ARTICLE

# Metabolic syndrome in long-term survivors of childhood acute leukemia treated without hematopoietic stem cell transplantation: an L.E.A. study

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## ABSTRACT

Cardiovascular conditions are serious long-term complications of childhood acute leukemia. However, few studies have investigated the risk of metabolic syndrome, a known predictor of cardiovascular disease, in patients treated without hematopoietic stem cell transplantation. We describe the overall and age-specific prevalence, and the risk factors for metabolic syndrome and its components in the L.E.A. (Leucémie de l'Enfant et de l'Adolescent) French cohort of childhood acute leukemia survivors treated without hematopoietic stem cell transplantation. The study included 650 adult patients (mean age at evaluation: 24.2 years; mean follow-up after leukemia diagnosis: 16.0 years). The prevalence of metabolic syndrome was 6.9% (95% CI 5.1-9.2). The age-specific cumulative prevalence at 20, 25, 30 and 35 years of age was 1.3%, 6.1%, 10.8% and 22.4%, respectively. The prevalence of decreased high-density lipoprotein cholesterol, increased triglycerides, increased fasting glucose, increased blood pressure and increased abdominal circumference was 26.8%, 11.7%, 5.8%, 36.7% and 16.7%, respectively. Risk factors significantly associated with metabolic syndrome in the multivariate analysis were male sex (OR 2.64; 95% CI 1.32-5.29), age at last evaluation (OR 1.10; 95% CI 1.04-1.17) and body mass index at diagnosis (OR 1.15; 95% CI 1.01-1.32). The cumulative steroid dose was not a significant risk factor. Irradiated and non-irradiated patients exhibited different patterns of metabolic abnormalities, with more frequent abdominal obesity in irradiated patients and more frequent hypertension in non-irradiated patients. Survivors of childhood acute leukemia are at risk of metabolic syndrome, even when treated without hematopoietic stem cell transplantation or central nervous system irradiation. A preventive approach with regular screening for cardiovascular risk factors is recommended. *clinicaltrials.gov identifier:01756599.*

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## Introduction

Acute leukemia (AL) accounts for one third of childhood cancers.[1] A significant improvement in patient survival has led to a heightened focus on the long-term complications associated with this disease and corresponding treatments. Notably, childhood AL survivors exhibit a more than 4-fold increase in cardiovascular-related mortality rates, including congestive heart failure, coronary artery disease including myocardial infarction, cardiac arrest and stroke, compared with siblings or the general population.[2,3] Anthracyclines, which have been linked to cardiac toxicity, are only partly responsible for this increased cardiovascular mortality.[4] Furthermore, childhood AL survivors have been shown to have early signs of atherosclerotic lesions.[5,6] The natural evolution of atheromatous disease begins years before the onset of a lesion with clinical impacts. Therefore, clinicians and researchers have aimed to identify early markers associated with an increased risk of developing cardiovascular disease. One of the most studied markers in the general population is metabolic syndrome (MetS).[7] It is defined as a combination of cardiovascular risk factors, including abdominal obesity, dyslipidemia, glucose intolerance and hypertension. This composite marker predicts coronary artery disease and stroke risk better than each of its components.[8]

Most of the published data concerning MetS prevalence among childhood AL survivors have been focused on patients treated with hematopoietic stem cell transplantation (HSCT). In this population, the prevalence of MetS is particularly high.[9–11] Previous studies have investigated MetS prevalence among childhood AL patients treated without HSCT,[12–18] although most of these studies had distinct limitations: (I) child or very young adult populations, (II) self-administered questionnaires, (III) single-center studies, (IV) small cohort size, or (V) retrospective design. Thus, the reported MetS prevalence among patients treated without HSCT is quite variable, with values ranging from 8.3% to 31.7%.[13,15,17,18] Consequently, the risk of MetS remains controversial, especially for patients treated without central nervous system (CNS) irradiation. This matter is all the more important as modern protocols tend to strongly limit the treatment modality of CNS irradiation.[19] Additionally, the pathophysiology and risk factors of increased metabolic and cardiovascular risk in this population remain poorly understood.

A previous study on MetS from the French Leucémie de l'Enfant et de l'Adolescent L.E.A. program[20] has described a cohort of patients treated either with or without HSCT. However, the number of patients was relatively small and precluded any specific analysis of each therapeutic subgroup. The further expansion of the L.E.A. cohort allowed us to perform the study herein, which focused on 650 patients treated without HSCT. Its aim was to prospectively describe the overall and age-specific prevalence and risk factors for MetS and its components among adult survivors of childhood AL who did not receive HSCT and were included in the L.E.A. multicenter French cohort.

## Methods

L.E.A. is a long-term follow-up program involving all childhood AL survivors treated in the French participating centers since 1980. As detailed elsewhere,[21] participants are summoned to the follow-up clinic at predefined dates, starting one year after completion of chemotherapy. These visits are repeated every two years until the age of 20 and at least 10 years of complete remission, and every four years thereafter. The program began in 2004 and rests on the constitution of a multicenter historical and prospective cohort, which includes both incident cases (diagnosed after the start date of the participation of the center in the L.E.A program) and prevalent cases (diagnosed between 01/01/1980 and the start date of the participation of the center in the L.E.A program). Since 2007, adult patients have systematically undergone a complete evaluation for MetS.

Patients were eligible for the present study if they had been included in the L.E.A. program between 2007 and 2013, were more than 18 years of age and were treated without HSCT. The eligible patients with complete evaluation for MetS were included in the study. All patients provided written informed consent. The study was approved by the French National Program for Clinical Research and the National Cancer Institute.

MetS was defined according to the National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATPIII) criteria revised in 2005[22] as the combination of at least three of the following criteria: (I) increased waist circumference (≥102 cm in men and ≥88 cm in women), (II) increased blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or treatment for hypertension, (III) decreased HDL cholesterol (<1.03 mmol/l in men and <1.3 mmol/l) in women), (IV) increased fasting glucose (≥5.5 mmol/l) or treatment for hyperglycemia, and (V) increased triglycerides (≥1.7 mmol/l) or treatment for hypertriglyceridemia. The body mass index (BMI) at diagnosis was expressed as standard deviation from the mean value of children of the same age in French references (z-score). Adult BMI was expressed in $kg.m^{-2}$. Overweight and obese patients were defined as BMI =25-30 $kg.m^{-2}$ and BMI ≥30 $kg.m^{-2}$, respectively. The cumulative steroid dose was calculated in equivalent of prednisone for each patient using the following formula:

*cumulative steroid dose = cumulative prednisone dose + (cumulative dexamethasone dose x 6.67) in* $mg.m^{-2}$

as previously described.[23]

Statistical analysis was performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) and Intercooled Stata 9.0 (StataCorp., College Station, TX, USA). Quantitative variables were expressed as mean ± standard deviation. Categorical variables were compared using the $\chi^2$ test or the Fisher's exact test. Quantitative variables were compared using the Student's *t*-test or the Mann-Whitney test. Prevalence rates are displayed with 95% confidence interval (CI). The associations between MetS or its components and potential risk factors were initially analyzed *via* univariate logistic regression. The variables associated with MetS in the univariate analysis with a *P*-value <0.05 were then included in a multivariate analysis. Odds ratios are displayed with 95% CI. The age-specific cumulative prevalence of MetS was estimated using the Kaplan-Meier method.

## Results

### Comparison between included patients and eligible but not included patients

The study flow chart is presented in Figure 1. Eight hundred and seventy patients from the L.E.A. program were eligible for the study. Among them, 650 underwent a complete evaluation for MetS and were ultimately included in the study cohort. The comparison between the character-

istics of patients included and those who were eligible but not included is presented in Table 1. Sex, age at diagnosis, age at last evaluation, time from diagnosis to last evaluation, BMI z-score at diagnosis, relapse rate, CNS irradiation rate and type of irradiation were similar in the two groups. In the studied cohort, the percentage of myeloblastic leukemia cases was significantly higher (9.5% *versus* 5.0%, *P*=0.033) and the mean cumulative steroid dose was significantly lower (4494±2578 mg/m$^2$ *versus* 5050±2216 mg/m$^2$, *P*=0.016) than among the eligible but not included patients.

### Description of the study cohort

The characteristics of the 650 included patients are shown in Table 1. The study population comprised 52.2% women and 47.8% men. The mean age at diagnosis was 8.2±4.8 years. The mean age at last evaluation was 24.2±5.2 years, and the time from diagnosis to last evaluation was 16.0±6.8 years. The mean BMI z-score at diagnosis was -0.15±1.72. CNS irradiation was performed in 18.0% of patients (n=117). When administered, the irradiation dose was 18 Gy (14.5%, n=94/650) or 24 Gy (3.2%; n=21/650). The mean BMI at last evaluation was 23.3±4.2

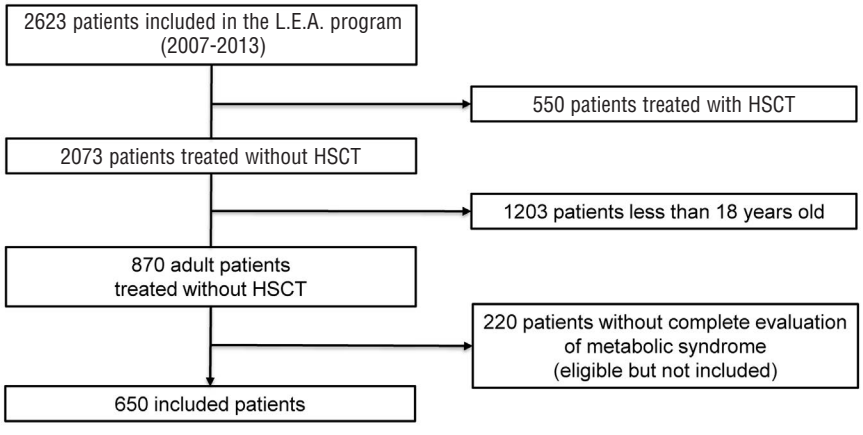


**Figure 1. Flow chart of the cohort.** HSCT: hematopoietic stem cell transplantation.

**Table 1. Description of the patient cohort and comparison with eligible but not included patients.**

| Patient characteristics | Total eligible patients n=870 (100%) n (%) or mean ± SD | Eligible but not included patients n=220 (25.3%) n (%) or mean ± SD | Patient cohort (included patients) n=650 (74.7%) n (%) or mean ± SD | *P* |
|---|---|---|---|---|
| Sex | | | | |
| Female | 456 (52.4%) | 117 (53.2%) | 339 (52.2%) | 0.792 |
| Male | 414 (47.6%) | 103 (46.8%) | 311 (47.8%) | |
| Leukemia type | | | | |
| ALL | 791 (90.9%) | 209 (95.0%) | 582 (89.5%) | **0.033** |
| AML | 73 (8.4%) | 11 (5.0%) | 62 (9.5%) | |
| Biphenotypic | 6 (0.7%) | 0 (0.0%) | 6 (0.9%) | |
| Age at diagnosis (years) | | | | |
| mean ± SD | 8.33±4.80 | 8.66±4.80 | 8.22±4.80 | 0.245 |
| Age at last evaluation (years) | | | | |
| mean ± SD | 24.22±5.23 | 24.22±5.39 | 24.23±5.18 | 0.983 |
| Time from diagnosis to last evaluation (years) | | | | |
| mean ± SD | 15.89±6.89 | 15.56±7.20 | 16.00±6.79 | 0.409 |
| BMI z-score at diagnosis | | | | |
| mean ± SD | -0.16±1.66 | -0.19±1.43 | -0.15±1.72 | 0.807 |
| Relapse | | | | |
| No | 828 (95.2%) | 210 (95.5%) | 618 (95.1%) | 0.821 |
| Yes | 42 (4.8%) | 10 (4.5%) | 32 (4.9%) | |
| CNS irradiation | | | | |
| No | 700 (80.5%) | 170 (77.3%) | 530 (81.5%) | 0.270 |
| 18 Gy | 132 (15.2%) | 38 (17.3%) | 94 (14.5%) | |
| 24 Gy | 32 (3.7%) | 11 (5.0%) | 21 (3.2%) | |
| Unknown‡ | 6 (0.7%) | 1 (0.5%) | 5 (0.8%) | |
| Type of irradiation† | | | | |
| Cranial | 123 (73.7%) | 36 (72.0%) | 87 (74.4%) | 0.837 |
| Craniospinal | 42 (25.1%) | 13 (26.0%) | 29 (24.8%) | |
| Unknown | 2 (1.2%) | 1 (2%) | 1 (0.9%) | |
| Cumulative prednisone-equivalent dose (mg/m$^2$) mean ± SD | 4623±2508 | 5050±2216 | 4494±2578 | **0.016** |

*SD: standard deviation; ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; BMI: body mass index; CNS: central nervous system; ‡unknown irradiation status or dose of irradiation; †expressed as % of irradiated patients (n=117);* ***significant values (P<0.05).***

kg.m$^{-2}$ (*Online Supplementary Table S1*). The number of complete MetS evaluations was one for 512 patients and two or more for 138 patients. The prevalence of overt diabetes was 0.8% (n=5/650).

### Overall and age-specific cumulative prevalence of MetS and its components

Overall, the prevalence of MetS was 6.9% (95% CI 5.1-9.2%; n=45/650). The Kaplan-Meier estimation describing the age-specific cumulative prevalence of MetS is shown in Figure 2. The age-specific cumulative prevalence at 20, 25, 30 and 35 years of age was 1.3% (95% CI 0.6-2.7), 6.1% (95% CI 4.0-9.1), 10.8% (95% CI 7.2-15.9) and 22.4% (95% CI 15.1-32.6), respectively. The prevalence of each component of MetS is shown in Table 2. Furthermore, 385 patients (59.2%) had at least one abnormal MetS component. A description of the BMI values as well as the overweight and obesity prevalence with respect to MetS status is reported in the *Online Supplementary Table S1*. The mean BMI at last evaluation was 22.9±3.7 kg/m$^2$ in patients without MetS and 29.5±5.8 kg/m$^2$ in patients with MetS ($P$<0.001). The rate of obese patients was 3.7% (n=22) in patients without MetS versus 45.2% (n=19) in patients with MetS ($P$<0.001).

### Univariate and multivariate analysis of risk factors for MetS and its components

The results of the univariate analysis of potential MetS risk factors are presented in the *Online Supplementary Table S2*. Leukemia type, age at diagnosis, relapse rate, type of CNS irradiation and cumulative steroid dose were not significantly associated with MetS in the univariate analysis. Consequently, these factors, along with the factor "time from diagnosis to last evaluation", which was highly correlated to the factor "age at last evaluation", were not included in the multivariate analysis. The results of the multivariate analysis are provided in Table 3. Three variables were found to be significantly associated with MetS in the multivariate analysis: male sex (OR 2.64; 95% CI 1.32-5.29; $P$=0.006), age at last evaluation (OR 1.10 per each additional year of follow-up; 95% CI 1.04-1.17; $P$=0.001) and BMI z-score at diagnosis (OR 1.15 per each additional z-score unit; 95% CI 1.01-1.32; $P$=0.037).

When each component of MetS was separately examined *via* multivariate analysis, several risk factors were highlighted. Undergoing 24 Gy CNS irradiation was a risk factor for a decreased HDL cholesterol (OR 2.76; 95% CI 1.03-7.40; $P$=0.044). Male sex was a risk factor for increased triglycerides and increased fasting glucose: OR 1.69 (95% CI 1.01-2.84; $P$=0.045) and 2.71 (95% CI 1.25-5.84; $P$=0.011), respectively. Risk factors for increased blood pressure were male sex (OR 3.47; 95% CI 2.41-4.99; $P$<0.001) and age at last evaluation (OR 1.08 for each additional year of follow-up; 95% CI 1.04-1.12; $P$<0.001). Undergoing 18 Gy and 24 Gy CNS irradiation were negatively associated with increased blood pressure, with OR 0.48 (95% CI 0.28-0.82; $P$=0.007) and 0.21 (95% CI 0.07-0.64; $P$=0.006), respectively. Age at last evaluation, BMI z-score at diagnosis and 24 Gy CNS irradiation were risk factors for increased waist circumference: OR 1.07 (95% CI 1.02-1.12; $P$=0.008), 1.44 (95% CI 1.23-1.70; $P$<0.001) and 4.84 (95% CI 1.63-14.44; $P$=0.005), respectively. Males were negatively associated with increased waist circumference (OR 0.38; 95% CI 0.22-0.64; $P$<0.001).

### Metabolic profile with regard to irradiation

The prevalence of each MetS component with respect to whether or not the patient had received CNS irradiation and radiation dose was analyzed for all patients with at least one abnormal component (n=385; 59.2%). The results are presented in Figure 3. Increased blood pressure was significantly more frequent in the non-irradiated group than in the 18 Gy and 24 Gy irradiated groups (63.4%, 50.0% and 35.7%, respectively; $P$=0.028). In contrast, increased waist circumference was significantly more frequent in the 24 Gy irradiated group than in the 18 Gy irradiated group and the non-irradiated group (64.3%, 37.3% and 22.4%, respectively; $P$<0.001). The other components of MetS were not significantly different with regard to the history of irradiation and corresponding dosage.

## Discussion

Our study aimed to precisely describe the overall and age-specific cumulative prevalence, and risk factors for MetS in a large cohort of childhood AL survivors treated without HSCT. Notably, the proportion of children who received CNS radiation was relatively low in our cohort. Therefore, the subgroup treated with chemotherapy alone

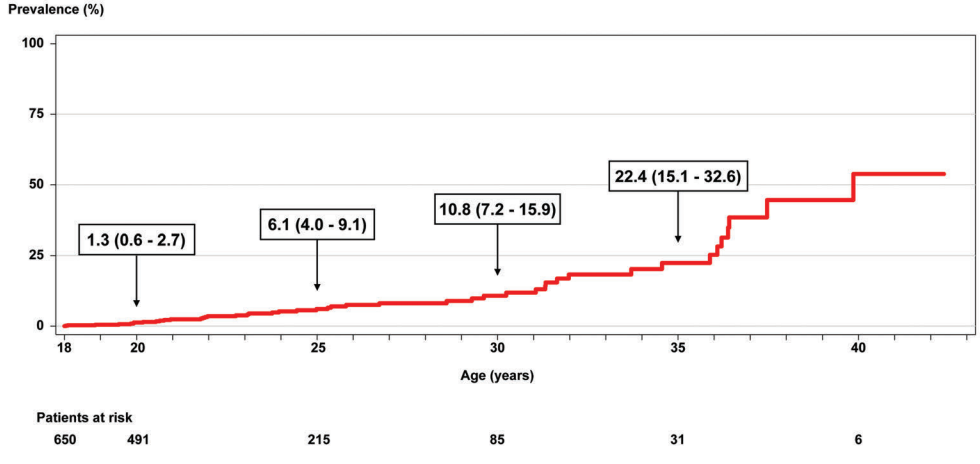


Figure 2. Age-specific cumulative prevalence of the metabolic syndrome.

(i.e., without CNS irradiation) is one of the largest ever published. As current protocols include very limited CNS irradiation indications, it is critical to evaluate MetS in non-irradiated patients.

The proportion of AML (acute myeloblastic leukemia) patients was higher among the included patients than among the eligible but not included patients, thereby explaining the lower mean cumulative steroid dose. This difference could be explained by the high severity of AML, which could have improved compliance for follow-up programs.

We report an overall MetS prevalence of 6.9% (95% CI 5.1-9.2) in our cohort, which involved relatively young patients (mean age of 24.2 years). This result is consistent with the results of a previously published L.E.A. study.[20] Prevalence was approximately two-fold higher than that observed in the adult French general population under 40 years of age, which ranges from 2.2% to 5.0%.[24,25] In the literature, the reported prevalence of MetS among adult survivors of childhood AL without HSCT is widely varied, ranging from between 8.3% and 31.7%.[13,15,17,18,20] Apart from the intrinsic limits of previous studies, direct comparison between the reported prevalence rates of MetS is difficult due to the heterogeneity of the studied populations with respect to leukemia type, age, follow-up duration and treatment modalities. Concerning the treatment modalities, some authors have reported data of patients primarily treated using protocols including CNS irradiation, which increases the risk of MetS.[13,18] Furthermore, the mean age of patients in previous studies ranged from 19 to 31.7 years, thereby rendering comparative analyses difficult as MetS prevalence tends to increase with age.[13,15,17,18,20] Overall however, the prevalence reported in our study appears lower than those reported in the literature, even after making an approximate correction for differences of age. We suggest that this difference could be partly explained by the observation that the prevalence of MetS observed in the general population in France is lower than that in other industrialized countries.[25]

We report a high rate of decreased HDL cholesterol in our cohort, which is consistent with the literature.[18,26] Little is known regarding the pathophysiology of HDL cholesterol diminution among childhood leukemia survivors. The commonly reported risk factors in the general population are genetic predisposition, smoking habits, low physical activity and obesity, and some of these factors are frequent among childhood acute leukemia survivors. Furthermore, interestingly, Canadian investigators have reported that several lipid abnormalities, including decreased HDL cholesterol, are already displayed by childhood leukemia patients at diagnosis.[27]

To our knowledge, no previous study has reported an age-specific analysis of MetS prevalence in this type of population. The age-specific cumulative prevalence of MetS was found to increase markedly, reaching 22.4% at 35 years of age, thereby highlighting the importance of a prolonged follow-up duration. The risk factors for MetS in adult survivors of childhood AL treated without HSCT have not been clearly established. Our multivariate analysis identified three significant risk factors of MetS: male sex, age at last evaluation and BMI at diagnosis. Interestingly, cumulative steroid dose was not significantly associated with MetS in this L.E.A. cohort. Moreover, MetS prevalence among acute myeloblastic leukemia survivors was not lower than that observed among acute lymphoblastic leukemia survivors, while AML protocols did not usually include any steroid therapy. Ongoing corticosteroid therapy induces many metabolic abnormalities, although limited data is available concerning the role that steroids play in the occurrence of MetS several years after treatment termination. In accordance with our results, the St Jude lifetime cohort study[18] has also suggested that there was no significant association between cumulative steroid dose and MetS occurrence.

In the present study, male sex was significantly associated with MetS (OR 2.64; 95% CI 1.32-5.29; *P*=0.006). This increased risk among men was also observed in the French general population. Indeed, the reported prevalence of MetS in French adult females and males under 40 years of age ranged from 2.2% to 3.1% and from 4.3% to 5.0%, respectively.[24,25] In the American population however, no difference between females and males has been reported,[28] and interestingly, sex was not a significant risk factor in the St Jude lifetime cohort study.[18] Notably, recent data suggest that the impact of cardiovascular risk factors may be more important for women.[29] Consequently, it remains necessary to monitor cardiovascular and metabolic risk in both male and female patients. In our study, male sex was also a risk factor for three components of MetS: the elevation of fasting glucose, elevated triglycerides and elevated blood pressure. Investigators from the St Jude lifetime cohort study also found male sex was a significant risk factor for elevated fasting glucose.[18] Inversely, investigators from Thailand have only reported "age at evaluation" as a significant risk factor for impaired glucose tolerance.[30] Several teams have shown that male survivors exhibit an increased risk of elevated triglyceride levels and other lipid abnormalities.[18,31] In our study, elevated blood pressure was significantly associated with male sex, which is also a known risk factor in the general population, especially among young and middle-aged adults.[32] This risk factor has already been described in adult survivors of childhood AL.[18,33] We found no clear evidence to explain a particularly increased risk of elevated blood pressure among male sur-

**Table 2. Prevalence of the metabolic syndrome and its components.**

| | Number of cases (%) | 95% CI |
|---|---|---|
| MetS prevalence | 45 (6.9%) | 5.1 - 9.2 |
| No. of abnormal MetS components | | |
| ≥1 | 385 (59.2%) | 55.3 - 63.0 |
| ≥2 | 149 (22.9%) | 19.8 - 26.4 |
| MetS components prevalence (among the entire cohort) | | |
| Decreased HDL cholesterol | 165 (26.8%) | 23.4 - 30.5 |
| Increased triglycerides | 75 (11.7%) | 9.3 - 14.5 |
| Increased fasting glucose | 36 (5.8%) | 4.2 - 8.1 |
| Increased blood pressure | 228 (36.7%) | 32.9 - 40.7 |
| Increased waist circumference | 93 (16.7%) | 13.7 - 20.1 |
| Decreased HDL cholesterol and increased triglycerides | 32 (5.2%) | 3.6 - 7.3 |
| MetS components prevalence (among MetS patients) | | |
| Decreased HDL cholesterol | 38 (88.4%) | 74.1 - 95.6 |
| Increased triglycerides | 30 (68.2%) | 52.3 - 80.9 |
| Increased fasting glucose | 10 (23.3%) | 12.3 - 39.0 |
| Increased blood pressure | 37 (88.1%) | 73.6 - 95.5 |
| Increased waist circumference | 33 (76.7%) | 61.0 - 87.7 |
| Decreased HDL cholesterol and increased triglycerides | 24 (55.8%) | 40.0 - 70.6 |

*CI: confidence interval; MetS: metabolic syndrome; HDL: high-density lipoprotein.*

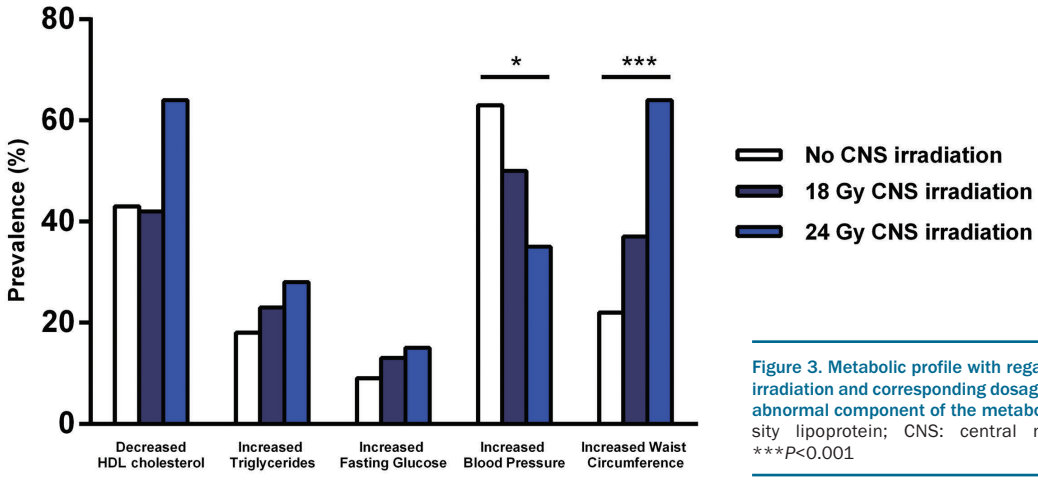


**Figure 3. Metabolic profile with regard to central nervous system irradiation and corresponding dosage in patients with at least one abnormal component of the metabolic syndrome.** HDL: high-density lipoprotein; CNS: central nervous system; *$P$<0.05; ***$P$<0.001

vivors of childhood AL. The St Jude lifetime cohort team showed that this increased risk was probably not related to chronic kidney disease, for which the prevalence was 2-8% in their cohort.[18] Interestingly, investigators in the USA have demonstrated that flow-mediated vasodilatation was better in female survivors of childhood AL compared with their male counterparts.[34] Finally, in our study, male sex was a protective factor of increased abdominal circumference (OR 0.38; 95% CI 0.22-0.64; $P$<0.001). It was striking to find this predisposition of abdominal obesity among the female subjects because such abdominal fat distribution is rather a male characteristic in the general population, especially among young and middle-aged adults.[35] It has already been reported that female adult survivors of childhood AL display an increased risk of obesity.[36] Female patients may have higher leptin levels.[37] Furthermore, it has been shown that female and male patients display significantly different BMI kinetics during treatment.[38]

Age at last evaluation was found to be a risk factor for MetS, increased blood pressure and increased abdominal circumference. This observation is consistent with published data concerning adult survivors of childhood AL[18] and other childhood cancers. Furthermore, as indicated above, MetS prevalence is also known to increase with age in the general population.

Increased BMI at diagnosis was also a risk factor for MetS in our study. We have shown that it was also a significant risk factor for increased abdominal circumference. Obesity, particularly abdominal obesity, is a major determinant of MetS in the general population.[22,39] It has been suggested that abdominal obesity could be a marker of impaired fat storage capacity in the subcutaneous adipose tissue, thereby resulting in the accumulation of ectopic visceral fat leading to metabolic disturbances.[40] This heightened risk of increased abdominal circumference and MetS could be explained by several observations. Children with an elevated BMI at diagnosis may have a genetic predisposition to obesity or certain metabolic disturbances. Likewise, such patients may have a familial and social environment that renders them more vulnerable to obesity or metabolic complications. A study has shown that being overweight or obese at the time of diagnosis of childhood AL was associated with a higher risk of obesity during long-term follow-up.[41] However, to our knowledge, BMI at diagnosis was never reported in the literature as a risk factor for MetS among adult survivors of childhood AL. These results indicate the importance of both monitoring the metabolic risk of children with an elevated BMI at the time of leukemia diagnosis and improving prevention and early treatment of associated complications.

In the univariate analysis, CNS irradiation was a significant risk factor for MetS only when administered at the 24 Gy dose, which could suggest a dose-effect relationship. However, in the multivariate analysis, CNS irradiation was not found to be a risk factor for MetS, neither at the 18 Gy nor at the 24 Gy dose. We hypothesize that the loss of effect in the univariate analysis can be explained by the observation that "age at last evaluation" was a confounding factor that has been corrected in the multivariate analysis. Indeed, CNS irradiation was more widely applied in older treatment protocols. In the literature however, brain irradiation has been frequently reported as a risk factor for MetS.[18,42,43] This can probably be explained in part by the observation that our irradiated patients displayed a lower risk of elevated blood pressure. We conducted an analysis of the prevalence of each MetS component among patients who had at least one abnormal component (Figure 3). We noted a greater prevalence of increased abdominal circumference among irradiated patients and, inversely, a greater prevalence of elevated blood pressure among non-irradiated patients. The irradiated patients may therefore have a different metabolic risk profile compared with the non-irradiated patients, thereby suggesting varying mechanisms of pathogenesis. The St Jude lifetime cohort study showed that CNS irradiation is a risk factor for MetS.[18] They did not find that irradiation had a significant effect on blood pressure; however, in agreement with our study, they found an increased risk of reduced HDL cholesterol and increased abdominal circumference among irradiated patients. Investigators in the USA have recently shown that CNS irradiation affects lipid profiles and in particular HDL cholesterol levels.[31] However, the long-term effect of CNS irradiation on blood pressure among adult survivors of childhood AL remains poorly understood. In several studies concerning acute lymphoblastic leukemia survivors, no significant difference in blood pressure between irradiated and non-irradiated patients has been described.[44,45] Another team has

**Table 3.** Multivariate analysis of potential risk factors for the metabolic syndrome and its components.

| Patients' characteristics | Metabolic syndrome OR (95% CI) | P | Decreased HDL cholesterol OR (95% CI) | P | Increased triglycerides OR (95% CI) | P | Increased fasting glucose OR (95% CI) | P | Increased blood pressure OR (95% CI) | P | Increased waist circumference OR (95% CI) | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | | | | | | | | | | | | |
| Female | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| Male | 2.64 (1.32-5.29) | **0.006** | 0.74 (0.51-1.07) | 0.112 | 1.69 (1.01-2.84) | **0.045** | 2.71 (1.25-5.84) | **0.011** | 3.47 (2.41-4.99) | **<0.001** | 0.38 (0.22-0.64) | **<0.001** |
| Age at last evaluation (years) | 1.10† (1.04-1.17) | **0.001** | 0.99† (0.96-1.03) | 0.799 | 1.04† (0.99-1.09) | 0.097 | 1.05† (0.98-1.12) | 0.132 | 1.08† (1.04-1.12) | **<0.001** | <1.07† (1.02-1.12) | **0.008** |
| BMI z-score at diagnosis | 1.15‡ (1.01-1.32) | **0.037** | 1.10‡ (0.99 - 1.21) | 0.076 | 1.02‡ (0.90 - 1.17) | 0.741 | 0.92‡ (0.73 - 1.16) | 0.482 | 1.00‡ (0.90 - 1.11) | 0.984 | 1.44‡ (1.23-1.70) | **<0.001** |
| CNS irradiation | | | | | | | | | | | | |
| No | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| 18 Gy | 0.92 (0.37-2.29) | 0.866 | 1.11 (0.65-1.90) | 0.712 | 1.27 (0.64-2.50) | 0.495 | 1.33 (0.54-3.32) | 0.534 | 0.48 (0.28-0.82) | **0.007** | 1.67 (0.87-3.24) | 0.122 |
| 24 Gy | 1.87 (0.56-6.27) | 0.309 | 2.76 (1.03-7.40) | **0.044** | 1.37 (0.41-4.60) | 0.61 | 1.31 (0.26-6.64) | 0.745 | 0.21 (0.07-0.64) | **0.006** | 4.84 (1.63-14.44) | **0.005** |

*HDL: high-density lipoprotein; OR: odds ratio; CI: confidence interval; BMI: body mass index; CNS: central nervous system; †OR per each additional year of follow-up; ‡OR per each additional z-score unit;* ***significant values (P<0.05).***

reported higher systolic blood pressure values among non-irradiated patients, albeit without performing a statistical analysis of the difference.[42] Finally, one study has shown that blood pressure was significantly higher in non-irradiated patients, which is consistent with our results.[45] Overall, the consequences of CNS irradiation on cardiovascular risk factors seem complex. We suggest that both irradiated and non-irradiated patients are at elevated risk for metabolic and cardiovascular disturbances, although their metabolic risk profile may vary.

Our study has several limitations. Other potential risk factors for MetS, such as genetic factors and behavioral factors (dietary factors, physical activity and smoking status), were not accounted for in the analysis herein. Furthermore, despite the comparison of the reported data to the latest available French data in the general population, this study lacks an appropriate comparison group.

The results of our study confirm the need for early, close and prolonged follow-up of adult survivors of childhood AL, even when treated without HSCT and without CNS irradiation. This prerequisite could enable both the early detection of metabolic abnormalities and the implementation of all appropriate therapeutic procedures to reduce the morbidity and mortality associated with cardiovascular complications in such patients. Upon initiation of the follow-up, the patient and his family should be advised to adopt general public health recommendations to reduce cardiovascular risk (e.g., increasing the consumption of fruit and vegetables, lowering the consumption of fat and carbohydrates, regular physical activity and quitting smoking). Indeed, adherence to these public health policies are known to be inversely associated with MetS among survivors of childhood cancer.[46] Several other therapeutic interventions can be considered, of which some have already been reported in the literature. A meta-analysis study has examined the effect of physical exercise programs for children with cancer.[47] Other investigators have examined the interest of growth hormone supplementation in a select population of patients.[48,49] A group of American investigators has shown that preventive therapeutic interventions limiting the increase in BMI and insulin resistance may be particularly important during maintenance therapy.[50] These therapeutic interventions will however require more expensive prospective studies for accurate evaluation.


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