Received: 16 February 2024 | Revised: 22 July 2024 | Accepted: 25 July 2024

DOI: 10.1002/pbc.31250

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

RESEARCH ARTICLE

Symptomatic osteonecrosis in children treated for Hodgkin lymphoma: A population-based study in Sweden, Finland, and Denmark

Mia Giertz[1,2] | Henri Aarnivala[3,4] | Sascha Wilk Michelsen[5] | Caroline Björklund[6] | Annika Englund[1,2] | Marika Grönroos[7] | Lisa Lyngsie Hjalgrim[5] | Pasi Huttunen[8] | Tuukka Niinimäki[4,9] | Eva Penno[10] | Tuuli Pöyhönen[11] | Päivi Raittinen[12] | Susanna Ranta[13,14] | Johan E. Svahn[15] | Lisa Törnudd[16,17] | Riitta Niinimäki[3,4] | Arja Harila[1,2]

[1]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

[2]Department of Pediatric Oncology and Hematology, Uppsala University Hospital, Uppsala, Sweden

[3]Department of Paediatrics, Oulu University Hospital, Oulu, Finland

[4]Research Unit of Clinical Medicine, University of Oulu, Oulu, Finland

[5]Department of Pediatric Hematology and Oncology, Department of Pediatric and Adolescence Medicine, Juliane Marie Centret, University Hospital Copenhagen, Copenhagen, Denmark

[6]Department of Pediatric Hematology and Oncology, Umeå University Hospital, Umeå, Sweden

[7]Department of Pediatrics, Turku University Hospital, Turku, Finland

[8]Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, New Children's Hospital, Helsinki University Hospital, Helsinki, Finland

[9]Department of Surgery, Oulu University Hospital, Oulu, Finland

[10]Department of Surgical Sciences, Unit of Radiology, Uppsala University, Uppsala, Sweden

[11]Department of Pediatrics, Kuopio University Hospital, Kuopio, Finland

[12]Centre for Child Health Research, Tampere University and University Hospital, Tampere, Finland

[13]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

[14]Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

[15]Department of Paediatric Oncology, Skåne University Hospital, Lund University, Lund, Sweden

[16]Division of Children's and Women's Health, Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

[17]Department of Pediatrics, H.R.H Crown Princess Victoria's Children's and Youth Hospital, Linköping, Sweden

Correspondence
Mia Giertz, Akademiska sjukhuset, 751 85 Uppsala, Sweden.
Email: mia.giertz@uu.se

Previous publication: Part of these data has been presented as a meeting abstract and oral

Abstract

Background: Osteonecrosis (ON) is a potentially disabling skeletal complication of cancer treatment. Although symptomatic osteonecrosis (sON) is well-known in acute lymphoblastic leukemia (ALL), with an incidence around 6%, studies on sON in pediatric

Abbreviations: ABVD, doxorubicin hydrochloride (adriamycin), bleomycin sulfate, vinblastine sulfate, and dacarbazine; ALL, acute lymphoblastic leukemia; BMI, body mass index; CI, confidence interval; EOT, end of treatment; EuroNet-PHL, European Network for Paediatric Hodgkin Lymphoma; GC, glucocorticoids; GPOH-HD, German Society of Pediatric Oncology and Hematology-Hodgkin's Disease; HL, Hodgkin lymphoma; IOTF, International Obesity Task Force; MRI, magnetic resonance imaging; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; ON, osteonecrosis; OR, odds ratio; SDS, standard deviation score; sON, symptomatic osteonecrosis; TJA, total joint arthroplasty.

Mia Giertz and Henri Aarnivala contributed equally as first authors.Riitta Niinimäki and Arja Harila contributed equally as last authors.

presentation at the virtual NOPHO 39th Annual meeting on May 9, 2022, with the title, "*Osteonecrosis in paediatric Hodgkin lymphoma, preliminary results from a cohort study in Sweden, Finland and Denmark.*" Not published at any official site.

Funding information
Mary Beve's Foundation; Gerd Ahlman's Fund; Swedish Childhood Cancer Fund; Alma and K. A. Snellman Foundation; Väre Foundation for Pediatric Cancer Research; Danish Childhood Cancer Foundation, Grant/Award Number: 2021-7439; Lion's Cancer Research Fund of Middle Sweden

Hodgkin lymphoma (HL) are scarce. The aim of this study was to examine the incidence, risk factors, and outcome of sON in children treated for HL.

Procedure: A total of 490 children under 18, diagnosed with HL between 2005 and 2019 in Sweden, Finland, and Denmark were eligible for the study. Data on patient characteristics, HL treatment, and development of sON were collected from patients' medical records. Magnetic resonance imaging scans were used to establish ON diagnosis and grade ON according to the Niinimäki grading system.

Results: Cumulative 2-year incidence of sON among the 489 included patients was 5.5% ($n = 30$). The risk for developing sON was higher for those with older age (odds ratio [OR] 1.25, 95% confidence interval [CI]: 1.05–1.49, $p < .010$), female sex (OR 4.45, CI 1.87–10.58, $p < .001$), high total cumulative glucocorticoid (GC) doses (OR 1.76, 95% CI: 1.21-2.56, $p = 0.003$), and advanced HL (OR 2.19, 95% CI: 1.03-4.65, $p = .042$). Four (13.3%) patients underwent major surgical procedures and 13 (43.3%) had persistent symptoms due to ON at follow-up.

Conclusions: This study shows that sON is as common in pediatric HL as in pediatric ALL, with risk factors such as older age, female sex, high cumulative GC doses, and advanced HL. Future HL protocol development should aim to reduce the burden of ON by modifying GC treatment.

KEYWORDS
children, Hodgkin lymphoma, osteonecrosis

1 | INTRODUCTION

Hodgkin lymphoma (HL) is one of the most common malignancies in teenagers and young adults aged 12–29, with approximately 80 new pediatric cases in the Nordic countries each year.[1–3] Over the past decades, treatment for pediatric HL has been adjusted to minimize toxicities and late complications, with a special focus on reducing radiation burden, without compromising the excellent 5-year survival of over 95%.[1,4–6] Treatment in the Nordic countries has for the last 15 years followed the European Network for Paediatric Hodgkin Lymphoma (EuroNet-PHL) protocols.[7] This treatment consists of intensive chemotherapy including high doses of glucocorticoids (GC) combined with consolidating radiation therapy (RT) for those with inferior positron emission tomography (PET) response to induction chemotherapy. There are numerous side effects to intensive GC treatment, one being osteonecrosis (ON).[8–10] ON is thought to be caused by compromised blood circulation to the bone that leads to degenerative changes and destruction of the joints, primarily the knees and hips.[11–13] Multiple sites are often affected, and symptoms range from asymptomatic to immobilizing pain, occasionally leading to major surgical procedures such as total joint arthroplasty (TJA).[9,14,15]

Although there are numerous studies describing ON in pediatric acute lymphoblastic leukemia (ALL), showing incidence rates around 6% in northern European cohorts,[13,14] studies analyzing ON in larger pediatric HL cohorts are lacking.[10,16–18] The German HL Study group reported a cumulative incidence of ON of 0.2%–1.0% (depending on HL stage) in patients 16–60 years of age. In their study, younger age at diagnosis, male sex, and higher cumulative GC were risk factors for ON.[18] Conversely, risk factors for ON in pediatric ALL have included higher age, female sex, and higher body mass index (BMI).[13,14,19] The risk of ON appears especially high in patients with cancer who were treated with high doses of GC from the start of puberty to early adulthood.[20] Most pediatric patients with HL are older than 10 at diagnosis and receive high doses of GC, suggesting that the risk of ON in children with HL may be higher than reported in adults.

The aim of this study was to systematically explore the incidence, risk factors, treatment, and outcome of symptomatic ON (sON) in a population-based Nordic cohort of children and adolescents treated for HL.

2 | METHODS

2.1 | Study design

This study was conducted as a population-based retrospective observational cohort study. All children under 18 who were diagnosed with HL from 2005 to 2019 in Sweden, Finland, and Denmark were eligible for the study. Diagnosis of HL was based on the World Health Organization (WHO) classification, including classic nodular sclerosis HL, lymphocyte-rich classical HL, mixed cellularity HL, lymphocyte-depleted HL, and nodular lymphocyte-predominant HL (NLPHL).[21] The

study was approved by the Ethical Review Authority in each participating country (Sweden: 2020-00174, 2021-03247, 2023-01174-02; Finland: 271/2019; Denmark: R-20073404). All data collection and analysis were managed according to the Declaration of Helsinki.

2.2 | Data collection

Patients were identified from either the National Childhood Cancer Registry (Sweden and Denmark) or hospital medical records (Finland) based on the International Classification of Disease—Tenth revision (ICD-10) for HL (C81.0-C81.9). Patient characteristics, HL diagnosis, and treatment, as well as presenting symptoms, diagnosis, and management of sON, were obtained from the registries and medical records between August 2020 and October 2022. Data were collected by a local clinician or research nurse, using a case report form (CRF).

All reported ON had been diagnosed with magnetic resonance imaging (MRI) at the local treatment center. The MRI scans were collected for centralized review by a pediatric radiologist (Eva Penno) and an orthopedic surgeon (Tuukka Niinimäki) to both confirm ON diagnosis and grade ON lesions sync the Niinimäki classification system (Table S1).[22] The two reviewers worked independently and were blinded to all patient data. The radiographic definition of ON was a circumscribed lesion with a distinct rim of low signal intensity on T1-weighted images (band sign), and high signal intensity on short tau inversion recovery images (double-line sign).[23] The definition of sON was persistence of pain in one or more locations of an extremity, in combination with confirmed osteonecrotic lesions on MRI.[11,24]

Date of developing sON was registered as the date of radiological confirmation of ON lesions in patients reporting pain or other symptoms leading to radiological examination. Date of last follow-up was set as date of last contact with healthcare, as documented in the patients' medical records at the local treatment center. For six patients, date for last follow-up was missing, and therefore end of treatment (EOT) was considered as last follow-up.

Cumulative GC doses given as part of HL treatment were calculated as prednisolone equivalents in mg/m^2. Dexamethasone doses were converted to GC equivalent of prednisolone by conversion factor 6.67.[25] Possible extra doses of GC given outside of the treatment protocol were not considered.

The International Obesity Task Force (IOTF) BMI cutoffs were used to assess BMI, in which BMI less than 17 kg/m^2 corresponds to underweight, BMI 17–25 as normal, BMI greater than 25 overweight, and greater than 30 obesity.[26] To compare changes in BMI at different time points, such as diagnosis of HL, diagnosis of sON and EOT, IOTF-BMI was transformed to standard deviation scores (SDS). Children under 5 years were defined as overweight or obese for SDS +2.[27] Children 5–18 years were defined as overweight for SDS +1, and obese for SDS +2.[28] Pubertal status was categorized as "not in puberty" or "in/completed puberty." For 99 patients (20.2%), pubertal status at HL diagnosis had not been reported, and it was therefore estimated when possible. Females ≥13 and males ≥14 were listed as "in/completed puberty" and females ≤8 and males ≤9 as "not in puberty."

2.3 | Data analysis and statistics

All data were analyzed with the Statistical Program for Social Sciences (SPSS), version 28.0.1.0. Patient characteristics were summarized by descriptive statistics. Categorical data were presented as numbers and fractions (%). Continuous data were presented as means and medians. Continuous variables were compared using the Mann–Whitney test, and categorical variables using the chi-square test. A competing risks analysis (for death prior to sON diagnosis) was not performed, as the single patient who died did so after being diagnosed with sON. Therefore, death was not a competing risk for observing sON in this group of patients. As the dependent variable (sON) is binary, simple and multiple logistic regression was used. All independent variables (age, sex, HL stage, GC doses, BMI, pubertal status, and radiotherapy) were analyzed separately to get unadjusted results (simple regression). Due to the small cohort and risk for overfitting, we could only adjust for age, sex, and HL stage (multiple regression). The independent variables were checked for multicollinearity, and showed no strong linear correlations. Kaplan–Meier survival analysis was performed to estimate cumulative incidence of sON. Associations with $p < .05$ were considered significant.

3 | RESULTS

3.1 | Patient characteristics

In total, 490 children were eligible for the study in Sweden ($n = 255$), Finland ($n = 122$), and Denmark ($n = 113$). Data were incomplete for one patient from Sweden; thus, 489 patients were included in the analyses (Figure 1). Descriptive data are presented in Table 1. All patients had been treated according to protocols as part of European clinical trials (GPOH-HD [German Society of Pediatric Oncology and Hematology-Hodgkin's Disease] 95, GPOH-HD 2002 pilot, EuroNet-PHL-C1 and EuroNet-PHL-C2, EuroNet-PHL-LP1), including combinations of different chemotherapeutic agents, with or without prednisone. Prednisone doses were given based on body surface, and varied both in total doses and treatment duration between patients, due to different HL stages and protocols. Radiotherapy was given to those with inadequate response to therapy and doses differed between protocols due to gradual reductions over time. Detailed information on treatment regimens are shown in Table S2.

3.2 | Incidence and timing of sON

ON lesions were reported in 44 (9%) patients. However, ON lesions in 14 patients were incidental findings detected by MRI performed due to other indications, and these asymptomatic ON cases were excluded

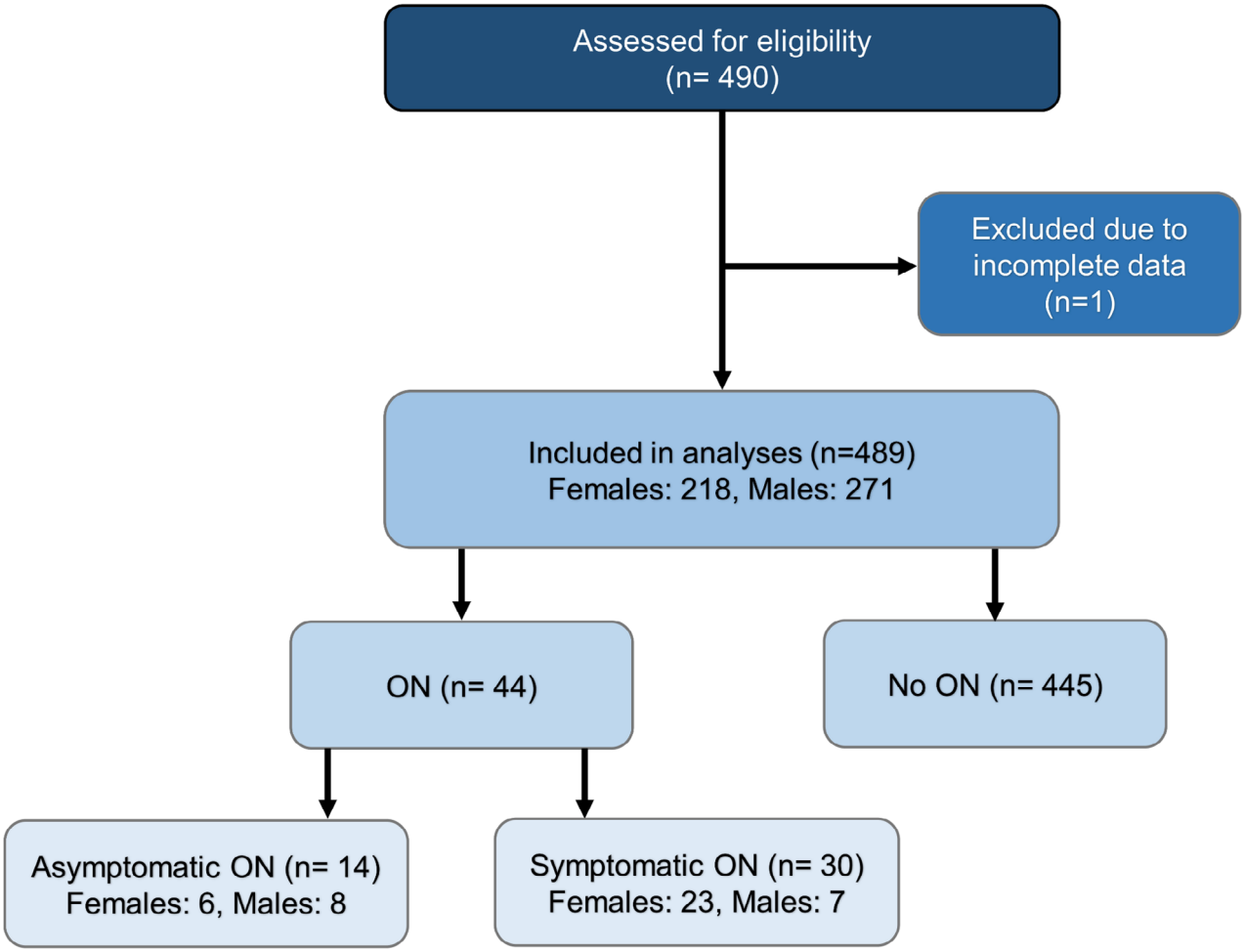

FIGURE 1 Study flowchart. Osteonecrosis (ON).

from further analysis. Hence, a total of 30 (6.1%) patients with sON were included in the statistical analyses. The cumulative 2- and 5-year incidence of sON was 5.5% (95% confidence interval [CI]: 3.34–7.66) and 6.4% (95% CI: 4.05–8.75), respectively. As shown in Table 2, median time from HL diagnosis to sON diagnosis by MRI was 9.3 months (range: 1.5–118.8). Eleven (36.7%) patients (eight females, three males) were diagnosed with sON during HL treatment, with a median time to sON of 4.1 months (range: 1.5–7.9). Out of the 19 (63.3%) patients who were diagnosed with sON after end of HL therapy, six patients reported symptoms consistent with sON already during therapy. One patient complained of knee pain already during HL treatment, but was not diagnosed with sON in the knees until 9 years later at a follow-up clinic.

3.3 | Sites and severity of sON

Joint ON was present in 23 (76.7%) patients. Two (6.7%) patients already had Niinimäki grade 5 ON (joint collapse) at initial diagnosis of sON. Details regarding sON location and severity are presented in Table 2.

3.4 | Age and puberty

Mean age of patients with sON was higher than in patients without sON (15.3 ± 1.6 vs. 13.8 ± 3.2 years, $p < .001$). One sON patient was 10.8 years old, while all others were older than 12. In multiple analysis, the odds of developing sON was 25% higher for each added year of age (odds ratio [OR] 1.25, 95% CI: 1.04–1.51, $p = .016$) (Table 3). Out of the 30 patients with sON, 27 were in puberty or had completed puberty. There were no differences in pubertal status between patients with or without sON with either chi-square test or logistic regression.

3.5 | Sex distribution

Females had a higher risk of developing sON than males, 23/218 versus 7/271 (10.6% vs. 2.6%, $p < .001$). The difference in sON incidence over time is visualized in Figure 2, which demonstrates a 2-year cumulative incidence in females of 9.5% (95% CI: 5.58–13.42) compared to 2.3% in males (95% CI: 0.54–4.06, $p < .001$). In the whole cohort, the odds of developing sON were four times higher for females than for males (OR 4.45, 95% CI: 1.87–10.58, $p < .001$), and 22 out of 177 (12.4%) pubertal females developed sON (Table 3).

TABLE 1 Descriptives of the cohort.

	All patients ($N = 489$)	No sON ($N = 459$)	sON ($N = 30$)	
	Mean ± SD	Mean ± SD	Mean ± SD	p[a]
Age at diagnosis	13.86 ± 3.13	13.76 ± 3.18	15.31 ± 1.59	<.001
Cumulative GC dose in mg	2857 ± 1280	2807 ± 1290	3623 ± 809	.002
BMI SDS at diagnosis[b]	0.26 ± 1.18	0.27 ± 1.17	0.09 ± 1.32	.431
BMI SDS change from diagnosis to end of therapy[c]	0.64 ± 0.76	0.63 ± 0.75	0.81 ± 0.71	.242
	N (%)	*N* (%)	*N* (%)	
Sex				<.001
Male	271 (55.4%)	264 (57.5%)	7 (23.3%)	
Female	218 (44.6%)	195 (42.5%)	23 (76.7%)	
Country				.038
Sweden	254 (51.9%)	245 (53.4%)	9 (30.0%)	
Denmark	113 (23.1%)	104 (22.7%)	9 (30.0%)	
Finland	122 (24.9%)	110 (24.0%)	12 (40.0%)	
BMI at diagnosis				.392
Underweight	17 (3.5%)	13 (2.8%)	4 (13.3%)	
Normal	355 (72.6%)	333 (72.6%)	18 (60.0%)	
Overweight	73 (14.9%)	69 (15.0%)	4 (13.3%)	
Obese	22 (4.5%)	21 (4.6%)	1 (3.3%)	
Unknown	22 (4.5%)	23 (5.0%)	3 (10.0%)	
BMI at end of therapy				.540
Underweight	9 (1.8%)	8 (1.7%)	1 (3.3%)	
Normal	230 (47.0%)	217 (47.3%)	13 (43.3%)	
Overweight	104 (21.3%)	96 (20.9%)	8 (26.7%)	
Obese	46 (9.4%)	43 (9.4%)	3 (10.0%)	
Unknown	100 (20.4%)	95 (20.7%)	5 (16.7%)	
Pubertal status at diagnosis				.076
Not in puberty	112 (22.9%)	109 (23.7%)	3 (10.0%)	
In/completed puberty	348 (71.2%)	322 (70.2%)	26 (86.7%)	
Unknown	29 (5.9%)	28 (6.1%)	1 (3.3%)	
Subtype				.218
Nodular sclerosis	357 (73%)	335 (73.0%)	22 (73.3%)	
Mixed cellularity	51 (10.4%)	46 (10.0%)	5 (16.7%)	
NLPHL	43 (8.8%)	43 (9.4%)	0 (0%)	
HL NOS	38 (7.8%)	35 (7.6%)	3 (10.0%)	
Stage				.118
I	36 (7.4%)	36 (7.8%)	0 (0%)	
II	246 (50.3%)	234 (51.0%)	12 (40%)	
III	100 (20.4%)	92 (20.0%)	8 (26.7%)	
IV	103 (21.2%)	93 (20.3%)	10 (33.3%)	
Unknown	4 (0.8%)	4 (0.9%)	0 (0%)	
Protocol				.210
EuroNet PHL C1/C2	364 (74.4%)	337 (73.4%)	27 (90%)	
GPOH-HD 95/2002	66 (13.5%)	65 (14.2%)	1 (3.3%)	
ABVD	22 (4.5%)	22 (4.8%)	0	

(Continues)

TABLE 1 (Continued)

	N (%)	*N* (%)	*N* (%)	
EuroNet PHL LP1	12 (2.5%)	12 (2.6%)	0	
Other	25 (5.1%)	23 (5.0%)	2 (6.7%)	
Radiotherapy				.813
Yes	183 (37.4%)	171 (37.3%)	12 (40%)	
No	299 (61.2%)	281 (61.2%)	18 (60%)	
Unknown	7 (1.4%)	7 (1.5%)	0 (0%)	
Relapse				N/A
Yes	64 (13.1%)	62 (13.5%)	2 (6.7%)	
No	425 (86.9%)	397 (86.5%)	28 (93.3%)	
Overall survival				N/A
Alive	477 (97.5%)	448 (97.6%)	29 (96.7%)	
Dead	12 (2.5%)	11 (2.4%)	1 (3.3%)	

Abbreviations: ABVD, doxorubicin hydrochloride (Adriamycinadriamycin), bleomycin sulfate, vinblastine sulfate, and dacarbazine; BMI SDS, body body mass index standard deviation score; EuroNet PHL, European Network Pediatric Hodgkin Lymphoma Study Group; GC, glucocorticoids; GPOH-HD, the *German* Society of *Pediatric* Oncology and Hematology––Hodgkin's Disease; N/A, not assessed due to small numbers of patients who relapsed/died in the sON group; NLPHL, nodular lymphocyte-predominant HL; NOS, not otherwise specified; SD, standard deviation; sON, symptomatic osteonecrosis.

[a]Significance level $p < .05$ with Mann–Whitney *U* or X^2 test.

[b]Data available for 464 patients.

[c]Data available for 387 patients.

3.6 | Treatment and stage of HL

There was no significant difference in the risk of developing sON between different treatment protocols (Table 1). GC was part of HL treatment and/or pre-phase in 464 patients (94.9%). Of the 25 patients who did not receive GC, 18 patients were treated with only ABVD (doxorubicin hydrochloride [adriamycin], bleomycin sulfate, vinblastine sulfate, and dacarbazine) courses, and the remaining seven patients had NLPHL treated with various regimens.

All sON patients were treated with GC, and they received significantly higher total GC doses during HL treatment compared to patients who did not develop sON (mean 3623 ± 809 vs. 2800 ± 1290 mg/m^2, $p = .002$). As seen in Table 3, the odds for sON were nearly doubled for each 1000 mg of total cumulative GC given during the whole HL treatment (OR 1.76, 95% CI: 1.21–2.56, $p = .003$).

There were no differences in sON when comparing the specific HL stages I–IV. However, when grouping HL stages into low stage (I+II) and advanced stage (III+IV), logistic regression analysis (Table 3) showed that patients with low stage HL had twofold increased odds of developing sON than patients with advanced stage HL (OR 2.19, 95% CI: 1.03–4.65, $p = .042$). The difference in cumulative 2-year incidence of sON between low and advanced HL stage is visualized in Figure 3.

3.7 | BMI

Information on BMI categories was available for 467 patients (94.7%) at HL diagnosis and for 389 (79.6%) patients at EOT. As seen in Table 1, there were no differences between patients who developed sON compared to those who did not develop sON, regarding IOTF-BMI categories at diagnosis, mean IOTF-BMI SDS at diagnosis, nor in the mean IOTF-BMI SDS change from diagnosis to EOT.

3.8 | Symptoms and management of ON

Pain was the first symptom of ON in 29 (96.7%) patients. One patient experienced fatigue in the shoulders. Treatment and recommendations at sON diagnosis are presented in Table 2. Four patients (three females, one male) underwent bilateral hip replacement. Of note, the sole male patient requiring hip TJA had undergone allogenic hematopoietic stem cell transplantation (HSCT) prior to HL treatment. HL treatment was modified in two patients, one who discontinued steroid treatment and one who was switched to ABVD treatment.

3.9 | Follow-up

In all patients, median follow-up time from diagnosis to last contact with healthcare was 5.1 years (range: 0.2–16.7). There were no differences in follow-up time between females (median 5.0 years, range: 0.2–13.8) and males (median 5.1 years, range: 0.3–16.7). Median time for follow-up concerning sON symptoms and radiographic evaluation was 3.8 years (range: 0.3–11.5). At last sON follow-up, symptoms persisted in nine females and four males (13 patients, 43.3%). Two patients relapsed after sON diagnosis, at 1 and 3 years, respectively. One patient died 5 years after sON diagnosis (death caused by large diffuse B-cell lymphoma).

TABLE 2 Characteristics of patients ($N = 30$) with HL and sON, severity and location of sON lesions, and therapeutic implications of sON.

Characteristics	Median (range)
Time to sON in months	9.3 (1.5–118.8)
Follow-up time (sON) in years	3.8 (0.3–11.5)
Total number of ON lesions per patient	3.6 ± 2.4
	***n* (%)**
Age	
<10 years	0 (0%)
10–13.9 years	6 (20%)
14–17.9 years	24 (80%)
Timing of sON	
During treatment	11 (36.7%)
After EOT	19 (63.3%)
Most common sites affected with ON	
Femur	20 (66.7%)
Tibia	17 (56.7%)
Knee	15 (50%)
Hip	11 (36.7%)
Highest Niinimäki grade at sON dx	
Grade 5	2 (6.7%)
Grade 4	9 (30%)
Grade 3	10 (33.3%)
Grade 2	9 (30%)
Modified HL treatment	
Yes	2 (6.7%)
No	21 (70%)
Unknown	7 (23.3%)
Weight-bearing restrictions	
Yes	12 (40%)
No	17 (56.7%)
Unknown	1 (3.3%)
Crutches for mobility	
Yes	7 (23.3%)
No	23 (76.7%)
Physiotherapy	
Yes	18 (60.0%)
No	11 (36.7%)
Unknown	1 (3.3%)
Pain medication other than opioids	
Yes	18 (60%)
No	11 (36.7%)
Unknown	1 (3.3%)
Oral opioids	
Yes	10 (34.5%)
No	18 (62.1%)
Unknown	1 (3.4%)
Bisphosphonate treatment	
Yes	6 (20%)
No	24 (80%)
Surgical intervention[b]	
Yes	7 (23.3%)
No	23 (76.7%)
Symptoms at last follow-up	
Yes	13 (43.3%)
No	13 (43.3%)
Unknown	4 (13.3%)

Abbreviations: HL, Hodgkin lymphoma; ON, osteonecrosis; sON, symptomatic osteonecrosis.

[a]Numbers (*n*) do not add up to 100% as most patients had multiple ON lesions at different sites.

[b]Including total joint arthroplasty (TJA), core decompression, arthroscopy, lengthening of tragus tendon.

4 | DISCUSSION

This systematic population-based study describes the largest complete pediatric HL cohort to date, assessing sON and risk factors in 489 children under 18 treated for HL in three Nordic countries. We report a 5.5% 2-year and a 6.4% 5-year cumulative incidence of sON. Risk factors for sON were older age, female sex, high GC doses, and advanced HL. Out of the patients with sON, as many as 43.3% had persisting symptoms at last follow-up, and 13% had undergone major hip surgery by the time of data collection.

Reports of sON in children with HL are scarce.[10,17,18,29] In the only cohort study consisting exclusively of children and adolescents with HL, ON was found by MRI screening in 10 of 24 patients (42%), but only one presented with symptoms.[17] Niinimaki et al. used MRI screening at EOT in 32 children with cancer, and found four of seven patients (57%) with HL to have ON, of whom two presented with symptoms.[10] In a retrospective study including mainly adults, Albano et al. found ON using MRI screening in seven of 42 patients (17%).[29] In a large study by Borchman et al. including 11,330 patients with HL aged 16–60 years, 0.2%–1.0% developed sON (depending on the grade of HL).[18]

Previous studies have not been able to define any specific risk factors for ON in children with HL, although higher GC dose was described as the main risk factor for ON in the aforementioned studies by Borchman et al. and Albano et al.[18,29] Borchman et al. also found teenagers and young adults to be at a higher risk of developing ON than older adults. Interestingly, male sex was described as a risk factor for ON in their cohort.[18] Rather, our results on incidence and risk factors of ON

TABLE 3 Analysis of risk factors for symptomatic osteonecrosis.

	Unadjusted				Adjusted			
		95% CI				95% CI		
	OR	Lower	Upper	p^a	OR	Lower	Upper	p^a
Age at diagnosis	1.25	1.05	1.49	.010	1.25	1.04	1.50	.016
Male (ref)		<0.001		.001				
Female	4.45	1.87	10.58		4.21	1.76	10.11	
HL stage I+II (ref)		0.042				0.031		
HL stage III+IV	2.19	1.03	4.65		2.34	1.08	5.08	
Cumulative GC dose[b]	1.76	1.21	2.56	.003	N/A			
BMI SDS change	1.39	0.80	2.39	.240	N/A			
Not in puberty (ref)		0.072	N/A					
In/completed puberty	0.33	0.99	1.1					
No radiotherapy (ref)				.813	N/A			
Radiotherapy	0.91	0.43	1.194					

Note: Unadjusted results analyzed with simple logistic regression. Adjusted results analyzed with multiple logistic regression.
Abbreviations: BMI SDS change, change in body mass index standard deviation score from diagnosis to end of treatment; CI, confidence interval; N/A, not assessed; OR, odds ratio.
[a]Significance level $p < .05$.
[b]Cumulative glucocorticoid doses in 1000 mg.

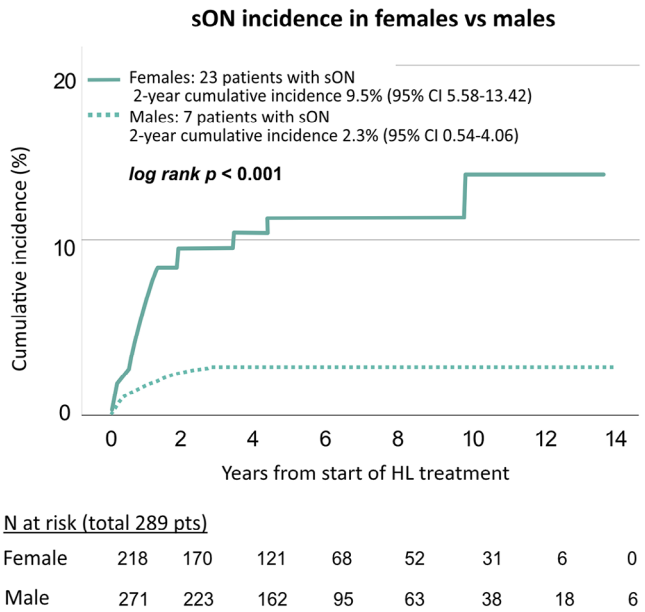

FIGURE 2 Incidence of symptomatic osteonecrosis (sON) in females versus males. CI, confidence interval.

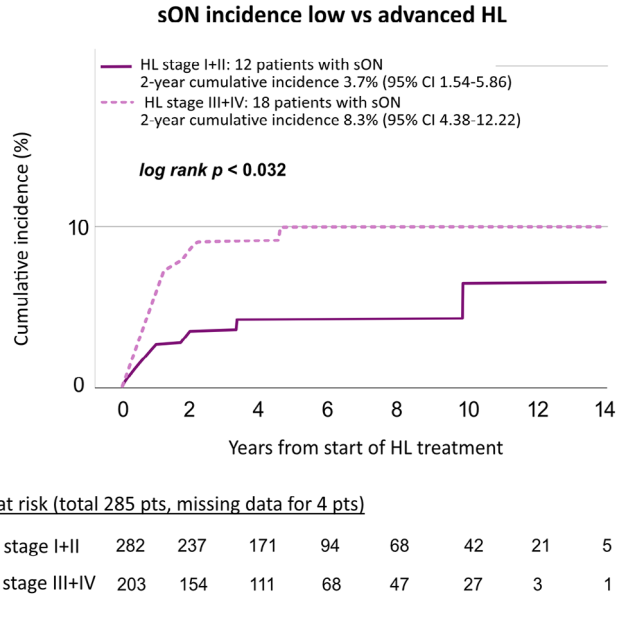

FIGURE 3 Incidence of symptomatic osteonecrosis (sON) in low versus advanced stages of Hodgkin lymphoma (HL). CI, confidence interval.

are in accordance with those reported by Mogensen et al. in children with ALL.[14] Mogensen et al. found a 5-year 6.3% cumulative incidence in pediatric ALL patients treated according to the Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL2008 protocol and a 28% incidence in females over 10, which is higher than the 12.4% incidence in pubertal females presented here. The elevated risk of sON in pubertal females might be explained by increased estrogen levels that promote intracortical bone remodeling, increase bone mass gain, and have procoagulatory effects.[30,31] All this can lead to an imbalance between osseous metabolic/blood supply demands and real osseous blood supply.[12,20,31]

Most treatment regimens for childhood HL worldwide include GC.[7] However, young adults with early stage HL have often been treated according to adult protocols generally consisting of ABVD courses

without GC. These patients appear to have a much lower risk for ON than young adults treated according to pediatric protocols containing GC.[17,18] In the present study, only patients who received GC within their treatment developed sON, which is in accordance with literature. GC have a lipid-altering effect that is thought to induce ON and hyperlipidemia has also been shown, by Mogensen et al., to be a risk factor for ON in children with ALL.[32–34] This suggests that patients with a lower BMI might have a lower risk for ON, as they usually have lower lipid levels than those with higher BMI. In our study, we did not observe any association between BMI at diagnosis and risk of developing sON. Nevertheless, as nine patients were diagnosed with sON already during chemotherapy, it is evident that not only the cumulative GC dose, but also host-related factors play a role in the development of sON. Differences in GC metabolism resulting in different GC exposure and side effects are an example of such factors, and there are some data on genetic variations predisposing to metabolic side effects of dexamethasone.[35]

As many as 14 incidental cases of asymptomatic ON were found, although no systematic screening for ON was performed. This highlights that asymptomatic ON is common, as shown in screening studies.[10,17,36] As asymptomatic ON does not always progress to sON, and can only be found at actual screening or incidentally through other MRI follow-up, there are no current recommendations for managing or treating asymptomatic ON.[15,36,37] According to present literature, there is little to be done to prevent ON progression, regardless of whether the lesions are symptomatic. This is supported in a review from 2014, in which Te Winkel et al. stated that there is no conclusive evidence to support the effectiveness of any specific intervention such as weight-bearing restrictions, bisphosphonates, hyperbaric oxygen therapy, or prostacyclin analogs. Te Winkel and colleagues therefore recommend only clinical screening of ON, focusing on persistent pain or limited joint mobility.[38] As no evidence-based conservative treatment alternatives are available, management of sON in children is mainly symptomatic and given on a case-by-case basis. Accordingly, treatment of sON within our cohort consisted of weight-bearing restrictions, pharmacological pain relief, and physiotherapy. All but two sON patients diagnosed during chemotherapy carried through their therapy with full GC doses.

With lack of options on secondary prevention and conservative treatment, the most appealing way to decrease the impact of sON would be to reduce GC doses in HL treatment protocols. Even in the present study, it was observed that patients receiving ABVD treatment without GC did not develop sON. However, ABVD carries a high risk of, for example, cardiac and pulmonary toxicity.[39–42] Hence, there should be an attempt to compare the overall toxicity profiles of different treatment protocols rather than single toxicities when deciding on future directions in HL therapy. This would require systematic registration and reporting of treatment-associated toxicities, where there still is much to be improved in clinical practice. Our results highlight the need for new treatment strategies for HL to reduce sON risk, especially considering the excellent outcome in both primary and relapsed HL. Future studies should focus on diminishing the risk of ON, either by modifying current chemotherapy alternatives or using targeted therapies already used in adults with HL.[43–45] For example, a recent adult study reported promising results on overall survival of early stage unfavorable HL, and reported no ON when combining nivolumab with conventional chemotherapy without GC, as well as nivolumab in monotherapy.[44] Furthermore, a recently published abstract from an American study including 976/994 adults and children from 12 years with stage III–IV HL, showed that nivolumab in combination with doxorubicin, vinblastine, and dacarbazine (AVD) was superior in progression-free survival after 1 year, compared to brentuximab vedotin combined with AVD (94% vs. 86%).[46]

The most important strength of the present study is the population-based design, including all HL patients treated in the three Nordic countries over the study period, thereby minimizing selection bias. Information from medical records were individually and thoroughly evaluated for all cases, which minimized information bias. Furthermore, due to an established Nordic collaboration and common pediatric oncology and hematology education system, clinical practice is similar in Sweden, Finland, and Denmark. Details on almost all patients' treatment regimens were available, and GC treatment was evaluated as total cumulative doses, regardless of treatment strategy. Even though patients were treated according to different protocols, the cohort was quite homogenous in terms of the used steroid regime, as it was the same for 88% of the patients (EuroNet PHL C1/C2 and GPOH-HD 95/2002).

Study limitations include its retrospective design, possible differences in data registration and ON awareness, as well as relying on documentation in patient medical records. Although cumulative GC doses for the whole treatment period were attained, exact doses of GC received at sON diagnosis were not available. However, higher HL stage reflects higher total cumulative GC doses, hence both variables are analyzed in this study. Finally, the median follow-up time of 5.1 years may have led to an underestimation of the number of late sON cases, although their number would likely have been small considering that sON generally developed during or the first years after treatment. Still, longer follow-up studies, preferably with prospective registration of sON within treatment protocols, are needed to elucidate the role of sON in children and young adults with HL in the very long-term.

Taken together, this study establishes the cumulative incidence of sON in pediatric HL, showing that sON is a common and relevant treatment complication. ON should be suspected, and screened for with MRI, in children reporting persisting skeletal pain during or after HL treatment. Reducing GC in HL therapy should be one of the main focuses in future HL protocol development, to minimize risk of developing ON, especially in patients at risk—adolescent females.

ACKNOWLEDGMENTS

We would like to thank Olle Lindinger, Umeå University Hospital (Sweden), Yvonne Håkansson, Lund University Hospital (Sweden), and Lars Kawan, Queen Silvia's Hospital in Gothenburg (Sweden), Steen Roshoej, Margrethe Ottosen Møller, and Hilde Dragland Galsgaard Aalborg, Aarhus and Odense (Denmark), for assistance in collecting data for the study. This study was supported by grants from theMary Beve's Foundation, Gerd Ahlman's Fund, Swedish Childhood Cancer

Fund, Alma and K. A. Snellman Foundation, and the Väre Foundation for Pediatric Cancer Research, Danish Childhood Cancer Foundation (no. 2021-7439), Lion's Cancer Research Fund of Middle Sweden.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Mia Giertz https://orcid.org/0009-0005-2767-1714
Henri Aarnivala https://orcid.org/0000-0002-2025-3676
Annika Englund https://orcid.org/0000-0001-5678-3719
Susanna Ranta https://orcid.org/0000-0001-7854-0371
Riitta Niinimäki https://orcid.org/0000-0003-0190-5664

REFERENCES

1. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(2):83-103. doi:10.3322/caac.21219
2. Larønningen SFJ, Beydogan H, Bray F, et al. *NORDCAN: cancer incidence, mortality, prevalence and survival in the Nordic countries*. NORDCAN; 2022. Accessed March 2, 2023. https://nordcan.iarc.fr/
3. Hjalgrim LL, Rostgaard K, Engholm G, et al. Aetiologic heterogeneity in pediatric Hodgkin lymphoma? Evidence from the Nordic countries, 1978–2010. *Acta Oncol*. 2016;55(1):85-90. doi:10.3109/0284186x.2015.1049660
4. Mauz-Korholz C, Hasenclever D, Dorffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in females have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. *J Clin Oncol*. 2010;28(23):3680-3686. doi:10.1200/JCO.2009.26.9381
5. Smith MA, Altekruse SF, Adamson PC, Reaman GH, Seibel NL. Declining childhood and adolescent cancer mortality. *Cancer*. 2014;120(16):2497-2506. doi:10.1002/cncr.28748
6. Mauz-Körholz C, Landman-Parker J, Fernández-Teijeiro A, et al. Response-adapted omission of radiotherapy in children and adolescents with early-stage classical Hodgkin lymphoma and an adequate response to vincristine, etoposide, prednisone, and doxorubicin (EuroNet-PHL-C1): a titration study. *Lancet Oncol*. 2023;24(3):252-261. doi:10.1016/s1470-2045(23)00019-0
7. Mauz-Körholz C, Metzger ML, Kelly KM, et al. Pediatric Hodgkin lymphoma. *J Clin Oncol*. 2015;33(27):2975-2985. doi:10.1200/jco.2014.59.4853
8. Mattano LA Jr, Devidas M, Nachman JB, et al. Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial. *Lancet Oncol*. 2012;13(9):906-915. doi:10.1016/S1470-2045(12)70274-7
9. Mattano LA Jr, Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *J Clin Oncol*. 2000;18(18):3262-3272. doi:10.1200/JCO.2000.18.18.3262
10. Niinimaki RA, Harila-Saari AH, Jartti AE, et al. Osteonecrosis in children treated for lymphoma or solid tumors. *J Pediatr Hematol Oncol*. 2008;30(11):798-802. doi:10.1097/MPH.0b013e31818ab29d
11. Niinimäki T, Harila-Saari A, Niinimäki R. The diagnosis and classification of osteonecrosis in patients with childhood leukemia. *Pediatr Blood Cancer*. 2015;62(2):198-203. doi:10.1002/pbc.25295
12. Toksvang LN, Andrés-Jensen L, Rank CU, et al. Maintenance therapy and risk of osteonecrosis in children and young adults with acute lymphoblastic leukemia: a NOPHO ALL2008 sub-study. *Cancer Chemother Pharmacol*. 2021;88(5):911-917. doi:10.1007/s00280-021-04316-z
13. te Winkel ML, Pieters R, Hop WC, et al. Prospective study on incidence, risk factors, and long-term outcome of osteonecrosis in pediatric acute lymphoblastic leukemia. *J Clin Oncol*. 2011;29(31):4143-4150. doi:10.1200/jco.2011.37.3217
14. Mogensen SS, Harila-Saari A, Mäkitie O, et al. Comparing osteonecrosis clinical phenotype, timing, and risk factors in children and young adults treated for acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2018;65(10):e27300. doi:10.1002/pbc.27300
15. Niinimäki R, Suo-Palosaari M, Pokka T, Harila-Saari A, Niinimäki T. The radiological and clinical follow-up of osteonecrosis in cancer patients. *Acta Oncol*. 2019;58(4):505-511. doi:10.1080/0284186x.2019.1566769
16. Hanif I, Mahmoud H, Pui CH. Avascular femoral head necrosis in pediatric cancer patients. *Med Pediatr Oncol*. 1993;21(9):655-660.
17. Littooij AS, Kwee TC, Enriquez G, et al. Whole-body MRI reveals high incidence of osteonecrosis in children treated for Hodgkin lymphoma. *Br J Haematol*. 2017;176(4):637-642. doi:10.1111/bjh.14452
18. Borchmann S, Müller H, Haverkamp H, et al. Symptomatic osteonecrosis as a treatment complication in Hodgkin lymphoma: an analysis of the German Hodgkin Study Group (GHSG). *Leukemia*. 2019;33(2):439-446. doi:10.1038/s41375-018-0240-8
19. Niinimaki RA, Harila-Saari AH, Jartti AE, et al. High body mass index increases the risk for osteonecrosis in children with acute lymphoblastic leukemia. *J Clin Oncol*. 2007;25(12):1498-1504. doi:10.1200/jco.2006.06.2539
20. Kunstreich M, Kummer S, Laws HJ, Borkhardt A, Kuhlen M. Osteonecrosis in children with acute lymphoblastic leukemia. *Haematologica*. 2016;101(11):1295-1305. doi:10.3324/haematol.2016.147595
21. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia*. 2022;36(7):1720-1748. doi:10.1038/s41375-022-01620-2
22. Niinimäki TNJ, Halonen J, Hänninen P, Harila-Saari A, Niinimäki R. The classification of osteonecrosis in patients with cancer: validation of a new radiological classification system. *Clin Radiol*. 2015;70:1439-1444.
23. Karimova EJ, Rai SN, Deng X, et al. MRI of knee osteonecrosis in children with leukemia and lymphoma: part 1, observer agreement. *AJR Am J Roentgenol*. 2006;186(2):470-476. doi:10.2214/AJR.04.1598
24. Saini A, Saifuddin A. MRI of osteonecrosis. *Clin Radiol*. 2004;59(12):1079-1093. doi:10.1016/j.crad.2004.04.014
25. Mager DE, Lin SX, Blum RA, Lates CD, Jusko WJ. Dose equivalency evaluation of major corticosteroids: pharmacokinetics and cell trafficking and cortisol dynamics. *J Clin Pharmacol*. 2003;43(11):1216-1227. doi:10.1177/0091270003258651
26. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr Obes*. 2012;7(4):284-294. doi:10.1111/j.2047-6310.2012.00064.x
27. WHO child growth standards based on length/height, weight and age. *Acta Paediatr Suppl*. 2006;95:76-85. doi:10.1111/j.1651-2227.2006.tb02378.x
28. de Onis M, Lobstein T. Defining obesity risk status in the general childhood population: which cut-offs should we use? *Int J Pediatr Obes*. 2010;5(6):458-460. doi:10.3109/17477161003615583
29. Albano D, Patti C, La Grutta L, et al. Osteonecrosis detected by whole body magnetic resonance in patients with Hodgkin lymphoma treated by BEACOPP. *Eur Radiol*. 2017;27(5):2129-2136. doi:10.1007/s00330-016-4535-8
30. Schoenau E. Bone mass increase in puberty: what makes it happen? *Horm Res*. 2006;65(2):2-10. doi:10.1159/000091748

31. Nowak-Göttl U, Kenet G. Challenging aspects of managing hemostasis in adolescents. *Acta Haematol*. 2014;132(3-4):326-330. doi:10.1159/000360237
32. Wang GJ, Cui Q, Balian G. The Nicolas Andry award. The pathogenesis and prevention of steroid-induced osteonecrosis. *Clin Orthop Relat Res*. 2000;370:295-310. doi:10.1097/00003086-200001000-00030
33. Chang C, Greenspan A, Gershwin ME. The pathogenesis, diagnosis and clinical manifestations of steroid-induced osteonecrosis. *J Autoimmun*. 2020;110:e102460. doi:10.1016/j.jaut.2020.102460
34. Mogensen SS, Schmiegelow K, Grell K, et al. Hyperlipidemia is a risk factor for osteonecrosis in children and young adults with acute lymphoblastic leukemia. *Haematologica*. 2017;102(5):e175-e178. doi:10.3324/haematol.2016.160507
35. Hu W, Jiang C, Kim M, et al. Individual-specific functional epigenomics reveals genetic determinants of adverse metabolic effects of glucocorticoids. *Cell Metab*. 2021;33(8):1592-1609.e7. doi:10.1016/j.cmet.2021.06.004
36. Kawedia JD, Kaste SC, Pei D, et al. Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia. *Blood*. 2011;117(8):2340-2347; quiz 2556. doi:10.1182/blood-2010-10-311969
37. Ojala AE, Paakko E, Lanning FP, Lanning M. Osteonecrosis during the treatment of childhood acute lymphoblastic leukemia: a prospective MRI study. *Med Pediatr Oncol*. 1999;32(1):11-17.
38. Te Winkel ML, Pieters R, Wind EJ, Bessems JH, van den Heuvel-Eibrink MM. Management and treatment of osteonecrosis in children and adolescents with acute lymphoblastic leukemia. *Haematologica*. 2014;99(3):430-436. doi:10.3324/haematol.2013.095562
39. Policiano C, Subirá J, Aguilar A, Monzó S, Iniesta I, Rubio Rubio JM. Impact of ABVD chemotherapy on ovarian reserve after fertility preservation in reproductive-aged women with Hodgkin lymphoma. *J Assist Reprod Genet*. 2020;37(7):1755-1761. doi:10.1007/s10815-020-01844-0
40. Amin MSA, Brunckhorst O, Scott C, et al. ABVD and BEACOPP regimens' effects on fertility in young males with Hodgkin lymphoma. *Clin Transl Oncol*. 2021;23(6):1067-1077. doi:10.1007/s12094-020-02483-8
41. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*. 2016;374(25):2419-2429. doi:10.1056/NEJMoa1510093
42. Taparra K, Liu H, Polley MY, Ristow K, Habermann TM, Ansell SM. Bleomycin use in the treatment of Hodgkin lymphoma (HL): toxicity and outcomes in the modern era. *Leuk Lymphoma*. 2020;61(2):298-308. doi:10.1080/10428194.2019.1663419
43. Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1–2 trial. *Lancet Oncol*. 2020;21(4):541-550. doi:10.1016/s1470-2045(20)30023-1
44. Bröckelmann PJ, Goergen H, Keller U, et al. Efficacy of nivolumab and AVD in early-stage unfavorable classic Hodgkin lymphoma: the randomized phase 2 German Hodgkin Study Group NIVAHL trial. *JAMA Oncol*. 2020;6(6):872-880. doi:10.1001/jamaoncol.2020.0750
45. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med*. 2018;378(4):331-344. doi:10.1056/NEJMoa1708984
46. Herrera AF, LeBlanc ML, Castellino SM, et al. SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). *J Clin Oncol*. 2023;41(17 suppl):LBA4. doi:10.1200/JCO.2023.41.17_suppl.LBA4

SUPPORTING INFORMATION

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

How to cite this article: Giertz M, Aarnivala H, Wilk Michelsen S, et al. Symptomatic osteonecrosis in children treated for Hodgkin lymphoma: A population-based study in Sweden, Finland, and Denmark. *Pediatr Blood Cancer*. 2024;e31250. https://doi.org/10.1002/pbc.31250