Correlation The Nutritional Status and Metabolic Profile in Children and Adolescent Post-Therapy Acute Lymphoblastic Leukemia (ALL)

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ABSTRACT

Background: Cardiometabolic dysfunction including obesity, dyslipidemia, and diabetes are becoming problem for ALL survivors. During ALL therapy, the prevalence of obesity increases five to ten times, increasing the risk of long-term comorbidity and mortality in children and adolescents with ALL.

Objective: The aim of this study is to analyze the relationship between nutritional status and metabolic profile in children and adolescents with ALL survivors.

Method: This research is a cross-sectional study of children and adolescents with ALL who are routinely checked at the hematology clinic at RSUD dr. Soetomo Surabaya, selected using consecutive sampling. After anthropometric examination, blood examination was carried out together with a complete blood count, which is routinely conducted at the Clinical Pathology Laboratory. Data analysis used the Chi square test with a p value <0.05 considered significant.

Result: A total of 26 children and adolescents participated in this study, consisting of 18/26 boys and 8/26 girls. Normal nutritional status in 16 patients (61.5%), with 2 patients (7.7%) having hypertension. There were no patients with hyperglycemia, but 7 patients (26.9%) experienced dyslipidemia. The Chi-square test for the relationship between nutritional status and hypertension, as dyslipidemia, yielded p-values of 0.126 and 0.440, respectively.

Conclusion: ALL survivors' nutritional status varied from undernutrition to normal and overnutrition, with more than 50% having normal nutrition. BMI correlated with waist circumference as the major causes of MetS components (blood pressure, HDL-c, and triglyceride), while HAZ correlated with triglyceride and exhibited a negative correlation with HDL-c. There is no correlation between age at diagnosis groups or actual age with nutritional status, but reference age at diagnosis (2-5 years old) protected the ALL children against the abdominal obesity development, as it correlated with medical therapy risk.
Keywords: Acute lymphoblastic leukemia, metabolic syndrome, nutritional status

Introduction

Acute lymphoblastic leukaemia (ALL) is one of the most common cancers in children, impacting on the mortality The 5-year survival rate after diagnosis has increased in recent years, reaching 80% in developed countries (1), while 10-year event free survival reaching 83.1% and the overall survival was 88.4% (2). But this reality differs with the developing country due to abandonment treatment or younger age, leading to the increment of mortality rates (3), and the cure rate was less than 35% (4). ALL treatment for survivors can have survived leaving a long-term effect, such as secondary malignant neoplasms (SMNs), cardiac toxicity, neurotoxicity, bone toxicity, hepatic dysfunction, visual changes, obesity and fertility (5), that affecting the morbidity and premature mortality. Factors contributing to the late effects include the type and duration of treatment, age at the time of treatment, gender, and overall health status. (6).

Obesity is one of the morbidities of ALL medical treatment, along with the metabolic disease, had been developed during therapy (7), placing the paediatric ALL survivors to have a higher risk of obesity by 11-40% (6), or 9-times higher than normal children (8). Moreover, they had a high risk of developing cardiovascular disease. (7). A meta-analysis study noted the increment of 0.83-BMI z-score that equivalent with 80^{th} BMI percentile, or higher BMI than reference population, that related with cranial irradiation, gender, and age at diagnosis (9). A study investigating ALL survivors aged above 18 years old noted that 12% of the survivors had hypertension, 25% had hyperglycemia, 29.1% hypertriglyceridemia, and 12.5% had low HDL-C (10). Other findings also strengthen these findings: the prevalence of metabolic syndrome (MetS) was 16% in ALL survivors, both adolescents and adults (11), highlighting the needs of monitoring, assessment and long-term treatment for ALL survivors (12). MetS is defined as the presence of 3 out of 5 risk factors, namely abdominal obesity, hyperglycemia, hypertriglyceridemia, high-density lipoprotein (HDL) and hypertension (13), that increase the risk of diabetes and cardiovascular disease (CVD) (14). Regarding the facts mentioned above, this study was conducted to investigate the correlation between nutritional status and the MetS profile in pediatric survivors of acute lymphoblastic leukemia (ALL).

Methods

Study Design and Subjects

An analytic observational study with a cross-sectional study design was conducted from June to October 2024 at Dr. Soetomo General Teaching Hospital, Surabaya, involving ALL survivors proven by laboratory tests and bone marrow aspiration (BMA) performed by a hematological doctor and had completing the chemotherapy. Children with congenital diseases, diabetes mellitus (proven by HbA1C value greater than 6.5%) and relapse were excluded from the study. The study was conducted only when the parents, as caregivers, gave permission by signing informed consent, and information for consent was provided by the researchers.

Sample Size

The sample size was calculated using the formula below:

$$n = \left[\frac{Z_{1-1/2\,\alpha} + Z_{1-\beta}}{\frac{1}{2}\ln\left(\frac{1+r}{1-r}\right)} \right]^2 + 3$$

Notes:
n = number of samples required
Z1-1/2α = standard value according to the error rate α=5% is 1.96.
Z1-β = standard value according to the error rate β=20% is 0.84
r = correlation coefficient in previous research.

According to previous references, r = 0.49 (15). Based on the formula above, the number of samples needed was 26 patients.

MetS Determination

MetS was only determined for those above 10 years-old, but the parameters were recommended to measure in high-risk groups (family history of MetS, T2DM, dyslipidemia, CVD, hypertension, and/or obesity), including waist circumference (WC), fasting blood glucose (FBG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), systolic blood pressure (SBP), diastolic blood pressure (DBP), and total cholesterol. All the markers were measured at Dr. Soetomo General Teaching Hospital laboratory, and the blood withdrawal was done by the nurse. MetS criteria were based on the International Diabetes Foundation (IDF); stating that MetS was diagnosed when there was abdominal obesity followed by the presence of at least 2 or more metabolic markers, namely hypertriglyceridemia, hyperglycemia, hypertension, and a low-level of HDL-C (16).

Abdominal Obesity Determination

Abdominal obesity was determined when waist circumference was >90^{th} percentile (16), based on the study conducted by Poh et al. (17).

Hypertension Determination

Hypertension was determined for children (≤ 13 years old), thresholds for the definitions of elevated blood pressure and hypertension according to age and height: blood pressure ≥ 90th and <95th percentile designates elevated blood pressure, and ≥ 95th percentile indicates hypertension. For adolescents ≥13 years old, measurements ≥ 120/80 indicate elevated blood pressure and ≥ 130/80 meet the criteria for hypertension, based on the *American Academy of Pediatrics* 2017 recommendation (18).

Dyslipidemia Determination

Subjects were determined to have dyslipidemia if there were high levels of plasma cholesterol and/or triglycerides (TG) or a low level of HDL-C (19). The reference value to determine hypercholesterolemia was if the cholesterol level was ≥ 200 mg/dL (18), hypertriglyceridemia was determined based on IDF criteria: 10-16 years old ≥ 110 mg/dL, and above 16 years old ≥ 150 mg/dL (16), and for subjects under 10 years old we determined as ≥ 100 mg/dL. HDL-C was categorized as low if > 40 mg/dL for those under 10 years old (18).

Hyperglycemia Determination

Hyperglycemia was determined when fasting blood glucose (FGB) ≥ 100 mg/dL for children aged 10-16 years old, and ≥ 110 mg/dL for < 16 years old (16), for children < 10 years old, the diagnosis based on American Diabetes Association criteria (20).

Statistical Analysis

The data were analyzed using descriptive statistics, while the correlation was determined using Pearson (or Spearman Rho) correlation with a significance level of <0.05, along with chi-square analysis and Mantle Haenszel.

Ethical Clearance:

The study was conducted after receiving ethical approval from Dr. Soetomo General Teaching Hospital, number 2999/105/3/VI/2024 at July 10th 2024.

Results

A total of 26 children aged more than 5 years old were included in the study, with male-to-female ratio of 9:4, indicating that the proportion of male was twice that of females. Subject characteristics were summarized in Table 1.

Table 1. Subject's Characteristics

Subject's Characteristics	Mean + SD	Min-max
Age, in months	130 ± 43.90	66.00-214.00
Age at diagnosis, in months	93.88 ± 49.94	24.00-180.00
Chemotherapy duration, in months	25.15 ± 1.41	24.00-29.00
Body weight, in kg	36.28 ± 12.28	17.00-66.30
Body height, in cm	136.73 ± 16.76	105.00-170.00
BMI, in kg/m^2	19.19 ± 4.77	12.80-38.10
HAZ	-0.86 ± 1.16	-4.40 - 1.12
BMI-for-age z-score	0.67 ± 1.86	-3.79 - 5.14
Waist circumference, in cm	73.54 ± 7.71	65.00-96.00
SBP, in mmHg	109.23 ± 9.77	100.00-130.00
DBP, in mmHg	71.92 ± 6.94	60.00-80.00
FBG, in mg/dL	85.92 ± 9.31	68.00-105.00
Cholesterol, in mg/dL	162.54 ± 30.56	103.00-232.00
TG, in mg/dL	99.58 ± 55.04	30.00-260.00
HDL-c	48.00 ± 10.80	25.00-75.00
LDL-c	95.69 ± 23.23	48.00-154.00

MetS was found in one subject, but MetS components were detected, namely abdominal obesity (14 subjects or 53.85%), hypertension (2 subjects or 7.69%), hypertriglyceridemia (8 subjects or 30.77%) and low levels of HDL-c (3 subjects or 3.54%). Nutritional status investigation revealed that the prevalence of undernutrition was 19.23% respectively; stunted/severely stunted was 15.38%, underweight/severely underweight was 7.69%, and overweight/obesity was 19.23%.

Table 2 summarizes the correlation of nutritional status with MetS markers, revealing that BMI was strongly correlated with waist circumference (r=0.744, *P*=0.000), and HAZ was correlated with triglycerides (r=0.390, *P*=0.049), but correlated negatively with HDL-C (r=-397, *P*=0.045). While BMIZ did not show any correlation with MetS markers. Surprisingly, waist

circumference correlated with blood pressure, namely systolic BP (r=0.670, *P*=0.000), diastolic BP (r=0.526, *P*=0.006), LDL-C (r=0.397, *P*=0.045) and cholesterol level (r=0.432, *P*=0.028).

Table 2. Correlation between nutritional status index with MetS markers

Nutritional status	WC		FBG		TG		HDL-c		Systole-BP		Diastole-BP	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
HAZ	-0.039	0.109	-0.046	0.288	0.390	0.049	-0.397	0.045	-0.208	0.313	-0.139	0.345
BMI	0.744	0.000	-0.183	0.732	0.091	0.660	0.176	0.390	0.322	0.109	0.270	0.182
BMIZ	0.322	0.109	-0.331	0.009	0.142	0.489	0.142	0.489	-0.093	0.650	-0.140	0.496

Table 3 summarized the prevalence of MetS, dyslipidemia, and MetS markers based on nutritional status, which showed that all overweight/obese subjects had abdominal obesity compared to others (r=0.513, *P*=0.027). even-thought no significant different as the consequences of minimal subjects in the underweight, it seems that a low level of HDL-C was associated with underweight.

Table 3. Prevalent of MetS, dyslipidemia, and MetS markers based on nutritional status

Markers	Normal (n=19)	Overweight/obesity (n=5)	Underweight (n=2)	*P* value
Dyslipidemia	6 (31.58%)	1 (20%)	0 (0%)	1.000
Abdominal obesity	9 (47.37%)	5 (100%)	0 (0%)	0.027
Hypertension	1 (5.26%)	1 (20%)	0 (0%)	0.474
Hyperglycemia	0 (0%)	0 (0%)	0 (0%)	-
Hypertriglyceridemia	7 (36.84%)	1 (20%)	0 (0%)	0.342
Low level of HDL-C	2 (10.53%)	0 (0%)	1 (50%)	0.218
MetS	0 (0%)	1 (20%)	0 (0%)	0.211

Table 4 expressed the correlation of chemotherapy type with MetS, especially abdominal obesity (r=0.573, *P*=0.005), hypertriglyceridemia (r=592, *P*=0.016), and low level of HDL-C (r=0.611, *P*=0.005). for the prediction of abdominal obesity, it revealed that standard risk chemotherapy had a protective effect on abdominal obesity development by 0.051 (95% CI [0.005-0.514], *P*=0.012), with an accuracy of 73.1%.

Table 4. The correlation between chemotherapy with MetS, dyslipidemia, and MetS markers

Markers	Standard risk (n=10)	High risk (n=16)	r	*P* value
Dyslipidemia	3 (30%)	4 (25%)	-0.055	1.000
Abdominal obesity	9 (90%)	5 (31.25%)	0.573	0.005
Hypertension	0 (0%)	2 (12.50%)	0.228	0.508
Hyperglycemia	0 (0%)	0 (0%)	-	-
Hypertriglyceridemia	2 (20%)	6 (37.5%)	0.592	0.016
Low level of HDL-C	0 (0%)	3 (18.75%)	0.611	0.005
MetS	0 (0%)	1 (6.25%)	0.122	1.000

Discussion

The higher prevalent of ALL in males than female has been well-known in several study (21–24), with poorer outcomes than female, marked by lower event-free (84.6% ± 0.5% vs. 86.0%

± 0.6%; p=0.009) and overall survival (91.3% ± 0.4% vs. 92.5% ± 0.4%; p=0.02) (22). This study also highlighted a frequent of undernutrition among ALL survivors, that in line with other: 40% were underweight, and 10% were stunted (25). Medical treatment exposure causes a decrease in adult height among survivors of acute lymphoblastic leukemia (ALL) and increases the risk of short stature by 3.4 times compared with their siblings. This short stature is also associated with the age of diagnosis (during puberty), cranial radiotherapy (greater than 20 Gy), and female sex. (26). A study noted there were a decrease of body height/ length (HAZ/LAZ) in the high-risk treatment group (27).

Age at diagnosis is a significant prognostic factor related to the treatment outcomes of acute lymphoblastic leukemia (ALL). (28). A study noted the onset of ALL at the age of 2 and 5 years, with the incidence rate of more than 80 cases/1,000,000 per year (29) while other noted the frequent cases in aged 1 to 10 years (28). Our study revealed the correlation of ALL age-onset with the development of abdominal obesity, highlighting the role of age as a prognostic factor (30), in which age-diagnosed between 1-4 years old had the highest survival rate (5-year event-free survival was 80% (30). The age during medical intervention impacts the metabolic profile, as it inhibits the normal growth pattern, leading survivors to develop endocrine disorders such as insulin resistance. This evidence notes a negative correlation between target height and age at treatment. (31). However other found the younger age at diagnosis and treatment, the better prognosis, especially at the age of 2-5 years old (32,33), while older children and adolescents had a bad prognosis (34). MetS also correlated with older age; for every 5-year increment, there was an increased risk of developing MetS by 1.13-times (35).

High prevalent of MetS and obesity in ALL survivors is related to the medical therapy (radiotherapy, chemotherapy, glucocorticoid therapy, and surgery) causing metabolic alterations, vascular changes, and hormone deficiencies (36). All of those treatment producing inflammatory and prothrombotic responses, leading on cardiovascular toxicity and atherosclerosis development, marked with the body weight gain (35). Thus, uncontrolled body weight gain highlights the importance of MetS development in the form of obesity (36). A study found the increment of overweight/obesity, 4.2% at diagnosis to 37.5% after intensive therapy, suggesting weight gain and increased BMI during treatment (27). Several factors are associated with obesity in ALL survivors, including cranial radiation, female gender, and glucocorticoid administration (36).

A study has shown that BMI correlates with the apolipoprotein profile (Apo-C1, Apo-C3, Apo-H, and Apo-J) (37). It was found that the risk of developing MetS and its components is related to cranial radiotherapy (38) and total body irradiation (TBI)-based hematopoietic cell transplantation (HCT) (39,40). The most frequent MetS found were abdominal obesity, hypertension, insulin resistance, and dyslipidemia (40). Overweight/obesity, dyslipidemia, and insulin resistance were frequently experienced by women, while hypertension occurred in men (38). Medical treatments such as brain surgery and radiotherapy casuing the hypothalamic-pituitary axis, with further consequences of pituitary hormone deficiencies, while local therapy in endocrine organs causes hormone deficiencies, meanwhile chemotherapeutic agents damage the vasculature by increasing the oxidative stress, increasing the possibility of MetS development. All of those were the pathological causes of obesity and dyslipidemia in ALL survivors (41).

Our study highlighted that the high risk of abdominal obesity was associated with age at diagnosis and treatment risk. Abdominal obesity correlated significantly with BMI. These findings are in line with others, that overweight/obese survivors had a higher risk of MetS

(39,42,43) with abdominal obesity as the onset of metabolic alterations (44). A study noted a higher prevalence of abdominal obesity than obesity itself, with 38.8% vs. 23.9% after treatment completion in ALL children, with sex, cranial radiotherapy, BMI-for-age z-score at diagnosis, treatment risk (high risk) dietary energy intake, and physical activity as the risk factors (45), that in line with our findings: age at diagnosis and treatment risk (high risk) correlated with the presence of abdominal obesity. The treatment risk is also associated with the presence of hypertriglyceridemia and a low level of HDL-C (46), that also noted in other study, 50% of ALL survivors had dyslipidemia (hypertriglyceride, high LDL-c and low HDL-c), with low level of Apo A-I, but high level of Apo B-100 and C-II (47). Even when diagnosed, 99% children with ALL have experienced dyslipidemia in the form of low HDL-C (98%) and mild hypertriglyceridemia (61%) (48).

Nutritional assessment, including HAZ, showed a correlation with TG and HDL-C. no study has highlighted the role of HAZ on the lipid profile so far, but taller male adolescents are more likely to have lower cholesterol levels and LDL-C, but higher blood pressures (49). Also, there is evidence that good growth trajectories during early childhood (aged 3 months to 36 months) were associated with lower HDL and higher TG in later adolescence (50). We suggest several other factors involved in this relationship, including the treatment risk, as high-risk chemotherapy was predominant in this study, along with the age group (predominantly age > 5 years old).

Our study had several limitations as we did not record the nutritional status at diagnosis, nutritional intake during therapy, and other therapies including radiotherapy, glucocorticoid therapy, and surgery). All of which limit our analysis regarding the study. Furthermore, our study did not enrolled insulin as one of the major causes of MetS and other related disease.

Conclusion

The nutritional status of ALL survivors ranged from undernutrition to normal and overnutrition, with more than 50% having a normal nutritional status. BMI correlated with waist circumference as the major causes of MetS components (blood pressure, HDL-c, and triglyceride), while HAZ correlated with triglyceride and exhibited a negative correlation with HDL-c. There is no correlation between the age at diagnosed groups or actual age and nutritional status. However, the reference age at diagnosis (2-5 years old) protected the ALL children against the development of abdominal obesity, as it correlated with the risk of medical therapy.

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Conflict of Interest

The authors declare they had no conflict of interest.

Authors Contribution

Conceptualization, methodology, and investigation, writing original draft; RI: methodology and investigation; MRA: conceptualization, methodology, editing

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