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Osteonecrosis in children and young adults treated for acute lymphoblastic leukemia: A scoping review

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ABSTRACT

Osteonecrosis (ON) is a common disabling complication of treatment for patients with acute lymphoblastic leukaemia (ALL). Reported incidence rates range from 1% to 61% and multiple possible risk factors have been identified. This review explored existing evidence to provide new perspectives and recommendations for future interdisciplinary research. PEDro, CINAHL, AMED, EMBSAE, OVID, EMCARE databases were systematically searched from their inception to March 2022. Published original research reporting the incidence rates of osteonecrosis in patients aged 10–25 with ALL were included. Study reporting quality was assessed against appropriate reporting guidelines (STROBE, CONSORT and CROSS). All relevant data reporting incidence rates and risk factors were extracted for narrative synthesis. 3146 report titles were screened, with 34 studies included (n = 12,056) (30 observational cohort studies, three randomised trials, and one questionnaire study). The median study quality reporting score was 68% (IQR 64–82%). Median overall incidence rate of ON was 51.8% (IQR 41.4–58.9%) and 15.65% (IQR 9.2–24.2%) for asymptomatic and symptomatic patient screening respectively. Five possible risk factor categories were identified: sex assigned at birth, age, ethnicity, steroid regimen, and genotype. The female sex and white ethnicity were consistently reported as risk factors independently associated with an increased risk of osteonecrosis in all studies. A heterogenous body of literature with moderate reporting quality identified a high incidence rate of osteonecrosis in patients with ALL. Future research investigating the efficacy of stratified treatments that focus on reducing the risk of osteonecrosis through modification of steroid regimen particularly in females of white ethnicity is needed. Obtaining multidisciplinary consensus with regards to screening methodologies and intervention outcomes may also help to improve evidence synthesis in this area. This may in turn facilitate early diagnosis and improve long term patient outcomes through treatment regimen modification and possible prevention of ON progression.

1. Introduction

Survival rates for Acute Lymphoblastic Leukemia (ALL) in children and young adults are currently around 90%, however, over 50% of ALL patients acquire at least one chronic medical condition secondary to treatment [9,17,65,48]. ALL patients aged 10–25 years old experience lower event-free survival rates, and higher rates of secondary complications when compared to those less than 10 years old [3,71].

Osteonecrosis (ON) is a common disabling secondary complication of ALL treatment, first identified in 1977 [33]. Incidence rates are reported as 1–17.6% in children and young adults aged 1–25 years old, with those aged 10–25 years old being at greater risk with ON incidence rates reported as high as 61.1% [30,39,53,63]. There has been limited synthesis of research into incidence rates of this population and the risk factors

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Table 1
Search Terms - As used within database searches.

Search Terms	
S1	*Paediatric OR Pediatric OR Children OR Child OR Infant OR Young Person*
S2	*Avascular Necrosis OR AVN OR Osteonecrosis OR Perthes*
S3	*Acute lymphoblastic leukemia OR acute lymphoblastic leukaemia OR acute lymphocytic leukemia OR acute lymphocytic leukaemia OR ALL*

Key: S1/2/3 = Search 1/2/3

that disproportionately impact them. Risk factor analysis of sex assigned at birth, genetic factors, and variations in corticosteroid treatment regimens have been discussed within research, but this has not been specific to adolescents [39]. Ethnicity has also been discussed as a possible risk factor with reports of Asian populations having a lower incidence of hip ON [5]. Greater awareness of these risk factors could facilitate tailored treatment protocols to best manage modifiable risk factors.

ON affects multiple joints, with ON of the hip and knee joints the most frequently reported, and hip ON reported as having worse long-term patient outcomes [54,82]. The onset of ON is multifactorial in the context of ALL treatment and there is a requirement for collaborative, interdisciplinary efforts to determine the scale of ON and associated risk factors [37]. Pain is the most common presenting symptom for ON, however, due to concurrent glucocorticoid prescription, pain is often masked and difficult to assess [64]. It can occur during stair climbing, sit to stand transfers or periods of prolonged walking [41]. These are all key aspects of rehabilitation within the paediatric cancer population. As key members of the multidisciplinary team, increased awareness of ON, and its associated risk factors by physiotherapists is necessary [26,56].

ON as a secondary complication of treatment also presents in other haematological diseases, including sickle cell anaemia. Physiotherapists have played a key role in the development of ON screening approaches prior to MRI scanning and subsequent clinical evaluation of ON [1]. However, thus far there have been no similar approaches within the ALL population.

To our knowledge, no structured reviews into the incidence rates and risk factors associated with ON have been published. Two peer-reviewed literature reviews have been published - Kunstreich et al. [39] and [37] - although, due to failure to follow a structured, repeatable methodology, both reviews are at high risk of selection and publication bias. There have been systematic reviews of pharmacological interventions for ALL, but these report high levels of confounding and selection bias secondary to limited level ≥ 3 evidence [59], with one Cochrane review by Vist et al. [80] calculating a heterogeneity of $I^2 = 42.2\%$. Due to the high levels of heterogeneity and bias within current research a scoping review methodology was implemented. Scoping reviews facilitate evidence synthesis, utilising transparent and repeatable methods to identify and analyse knowledge gaps, along with identifying key characteristics of related concepts [52]. This scoping review therefore aimed to provide new perspectives on ON within the ALL population to guide interdisciplinary research and clinical management.

2. Methodology

2.1. Overview

The methodology implemented was in accordance with Arksey and O'Malley's [7] framework for scoping reviews, in which five stages are outlined (forming subsequent sub-headings).

2.2. Stage 1 - Identifying the research question

This scoping review aimed to answer the following question:

What is the extent of original research reporting incidence and/or risk factors for ON in children and young adults (aged 10–25 years old) treated for ALL?

The secondary aims of the study included:

I. *What are the incidence rates for ON secondary to treatment for ALL?*
II. *What risk factors have been identified for ON within the ALL population?*

2.3. Stage 2 – Identifying relevant Studies

Following consultation with a specialist health-care librarian, a comprehensive search strategy was developed (Table 1). This was adapted for Physiotherapy Evidence Database (PEDro) and Grey Literature searches. The Healthcare Database Advanced Search tool was used to search the following databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine Database (AMED), Exerpta Medica database (EMBASE) and OVID Emcare. Additional records were sourced through PEDro, NHS, WHO, TRIP and Open Grey Searches in addition to back reference searches of included studies. The first and final search of databases were completed on the 26th of January 2022 and 14th March 2022 respectively.

2.4. Stage 3 - Study Selection

The research questions underpinned the inclusion criteria (Table 2) which utilised the population-concept-context mnemonic [60]. '*Population*' – Patients treated for ALL aged between 10 and 25; '*Concept*' - Studies assessing the incidence rate of and/or the risk factors for ON of the hip and other joints; '*Context*' – Original research published in

Table 2
Selection Criteria - Inclusion/exclusion criteria with justification in keeping with the population-concept-context pneumonic.

Category	Subcategory	Inclusion	Exclusion	Justification
Population	**Participants**	Human Participants	Murine or In Vitro Models	Justified by the research question
	Age Range	10–25 years old	Failure to report data exclusively to the included population	Due to increased prevalence of osteonecrosis within 10–25 year olds
	Exposure	Patients treated for ALL	Other malignancies or haematological disorders	To ensure that ALL was an independent variable
Concept	**Incidence Rates**	Incidence rate of osteonecrosis of the hip or all joints	Incidence rates of ONLY non-weight bearing joints or ankle	Due to increased prevalence of ON within the Hip and greater impact on patients' lives
	Risk Factors	Identified risk factors of ON and their associated risk	Failure to report data exclusively to the included population	Justified by the research question
Context	**Geographical Location of Study**	All considered		In-keeping with a scoping review methodology allow for comparisons between geographical location
	Setting of Research	All settings considered		In-keeping with a scoping review methodology
	Study Design	All considered		In-keeping with a scoping review methodology
	Publication Language	Full text citation in English		English is the working language of reviewers
	Year of Publish	All considered		Changes in treatment protocols over time may provide insight into risk factors for osteonecrosis, i.e., increased cumulative steroid dose

Table 3
Key to Colour Coding - Colour coding used within narrative synthesis of risk factors, in-keeping with [61].

Statistically Significantly Risk Increase for the Female Gender	Higher Risk Reported. Although Not Statistically Significant	No Difference in Risk	Lower Risk Reported. Although Not Statistically Significant	Statistically Significantly Decreased Risk for Females	Data Not Provided

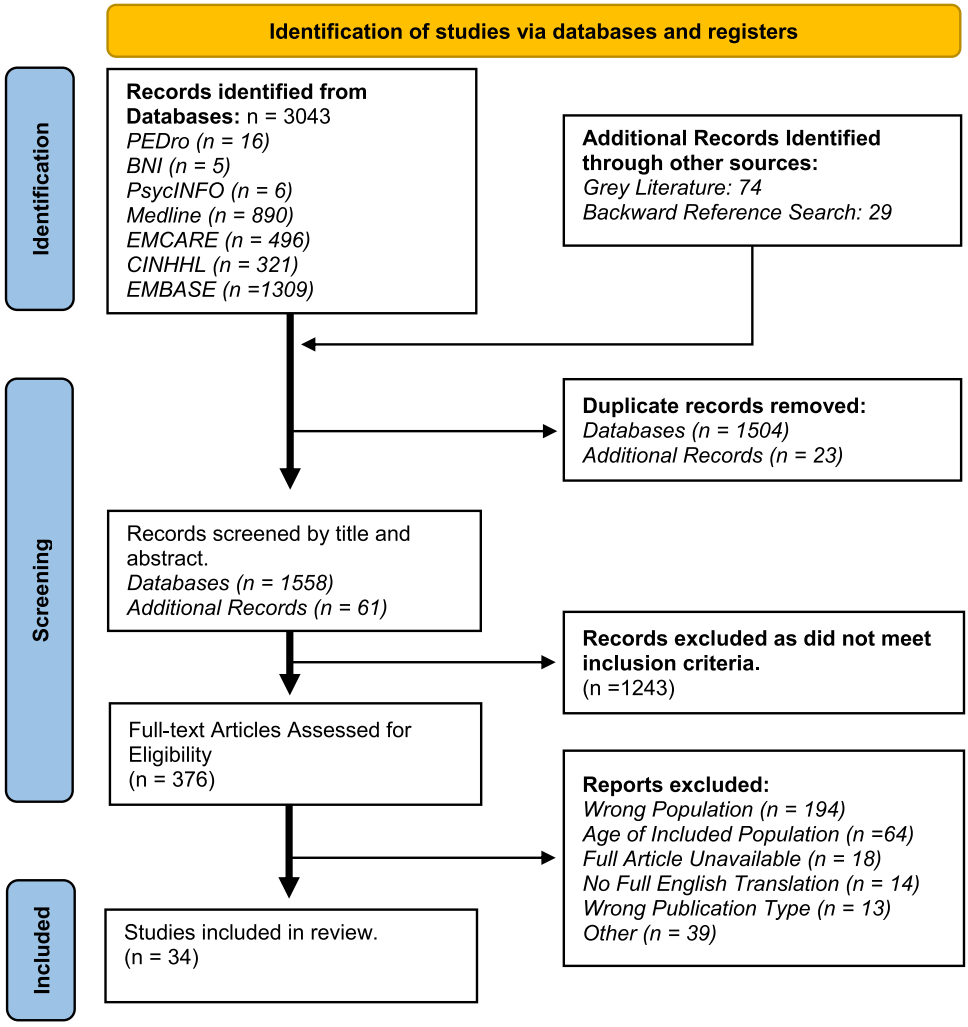


Fig. 1. PRISMA Flow Diagram for Included Studies - *Reported within the PRISMA Extension for Scoping Reviews* [77].

English with no exclusion based on publication date, study design or geographical location. Search results were imported into the Rayyan research tool for screening, with duplicates deleted at this stage [57]. Two reviewers (MC and MT) screened titles and abstracts, then full-text citations of the remaining studies were individually reviewed (by MT and MC). Final selection was agreed by both reviewers with mediation by a third reviewer (RS) required for five studies. When the full text of potential publications could not be located, a specialist librarian was consulted. The study selection process is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews guidelines [77].

2.5. Stage 4 – charting the data

Data extraction was completed by MT and MC, using the charting table (Supplementary Table S1) to identify key information from articles relevant to the research questions. The studies were appraised for quality independently by MT and MC, with conflicts solved through discussion. Reporting guidelines were adapted to study methodology according to the EQUATOR (enhancing the quality and transparency of health research) network: Observational studies using STROBE Guidelines, with an adapted version for conference articles [79,81]; Randomised controlled trials (RCT) using CONSORT [69]; Survey Studies using CROSS [70]. The completeness of reporting for each study was calculated as the quotient of the reported items from the relevant guideline, and the total items included in the guideline minus items not applicable to the study [22].

2.6. Stage 5 – collating, summarising and reporting the results

Narrative Synthesis utilising colour coding to denote trends and statistical significance of associated risk factors, in-keeping with Popay

Table 4
Study Characteristics and Critical Appraisal Scores.

Author, Year and Country	Study Type	Study Cohort (Number of patients, Age Range, Total Study Participants)	Follow Up	Critical Appraisal Type	Critical Appraisal Reporting Score
Prospective					
[27], Canada, United States, including Puerto Rico	Prospective Cohort Study	185, 10–18 yrs, 730	5 yrs	STROBE	82%
[32], United States	Prospective Cohort Study	96, 11–20 yrs, 744	4 yrs	STROBE	82%
[16], Netherlands	Prospective Cohort Study	127, 10–18 yrs, 693	3 yrs	STROBE	82%
[31], United States	Prospective Cohort Study	1855, 10–20 yrs, 2285	NS	STROBE	77%
[34], United States	Prospective Cohort Study	92, 10–20 yrs, 365	5 yrs	STROBE	68%
[6], Italy	Prospective Cohort Study	249, 10–17 yrs, 1421	5 yrs	STROBE	68%
[20], United States	Prospective Cohort Study	51, 10–20 yrs, 980	NS	STROBE	68%
[19], United States	Prospective Cohort Study	147, 10–18 yrs, 615	5 yrs	STROBE	63%
[63], United States	Prospective Cohort Study	36, 10–18.8 yrs, 64	6.4 yrs	STROBE	63%
[36], Germany	Prospective Cohort Study	30, 10–17 yrs, 30	6 months	STROBE	59%
[75], Sweden, Norway, Denmark, Finland, Iceland, Estonia, Lithuania	Prospective Cohort Study	195, 10–18 yrs, 1162	2.5 yrs	STROBE	54%
[38], Germany	Prospective Conference Abstract	NS, 10–23, 359	5 yrs	STROBE for Conference Abstracts	27%
Prospective Studies Overall		**Range:**	*27–82%*	**Median**	68%
Randomised Trial					
[47], United States, Canada, and Australia	Randomised Trial	1287, 10–21 yrs, 2056	5 yrs	CONSORT	84%
[83], United States	Randomised Control Trial	112, 10–18 yrs, 492	5 yrs	CONSORT	72%
[50], Austria, Germany, Italy, and Switzerland	Randomised Trial	431, 10–18 yrs, 3720	5 yrs	Consort	76%
Randomised Trials Overall		**Range:**	*72–84%*	**Median**	76%
Retrospective					
[49], Denmark	Retrospective Cohort Study	282 (Including 67 matched controls), 10–19 yrs, 1489	5 yrs	STROBE	91%
[76], Denmark, Estonia, Finland, Iceland, Lithuania, Norway, and Sweden	Retrospective Cohort Study	266, 10–17 yrs, 1591	5 yrs	STROBE	86%
[35], United Kingdom	Retrospective Conference Abstract	10, 11–16 yrs, 10	NS	STROBE for Conference Abstracts	77%
[46], United States, Canada, and Australia.	Retrospective Cohort Study	893, 10–20 yrs, 1490	3 yrs	STROBE	72%
[64], United Kingdom	Retrospective Cohort Study	NS 10–20 yrs, 235	5 yrs	STROBE	68%
[11], Germany	Retrospective Cohort Study	392, 10–18 yrs, 1951	5 yrs	STROBE	68%
[8], United States	Retrospective Cohort Study	177, 10–18 yrs, 208	NS (Study period 1992–2010)	STROBE	68%
[10], Italy	Retrospective Conference Abstract	262, 10–17 yrs, 469	NS	STROBE for Conference Abstracts	64%
[58], Australia	Retrospective Cohort Study	55, 10–17 yrs, 251 total	1 Year After Completion of Treatment	STROBE	59%
[29], Slovenia	Retrospective Cohort Study	33, 12.9–17 yrs, 131	NS (Study period 1970–2004)	STROBE	59%
[14], United States	Retrospective Conference Abstract	NS, 10–18 yrs, 637	5 yrs	STROBE for Conference Abstracts	55%
[51], Japan	Retrospective Cohort Study	243, 10–18 yrs, 1195	3.5 yrs	STROBE	68%
[13], Taiwan	Retrospective Cohort Study	55, 10–18 yrs, 245	8.7 yrs	STROBE	64%
[5], Japan	Retrospective Cohort Study	39, 10–18 yrs, 175	1 yr	STROBE	86%
[67], Japan	Retrospective Cohort Study	375, 10–18 yrs, 1162	5 yrs	STROBE	68%
[24], Japan	Retrospective Cohort Study	249, 10–18 yrs, 1095	5 yrs	STROBE	73%
[23], USA	Retrospective Cohort Study	2854, 10–22 yrs, 10729	5 yrs	STROBE	68%
Retrospective Trials Overall		**Range:**	*55–91%*	**Median**	68%
Retrospective Questionnaire Study					
[4], United Kingdom	National Questionnaire Study, Retrospective Cohort	793, 10–18 yrs, 3207	7 yrs	CROSS	100%

Key: NS = Not Stated; STROBE = Strengthening the Reporting of Observational studies in Epidemiology; CROSS = A Consensus-Based Checklist for Reporting of Survey Studies; yrs = Years Old

et al. [61] and Rogers *et al.*'s[66]recommendations. Where there was no statistical analysis, associated incidence rates were reported and interpreted by reviewers, however, when this data was not provided studies were marked in grey within colour coding analysis (Table 3). The median and interquartile ranges of included incidence rates were calculated, studies standard deviation (SD) informed this calculation however there was no statistical weighting secondary to cohort size.

Table 5
Components of Included Studies x marking the presence of data and/or analysis of reported osteonecrosis incidence rates or independent risk factors.

Reference	Incidence Rate	Risk Factors					
		Gender	Ethnicity	Age	Steroid Regimen	Genetic	Other
[4]	x	x	x	x			
[5]	x	x	x		x		
[6]	x	x			x		
[8]	x				x		
[10]	x	x			x		
[11]	x			x			
[13]	x	x					
[14]	x					x	
[16]	x						x
[19]	x					x	
[20]	x	x	x			x	
[23]	x	x		x	x		
[24]	x	x			x		
[27]		x	x				x
[29]	x			x		x	
[31]	x	x				x	
[32]	x		x	x	x		x
[34]	x	x	x		x	x	x
[35]							x
[36]	x						x
[38]				x			x
[47]	x			x	x		
[46]	x	x	x	x	x		
[49]	x	x			x		x
[50]	x			x	x		
[51]	x	x			x		
[58]	x						
[63]	x					x	
[64]	x						
[67]	x				x		
[75]	x			x			
[76]	x						
[83]	x	x			x		

3. Results

3.1. Study characteristics

3146 potentially eligible citations were identified; 34 studies met the inclusion criteria, recorded in a PRISMA flow diagram [77] (Fig. 1).

30 observational cohort studies (13 prospective and 17 retrospective), three randomised trials, and one national questionnaire study were included. Study characteristics and their associated critical appraisal scores are reported in Table 4. A total of 12,056 patients were included within this scoping review, however Cole et al. [14], Rhodes et al. [64] and Kuhlen et al. [38] all failed to report the size of the 10–25 years old cohort. High variability between studies was evident, notably study cohort size ranged from 10 to 2854 patients and the year of publication from 2000 to 2022, including patients treated as early as in 1989. Follow-up time ranged from 6 to 104 months, with multiple studies failing to report their follow-up time (see Table 4). Most studies reported their incidence rates and at least one risk factor, summarised in Table 5.

STROBE, CONSORT and CROSS quality appraisals were completed for all included studies (Table 4). The overall median was 68% (IQR 64–82%). The STROBE reporting scores of included observational studies ranged from 27% to 91% (prospective overall median 68% (IQR 61–82%); retrospective overall median 68% (IQR 64–75%)). The majority failed to report on: participant flow charts (21/27), sources of bias (21/27) and description of study type in the title and/or abstract (17/27). Three randomised studies were included with CONSORT scores of 72%, 76% and 84%, the only national questionnaire study Amin et al. [4] had a 100% CROSS appraisal.

3.2. Narrative Synthesis - Incidence Rates

Incidence rates for ON ranged from 5.3% to 61.1% in all included studies (Supplementary Table S2). ON diagnostic and grading guidelines varied between studies. The most common being the National Cancer Institute Common Terminology Criteria for Adverse Events [15] (9/34), but 13/34 studies failed to outline their chosen ON diagnostic and grading guideline. Other included studies used Niinimäki, ARCO (association research circulation osseous classification), ICD-9 (International classification of diseases) Codes, PTWG (Ponte di Legno toxicity working group), Ficat classification and radiographer assessment approaches to diagnose and grade ON. When data was synthesized by study methodology (Fig. 2), there was a trend within reported incidence rates of Prospective > Retrospective > Survey > Randomised (although ranges overlap). However, this appears to be due to ON screening methodologies, rather than study design. Five included studies completed asymptomatic screening (4 prospective and 1 retrospective). Kawedia et al. [34] used NCI CTCAE guidelines for asymptomatic screening, but within their reported incidence rates only grade 2–4 ON was included. Grade 2–4 NCI CTCAE (2006) includes only symptomatic disease, which removes the asymptomatic nature of presentation. When distinguishing between asymptomatic and symptomatic patient screening the median incidence rates were 51.8% (IQR 41.4–58.9%) and 15.62% (IQR 9.2–24.2%) respectively (Fig. 3). There also appears to be variance secondary to geographical location (Table S2). Of included eastern studies (Japan (6), Taiwan (1)) the median ON incidence rate is 10.6% (IQR 6.85–15.6) compared to 17.35% (IQR 11.9–24.2) within western studies (Europe(11), North America (13), Oceania (3)).

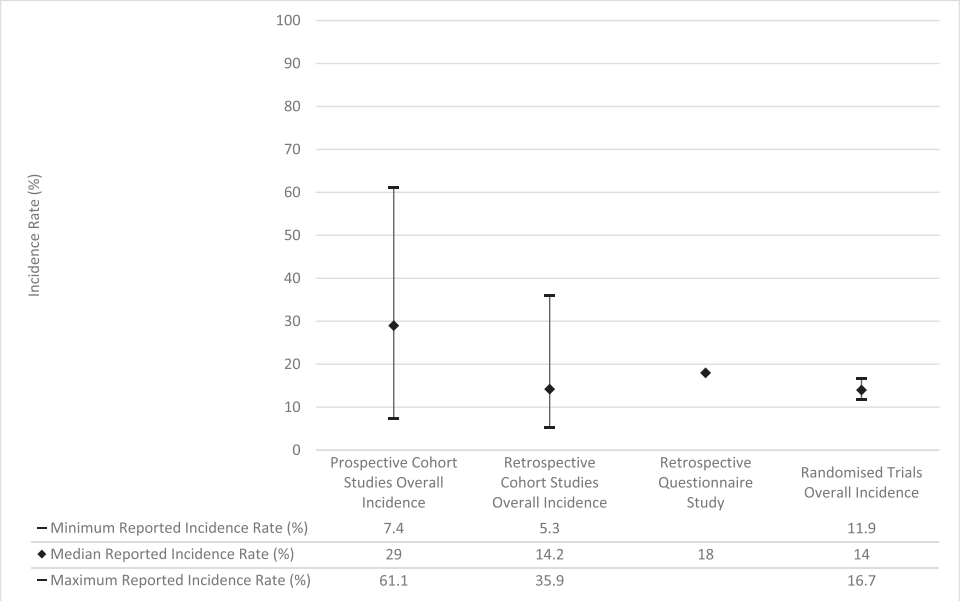


Fig. 2. Medians of Reported Incidence with Range Bars Separated by Study Design - Sources of data reported within Table S2.

3.3. *Narrative synthesis - risk factors*

Within the selected studies a variety of associated risk factors for ON within the ALL population were identified. Analysed herein within six subsets: sex assigned at birth, genotype, age, treatment regimen, ethnicity and other, with overall analysis of these six subsets then presented (Table 12). When reporting the impact of risk factors some studies calculated odds ratios (OR) or hazard ratios (HR), although the majority reported incidence rates and SD only.

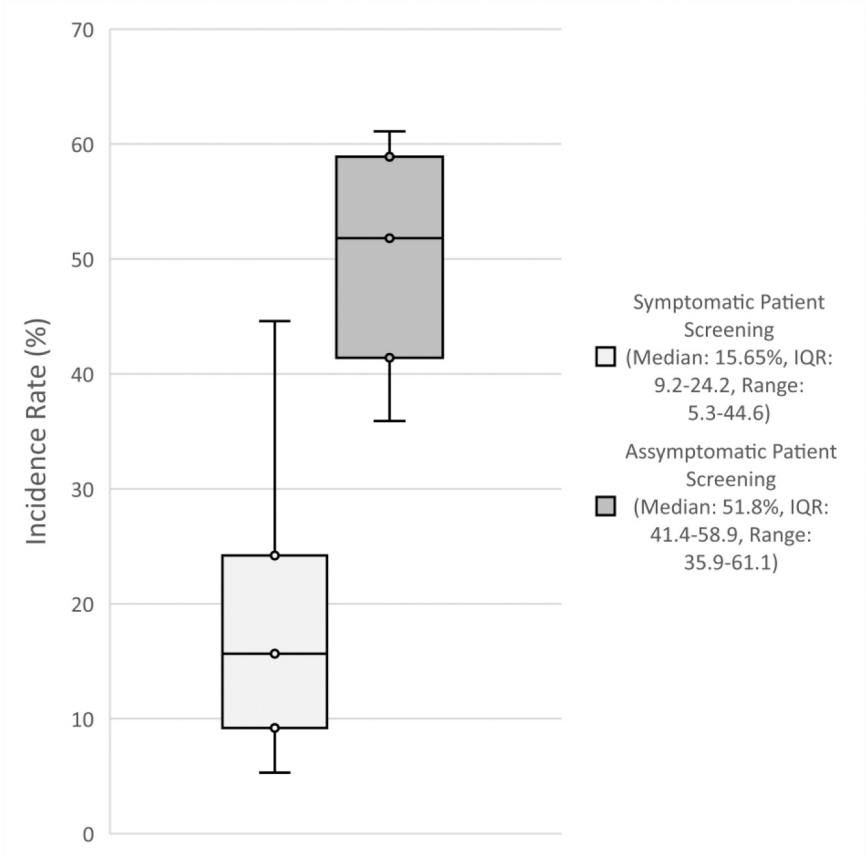


Fig. 3. Box Plot Diagram of Reported Incidence Rates of Osteonecrosis for symptomatic and asymptomatic patient screening - Calculated from reported incidence rates from all included studies separated secondary to screening methodology.

Table 6
Risk Factor Analysis of The Impact of Sex assigned at birth - Reported incidence rates and/or statistical analysis secondary to the impact of gender. Comparisons made of males compared to females in-keeping with the majority of research.

Reference	Treatment Protocol	Follow Up	Study Cohort (Number of Patients, Age Range)	Incidence Rate in Females	Incidence Rate in Males	Odds Ratio (Female Vs Male)
Mattano et al., 2000	CCG-1882	3 yrs	893, 10-20yrs **Full Cohort**	**17.4%** (SD 2.1%)	**11.7%** (SD 1.6%)	NS
			736, 10-15 *Subgroup*	**19.2%** (SD 2.3%)	**9.8%** (SD 2.3%)	
			157, 16-20 *Subgroup*	**13.2%** (SD 5.1%)	**20.7%** (SD 4.7%)	NS
Arico et al., 2003	AIEOP- ALL 95	5 yrs	249, 10-17yrs	0.0855	0.015	NS
French et al., 2008	CCG-1882	NS	51, 10-20yrs	0.228	0.118	NS
Kawedia et al., 2011	St Jude Total XV	5 yrs	92, 10-20yrs	NS		**1.29** (CI 0.71-2.4, p = 0.39)
Vrooman et al., 2013	DFCI ALL 00-01	5 yrs	112 10-18yrs	*No Statistical Difference Found (Data not Provided)*		
Biddeci et al., 2016	AIEOP p2000, BFM ALL 2009	NS	262, 10- 17yrs	*No Statistical Difference Found (Data not Provided)*		
Amin et al., 2017	UK ALL 2003	7 yrs	793, 10-20yrs	NS		**1.04** (CI 0.76-1.32, p = 0.79)
Kahn et al., 2018	DFCI 05-001	5 yrs	185 10-18yrs	NS		**HR 0.34** (Male Vs Female) (CI 0.13-0.84)
Mogensen et al., 2018	NOPHO ALL 2008	5 yrs	282, 10-18.9yrs	**28%** (CI 19-41)	**15%** (CI 9.0-24)	NS
Karol et al., 2022	COG ALL0232	NS	1468, 10-20 yrs	NS		**1.39** (CI 1.08- 1.78, p = 0.00982)
Karol et al., 2022	SJ Total XV NCT00137111	NS	91, 10-20 yrs	NS		**1.40** (CI 0.77- 2.55, p = 0.27)
Moriya *et al*., 2021	JACLS ALL 2002 & 2008	3.5 yrs	243, 10-18yrs	Females at increased risk of developing ON (Data not provided for our population)		
Chen *et al*., 2015	Taiwan Pediatric Oncology Group-ALL-2002 protocol	5yrs	55, 10-18yrs	Females at increased risk of developing ON (Data not provided for our population)		
Arakawa *et al*., 2021	Modified Berlin–Frankfurt–Munster (BFM)-95 regimen	1yr	39, 10-18yrs	Females at increased risk of developing ON (Data not provided for our population)		
Badhiwala, Nayiager and Athale, 2015	DFCI ALL 91-01, 95-01, 00-01, or 05-01	2yrs	31, 10-18yrs	Females at increased risk of developing ON (Data not provided for our population)		
Hyakuna *et al*., 2014	JCCLSG - ALL941, ALL2000, and ALL2004	5yrs	249, 10-18yrs	**25.6%** (SE, 8.4%)	**2.14%** (n = 3/140)	**NS**
Heneghan *et al*., 2017	CHOP ALL 2004-2012	5yrs	2854, 10-22yrs	Females at increased risk of developing ON (Data not provided for our population)		

Key to colour coding:	Statistically Significantly Risk Increase for the Female Gender	Higher Risk Reported. Although Not Statistically Significant	No Difference in Risk	Lower Risk Reported. Although Not Statistically Significant	Statistically Significantly Decreased Risk for Females	Data Not Provided

Key: NS = Not stated; yrs = Years Old; CI = 95% Confidence Interval; SE = Standard Error; SD = Standard Deviation, HR = Hazard Ratio

3.3.1. *Sex assigned at birth*

16 studies (17 treatment protocols) assessed effects of sex assigned at birth on the incidence of ON (Table 6). 16/17 studies which included their data showed results in-keeping with higher incidence of ON in females overall, with six studies showing this as statistically significant. Within these six studies, four compared incidence rates using standard deviation to show statistical significance only, with incidence rates increased in females by 5.7–13%. Two studies included further statistical analysis, Kahn et al. [27] calculated a hazard ratio (male vs female) of 0.34 (CI 0.13–0.84) and [31] calculated an odds ratio (female vs male) of 1.39 (CI 1.08–1.78). Three other studies [4,31,34] calculated odds ratios, ranging from 1.04 to 1.4, albeit all three reported this as not being statistically significant. Five studies [5,8,13,23,51] reported that females > 10 yrs were at higher risk of developing ON, however they failed to provide their data specific to the > 10 yrs populations. Hyakuna et al. [24] calculated incidence rates of 25.6% (SE 8.4%) in females compared to 2.14% in males but failed to complete statistical analysis for > 10 yrs males. Two studies [10,83] both failed to provide their primary data, concluding that there was no statistical difference in incidence of ON between sexes, although it is unclear whether their incidence rates demonstrate a trend in line with the findings of other studies. Mattano *et al.*'s [46] 16–20-year-old cohort showed males to have increased incidence of ON 20.7% (SD 5.1%) vs 13.2% (SD 4.7%), however this failed to show statistical significance.

3.3.2. *Ethnicity*

Ethnic groupings varied highly between studies. In keeping with the majority studies, the colour coding analysis used 'other ethnicities' as

Table 7
Risk Factor Analysis of The Impact of Ethnicity - Reported incidence rates and/or statistical analysis secondary to the impact of ethnicity. Comparisons made of other ethnicities compared to the white ethnicity in-keeping with the majority of research.

Reference	Treatment Protocol	Follow Up	Ethnicity	ON Incidence Rates	Univariate Odds Ratio	Multivariate Odds Ratio
Mattano et al., 2000	CCG-1882	3 yrs	White	**16.7%** (SD 1.4)	**~5** "Fold increase"	NS
			Black & Other	**3.3%** (SD 2.3) **& 6.7%** (SD 2.2%)	**Reference**	
French et al., 2008	CCG-1882	NS	White	**7.00%**	**~2.5** "Fold increase"	NS
			Other	**6.10%**	**Reference**	
Kawedia et al., 2011	St Jude Total XV	5 yrs	White	**21%**	NS	**1.8** (CI 0.9-4, P = 0.43)
			Black and Other	**11.7% and 13.3%**		**Reference**
Kaste et al., 2015	Total Therapy Study XV	4 yrs	*No Statistical Difference Found (Data not Provided for our Population)*			
Amin et al., 2017	UK ALL 2003	7 yrs	*Increased Prevalence of ON in patients of Asian Ethnicity (Data not Provided for our Population)*			
Kahn et al., 2018	DFCI 05-001	5 yrs	Non-Hispanic		**Reference**	
			Hispanic		**0.28** (CI 0.1-0.76, p = 0.013)	**0.23** (CI 0.08-0.66, p = 0.006)

Key to colour coding:	Statistically Significantly Risk Increase for the White Ethnicity	Higher Risk Reported. Although Not Statistically Significant	No Difference in Risk	Lower Risk Reported. Although Not Statistically Significant	Statistically Significantly Decreased Risk for the White Ethnicity	Data Not Provided

Key: NS = Not stated; yrs = Years Old; CI = 95% Confidence Interval; SD = Standard Deviation

the reference against 'white ethnicity'(Table 7). Only studies which reported comparisons in ethnicity-specific incidence rates were included within Table 7. Mattano et al. [46] and French et al. [20] both showed statistically significant increases in prevalence of ON within white patients with a 5- and 2.5-fold increase respectively. Two included studies calculated OR/HR. Firstly, Kawedia et al. [34] found a non-statistically significant OR of white vs other ethnicities of 1.8 (CI 0.9–1.4). Secondly Kahn et al. [27] reported a statistically significant decrease of ON incidence within Hispanic patients compared to white counterparts with multivariant hazard ratio of 0.23 (CI 0.08–0.66). The remaining two studies [32,4] both failed to present data of our population age group. Although, within their conclusions, Amin et al. [4] stated that there was a statistically significant increase of ON incidence within the Asian population and Kaste et al. [32] reported no statistically significant change in incidence rates secondary to ethnicity.

3.3.3. Age

Ten studies completed analysis of age groups within this studies population (Table 8). There was high variation within the results. Burger et al. [11], Möricke et al. [50] and Mattano et al. [47] showed the only statistically significant increases in the incidence rates of ON in > 15 year olds versus those < 15 years old, 7% (SE 2%) Vs 16.67% (SE 5.2%); 14.5% (SE 2%) Vs 22.7% (SE 4.2%) and 9.9% (SE 1.5%) Vs 20% (SE 4.3%) respectively. Three ([29,46]; Kuhlen *et al.*, [38] other studies found similar ON incidence increases due to age, however reported this as not being statistically significant. Toft et al. [75], Kaste et al. [32] and Amin et al. [4] both reported decreased incidence in those > 15 years old, however this was found to not be statistically significant. [23]) compared incidence rates of 10–19 yrs to 19–22 yrs and found no difference in ON incidence between these groups (6.2% Vs 6.25%). As reported within Table 8 only two studies calculated odds and/or hazard ratios (OR and/or HR), however these were excluded as they used under 10-year-olds as their reference incidence rates.

3.3.4. Treatment Regimen

Table 9 summarises the impact of 30 different treatment regimens on the incidence rates of ON. Increased dexamethasone (DEX) cumulative dose resulted in a subsequent increase in ON incidence rates within 10 studies. Kawedia et al. [34] was the sole study demonstrating significantly increased rates of osteonecrosis following greater DEX exposure in the over 10 yrs group (29.7% (DEX cumulative dose 3360 mg/m^2) Vs 9% (DEX cumulative dose 672 mg/m^2)). Four other studies [5,23,24,51] drew similar conclusions, associating higher DEX exposure with an increased risk of ON. Although, these studies failed to provide data for the over 10 yrs group. Moreover, four other studies [32,46,67,6] reported this trend, however their associations were not deemed to be statistically significant. Bidecci *et al.*[10] also showed a statically significant difference between protocols on ON incidence rate 3.1% Vs 25% with the implication this was due to increased DEX cumulative dose, however there was no such statistically significant difference between total steroid cumulative doses.

Modifications of treatment regimens independent of cumulative steroid dose can be seen to impact the incidence ON. Mattano et al. [47] demonstrated three such factors. Firstly, bone marrow response following treatment (slow versus rapid early responders (SER and RER)). The SER cohort had a greater DEX cumulative dose, but a reduction in ON rate, 11.8% (SE 3.3%) vs 12.8% (SE 1.8%). Secondly, alternative week vs continuous treatment, where alternative week treatment

Table 8
Risk Factor Analysis of The Impact of Age - Reported incidence rates and/or statistical analysis secondary to the impact of age. Comparisons made of younger patients compared to older in-keeping with the majority of research.

Reference	Treatment Protocol	Follow Up	Age Range	ON Incidence Rate	Univariate Odds Ratio or Hazard Ratio	Multivariate Odds Ratio or Hazard Ratio
Mattano et al., 2000	CCG-1882	3 yrs	10-15yrs 16-20yrs	**13.50%** (SD 1.4%) **18.00%** (SD 3.6%)	NS	
Kuhlen et al., 2017	ALL-SCT-BFM 2003	5 yrs	10-14 yrs 15-23yrs	**10.00%** (SD 3%) **13.00%** (SD 4%)	NS	
Burger et al., 2005	ALL-BFM 95	5 yrs	10-15yrs 15-18yrs	**7.00%** (SE 2%) **16.67 %** (SE 5.2%)	NS	
Mattano et al., 2012	CCG-1961	5 yrs	10-15yrs 16-21yrs	**9.90%** (SE 1.5) **20.00%** (SE 4.3)	Used patients aged <10 as reference for OR calculation	NS
Kaste et al., 2015	Total Therapy Study XV	4 yrs	11-15 yrs 16-20yrs	**47.10%** **46.20%**	Used patients aged <10 as reference for OR/HR calculation	
Toft et al., 2016	NOPHO ALL2008	2.5 yrs	10-14 yrs 15-17 yrs	**11.00%** **6.50%**	NS	
Karas-Kuzelicki et al., 2016	POG, BFM-83, BFM-86, BFM-90, BFM-95, IC-BFM 2002	NS	12.9-14.5 yrs 14.5-17yrs	**12.50%** **28.00%**	NS	
Amin et al., 2017	UK ALL 2003	7 yrs	10-15yrs 16-20yrs	**22.96%** **21.31%**	NS	
Möricke *et al*., 2016	AIEOP-BFM ALL 2000	5yrs	10-15yrs 15-18yrs	**14.5%** (SE 2.0) **22.7%** (SE 4.2)	NS	
Heneghan *et al*., 2017	CHOP ALL 2004-2012	5yrs	10-19yrs 19-22yrs	6.20% 6.25%		

Key to colour coding:	Statistically Significantly Risk Increase for Older Patients	Higher Risk Reported. Although Not Statistically Significant	No Difference in Risk	Lower Risk Reported. Although Not Statistically Significant	Statistically Significantly Decreased Risk for Older Patients

Key: NS = Not stated; yrs = Years Old; CI = 95% Confidence Interval; SE = Standard Error; SD = Standard Deviation, HR = Hazard Ratio; RHR = Risk Hazard Ratio

experienced a statistically significant decrease ON incidence rates, 8.7% (SD 2.1%) Vs 17% (2.9%), but had higher DEX cumulative dose. Mogensen et al. [49] similarly investigated the difference between alternative week vs continuous treatment, but reported those following the alternative week treatment had increased ON incidence. Finally, Mattano et al. [47] compared intensified Vs standard treatment, where both cohorts had the same DEX cumulative dose, but standard treatment included additional asparaginase therapy, which reportedly led to a statistically significant increase in ON prevalence (12.4% (SE 2.1%) Vs 21.4% (4.3% SE)). Asparaginase therapy was also linked with increased incidence of ON by [5] and [51], however both failed to provide their primary data.

Three studies assessed the impact of DEX Vs prednisolone (PDN) during treatment induction. Vrooman et al. [83] demonstrated increased ON incidence rates in those treated with DEX compared to PDN (23% vs 5%). This was similarly shows by [23], albeit they failed to provide their primary data to > 10 yrs only. Mogensen et al. [49] found no difference between induction using PDN and DEX with an OR of 1.00 (CI 0.2–2.1, p = 0.990). Möricke et al. [50] showed the DEX cohort had a decreased incidence of ON compared to PDN during induction, but this was not statistically significant with incidence rates of 13.8% (SE 2.4) Vs 19.2% (SE 2.7%) respectively.

3.3.5. *Genotype*

Table 10 provides a summary of the 14 potential risk factor genotypes assessed for influencing ON prevalence. Within the colour coding analysis, the limited repeatability between studies and reduced reliability (secondary to failure to produce data) is evident. French et al.

Table 9
Risk Factor Analysis of The Impact of Treatment Regime - Reported incidence rates and/or statistical analysis secondary to the impact of different treatment regimes. Where statistical analysis was completed comparisons were made between study cohorts and are stated in the above table.

Reference	Follow Up	Treatment Protocol	Protocol Subset	Steroid Type	Cumulative Steroid Dose (mg/m^2)	ON Incidence Rate	Additional Statistical Analysis
Mattano et al., 2000	3 Years	**CCG-1882**	**Standard BFM**	*Induction:* PDN Delayed Intensification: DEX	1815 235	**16.4%** (SD 4.3%)	Standard Vs Augmented **- OR 1.4**
			Augmented BFM	*Induction:* PDN Delayed Intensification: DEX	1815 470	**23.20%** (SD 4.8%)	
Arico et al., 2003	5 Years	**AIEOP- ALL 95**	**Intermediate Risk** **High Risk**	PDN & DEX, Calculated as Prednisone Equivalent	3250-4762 6460	**3.20%** **15.60%**	NS
Kawedia et al., 2011	5 Years	**St Jude Total XV**	**Low Risk** **High Risk**	DEX DEX	672 3360	**9%** **29.70%**	Low Vs High Risk **OR 2.5** (CI,1.2-4.9, P =0.011)
Mattano et al., 2012	5 Years	**CCG-1961**	**RER** **SER**	DEX DEX	210-280 280	**12.80%** (SE 1.8%) **11.8%** (SE 3.3%)	NS
Mattano et al., 2012	5 Years	**CCG-1961**	**RER Intensified Continuous** **RER Standard Continuous**	DEX Asparaginase DEX Asparaginase	210-280 0 210-280 36'000	**12.40%** (SE 3.7%) **21.4%** (SE 4.3%)	Intensified Vs Standard - **OR 1.8**
			RER Alternate Week (AW) **RER Continuous (C)**	DEX DEX	280 210	**8.70%** (SD 2.1%) **17%** (SD 2.9%)	Alternate Week Vs Continuous - **OR 2.1**
Vrooman et al., 2013	5 Years	**DFCI ALL 00-01**	**Corticosteroid Random Assignment**	DEX PDN	Standard Risk- 6 High Risk- 18 Standard Risk- 40 High Risk- 120	**23.00%** (p = 0.02) **5.00%** (p = 0.02)	NS
Kaste et al., 2015	4 Years	**Total Therapy Study XV**	**Low Risk** **High Risk**	DEX DEX	360 420	**18.50%** (SE 4.3%) **20.00%** (SE 10.7%)	<10yrs used as reference in HR calculation
Biddeci et al., 2016	NS	**AIEOP: p2000**		DEX PDN	1730-1960 141-580	**3.10%** (p=0.001)	**Z -Test = 5** (p < 0.001)
		BFM ALL 2009		DEX PDN	1632-2040 223-556	**25.00%** (p = 0.001)	

(*continued on next page*)

Table 9 (*continued*)

Mogensen et al., 2018	5 Years	**NOPHO ALL 2008**	**Induction randomisation**	DEX PDN	210 1740	NS	DEX Vs PDN - **OR 1** (CI 0.2-2.1, p = 0.990)
Mogensen et al., 2018	5 Years	**NOPHO ALL 2008**	**Standard Risk**	DEX PDN	238 866	**16.30%**	NS
			Intermediate Risk	DEX PDN	503 581	**13.80%**	
			High Risk (non-SCT)	DEX PDN	664-748 227	**10.20%**	
Möricke *et al*., 2016	AIEOP-BFM ALL 2000	5yrs	Induction Randomisation	DEX PDN	210-300 1260-1800	**13.8%** (SE 2.4) **19.2%** (SE 2.7%)	p = 0.23
Moriya *et al*., 2021	JACLS ALL 2002 & 2008	3.5 yrs	Increased DEX and L-asp dosage increases ON incidence (Data not provided for our population)				
Arakawa *et al*., 2021	Modified Berlin–Frankfurt–Munster (BFM)-95 regimen	1yr	Increased DEX and L-asp dosage increases ON incidence (Data not provided for our population)				
Sakamoto *et al*., 2018	JACLS ALL-97	167, 10-15yrs	High Risk	DEX PDN Total Corticosteroid	70 7360 7827	**9.50%**	NS
			Extremely High Risk	DEX PDN Total Corticosteroid	670 6680 11629	**16.40%**	NS
	JACLS ALL 2002	209, 10-18yrs	High Risk	DEX PDN Total Corticosteroid	70-120 5945 6412-6745	**7.30%**	NS
			Extremely High Risk	DEX PDN Total Corticosteroid	670 6505 10974	**8.20%**	NS
Hyakuna *et al*., 2014	JCCLSG - ALL941, ALL2000, and ALL2004	249, 10-18yrs	Increased DEX increases ON incidence (Data not provided for our population)				
Heneghan *et al*., 2017	CHOP ALL 2004-2012	2854, 10-22yrs	Increased DEX increases ON incidence (Data not provided for our population)				

Key to colour coding:	Statistically Significantly Risk Increase Secondary to Treatment Regime	Higher Risk Reported. Although Not Statistically Significant	No Difference in Risk	Data not provided

Key: DEX = Dexamethasone; PDN = Prednisolone; NS = Not Stated; yrs = Years Old; CI = 95% Confidence Interval; HR = Hazard Ratio; OR = Odds Ratio; SCT = Stem Cell Transplant

[20] showed increased incidence of ON in those with the *PAI-1* AA/AG genotype, with an associated multivariant OR of 2.89 (CI 1.48–5.62). This was not repeated by Finklestein *et al.* [19] who failed to provide primary data. Karol et al. [31] assessed the impact of the *GRIN3A* genotype within the COG ALL0232 cohort. This was shown to statistically significant in increasing ON incidence, calculating a HR 2.07 (CI 1.59–2.70), although within the SJ Total XV cohort despite a similarly increased HR of 1.67 (CI 0.55–2.7), this was not found to be statistically significant.

French et al. [20] found an OR of 1.42 (CI 0.72–2.74) secondary to the *TYMS* 2/2 genotype, however this was not statistically significant. Relling et al. [63] reported a 100% incidence rate of ON secondary to the *TYMS* 2/2 genotype, whilst also finding a 51.7% incidence rate in patients with the 2/3 or 3/3 genotype, although due limited cohort size (7 and 29 respectively) no statistical analysis was completed. Cole et al. [14] and Finklestein *et al.* [19], both with larger cohorts, concluded that the 2/2 *TYMS* genotype had no influence ON incidence rates, albeit both failed to present their data on this. Karas-Kuzelicki et al. [29] found 2/2

Table 10
Risk Factor Analysis of The Impact of Genetic Factors - Reported incidence rates and/or statistical analysis secondary to the impact of different genotypes. Where statistical analysis was completed comparisons were made between genotypes within the same study and are stated in the above table.

Reference	Treatment Protocol	Follow Up	Gene		Genotype	Number of Patients (with ON/ALL + Controls)	ON Incidence Rates	Additional Statistical Analysis	
Relling et al., 2004	St Jude Total XIIIB, XIV	6.4 yrs	*TYMS* Enhancer Repeat		2R/2R	7/7	**100%**	NS	
					2/3 or 3/3	15/29	**51.70%**		
			Population with: *TYMS* enhancer repeat (2/3 or 3/3)	VDR Start Site	T/C or T/T	5/14	**35.70%**	NS	
					C/C	10/15	**66.70%**		
French et al., 2008	CCG-1882	NS	*TYMS* Enhancer Repeat		2R/2R	16/80	**20%**	Univariant OR **1.4** (CI 0.72-2.74, p = 0.326)	Multivariate OR **1.42** (CI 0.72-2.8, 0.319)
					Other	27/189	**14.30%**	Reference	Reference
French et al., 2008	CCG-1882	NS	*VDR, BGLAP, ESR1, MTHFR, ABCB1, PTH, PTHR, ACP5, ACP5*					No Statistical Significance Found in any of the Adjacent Genes *(See table 2 from French et al., 2008)*	
French et al., 2008	CCG-1882	NS	*PAI - 1*		AA/AG	21/57	**36.80%**	Univariant OR **2.79** (CI 1.45-5.34, p = 0.002)	Multivariate OR **2.89** (CI 1.48-5.62, p = 0.002)
					GG	25/189	**13.20%**	Reference	Reference
Kawedia et al., 2011	St Jude Total XV	5 yrs	*A PAI-1*			NS		No Statistical Significance (Data Not Provided)	P= 0.9
Kawedia et al., 2011	St Jude Total XV	5 yrs	*SH3YL1*		TT /AT	12/13	**92.30%**	NS	
					AA	29/79	**36.70%**		
Cole et al., 2015	DCFI ALL 05-001	5 yrs	*TYMS*	2R		NS		No Statistical Significance (Data Not Provided)	
Finkelstein et al., 2017	DFCI ALL 05-001	5 yrs	*IL1B*			NS		Multivariable HR **- 0.44** (CI 0.13–1.44, p = 0.17)	
Finkelstein et al., 2017	DFCI ALL 05-001	5 yrs	*PAI - 1*			NS		No Statistical Significance (Data Not Provided)	
			TYMS	2R		NS		No Statistical Significance (Data Not Provided)	
Karas-Kuzelicki et al., 2016	POG, BFM-83, BFM-86, BFM-90, BFM-95, IC-BFM 2002	NS (Study period 1970-2004)	*TPMT*		*1/*3	2/2	**100%**	p = 0.001	
					1*1*	5/23	**21.70%**		
Karol et al., 2022	COG ALL0232	NS	*GRIN3A*		NS	230/1468	NS	RAF Cases 0.152 RAF Controls 0.0905	**HR = 2.07** (1.59-2.70 CI, p = 1.44 x 10^6;
Karol et al., 2022	SJ Total XV NCT00137111	NS	*GRIN3A*		NS	45/91	NS	RAF Cases 0.10 RAF Controls 0.077	**HR =1.67** (0.55-5.10 CI, P = 0.37)

Key to colour coding:	Significantly Increased Risk Secondary to Genotype	Higher Risk Although No Statistical Significance	No Difference in Risk	Data Not Provided

Key: NS = Not stated; yrs = Years Old; CI = 95% Confidence Interval; SE = Standard Error; SD = Standard Deviation; RAF = Random Allele Frequency; TPMT = Thiopurine S-methyltransferase, TYMS = Thymidylate synthase, PAI - 1 = Plasminogen activator inhibitor-1, IL1B = Interleukin 1 beta, GRIN3A = Glutamate Ionotropic Receptor NMDA Type Subunit 3A

patients with the *TPMT* * 1/* 3 genotype developed ON, although this small sample cannot be taken as conclusive, and no other included study assessed the TPMT gene.

3.3.6. Other

In addition to the above risk factors, some included studies presented data on other risk factors (Table 11), including: four studies finding that BMI demonstrated no impact on ON incidence rates; den Hoed et al. [16] concluded reduced bone mineral density and ON develop independently; Krull et al. [36] reported a significant increase in the incidence of ON in patients without Leukemic infiltration of bone marrow (41.6% Vs 18.7%); Kuhlen *et al.* [38] found increased incidences of ON following hematopoietic stem cell transplantation in those with past medical history of ON (58% Vs 7%).

Kim and Stohr [35] investigated the morphological predictors of ON, finding acetabular retroversion as the only significant predictor of ON, although data of controls was not stated, and it was only a 10-patient cohort. Finally, Kawedia et al. [34], analysed the impact of lipid levels on ON incidence rate. Finding high serum cholesterol at week 8 to be associated with a statistically significant in increase in the risk of developing ON (OR 1.11 (CI 1.02–1.21)). Similarly finding high serum cholesterol levels at week 12 increased ON incidence with a OR of 1.05 (CI 0.97–1.14), albeit this no longer was statistically significant. No such relationship was found with high albumin levels. However, within the SH3L1 AA genotype cohort there was an increased ON incidence rate of 73.3% in those with low albumin levels compared to 28.1% in controls, but there was no additional statistical analysis on this data.

3.3.7. Overall analysis

Table 12 uses colour coding (Table 5) to provide a summary of the evidence. It is evident that patients of the female 'sex' (assigned at birth) and 'white ethnicity' have no data which appears to contradict the hypotheses of both characteristics result in an increased incidence of ON. Mattano et al. [46] found one cohort of 16–20 yrs to have increased incidence of ON in males but reported the full 10–20 yrs cohort to have increased incidence in females. 'Older age' and 'other' risk factors have high variability within their results, therefore there is limited ability to identify any independent risk factors. Finally, 'treatment regimen' and 'genetic' risk factors appear to show an impact on ON incidence rates, although included studies had high variability in methods and assessed different variables leading to minimal generalisability of this data.

4. Discussion

This scoping review is the first of its kind investigating the extent of research of the incidence rates and risk factors of ON within patients treated for ALL. 34 studies and 12,056 patients were included within our review. Increased awareness of ON as a secondary complication to

Table 11
Risk Factor Analysis of The Impact of Other Factors - Reported incidence rates and/or statistical analysis secondary to the impact of independent variables. Where statistical analysis was completed comparisons odds ratios were calculated against control groups without the independent variable.

Reference	Treatment Protocol	Follow Up	Variable	Risk Factor	Number of Patients (with ON/ ALL + Controls)	ON Incidence Rates	Additional Statistical Analysis	
den Hoed et al., 2015	DCOG-ALL9	3 yrs	Bone Mineral Density	BMD Lumbar Spine	Control - 0/99	N/A	Mean BMD: 0.9	No significant difference between patients who did or did not develop ON (p = 0.359)
					ON - 28/28	N/A	Mean BMD:1.14	
				BMD Total Body	Control - 0/99	N/A	Mean BMD: 007	No significant difference between patients who did or did not develop ON (p = 0.650)
					ON - 28/28	N/A	Mean BMD: 0.25	
Kim and Stohr, 2018	UKALL	ON Patients only	Morphological Predictors	Centre Edge Angle	10/0	NS	Mean: **35.7°** Range: **20-50°** SE: **2.2°**	Within the Range of General Population
				Acetabular Index	10/0	NS	Mean: **11.1°** Range: **7-14°** SE: **2.4°**	Within the Range of General Population
				Neck-Shaft Angles	10/0	NS	Mean: **134.7°** Range: **125-142°** SE: **1.1°**	Within the Range of General Population
Kim and Stohr, 2018	UKALL	ON Patients only	Morphological Predictors	Acetabular Retroversion	10/0	NS	**Mean >6°**	50% Higher than General Population
Krull et al., 2017	IEOP-BFM 2009, CoALL-08-08	6 Months	Leukemic Infiltration (LI)	LI	3/24	12.50%	p = 0.016	Further analysis of susceptible joints (4 per patient). 41.6% Vs 18.7% (p=0.028) incidence rates in NO LI Vs LI
				No LI	4/6	66.70%		
Kuhlen et al., 2017.	ALL-SCT-BFM 2003	5 yrs	PMH of ON prior to HSCT	PMH ON	NS	**58.00%** (SD 19%)	NS	
				no PMH of ON	NS	**7%** (SD 2%)		
Kawedia et al,. 2011	St Jude Total XV	5 yrs	Higher Serum Cholesterol (mg/dl) Week 8	**Control** Median: 146.0 mg/dl Range: 12–453mg/dl	0/275	N/A	Reference	
				ON Grade 2-4 Median: 181.0mg/dl Range: 70–464mg/dl	63/63	N/A	**Univariant Logistic Regression 1.18** (CI 1.02–1.21, p < 0.0206) **Multivariant Logistic Regression 1.11** (CI 1.02–1.21, p = 0.0206)	

(*continued on next page*)

Table 11 (*continued*)

Kawedia et al,. 2011	St Jude Total XV	5 yrs	Higher Serum Cholesterol (mg/dl) Week 12	**Control** Median: **164.0mg/dl** Range: **4–496mg/dl**	0/257	N/A	Reference
				ON Grade 2-4 Median: **187mg/dl** Range: **32–736mg/dl**	61/61	N/A	**Univariant Logistic Regression 1.12** (CI 1.03–1.21, p < 0.0074) **Multivariant Logistic Regression 1.05** (CI 0.97–1.14, p = 0.2391)
Kawedia et al,. 2011	St Jude Total XV		Albumin Levels (mg/dl) at Week 8	**Control** Median: **3.7mg/dl** Range: **2.2–4.8mg/dl**	0/251	N/A	Reference
				ON Grade 2-4 Median: **3.3mg/dl** Range: **2.2–4.5mg/dl**	60/60	N/A	**Univariant Logistic Regression 0.43** (CI 0.26-0.72, p < 0.0.001) **Multivariant Logistic Regression 0.58** (CI 0.0.34–1.00, p = 0.05)
Kawedia et al,. 2011	St Jude Total XV - With SH3YL1 AA Genotype	5 yrs		Albumin <2.75 mg/dl	11/15	**73.30%**	NS
				Albumin >2.75 mg/dl	18/64	**28.10%**	
				BMI			
Kahn et al., 2018	DFCI 05-001	Symptomatic	BMI	**Not Obese**: BMI < 95th percentile for age and sex	NS/721	NS	Reference
				Obese: BMI > 95th percentile for age and sex	NS/102	NS	**Univariant HR 0.42** (CI 0.13-1.39, p = 0.16)
Mogensen et al., 2018	NOPHO ALL 2008	5 yrs	BMI-SDS (time varying, weighted)	No Statistical Significance (Data not provided for this studies population)			
Kaste et al., 2015	Total Therapy Study XV	4 yrs	BMI	No Statistical Significance (Data Not Provided)			
Badhiwala, Nayiager and Athale, 2015	DFCI ALL 91-01, 95-01, 00-01, or 05-01	2yrs	BMI	No Statistical Significance (Data Not Provided)			

Key to colour coding:	Statistically Significantly Increased Risk Secondary to an Identified Risk Factor	Higher Risk Reported. Although Not Statistically Significant	No Difference in Risk	Lower Risk Reported. Although Not Statistically Significant	Statistically Significantly Decreased Risk Secondary to an Identified Risk Factor	Data Not Provided

Key: NS = Not stated; yrs = Years Old; CI = 95% Confidence Interval; SE = Standard Error; SD = Standard Deviation; BMI = Body Mass Index; deg = degrees; ON = osteonecrosis; PMH = Past Medical History; HSCT = Hematopoietic stem-cell transplantation; BMD = Bone Mineral Density; LI = Leukemic Infiltration of the Bone Marrow

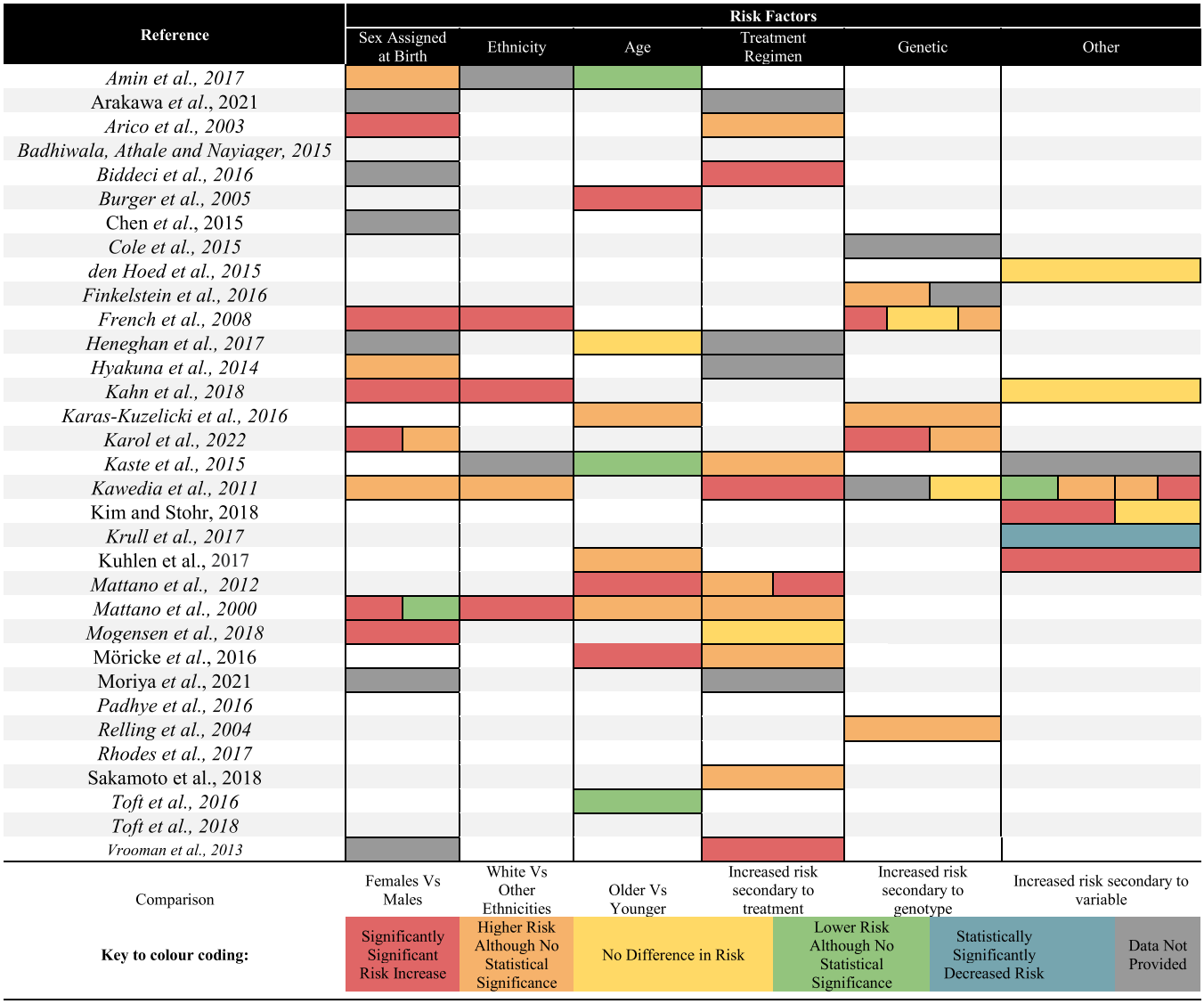
treatment in the ALL population has resulted in a subsequent increase in the quantity of research. However, variance between treatment regimens and research methodologies result in difficulty synthesising this data. The median of study reporting quality scores of included studies was 68% (IQR 64–82%). With > 70% reported as adequate [62], there is the opportunity for an improvement in the quality of research, notably by increased use of patient flow charts, improved reporting and recognition of the possible sources of bias. Study design varied within this review with the majority being retrospective observational research. ALL treatment protocols are constantly evolving in-line with best research. This leads to over 60% of ALL patients being enrolled on RCTs and therefore treated on new treatment protocols [68]. The majority of RCTs fail to provide and analyse data on ON incidence and associated risk factors, leading to a large proportion of the research on ON being retrospective. Due to the high prevalence of ON researchers should be encouraged to report ON rates within their RCT design, thus improving the quality of ON research. Our findings indicated a variation in results secondary to this research and screening methodology. Prospective research reduces the risk of bias and has an increased capability for the identification of asymptomatic disease; therefore, larger prospective studies would provide the best evidence [18].

ON diagnostic and grading guidelines varied between studies. The most common guideline being the National Cancer Institute Common Terminology Criteria for Adverse Events (9/34), but 13/34 studies failed to outline their chosen ON diagnostic and grading guideline. Asymptomatic screening facilitated an earlier diagnosis of ON. Kawedia et al. [34] found that patients (aged 1–20 years old) who presented with asymptomatic grade 1 ON had an increased risk of developing grade 2–4 ON (34 of 130; 26%) compared with controls (27 of 194; 14%, $P = .008$). Progression from NCI CTCAE grade 1 ON to symptomatic disease has been estimated at up to 55.9% within the ALL population [28]. Whilst ON progression is not inevitable, recent research has identified possible preventative pharmacological treatments such as bisphosphonates and hyperbaric oxygen therapy [73], which could be used to prevent further deterioration in the treatment of patients with grade 1 ON. Early diagnosis of ON also facilitates adaptations of treatment regimens, which have the potential help to slow or reverse ON progression [25]. Arakawa et al.[5] found four cases of asymptomatic ON which had necrosis of > 30% of the epiphyseal surface of the femoral head. All four of these patients went on to require joint replacement surgery. A child or young adolescent with > 30% femoral head necrosis is at very high risk femoral head collapse and the severe complications from this, including reduced quality of life. This reinforces the need for early diagnosis and adaptation of treatment protocols to those with grade 1 ON to minimise the potential impact on a patient's mobility and therefore quality of life. There is a need for greater research into this area and Amin *et al.* (2019) are currently assessing this within the BONES study (protocol published 2019).

Physiotherapists have the potential to play a key role in screening prior to MRI. Since early 2005, physiotherapists treating patients for sickle cell anaemia have used the Children's Hospital Oakland Hip Evaluation Scale (CHOHES) as a screening tool and outcome measure for patients at risk of developing ON; similarly, used in the developmental dysplasia population [2,45]. Within this review CHOHES has not been used in any studies looking into ON within the ALL population, providing a potential new area of research for physiotherapists which could help improve outcomes. There has been one physiotherapy-led cohort study of ON in the ALL population, where range of motion and functional mobility was assessed. This study concluded that functional mobility assessments should be used in combination with MRI screening, although there was no reference to CHOHES [44].

Within this review the incidence rates of ON in the ALL population were 51.8% (IQR 41.4–58.9%) and 15.62% (IQR 9.2–24.2%) for asymptomatic and symptomatic patient screening respectively (Fig. 3). The large range is likely due to the variance between treatment regimens, demonstrating the limitation of the generalisability of this data. The identification of those at higher risk has potential to inform asymptomatic patient screening and treatment choices. Within this

Table 12
Colour Coded Table of Analysed Characteristic of Included Studies - Adapted from Table 5, with colour coding to give overall picture of the quantity and quality of the data for the identified risk factors.



review all included primary data indicated the female sex and the white ethnicity as both being independently associated with increases in ON incidence rates. This was independent of ALL incidence being recognised as higher in males, notably in the GLOBOCAN 2020 statistics [12,72]. There are two main hypotheses as to why females are at higher risk of developing ON, firstly that earlier onset of puberty in females results in an increased risk [21], and secondly that the oestrogenic effects on bone mass and the procoagulant effects of oestrogen predispose patients to osteonecrosis [39]. The cohort size of ethnic minorities within western research is significantly lower than that of white patients, leading to a high probability of selection bias within these results. When comparing the incidence rates of symptomatic disease between western research and that completed in Asia, ON incidence rates are 17.4% (IQR 11.9–24.2) and 10.6% (IQR 6.85–15.6) respectively. Whilst this cannot be proven to be solely as a result of ethnicity, these results appear to be in-keeping with the white ethnicity patients being at higher risk of developing ON. One possible explanation for this was postulated by Arakawa et al. [5] reporting that the JACLS (Japan Childhood Leukemia Study Group) cohorts reduced asparaginase and corticosteroid dose may cause this reduction in incidence rather than ethnicity. There is a need for improved research into this, reducing both selection bias and confounding variables secondary to treatment regimen.

The impact of ethnicity on presenting genotypes was assessed in all studies assessing genotypes as a risk factor for ON, but no studies found this to be statistically significant. The authors are aware of only one case study from non-western research reporting genetic risk factors. Nozaki, Matsubara, and Mori [55] reported a case of a 12 year old female with bilateral tali ON, who presented with the *TYMS 2/2* genotype. This provides a potential area for future research to evaluate if ethnic differences in ON incidence are due to genetic factors. The influence of genetic risk factors in < 10 year olds is well documented [30]. Although when the same genotypes (*BMP7* and *PROX1-AS1*) are assessed within > 10 years old there is no similar relationship. Although the impact of age is well documented, most larger research studies on genetic risk factors for ON failed to separate their results into < 10 and > 10 years old cohorts, reducing the clinical relevance of their results. Both increased age and some genotypes influence the rate of DEX clearance from the blood stream, thereby increasing risk of developing ON [42,84].

This reviews results indicate no direct relationship between cumulative DEX dose and ON incidence rates. Mattano et al. [47] demonstrated this when comparing standardised and intensive treatment,

concluding it was asparaginase which influenced ON incidence not DEX; similarly evidenced in murine models by Lui *et al.*[40] and human models by Atteveld et al. [78]. Lynggaard et al. [43] have published a protocol for a meta-analysis looking into this impact asparaginase which will help to progress treatment. It is crucial to recognise DEX has higher efficacy and improved survival rates from ALL, when compared against other steroids including PDN [74]. Combined cumulative corticosteroid dosage of DEX and PDN has been shown to impact ON incidence. However, variance within this calculation makes comparison of this data extremely complex, with included studies using a 1:5.5, 1:6 or 1:7 DEX to PDN equivalent dosage. In more recent protocols like the UKALL 2011 protocol, which is currently being evaluated (study period ending in 2027), DEX is given on alternative weeks to aid clearance, aiming to reduce ON incidence rates (Taylor, 2013).

This was the first review that followed systematic searching and reporting methodology resulting in an increased repeatability. Although there are several limitations to this study, within reported incidence rates there was no statistical weighting to studies based on cohort size. This review solely focussed on secondary impacts of treatment and failed to compare this to treatment efficacy, acting as a significant limitation as treatment efficacy must continue to be prioritised. Thirdly as date of publication was not used as an exclusion criterion, the generalisability of this review is limited secondary to the development/improvements to treatments. Finally, many studies who calculated OR of risk factors were excluded due to using < 10 years old as the reference, significantly reducing the cohort size within the narrative synthesis.

5. Conclusion

Future research is needed to investigate the efficacy of stratified treatment interventions, particularly in female patients of white ethnicity who have been found to be at increased risk of developing ON, to reduce the risk of ON through modifying steroid dose and treatment regimens. This study found a median incidence rate of ON in patients treated for ALL as 51.8% (IQR 41.4–58.9%) and 15.6% (IQR 9.2–24.2%) for asymptomatic and symptomatic patient screening respectively with female sex (assigned at birth) and patients of white ethnicity independently associated with being at higher risk of developing ON. This review has demonstrated the high heterogeneity within current research. Greater consensus within research methods would facilitate, systematic comparison and data synthesis between treatment protocols, to better identify risk factors thereby informing clinical practice to improve patient outcomes. Future research should be multidisciplinary in nature, extrapolating knowledge from other haematological disorders to inform practice, focusing on developing screening tools/methodologies to facilitate the implementation of adapted treatment methodologies to prevent and reduce the progression of ON.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

MC: Conception and design, data collection, data analysis, drafting, critical revision MT: Conception and design, data collection, data analysis and final approval of the version to be published. JW & MW: critical revision during the drafting process. RS: Supervision throughout the research process. All authors contributed to the article and approved the final submitted version.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2023.100121.

References

[1] O.O. Adesina, L.D. Neumayr, 'Osteonecrosis in sickle cell disease: an update on risk factors, diagnosis, and management', Hematology 2019 (1) (2019) 351–358, https://doi.org/10.1182/hematology.2019000038.

[2] C.M. Aguilar, L.D. Neumayr, B.E. Eggleston, A.N. Earles, S.M. Robertson, H. E. Jergesen, B.N. Stulberg, E.P. Vichinsky, 'Clinical evaluation of avascular necrosis in patients with sickle cell disease: children's Hospital Oakland Hip Evaluation Scale–a modification of the Harris Hip Score', Arch. Phys. Med. Rehabil. 86 (7) (2005) 1369–1375, https://doi.org/10.1016/j.apmr.2005.01.008.

[3] E.M. Alvarez, M. Malogolowkin, J.S. Hoch, Q. Li, A. Brunson, B.H. Pollock, L. Muffly, T. Wun, T.H.M. Keegan, Treatment complications and survival among children and young adults with acute lymphoblastic leukemia, JCO Oncol. Pract. 16 (10) (2020) e1120–e1133, https://doi.org/10.1200/JOP.19.00572.

[4] N.L. Amin, R. Feltbower, S. Kinsey, A. Vora, B. James, Osteonecrosis in patients with acute lymphoblastic leukaemia: a national questionnaire study, BMJ Paediatr. Open 1 (1) (2017), e000122.

[5] Y. Arakawa, S. Masutani, K. Oshima, Y. Mitani, M. Mori, K. Fukuoka, K. Moriwaki, M. Kato, K. Taira, Y. Tanami, A. Nakazawa, K. Koh, Asian population may have a lower incidence of hip osteonecrosis in childhood acute lymphoblastic leukemia, Int. J. Hematol. 114 (2) (2021) 271–279, https://doi.org/10.1007/s12185-021-03163-1.

[6] M. Aricò, M.F.P. Boccalatte, D. Silvestri, E. Barisone, C. Messina, R. Chiesa, N. Santoro, P. Tamaro, A. Lippi, D. Gallisai, G. Basso, G. De Rossi, Associazione Italiana di Ematologia ed Oncologia Pediatrica, Osteonecrosis: an emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia, Haematologica 88 (7) (2003) 747–753.

[7] H. Arksey, L. O'Malley, Scoping studies: towards a methodological framework, Int. J. Soc. Res. Methodol. 8 (1) (2005) 19–32, https://doi.org/10.1080/1364557032000119616.

[8] J.H. Badhiwala, U.H. Athale, T. Nayiager, The development of thromboembolism may increase the risk of osteonecrosis in children with acute lymphoblastic leukemia, Pediatr. Blood Cancer 62 (10) (2015) 1851–1854.

[9] J. Bartram, P. Veys, A. Vora, Improvements in outcome of childhood acute lymphoblastic leukaemia (ALL) in the UK – a success story of modern medicine through successive UKALL trials and international collaboration, Br. J. Haematol. 191 (4) (2020) 562–567, https://doi.org/10.1111/bjh.17162.

[10] G. Biddeci, E. Varotto, M.P. Boaro, S. Varotto, A. Marzollo, M. Gabelli, R. Assadi, G. Garetto, C. Gigante, G. Basso, M.C. Putti, Features of avascular osteonecrosis in children treated for acute lymphoblastic leukaemia: Experience in a single center, Blood 128 (22) (2016).

[11] B. Bürger, R. Beier, M. Zimmermann, J.D. Beck, A. Reiter, M. Schrappe, Osteonecrosis: a treatment related toxicity in childhood acute lymphoblastic leukemia (ALL)—experiences from trial ALL-BFM 95', Pediatr. Blood Cancer 44 (3) (2005) 220–225.

[12] Cancer Research UK (2021) *Acute lymphoblastic leukaemia (ALL) incidence statistics*, Cancer Research UK. Available at: ⟨https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence⟩ (Accessed: 25 March 2022).

[13] S.-H. Chen, T.-Y. Chang, T.-H. Jaing, M.S. Lee, C.-J. Wang, I.-J. Hung, C.-P. Yang, Incidence, risk factors, and treatment outcome of symptomatic osteonecrosis in Taiwanese children with acute lymphoblastic leukemia: a retrospective cohort study of 245 patients in a single institution, Int. J. Hematol. 102 (1) (2015) 41–47, https://doi.org/10.1007/s12185-015-1790-4.

[14] P.D. Cole, T.M. Blonquist, D.S. Neuberg, V. Vijayanathan, L.M. Vrooman, S. E. Sallan, L.B. Silverman, Y. Finkelstein, Homozygosity for the 2R tandem repeat polymorphism in the thymidylate synthase (TS) promoter is associated with increased risk for bony morbidity among children treated for acute lymphoblastic leukemia on DFCI protocol 05-001, Blood 126 (23) (2015) 251.

[15] DCTD, NCI, NIH, DHHS (2006) *'Common Terminology Criteria for Adverse Events (CTCAE)'*, Version 3.0. Available at: ⟨https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf⟩.

[16] M.A.H. den Hoed, S.M.F. Pluijm, M.L. te Winkel, I.M. van der Sluis, H.A. de Groot-Kruseman, J.A. Leeuw, M.C.A. Bruin, D. Bresters, A.J.P. Veerman, M.M. van den Heuvel-Eibrink, M. Fiocco, P. Hoogerbrugge, M.H. Lequin, J.C. Roos, R. Pieters, Aggravated bone density decline following symptomatic osteonecrosis in children with acute lymphoblastic leukemia, Haematologica 100 (12) (2015) 1564–1570.

[17] T. Eleanor, 'ISRCTN - ISRCTN64515327: United Kingdom trial for children and young adults with acute lymphoblastic leukaemia and lymphoma *2011'*, ISRCTN64515327, BMC ISRCTN Regist. (2011), https://doi.org/10.1186/ISRCTN64515327.

[18] A.M. Euser, C. Zoccali, K.J. Jager, F.W. Dekker, Cohort studies: prospective versus retrospective, Nephron Clin. Pract. 113 (3) (2009) c214–c217, https://doi.org/10.1159/000235241.

[19] Y. Finkelstein, T.M. Blonquist, K.E. Stevenson, D.S. Neuberg, L.B. Silverman, L. M. Vrooman, S.E. Sallan, V. Vijayanathan, P.D. Cole, A thymidylate synthase polymorphism is associated with increased risk for bone toxicity among children treated for acute lymphoblastic leukemia, Pediatr. Blood Cancer 64 (7) (2017).

[20] D. French, L.H. Hamilton, M.V. Relling, L.A. Mattano Jr., H.N. Sather, M. Devidas, J.B. Nachman, 'A PAI-1 (SERPINEI) polymorphism predicts osteonecrosis in children with acute lymphoblastic leukemia: a report from the children's oncology group', Blood 111 (9) (2008) 4496–4499.

[21] N.H. Golden, S.A. Abrams, Optimizing bone health in children and adolescents, Pediatrics 134 (4) (2014) e1229–e1243, https://doi.org/10.1542/peds.2014-2173.

[22] O.D. Gustafson, M.A. Williams, S. McKechnie, H. Dawes, M.J. Rowland, Musculoskeletal complications following critical illness: a scoping review, J. Crit. Care 66 (2021) 60–66, https://doi.org/10.1016/j.jcrc.2021.08.002.

[23] M.B. Heneghan, S.R. Rheingold, Y. Li, A.E. Seif, Y.-S. Huang, L. McLeod, L. Wells, B.T. Fisher, R. Aplenc, Treatment of Osteonecrosis in Children and Adolescents with Acute Lymphoblastic Leukemia, Clin. Lymphoma, Myeloma Leuk. 16 (4) (2016) 223–229.e2, https://doi.org/10.1016/j.clml.2015.12.009.

[24] N. Hyakuna, Y. Shimomura, A. Watanabe, T. Taga, A. Kikuta, T. Matsushita, K. Kogawa, C. Kawakami, Y. Horikoshi, T. Iwai, Y. Okamoto, M. Tsurusawa, K. Asami, Group (JCCLSG), for T.J.C.C. and L.S, Assessment of corticosteroid-induced osteonecrosis in children undergoing chemotherapy for acute lymphoblastic leukemia: a report from the Japanese childhood cancer and leukemia study group, J. Pediatr. Hematol. /Oncol. 36 (1) (2014) 22, https://doi.org/10.1097/MPH.0000000000000039.

[25] K Issa, R Pivec, BH Kapadia, S Banerjee, MA Mont, Osteonecrosis of the femoral head, Bone Joint J 95 (2013) 46–50, https://doi.org/10.1302/0301-620X.95B11.32644.

[26] L.C. Jones, S.C. Kaste, S.E. Karol, B. DeFeo, H.K.W. Kim, M.D. Neel, A.S. Levin, Team approach: management of osteonecrosis in children with acute lymphoblastic leukemia, Pediatr. Blood Cancer 67 (11) (2020), e28509, https://doi.org/10.1002/pbc.28509.

[27] J.M. Kahn, K.M. Kelly, P.D. Cole, T.M. Blonquist, K. Stevenson, D.S. Neuberg, Z. Jin, S. Barrera, R. Davila, E. Roberts, U.H. Athale, L.A. Clavell, C. Laverdiere, J.-M. Leclerc, B. Michon, M.A. Schorin, J.J.G. Welch, S.E. Sallan, L.B. Silverman, An investigation of toxicities and survival in Hispanic children and adolescents with ALL: results from the dana-farber cancer institute all consortium protocol 05-001, Pediatr. Blood Cancer 65 (3) (2018).

[28] J.S. Kang, K.H. Moon, D.G. Kwon, B.K. Shin, M.S. Woo, The natural history of asymptomatic osteonecrosis of the femoral head (Available at:), Int. Orthop. 37 (3) (2013) 379–384, https://doi.org/10.1007/s00264-013-1775-y.

[29] N. Karas-Kuzelicki, S. Mencej-Bedrac, J. Marc, I. Mlinaric-Rascan, J. Jazbec, Risk factors for symptomatic osteonecrosis in childhood ALL: a retrospective study of a Slovenian pediatric ALL population between 1970 and 2004, Exp. Ther. Med. 12 (2) (2016) 840–846.

[30] S.E. Karol, L.A. Mattano Jr, W. Yang, K.W. Maloney, C. Smith, C. Liu, L.B. Ramsey, C.A. Fernandez, T.Y. Chang, G. Neale, C. Cheng, E. Mardis, R. Fulton, P. Scheet, F. A. San Lucas, E.C. Larsen, M.L. Loh, E.A. Raetz, S.P. Hunger, M. Devidas, M. V. Relling, Genetic risk factors for the development of osteonecrosis in children under age 10 treated for acute lymphoblastic leukemia, Blood 127 (5) (2016) 558–564, https://doi.org/10.1182/blood-2015-10-673848.

[31] S.E. Karol, T.Y. Chang, S. Jeha, C.-H. Pui, W. Yang, C.A. Fernandez, C. Liu, C. Smith, W.E. Evans, M.V. Relling, S.L. Van Driest, S. Kaste, E. Bowton, M. Basford, L. Bastarache, J.C. Denny, D.M. Roden, E. Larsen, N. Winick, W. L. Carroll, C. Cheng, D. Pei, M.L. Loh, E.A. Raetz, S.P. Hunger, P. Scheet, M. Devidas, L.A. Mattano, Genetics of glucocorticoid-associated osteonecrosis in children with acute lymphoblastic leukemia, Blood 126 (15) (2015) 1770–1776.

[32] S.C. Kaste, D. Pei, C. Cheng, M.D. Neel, W.P. Bowman, R.C. Ribeiro, M.L. Metzger, D. Bhojwani, H. Inaba, P. Campbell, J.E. Rubnitz, S. Jeha, J.T. Sandlund, J. R. Downing, M.V. Relling, C.-H. Pui, S.C. Howard, Utility of early screening magnetic resonance imaging for extensive hip osteonecrosis in pediatric patients treated with glucocorticoids, J. Clin. Oncol. 33 (6) (2015) 610–615.

[33] U. Kaufmann, F. Lampert, '[Necrosis of the caput femoris in complete remission of lymphoblastic leukaemia (author's transl)]', Klin. Padiatr. 189 (8) (1977) 37–40.

[34] J.D. Kawedia, S.C. Kaste, D. Pei, J.C. Panetta, X. Cai, C. Cheng, G. Neale, S. C. Howard, W.E. Evans, C.-H. Pui, M.V. Relling, Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia, Blood 117 (8) (2011) 2340–2347.

[35] S. Kim, K. Stohr, Investigation of morphological predictors of avascular necrosis, Br. J. Haematol. 181 (2018) 118.

[36] K. Krull, M. Kunstreich, A. Kloetgen, A. Borkhardt, M. Kuhlen, J. Klasen-Sansone, D. Klee, F. Gruener, G. Escherich, K. Bleckmann, A. Moericke, M. Schrappe, N. Jorch, D. Steinbach, C.-F. Classen, A. Guggemos, R. Kolb, Osteonecrosis develops independently from radiological leukemic infiltration of bone in adolescents with acute lymphoblastic leukemia-first findings of the OPAL trial, Leuk. Lymphoma 58 (10) (2017) 2363–2369.

[37] M. Kuhlen, M. Kunstreich, N. Gökbuget, Osteonecrosis in adults with acute lymphoblastic leukemia: an unmet clinical need, HemaSphere 5 (4) (2021), e544, https://doi.org/10.1097/HS9.0000000000000544.

[38] M. Kuhlen, M.H. Albert, P. Bader, K. Ehlert, T. Guengoer, T. Klingebiel, P.J. Lang, M. Schrappe, J. Schrum, A.S. Schulz, A. Von Stackelberg, B. Strahm, K.-W. Sykora, I. Teichert-Von Luettichau, A. Borkhardt, R. Meisel, U. Poetschger, E. Glogova, C. Peters, 'Osteonecrosis after allogeneic hsct in children with high-risk or relapsed ALL treated in the ALL-SCT 2003 trial', Blood (2017) 130.

[39] M. Kunstreich, S. Kummer, H.-J. Laws, A. Borkhardt, M. Kuhlen, Osteonecrosis in children with acute lymphoblastic leukemia, Haematologica 101 (11) (2016) 1295–1305, https://doi.org/10.3324/haematol.2016.147595.

[40] C. Liu, L.J. Janke, J.D. Kawedia, L.B. Ramsey, X. Cai, L.A. Mattano, K.L. Boyd, A. J. Funk, M.V. Relling, Asparaginase potentiates glucocorticoid-induced osteonecrosis in a mouse model, PLoS ONE 11 (3) (2016), e0151433, https://doi.org/10.1371/journal.pone.0151433.

[41] L.H. Liu, Q.-Y. Zhang, W. Sun, Z.R. Li, F.-Q. Gao, Corticosteroid-induced osteonecrosis of the femoral head: detection, diagnosis, and treatment in earlier stages, Chin. Med. J. 130 (21) (2017) 2601–2607, https://doi.org/10.4103/0366-6999.217094.

[42] L. Lu, Y. Cai, X. Luo, Z. Wang, S.H. Fung, H. Jia, C.L. Yu, W.Y. Chan, K.K. Miu, W. Xiao, A core omnigenic non-coding trait governing dex-induced osteoporotic effects identified without DEXA, Front. Pharmacol. 12 (2021), 750959, https://doi.org/10.3389/fphar.2021.750959.

[43] L.S. Lynggaard, C.U. Rank, B. Als-Nielsen, S.G. Hoejfeldt, M. Heyman, K. Schmiegelow, B.K. Albertsen, PEG-asparaginase treatment for acute lymphoblastic leukaemia in children: a network meta-analysis, Cochrane Database Syst. Rev. [Prepr.] (6) (2021), https://doi.org/10.1002/14651858.CD014570.

[44] V.G. Marchese, B.H. Connolly, C. Able, A.R. Booten, P. Bowen, B.M. Porter, S. N. Rai, M.L. Hancock, C.-H. Pui, S. Howard, M.D. Neel, S.C. Kaste, Relationships among severity of osteonecrosis, pain, range of motion, and functional mobility in children, adolescents, and young adults with acute Lymphoblastic Leukemia, Phys. Ther. 88 (3) (2008) 341–350, https://doi.org/10.2522/ptj.20070108.

[45] A. Marks, M. Cortina-Borja, D. Maor, A. Hashemi-Nejad, A. Roposch, Patient-reported outcomes in young adults with osteonecrosis secondary to developmental dysplasia of the hip - a longitudinal and cross-sectional evaluation, BMC Musculoskelet. Disord. 22 (1) (2021), 42, https://doi.org/10.1186/s12891-020-03865-3.

[46] L.A. Mattano, H.N. Sather, M.E. Trigg, J.B. Nachman, Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the children's cancer group, J. Clin. Oncol. 18 (18) (2000) 3262–3272.

[47] L.A. Mattano, M. Devidas, J.B. Nachman, H.N. Sather, S.P. Hunger, P.G. Steinherz, P.S. Gaynon, N.L. Seibel, 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. 13 (9) (2012) 906–915.

[48] R. Mody, S. Li, D.C. Dover, S. Sallan, W. Leisenring, K.C. Oeffinger, Y. Yasui, L. L. Robison, J.P. Neglia, 'Twenty-five–year follow-up among survivors of Childhood Acute Lymphoblastic Leukemia: A report from the childhood cancer survivor study', Blood 111 (12) (2008) 5515–5523, https://doi.org/10.1182/blood-2007-10-117150.

[49] S.S. Mogensen, L.R. Helt, K. Schmiegelow, T.L. Frandsen, A. Harila-Saari, I. H. Myrberg, O. Makitie, R. Niinimaki, A. Vestli, S. Hafsteinsdottir, L. Griskevicius, K. Saks, H. Hallbook, J. Retpen, N. Toft, Comparing osteonecrosis clinical phenotype, timing, and risk factors in children and young adults treated for acute lymphoblastic leukemia, Pediatr. Blood Cancer 65 (10) (2018).

[50] A. Möricke, M. Zimmermann, M.G. Valsecchi, M. Stanulla, A. Biondi, G. Mann, F. Locatelli, G. Cazzaniga, F. Niggli, M. Aricò, C.R. Bartram, A. Attarbaschi, D. Silvestri, R. Beier, G. Basso, R. Ratei, A.E. Kulozik, L. Lo Nigro, B. Kremens, J. Greiner, R. Parasole, J. Harbott, R. Caruso, A. von Stackelberg, E. Barisone, C. Rössig, V. Conter, M. Schrappe, Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000 (Available at:), Blood 127 (17) (2016) 2101–2112, https://doi.org/10.1182/blood-2015-09-670729.

[51] K. Moriya, T. Imamura, S. Katayama, A. Kaino, K. Okamoto, N. Yokoyama, S. Uemura, H. Kitazawa, M. Sekimizu, H. Hiramatsu, I. Usami, H. Ishida, D. Hasegawa, A. Hama, A. Moriya-Saito, A. Sato, Y. Sasahara, S. Suenobu, K. Horibe, J. Hara, Group (JACLS), J.A. of C.L.S, The incidence of symptomatic osteonecrosis is similar between Japanese children and children in Western countries with acute lymphoblastic leukaemia treated with a Berlin-Frankfurt-Münster (BFM)95-based protocol (Available at:), Br. J. Haematol. 196 (5) (2022) 1257–1261, https://doi.org/10.1111/bjh.17988.

[52] Z. Munn, M.D.J. Peters, C. Stern, C. Tufanaru, A. McArthur, E. Aromataris, Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach, BMC Med. Res. Methodol. 18 (1) (2018), 143, https://doi.org/10.1186/s12874-018-0611-x.

[53] J.B. Nachman, 'Adolescents with acute lymphoblastic leukemia: a new "age"', Rev. Clin. Exp. Hematol. 7 (3) (2003) 261–269.

[54] Z.A. Naseer, M. Bachabi, L.C. Jones, R.S. Sterling, H.S. Khanuja, Osteonecrosis in Sickle Cell Disease, South. Med. J. 109 (9) (2016) 525–530, https://doi.org/10.14423/SMJ.0000000000000516.

[55] H. Nozaki, K. Matsubara, S. Mori, Osteonecroses of the bilateral tali during maintenance therapy in a child with acute lymphoblastic leukemia, Jpn. J. Clin. Hematol. 47 (2) (2006) 106–110.

[56] P.A. Ospina, M.L. McNeely, A scoping review of physical therapy interventions for childhood cancers, Physiother. Can. 71 (3) (2019) 287–296, https://doi.org/10.3138/ptc.2018-13.pp.

[57] M. Ouzzani, H. Hammady, Z. Fedorowicz, A. Elmagarmid, Rayyan—a web and mobile app for systematic reviews, Syst. Rev. 5 (1) (2016), https://doi.org/10.1186/s13643-016-0384-4.

[58] B. Padhye, L. Dalla-Pozza, D. Little, C. Munns, Incidence and outcome of osteonecrosis in children and adolescents after intensive therapy for acute lymphoblastic leukemia (ALL)', Cancer Med. 5 (5) (2016) 960–967.
[59] J.M. Peppercorn, J.C. Weeks, E.F. Cook, S. Joffe, Comparison of outcomes in cancer patients treated within and outside clinical trials: Conceptual Framework and Structured Review, The Lancet 363 (9405) (2004) 263–270, https://doi.org/10.1016/s0140-6736(03)15383-4.
[60] M.D.J. Peters, C.M. Godfrey, P. McInerney, C.B. Soares, H. Khalil, D. Parker (2015) *'Joanna Briggs Institute Reviewers' Manual: 2015 edition / Supplement'*, The Joanna Briggs Institute [Preprint]. Available at: ⟨https://nursing.lsuhsc.edu/JBI/docs/ReviewersManuals/Scoping-.pdf⟩ (Accessed: 22 March 2022).
[61] J. Popay, H. Roberts, A. Sowden, M. Petticrew, L. Arai, Guidance on the conduct of narrative synthesis in systematic reviews, A Prod. ESRC Methods Program. Version 1 (b92) (2006) (Available at), ⟨https://www.lancaster.ac.uk/media/lancaster-university/content-assets/documents/fhm/dhr/chir/NSsynthesisguidanceVersion1-April2006.pdf⟩.
[62] J. Reid, J. Unger, D. McCaskell, L. Childerhose, D. Zorko, M. Kho, Physical rehabilitation interventions in the intensive care unit: a scoping review of 117 studies, J. Intensive Care 6 (1) (2018).
[63] M.V. Relling, W. Yang, S. Das, E.H. Cook, G.L. Rosner, M. Neel, S. Howard, R. Ribeiro, J.T. Sandlund, C.-H. Pui, S.C. Kaste, Pharmacogenetic risk factors for osteonecrosis of the hip among children with leukemia, J. Clin. Oncol. 22 (19) (2004) 3930–3936.
[64] A. Rhodes, J. Gray, N. Harvey, J.H. Davies, R.O.C. Oreffo, I. Reading, N.M. P. Clarke, A. Aarvold, Osteonecrosis following treatment for childhood acute lymphoblastic leukaemia: the Southampton Children's Hospital experience, J. children's Orthop. 11 (6) (2017) 440–447.
[65] L.L. Robison, Late effects of acute lymphoblastic leukemia therapy in patients diagnosed at 0-20 years of age, Hematology 2011 (1) (2011) 238–242, https://doi.org/10.1182/asheducation-2011.1.238.
[66] M. Rodgers, A. Sowden, M. Petticrew, L. Arai, H. Roberts, N. Britten, J. Popay, Testing methodological guidance on the conduct of narrative synthesis in systematic reviews: effectiveness of interventions to promote smoke alarm ownership and function, Evaluation 15 (1) (2009) 49–73, https://doi.org/10.1177/1356389008097871.
[67] K. Sakamoto, T. Imamura, K. Kihira, K. Suzuki, H. Ishida, H. Morita, M. Kanno, T. Mori, H. Hiramatsu, K. Matsubara, K. Terui, Y. Takahashi, S. Suenobu, D. Hasegawa, Y. Kosaka, K. Kato, A. Moriya-Saito, A. Sato, H. Kawasaki, K. Yumura-Yagi, J. Hara, H. Hori, K. Horibe, Low incidence of osteonecrosis in childhood acute lymphoblastic leukemia treated with ALL-97 and ALL-02 study of Japan association of childhood leukemia study group, J. Clin. Oncol. 36 (9) (2018) 900–907, https://doi.org/10.1200/JCO.2017.75.5066.
[68] M. Schrappe, A. Möricke, A. Reiter, G. Henze, K. Welte, H. Gadner, W.-D. Ludwig, J. Ritter, J. Harbott, G. Mann, T. Klingebiel, B. Gruhn, C. Niemeyer, B. Kremens, F. Niggli, K.-M. Debatin, R. Ratei, M. Stanulla, R. Beier, G. Cario, A. Schrauder, M. Zimmermann, Key treatment questions in childhood acute lymphoblastic leukemia: results in 5 consecutive trials performed by the ALL-BFM study group From 1981 to 2000, Klin. Pädiatrie 225 (S 1) (2013) S62–S72, https://doi.org/10.1055/s-0033-1337966.
[69] K.F. Schulz, D.G. Altman, D. Moher, CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials, Ann. Intern. Med. 152 (11) (2010) 726–732, https://doi.org/10.7326/0003-4819-152-11-201006010-00232.
[70] A. Sharma, N.T. Minh Duc, T. Luu Lam Thang, N.H. Nam, S.J. Ng, K.S. Abbas, N. T. Huy, A. Marušić, C.L. Paul, J. Kwok, J. Karbwang, C. de Waure, F.J. Drummond, Y. Kizawa, E. Taal, J. Vermeulen, G.H.M. Lee, A. Gyedu, K.G. To, M.L. Verra, É. M. Jacqz-Aigrain, W.K.G. Leclercq, S.T. Salminen, C.D. Sherbourne, B. Mintzes, S. Lozano, U.S. Tran, M. Matsui, M. Karamouzian, A consensus-based checklist for reporting of survey studies (CROSS*)'*, J. Gen. Intern. Med. 36 (10) (2021) 3179–3187, https://doi.org/10.1007/s11606-021-06737-1.
[71] L. Smith, A.W. Glaser, S.E. Kinsey, D.C. Greenwood, L. Chilton, A.V. Moorman, R. G. Feltbower, Long-term survival after childhood acute lymphoblastic leukaemia: population-based trends in cure and relapse by clinical characteristics, Br. J. Haematol. 182 (6) (2018) 851–858, https://doi.org/10.1111/bjh.15424.
[72] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries (Available at:), CA: A Cancer J. Clin. 71 (3) (2021) 209–249, https://doi.org/10.3322/caac.21660.
[73] M.L. te Winkel, R. Pieters, E-J.D. Wind, J.H.J.M. Bessems, M.M. van den Heuvel-Eibrink, Management and treatment of osteonecrosis in children and adolescents with acute lymphoblastic leukemia (Available at:), Haematologica 99 (3) (2014) 430–436, https://doi.org/10.3324/haematol.2013.095562.
[74] O. Teuffel, S.P. Kuster, S.P. Hunger, V. Conter, J. Hitzler, M.-C. Ethier, P.S. Shah, J. Beyene, L. Sung, Dexamethasone versus prednisone for induction therapy in childhood acute lymphoblastic leukemia: a systematic review and meta-analysis, Leukemia 25 (8) (2011) 1232–1238, https://doi.org/10.1038/leu.2011.84.
[75] N. Toft, H. Birgens, T.W. Klausen, J. Abrahamsson, L. Griskevicius, H. Hallbook, M. Heyman, O.G. Jonsson, K. Palk, K. Pruunsild, P. Quist-Paulsen, G. Vaitkeviciene, K. Vettenranta, A. Asberg, L.R. Helt, T. Frandsen, K. Schmiegelow, Toxicity profile and treatment delays in NOPHO ALL2008-comparing adults and children with Philadelphia chromosome-negative acute lymphoblastic leukemia, Eur. J. Haematol. 96 (2) (2016) 160–169.
[76] N. Toft, H. Birgens, T.W. Klausen, J. Abrahamsson, L. Griskevic Ius, H. Hallbook, M. Heyman, O. Jonsson, K. Palk, K. Pruunsild, P. Quist-Paulsen, G. Vaitkeviciene, K. Vettenranta, A. Asberg, T.L. Frandsen, K. Schmiegelow, H.V. Marquart, H. O. Madsen, U. Noren-Nystrom, Results of NOPHO ALL2008 treatment for patients aged 1-45 years with acute lymphoblastic leukemia, Leukemia 32 (3) (2018) 606–615.
[77] A.C. Tricco, E. Lillie, W. Zarin, K.K. O'Brien, H. Colquhoun, D. Levac, D. Moher, M. D.J. Peters, T. Horsley, L. Weeks, S. Hempel, E.A. Akl, C. Chang, J. McGowan, L. Stewart, L. Hartling, A. Aldcroft, M.G. Wilson, C. Garritty, S. Lewin, C. M. Godfrey, M.T. Macdonald, E.V. Langlois, K. Soares-Weiser, J. Moriarty, T. Clifford, Ö. Tunçalp, S.E. Straus, PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation, Ann. Intern. Med. 169 (7) (2018) 467–473, https://doi.org/10.7326/M18-0850.
[78] J.E. van Atteveld, H.A. de Groot-Kruseman, M. Fiocco, M.H. Lequin, S.J.C.M. M. Neggers, S.M.F. Pluijm, I.M. van der Sluis, R. Pieters, M.M. van den Heuvel-Eibrink, Effect of post-consolidation regimen on symptomatic osteonecrosis in three DCOG acute lymphoblastic leukemia protocols, Haematologica 106 (4) (2021) 1198–1201, https://doi.org/10.3324/haematol.2020.257550.
[79] J.P. Vandenbroucke, E. von Elm, D.G. Altman, P.C. Gøtzsche, C.D. Mulrow, S. J. Pocock, C. Poole, J.J. Schlesselman, M. Egger, Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration, PLoS Med. 4 (10) (2007), e297, https://doi.org/10.1371/journal.pmed.0040297.
[80] G.E. Vist, D. Bryant, L. Somerville, T. Birminghem, A.D. Oxman, Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate, Cochrane Database Syst. Rev. [Prepr.] 3 (2008), https://doi.org/10.1002/14651858.MR000009.pub4.
[81] E. von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gøtzsche, J. P. Vandenbroucke, The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies, Lancet (Lond., Engl.) 370 (9596) (2007) 1453–1457, https://doi.org/10.1016/S0140-6736(07)61602-X.
[82] A. Vora, Management of osteonecrosis in children and young adults with acute lymphoblastic leukaemia, Br. J. Haematol. 155 (5) (2011) 549–560, https://doi.org/10.1111/j.1365-2141.2011.08871.x.
[83] L.M. Vrooman, K.E. Stevenson, J. O'Brien, S.E. Dahlberg, D.S. Neuberg, S.E. Sallan, L.B. Silverman, J.G. Supko, J.L. Kutok, B.L. Asselin, K.M. Kelly, L.A. Clavell, S. E. Lipshultz, M. Schorin, M.V. Relling, H.J. Cohen, U.H. Athale, C. Laverdiere, B. Michon, Postinduction dexamethasone and individualized dosing of Escherichia coli l-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: Results from a randomized study - Dana-Farber Cancer Institute ALL Consortium Protocol 00-01', J. Clin. Oncol. 31 (9) (2013) 1202–1210.
[84] L. Yang, J.C. Panetta, X. Cai, W. Yang, D. Pei, C. Cheng, N. Kornegay, C.-H. Pui, M. V. Relling, Asparaginase may influence dexamethasone pharmacokinetics in acute Lymphoblastic Leukemia, J. Clin. Oncol. 26 (12) (2008) 1932–1939, https://doi.org/10.1200/JCO.2007.13.8404.