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Systematic Review and Meta-Analysis of the Proportion of Pediatric Acute Lymphoblastic Leukemia (ALL) Cases that Develop Osteonecrosis

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer and accounts for roughly 30% of malignancies in the pediatric population[9]. Despite the relatively high occurrence of ALL in the pediatric population, outcomes are favorable with an overall survival rate reported as high as 90%[10, 11, 18, 22, 23]. Advances in chemotherapeutic agents in combination with risk stratification by disease burden, greater accessibility to supportive care, and ongoing clinical and laboratory investigations are largely credited for these improvements. Due to the various challenges and toxicities associated with medical management of ALL, there is currently no standard treatment protocol. Instead, several treatment protocols exist and are under continuous clinical investigation for evaluation of their efficacy and toxicity profiles. A common factor among treatment protocols is medical management that is based largely on the risk of disease burden as determined by various clinical and laboratory findings. Information including immunophenotype, cytogenic analysis, patient age, white blood cell (WBC) count at time of diagnosis, and response to initial therapy can be used to stratify patients by risk[9]. Intuitively the higher risk of disease burden requires a more aggressive treatment protocol to eradicate disease whereas a lower risk disease burden requires a less aggressive protocol and reduces the risk of treatment related toxicity. Regardless of risk stratification, however, the ultimate goal of medical management for ALL is to maximize survival while minimizing medication related toxicities impairing quality of life. It is reported that roughly 75-80% of children diagnosed with ALL are enrolled into an ongoing clinical trial aim at achieving these treatment related goals[9].

Although advances in medical management of ALL have improved survival rates, debilitating side effects of anti-leukemic treatment may result in significant consequences

regarding quality of life. Of these side effects, one of the most significant and debilitating is osteonecrosis (ON)[11, 22, 23]. ON is also referred to as "avascular necrosis" or "aseptic necrosis" and can be defined as the death of bone tissue resulting from the loss or disruption of vascular supply. The presentation of ON is variable and can range from asymptomatic to debilitating with severe pain in the affected limb due to degenerative changes. This adverse effect of management can lead to loss or restricted motion and reduced quality of life. Management of this condition remains difficult with the primary goal of treatment aimed at preserving the native joint. Currently, treatment can include bed-rest, supportive care, non-weight bearing on the affected extremity, physical therapy exercises, and in some cases surgical intervention. Despite the various non-operative measures, failure to diagnosis ON in early stages may lead to bone collapse often requiring joint replacement even at young ages. Due to these reasons clinicians need a high-index of suspicion to monitor those with high risk for disease development.

In the pediatric ALL population, development of ON is not completely understood. Currently, corticosteroid induced ischemia is largely hypothesized to be a contributing factor to the development of ON[11]. Additionally, the current literature reports multiple risk factors for the development of ON to varying degrees. Some of these reported risk factors include female gender, age $\geq$ 10 at time of ALL diagnosis, dexamethasone use, and increased dosages of corticosteroid during induction and delayed intensification phases of medical management[11, 22]. Despite these associated risk factors, variability in reported rates of ON exist among studies with overall incidence rates ranging from <1-17% in study populations[14, 22, 23].

Objective

The purpose of this project was to systematically review the current literature and to report a pooled analysis on the rates of ON following anti-leukemic treatment in the pediatric population. Analysis of the current literature was aimed at recognizing any relation between ON development and patient age at time of ALL diagnosis, gender of patient, aggressiveness of medical therapy utilized, and to identify any other factors related to the development of ON.

Hypothesis

In pediatric patients receiving medical management for ALL, rates of osteonecrosis will vary with an increased risk associated with female gender, age $\geq$ 10 years at time of ALL diagnosis, and increased aggressiveness of medical management as determined by protocol specific ALL risk stratification.

Methods

A single investigator (JMA) conducted a search of the PubMed database on January 26, 2017 using the search terms "(Leukemia or Cancer or steroids) AND (AVN or avascular necrosis or osteonecrosis) AND (pediatric or childhood or children)". The search was limited to articles published in English. To increase thoroughness, this search was augmented with searches of the Scopus and Cochrane databases on March 28, 2017 using identical search terms and limits. Studies were included if they reported on rates of clinically symptomatic ON throughout the entirety of treatment in ALL patient populations $\leq$ 18 years of age. Exclusion criteria included Level V evidence, laboratory studies, radiographic studies, systematic reviews, clinical development trials, and studies reporting preliminary results.

Studies meeting all inclusion criteria were reviewed individually and the following data was extracted: year of publication, study design, enrollment time period, geographical location,

number of enrolled patients (total, male, and female), mean age at ALL diagnosis, treatment protocol, total number and incidence rates of ON development (total, male, and female), number and incidence rates of ON in patients $\geq$ 10 years at time of ALL diagnosis, number and incidence of ON in patients < 10 years at time of ALL diagnosis, mean age of ALL diagnosis for patients who developed ON, mean duration of time from ALL diagnosis and development of ON, number and incidence of ON development based on disease risk stratification, number and incidence of ON development based on immunophenotype, anatomical location of ON, and mean number of joints affected per patient.

Search Results

The search resulted in 764 cumulative citations (Figure 1). Of these citations, 117 were immediately excluded as they were determined to be duplicate studies. The titles of the remaining 647 citations were reviewed and 375 studies were excluded based on the manuscript title being obviously unrelated to this review. Abstracts were then reviewed for the remaining 272 citations which resulted in an additional 160 articles excluded. The final 112 citations were reviewed in their entirety which resulted in 86 additional exclusions based on the manuscript. The final number of studies meeting inclusion criteria for this systematic review and meta-analysis was 26. Each manuscript was reviewed individually and data for each was extracted as described in the methods section. After review of the 26 articles it was determined that two of the included studies were published by the same author, under the same treatment protocol, in the same geographical region, and during overlying time periods. Therefore, it was determined that the two studies reported on identical patient populations and data from the most recently published article was used for this review as to not duplicate patient outcomes. This exclusion resulted in a total of 25 studies included in this review (Tables 1-4).

Statistics

A meta-analysis was conducted on the pooled proportions of symptomatic ON in the included studies. A random effects model was used to calculate the pooled estimated proportions and 95% confidence intervals (CI). Heterogeneity between the studies was quantified with the I^2 statistic. Separate forest plots were generated to explore the rates of ON in various subgroups including gender, age (<10 years vs. $\geq$ 10 years), and risk of disease burden of ALL. These included proportional estimates for each subgroup as well as the risk ratio between the subgroups. Meta-regression was used to explore the effect of time (based on date of manuscript publication) and geographical location (all other countries versus European countries) on the proportion of symptomatic ON. The alpha level of all statistics was set at 0.05. All statistical analysis was performed using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Statistical Results

The 25 included studies reported on 14,043 children treated for ALL and revealed a total of 509 cases of ON accounting for a pooled incidence rate of 4.4% (CI 3.5 – 5.3%, Figure 2). The mean age of ALL diagnosis for those who developed ON was reported in 20 studies and resulted in a pooled mean of 12.46 years. The mean onset of timing from ALL diagnosis to clinical diagnosis of ON was reported in 19 studies with a pooled mean of 16.58 months.

Female versus Male Gender

The included studies reported on 5987 male and 4612 female patients with the greater proportion of ON presenting in females compared to males (6.6%, CI 4.4 – 9.3% compared to 4.2%, CI 2.5 – 6.3%; Figure 3). Further statistical analysis of these studies revealed increased

relative risk for patients of female gender compared to male gender in the development of ON (RR 1.56, CI 1.28 – 1.90; Figure 4).

Age < 10 Years versus Age ≥ 10 Years at ALL Diagnosis

Twenty of the included studies reported ON rates specific to age ≥ 10 years compared to age < 10 years at time of ALL diagnosis. Cumulatively, 750 patients diagnosed at age ≥ 10 years were compared to 2573 patients at age < 10 years at time of ALL diagnosis. The greater proportion of ON occurred in patients aged ≥ 10 years compared to aged < 10 years at time of ALL diagnosis (13.5%, CI 9.3 – 18.3% compared to 1.2%, CI 0.5 – 2.1%; Figure 5). Further statistical analysis of these studies revealed increased risk for patients aged ≥ 10 years at time of ALL diagnosis as compared to those < 10 years of age at time of ALL diagnosis in the development of ON (RR. 9.35, CI 5.67 – 15.43; Figure 6).

Risk of Disease Burden

Nineteen studies reported on the rates of ON by disease risk stratification as determined by treatment protocol. Statistical analysis was conducted by pooling data from "low" to "medium" risk (or equivalent) versus "high" to "very high" risk. Cumulatively, 155 patients were classified as "low" to "medium" risk while 247 were categorized as "high" or "very high" risk. The greater proportion of ON occurred in high risk disease burden compared to low risk disease burden (7.5%, CI 5.2 – 10.1% compared to 2.9%, CI 1.5 – 4.8%; Figure 7). Further statistical analysis of these studies revealed increased risk for patients stratified as "high" or "very high" risk as compared to "low" or "medium" risk in the development of ON (RR 2.16, CI 1.47 – 3.18; Figure 8).

Immunophenotype

Only 8 of the included studies reported on the rates of ON development based on immunophenotype. Pooling of this data resulted in 128 patients classified as B-cell leukemia while 36 were categorized as T-cell leukemia with the greater proportion of ON occurring in T-cell versus B-cell (5.88% compared to 4.76%).

Affected Limbs

Eighteen studies reported on the specific limb(s) affected by ON per patient. Overall, the studies reported on 399 patients who developed 994 clinically symptomatic cases of ON (mean, 2.66 affected limbs per patient). Based on the specific limb(s) involved, ON developed in the hip/femoral head (337), knee (309), foot/ankle (162), shoulder/scapula (79), elbow (44), femur (28), tibia (19), and wrist/hand (16).

Meta-Regression Analysis

Meta-regression was conducted on rates of ON over time (0.0129 increase per year, $p = 0.159$; Figure 9) and rates of ON based on geographic location of study (0.0027 increase in European countries, $p = 0.876$; Figure 10).

Discussion

The goal of this systematic review with meta-analysis was to consolidate the available literature in order to report on overall incidence rates and risk factors for the development of ON in pediatric patients being medically managed for ALL. The search criteria and multiple databases were specifically chosen in an attempt to be as comprehensive as possible. Although previous studies have already reported associations between risk of ON development and female gender, age $\geq$ 10 years at time of ALL diagnosis, and increased corticosteroid use there is

currently no wide-ranging systematic review with meta-analysis to investigate these associations in totality and to report on the pooled results of these studies. To the best of the authors' knowledge, this investigation is the first to do so.

Overall, the cumulative proportion of symptomatic ON development in this patient population was determined to be 4.4% (CI 3.4 – 5.3%). This investigation reported on the cumulative incidence in an aggregated pool of 14,043 patients and, to the best of the authors' knowledge, is the most inclusive report on rates of ON in the pediatric population. Of the included studies the number of included patients ranged from 109 in the investigation by Hogler et al.[8] to 1,951 in the investigation reported by Burger et al.[4] In addition, rates of ON from the included studies ranged from just 0.81% in the investigation by Madadi et al[16] to 17.74% in the investigation reported by Kuhlen et al.[14] This wide variation across studies is similarly cited in the literature and is precisely the reason the efforts of this meta-analysis were necessary. All four studies were conducted between the years 2005-2014 and reported on clinically symptomatic development of ON that was confirmed radiographically. Although all studies used different treatment protocols, all protocols utilized corticosteroids and stratified patients by risk to determine specific treatment pathways within the protocols. The variance among incidence rates may be due to random chance between studies or may be related to other risk factors that were not investigated in this review.

From the pooled analysis of the 25 included studies, our results support the current literature as we report increased risk for female gender and those $\geq$ 10 years of age at time of ALL diagnosis. In regards to gender, 229 females were found to have developed symptomatic ON attributing to an accumulative incidence rate of 6.6% (CI 4.4 – 9.3%) as compared to 191 males attributing to an accumulative incidence rate of 4.2% (CI 2.5 – 6.3%). From this it was

determined that females have a 1.56 RR (CI 1.28 – 1.90) of developing symptomatic ON as compared to males. In regards to age, 339 patients aged ≥ 10 at time of ALL diagnosis were found to have developed symptomatic ON attributing to an accumulative incidence rate of 13.5% (CI 9.3 – 18.3%) as compared to 79 patients aged < 10 at time of ALL diagnosis attributing to an accumulative incidence rate of only 1.2% (CI 0.5% - 2.1%). From this it was determined that those aged ≥ 10 years at time of ALL diagnosis have a 9.35 RR (CI 5.67 – 15.43) of developing symptomatic ON as compared to those < 10 years at time of ALL diagnosis. The risk attributed to age was the greatest risk factor associated with the development of symptomatic ON revealed in this investigation. The association between female gender and age ≥ 10 at time of ALL diagnosis with the development of ON is well reported in the literature, however complete understanding of the pathophysiological mechanisms behind these relationships has not been fully understood. Possible mechanisms behind these associations may include hormones, timing of skeletal development, and genetic predispositions which may become the basis for future investigations.

In regards to chemotherapeutic agent and corticosteroid use, this meta-analysis utilized risk stratification as determined by the treatment protocol as a surrogate for level of aggressiveness in medicinal treatment. Essentially, the treatment protocols described in each manuscript were extremely detailed with various clinical and laboratory variables used to determine the appropriate course of treatment. In addition, determining the dosage and frequency of medication administration to each patient was essentially impossible unless it was specifically reported by the investigators. Part of the reason for this difficulty is that the stratification of patients is not only based on clinical and laboratory values at the time of ALL diagnosis, but can also be changed based on initial response to therapy. Even patients within the same stratification

group within an identical study protocol may have been exposed to varying dosages and frequencies of medications. Therefore, based on the variability between protocols and extreme detail within protocol without specific reporting of dosage and frequency of medication administration it was not plausible to compare studies and draw overall conclusions based on specific drug therapy. Consequently, it was decided to use level of risk stratification as a surrogate for aggressiveness of treatment. The theory behind this decision was that regardless of protocol utilized, the aggressiveness of medical treatment as determined by dosage, frequency, and drug utilized is correlated with risk (i.e., the higher the risk stratification the more aggressive the medical treatment of the disease). Based on this, patients were classified into "high" or "very high" risk versus "low" or "medium" risk for comparison. From the pooled analysis those with higher risk of disease burden were found to have an overall incidence of 7.5% (CI 5.2 – 10.1%) as compared to those determined to be "low" or "medium" risk who suffered an incidence rate of 2.9% (CI 1.5 – 4.8%). From this it was determined that those with higher risk of disease burden had a 2.16 RR (CI 1.47 – 3.18) of developing symptomatic ON as compared to those with low risk of disease burden. From these results, this study supports the theory that more aggressive medical management is associated with higher proportions of symptomatic ON development.

In an attempt to determine if the rates of symptomatic ON are related to time or geographic location of the patient population a meta-regression analysis was performed. When evaluating rates of ON over time, analysis revealed a 0.0129 increase per year ($p = 0.159$) based on the included studies. A potential reason for this increase could be an association between ON development and the correlated improvement in patient survival. In other words, the rates of ON may be slightly increasing as the rates of survival increase due to various factors such as extended exposure to medical therapy and more prolonged follow-up for survivors. In regards to

meta-regression of geographical location all other countries were compared to European countries with a 0.0027 increase (p = 0.876) in European studies. There does not appear to be a significant effect of ON rates based on this evaluation.

Finally, this investigation found that of the 20 studies that reported on limb involvement there was a mean of 2.66 limbs affected per patient presenting with symptomatic ON. This is important for a clinician to consider as it appears that the individuals who develop symptomatic ON may be at risk in multiple sites. This could lead a clinician to consider radiographically screening other limbs of an affected patient to rule out involvement in asymptomatic sites. Additionally, the most commonly affect joints/limbs were the hip or proximal femur (348), knee (323), and foot/ankle (169) which is consistent with the current literature. The weight bearing joints of the body appear to be more commonly affected in patients which may be the result of increased strain and trauma to these joints and also may be in part due to the increased likelihood of complaining of pain in these joints

Study Limitations

The greatest limitation to this systematic review and meta-analysis is the variability in treatment protocol used during treatment. The variability between study protocols, lack of reported detail on dosage and frequency of medicinal administration in investigations, and re-stratification of disease and treatment based on initial response made it extremely difficult to extract information for caparison of drug, dosage, and frequency of administration. In addition, this review and meta-analysis was specific to clinically symptomatic pain which was confirmed radiographically to be ON. Due to the fact that ON can present with varying degree of pain, this

analysis may underestimate the true rate of ON in this population as all studies reporting on screening or preventative measures for diagnosis of asymptomatic ON were excluded.

Conclusions and Future Work

Based on analysis of the current literature, ON as an adverse effect of pediatric ALL treatment occurs in 4.4% of patients with increased risk in females, those $\geq$ 10 years at diagnosis, and those with high risk disease burden which is correlated with more aggressive medicinal treatment. Further investigations into this subject should be focused on determining any association between cumulative dosages of medical therapies and the development of ON. In addition, due to the importance of early diagnosis in patients with ON further investigations into preventative screening modalities for cases of asymptomatic ON in susceptible populations are necessary. The benefits of screening for asymptomatic cases of ON need to be weighed against the financial implications of conducting screening tests and, more importantly, against the risks involved in exposing young children to radiation.

Figures and Tables

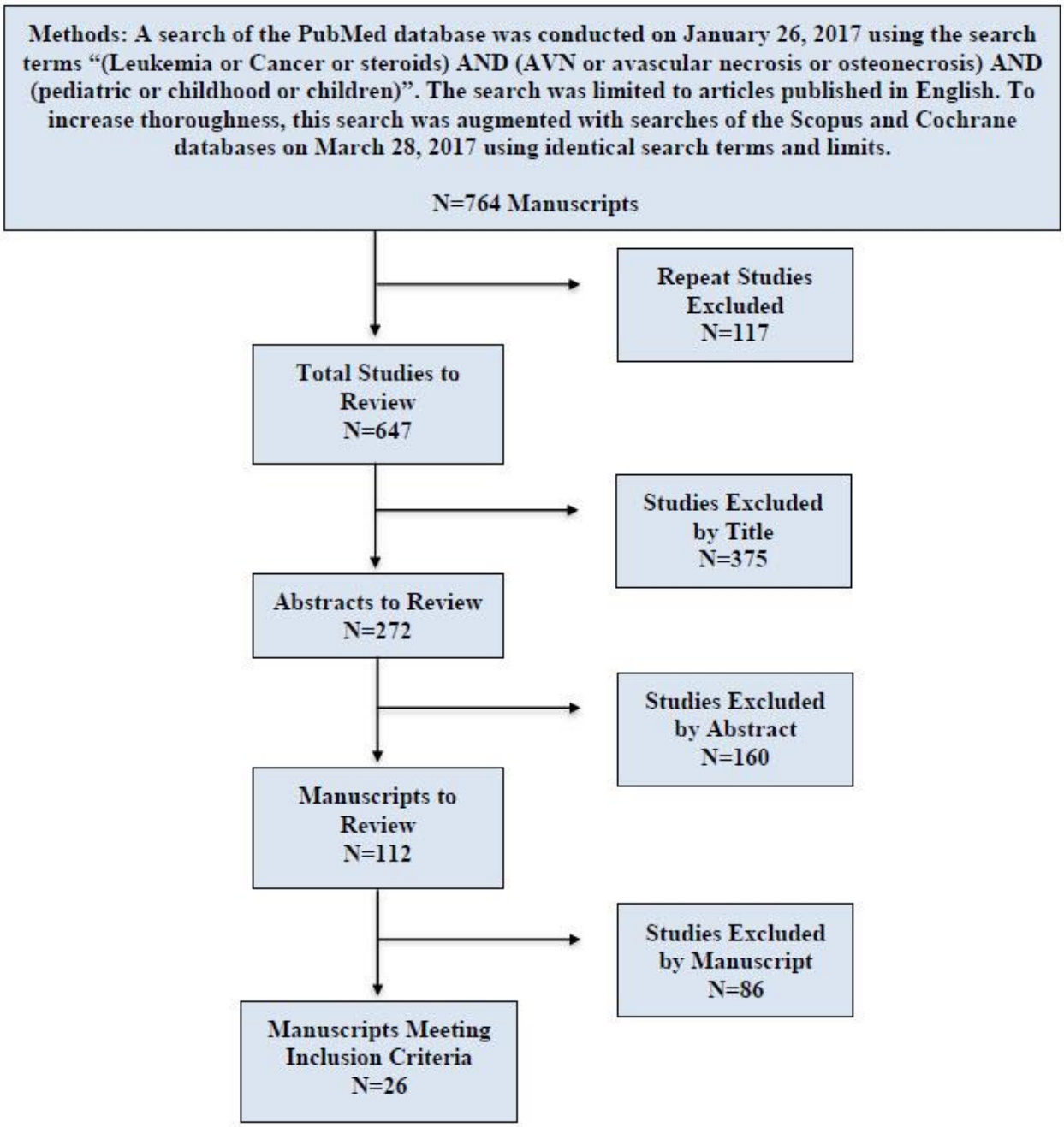

Figure 1: Flow dagram for enrollement of eligibile studies.

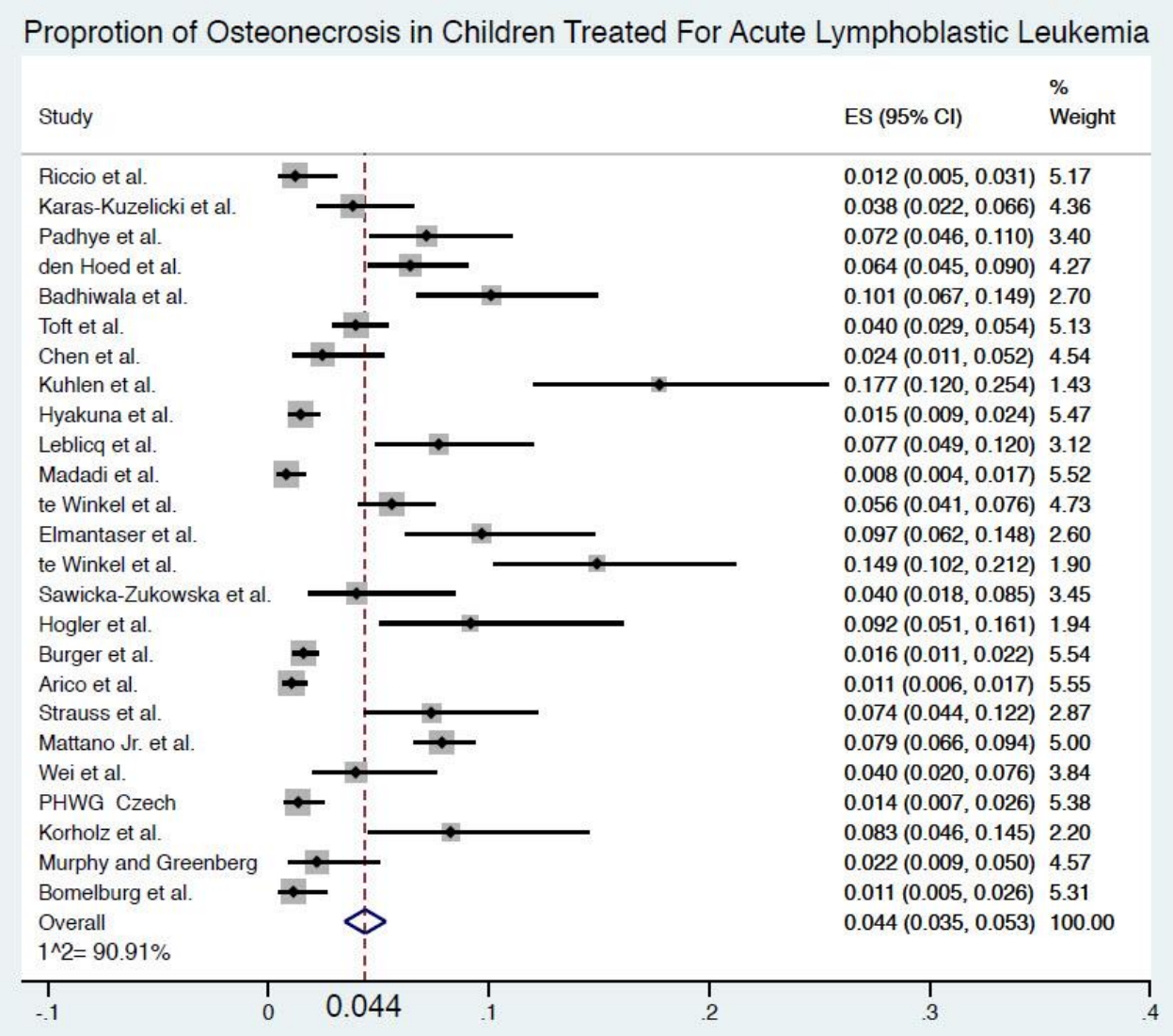

Figure 2: Forest plot for cumulative proportion of ON development in children treated for ALL in included studies.

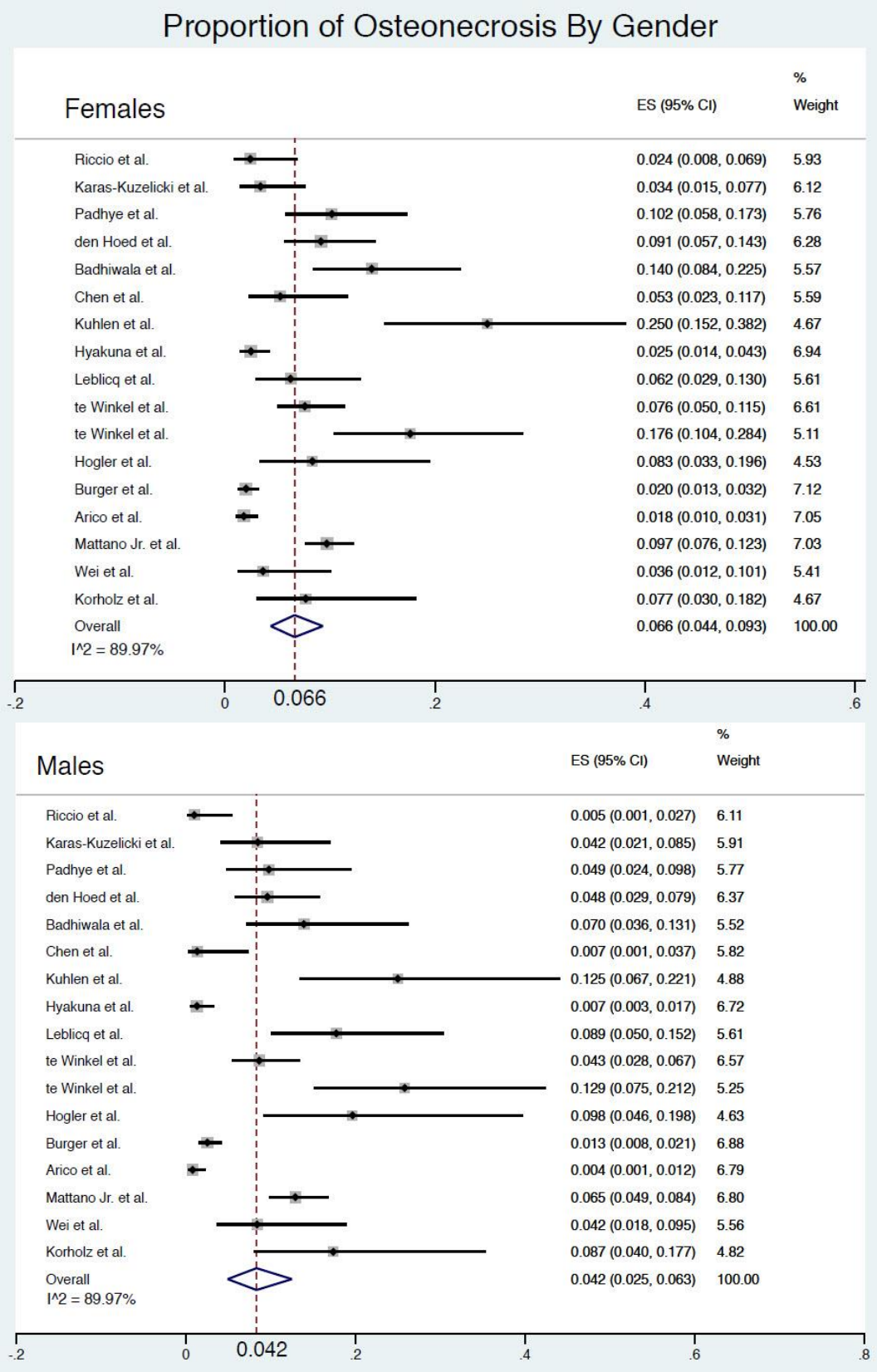

Figure 3: Proportion of ON based on gender.

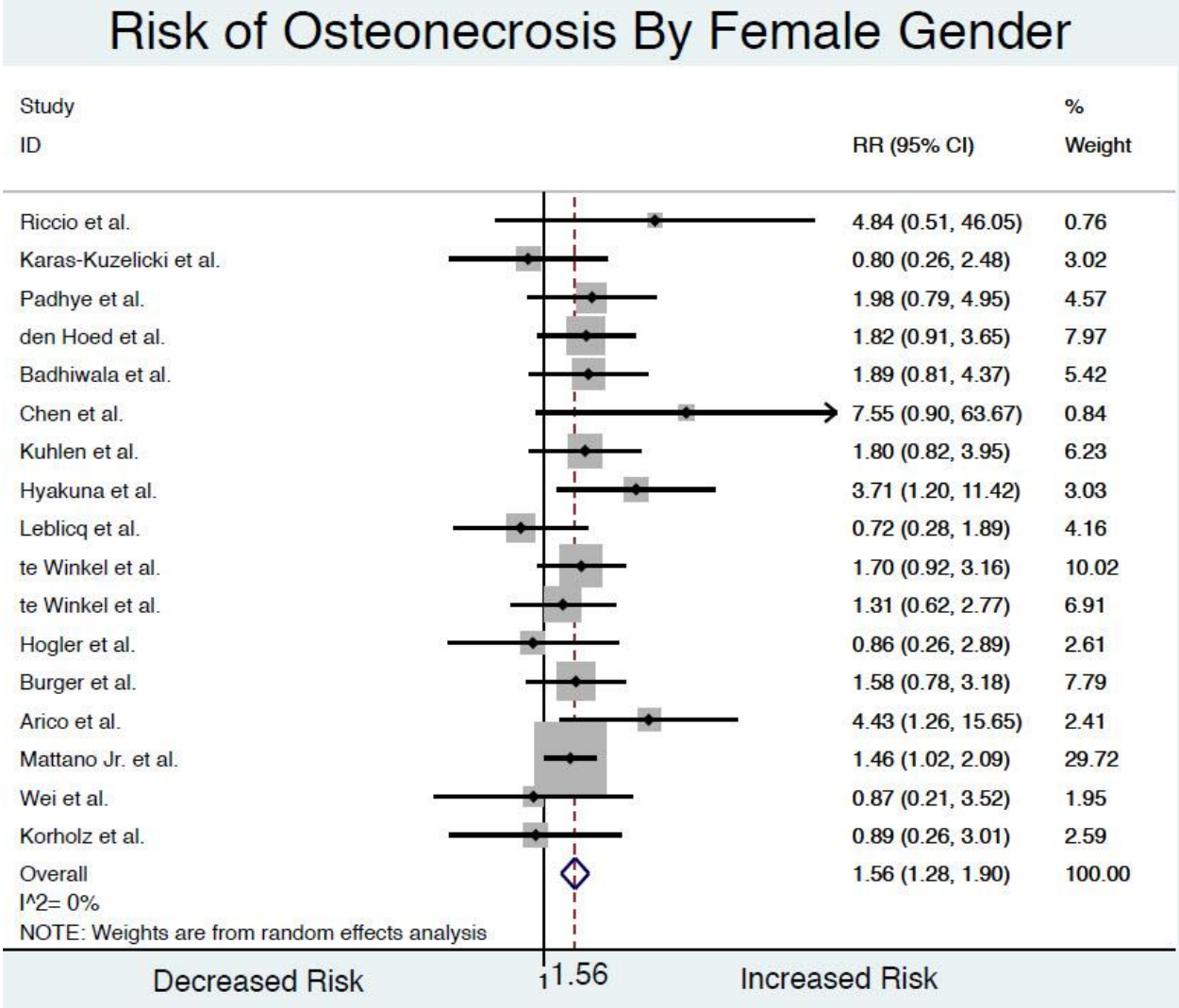

Figure 4: Relative risk of developing ON by gender.

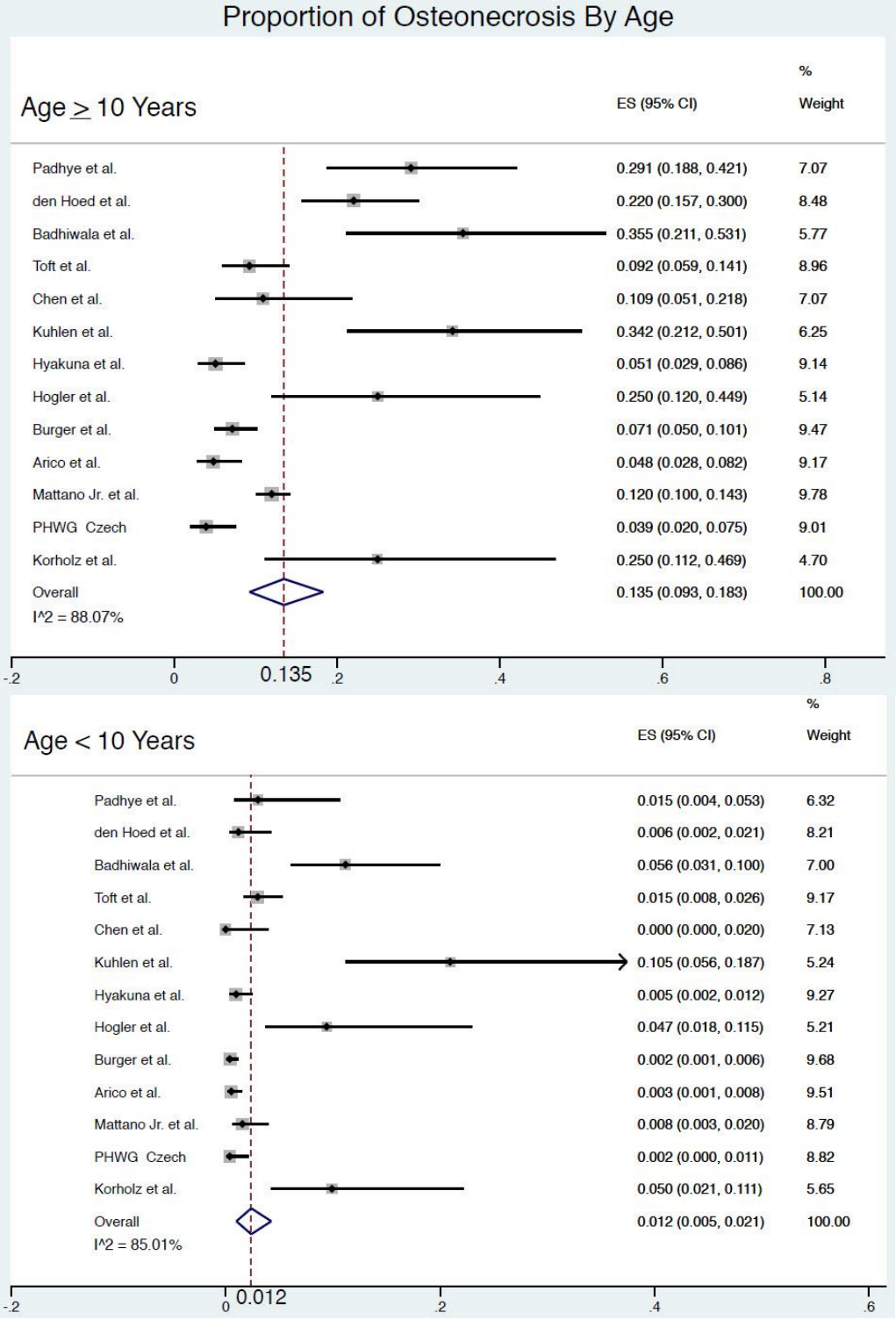

Figure 5: Proportion of ON development by age at time of ALL diagnosis.

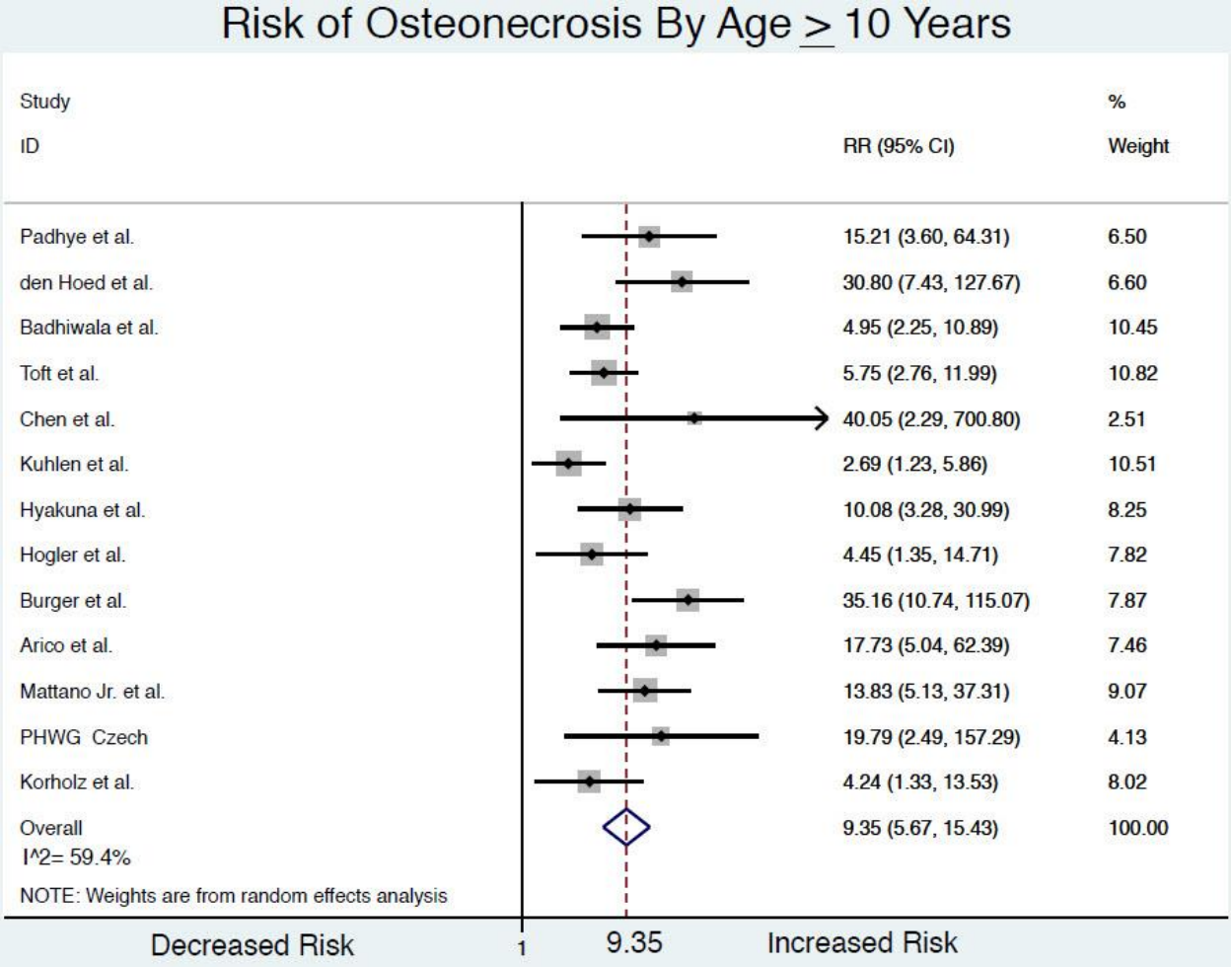

Figure 6: Relative risk for development of ON based on age at time of ALL diagnosis.

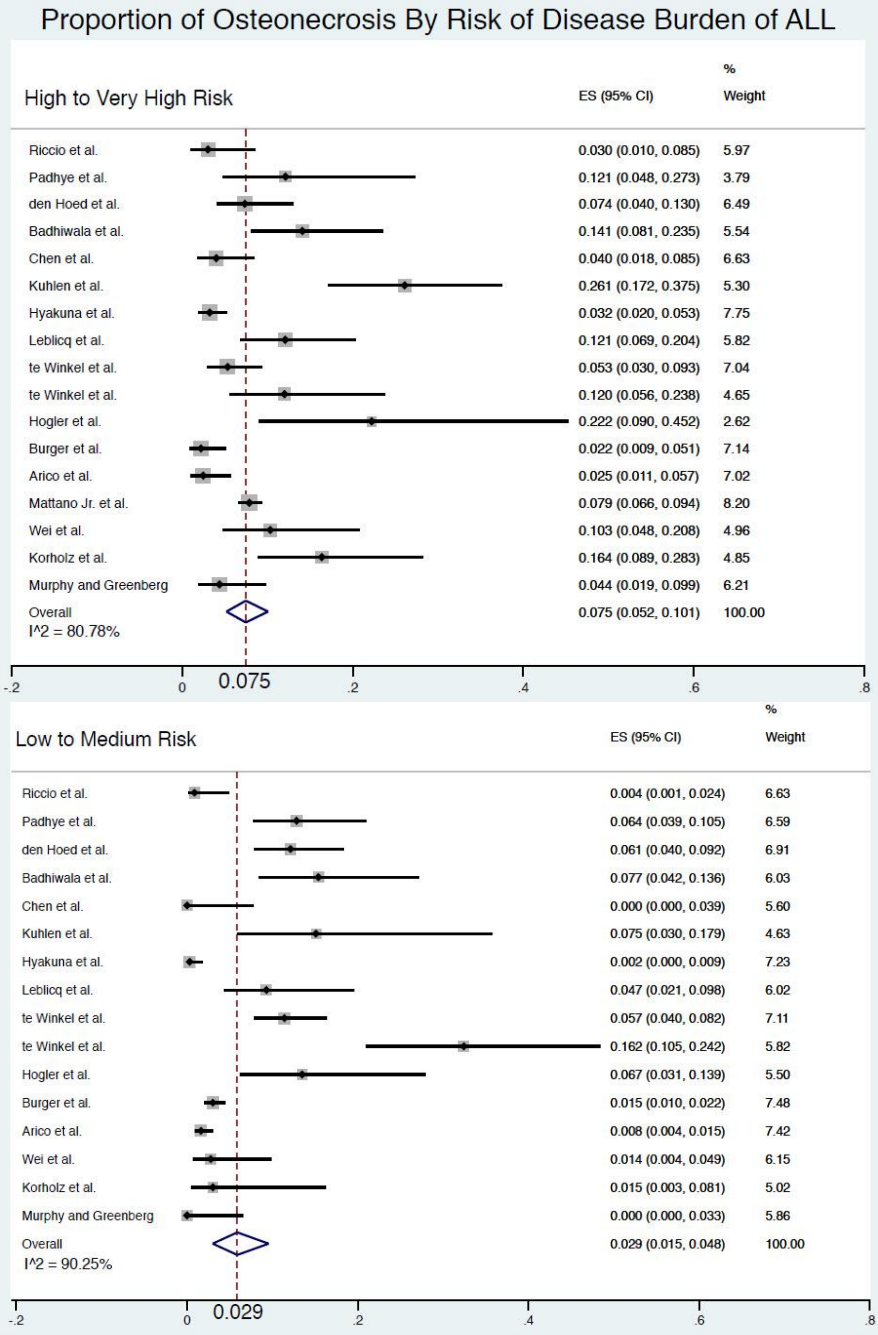

Figure 7: Proportion of ON development by risk of disease burden.

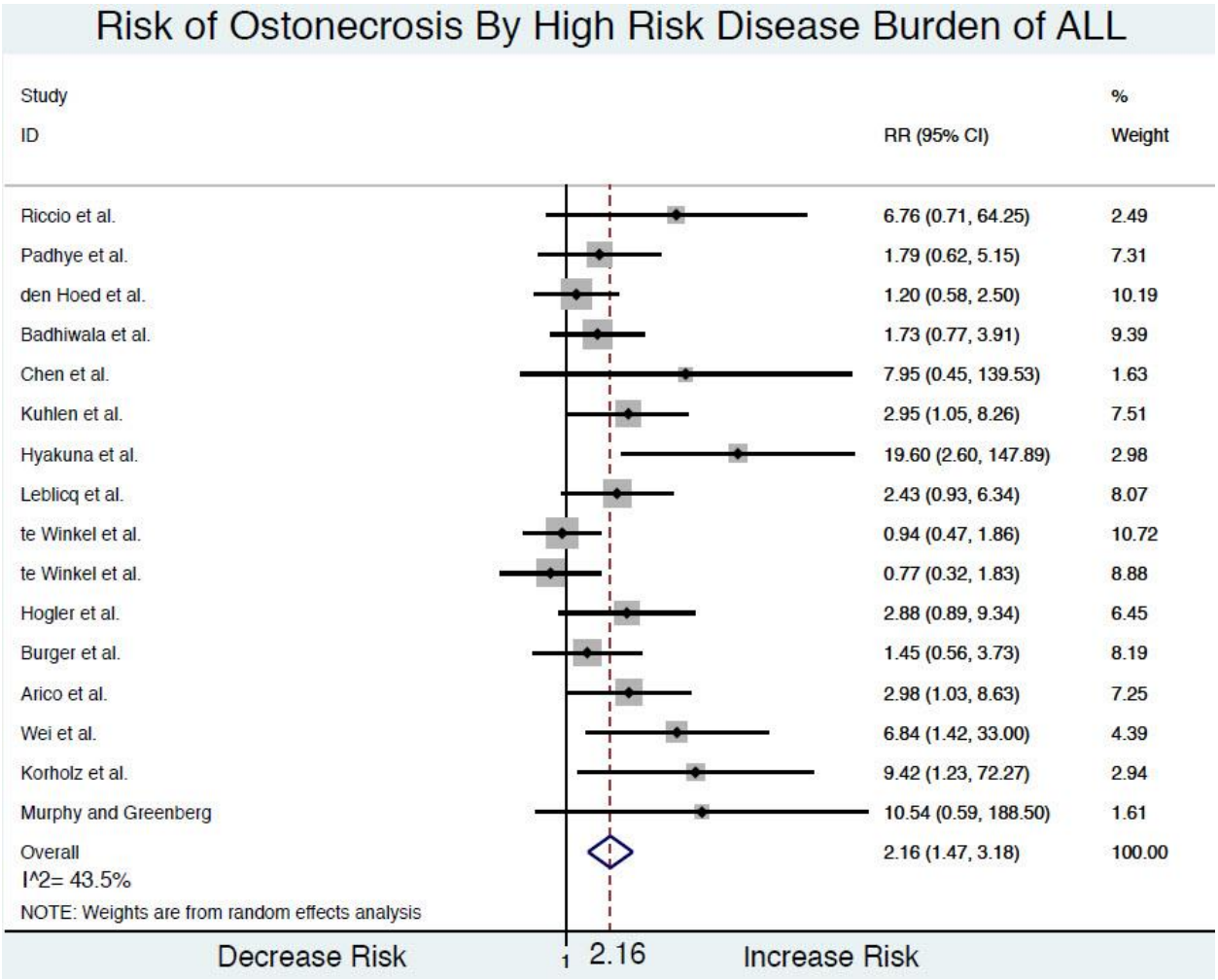

Figure 8: Relative risk for development of ON based on risk of disease burden.

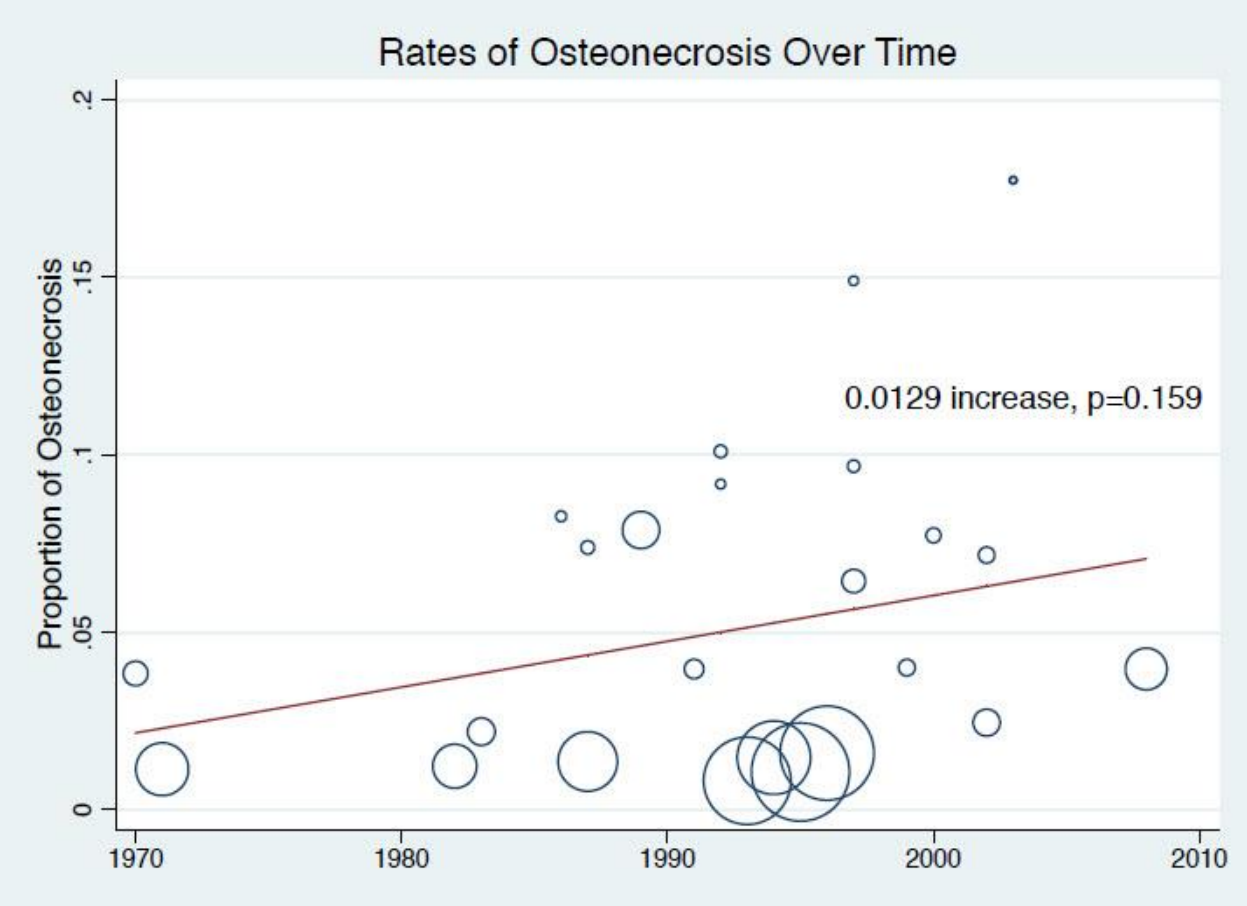

Figure 9: Meta-regression, rates of ON over time.

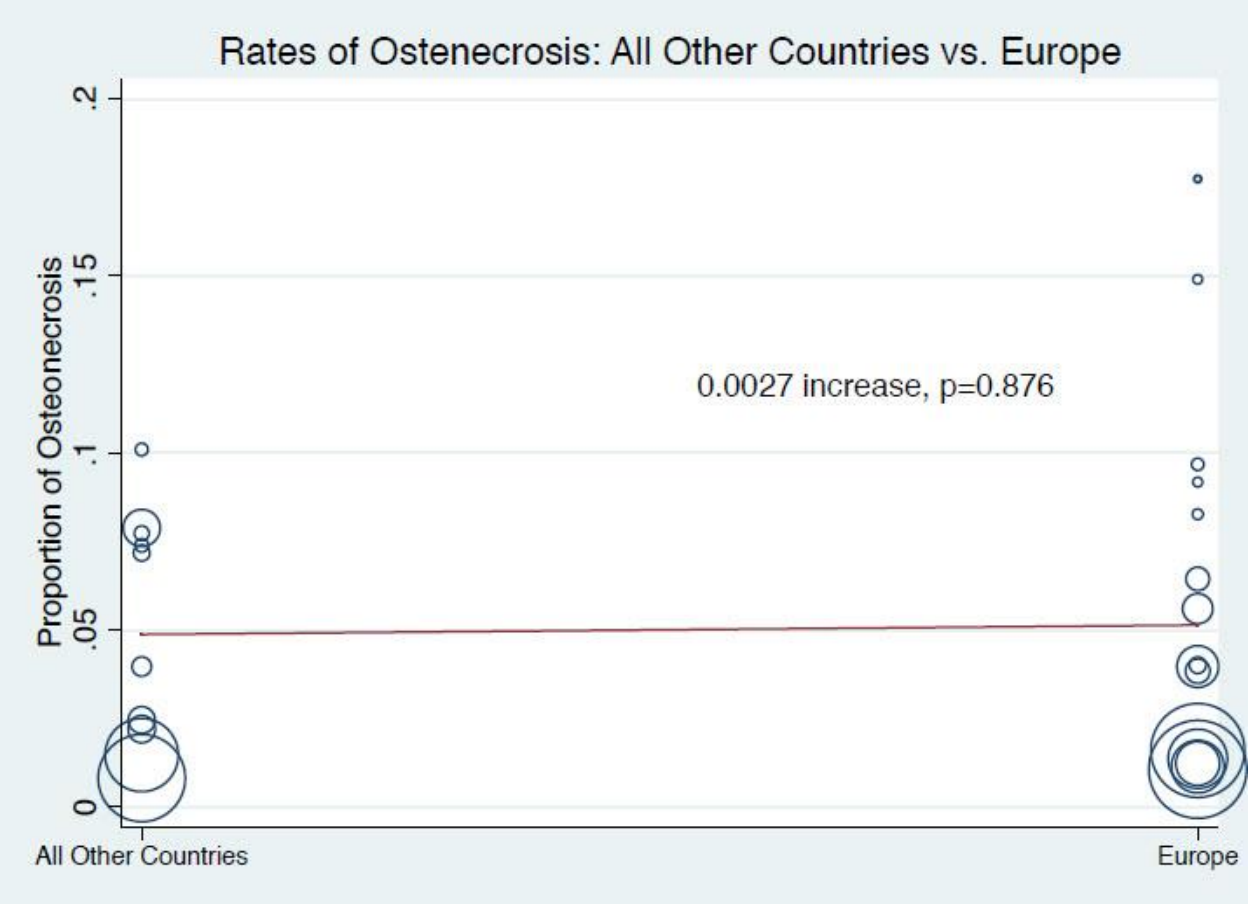

Figure 10: Meta-regression, rates of ON based on geographical location of study.

Authors	Study Design	Geographic Location	Treatment Regimen
Riccio et al.[22] (2016)	Retrospective Cohort	Naples, Italy	Corticosteroids and Cytostatic Agents
Karas-Kuzelicki et al.[12] (2016)	Retrospective Cohort	Ljubljana, Slovenia	Various Pediatric Oncology Group (POG) and Berlin-Frankfurt-Munster (BFM) Protocols
Padhye et al.[20] (2016)	Retrospective Cohort	Sydney, Australia	ANZCHOG ALL8 Trial
den Hoed et al.[6] (2015)	Prospective Cohort	The Netherlands	Dexamethasone based Dutch Child Oncology Group- ALL9 Protocol
Badhiwala et al.[2] (2015)	Retrospective Cohort	Ontario, Canada	Dana-Farber Cancer Institute (DFCI) ALL Consortium Protocols
Toft et al.[28] (2015)	Prospective Cohort	Sweden, Norway, Denmark, Finland, Iceland, Estonia, Lithuania	NOPHO ALL2008
Chen et al.[5] (2015)	Retrospective Cohort	Northern Taiwan	Taiwan Pediatric Oncology Group- ALL-2002 Protocol
Kuhlen et al.[14] (2014)	Retrospective Cohort	Germany	CoALL 07-03 Protocol
Hyakuna et al.[11] (2014)	Retrospective Cohort	Okinawa, Japan	ALL941, ALL2000, and ALL2004 Protocols
Subset of 3 Clinical Trials	Retrospective Cohort	Okinawa, Japan	ALL941
	Retrospective Cohort	Okinawa, Japan	ALL2000
	Retrospective Cohort	Okinawa, Japan	ALL2004
Leblicq et al.[15] (2013)	Retrospective Cohort	Quebec, Canada	DFCI 2000-01 and 2005-001 Protocols
Madadi et al.[16] (2011)	Retrospective Cohort	Tehran, Iran	Corticosteroids and Cytostatic Agents
te Winkel et al.[27] (2011)	Prospective Cohort	The Netherlands	Dexamethasone based Dutch Child Oncology Group- ALL9 Protocol
Elmantaser et al.[7] (2010)	Retrospective Cohort	Glasgow, UK	UKALL97, UKALL97/01, or UKALL2003
te Winkel et al.[26] (2008)	Retrospective Cohort	The Netherlands	Dutch Childhood Oncology Group (DCOG)-ALL9 Treatment Protocol
Hogler et al.[8] (2007)	Retrospective Cohort	Austria	ALL BFM 90, 95, 99 (Pilot), and 2000 Protocols
Sawicka-Zukowska et al.[24] (2006)	Retrospective Cohort	Poland	ALL BFM 95, BFM ALL IC 2002, and New York Protocols
Burger et al.[4] (2005)	Retrospective Cohort	Germany	ALL-BFM 95 Protocol
Arico et al.[1] (2003)	Retrospective Cohort	Palemo, Italy	AIEOP-ALL 95 Protocol
Strauss et al.[25] (2001)	Retrospective Cohort	Boston, Mass. (USA)	DFCI ALL 87-01 and 91-01 Protocols
Mattano Jr. et al.[17] (2000)	Retrospective Cohort	Kalamazoo, MI; Los Angeles, CA; and Chicago, IL (USA)	Children's Cancer Group (CCG-1882) Protocol
Wei et al.[29] (2000)	Retrospective Cohort	Philadelphia, PA (USA)	CCG-1882 Protocol
Report from the PHWGCRC*[21] (1999)	Retrospective Cohort	Czech Republic	ALL-BFM 83, 90, 95. ALL-Slovak Protocols 0276, 0380, 0486, 0491, and 0591
Korholz et al.[13] (1998)	Retrospective Cohort	Germany	CoALL 3-85, 4-89, 5-92. BFM-ALL 86 and 90.
Murphy and Greenberg[19] (1990)	Retrospective Cohort	Ontario, Canada	Modified BFM Protocol
Bomelburg et al.[3] (1990)	Retrospective Cohort	Germany	DAL and BFM Protocols
TOTAL (n=25)			

Table 1: Included studies, study design, geographic location of study, and treatment protocol utilized.
*Pediatric Hematology Working Group of the Czech Republic and Collaborators

Authors	No. Enrolled Patients (M/F)	Mean Age at ALL Diagnosis	No. ON Events (M/F)	Incidence % (M/F)	Mean Age Patients Diagnosed (ALL) Developed ON	Onset Timing of ON (From ALL Diagnosis)
Riccio et al.[22] (2016)	328 (204/124)	6.17 years	4 (1/3)	1.2% (0.005%, 2.42%)	12 years (mean)	12.5 months (mean)
Karas-Kuzelicki et al.[12] (2016)	313 (165/148)	5.9 years	12 (7/5)	3.83% (4.24%, 3.38%)	11.3 +/- 5.9 years (mean)	
Padhye et al.[20] (2016)	251 (143/108)		18 (7/11)	7% (5.2%, 11.2%)	13.05 years (median, 4.3-16.7)	1.15 years (median, 0.25-2.12)
den Hoed et al.[6] (2015)	466 (291/175)	6.02 years	30 (14/16)	6.4% (0.05%, 10.06%)	13.5 years (median, 5-17.1)	14 months (median, 1-33)
Badhiwala et al.[2] (2015)	208 (115/93)	5.4 years	21 (8/13)	10.1% (6.96%, 13.98%)	9.3 years (mean)	69.2 weeks (mean)
Toft et al.[28] (2015)	934 (502/432)	5.3 years	37 (not reported)	3.96% (not reported)		
Chen et al.[5] (2015)	245 (150/95)		6 (1/5)	2.45% (0.67%, 5.26%)	13.3 years (median age, 11.6-16.4)	2.5 years (median, 1.1-7.5)
Kuhlen et al.[14] (2014)	124 (72/52)		22 (9/13)	17.74% (12.5%, 25.0%)	11 years (median age)	13.9 months (median, 3.6-52.2)
Hyakuna et al.[11] (2014)	1095 (610/485)		16 (4/12)	1.46% (0.66%, 2.47%)	11.5 years (median, 5-16y)	
Subset of 3 Clinical Trials	464 (not reported)		4 (not reported)	0.86%		56.5 weeks (median, 32-264)
	305 (not reported)		2 (not reported)	0.66%		
	326 (not reported)		10 (not reported)	3.07%		66 weeks (median, 37-120)
Leblicq et al.[15] (2013)	220 (124/96)	4.8 years (median, 1.2-18)	17 (11/6)	7.73% (8.87%, 6.25%)	11 years (median, 2.7-16.6)	13.4 months (median, 2.5-34)
Madadi et al.[16] (2011)	865 (not reported)		7 (4/3)	0.81%	10.2 years (mean, 5-13)	20 months (median, 10-91)
te Winkel et al.[27] (2011)	679 (416/263)	6.36 years	38 (18/20)	5.6% (4.33%, 7.60%)	12.5 years (mean), 13.5 years (median)	1.2 years (mean, 0.1 to 2.7)
Elmantaser et al.[7] (2010)	186 (110/76)	5.3 years (median, 1.7-13.6)	18 (not reported)	9.70%	12.2 years (median, 6.8-14.9)	29 months (median, 8.8-48)
te Winkel et al.[26] (2008)	161 (93/68)		24 (12/12)	14.91% (12.90%, 17.65%)	13.8 years (median, 4.0-17.2)	
Hogler et al.[8] (2007)	109 (61/48)	5.16 years (median, 0.07-17.33)	10 (6/4)	9.17% (9.84%, 8.33%)	12.78 years (median, 6.93-16.30) [this is age at event]	15.85 months (median, 1.15-52.01)
Sawicka-Zukowska et al.[24] (2006)	150 (not reported)		6 (5/1)	4% (not reported)	16.23 years (mean)	1.47 years (mean)
Burger et al.[4] (2005)	1951 (1106/845)		31 (14/17)	1.59% (1.27%, 2.01%)		
Arico et al.[1] (2003)	1421 (752/669)		15 (3/12)	1.06% (0.4%, 1.79%)		17 months (median, 8-45)
Strauss et al.[25] (2001)	176 (95/81)		13 (not reported)	7.39% (not reported)		14 months (median, 10-24)
Mattano Jr. et al.[17] (2000)	1409 (790/619)	10.1 years (mean)	111 (51/60)	7.88% (6.46%, 9.69%)	13.6 years (mean, 3.8-18.5)	
Wei et al.[29] (2000)	202 (119/83)	6.5 years (mean, 1-18)	8 (5/3)	3.96% (4.20%, 3.61%)	9.92 years (mean, 3.58-15.67)	30 months (mean, 8-74)
Report from the PHWGCRC*[21] (1999)	665 (not reported)		9 (2/7)	1.35% (not reported)	13.75 (median, 9.25-17.0), 13.65 (mean)	13 months (median, 5-25), 13 months (mean)
Korholz et al.[13] (1998)	121 (69/52)	4 years (median, 1-17)	10 (6/4)	8.26% (8.70%, 7.69%)	9.55 years (mean, 3-17) [this is age at event]	21.3 months (mean, 7-40)
Murphy and Greenberg[19] (1990)	228 (not reported)		5 (3/2)	2.19% (not reported)	13.08 years (mean, 9.5-16.7)	12.4 months (mean, 10.5-18)
Bomelburg et al.[3] (1990)	441 (not reported)		5 (not reported)	1.13% (not reported)	7.8 years (mean, 1-13)	13.6 months (mean, 12-15 for first ON lesion)
TOTAL (n=25)	**14043 (5987/4612)**	**6.90 years**	**509 (191/229)**	**4.4% (4.2%, 6.6%)**	**12.46 years**	**16.58 months**

Table 2: Included studies, enrolled patients, mean age, incidence rates of ON, mean age of ALL diagnosis for those who developed ON, and onset of ON timing.
*Pediatric Hematology Working Group of the Czech Republic and Collaborators

Authors	Incidence (%) ≥10y	Incidence (%) <10y	Rates of ON Based on Risk Stratification				Rates of ON Based on Immunophenotype	
							BCP	T
Riccio et al.[22] (2016)	4 (not reported)	0	Standard- 0/180 (0%)	Intermediate- 1/49 (2.04%)	High- 3/99 (3.03%)			
Karas-Kuzelicki et al.[12] (2016)								
Padhye et al.[20] (2016)	16 (29%)	2 (1.02%)	Standard- 2/59 (3.39%)	Medium- 12/159 (7.55%)	High- 0/5 (0%)	Very High- 4/28 (14.29%)		
den Hoed et al.[6] (2015)	28 (22.05%)	2 (0.59%)	Non-High Risk- 20/330 (6.06%)		High Risk- 10/136 (7.35%)		25/379 (6.60%)	5/68 (7.35%)
Badhiwala et al.[2] (2015)	11 (35.5%)	10 (5.6%)	Standard Risk- 10/130 (7.69%)		High- 11/78 (14.1%)			
Toft et al.[28] (2015)	18 (9.23%)	11 (1.49%)						
Chen et al.[5] (2015)	6 (10.91%)	0 (0%)	Standard- 0/90 (0%)	High- 5/86 (5.81%)	Very High- 1/69 (1.45%)		6/217 (2.76%)	0/28 (0%)
Kuhlen et al.[14] (2014)	13 (34.21%)	9 (10.47%)	Low- 4/53 (7.55%)		High- 18/69 (26.09%)		16/102 (15.69%)	5/20 (25.0%)
Hyakuna et al.[11] (2014)	12 (4.82%)	4 (0.47%)	Standard- 1/630 (0.16%)		High and High-High- 15/465 (3.23%)		9/748 (1.20%)	3/102 (2.94%)
Subset of 3 Clinical Trials								
Leblicq et al.[15] (2013)	10 (not reported)	7 (not reported)	Standard- 6/129 (4.65%)		High- 11/91 (12.09%)			
Madadi et al.[16] (2011)	5 (not reported)	2 (not reported)	Standard- 2 (not reported)		High- 5 (not reported)			
te Winkel et al.[27] (2011)	33 (not reported)	5 (not reported)	Non-High Risk- 27/473 (5.71%)		High-Risk- 11/206 (5.34%)			
Elmantaser et al.[7] (2010)								
te Winkel et al.[26] (2008)			Non-High Risk- 18/111 (16.22%)		High-Risk- 6/50 (12.0%)		20/136 (14.71%)	4/25 (16.0%)
Hogler et al.[8] (2007)	6 (25.0%)	4 (4.71%)	Standard- 2/36 (5.56%)	Medium- 4/53 (7.55%)	High- 4/18 (22.22%)			
Sawicka-Zukowska et al.[24] (2006)	6 (not reported)	0						
Burger et al.[4] (2005)	28 (7.14%)	3 (0.19%)	Standard- 1/679 (0.15%)	Medium- 25/1046 (2.39%)	High- 5/226 (2.21%)		5/450 (1.11%)	5/250 (2.0%)
Arico et al.[1] (2003)	12 (4.82%)	3 (0.26%)	Standard- 1/98 (1.02%)	Intermediate- 9/1121 (0.8%)	High- 5/202 (2.48%)			
Strauss et al.[25] (2001)			Standard- not reported		High- not reported			
Mattano Jr. et al.[17] (2000)	107 (11.98%)	4 (0.78%)	All patients evaluated in this study were considered "High" risk				47/656 (7.16%)	11/109 (10.09%)
Wei et al.[29] (2000)	5 (not reported)	3 (not reported)	Low- 2/144 (1.39%)		High- 6/58 (10.34%)			
Report from the PHWGCRC*[21] (1999)	8 (3.90%)	1 (0.19%)	Standard- 2 (not reported)	Medium- 5 (not reported)	High- 2 (not reported)			
Korholz et al.[13] (1998)	5 (25%)	5 (4.72%)	Standard 1/66 (1.52%)		High- 9/55 (16.36%)		0/3 (0%)	3/10 (30%)
Murphy and Greenberg[19] (1990)	4 (not reported)	1 (not reported)	Standard- 0/115 (0%)		High- 5/113 (4.4%)			
Bomelburg et al.[3] (1990)	2 (not reported)	3 (not reported)						
TOTAL (n=25)	**339 (13.5%)**	**79 (1.2%)**	**Low to Medium (or Standard to Intermediate) Risk: 155 (2.9%)**		**High or Very High Risk: 247 (7.5%)**		**128 (4.76%)**	**36 (5.88%)**

Table 3: Included studies and incidence of ON by various risk factors (age, risk stratification, and immunophenotype).
*Pediatric Hematology Working Group of the Czech Republic and Collaborators

Authors	Cumulative Number of Joint Affected by Location								Joints Affected Per Patient Diagnosed with ON
	Hip	Femur	Tibia	Knee	Foot/Ankle	Shoulder/Scapula	Elbow	Wrist/Hand	
Riccio et al.[22] (2016)	7	0		0	0	1	0	0	2
Karas-Kuzelicki et al.[12] (2016)									
Padhye et al.[20] (2016)	18			27	12	7	1		3.61
den Hoed et al.[6] (2015)	19			22	6	4	1	1	1.76
Badhiwala et al.[2] (2015)	14			18	19				2.43
Toft et al.[28] (2015)									
Chen et al.[5] (2015)	11		2	1	2	1			2.83
Kuhlen et al.[14] (2014)	17			32	12	8	1		3.18
Hyakuna et al.[11] (2014)	16	2		12	1				1.94
Subset of 3 Clinical Trials	7								1.75
	1			2	1				2
	8	2		10					2
Leblicq et al.[15] (2013)	11			8	23				2.47
Madadi et al.[16] (2011)	11								1.57
te Winkel et al.[27] (2011)	45			56	19	8	1	1	3.42
Elmantaser et al.[7] (2010)	9			13		7			1.61
te Winkel et al.[26] (2008)									
Hogler et al.[8] (2007)	8		8		10	4			3
Sawicka-Zukowska et al.[24] (2006)									
Burger et al.[4] (2005)	*11*	*2*		*14*	*7*	*4*			*#*
Arico et al.[1] (2003)	19		2	1	5	2			1.93
Strauss et al.[25] (2001)		7	7			3	13	3	2.54
Mattano Jr. et al.[17] (2000)	86			99	46	29	24	11	2.66
Wei et al.[29] (2000)	12			8	3	2	2		3.38
Report from the PHWGCRC*[21] (1999)	7	7			1				1.67
Korholz et al.[13] (1998)									6.6
Murphy and Greenberg[19] (1990)	5	6			2	2	1		3.2
Bomelburg et al.[3] (1990)	6	4				1			2.2
TOTAL (n=25)	**348**	**30**	**19**	**323**	**169**	**83**	**44**	**16**	**2.66**

Table 4: Included studies, enrolled patients, mean age, incidence rates of ON, mean age of ALL diagnosis for those who developed ON, and onset of ON timing.
*Pediatric Hematology Working Group of the Czech Republic and Collaborators
#This data was reported in number of patients affected instead of cumulative joints affected (not included in pooled analysis)

References

1. Arico M, Boccalatte MF, Silvestri D, et al. Osteonecrosis: An emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia. *Haematologica.* 2003;88(7):747-753.
2. Badhiwala JH, Nayiager T, Athale UH. The development of thromboembolism may increase the risk of osteonecrosis in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2015;62(10):1851-1854.
3. Bomelburg T, von Lengerke HJ, Ritter J. Incidence of aseptic osteonecrosis following the therapy of childhood leukemia. *Haematol Blood Transfus.* 1990;33:577-579.
4. Burger B, Beier R, Zimmermann M, Beck JD, Reiter A, Schrappe M. Osteonecrosis: a treatment related toxicity in childhood acute lymphoblastic leukemia (ALL)--experiences from trial ALL-BFM 95. *Pediatr Blood Cancer.* 2005;44(3):220-225.
5. Chen SH, Chang TY, Jaing TH, et al. 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.* 2015;102(1):41-47.
6. den Hoed MA, Pluijm SM, te Winkel ML, et al. Aggravated bone density decline following symptomatic osteonecrosis in children with acute lymphoblastic leukemia. *Haematologica.* 2015;100(12):1564-1570.
7. Elmantaser M, Stewart G, Young D, Duncan R, Gibson B, Ahmed SF. Skeletal morbidity in children receiving chemotherapy for acute lymphoblastic leukaemia. *Arch Dis Child.* 2010;95(10):805-809.
8. Hogler W, Wehl G, van Staa T, Meister B, Klein-Franke A, Kropshofer G. Incidence of skeletal complications during treatment of childhood acute lymphoblastic leukemia: comparison of fracture risk with the General Practice Research Database. *Pediatr Blood Cancer.* 2007;48(1):21-27.
9. Horton T, Steuber C. Overview of the presentation and diagnosis of acute lymphoblastic leukemia in children and adolescents. UpToDate: Wolters Kluwer; 2017.
10. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol.* 2012;30(14):1663-1669.
11. Hyakuna N, Shimomura Y, Watanabe A, et al. 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.* 2014;36(1):22-29.
12. Karas-Kuzelicki N, Mencej-Bedrac S, Jazbec J, Marc J, Mlinaric-Rascan I. Risk factors for symptomatic osteonecrosis in childhood ALL: A retrospective study of a Slovenian pediatric ALL population between 1970 and 2004. *Exp Ther Med.* 2016;12(2):840-846.
13. Korholz D, Bruder M, Engelbrecht V, Ruther W, Gobel U. Aseptic osteonecrosis in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol.* 1998;15(4):307-315.
14. Kuhlen M, Moldovan A, Krull K, Meisel R, Borkhardt A. Osteonecrosis in paediatric patients with acute lymphoblastic leukaemia treated on Co-ALL-07-03 trial: a single centre analysis. *Klin Padiatr.* 2014;226(3):154-160.
15. Leblicq C, Laverdiere C, Decarie JC, et al. Effectiveness of pamidronate as treatment of symptomatic osteonecrosis occurring in children treated for acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2013;60(5):741-747.

16. Madadi F, Shamsian BS, Alavi S, Madadi F, Eajazi A, Aslani A. Avascular necrosis of the femoral head in children with acute lymphoblastic leukemia: a 4- to 9-year follow-up study. *Orthopedics.* 2011;34(10):e593-597.

17. Mattano LA, Jr., Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *J Clin Oncol.* 2000;18(18):3262-3272.

18. Moricke A, Zimmermann M, Reiter A, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. *Leukemia.* 2010;24(2):265-284.

19. Murphy RG, Greenberg ML. Osteonecrosis in pediatric patients with acute lymphoblastic leukemia. *Cancer.* 1990;65(8):1717-1721.

20. Padhye B, Dalla-Pozza L, Little D, Munns C. Incidence and outcome of osteonecrosis in children and adolescents after intensive therapy for acute lymphoblastic leukemia (ALL). *Cancer Med.* 2016;5(5):960-967.

21. Pediatric Hematology Working Group of the Czech R, Collaborators. Osteonecrosis in children treated for acute leukemia. *Med Pediatr Oncol.* 1999;32(6):474-476.

22. Riccio I, Pota E, Marcarelli M, et al. Osteonecrosis as a complication in pediatric patients with acute lymphoblastic leukemia. *Pediatr Med Chir.* 2016;38(3):118.

23. Salem KH, Brockert AK, Mertens R, Drescher W. Avascular necrosis after chemotherapy for haematological malignancy in childhood. *Bone Joint J.* 2013;95-B(12):1708-1713.

24. Sawicka-Zukowska M, Kajdas L, Muszynska-Roslan K, Krawczuk-Rybak M, Sonta-Jakimczyk D, Szczepanski T. Avascular necrosis--an antineoplastic-treatment-related toxicity: the experiences of two institutions. *Pediatr Hematol Oncol.* 2006;23(8):625-629.

25. Strauss AJ, Su JT, Dalton VM, Gelber RD, Sallan SE, Silverman LB. Bony morbidity in children treated for acute lymphoblastic leukemia. *J Clin Oncol.* 2001;19(12):3066-3072.

26. te Winkel ML, Appel IM, Pieters R, van den Heuvel-Eibrink MM. Impaired dexamethasone-related increase of anticoagulants is associated with the development of osteonecrosis in childhood acute lymphoblastic leukemia. *Haematologica.* 2008;93(10):1570-1574.

27. te Winkel ML, Pieters R, Hop WC, et al. Prospective study on incidence, risk factors, and long-term outcome of osteonecrosis in pediatric acute lymphoblastic leukemia. *J Clin Oncol.* 2011;29(31):4143-4150.

28. Toft N, Birgens H, Abrahamsson J, et al. Toxicity profile and treatment delays in NOPHO ALL2008-comparing adults and children with Philadelphia chromosome-negative acute lymphoblastic leukemia. *Eur J Haematol.* 2016;96(2):160-169.

29. Wei SY, Esmail AN, Bunin N, Dormans JP. Avascular necrosis in children with acute lymphoblastic leukemia. *J Pediatr Orthop.* 2000;20(3):331-335.