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Original article

High prevalence of metabolic syndrome and insulin resistance in adolescents receiving chemotherapy for acute lymphoblastic leukemia

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Abstract. *Background and aim:* Acute lymphoblastic leukemia (ALL) is a common pediatric cancer with improved survival rates due to advancements in chemotherapy. However, adolescents with ALL face an elevated risk of insulin resistance and metabolic syndrome, complicating treatment outcomes and increasing long-term risks for cardiovascular disease and type 2 diabetes. This study aimed to assess the prevalence of insulin resistance and metabolic syndrome in overweight and obese adolescents undergoing maintenance chemotherapy for ALL, compared to a control group without ALL. *Methods:* An observational case-control study was conducted involving 45 adolescents, with 9 in the case group (overweight and obese adolescents with ALL) and 36 in the control group (overweight and obese adolescents without ALL). Insulin resistance was assessed using the HOMA-IR, and metabolic syndrome was diagnosed based on the IDF criteria. The statistical analysis included independent-sample t-tests, chi-square tests, and logistic regression. *Results:* The prevalence of insulin resistance was significantly higher in the case group compared to the control group (88.9% vs. 47.2%, $P < 0.05$), with a mean HOMA-IR score of 5.94 ± 3.98 in the case group and 2.73 ± 1.20 in the control group. Metabolic syndrome prevalence was also higher in the case group (66.7% vs. 22.2%, $P < 0.05$). Adolescents with ALL had a 10-fold increased risk of developing insulin resistance and metabolic syndrome simultaneously (95% CI: 1.8–53.4; $P < 0.05$). *Conclusions:* Overweight and obese adolescents undergoing chemotherapy for ALL were at significantly higher risk of insulin resistance and metabolic syndrome. Early screening and intervention during chemotherapy are essential to mitigate long-term metabolic risks and improve overall outcomes. Limited number of participants indicates the necessity for more extensive research. (www.actabiomedica.it)

Key words: acute lymphoblastic leukemia, insulin resistance, metabolic syndrome, adolescent, antineoplastic agents

Introduction

Acute lymphoblastic leukemia (ALL) is among the most common pediatric cancers, accounting for more than 80% of leukemia cases in children and adolescents. Over recent decades, advancements in chemotherapy and supportive care have dramatically improved survival rates in pediatric ALL. However, long-term survivors face an increased risk of metabolic disorders, including obesity, insulin resistance, and metabolic syndrome, which can negatively impact their quality of life and long-term health outcomes (1,2). These conditions are particularly concerning in pediatric ALL survivors due to the early onset of such metabolic dysfunctions, which may exacerbate the risk of cardiovascular diseases and type 2 diabetes in later

life. The incidence of obesity in ALL survivors has been well-documented. Study reported that up to 38% of children treated for ALL develop obesity, compared to 31% of the general pediatric population (3). The etiology behind this increased obesity risk is multifactorial, involving prolonged exposure to corticosteroids, reduced physical activity, and altered energy metabolism as a result of both the disease and its treatment (4). Corticosteroids such as prednisolone and dexamethasone, commonly used during ALL treatment, are known to contribute to hyperglycemia and insulin resistance, further predisposing survivors to metabolic syndrome (5). Although several studies have examined the long term prevalence of obesity and metabolic syndrome in ALL survivors, limited data exist on the prevalence of insulin resistance and metabolic syndrome during the active chemotherapy phase, particularly in overweight and obese adolescents undergoing maintenance chemotherapy (2). Few studies focusing on active treatment predominantly report younger children, with minimal emphasis on high risk adolescent who may present more pronounced metabolic dysfunction due to intensive chemotherapy regimens (6). The novelty of this study lies in addresing specific population and treatment phase, providing critical insights for metabolic risks during active chemotherapy. Early identification and intervention in this population are essential to prevent further progression and reduce long-term risks (3). The objectives of this study were to analyze the risk of developing insulin resistance and metabolic syndrome in overweight and obese adolescents with ALL who were currently undergoing maintenance chemotherapy, determine the incidence of these metabolic conditions, identify risk factors, and compare findings with a control group of overweight adolescents without ALL. This study aims to bridge the knowledge gap regarding metabolic dysfunctions during active treatment and provides insights for early screening and management strategies to improve outcomes and quality of life for ALL survivors (6).

Patients and Methods

This was an observational case-control study aimed at assessing the risks of insulin resistance and metabolic syndrome in overweight and obese adolescents with ALL undergoing maintenance chemotherapy. The study population comprised adolescents aged 10–18 years, recruited from the Pediatric Hematology and Oncology Department at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. A total sampling method was used during the 9-month recruitment period, yielding a sample size of 45, with 9 participants in the case group and 36 in the control group (ratio 1:4) due to limitation of finding subjects in case group that meet the inclusion criteria. Given the relatively small sampel size, a power calculation was performed, showing that sample size offers sufficient power to detect significant differences in primary outcomes, although it may limit the generalizability of findings. The control group consisted of overweight and obese adolescents without ALL, matched by age and body mass index (BMI). Control group participants were additionally matched on lifestyle factors, where possible, such as socioeconomic status and general activity level to enhance comparability. However, variations in diet, physical activity, and family history of metabolic disorders between groups were not controlled for and are acknowledged as potential confounders. The inclusion criteria for the case group were adolescents diagnosed with ALL who were currently undergoing maintenance chemotherapy and had a BMI indicating overweight or obesity (BMI ≥85th percentile for age and sex based on CDC growth charts). The control group included adolescents who were also overweight or obese but without any history of leukemia or chemotherapy. The exclusion criteria for both groups were a history of congenital disorders, genetic syndromes, or any other chronic conditions that could independently influence insulin resistance or metabolic syndrome. Ethical approval for this study was obtained from the Ethics Committee of RSUD Dr. Soetomo, Surabaya, Indonesia (approval number: 0631/KEPK/III/2023). Informed consent was obtained from all participants and their guardians before enrollment in the study. Anthropometric measurements, comprising weight, height, and waist circumference, were taken for all participants. BMI was calculated as weight (kg) divided by height squared (m^2) and categorized according to the CDC growth charts. Insulin resistance was assessed using the Homeostasis Model Assessment of Insulin

Resistance (HOMA-IR), calculated using fasting insulin and fasting glucose levels. Metabolic syndrome was diagnosed based on the International Diabetes Federation (IDF) criteria: central obesity, elevated triglycerides, low high-density lipoprotein cholesterol (HDL-c), high blood pressure, and elevated fasting glucose levels. The data were analyzed using SPSS version 25.0. Descriptive statistics were used to summarize the baseline characteristics of the case and control groups. Continuous variables were compared using independent-sample t-tests or the Mann–Whitney U test, depending on the distribution of the data. Categorical variables were analyzed using chi-square tests. Multivariate logistic regression was conducted to identify factors associated with insulin resistance and metabolic syndrome, adjusting for the potential confounders of age, sex, and BMI. Additional potential confounders, such as diet, physical activity, and family history, were not adjusted for, given data limitations, and are recognized as study limitations. A *P*-value of less than 0.05 was considered statistically significant.

Results

A total of 45 participants were enrolled in this study, with nine in the case group (overweight and obese adolescents with ALL undergoing maintenance chemotherapy) and 36 in the control group (overweight and obese adolescents without ALL). A 1:4 ratio was used between the numbers of cases and controls. Baseline characteristics, including age, sex, and BMI, are shown in Table 1. The mean waist circumference was larger in the case group (90.22 ± 11.41 cm vs. 86.1 ± 7.24 cm), as was the waist-to-hip ratio (Table 1).

Significant differences existed between the groups in insulin, HOMA-IR, and HDL values (Figure 1). The case group had significantly lower HDL levels and higher insulin levels, thus creating higher HOMA-IR values, compared to the control group ($P < 0.05$). Triglyceride, total cholesterol, and fasting blood sugar levels were higher for the case group than the control group, but they were not statistically different (Table 2).

The prevalence of insulin resistance, as measured by the HOMA-IR, was significantly higher in the case group compared to the control group

Table 1. Characteristics and Anthropometric Measurements of Case Group and Control Group

Parameter	Case Group (Mean ± SD) n = 9	Control Group (Mean ± SD) n = 36
Sex	Male (n=7) Female (n=2)	Male (n=17) Female (n=19)
Age (years)	15.3 ± 1.77	15.1 ± 1.82
Weight (kg)	53.88 ± 9.38	76.95 ± 11.51
Height (cm)	1.44 ± 0.11	1.57 ± 0.07
BMI (kg/m²)	26.08 ± 4.60	30.51 ± 2.86
Waist circumference (cm)	90.22 ± 11.41	86.1 ± 7.24
Hip circumference (cm)	88.05 ± 7.92	104.03 ± 7.65
Waist-to-hip ratio	1.02 ± 0.79	0.94 ± 0.50
Waist-to-height ratio	0.62 ± 0.11	0.62 ± 1.34

(88.9% vs. 47.2%, $P < 0.05$). Multivariate logistic regression showed that adolescents with ALL had an 8.9-fold increased risk of developing insulin resistance (95% CI: 1.011–79.049; $P < 0.05$), as shown in Table 3. The prevalence of metabolic syndrome, defined according to IDF criteria, was also significantly higher in the case group (66.7%) compared to the control group (22.2%), with a 7-fold increased risk (95% CI: 1.4–34.4; $P < 0.05$). The incidence of insulin resistance and metabolic syndrome occurring simultaneously was significantly higher in the case group compared to the control group (55.6% vs. 11.1%, $P < 0.05$). Adolescents with ALL were 10 times more likely to develop both conditions compared to the control group (95% CI: 1.8–53.4; $P < 0.05$; Figure 2).

Discussion

Insulin resistance was significantly higher in the case group (88.9%) compared to the control group (32.3%). Adolescents with ALL had a mean HOMA-IR score of 5.94 ± 3.98, which was substantially higher than the control group's mean score of 2.73 ± 1.20. The prevalence of metabolic syndrome was also markedly higher in the case group (66.7%) compared to

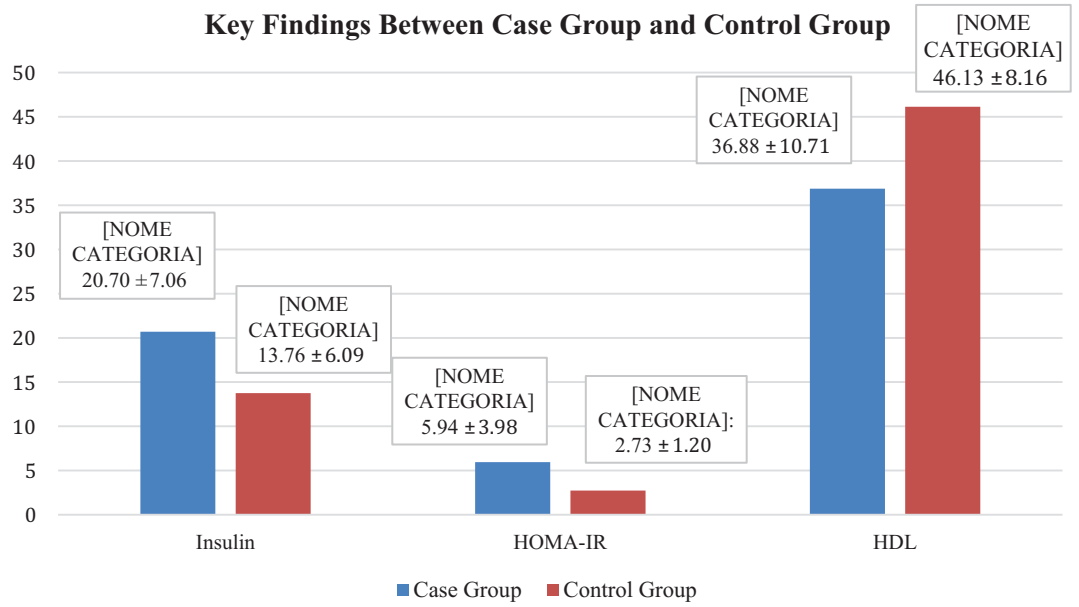

Figure 1. Key Findings Between Overweight and Obese Adolescents with and Without ALL

Table 2 Metabolic Parameters of Participants

Parameter	Case Group (Mean ± SD)	Control Group (Mean ± SD)	*P*-value
Insulin (μU/mL)	20.70 ± 7.06	13.76 ± 6.09	0.020[a*]
HOMA-IR	5.94 ± 3.98	2.73 ± 1.20	0.005[b]
HDL (mg/dL)	36.88 ± 10.71	46.13 ± 8.16	0.035[a*]
LDL (mg/dL)	111.77 ± 35.65	113.00 ± 28.47	0.921[b]
Triglycerides (mg/dL)	140.22 ± 71.63	101.33 ± 51.03	0.156[a]
Total cholesterol (mg/dL)	179.77 ± 25.31	171.00 ± 31.12	0.390[a]
Fasting blood sugar (mg/dL)	106.77 ± 37.23	79.91 ± 6.12	0.063[a]

[a] Independent-sample t-test; [b] Mann–Whitney U test, [*]significant if $P < 0.05$

Table 3. Prevalence of Insulin Resistance and Metabolic Syndrome in Case and Control Groups

Parameter	Case Group (%)	Control Group (%)	Odds Ratio	P-value
Insulin resistance	88.9	47.2	8.9 (95% CI: 1.011–79.049)	**0.049**[ab*]
Metabolic syndrome	66.7	22.2	7.0 (95% CI: 1.4–34.4)	**0.017**[ab*]
Insulin resistance with metabolic syndrome	55.6	11.1	10.0 (95% CI: 1.8–53.4)	**0.007**[ab*]

[a] Chi-square test; [b] logistic regression, [*]significant if $P < 0.05$

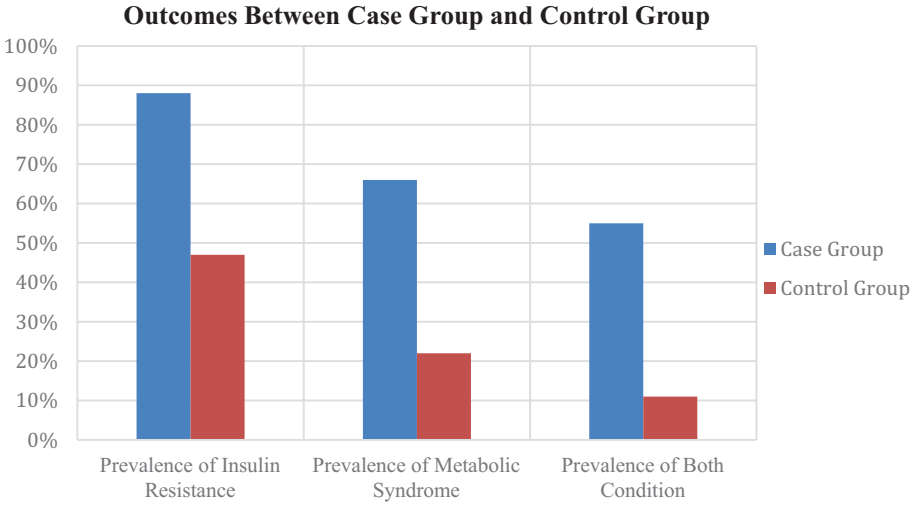

Figure 2. Comparison of Outcomes Between Overweight and Obese Adolescents With and Without ALL

the control group (19.4%), with central obesity and elevated fasting glucose levels being the most common components. These findings underscore the heightened risk of metabolic dysfunction in adolescents undergoing chemotherapy for ALL, with a notable 8.9-fold increased risk of insulin resistance and a 10-fold increased risk of developing insulin resistance and metabolic syndrome simultaneously. The findings of this study align with prior research indicating that survivors of pediatric ALL face an elevated risk of metabolic disorders, primarily due to the extended use of corticosteroids such as prednisolone and dexamethasone, which can impair glucose metabolism and contribute to obesity (3). Previous studies have also demonstrated that hematopoietic stem cell transplantation in children with leukemia poses significant risks for metabolic syndrome, further corroborating the findings in this study, particularly regarding increased metabolic dysfunction due to age and treatment regimens (7). Our study extends current knowledge by focusing on adolescents actively undergoing chemotherapy, rather than solely on post-treatment survivors. This distinction is crucial because it highlights the development of metabolic abnormalities during active treatment, which may require earlier intervention. Studies have predominantly focused on long-term metabolic outcomes in ALL survivors, noting similar risks for insulin resistance and obesity (8,9). However, our findings suggest that these metabolic risks, such as insulin resistance and metabolic syndrome, are already present during the maintenance chemotherapy phase, rather than manifesting only after treatment completion (10). Interestingly, the magnitude of insulin resistance observed in our cohort exceeded some previous estimates. This discrepancy may be attributed to differences in population characteristics, treatment regimens, or the younger age and higher doses of corticosteroids administered in our cohort. Previous research has indicated that younger ALL patients exposed to corticosteroids are particularly susceptible to disruptions in glucose metabolism and weight gain during treatment (11). These discrepancies underscore the need for further investigation into how specific treatment protocols and patient characteristics influence metabolic outcomes in ALL patients (12). The practical implications of these findings are significant, particularly in the context of early intervention strategies for metabolic dysfunction in adolescents with ALL. Clinicians should be aware of the heightened risk for insulin resistance and metabolic syndrome during active chemotherapy, not just in post-treatment survivors. Given that metabolic syndrome is associated with an increased risk of cardiovascular disease and type 2 diabetes, early screening and intervention for these metabolic conditions are crucial to improve long-term health outcomes in ALL patients (1). From a clinical perspective, routine

monitoring of glucose metabolism and lipid profiles should be integrated into the treatment protocols for adolescents undergoing chemotherapy for ALL. Lifestyle interventions, such as dietary modification and physical activity promotion, may help mitigate some of the metabolic side effects of chemotherapy (2). Special attention for children of 10 years of age and older, who are at higher risk, HbA1c dan fasting blood glucose can be measured every 3 months (13). Pharmacological interventions, such as metformin, may also be considered for improving insulin sensitivity in patients who exhibit early signs of metabolic dysfunction (14). Theoretically, these findings contribute to a growing body of literature on the metabolic complications of pediatric cancer treatments. They highlight the need to consider not only the long-term health outcomes of cancer survivors but also the metabolic risks that arise during treatment itself. Future research should explore whether early metabolic intervention during chemotherapy could improve survival outcomes and reduce the incidence of long-term comorbidities such as cardiovascular disease (15). A key strength of this study is its focus on adolescents undergoing active chemotherapy, a population that has been under-researched in terms of metabolic complications. By comparing overweight and obese adolescents with ALL to a control group of similarly overweight adolescents without cancer, we isolated the impact of chemotherapy on metabolic outcomes. The use of objective measures, such as HOMA-IR and waist circumference, also strengthens the validity of our findings (16). These indicators are essential in predicting metabolic syndrome and insulin resistance, ensuring robust and reliable results. Several limitations must be acknowledged. First, the sample size may limit the generalizability of our findings. Larger studies are needed to confirm the results and explore potential interactions between other variables, such as treatment intensity and duration. Second, the cross-sectional design of this study prevents us from drawing conclusions about the causal relationship between chemotherapy and metabolic dysfunction. Longitudinal studies are necessary to determine whether the observed metabolic abnormalities persist or worsen after treatment completion (17). Lastly, although we adjusted for age, sex, and BMI, other confounding factors, such as genetic predispositions or dietary habits, were not considered and may have influenced the results (18). Given the findings and limitations of this study, several avenues for future research are suggested. First, larger, multi-center studies should be conducted to confirm the prevalence of insulin resistance and metabolic syndrome in adolescents undergoing chemotherapy for ALL. These studies should include longitudinal follow-up to assess the persistence of metabolic dysfunction after treatment and identify potential long-term cardiovascular risks (17). Future research should also explore the mechanisms underlying the development of metabolic syndrome during chemotherapy. Specifically, studies investigating the role of corticosteroids in disrupting glucose metabolism, as well as potential genetic factors that may predispose certain individuals to metabolic dysfunction, would be valuable. Understanding these mechanisms could inform the development of targeted interventions aimed at reducing the metabolic side effects of chemotherapy (19). Intervention studies are also needed to determine the efficacy of early lifestyle or pharmacological interventions in preventing or mitigating metabolic syndrome in ALL patients. Randomized controlled trials assessing the impact of dietary interventions, physical activity, and pharmacological agents such as metformin or insulin sensitizers could provide valuable insights into how best to manage these metabolic risks during treatment (14). Finally, exploring the psychological and behavioral factors that contribute to metabolic dysfunction in adolescents undergoing cancer treatment may be beneficial. Research into how cancer-related fatigue, stress, and reduced physical activity contribute to weight gain and insulin resistance could inform the development of holistic care approaches that address the physical and mental health needs of these patients (20).

Conclusion

This study highlights the significant metabolic risks faced by overweight and obese adolescents undergoing chemotherapy for ALL, with a markedly higher prevalence of insulin resistance and metabolic syndrome compared to their peers without cancer. These findings emphasize the need for early screening and intervention during chemotherapy to mitigate long-term health risks associated with metabolic dysfunction.

Given the relatively small sample size, multi-center studies or collaborative research efforts are essential to confirm these findings and ensure broader applicability. Both healthcare providers and families play a critical role in addressing the metabolic challenges during ALL treatment, from implementing regular metabolic screenings to supporting dietary and lifestyle modifications that can reduce risk. Although this study provides important insights, further research is required to confirm these findings, explore underlying mechanisms, and develop effective intervention strategies. By addressing these gaps, we can improve the short- and long-term health outcomes of adolescents with ALL, ultimately enhancing their quality of life and survival.

Abbreviations: ALL: acute lymphoblastic leukemia; BMI: body mass index; CDC: Centers for Disease Control and Prevention; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IDF: International Diabetes Federation.

Ethic Approval: Ethical approval for this study was obtained from the Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (approval number: 0631/KEPK/III/2023).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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