Associations between pretherapeutic body mass index, outcome, and cytogenetic abnormalities in pediatric acute myeloid leukemia

Ditte J. A. Løhmann1 | Peter H. Asdahl1 | Jonas Abrahamsson2 | Shau-Yin Ha3 | Ólafur G. Jónsson4 | Gertjan J. L. Kaspers5,6,7 | Minna Koskenvuo8 | Birgitte Lausen9 | Barbara De Moerloose10 | Josefine Palle11 | Bernward Zeller12 | Lillian Sung13 | Henrik Hasle1

1Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus N, Denmark
2Department of Pediatrics, Institution for Clinical Sciences, Queen Silvia Children's Hospital, Gothenburg, Sweden
3Department of Pediatrics, Queen Mary Hospital and Hong Kong Pediatric Hematology and Oncology Study Group (HKPHOSG), Hong Kong, China
4Department of Pediatrics, Landspitali University Hospital, Reykjavik, Iceland
5Department of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands
6Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
7Dutch Childhood Oncology Group, The Hague, The Netherlands
8Division of Hematology-Oncology and Stem Cell Transplantation, Children's Hospital and Helsinki University Central Hospital, Helsinki, Finland
9Department of Pediatrics and Adolescent Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
10Department of Pediatrics, Ghent University Hospital, Ghent, Belgium
11Department of Woman's and Children's Health, Uppsala University, Uppsala, Sweden
12Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway
13Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Canada

Abstract

Background: Associations between body mass index (BMI), outcome, and leukemia-related factors in children with acute myeloid leukemia (AML) remain unclear. We investigated associations between pretherapeutic BMI, cytogenetic abnormalities, and outcome in a large multinational cohort of children with AML.

Methods: We included patients, age 2-17 years, diagnosed with de novo AML from the five Nordic countries (2004-2016), Hong Kong (2007-2016), the Netherlands and Belgium (2010-2016), and Canada and USA (1995-2012). BMI standard deviations score for age and sex was calculated and categorized according to the World Health Organization. Cumulative incidence functions, Kaplan-Meier estimator, Cox regression, and logistic regression were used to investigate associations.

Results: In total, 867 patients were included. The median age was 10 years (range 2-17 years). At diagnosis, 32 (4%) were underweight, 632 (73%) were healthy weight,
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INTRODUCTION

Acute myeloid leukemia (AML) in children is a clinically and genetically heterogeneous disease with a long-term overall survival of around 70%, and few known causative factors. Overweight in children is increasing globally and, as a consequence, so are overweight-related diseases. Overweight at diagnosis has been associated with inferior outcome in pediatric AML in two North American studies, but in a recent study on mainly Nordic patients, we failed to confirm this association. Likewise, results from studies on the effect of pretherapeutic body mass-index (BMI) in adults with AML have been conflicting. In our previous study, we saw indications of cytogenetic abnormalities being associated with weight group, an association that, to our knowledge, has not been reported in children before.

In this study, we aimed to investigate associations between pretherapeutic BMI and outcome in a large, multinational cohort of children diagnosed with AML and treated on several protocols. Second, we aimed to confirm a possible association between BMI group and cytogenetic abnormalities as suggested by our previous study.

MATERIALS AND METHODS

Patients

We included patients less than 18 years of age diagnosed with de novo AML before November 1st 2016, but without Down syndrome, acute promyelocytic leukemia, or isolated granulocytic sarcoma. Patients originated from the five Nordic countries (Sweden, Denmark, Norway, Finland and Iceland), the Netherlands, Belgium, Hong Kong (NOPHO-DBH cohort) and Canada and USA. Included patients from the Nordic countries were diagnosed from 2004 to 2016, Hong Kong from 2007 to 2016, Belgium and the Netherlands from 2010 to 2016, Canada from 1995 to 2012 and USA from 2005 to 2012. Included patients from Canada and USA diagnosed from 2005 to 2012 came from a prospective study on host genome variants and infection. We excluded patients below 2 years of age (BMI calculations in this age group is not standardized), and patients with missing data on BMI at diagnosis (Figure 1).

Data collection and registration

In the NOPHO-DBH cohort data on demographics, cytogenetic abnormalities, and follow-up information were prospectively registered by the treating center. In Canada and USA, clinical research associates conducted site visits in order to abstract the required data from medical records. Centers were contacted at later time points to update follow-up information. The Research Ethics Boards at all participating institutions/countries approved data collection and written informed consent was obtained from all patients/parents/guardians. For Canadian children diagnosed between 1995 and 2004, the need for informed consent was waived given the retrospective nature of the study.

Definitions and statistics

BMI was calculated using height and weight measured at time of diagnosis. BMI standard deviation (SD) score for age and sex was calculated and categorized according to the World Health Organization Child Growth Standards as following: underweight: $<-2$ SD, healthy weight: $-2$ up to $+2$ SD for age 2-5 and $-2$ up to $+1$ SD for age 6-17, overweight: $>2$ up to $3$ SD for age 2-5 and $>1$ up to $2$ SD for age 6-17, and obese: $>3$ SD for age 2-5 and $>2$ SD for age 6-17.
For all analyses, the healthy weight group was used as reference.

Treatment-related mortality was defined as death not related to disease progression.\textsuperscript{12} Patients with unknown reason for death were excluded from treatment-related mortality analyses. Associations between BMI groups and relapse, treatment-related mortality, and overall survival were investigated using the cumulative incidence function with pseudo-observations under competing risks and the Kaplan-Meier estimator. Death was included as a competing risk in the calculation of cumulative incidence of relapse, and death from progressive disease in the calculation of cumulative incidence of treatment-related mortality. Multiple Cox regression was used to compare groups. Follow-up started at diagnosis and ended at event, death, or last follow-up. Cases were censored on November 5, 2016, 6 months before data cutoff (May 5, 2017) to ensure independent censoring (relapse and death could be reported sooner than ongoing follow-up for patients in continuing remission).

\text{Inv(16)/t(16;16) (in the following referred to as inv(16)), t(8;21) and KMT2A rearrangements were selected for the study due to these abnormalities being common and with prognostic significance.\textsuperscript{1,13} Core-binding factor AML, t(8;21) and inv(16), has generally been associated with a favorable prognosis, whereas the prognostic significance of KMT2A rearrangements depends on the fusion partner.\textsuperscript{1} Logistic regression was used to investigate associations between BMI groups and cytogenetic abnormalities. Cases with missing data on cytogenetic abnormalities were excluded from analyses.}

BMI standard deviation score as a continuous variable and outcomes were modeled using restricted cubic splines with four knots at BMI SD score −2, 0, 1, and 2.\textsuperscript{14} Confounders incorporated into statistical models were defined as factors, which could influence both the independent variable (BMI group) and dependent variables (treatment-related mortality, relapse, survival, and cytogenetic abnormalities). Age, sex, and country group (Nordic countries, Belgium/the Netherlands, Hong Kong or Canada/USA) was included in all adjusted models. Year of diagnosis was included in the adjusted models for treatment-related mortality, relapse, and overall mortality.

3 | RESULTS

A total of 867 patients included were treated in 10 different countries (Canada n = 394, Sweden n = 116, the Netherlands n = 92, Denmark n = 53, Finland n = 51, Hong Kong n = 50, Belgium n = 48, Norway n = 41, USA n = 17, and Iceland n = 5). Of included cases, n = 692 (80%) were population based, and n = 239 (28%) were included in our previously study of associations between BMI group and outcome.\textsuperscript{6} The median age of diagnosis was 10 years of age (range: 2-17 years), 53% of cases were male and the median follow-up time for cases alive at end of follow-up (n = 615) was 3.9 years (range: 0.1-13.3 years). Patients were treated on 17 different protocols with AAML0531,\textsuperscript{15} COG9421,\textsuperscript{16} NOPHO-AML 2004,\textsuperscript{17} DB AML-01,\textsuperscript{18} and NOPHO-DBH AML 2012 (ClinicalTrials.gov identifier: NCT01828489, ongoing accrual) accounting for 79%. Table 1 shows baseline characteristics according to BMI group. The frequency of underweight and obesity was higher among males, and the median age was higher for the nonhealthy BMI groups. The frequency of obesity was higher in the North American countries.
3.1 | BMI group and risk of relapse, treatment-related mortality, and overall mortality

Within the follow-up period, 324 patients suffered a first relapse, 102 died from treatment-related causes, and 244 died for any reason. Of the 102 patients that died from treatment-related causes, 42 died without previous hematopoietic stem cell transplantation or relapse, 14 died after hematopoietic stem cell transplantation in first complete remission and 46 died after relapse from causes other than disease progression. In two cases, reason for death was unknown (excluded from treatment-related mortality analyses). The remaining 140 deaths were due to disease progression.

Overall, in the cohort the 5-year cumulative incidence of relapse was 43% (95% confidence interval (CI) 40-47), the 5-year cumulative incidence of treatment-related mortality was 13% (95% CI 10-15), and 5-year overall survival was 67% (95% CI 64-71). The results for associations between BMI group and risk of relapse, treatment-related mortality, and overall mortality are presented in Table 2 and Figure 2.

We found no evidence of associations between BMI group and risk of relapse, risk of treatment-related mortality, or risk of death for any reason (Figure 2, Table 2, and Supporting Information). Including cytogenetic abnormalities in the models, as mediation analyses did not change the results (Table S2). Combining the overweight and obese group, we saw similar results with no evidence of association between overweight/obesity and risk of relapse, risk of treatment-related mortality, or risk of death for any reason (Table S3).

3.2 | BMI group and cytogenetic abnormalities

In 36 (4.2%) cases, information on t(8;21) and inv(16) were missing, and in 38 (4.4%) cases information on KMT2A
rearrangements were missing. In the remaining cases, 155 (19%) of patients had t(8;21), 80 (10%) had inv(16) and 100 (12%) had a KMT2A rearrangement. Patients with KMT2A rearrangements were younger, the three cytogenetic abnormalities groups showed a different pattern of white blood cell count at diagnoses and fewer with the cytogenetic abnormalities were transplanted in first complete remission compared to the entire cohort (Table S4). The results for associations between BMI group and cytogenetic abnormalities are presented in Table 3. The frequency and odds ratio of t(8;21) and inv(16) increased with increasing BMI group (Table 3). For KMT2A rearrangements, the association with BMI group was less clear: overweight cases had higher frequency and obese cases had a lower frequency (Table 3). Figure 3 shows the association between BMI standard deviation score examined continuously and the adjusted odds ratio for cytogenetic abnormalities.

4 | DISCUSSION

In this multinational study of 867 pediatric AML patients diagnosed within the last two decades, we found no evidence of associations between BMI group and risk of relapse, treatment-related, or overall mortality. We found associations of obesity and a higher frequency of t(8;21) and inv(16).

We used the World Health Organization (WHO) Child Growth Standard for calculating BMI SD score based on age and sex, due to the multinational design of our study. The growth standard is based on data from children from six different countries (Brazil, Ghana, India, Norway, Oman and the USA) with different ethnic backgrounds and cultural settings and therefore the standard is the most relevant when doing a multinational study. The WHO classification has been shown to have a higher prevalence of overweight and obesity but with similar trends when compared with the International Obesity Task Force and the US Centers for Disease Control and Prevention classifications.

In contrast to two previous North American studies (including mainly patients from the US) that showed that overweight/obesity was associated with increased treatment-related mortality, we found no evidence of associations between BMI group and treatment-related mortality, or overall mortality. We found associations of obesity and a higher frequency of t(8;21) and inv(16).
and while all patients in the two North American studies were treated up to 2008, approximately half the patients included in our study were treated after 2008. In a previous study, we showed that overweight children were at higher risk for toxicity, but the mortality rate from severe toxicity could have decreased in recent years. Both North American studies included patients up to 20 years of age, whereas this study only included patients up to 17 years of age (upper age limit for the pediatric AML protocols in the NOPHO-DBH countries). The frequency of obesity and toxicity increases with age and therefore the difference in age distribution could be part of the explanation for difference in treatment-related mortality. Due to our cohort consisting of patients treated on 17 different protocols, we did not find it feasible to stratify on protocol. Therefore it is possible that an association between BMI group and outcome exist for some treatment regimes. Finally it is important to note that our finding of no association between BMI group and outcome was based on a relatively small cohort and therefore could be a type II error (failure to reject a false null hypothesis). We may have failed to show an association between obesity and outcome because of the relatively low prevalence of obesity in this study, likely reflecting the prevalence of obesity in participating countries. If an association between BMI and outcomes does exist, its effect could be magnified in countries where the prevalence of obesity is higher. A future meta-analysis may overcome the challenges related to small sample size and the relatively low prevalence of obesity in this study.

The frequency of cytogenetic abnormalities in our study was comparable to previous reported frequencies. The frequency of t(8:21) was slightly higher and the frequency of KMT2A rearrangement slightly lower compared to what was previously published, but this was probably due to these abnormalities being age-dependent and the fact that children below 2 years were excluded from this study. Increasing BMI standard deviation score was associated with increasing frequency of inv(16) and t(8:21) (Table 3 and Figure 3). This is the first report of associations of BMI standard deviation score and cytogenetic abnormalities in children, but in adults, obesity has been associated with AML with recurrent cytogenetic abnormalities (including t(8,21) and inv(16)/t(16;16)), though the study did not specify which cytogenetic abnormalities. Our results indicate that either a common etiology for overweight and certain types of AML exist or that obesity is associated with developing certain leukemic cytogenetic abnormalities.

A common variant in the gene coding for the fat mass- and obesity-associated protein (FTO) is known to predispose to obesity in adults and children. Recently, it has been shown that FTO, an RNA demethylase, plays an oncogenic role in AML in adults. It might therefore be biologically plausible that obesity and (certain types of) AML could have a common etiology in children as well.

If, instead, obesity is associated with developing core-binding factor leukemia, it is possible that obese children have a higher risk of developing AML, comparable to obese adults. A recent study showed that bone marrow adipocytes support the survival and proliferation of AML

FIGURE 2 Cumulative incidence of relapse, treatment-related mortality, and overall survival according to body mass index group. A, Cumulative incidence of relapse. B, Cumulative incidence of treatment-related mortality (TRM). C, Kaplan-Meier estimator of overall survival.
blasts. Also, there is growing evidence that higher birth-weight is associated with developing both acute lymphoid leukemia and AML in childhood and young adulthood, but studies of associations between birth-weight and cytogenetic subgroups of AML are lacking. However, it is important to note, that this study was not designed to examine the effect of obesity on the risk of developing leukemia. Studies of incidence of AML in overweight children compared to healthy weight children are needed in general, and with a focus on specific cytogenetic subtypes in particular. As opposed to our study, future studies would also benefit from collecting BMI SD score at several time points before AML diagnosis.

Ethnicity could be a confounder in this study. Gramatges et al demonstrated a higher frequency of t(8;21) in Hispanic children with AML compared to non-Hispanic whites. However, the study did not show frequency of overweight in the two groups, and Hispanic children are more overweight in the US. We did not have information on ethnicity for about half our cases, and because of our multinational cohort, ethnicity groups were difficult to define. Therefore, we chose not to include ethnicity in our models. As opposed to our study, future studies would also benefit from collecting BMI SD score at several time points before AML diagnosis.

| Table 3 Cytogenetic abnormalities according to body mass index groups |
|-----------------|-----------------|-----------------|-----------------|
|                | Underweight     | Healthy weight  | Overweight      | Obese           |
| **t(8;21)**    |                 |                 |                 |                 |
| N (%)          | 2 (7)           | 106 (17)        | 26 (21)         | 21 (31)         |
| Crude OR (95% CI) | 0.3 (0.08-1.4)  | 1               | 1.2 (0.8-2.0)   | 2.1 (1.2-3.7)   |
| Adjusted OR (95% CI) | 0.3 (0.08-1.4)  | 1               | 1.2 (0.7-1.9)   | 1.9 (1.1-3.4)   |
| **inv(16)/t(16;16)** |                |                 |                 |                 |
| N (%)          | 1 (3)           | 53 (9)          | 14 (11)         | 12 (18)         |
| Crude OR (95% CI) | 0.4 (0.05-2.7)  | 1               | 1.3 (0.7-2.5)   | 2.2 (1.1-4.4)   |
| Adjusted OR (95% CI) | 0.3 (0.05-2.6)  | 1               | 1.6 (0.8-3.0)   | 2.8 (1.3-5.8)   |
| **KMT2A rearrangements** |             |                 |                 |                 |
| N (%)          | 5 (17)          | 70 (12)         | 22 (18)         | 3 (4)           |
| Crude OR (95% CI) | 1.5 (0.6-4.1)   | 1               | 1.7 (1.0-2.8)   | 0.4 (0.1-1.2)   |
| Adjusted OR (95% CI) | 1.8 (0.6-4.9)   | 1               | 2.0 (1.1-3.5)   | 0.5 (0.1-1.5)   |

Note: Underweight: <-2 SD, Healthy weight: -2 to +2 SD for age 2-5 and -2 to +1 SD for age 6-17, Overweight: >2-3 SD for age 2-5 and >1-2 SD for age 6-17, Obesity >3 SD for age 2-5 and >2 SD for age 6-17.
Abbreviations: CI: confidence interval, OR: odds ratio.

aAdjusted for age (continuously), sex and country group (Nordic countries, Belgium/the Netherlands, Hong Kong, or Canada/USA).

In conclusion, in this large multinational cohort, we found that, in children with AML, overweight and obesity were not
associated with outcome, which is in contrast to previous studies. We found that obesity was associated with a higher frequency of core-binding factor leukemia. This finding raises the question whether overweight in children increases the risk of developing core-binding factor AML, but further studies are needed.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

DJAL, LS, and HH designed the project; DJAL, PHA, LS, and HH interpreted the data, and drafted the manuscript; DJAL performed statistical analyses; JA, GJLK, SY.H., OGJ, MK, BL, BDM, JP, and BZ collected the data and contributed to the writing of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Ditte J. A. Løhmann https://orcid.org/0000-0002-9935-9157

Lillian Sung https://orcid.org/0000-0003-0951-3091

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