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ORIGINAL PAPER

Haematological Malignancy – Clinical

Follow-up of osteonecrosis in paediatric acute lymphoblastic leukaemia patients treated with the NOPHO ALL2008 protocol

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Summary

Although osteonecrosis (ON) is a common sequel after childhood acute lymphoblastic leukaemia treatment and may cause debilitating symptoms, its prognosis remains underexplored. We describe the radiological evolution of ON lesions in a Finnish patient cohort treated according to the The Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL2008 protocol. We aimed to identify the factors influencing the outcome of ON. We collected data from 37 patients diagnosed with ON treated in five tertiary centres. We analysed magnetic resonance imaging scans containing 235 ON lesions (109 affecting joints) and graded them using the Niinimäki classification system. The mean follow-up time from an ON diagnosis was 3.3 years (SD 3.4 range: 0.04–13.5). Among the lesions with follow-up scans, 55% remained stable, 35% resolved, 8% improved to lower grade and 2% progressed. Joint collapse was observed in 18 joint lesions (17%). Factors associated with unfavourable outcomes were female sex, older age at diagnosis and haematopoietic stem cell transplantation (HSCT). The chance for spontaneous resolution of ON was lower in females (adjusted odds ratio [aOR] 10.3, 95% CI 2.0–52.6) and decreased with age (aOR 1.4, 95% CI 1.1–1.7), whereas HSCT was associated with joint collapse already at ON diagnosis (aOR 8.3, 95% CI 2.6–27.0).

KEYWORDS
acute lymphoblastic leukaemia, children, magnetic resonance imaging, osteonecrosis

Abbreviations: ALL, acute lymphoblastic leukaemia; AOR, adjusted odds ratio; CI, confidence interval; GEE, generalized estimating equation; HSCT, haematopoietic stem cell transplantation; MRI, magnetic resonance imaging; NOPHO, The Nordic Society of Paediatric Haematology and Oncology; ON, osteonecrosis; SD, standard deviation; TJA, total joint arthroplasty.

INTRODUCTION

Osteonecrosis (ON) is widely recognized as one of the most common treatment-related toxicities in children with acute lymphoblastic leukaemia (ALL).[1–3] The reported ON incidence has varied significantly across studies, ranging from 1.6% to 17.6% in symptomatic patients to as high as 72% in systematic screening studies.[4–6] The risk factors for ON development have been extensively studied in children with leukaemia and lymphoma, including the use of glucocorticoids, female sex and age over 10 years.[5,7–12] Both medical professionals and survivors consider ON to be one of the most significant adverse events among ALL survivors.[13] ON may cause intense pain, limit daily activities and necessitate surgical intervention due to joint collapse resulting in pain and restricted mobility.[1,7,14]

In the past, radiological grading of ON primarily relied on joint-specific grading systems.[15] Magnetic resonance imaging (MRI) is the standard radiological method for diagnosing and monitoring ON in cancer patients. In 2015, the Niinimäki grading system was introduced as a joint-independent method for assessing ON lesions and has been widely adopted as a classification tool for oncological patients.[14,16,17]

The location of ON is crucial in terms of its clinical significance. Lesions in weight-bearing joints are more likely to result in significant symptoms compared to lesions in smaller bones, which are often asymptomatic.[6,18,19] It is known that ON in the femoral head most commonly progresses to joint collapse, necessitating surgical intervention.[6] The natural course of other clinically significant lesions, such as those in the knee or ankle, is not as well understood. A recent study on ON in ALL patients focusing on joint lesions suggested that lesions on concave joint surfaces may have better outcomes than those on convex surfaces.[16]

Although numerous studies have investigated ON risk factors, the determinants of ON progression and the potential for spontaneous healing remain unclear.[1,20] This study aimed to describe the radiological evolution of ON and identify factors influencing the outcome of ON in a multicentre cohort of paediatric patients with ALL.

PATIENTS AND METHODS

Study design

This study was conducted in all five Finnish tertiary-level hospitals treating children with ALL according to The Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL2008 protocol between 2008 and 2020. During the study period, a total of 458 paediatric ALL patients were treated in the participating centres. Of these patients, all those with ON reported in the NOPHO ALL2008 toxicity registry were included in the study.[21] Data on ALL background information were collected from medical records.

All ON lesions were diagnosed with MRI. To be diagnosed as ON, lesions had to exhibit characteristic imaging findings, such as the double-line sign, consisting of two serpentine lines representing the border between a viable and a nonviable bone, or the rim sign resulting from osteochondral fragmentation.[22,23] Evaluation of the findings did not require a contrast agent. Lesions affecting both concave and convex surfaces within a joint were considered separate lesions. MRI scans were evaluated by a general radiologist (SH) and a consultant-level paediatric radiologist (MS-P) to grade the lesions according to the Niinimäki classification system. The Niinimäki grading criteria are provided in Table S1.

Follow-up outcomes were categorized as 'stable', 'improved' or 'resolved'. 'Stable' was defined as no change in the Niinimäki grade during follow-up. 'Improved' indicated a decrease in the Niinimäki grade over time. 'Resolved' was defined as a final Niinimäki grade of 0, indicating complete disappearance of the lesion.

Statistical analysis

Generalized estimating equation (GEE) models were employed to analyse the relationship between HSCT, age at ALL diagnosis, sex and joint surface shape and both spontaneous resolution of ON and presenting with joint collapse (grade 5 ON) at diagnosis. All analyses were performed using IBM SPSS Statistics for Windows Version 29.01.1.1 (Armonk, NY: IBM Corp.).

RESULTS

Of the 458 patients considered, the final cohort included 37 patients, resulting in an ON incidence of 8%. A total of 235 osteonecrotic lesions were identified, with convex and concave lesions considered as separate sites. Most patients were female (65%) and the mean age at ALL diagnosis was 10.3 (standard deviation [SD]: 4.5, range: 2.0–16.0) years, while the mean age at ON diagnosis was 11.9 (SD: 4.8, range: 2.8–18.4) years. A mean of 6.4 (SD: 5.1, range: 1–20) lesions were diagnosed per patient. As many as 179 lesions (76%) were found in 24 female patients, and the number of lesions per patient was significantly higher in females compared to males, with a mean of 7.5 (SD: 5.5, range: 1–20) lesions in females and 4.2 (SD: 3.3, range 1–11) lesions in males ($p < 0.05$). Symptomatic ON was reported in 85% of the patients. The patients' background data are presented in Table 1.

Sites of osteonecrosis

ON occurred at 15 different anatomic sites, and its distribution is presented in Figure 1. Among all lesions, 109 affected the joints in 28 patients, with convex joint surface involvement in 66 (61%) cases. Weight-bearing joints accounted for 40% of all joint lesions, including the hip ($n = 21$), knee

($n = 52$) and ankle ($n = 22$). Among the non-weight-bearing joints, the shoulder ($n = 8$) and elbow ($n = 6$) were the affected sites. The most common non-articular locations were the tibia ($n = 49$), femur ($n = 39$) and foot ($n = 11$). Most of the patients had multiple lesions, as 81% of the cohort were diagnosed with two or more lesions (mean: 6.4, SD: 5.1, range: 1–20).

TABLE 1 Background information on the 37 patients with osteonecrosis.

	Values expressed as *n* (%) or mean ± SD
Female	24 (65)
Age at ALL diagnosis, years	10.3 ± 4.5
Age at ON diagnosis, years	11.9 ± 4.8
Time from ALL diagnosis to ON, years	1.6 ± 0.96
ALL lineage	
Pre-B cell	31 (84)
T cell	6 (16)
Final treatment stratification	
SR	17 (46)
IR	13 (35)
HR-CHEMO	3 (9)
HR-HSCT[a]	4 (11)
Relapse (after ON)	3 (8)
Symptomatic ON	31 (84)
Time from HSCT to ON, years	0.36 ± 1.6
Number of ON lesions	6.4 ± 5.1
Grade 5 ON in 1 ≥ joint	11 (30)

Abbreviations: ALL, acute lymphoblastic leukaemia; CHEMO, chemotherapy; HR, high risk; HSCT, haematopoietic stem cell transplantation; MRI, magnetic resonance imaging; IR, intermediate risk; ON, osteonecrosis; SR, small risk.

[a]TBI 12Gy + etoposide or TreoFluTT preconditioning.

Initial grades of osteonecrosis

The initial ON grades in the weight-bearing joints are presented in Table 2. At the time of diagnosis, nine patients already had grade 5 lesions (joint surface collapse). These patients had a total of 14 grade 5 joint lesions, all of which involved convex joint surfaces. In a GEE model, HSCT was associated with an increased risk of having Grade 5 ON at diagnosis rather than only Grade ≤4 ON (aOR: 8.3, $p < 0.001$ 95% CI: 2.6–27.0), while age at diagnosis (aOR: 1.1, 95% CI: 1.0–1.3, $p = 0.072$) and female sex (aOR: 2, 95% CI: 0.59–6.7, $p = 0.26$) were not.

Evolution of osteonecrosis lesions during follow-up

Follow-up imaging was available for 191 lesions (81%) across 26 patients, of whom 23 were symptomatic with ON. The median number of follow-up images per lesion was 2 (interquartile range [IQR] 2–3; range 1–11). The mean follow-up period was 3.3 (SD: 3.4, range: 0.04–13.5) years. Among lesions with follow-up images, 55% remained stable, 35% resolved completely, 8% improved to a lower grade and 2% progressed. Among males, 55% of lesions resolved completely, compared to 34% of lesions resolved in females.

Table 3 presents the evolution of lesions in weight-bearing joint lesions during follow-up. Only four joint lesions (4% of all lesions with follow-up imaging) in three patients progressed over time: one affecting the hip, two affecting the knee and one affecting the ankle. All of these lesions advanced to Grade 5. At last follow-up, 18 lesions in 11 patients were grade 5, of which 17 affected convex and one a concave surface. ON grades at initial diagnosis and last follow-up, categorized by ON site, are presented in Table 4.

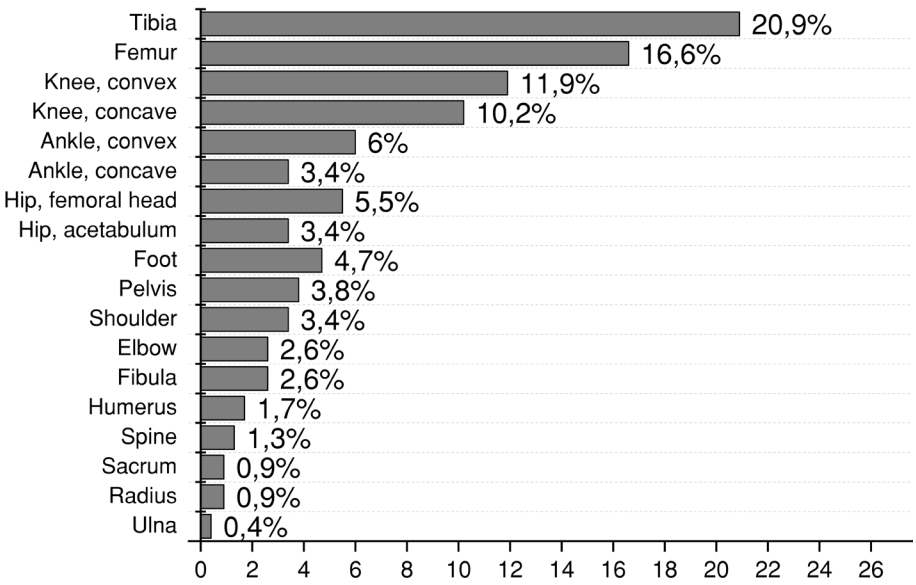

FIGURE 1 The relative proportion of osteonecrosis lesions ($N = 235$) across anatomic sites.

Figure 2 demonstrates the correlation between the highest Niinimäki grade of ON and the time from ALL diagnosis to ON diagnosis.

A GEE model including lesions with follow-up imaging was constructed in a forward stepwise manner, and the final model consisting of sex, age, HSCT and joint surface shape showed that female sex (aOR: 10.3, 95% CI: 2.0–52.6, $p < 0.01$) and older age (aOR: 1.4, 95% CI: 1.1–1.7, $p < 0.01$) were associated with lower odds of spontaneous ON resolution. In contrast, HSCT (aOR: 1.8, 95% CI: 0.22–14.5, $p = 0.59$) and joint surface shape (aOR: 0.43, 95% CI 0.14–1.4, $p = 0.15$) did not have a significant impact on the odds of spontaneous resolution.

Surgical and pharmacological interventions

Surgical treatment was performed on 10 joints across 10 patients, all of which had involvement of convex joint surfaces. Surgery was performed on six female patients, and the majority of the procedures involved the femoral head. All but one of the operated lesions were Niinimäki Grade 5. The mean time from ON diagnosis to surgery was 3.7 (SD: 1.0, range: 2.3–6.0) years, and the mean age at the time of surgery was 15.0 (SD: 3.5, range: 10.4–18.6) years. Details of the surgical procedures are presented in Table 5.

TABLE 2 The Niinimäki grades of osteonecrosis in the most clinically relevant joint sites at the time of diagnosis.

Grade	Site	Concave	Convex
	Hip	$n = 8$	$n = 13$
3		7	3
4		1	4
5		0	6
	Knee	$n = 24$	$n = 28$
3		16	17
4		8	9
5		0	2
	Ankle	$n = 8$	$n = 14$
3		4	6
4		4	5
5		0	3

Total joint arthroplasty (TJA)

Total joint arthroplasty was performed exclusively for Grade 5 ON of the femoral head, accounting for four patients. All patients with TJA were female. The procedure was performed at a mean age of 16.7 (SD: 1.2, range: 15.0–17.9) years and an average age of 4.0 (SD: 1.4, range: 2.8–6.0) years after an ON diagnosis.

Other procedures

Six of the surgical procedures were non-TJA. In the hips, two Grade 5 lesions were treated with osteotomy instead of TJA. In the ankles, two lesions were treated with drilling. One ankle joint had lesions on both the convex and concave sides, with the convex lesion classified as Grade 5 and the concave lesion classified as Grade 4. After osteotomy, the lesion on the concave side fully resolved, but the Grade 5 lesion with joint collapse did not resolve. A single Grade 4 ankle lesion involving a convex surface was fully resolved following drilling.

Bisphosphonates

Bisphosphonate treatment was administered to six patients. The majority received it for pain management, while one patient was treated for concomitant osteoporosis. Among four patients who underwent bisphosphonate treatment, 18/43 lesions completely resolved. One of these patients experienced full resolution of all lesions ($n = 9$), with the highest initial ON grade being 3. Additionally, the grade of five lesions in three patients improved to a lower grade. As the number of patients receiving bisphosphonate treatment was small, and most received it solely for pain management, no statistical analyses were performed regarding its effect.

DISCUSSION

In this study, grade 5 ON was diagnosed in 11 patients and was notably prevalent in this cohort treated for childhood ALL. Of 458 patients treated for ALL under the NOPHO ALL2008 protocol in the participating centres during the study period, ON was identified in 37 patients, resulting in

TABLE 3 Evolution of the weight-bearing joint lesions during follow-up.

	Hip concave ($n = 8$)	Hip convex ($n = 13$)	Knee concave ($n = 24$)	Knee convex ($n = 28$)	Ankle concave ($n = 7$)	Ankle convex ($n = 14$)
Resolution	6	2	10	8	3	6
Improvement	0	2	1	6	0	0
Stable	2	8	7	10	0	3
Progression	0	1	0	1	1	1
No follow-up	0	0	6	5	4	4

TABLE 4 Changes in the Niinimäki grade during follow-up by site represented as n/n. The left n indicates the number of osteonecrosis (ON) lesions with the respective grade at diagnosis, and the right n at last follow-up.

Grade	Hip concave ($n=8$)	Hip convex ($n=13$)	Knee concave ($n=24$)	Knee convex ($n=28$)	Ankle concave ($n=7$)	Ankle convex ($n=14$)	Shoulder concave ($n=2$)	Shoulder convex ($n=6$)	Elbow concave ($n=1$)	Elbow convex ($n=5$)
5	—	6/7	—	2/3	0/1	3/4	—	2/2	—	1/1
4	1/0	4/1	8/5	9/3	4/3	5/1	—	—	—	1/0
3	7/2	3/3	16/9	17/14	4/1	6/3	2/2	4/4	1/0	3/0
2	—	—	—	—	—	—	—	—	0/1	0/2
1	—	—	—	—	—	—	—	—	—	—
No ON	–/6	–/2	–/10	–/8	–/3	–/6	—	—	—	–/2

Abbreviation: ON, osteonecrosis.

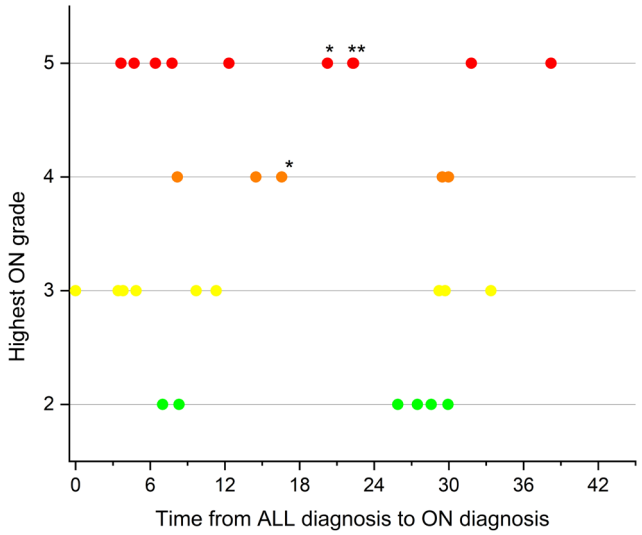

FIGURE 2 The highest Niinimäki grade of ON in relation to the time from ALL diagnosis to ON. *Patient treated with HSCT. ALL, acute lymphoblastic leukaemia; HSCT, haematopoietic stem cell transplantation; ON, ON, osteonecrosis.

an overall incidence of 8.1%. Of the 235 ON lesions identified in these patients, as many as 14 (6%) were already classified as Grade 5 in the first MRI scan, indicating joint surface collapse. The majority of lesions remained stable during follow-up (55%), but a significant proportion (35%) resolved completely over time. Females and older patients had a notably lower likelihood of ON resolution during follow-up. HSCT was identified as a significant factor associated with poorer outcomes through increasing the likelihood of joint collapse already at the time of ON diagnosis.

In previous studies, the incidence of Grade 5 lesions at the time of ON diagnosis was remarkably lower. For example, in studies involving paediatric patients with ALL and Hodgkin lymphoma, the reported incidences of joint collapse at ON diagnosis were 4% and 0.7% respectively.[6,16,24] In contrast, in the present study, 18 lesions in 11 patients were classified as Grade 5 at some point during follow-up. The observed proportion of 6% may, in part, be due to the retrospective, registry-based study design. According to previous studies, HSCT, female sex and older age are among the most significant risk factors for worse outcomes and ON requiring surgical intervention in paediatric ALL patients.[1,3,25] The present results indicate that patients undergoing HSCT for ALL who develop ON more frequently present with joint collapse at ON diagnosis. In HSCT patients, the importance of early MRI at the onset of symptoms suggestive of ON is emphasized.

Due to the lack of potential for spontaneous resolution, lesions that were already Grade 5 at diagnosis were excluded from the GEE models. This likely was the reason why HSCT showed no impact on ON resolution. Consistent with prior research, older age and female sex were identified as significant factors that reduced the likelihood of spontaneous ON resolution. The association of female sex and older age (adolescence) with increased susceptibility to ON and poorer prognosis may be attributed to sex-dependent hormonal differences. Oestrogen and insulin-like growth factors play crucial roles in pubertal bone mass acquisition and likely influence ON risk during puberty.[26] Additionally, males develop larger and denser bones than females from an early age, potentially giving adolescent males a bone-strength advantage that may influence ON prognosis, especially in weight-bearing bones.[27]

Recent studies on ON in ALL and Hodgkin lymphoma patients focusing on joint ON have suggested that lesions on concave joint surfaces may have better outcomes compared to those on convex surfaces.[16,24] This observation is believed to result from convex joint surfaces being less resistant due to thinner subchondral bone and greater exposure to convergent forces.[28] Here, incorporating joint surface shape improved the fit of the GEE model for ON resolution, but joint surface shape had no statistically significant impact on the likelihood of ON resolution. Then again, progression was so rare in this cohort that it precluded any meaningful statistical analysis, leaving open the possibility that joint surface shape may influence the risk of progression. However, it is likely not the shape of the affected joint surface that determines the clinical significance and outcome of a joint ON lesion, but rather the grade of ON itself and the anatomical site—ON of the femoral head invariably presenting with the greatest morbidity. Since the classification is intended to be universal and applicable to any skeletal site, there is not enough supporting evidence to justify revising

TABLE 5 Surgical procedures by cases.

Sex	Age at ALL diagnosis (years)	Time from ALL diagnosis to surgery (years)	Site of ON	Niinimäki grade prior to surgery	Procedure
F	14	2.9	Hip	5	Total hip replacement
F	14	4.0	Hip	5	Total hip replacement
F	9	6.0	Hip	5	Total hip replacement
F	14	3.1	Hip	5	Total hip replacement
F	8	2.3	Ankle	4	Drilling
F	8	2.5	Ankle	5	Drilling
M	7	3.5	Ankle[a]	5	Osteotomy
M	14	4.4	Hip	5	Osteotomy
M	14	4.4	Hip	5	Osteotomy
M	15	3.9	Elbow	5	Cartilage graft

Abbreviations: ALL, acute lymphoblastic leukaemia; F, female; M, male; ON, osteonecrosis.

[a]In one ankle, both convex and concave surfaces were affected; other operated joints had only convex surface involvement.

the Niinimäki scoring system to account for joint surface shape.[24]

In the present cohort, females and males underwent surgery approximately at the same rate. This was not unexpected, as although females had more lesions on average, most lesions were located outside the joints. However, despite the similar number of procedures performed on both sexes, all patients who underwent TJA were female. However, no statistically significant differences between sexes in relation to operative treatment were identified in the study, which is likely attributable to the limited sample size. HSCT and older age have been previously described as risk factors for TJA in leukaemia and lymphoma patients, but research on sex as a risk factor for TJA remains limited.[25] In non-hip lesions, surgical treatments varied significantly, with drilling being the only intervention followed by any radiological improvement in an affected lesion. In one patient, osteotomies had been performed due to femoral head ON, despite previous data advocating TJA as the preferable treatment option.[29,30]

Bisphosphonate treatment was administered to only six patients (16%) in our cohort. Previous studies have not found any impact of bisphosphonates on ON progressing to joint destruction, but prospective interventional studies are lacking.[31] In addition to ON, ALL treatment also conveys a significant risk of osteoporosis.[32,33] It has been recommended that bone density should be evaluated in all ALL patients using dual-energy X-ray absorptiometry at the diagnosis of ON, to screen for osteoporosis.[34,35] Additionally, the use of bisphosphonates for primary prevention of ON during ALL induction therapy has been discussed.[35] However, a preclinical mouse model comparing the lifespan of mice receiving only chemotherapy as part of ALL treatment to those receiving both chemotherapy and bisphosphonates found a statistically significant reduction in the lifespan of the group receiving bisphosphonates.[36] For this reason, bisphosphonates have not been recommended solely as a preventive treatment, although no additional evidence from preclinical or clinical studies linking bisphosphonate use with worse outcomes in ALL has since been published. Hence, if a patient with ALL is diagnosed with osteoporosis alongside ON, bisphosphonate use may be justified as secondary osteoporosis increases fracture risk and early intervention might convey some benefit regarding ON outcomes.[37,38] Such a question could best be answered by a clinical study on preventing ON progression with bisphosphonates in paediatric ALL patients presenting with Grades 3–4 ON. However, considering the number of patients presenting with Grade 5 ON to begin with, a clinical trial with bisphosphonates for primary prevention of ON would be more feasible.

When planning the current study, we initially sought to conduct a collaborative investigation involving most Nordic countries. However, even within participating centres in Finland, imaging methods and MRI scan quality varied greatly. Additionally, obtaining information about surgical procedures proved challenging, especially when procedures other than TJA were involved. Based on this research, standardization of clinical practices across hospitals treating ON is needed, particularly regarding imaging protocols and surgical treatment approaches. This would ensure consistent diagnostics, appropriate patient selection and optimal surgical intervention.

The main limitation of this study was its retrospective nature. The results are likely subject to selection bias, and severe cases are probably overrepresented in the cohort. The small cohort size made it challenging to identify factors associated with a poorer prognosis. Also, follow-up imaging was not conducted systematically and differed between centres. The main strengths of this study were the significant proportion of lesions with at least one follow-up image available, along with the systematic centralized review of all MRI scans and standardized registration of all ON cases.

In conclusion, ON remains a clinically significant, common adverse event of childhood ALL treatment, with its risk factors becoming increasingly well understood. The greatest risk factors preventing spontaneous healing are female sex and older age at diagnosis. Grade 5 lesions, indicating joint collapse, are more likely to develop early in ALL patients who undergo HSCT. There is a need for prospective

interventional trials involving paediatric patients with ALL, preferably with a clinical question of preventing ON development with bisphosphonates or preventing joint collapse in patients with Grades 3–4 ON.

AUTHOR CONTRIBUTIONS

Roosa Rokkanen: Writing—original draft and investigation data curation; Henri Aarnivala: Writing—review and editing, methodology and investigation; Sanna Huhtaniska: Data curation, review and editing; Maria Suo-Palosaari: Data curation, review and editing; Pauliina Utriainen: Data curation, review and editing; Liisa Järvelä: Data curation, review and editing; Sauli Palmu: Data curation, review and editing; Tuuli Pöyhönen: Data curation; Tytti Pokka: Formal analysis and data curation; Riitta Niinimäki: Conceptualization; writing—review and editing, project administration, supervision, methodology and investigation.

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CONFLICT OF INTEREST STATEMENT

All the authors declare no conflicts of interest.

ETHICS STATEMENT

This study was approved by the Regional Ethics Committee of the Northern Ostrobothnia Hospital District, Finland, and it was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the patients or their legal guardians before their participation in the study.

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SUPPORTING INFORMATION

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

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