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Metabolic Syndrome in Survivors of Pediatric Acute Lymphoblastic Leukemia in a Tertiary Care Hospital in Bangladesh

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Abstract:

Background: *Acute Lymphoblastic Leukemia (ALL) is indeed the most common childhood malignancy, and advancements in multi-modality therapies and supportive care have significantly improved survival rates. However, survivors are at a lifelong risk for treatment-related complications, which can impact their quality of life. This study aimed to evaluate the prevalence and contributing factors of metabolic syndrome in survivors of pediatric acute lymphoblastic leukemia*

Methods: *This cross-sectional study was conducted in the Department of Pediatric Hematology & Oncology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh from January 2023 to December 2023. Forty-eight children who were survivors of acute lymphoblastic leukemia (ALL) were included in the study purposively. Detailed history, physical examination, and relevant laboratory investigations to diagnose metabolic syndrome were performed. Statistical analysis was conducted using the SPSS version 23.0 software*

Results: *The prevalence of metabolic syndrome (MS) among participants was 20.8%. Logistic regression analysis showed a strong association between central obesity and MS ($p<0.001$). Individuals who were overweight or obese were about 5.7 times more likely to develop MS ($p=0.017$). Elevated blood pressure significantly increased the likelihood of MS by 12.75 times ($p=0.001$). Furthermore, low HDL cholesterol, elevated triglyceride levels, and elevated fasting glucose levels were significantly associated with a higher risk of MS ($p<0.05$).*

Conclusion: *One in five pediatric survivors of acute lymphoblastic leukemia may develop metabolic syndrome. Clinical indicators include central obesity, obesity, overweight, and elevated blood pressure, with central obesity posing the highest risk for developing metabolic syndrome.*

Keywords: *Acute lymphoblastic leukemia, Bangladesh, Metabolic syndrome, Pediatric, Prevalence, Survivors*

1. INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) indeed represents about 25% of childhood cancers, as highlighted by Kakaje et al. (2020) [1]. Over the past few decades, treatment outcomes for childhood ALL have improved significantly, even resource-limited countries, showed remarkable success as noted by Arora et al. (2020) [2]. The average five-year survival rate for ALL in developed countries is around 93.5% [3], while it ranges from 45% to 81% in developing countries [2]. Despite the lower survival rates in some low and middle-income countries, many are showing promising improvements. However, as survival rates increase, there is a growing emphasis on the long-term adverse effects. A high or severe burden of adverse events is observed in 55% of survivors, making them potential candidates for treatment-related complications [4]. Studies suggest that ALL survivors face risks for obesity, diabetes, dyslipidemia, and metabolic syndrome, each contributing to an increased risk of cardiovascular disease, which can be potentially preventable [5]. Previous studies indicate that the prevalence of metabolic syndrome (MS) among adult survivors of pediatric ALL ranges from 6.9% to 33.6% [6]. MS is characterized by a combination of cardiovascular risk factors, including abdominal obesity, dyslipidemia, impaired glucose tolerance, and elevated blood pressure. Its development in childhood cancer survivors is a potential marker for cardiovascular morbidity and early mortality [7]. Since MS is preventable, early identification is crucial. A study by Zareifar et al. (2017) [8] assessed metabolic syndrome prevalence among 53 survivors by evaluating serum triglycerides, cholesterol, FBS, insulin, leptin, blood pressure, and BMI. They found that 24.53% of participants were overweight and 39.6% had metabolic syndrome. The study highlighted that being overweight, linked to higher blood leptin levels and BMI. The authors stressed the importance of incorporating metabolic syndrome criteria, including triglycerides, into follow-up visits for pediatric ALL survivors. The study by Kartal et al. (2022) [9] investigated long-term complications among childhood leukemia and lymphoma survivors, including 89 patients treated from 2000 to 2012. This study evaluated family history, demographics, anthropometrics, and lab results, finding that 20% of patients were obese, 15.7% had increased blood pressure, and 15% showed impaired glucose tolerance. Those with metabolic issues often had family histories of hypertension, dyslipidemia, and cardiovascular diseases. The study pointed out that metabolic syndrome progressively increases from the start of treatment, highlighting the need for regular follow-ups to monitor and manage these late effects. There is currently no published data from Bangladesh on the prevalence of metabolic syndrome among pediatric ALL survivors. Therefore, this study aimed to determine the prevalence and contributing factors of metabolic syndrome in pediatric acute lymphoblastic leukemia survivors.

2. METHODOLOGY

This study employed a cross-sectional design and was conducted within the Department of Pediatric Hematology & Oncology at Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh, spanning from January2023 to December 2023. The study sample comprised 48 children who were survivors of Acute Lymphoblastic Leukemia (ALL). Participants were selected using a convenient purposive sampling method. We excluded individuals displaying psychomotor delays, mental retardation, or pre-existing thyroid disorders, based on the study's exclusion criteria. For each participant, detailed medical histories were taken, followed by physical examinations and relevant laboratory tests to diagnose metabolic syndrome. The study adhered to the ethical principles outlined in the Declaration of Helsinki and was conducted following relevant regulations and the General Data Protection Regulation (GDPR). The study posed minimal physical risk, and informed consent was obtained from the parents or participants after a clear explanation of the study's purpose and procedures was provided. Approximately 5 ml of fasting blood was drawn from each participant, with samples sent to the laboratory for analysis. Lipid profiles and fasting blood sugar (FBS) levels were assessed using established protocols, and components of metabolic syndrome were evaluated. Data analysis was performed using SPSS software, version 23.0.

3. RESULT

In this study, most patients (87.5%) were diagnosed before age 10, with 12.5% diagnosed at 10 or older, and a mean diagnosis age of 5.53±3.31 years. At survivor enrollment, 27.1% were under 10, 60.4% were aged 10-18, and 12.5% were over 18, with a mean enrollment age of 13.2±3.54 years. Among 48 patients, 30 (62%) were male and 18% (38) were female. The diagnosis breakdown showed that 87.5% of patients were diagnosed with ALL-B, while 12.5% had ALL-T. Among survivors, 54.2% received the UK ALL-B regimen and 45.8% received the UK ALL-A regimen, following UKALL-2019 guidelines. The prevalence of having one, two, or three or more components of metabolic syndrome was 58.3%, 20.8%, and 20.8%, respectively. The prevalence of metabolic syndrome among participants was 20.8% (n=10). In analyzing the association of demographic risk factors with MS in survivors of pediatric ALL we did not find any significant correlation. The study found significant associations between clinical risk factors and metabolic syndrome (MS) in pediatric ALL survivors. Overweight/obesity was more common in those with MS (70.0%) compared to those without (29.0%; $p = 0.017$). Central obesity was also significantly higher in MS individuals (90.0% vs. 10.5%; $p < 0.001$). Additionally, elevated blood pressure was more prevalent in the MS group (60.0% vs. 10.5%; $p < 0.001$). The study showed that individuals with metabolic syndrome (MS) had significantly higher rates of low HDL cholesterol (80% vs. 34.2%; $p = 0.009$) and elevated triglyceride levels (100.0% vs. 39.5%; $p < 0.001$) compared to those without MS, underscoring dyslipidemia as a key feature of MS. Elevated fasting glucose levels were also significantly more common in MS individuals (20.0% vs. 2.6%; p=0.044), indicating impaired glucose metabolism. The study found that patients with metabolic syndrome (MS) had significantly higher triglyceride levels (158.8±47.2 mg/dl) than those without MS (87.9±24.1 mg/dl; p=0.003). HDL levels were notably lower in the MS group (38.2±8.3 mg/dl) compared to the non-MS group (51.1±23.0 mg/dl; p=0.043). However, no significant differences were observed in cholesterol and LDL levels between the groups. As per the logistic regression analysis, central obesity demonstrates an association with individuals exhibiting central obesity having a remarkably elevated risk of MS ($p< 0.001$). Overweight/obesity emerges as a significant risk factor, with individuals in this category being approximately 5.7 times more likely to develop MS compared to those without overweight/obesity (p=0.017). Elevated blood pressure was another significant predictor, with individuals having elevated blood pressure showing a 12.75 times higher likelihood of MS ($p = 0.001$). Additionally, low HDL cholesterol, elevated triglyceride levels, and elevated fasting glucose levels were significantly associated with an increased risk of MS ($p<0.05$).

Table 1. *Distribution of diagnosis and treatment protocol among survivors (N=48)*

Characteristics	n	%
Diagnosis		
ALL-B	42	87.5
ALL-T	6	12.5
Treatment protocol		
UK ALL-A	22	45.8
UK ALL-B	26	54.2

Table 2. *Distribution of metabolic syndrome components by gender (N=48)*

Prevalence of components of MS	Male	Female	Total
	(n=30)	(n=18)	(n=48)
	No. (%)	No. (%)	No. (%)
One component	15(50.0%)	13(72.2%)	28(58.4%)
Two-component	7(23.3%)	3(16.7%)	10(20.8%)

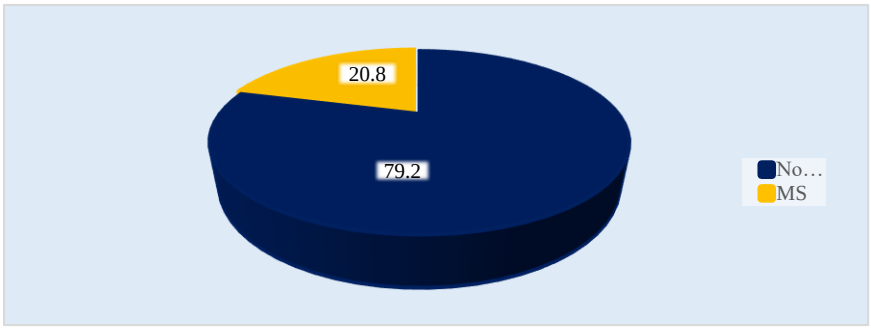

Figure 1. *Pie chart showed prevalence of metabolic syndrome among participants (N=48)*

Table 3. *Association of demographic risk factors with MS in survivors of pediatric ALL (N=48)*

Outcome Variable: MS	MS	Not MS	P value
Age at initial ALL diagnosis			
<10 year	<10 year	<10 year	<10 year
≥10 years	≥10 years	≥10 years	≥10 years
Age at survivor enrollment(years)			
Mean ±SD	15.0±4.05	12.8±3.0	0.061
Duration after Rx completion	4.46±1.60	4.16±1.63	0.605
Gender			
Male	8(80.0%)	22(57.9%)	0.199
Female	2(20.0%)	16(42.0%)	
UK ALL 2019 guideline			
Standard risk	6(60.0%)	29(76.3%)	0.302
High risk	4(40.0%)	9(23.7%)	

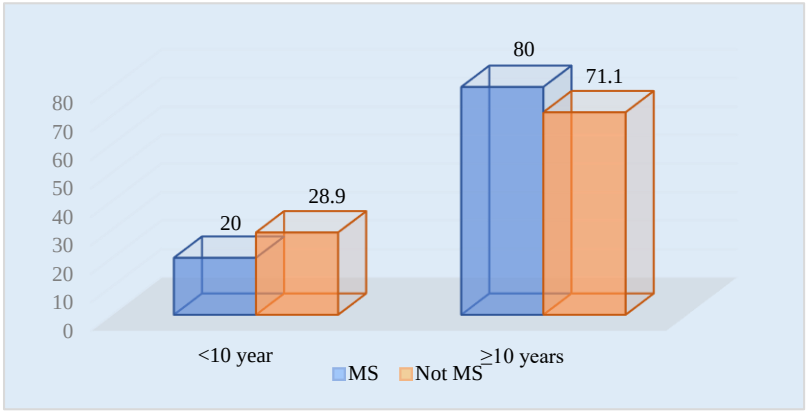

Figure 2. *Column chart showed group wise age at initial ALL diagnosis (N=48)*

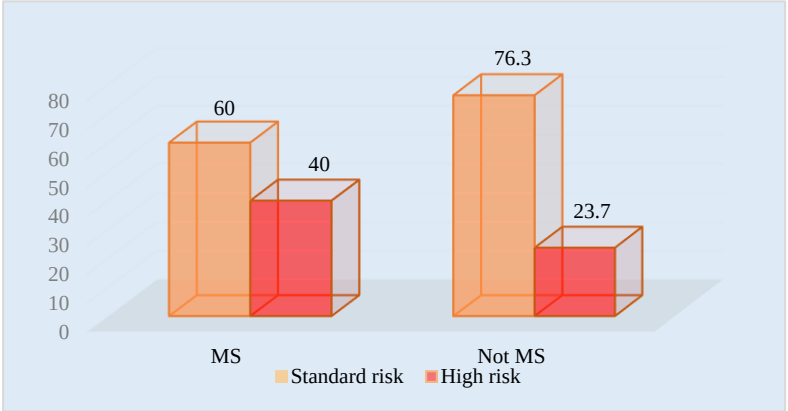

Figure 3. *Column chart showed group wise age at initial ALL diagnosis (N=48)*

Table 4. *Association of clinical components with MS in survivors of pediatric ALL (N=48)*

Clinical Component	MS (n=10)	Not MS (n=38)	P value
Obesity (by BMI)			
Yes	7(70.0%)	11(29.0%)	0.017
No	3(30.0%)	27(71.0%)	
Central obesity (by WC)			
Yes	Yes	Yes	<0.001
No	No	No	
Elevated blood pressure			
Present	Present	Present	<0.001
Absent	Absent	Absent	

Table 5. *Association of laboratory components in MS of study subjects ALL (N=48)*

Laboratory component	MS (n=10)	Not MS (n=38)	p-value
Low HDL cholesterol			
Present	8(80.0%)	13(34.2%)	0.009
Absent	2(10.0%)	25(65.8%)	
Elevated triglyceride			
Present	10(100.0%)	15(39.5%)	<0.001
Absent	0(0.0%)	23(60.5%)	
Elevated fasting glucose			
Present	2(20.0%)	1(2.6%)	0.044
Absent	8(80.0%)	37(97.4%)	

Table 6. *Comparison of lipid profile between MS and Non-MS of survivors of pediatric ALL (N=48)*

Lipid profile	MS	Not MS	p-value
	Mean ±SD		
Triglyceride (mg/dl)	158.8±47.2	87.9±24.1	0.003
Cholesterol (mg/dl)	213.2±70.7	165.7±36.4	0.104
HDL (mg/dl)	38.2±8.3	51.1±23.0	0.043
LDL (mg/dl)	143.2±76.3	94.3±35.3	0.106

Table 7. *Logistic regression performed to measure risk factors of MS in survivors of ALL (N=48)*

Parameters	p-value	OR	95%CI	
			Lower	Upper
obesity	0.017	5.727	1.248	26.276
Central obesity	<0.001	76.5	7.584	771.617
Elevated blood pressure	0.001	12.75	2.485	65.415
Low HDL cholesterol	0.009	7.692	1.422	41.614
Elevated triglyceride	<0.001	0.6	0.436	0.826
Elevated fasting glucose	0.044	9.25	0.745	114.869

3. DISCUSSION

To evaluate the prevalence of metabolic syndrome (MS) among childhood ALL cancer survivors in a tertiary care hospital, a total of 48 patients who had completed at least two years post-treatment were selected. Among these cases, the prevalence of MS was found to be 20.8%, which is higher than the rates observed in the general pediatric population in developing countries, typically ranging from 3.6% to 4.8% [12]. A higher prevalence rates were noted by Singh et al. (2013) [13] at 33.3%. Conversely, lower prevalence rates were reported by Mohapatra et al. (2016) [14] at 13%. In this study, the majority of patients (87.5%) were diagnosed with ALL before the age of 10, while only 12.5% were diagnosed at age 10 or older. At the time of survivor enrollment, most participants (60.4%) were aged between 10-18 years, with an average age of 13.3 ± 3.33 years. Participants who developed MS had a mean age of 15.0 ± 4.05 years. These findings are consistent with those of Mohamed et al. (2022) [15], who reported that patients with MS had an average age at diagnosis

of 11.0 ± 2.0 years. Among the studied cases, a higher prevalence of metabolic syndrome (MS) was observed in males at 26% compared to females at 11%, although the difference was not statistically significant (p=0.199). This observation suggests a potential trend towards a higher MS prevalence among male survivors, which aligns with findings from Barbosa et al. (2017) [16]. These findings reflect the variability in MS prevalence among ALL survivors, likely influenced by differences in population demographics, healthcare systems, lifestyle factors, and genetic predispositions across various geographical regions. The present study indicates that there is no significant difference in the development of metabolic syndrome (MS) among survivors of children who received either standard or high-risk treatment protocols. This finding was comparable to the report by Mohapatra et al. (2016) [14], which noted that, among high-risk ALL survivors, a higher proportion had MS compared to those with standard-risk ALL (50% vs. 31%), but this difference was not statistically significant (p=0.62). This suggests that high-risk treatment protocols may not significantly impact MS development in this population. These observations suggest a potential association between higher BMI scores and the development of metabolic syndrome (MS) in pediatric ALL survivors. This finding was consistent with the research of Kartal et al. (2022) [9], and Karakaya et al. (2013) [17], all of which demonstrate a significant association between BMI and MS. The present study also indicates a strong correlation between obesity, as measured by BMI, and the development of MS. Additionally, central obesity, as assessed by waist circumference (WC), is significantly more prevalent among individuals with MS compared to those without MS (90.0% vs. 10.5%, respectively; $p < 0.001$). Elevated blood pressure shows a strong association with metabolic syndrome (MS), with a significantly higher prevalence among individuals with MS compared to those without MS (60.0% vs. 10.5%; $p < 0.001$). This observation was consistent with findings from Oudin et al. (2018) [18]. Additionally, individuals with MS exhibit significantly higher rates of low HDL cholesterol compared to those without MS (80% vs. 34.2%; $p = 0.009$). Elevated triglyceride levels were also notably more prevalent among MS individuals than non-MS individuals (100.0% vs. 39.5%; $p < 0.001$), emphasizing the role of dyslipidemia as a key feature of MS. Elevated fasting glucose levels were significantly associated with metabolic syndrome (MS), with a much higher prevalence among individuals with MS compared to those without MS (20.0% vs. 2.6%; p=0.044). This suggests an impairment in glucose metabolism among individuals with MS. These findings were consistent with another previous study [18], which highlighted the connection between elevated fasting glucose and MS. The logistic regression analysis revealed significant associations between various risk factors and metabolic syndrome (MS) in survivors of pediatric Acute Lymphoblastic Leukemia (ALL). Overweight/obesity (OR: 5.727, $p = 0.017$), central obesity (OR: 76.500, $p < 0.001$), elevated blood pressure (OR: 12.750, $p = 0.001$), low HDL cholesterol (OR: 7.692, $p = 0.009$), elevated triglycerides (OR: 0.600, $p < 0.001$), and elevated fasting glucose (OR: 9.250, p=0.044) were identified as significant predictors of MS. These findings were consistent with previous studies by Mohamed et al. (2022) [15], and Zhang et al. (2014) [19].

4. Limitation Of The Study

The study was conducted in a single tertiary care hospital, which may limit the generalizability of the findings to other healthcare settings or populations with different demographic and clinical characteristics. Furthermore, the study lacked detailed information on potential confounding factors, such as socioeconomic status, lifestyle factors, and genetic predispositions, which might restrict the ability to fully understand and interpret the metabolic consequences in acute lymphoblastic leukemia survivors

5. Conclusion And Recommendation

Among the pediatric survivors of acute lymphoblastic leukemia (ALL), one in five may develop metabolic syndrome.Clinical indicators of this syndrome include central obesity, obesity, being overweight, and elevated blood pressure.

Central obesity, in particular, poses the highest risk for developing metabolic syndrome among these factors. Thisunderscores the importance of monitoring and managing weight and related health parameters in pediatric acute lymphoblastic leukemia survivors to reduce the risk of subsequent metabolic complications.

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