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Original Article

# Assessment of Obesity and Hepatic Late Adverse Effects in the Egyptian Survivors of Pediatric Acute Lymphoblastic Leukemia: a Single Center Study

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**Abstract.** ***Background*: Childhood acute lymphoblastic leukemia (ALL) with current cure rates reaching 80% emphasizes the necessity to determine treatment-related long-term effects. The aim of this study is to estimate the prevalence of overweight, obesity, and hepatic late adverse effects in a cohort of ALL survivors treated at the Hematology and Oncology Unit, Pediatrics Department, Menoufia University, Egypt.**

***Methods*: In this case-control study, height, weight, and body mass index (BMI) were assessed for 35 pediatric ALL survivors and 35 healthy children. These parameters were plotted on the growth and WHO standard deviation charts for both males and females. Overweight and obesity were defined by BMI > 85$^{th}$ and 95$^{th}$ percentile respectively. Laboratory investigations were done in the form of iron profile, liver enzymes, total and direct bilirubin levels, serum urea &creatinine and detection of hepatitis C virus antibodies by ELISA.**

***Results*: The weight and BMI were significantly greater in the survivors than controls (P value =0.002 and 0.039 respectively). ALT, total & direct bilirubin, serum ferritin and transferrin saturation were considerably higher in the survivors than the controls (P value = 0.03, 0.036, 0.044, 0.006 and 0.03 respectively). Ten (28.6%) of survivors had hepatitis C antibodies with none (0%) of controls (P value =0.02)**

***Conclusions*: Pediatric ALL survivors are at increased risk of overweight/obesity, hepatic dysfunction in the form of elevated liver enzymes, bilirubin levels, and C viral hepatitis. Screening of those survivors for such complications should be considered.**

**Keywords:** ALL, Survivors, Obesity, Liver function.

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**Introduction.** In Egypt, childhood acute lymphoblastic leukemia (ALL) is the most common cancer in children, accounting for almost one-third of newly diagnosed pediatric cancer cases. The annual incidence of pediatric ALL is approximately four cases per 100,000 children per year in the National Cancer Institute NCI, Cairo University, Egypt. Cases show male to female ratio of 2.3:1. The 2-10 years age group constitutes 68.5%.[1,2]

Fortunately, improvements in treatment, including multimodal therapy and hospital care,

have improved survival such that over 80% of children diagnosed with ALL survive at least five years.[2,3]

However, childhood cancer survivors are at increased risk of developing chronic health conditions, some of which manifest during or soon after treatment whereas others emerge years after therapy.[4] Obesity is a particularly significant problem among ALL survivors, which can intensify cardiovascular outcomes and place these individuals at greater risk for other chronic health conditions.[5]

Evidence from the Childhood Cancer Survivor Study (CCSS) suggests that survivors of ALL (who lived 5ys after treatment) experience a higher rate of obesity than their same-sex siblings, especially for female survivors (ALL: 31.7% vs. siblings: 22.2%).[6] Obesity may further compound the risk of other late effects, such as increased rate of cardiovascular diseases observed in childhood cancer survivors.[7]

Previous studies have attributed obesity to the cranial irradiation (CRT) patients received to prevent central nervous system (CNS) relapse, However, since the 1990s, CNS prophylaxis with CRT protocols has gradually been replaced with intrathecal and systemic chemotherapy by several consortia.[8] A study of the Children's Oncology Group (COG) found excessive weight gain also occurred in children receiving chemotherapy alone.[9] Treatment with glucocorticoids has been implicated in the physiology of adiposity, and there is data that dexamethasone may act more potently than prednisone.[10] Prolonged use of corticosteroids has shown effects on body composition associated with increases in the percentage of body fat in pediatric ALL survivors.[11]

Also, Hepatic abnormalities are well documented in survivors of childhood malignancies. A spectrum of liver diseases has been described including hepatitis B and C, iron overload, hepatic fibrosis, cirrhosis and hepatocellular carcinoma.[12] Less commonly reported hepatobiliary complications include cholelithiasis, focal nodular hyperplasia (FNH), nodular regenerative hyperplasia, hepatic microvesicular fatty change and siderosis.[13] The Childhood Cancer Survivor Study (CCSS) noted an almost two-fold excess risk of gallbladder disease among childhood cancer survivors compared to sibs (1.9 95 % 1.7–2.2).[13]

Acute or sub-acute hepatobiliary injury is recognized with varying incidence following radiation, multiple chemotherapies, or hematopoietic stem cell transplantation (HSCT).[14] Additionally, hepatobiliary toxicity is associated with supportive care measures, such as transfusion-acquired hepatitis, transfusion-associated iron overload or cholestatic disease from total parenteral nutrition (TPN). These conditions may predispose to clinically significant liver disease in aging childhood cancer survivors.[15] In this study, we aimed to estimate the prevalence of overweight, obesity, and hepatic late adverse effects in pediatric ALL survivors who lived 5 years after treatment.

**Patients and Methods.** A comparative cross-sectional case-control study was performed on thirty-five ALL survivors, treated at Hematology and Oncology Unit, pediatric department, Menoufia University Hospital. All of them completed treatment with St Jude Total XV Chemotherapy Protocol 5 years before the time of examination. In that protocol, the remission induction therapy began with prednisone, vincristine, daunorubicin, and asparaginase. Subsequent remission induction therapy included cyclophosphamide, mercaptopurine, and cytarabine. On hematopoietic recovery, consolidation therapy with high-dose methotrexate, mercaptopurine, triple intrathecal treatment began, and the dose of methotrexate was based on risk classification. During initial continuation therapy, patients with low-risk disease received daily mercaptopurine and weekly methotrexate with pulses of mercaptopurine, dexamethasone, and vincristine**.** Two re-induction treatments were given between weeks 7 to 9 and weeks 17 to 19. Patients with standard-risk disease received weekly asparaginase and daily mercaptopurine with pulses of doxorubicin plus vincristine plus dexamethasone. They also received two re-induction treatments between weeks 7 to 9 and weeks 17 to 20**.** For the remaining part of continuation therapy, patients with low-risk disease received mercaptopurine and methotrexate, with pulses of dexamethasone, vincristine, and mercaptopurine, and patients with standard-risk disease received three rotating drug pairs mercaptopurine plus methotrexate, cyclophosphamide plus cytarabine, and dexamethasone plus vincristine. Continuation

treatment lasted 120 weeks for girls and 146 weeks for boys.[16]

None of those survivors received radiotherapy. The study was done in the period between March 2015 and December 2015. A control group of 35 healthy children with matched age and sex was selected from volunteers from a local school. They were apparently healthy with no history of chronic illnesses or previous history of steroid intake. A written informed consent was obtained from the parents of all children, and oral assent was obtained from children of both groups. This study was approved by the ethical committee of the Faculty of Medicine, Menoufia University.

The survivors and controls were subjected to anthropometric measurements and laboratory investigations:

Anthropometric measurements (weight, height, and body mass index), BMI was assessed by Z-score. Body Mass Index = Weight in Kilograms/ (Height in meters) ² was plotted on age and gender-specific percentile charts (for 2 to 20-year-olds). BMI over the 95$^{th}$ percentile indicates obesity, between 85$^{th}$ and 95$^{th,}$ indicates risk of overweight.[17] We evaluated longitudinal changes in obesity rate and BMI Z scores in survivors of pediatric ALL as for survivors of childhood cancer aged <20 y. The BMI Z-score or percentile is often used to evaluate weight status, rather than the absolute BMI because an increased BMI is part of the normative/adolescent development and also varies by sex.[18] The BMI Z-score or percentile can be calculated on the basis of age and sex-specific mean BMI of a reference population.[19] 7 ml of venous blood were withdrawn from every child then transferred into a plain tube, centrifuged for 10 min at 4000 r.p.m. The serum obtained was kept frozen at - 20 ºC till analysis (Liver, kidney function tests, iron profile and HCV antibodies detection). Serum ALT & AST were estimated by enzymatic colorimetric method using Randox kit, United Kingdom.[20] Serum total and direct bilirubin were estimated by enzymatic colorimetric method using Diamond Diagnostics kit, Germany.[20] Serum urea was determined by Mod Berthelot enzymatic colorimetric method using Diamond Diagnostics Kit, Germany.[21] Serum creatinine was determined by the fixed rate kinetic chemical method, using Diamond Diagnostics Kit, Germany.[22] Serum iron and total iron binding capacity (TIBC) were determined by a colorimetric method using SPECTRUM diagnostics kit (Germany).[23,24] Transferrin saturation index (TSI) was calculated by the following formula: iron concentration divided by TIBC and multiplied by 100. The TSI > 16% values were regarded as correct ones.[25] Serum ferritin levels were measured to assess the iron status of our patients by Enzyme Linked Immune Sorbent Assay (ELISA) technique using (RAMCO LABORATORIES kit, INC., USA), and HCV antibodies were detected by ELISA using (AUTOBIO DIAGNOSTICS, China) kit on microplate reader (Bio-Rad 680 Hercules, California, USA).

**Statistical Analysis.** The statistical presentation and analysis of the present study were conducted using SPSS V.20 (SPSS Inc., Chicago, IL, USA). Data were expressed in two phases: Continuous parametric variables were presented as means± SD while for categorical variables numbers (%) were used. Chi-square ($\chi^2$ test) and Fisher's exact test were used for qualitative variables, student's t-test for parametric continuous variables and Man Whitney (U) test for non-parametric variables

**Results.** The mean age of the survivors at the time of the study was (11.01±4.6) years. Fourteen of them (40%) are females, and 21 (60%) are males. Sixty % were leukemia of low risk, and 40 % were of standard risk The mean age of them at diagnosis was (5.86±1.5) years. The mean age of controls was (9.6±3.3). Nine (60%) are males, and 6(40%) are females. The weight and BMI were significantly higher in the survivors' controls (P value =0.002 and 0.039 respectively) while no significant difference was found between the two groups regarding the height (P-value = 0.351) (**Table 1**). Survivors had a significant positive correlation with younger age at diagnosis and BMI (P-value = 0.003) and highly significant correlation with weight at diagnosis and after chemotherapy (P value = <0.001). Also, a highly significant value was detected between obese survivors and positive family history of obesity (P value = <0.001) (**Table 2**). ALT, total & direct bilirubin, serum ferritin and transferrin saturation were significantly higher in the survivors than controls (P value = 0.03, 0.036, 0.044, 0.006 and 0.03 respectively) (**Table 3**). While no significant difference was found between the two groups regarding AST, albumin, creatinine, BUN, serum iron and TIBC (**Table 3**). Ten (28.6%) of

**Table 1.** Z-score of anthropometric measures of studied groups.

| Z score | Patients | | Controls | | $\chi^2$ test | P value |
|---|---|---|---|---|---|---|
| | N(35) | % | N (35) | % | | |
| ***Height*** | | | | | | |
| Below 2 SD | 15 | 42.9 | 21 | 60 | 2.1 | 0.351 |
| From 2 to-2 SD | 3 | 8.6 | 0 | 0 | | |
| Above 2 SD | 17 | 48.6 | 14 | 40 | | |
| ***Weight*** | | | | | | |
| Below 2 SD | 12 | 34.3 | 14 | 40 | 12.3 | 0.002* |
| From 2 to-2 SD | 3 | 8.6 | 16 | 46.7 | | |
| Above 2 SD | 20 | 57.1 | 5 | 13.3 | | |
| ***BMI*** | | | | | | |
| Below 2 SD | 9 | 25.7 | 21 | 60 | 6.5 | 0.039* |
| From 2 to-2 SD | 10 | 28.6 | 9 | 26.7 | | |
| Above 2 SD | 16 | 45.7 | 5 | 13.3 | | |

* = Significant difference $\chi^2$ test: Chi-square test SD: Standard deviation

**Table 2.** Multivariate analysis of predicting risk factors for obesity.

| | Overweight | | | | $X^2$ | P value | Odds ratio (CI 95%) |
|---|---|---|---|---|---|---|---|
| | +ve | | -ve | | | | |
| | N(13) | % | N(22) | % | | | |
| **Age at diagnosis** | | | | | 0.16 | 0.689 | 0.747(0.2-3.1) |
| **≤6 yrs.** | 8 | 61.5 | 15 | 68.2 | | | |
| **>6 yrs.** | 5 | 38.5 | 7 | 31.8 | | | |
| **Family history** | | | | | **13.8** | **<0.001*** | **32 (3.4-302.2)** |
| **+ve** | 12 | 92.3 | 6 | 27.3 | | | |
| **-ve** | 1 | 7.7 | 16 | 72.7 | | | |
| **Wt. at diagnosis** | | | | | 0.02 | 0.886 | 1.15(0.2-8) |
| **Obese** | 2 | 15.4 | 3 | 13.6 | | | |
| **Normal** | 11 | 84.6 | 19 | 86.4 | | | |

* = Significant difference $\chi^2$ test: Chi-square test

**Table 3.**Laboratory investigations of studied groups.

| | Patients ± SD | Controls ± SD | t test ± SD | P value ± SD |
|---|---|---|---|---|
| **ALT(IU/L)** | 51.8±29.67 | 26±4.81 | 2.12 | 0.03* |
| **AST(IU/L)** | 47.85±27.86 | 30±4.41 | 1.8 | 0.073 |
| **T. bilirubin (mg/dl)** | 0.6057±.23508 | 0.46±0.12 | 2.15 | 0.036* |
| **D. bilirubin (mg/dl)** | 0.18±0.14 | 0.09±0.05 | 2.06 | 0.044* |
| **S. creatinine (mg/dl)** | 0.58±0.2 | 0.54±0.2 | 0.726# | 0.472 |
| **S. urea (mg/dl)** | 12.1±4.1 | 12.7±3.6 | 0.449 | 0.655 |
| **S. ferritin (ng/ml)** | 737.6±99.2 | 51.6±18.2 | 2.8# | 0.006* |
| **S. iron (µg/dl)** | 100.2±36.4 | 85.8±17.4 | 1.4# | 0.152 |
| **TIBC (µg/dl)** | 273.3±72.7 | 261.9±55.9 | 0.541# | 0.591 |
| **TSI (%)** | 46.9±21.1 | 34.7±1.7 | 2.2# | 0.03* |

#= U test (Mann-Whitney test), ±SD= mean ± standard deviation ALT= alanine transaminase, AST= aspartate transaminase, TIBC= total iron binding capacity.

**Table 4.** HCV Antibodies in studied groups.

| | Patients | | Controls | | Fisher's exact test | P value |
|---|---|---|---|---|---|---|
| **HCV Antibodies** | N(35) | % | N(35) | % | | |
| **+ve** | 10 | 28.6 | 0 | 0 | **5.3** | **0.02*** |
| **-ve** | 25 | 71.4 | 35 | 100 | | |

HCV= hepatitis C virus' * = Significant difference

survivors had hepatitis C antibodies with none (0%) of controls (P value =0.02) (**Table 4**). A correlation was calculated between cumulative doses of asparaginase and ALT, AST, total bilirubin, direct bilirubin. A positive highly significant correlation was found between cumulative dose of asparaginase and liver enzymes (ALT, AST) (P value = <0.001) and with

**Table 5.** Correlation between risk of liver abnormalities in patients and higher asparaginase cumulative dosage.

| | Asparaginase cumulative dosage. | | U test | P value |
|---|---|---|---|---|
| | Low (21) | Standard (14) | | |
| **ALT(IU/L)** | 22.7±6.7 | 95.4±47 | 7.03 | <0.001 |
| **AST(IU/L)** | 29.9±7.3 | 74.9±44.1 | 4.6 | <0.001 |
| **T. bilirubin (mg/dl)** | 0.51±0.2 | 0.74±0.3 | 3.2 | 0.003 |
| **D. bilirubin (mg/dl)** | 0.09±0.02 | 0.14±0.1 | 2.02 | 0.052 |

[#]= U test (Mann-Whitney test), ALT= alanine transaminase, AST= aspartate transaminase, T. bilirubin= total bilirubin, D. bilirubin= direct bilirubin

**Table 6.** Correlation between liver abnormalities and increased ferritin level.

| | S. ferritin level (ng/ml) | |
|---|---|---|
| | r | P-value |
| **ALT(IU/L)** | -0.135 | 0.44 |
| **AST(IU/L)** | -0.155 | 0.374 |
| **T.bilirubin (mg/dl)** | -0.149 | 0.393 |
| **D.bilirubin (mg/dl)** | 0.027 | 0.877 |

r = correlation coefficient

total bilirubin (P-value = 0.003) but not with direct bilirubin (P-value = 0.052) (**Table 5**). No significant correlation was found between liver function (transaminases and hyperbilirubinemia) and ferritin levels in survivors (**Table 6**).

**Discussion.** The first aim of this study was to assess the prevalence of overweight and obesity in pediatric ALL survivors. Our results revealed that survivors of pediatric ALL were at risk becoming overweight or obese with long-term follow-up. Based on U.S. Centers for Disease Control and Prevention (CDC) definition growth charts, Salazar-Martinez et al.[26] said that the prevalence of overweight and obesity was 12.1% and 6.2%, respectively, among the healthy Egyptian adolescents. This study revealed that overweight and obesity were more prevalent in ALL survivors compared to general Egyptian population, suggesting an impact of chemotherapy on weight gain in ALL survivors. This datum is in agreement with Asner et al.[27] who examined the prevalence and the risk factors for overweight and obesity in a cohort of ALL survivors treated and living in the French speaking part of Switzerland reported that there is a significant prevalence of obesity in young ALL survivors.

Fang et al.[28] indicated a significantly higher BMI in pediatric ALL survivors than the reference population. However, a study by Murphy et al.[29] found that on-treatment and survivor groups had a significantly lower body cell mass index than matched controls, and 53% of the survivors were considered undernourished.

In a study done on 56 adolescent, ALL survivors in Saudi Arabia, with a mean age of 13.4 years an average of 9.1 years post-diagnosis who did not receive CRT, the prevalence of BMI for age defined overweight, and obesity (combined 28.5%) were lower than in the general population in Saudi Arabia. The authors supposed that overweight and obesity observed were probably not an ALL specific problem.[30]

Our results demonstrated that the survivors who had high BMI z-score at diagnosis also had increased risk of being overweight /obese after treatment completion. This result was in line with Fang et al. study which is a retrospective cohort of 83 pediatric patients with ALL; they examined BMI status at several key time points: diagnosis; end of induction; end of consolidation; every 6 months during maintenance; and yearly for up to 5 years post-treatment. At diagnosis, 21% were overweight (BMI = 85–94.9th percentile) or obese (BMI ≥95th percentile). At the end of treatment and 5 years post-treatment, approximately 40% were overweight or obese. Weight gain during treatment was associated with being overweight/obese 5 years post-treatment (OR = 3.8, 95% CI: 1.1–12.5).[31]

All of the involved survivors had received dexamethasone with the mean cumulative dose of $927 \pm 135$ mg/m$^2$ which may be the cause of weight gain. It is not entirely understood why ALL survivors gain excess fat mass. One theory is that, during glucocorticoid treatment, ALL patients have an increased energy intake[32] and reduced energy expenditure on habitual physical activity[33] and that this effect continues after treatment ceases. Other theories are that glucocorticoid treatment causes increased adiposity by suppressing growth hormone secretion or that it causes resistance to leptin.[34]

The second aim of this study was to assess the hepatic late adverse effects in pediatric ALL survivors. At our study, there was a significant increase in D. Bilirubin, T. Bilirubin, ALT, serum ferritin and soluble transferrin saturation in the

survivors' group more than the control group. Ten of our survivors (28.6 %) have HCV positive antibodies detected by ELISA. These results go with the previous findings of Mulder et al.[35] who concluded that abnormal high ALT level was detected in survivors of childhood cancer. Also, Schempp et al.[36] found elevated levels of serum ferritin and soluble transferrin (iron overload) in survivors of childhood cancer and attributed this to Transfusion volume. This iron overload causes tissue damage through the chronic formation of free radicals leading to liver dysfunction.[37]

In a study of 118 children (with standard-risk leukemia) receiving native E. coli asparaginase or PEG-asparaginase, abnormal liver function (grade 3/4), including elevated transaminases and hyperbilirubinemia, was found in 8% of patients receiving native E. coli asparaginase and in 5% of patients receiving PEG-asparaginase.[38]

There are no clear pediatric guidelines for the management of asparaginase in patients with hepatic toxicity, and treatment recommendations vary across protocols. In the DCOG ALL-11 pediatric protocol, patients are required to display aspartate aminotransferase/alanine aminotransferase < 10×ULN and no signs of jaundice with bilirubin < 3× ULN before starting asparaginase treatment.[39]

Patients with hematologic malignancies were at a very high risk of HCV infection due to the large transfusional support they often needed.[40] The previously immunocompromised status of the leukemia survivors may have promoted more rapid viral replication or impaired host viral clearance and led to rapidly progressive liver disease.[41]

Moreover, it is known that chemotherapeutic drugs (methotrexate and 6-mercaptopurine) increase the risk of liver toxicity during or soon after cancer treatment.[13]

**Study Limitations.** This study had some limitations as small sample size and short duration.

**Conclusions.** Pediatric ALL survivors are at increased risk of overweight/obesity, iron overload, HCV infection and delayed hepatic complications.

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