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Obesity as a predictor of treatment-related toxicity in children with acute lymphoblastic leukaemia

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Summary

Obesity is associated with poor outcomes in childhood acute lymphoblastic leukaemia (ALL). We explored whether severe treatment-related toxicity and treatment delays could explain this observation. This study included 1 443 children aged 2·0–17·9 years with ALL treated with the Nordic Society of Pediatric Haematology and Oncology (NOPHO) ALL2008 non-high-risk protocol. Prospective treatment-related toxicities registered every three-month interval were used. Patients were classified according to sex- and age-adjusted international childhood cut-off values, corresponding to adult body mass index: underweight, <17 kg/m^2; healthy weight, 17 to <25 kg/m^2; overweight, 25 to <30 kg/m^2; and obese, ≥30 kg/m^2. Obese children had a higher incidence rate ratio (IRR) for severe toxic events {IRR: 1·55 [95% confidence interval (CI) 1·07–2·50]}, liver and kidney failures, bleeding, abdominal complication, suspected unexpected severe adverse reactions and hyperlipidaemia compared with healthy-weight children. Obese children aged ≥10 years had increased IRRs for asparaginase-related toxicities compared with healthy-weight older children: thromboses [IRR 2·87 (95% CI 1·00–8·21)] and anaphylactic reactions [IRR 7·95 (95% CI 2·15–29·37)] as well as higher risk for truncation of asparaginase [IRR 3·54 (95% CI 1·67–7·50)]. The high prevalence of toxicity and a higher risk of truncation of asparaginase may play a role in the poor prognosis of obese children aged ≥10 years with ALL.

Keywords: body mass index, obesity, childhood acute lymphoblastic leukaemia, adverse events, toxicity.

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Introduction

Severe toxicities that increase both morbidity and mortality are common during the treatment of childhood acute lymphoblastic leukaemia (ALL). In addition to deaths from toxicity, severe toxicity often leads to therapy interruptions and protocol deviations, which compromise treatment outcomes by increasing the risk of relapse.[1,2] Identification of prognostic risk factors for severe toxicities is thus essential for improving treatment.

The prevalence of overweight and obesity has increased in the general population.[3] Studies in children with ALL have demonstrated that the presence of obesity at diagnosis is associated with an increased risk of relapse [4,5] and lower survival rates.[6–9] The underlying reasons for the inferior outcomes in obese children are most likely multifactorial, including pharmacokinetic differences leading to under- or overtreatment, increased chemotherapy resistance and variations in genetic susceptibility.[10] Data on the frequency of severe treatment-related complications in extreme body mass index (BMI) categories in children with ALL are limited.[11–14] Previous studies have shown associations between high BMI and hepatic and pancreatic toxicities,[5,12,14,15] central nervous system (CNS) thrombosis,[16] venous thromboembolism (VTE)[17] and osteonecrosis.[18] In contrast, a Danish study based partly on the Nordic Society of Pediatric Haematology and Oncology (NOPHO) ALL2008 cohort found no association between pancreatitis and obesity in children,[19] and Meenan *et al.* did not find an association between an increased BMI and thrombosis, hepatotoxicity, or pancreatitis.[20]

In our previous study, we concluded that obesity at diagnosis was associated independently with the risk of relapse in older children with ALL.[4] We hypothesised that obese older children experience more severe toxic events than healthy-weight children and therefore their treatment may have been modified, contributing to the increased risk of relapse. To explore the underlying factors behind the higher relapse risk and inferior outcomes in this patient group, we studied the role of obesity in the occurrence of severe adverse events and treatment delays in children with ALL treated according to the non-high-risk arm of the NOPHO ALL2008 study.

Material and methods

Study group

Patients aged 2·0–17·9 years, diagnosed with precursor B-cell (BCP) or T-cell ALL between July 2008 and December 2017 in the Nordic (Sweden, Norway, Denmark, Finland, Iceland) and Baltic (Estonia and Lithuania) countries and treated according to the paediatric NOPHO ALL2008 protocol, were included in the study. The children in the study were followed up until March 2019. Details on the NOPHO ALL2008 treatment protocol (EudraCT 2008-003235-20) have been published previously.[21–23] As intensive high-risk block therapy differs significantly from non-high-risk therapy, the children in the high-risk treatment arm were excluded from the current study. Other exclusion criteria were: missing data on BMI, modified treatment including patients with Down syndrome or other predisposition syndromes. Patients below two years of age were excluded as the BMI cut-off values used in this study were defined from two years of age. Body surface area (BSA) was used to administer systemic chemotherapy; however, a maximum dose of 2·5 mg was used for vincristine. No dose adjustments were recommended for obese patients.

The NOPHO ALL2008 study was approved by the Scientific Ethical Review Boards of each respective country. Verbal and written consent was obtained for the registration of treatment-related data, including the toxicities. This substudy was approved by the NOPHO Scientific Board and a separate ethical approval was obtained from the Regional Ethics Review Board in Stockholm (approval no: 2018/1888-31).

Toxicity registration

The NOPHO ALL2008 registry includes information on treatment details, including asparaginase administration, the start date for each treatment phase (induction, consolidation, delayed intensification 1, consolidation 2 and maintenance 1), the response to treatment and the occurrence of predefined severe adverse events of special interest (SAEs). The registration was prospective; SAEs were registered after induction and every third month for all patients. Definitions of the registered SAEs are listed in Table I.

Body mass index

The BMI values at diagnosis were recorded as four categorical variables (underweight, healthy weight, overweight, obesity) with reference to age- and gender-adjusted cut-offs according to Cole *et al.* and the International Obesity Task Force (IOTF) Guidelines, corresponding to BMIs of <17 kg/m^2, 17 to <25 kg/m^2, 25 to <30 kg/m^2 and >30 kg/m^2 respectively, in the adult population.[24,25] Analyses were also performed using BMI standard deviation score (BMISD) as a continuous variable.[25]

Statistics

We calculated the incidence rate ratios (IRR) of the different SAEs during treatment (2.5 years) and treatment delays from diagnosis to the start of maintenance-1 (in the standard-risk arm corresponding to protocol day 134 and in the intermediate-risk arm to protocol day 148) in relation to the BMI.

The IRRs were estimated with a Poisson regression model, offsetting for the logarithm of time at risk for toxicity, adjusted for age. When calculating the timespan for toxicity in the IRR analyses, all patients were censored at the end of therapy (2·5 years), time of early relapse, or death from any cause during the period of treatment. Median follow-up in

Table I. List of the registered toxicities.

Abdominal complication	Complication leading to abdominal laparotomy/surgery
Anaphylactic reaction	Allergy/life-threatening anaphylaxis leading to changes in the leukaemia treatment, CTC grades 3–4
Bleeding	Intracranial or other catastrophic bleeding requiring acute major intervention
Coma	
Kidney dysfunction	Dialysis or permanently increased s-creatinine levels not present prior the leukaemia treatment
Fungal infection	Suspected or verified fungal infection, requiring systemic antifungal treatment excluding Pneumocystis jirovecii
Pancreatitis	Symptomatic pancreatitis, CTC grade 2–4
Heart failure	Severe/refractory congestive heart failure or life-threatening arrhythmia
Hyperglycaemia	Hyperglycaemia during leukaemia induction therapy with insulin treatment
Hyperlipidaemia	Severe lipid disorder, >5 times upper normal limit
Hypertensive crisis	Hypertensive crisis, CTC grade 4
Intensive care	Admission to intensive care unit
Liver dysfunction	Hepatic dysfunction with encephalopathy, or bilirubin >5 times upper normal limit
Osteonecrosis	Symptomatic osteonecrosis, CTC grade 2–4
Paralysis	Vincristine-related/suspected peripheral neurotoxicity leading to reduction of vincristine treatment
Pneumocystic jirovecii	Suspected or verified *Pneumocystic jirovecii* infection with systemic antipneumocytic treatment
PRES	Posterior reversible encephalopathy syndrome
Seizures	Seizures, CTC grades 2–4
Septic shock during induction	Severe septic infection, requiring inotropes
SUSAR	Suspected unexpected serious adverse event resulting in death or persistent/significant disability/incapacity *or* life-threatening event *or* requiring either inpatient hospitalisation or prolongation of existing hospitalisation
Thrombosis	Any symptomatic thromboembolism leading to intervention, for example, surgery or anticoagulation therapy
VOD	Veno-occlusive disease or severe sinusoidal obstruction syndrome of the liver

CTC, common toxicity criteria.

survivors was analysed with the reverse Kaplan–Meier method. Children were divided into two age groups: 2·0–9·9 years and 10·0–17·9 years at diagnosis. Differences in the proportions of toxic events and clinical patient characteristics were tested using a chi-squared test or Fisher's exact test. In the categorical analyses, the median treatment duration for each treatment phase until maintenance-1 and treatment duration from diagnosis to start of maintenance-1 in underweight, overweight and obese patients were compared with healthy-weight patients. Linear regressions of BMISD and the correlation to IRR of SAEs, adjusted for age, was analysed and presented as a correlation coefficient (r) and P value. The statistical significance was set at $P < 0{\cdot}05$. All statistical analyses were performed using IBM SPSS Statistics version 26·0 for Windows (SPSS Inc., Chicago, IL, USA) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria; version 4·1.0) in the forest plot figure.

Results

Patient characteristics and body mass index

A total of 1 443 patients were included in the study cohort (Fig 1). The median age at diagnosis was 4·7 years and the median follow-up time for the survivors was 5·2 years (range 19 days–10·6 years).

Patient characteristics are summarised in Table II. The older age group had a higher proportion of overweight and obese children (19·3%) compared to the younger age group (10·8%). There were no significant differences in the different BMI categories regarding sex, risk group, white blood cell count at diagnosis, immunophenotype, minimal residual disease (MRD) on day 29, cytogenetics or CNS disease. None of the patients had registered obesity-related comorbidities including type 2 diabetes at diagnosis.

Treatment delays

There were no significant differences in median duration of the individual treatment phases between the BMI categories, nor a significant correlation between BMISD and treatment duration. When the whole time period from diagnosis to the start of maintenance-1 was analysed, there was a tendency for a longer median delay in the obese compared with healthy-weight children (16 and 11 days respectively, $P = 0{\cdot}09$). A tendency to longer delay of more than four weeks (20% of the time period) from diagnosis until start of maintenance-1 was observed in obese compared to healthy-weight children [IRR 1·84 (95% CI 0·96–3·51), $P = 0{\cdot}07$)], but not when comparing underweight [IRR 0·75 (95% CI 0·33–1·71)] and overweight [IRR 0·77 (95% CI 0·44–1·33)] to healthy-weight children.

Severe adverse events

In the entire cohort, 764/1443 (52·9%) patients had at least one SAE during the treatment period (Table III). The

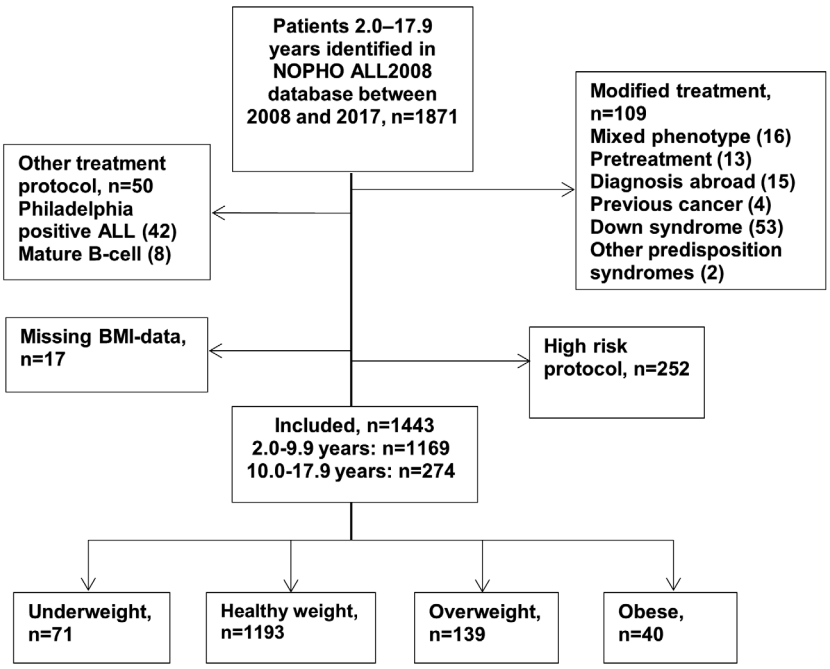

Fig 1. Consort diagram for acute lymphoblastic leukaemia (ALL) patients aged 2·0 to <18 years.

prevalence increased with age: 575 (49·2%) children aged 2·0–9·9 years and 189 (69·0%) children aged 10·0–17·9 years experienced one or more SAEs.

There was no linear association between BMISD and the IRR for any or individual SAEs after adjusting for age in the whole cohort, except for an increased tendency for bleeding ($r = 1·27$, $P = 0·07$). There was a correlation between increasing BMISD and IRR for abdominal complications ($r = 1·42$, $P = 0·01$), bleeding ($r = 2·02$, $P \leq 0·001$) and thromboses ($r = 1·18$, $P = 0·01$) and a decreasing BMISD and IRR for seizures ($r = 0·80$, $P = 0·001$) and paralysis ($r = 0·85$, $P < 0·001$) in children aged 10·0–17·9 years. The younger children aged 2·0–9·9 years showed a positive correlation between BMISD and IRR for kidney dysfunction ($r = 1·79$, $P < 0·001$).

Obesity and severe adverse events

Obese patients experienced SAEs more frequently than healthy-weight children [IRR 1·55 (95% CI 1·06–2·25), $P = 0·022$] (Fig 2). When separated into the two age groups, the IRR remained significant only for obese children aged 10·0–17·9 years [1·85 (95% CI 1·02–3·34)] (Figure S1).

When the different SAEs were analysed separately, the obese children showed an increased risk of hyperlipidaemia [IRR 3·12 (95% CI 1·56–6·22)], abdominal complications [IRR 11·68 (95% CI 3·66–37·27)], liver dysfunction [IRR 3·88 (95% CI 1·52–9·92)], kidney dysfunction [IRR 5·89 (95% CI 1·66–20·90)] and bleeding [IRR 5·30 (95% CI 1·1.17–24·00)], compared to those with healthy weight. In addition, suspected unexpected serious adverse reactions (SUSARs) [IRR 4·01 (95% CI 1·20–13·45)] were more frequent in obese children than healthy-weight children (Fig 2).

When analysing the children in the two separate age groups, the IRR for abdominal complications [IRR 12·66 (95% CI 2·26–71·05)], bleeding [IRR 25·23 (95% CI 3·41–186·71)], SUSAR [IRR 11·39 (95% CI 2·70–48·01)] and kidney dysfunction [IRR 5·19 (95% CI 1·09–24·66)] remained significant for the older obese children, but not for liver dysfunction [IRR 3·04 (95% CI 0·69–13·37)]. In this older age category, there was also an increased risk of thromboses [IRR 2·87 (95% CI 1·00–8·21)] and severe anaphylaxis [IRR 7·95 (95% CI 2·15–29·37)], which was not observed in the younger children (Figure S1). In the younger children, almost one fourth of those who were obese had hyperlipidaemia [23·1%, IRR of 3·25 (95% CI 1·39–7·58)]. Abdominal complications [IRR 13·36 (95% CI 2·76–64·77)] and liver dysfunction [IRR 5·09 (95% CI 1·51–17·11)] also remained significantly more common in younger obese children compared to healthy-weight children. There was a tendency for kidney dysfunction in the younger obese children [IRR 7·03 (95% CI 0·80–61·36), $P = 0·079$].

During the induction period, 12·4% (179/1443) of the children experienced SAEs. Ten obese children (25·0%) experienced an adverse event during the induction period compared with 138/1 193 (11·8%) children with healthy weight. The IRR for induction toxicity in the obese children was 1·70 (95% CI 0·86–3·73).

Furthermore, obese children had a higher risk of the truncation of asparaginase than children with a healthy weight [IRR 1·95 (95% CI 1·17–3·23)]. When younger and older children were analysed separately, the increased IRR remained significant only in older obese children [IRR 3·54 (95% CI 1·67–

Table II. Distribution of patients according to baseline characteristics across BMI categories.

	Overall population No. (%)	Under-weight No. (%)	Healthy weight No. (%)	Over-weight No. (%)	Obese No. (%)	*P* value
Cohort	1 443	71 (4·9)	1 193 (82·7)	139 (9·6)	40 (2·8)	
Age at diagnosis, median age: 4·7 years						
2·0–9·9 (median age: 4·0 years)	1 169 (81·0)	59 (83·1)	984 (82·5)	100 (71·9)	26 (65·0)	0·001
10·0–17·9 (median age: 14·0 years)	274 (19·0)	12 (16·9)	209 (17·5)	39 (28·1)	14 (35·0)	
Sex						
Male	797 (55·2)	40 (56·3)	660 (55·3)	76 (54·7)	21 (52·6)	0·981
Female	646 (44·8)	31 (43·7)	533 (44·7)	63 (45·3)	19 (47·5)	
Risk group						
Standard risk	844 (58·5)	40 (56·3)	704 (59·0)	81 (58·3)	19 (47·5)	0·706
Intermediate risk	595 (41·2)	30 (42·3)	487 (40·8)	58 (41·7)	20 (50·0)	
Induction death	4	1	2	0	1	
White blood cell count ($\times 10^9$/l) at diagnosis						
<50	1 196 (82·9)	58 (81·7)	995 (83·4)	111 (79·9)	32 (80·0)	0·764
>50 to <100	142 (9·8)	8 (11·3)	111 (9·3)	19 (13·7)	4 (10·0)	
>100	105 (7·3)	5 (7·0)	87 (7·3)	9 (6·5)	4 (10·0)	
Immunophenotype						
B lineage (90·3%)	1 312 (90·9)	64 (90·1)	1 087 (91·1)	126 (90·6)	35 (87·5)	0·876
T cell (9·7%)	131 (9·1)	7 (9·9)	106 (8·9)	13 (9·4)	5 (12·5)	
Response MRD, day 29						
MRD < 0·1%	1 130 (78·8)	52 (75·4)	938 (79·0)	114 (82·0)	26 (66·7)	0·185
MRD > 0·1-5%	304 (21·2)	17 (24·6)	249 (21·0)	25 (18·0)	13 (33·3)	
Unknown/missing data	9 (0·6)	2 (2·8)	6 (0·5)	0	1 (2·5)	
Cytogenetics‡,§						
Low risk	872 (60·4)	46 (64·8)	732 (61·4)	74 (53·2)	20 (60·4)	0·371
Intermediate risk	95 (6·6)	2 (2·8)	80 (6·7)	10 (7·2)	3 (7·5)	
Other/not stratifying	431 (29·9)	21 (29·6)	343 (28·8)	50 (36·9)	17 (42·5)	
No result/missing data	87 (4·3)	2 (2·5)	64 (4·0)	16 (6·1)	5 (5·2)	
CNS disease						
No	1 387 (96·1)	69 (97·2)	1 148 (97·2)	132 (95·0)	38 (95·0)	0·962
Yes	54 (3·7)	2 (2·8)	43 (3·6)	7 (5·0)	2 (5·0)	
Missing data	2 (0·2)	0	2	0	0	

Pearson´s chi-square test for distribution of predictors across BMI categories. CNS, central nervous system; MRD, minimal residual disease.
‡Day 29 is a response evaluation.
§Low risk: hyperdiploidy, t(12;21); Intermediate risk: t(1;19), dic(9;21), iAmp21.

7·50)]. Asparaginase treatment was discontinued in 8/14 (57·1%) of the older obese and 48/194 (24·7%) of the healthy-weight children. The reasons for discontinuing asparaginase in the older obese patients were thromboses (n = 3), anaphylactic reactions (n = 3) and pancreatitis (n = 2). Of these eight patients, two patients relapsed, one died after first remission and one after a secondary malignant neoplasm. Of the obese older children, 50% (7/14 patients) experienced relapses (n = 4), death in the first remission (n = 2), or secondary malignant neoplasm (n = 1), compared to 11% (22/209; 18 of the 22 were relapses) of the healthy-weight older children. None of the younger obese children died in the first complete remission and only one patient (1/26) relapsed.

Overweight and severe adverse events

Overweight children aged 2·0–17·9 years did not have a significantly higher IRR for one or more SAEs compared with healthy-weight children [IRR 1·01 (95% CI 0·80–1·29), P = 0·91] (Table IV) or when the younger and older age groups were analysed separately [IRR 1·07 (95% CI 0·80–1·43), P = 0·66 and 0·91 (95% CI 0·59–1·39), P = 0·66 respectively].

Underweight and severe adverse events

In underweight children, the IRR of one or more SAEs was 1·31 (95% CI 0·97–1·77), P = 0·077, compared with healthy-weight children (Table IV). Younger underweight children tended to have increased IRR for one or more SAEs during the treatment period [1·38 (95% CI 0·99–1·92), P = 0·059]. Younger underweight children had a significantly higher risk of thromboses [IRR 2·90 (95% CI 1·22–6·90), P = 0·02], whereas the older underweight patients had an increased risk of fungal infections [IRR 3·83 (95% CI 1·10–13·36), P = 0·035] compared to children with healthy BMI.

Table III. Number of patients with one or more severe adverse event during ALL-treatment, according to BMI category.

	Total number of patients	Under-weight n = 71 (%)	Healthy weight n = 1193 (%)	Over-weight n = 139 (%)	Obese n = 40 (%)	P value
Children						
2·0–17·9 years	1443	46 (64·8)	613 (51·4)	76 (54·7)	29 (72·5)	0·01
2·0–9·9 years	1169	38 (64·4)	469 (47·7)	51 (51·0)	17 (65·4)	0·03
10·0–17·9 years	279	8 (66·7)	144 (66·7)	25 (64·1)	12 (85·7)	0·51

ALL, acute lymphoblastic leukaemia; BMI, body mass index.

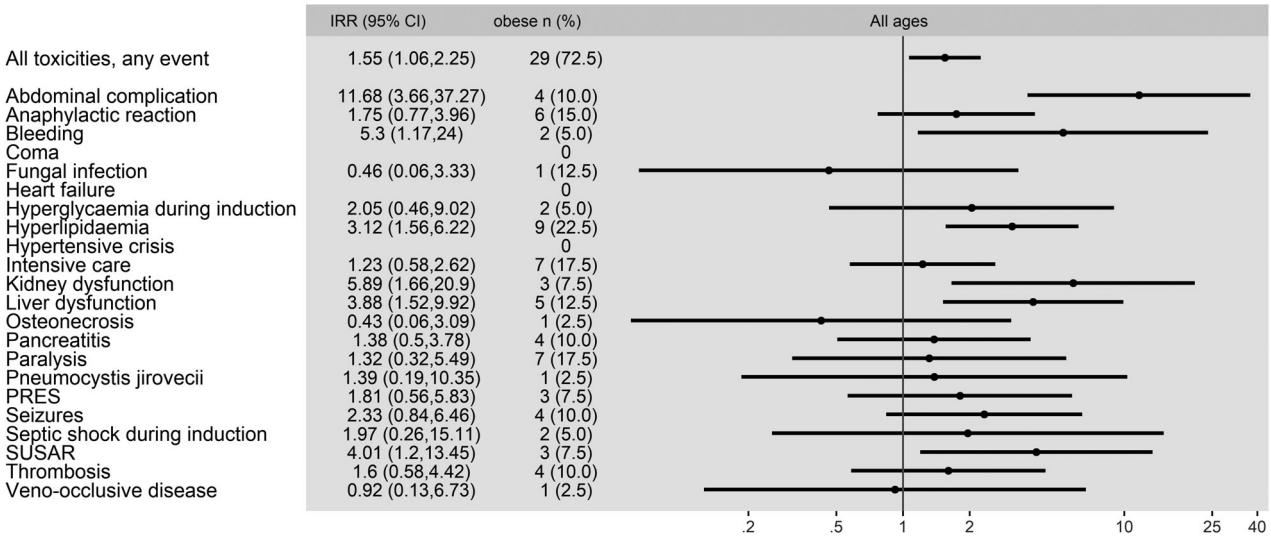

Fig 2. Comparison of incidence rate ratio (IRR) of severe adverse events of special interest between obese and healthy-weight children. PRES, posterior reversible encephalopathy syndrome; SUSAR, suspected unexpected serious adverse reaction.

Discussion

Previous studies have shown that older obese children have worse event-free survival (EFS) compared to children of healthy weight.[4,5] To better understand the underlying mechanisms, we studied the role of BMI in treatment-related severe toxicity in children with ALL. We observed an association between obesity at diagnosis and an increased risk of severe toxicity during leukaemia treatment. In our study, older obese children had a higher risk of thromboses, abdominal complications, kidney failure and bleeding than older healthy-weight children. Furthermore, older obese children had a high risk of truncation with asparaginase treatment, which has been associated with inferior outcomes.[1,2] These factors may underlie the inferior outcomes observed in older obese children.

In an earlier NOPHO ALL2008 study, a higher risk of toxicity was shown in adolescents than in young children.[26] In our cohort, older obese patients experienced SAEs more frequently than older healthy-weight children, such as an increased risk of thromboses. This was in line with previous findings[16,17] as well as our expectations that increasing age is a risk factor for thromboses in children with ALL,[27] and obesity a risk factor for thrombosis in the general population.[28]

Denton *et al.* showed that older obese children with ALL were at a high risk of developing liver toxicity or pancreatitis.[12] In their study, pancreatitis, but not liver toxicity, was associated with worse EFS. Our study also demonstrated a high risk of liver toxicity, especially in younger obese patients, whereas the risk of pancreatitis was not significantly higher in obese children compared to healthy-weight children. This could be explained by differences in the treatment protocols between studies, with intensive continuous asparaginase treatment for all children in the NOPHO ALL2008 study. Our results suggest that older obese children have an increased incidence of asparaginase-associated anaphylaxis. As the number of obese patients in this study is limited, our observation should be replicated in a larger group. Overall, asparaginase-related toxicities were common in older obese patients, leading to a high risk of a truncation of asparaginase. Our findings emphasise the importance of drug substitution in case of hypersensitivity or silent inactivation of asparaginase activity in this patient group.

Treatment delays may reflect treatment toxicity and modified treatment indirectly. Obese children did not have

Table IV. Incidence rate ratio of registered severe adverse events across the BMI categories. Adjustment for age in the analysis. Significant results are bold.

	Number of patients	Underweight *versus* healthy weight IRR (95% CI)	Healthy weight IRR (95% CI)	Overweight *versus* healthy weight IRR (95% CI)	Obese *versus* healthy weight IRR (95% CI)
Abdominal complication	18 (1·2)	3·20 (0·71, 14·46)	1	0·73 (0·09, 5·71)	**11·68 (3·66, 37·27)**
Anaphylactic reaction	165 (11·4)	1·05 (0·53, 2·05)	1	0·82 (0·46, 1·49)	1·74 (0·77, 3·96)
Bleeding	16 (1·1)	No event	1	1·33 (0·30, 6·00)	**5·30 (1·17, 24·00)**
Coma	19 (1·3)	1·26 (0·17, 9·60)	1	2·29 (0·75, 7·02)	No event
Kidney dysfunction	20 (1·4)	No event	1	2·06 (0·67, 6·38)	**5·89 (1·66, 20·90)**
Fungal infection	95 (6·6)	1·85 (0·89, 3·85)	1	1·37 (0·74, 2·53)	0·46 (0·06, 3·33)
Pancreatitis	105 (7·3)	1·11 (0·45, 2·74)	1	1·15 (0·64, 2·08)	1·38 (0·51, 3·79)
Heart failure	10 (0·7)	No event	1	0·82 (0·10. 6·54)	No event
Hyperglycaemia	27 (1·9)	1·08 (0·14, 8·10)	1	2·38 (0·93, 6·08)	2·05 (0·46, 9·02)
Hyperlipidaemia	114 (7·9)	0·62 (0·20, 1·97)	1	1·32 (0·76, 2·29)	**3·12 (1·56, 6·22)**
Hypertensive crisis	15 (1·0)	No event	1	1·26 (0·28, 5·66)	No event
Intensive care	266 (15·7)	1·34 (0·78, 2·30)	1	0·92 (0·59, 1·45)	1·23 (0·58, 2·62)
Liver dysfunction	50 (3·5)	0·46 (0·06, 3·36)	1	0·99 (0·39, 2·51)	**3·88 (1·52, 9·92)**
Osteonecrosis	69 (4·8)	0·33 (0·05, 2·38)	1	0·90 (0·43, 1·89)	0·43 (0·06, 3·09)
Paralysis	185 (12·8)	1·12 (0·59, 2·12)	1	0·70 (0·40, 1·23)	1·51 (0·71, 3·23)
Pneumocystic jirovecii	33 (2·3)	1·63 (0·38, 6·95)	1	**2·82 (1·24, 6·38)**	1·39 (0·19, 10·35)
PRES	62 (4·3)	1·37 (0·49, 3·78)	1	0·46 (0·14, 1·47)	1·81 (0·56, 5·83)
Seizures	70 (4·9)	1·31 (0·48, 3·63)	1	1·17 (0·56, 2·48)	2·33 (0·84, 6·46)
Septic shock during induction	26 (1·8)	1·01 (0·13, 7·64)	1	0·57 (0·07, 4·30)	1·96 (0·26, 15·11)
SUSAR	31 (2·1)	0·73 (0·10, 5·42)	1	1·01 (0·30, 3·36)	**4·01 (1·20, 13·45)**
Thrombosis	89 (6·2)	2·05 (0·94, 4·47)	1	1·13 (0·60, 2·15)	1·66 (0·60, 4·52)
VOD	46 (3·2)	0·46 (0·06, 3·39)	1	1·59 (0·71, 3·59)	0·92 (0·13,6·73)

BMI, body mass index; CI, confidence interval; IRR, incidence rate ratio; PRES, posterior reversible encephalopathy syndrome; SUSAR, suspected unexpected serious adverse event reaction; VOD, veno-occlusive disease. [Correction added on 30 May 2022, after first online publication: The data in the number of patients' column of this table were corrected in this version.]

significantly longer treatment delays than healthy-weight children. Butturini *et al.* demonstrated a higher risk for relapse in older obese children with ALL, unrelated to changes in chemotherapy doses, length of intervals between chemotherapy cycles and the incidence and severity of therapy-related toxicities.[5] Furthermore, neither Yeoh *et al.*[29] nor Laughton *et al.*[30] found an association between an increased risk of relapse and treatment delays within the first three months of treatment in children with ALL. In our study cohort, two of the 14 obese older patients died in the first complete remission and 4/14 experienced relapse, suggesting that both high risk of treatment-related toxicity and insufficient treatment contribute to the poor outcome in this group.

The number of children with hyperglycaemia requiring insulin treatment was low in general with no significant increase in obese children. In contrast, in a study by Meenan *et al.* the prevalence of insulin-requiring hyperglycaemia during pre-maintenance in obese patients was 25% compared to 11% in non-obese patients.[20] In our study, the registration of hyperglycaemia with insulin treatment was restricted to the induction phase, missing hyperglycaemia in later treatment phases.

The reason for the increased toxicities in obese compared to healthy-weight patients remains unclear. Overtreatment due to the different pharmacokinetics in obese patients can lead to treatment-related toxicity, which in turn may lead to delayed or modified treatment, that is, to undertreatment. In addition, extreme overweight in adolescents can be a surrogate marker for the underlying predisposing conditions and chemosensitivity, leading to toxicity, that is, overtreatment.

We also observed a negative impact of underweight on occurrence of SAEs. Younger underweight children had a significantly increased risk of thromboses. While risk for thrombosis is frequently associated with overweight/obesity, another previous study in adults with cancer also showed increased risk of thrombosis in underweight patients.[31] Furthermore, older underweight children had a higher risk of seizures and paralysis with decreasing BMISD. Older underweight patients also had a higher risk of fungal infections compared with their healthy-weight peers, in line with previous findings by Orgel *et al.*[14] Their study also demonstrated that underweight patients had increased risk of pulmonary toxicity, which was not assessed in our cohort as it was not a predefined toxicity.

The strength of this study stems from its prospective registration and the large number of patients treated with the same protocol. The main limitation was the lack of a detailed registration of treatment modifications and the exact time points for toxicity preventing definite conclusions on the consequences of toxicities on therapy and survival. Moreover,

only serious predefined toxicities were registered, leaving out common toxicities such as febrile neutropenia, which often leads to treatment delays and is more frequent in obese children than healthy-weight children with ALL.[20] Also, the quality of the registrations of SAEs can vary. For example, as mild liver dysfunction is common during the course of leukaemia treatment, we suspect that not all events with elevated bilirubin above the threshold for definition of liver dysfunction were registered. Similarly, as the vincristine dose in the NOPHO ALL2008 protocol is relatively high, dose reductions were common and possibly underregistered. Further, testing for lipids was not part of the protocol and therefore hyperlipidaemia may be underdiagnosed. However, possible registration errors apply to all patients and are most likely not influenced by BMI. We did not have data on changes in BMI during the treatment period, which may impact the risk of SAEs, or the body composition, that is, the amount of excess fat and lean mass. Additionally, as the number of obese patients was low and the testing of multiplicity is not adjusted for, the results should be interpreted with caution especially when considering specific toxicities. As there were no registered obesity-related comorbidities at diagnosis, we could not provide information about the treatment-independent metabolic risk profile.

Chemotherapy dose is calculated according to BSA. Children with similar BSA receive the same chemotherapy dose, regardless of body composition. Therapeutic drug monitoring in the future can help to optimise the chemotherapy dosing regimen in patients with unhealthy BMI.

In conclusion, our study demonstrated a higher risk of toxicities and truncated asparaginase treatment in obese older children with ALL, which can contribute to poorer survival in this group. Obese children can benefit from dietary- and physical training interventions or new immunological treatment strategies to decrease serious treatment-related toxicities.

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Author contributions

Authors' contributions to the work performed in this manuscript: CE, SR and AHS designed the research study, interpreted the data and wrote the draft of the paper. CE analysed the data. MH, RN, OJ, RR, GV, KS, BKA and KL contributed essential data. All the authors revised the paper critically and accepted the final version.

Conflicts of interest

The authors have no competing interests.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Comparison of incidence rate ratio of severe adverse events between obese and healthy weight, separated in younger and older children.

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