BMC Pediatrics

RESEARCH Open Access

Musculoskeletal manifestations of childhood malignancies: a systematic review and meta-analysis

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Abstract

Background Timely diagnosis of malignancies in children is very important. Knowing the clinical manifestations of malignancies help in timely diagnosis. The aim of this study is to investigate the prevalence of musculoskeletal manifestations of malignancies in children.

Methods we searched the manuscript databases including Scopus, Web of science, Google scholar, Medline, and Cochrane for all studies in accordance with the relevant keywords. The nine-star Newcastle-Ottawa Scale (NOS) scoring system was employed to assess the methodological quality of all eligible studies. Statistical analysis was performed using the Comprehensive Meta-Analysis (CMA) software.

Results Of 96 articles initially collected by database searching, 13 articles were eligible for the final analysis. The major musculoskeletal manifestations related to childhood malignancies include bone pain, bone swelling, bone tenderness, bone fracture, vertebral collapses, joint effusion and joint tenderness. Manifestations related to these malignancies also include septic arthritis-type symptoms, osteomyelitis-type symptoms, and osteomyelitis. The overall pooled prevalence of musculoskeletal manifestations in children suffering hematopoietic tumors (acute lymphoblastic leukemia and acute myeloid leukemia) was 32.1% (95%CI: 24.0–41.3%). The overall prevalence of musculoskeletal manifestations due to neuroblastoma was also 30.5% (95%CI: 19.2–44.9%). The rate of musculoskeletal manifestations due to other childhood cancers range from 23.5 to 80.3%.

Conclusion A significant part of childhood malignancies are associated with musculoskeletal manifestations. Clinicians should carefully evaluate and closely follow children with musculoskeletal manifestations to timely diagnosing of malignancies.

Trial registration number Not applicable.

Keywords Neoplasms, Child, Prevalence, Leukemia, Diagnosis

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Introduction

Malignancies are rare in children but may be associated with morbidity and mortality. Therefore, their proper diagnosis and treatment are very important in preventing these complications [1, 2]. Despite the increasing progress in diagnostic methods and cancer treatment approaches in children, this event is associated with adverse consequences, especially in the first decade of life [3]. In fact, early diagnosis of the disease and control of its progress not only leads to reducing the burden of the disease on the patients and their families, but also minimizes the complications and disabilities caused by the disease [4]. However, early diagnosis of the disease in children is a major challenge, and in contrast to adult cancer, which mainly faces early clinical manifestations, in children, these clinical manifestations sometimes cannot be traced until the advanced stages of the disease [5]. Also, the occurrence of general clinical symptoms caused by cancer in children can be observed with a higher prevalence than in adults, which makes it difficult to differentiate between cancer and systemic disorders [6].

Many common types of childhood cancers such as hematopoietic malignancies, sarcoma and central nervous system tumors present with musculoskeletal manifestations and complications [7, 8]. Articular symptoms such as arthritis, bone pain, intra-articular hemorrhage, joint infiltration, synovial reaction, and infections are the prominent musculoskeletal manifestations related to cancers that may be in the differential diagnosis with bone or muscle inflammatory disorders and therefore hide the diagnosis of cancer [9, 10]. It has been indicated that about 0.25 to 2% of children referred to pediatric rheumatology clinics due to appearance of musculoskeletal manifestations were finally diagnosed as a cancer. These patients may be misdiagnosed commonly by juvenile arthritis, however, their definitive diagnosis can be leukemia or tumors of the nervous system such as neuroblastoma [11, 12]. Such a diagnostic error is sometimes associated with a delay in the final diagnosis of cancer due to anti-inflammatory treatment and the use of corticosteroids, as well as a worsening of the related outcome [13]. Therefore, it is necessary for all specialists to evaluate and differentiate musculoskeletal manifestations caused by systemic inflammatory disorders and those caused by malignancies and to manage these manifestations in the field of childhood cancers as soon as possible. What was discussed in this systematic review of the musculoskeletal manifestations related to childhood malignancies and the examination of points so that by taking them into account, it is possible to distinguish clinical manifestations related to cancer and manifestations related to other systemic disorders.

Materials and methods

Search strategy

This study was done according to established methods and in accordance with PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis) Protocols [14]. Two researcher searched the article databases including Web of science, Medline, Google scholar, Cochrane and Scopus for all eligible studies in accordance with the considered keywords including: "cancer", "children", "malignancy", "childhood cancer", acute lymphoblastic leukemia"(ALL), acute myeloid leukemia"(AML), "lymphoma", "manifestation", "musculoskeletal", "bone", "muscle", and "joint". The studies were restricted to English language. The inclusion criterion for retrieved the studies assessed musculoskeletal manifestations of the different types of childhood cancers. The exclusion criteria were thus as follows: (1) a lack of clear and reproducible results, (2) lack of access to the manuscripts full texts and (3) review papers, case reports and case series.

Data abstraction and validity assessment

Data abstraction was independently performed by two un-blinded researchers on structure collection forms without divergences in data collection. The study quality was evaluated based on the following criteria: (1) the systematic review and meta-analysis based on the questions primarily formulated and described; (2) inclusion and exclusion criteria predefined in the studies as eligibility criteria; (3) searching the studies performed on a systematic and comprehensive approach; (4) the full texts were dually reviewed to minimize the bias; (5) the quality of included studies were rated independently by the researchers for appraising internal validity; (6) the risk of bias and heterogeneity were listed. The nine-star Newcastle-Ottawa Scale (NOS) scoring system was employed to assess the methodological quality of all eligible studies.

Statistical analysis

Dichotomous variables are reported as proportions and percentages, and continuous variables as mean values. Binary outcomes from individual studies were to be combined with both the Mantel-Hansel fixed effect model. The pooled prevalence and 95% confidence interval (CI) were used as summary statistics for describing the prevalence of musculoskeletal manifestations in the cancers. To determine the statistical heterogeneity of this study Cochran's Q test was used. This test was complemented with the I2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I2 of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and 76–100% high heterogeneity. Publication bias was assessed by the rank correlation test and also confirmed by the funnel plot

analysis. Reported values were two-tailed, and hypothesis testing results were considered statistically significant at $p = 0.05$. Statistical analysis was performed using the Comprehensive Meta-Analysis (CMA) software version 3.0 (Biostat, Englewood, NJ 07631 USA).

Results

Study selection and quality assessment

As shown in Fig. 1, initially 96 articles were included in the study, but eventually a large number of them were excluded from the study, and finally 13 articles were analyzed [14–26]. Table 1 describes baseline characteristics of the studies included. Quality assessment showed a NOS score of 7 or higher for all studies, indicating the presence of high methodological quality (Fig. 2).

Systematic reviewing the literature

In total, the studies regarding musculoskeletal manifestations in relation to malignancies in children were designed and implemented in two formats. In the first group, cancer patients referred to clinics or hospitals were the target of the study, who were examined in terms of musculoskeletal characteristics, and in the second group, patients who referred with musculoskeletal manifestations were the target, who were examined in terms of the prevalence of malignancies was studied. The present study considered the first group as the target group (Table 1). In the evaluated studies, a wide range of children's malignancies were investigated, which mainly included types of leukemia, neuroblastoma and other tumors of the central nervous system, bone tumors, especially malignant spinal cord lesions, and soft tissue tumors in a few studies. Manifestations were also investigated in the studies in two forms of clinical manifestations and musculoskeletal radiological manifestations.

In studies that focused on hematopoietic tumors (ALL and AML), the major musculoskeletal clinical manifestations of reported included bone pain (back, neck, and the extremities), limping and bone swelling, bone tenderness, bone fracture, vertebral collapses, joint effusion and joint tenderness. With less prevalence, other clinical manifestations including joint compression in the tibia-tarsus, knee, coxofemoral, and elbow, scoliosis and limited flexor and extensor muscle capacity. The

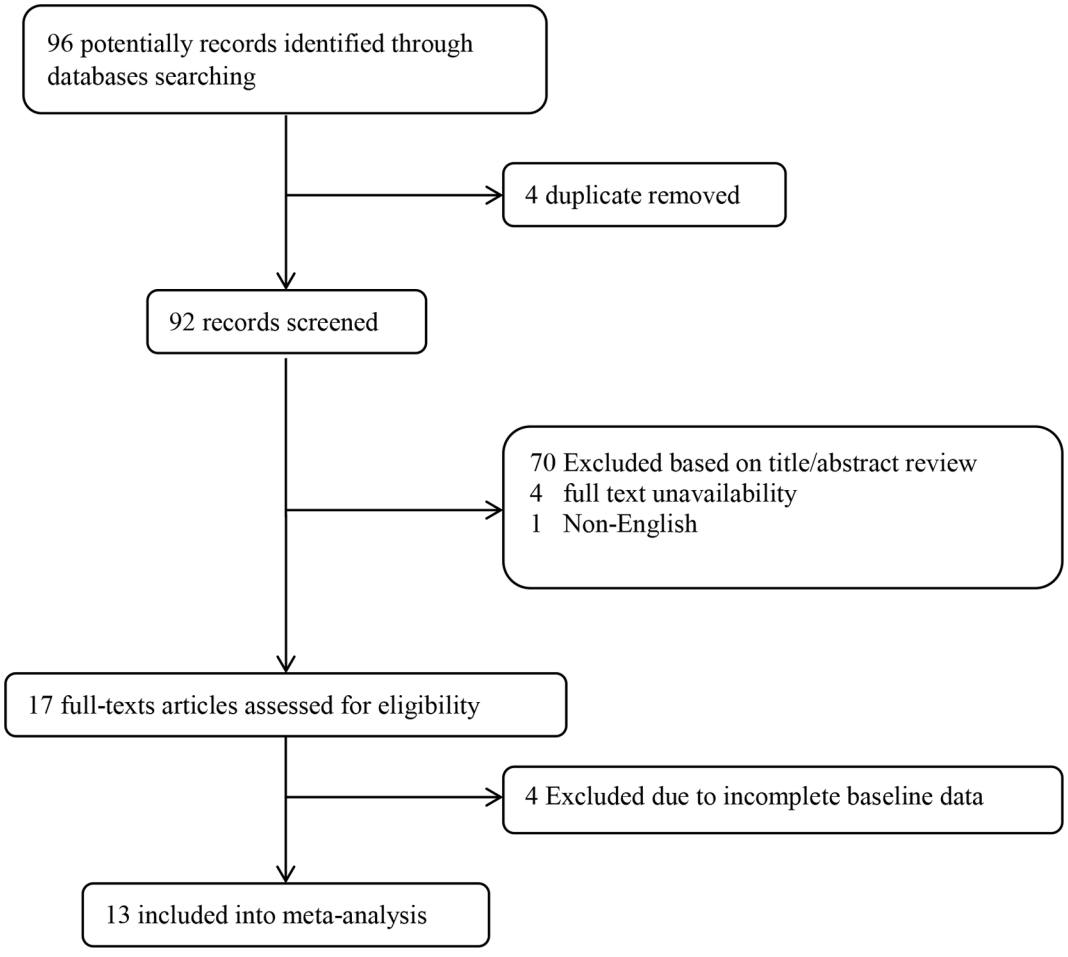

Fig. 1 PRISMA 2020 flow diagram. The flowchart of screening the eligible studies

Table 1 The details of studies assessed, number of patients and type of malignancy

Author, year	No. population	Cancers assessed
Roser et al., 2024 [14]	756	Leukemia
	577	Lymphoma
	417	CNS tumors
	87	Neuroblastoma
Dybedokken et al., 2024 [15]	58	Spinal tumors
Civino et al., 2021 [16]	1277	Bone tumors, Langerhans histiocytosis, leukemia, soft-tissue sarcomas, neuroblastoma
Kang et al., 2017 [17]	125	Acute lymphoblastic leukemia
Riccio et al., 2013 [18]	328	Acute lymphoblastic leukemia, Acute myeloid leukemia
Sinigaglia et al., 2008 [19]	122	Acute lymphoblastic leukemia, Acute myeloid leukemia
Campos et al., 2008 [20]	13	Acute lymphoblastic leukemia
	12	Neuroblastoma
Robazzi et al., 2007 [21]	406	Acute lymphoblastic leukemia, Acute myeloid leukemia
Murthi et al., 2001 [22]	128	Neuroblastoma
Mehlman et al., 1999 [23]	52	Vertebral and spinal cord tumors
Kai et al., 1996 [24]	168	Acute lymphoblastic leukemia
	57	Acute myeloid leukemia
Rogalsky et al., 1986 [25]	107	Leukemia
Costello et al., 1983 [26]	28	Acute lymphoblastic leukemia, Acute myeloid leukemia

rheumatologic manifestations related to these malignancies also included septic arthritis-type symptoms, osteomyelitis-type symptoms, and osteomyelitis. The prominent radiological manifestations related to hematopoietic malignancies included osteolysis, osteopenia, osteosclerosis, periosteal reactions. With less prevalence, pathological fractures, metaphyseal bands, periosteal new bone, sclerotic lesions, periosteal reaction, leukemic infiltration of bone marrow and avascular necrosis may be seen (Table 2).

In cases with neuroblastoma, the most common musculoskeletal manifestations have been found to be multiple bone and joint pains, dislocation of a hip, paraplegia, joint swelling, scoliosis, arthritis and/or arthralgia (Table 2).

In patients suffering endocrine neoplasia, marfanoid habitus, pes cavus, talipes equinovarus, slipped capital femoral epiphysis, kyphosis, scoliosis, lordosis, increased joint laxity, and weakness of the proximal muscles of the extremities were revealed as the prominent musculoskeletal manifestations. In a study by Vitale et al. on children with neuroblastoma, approximately 50% of patients had significant musculoskeletal manifestations. Congenital pseudarthrosis of the tibia and scoliosis were most common. Also, 20% of patients with Type I neuroblastoma, presented with scoliosis with or without the classic dystrophic features, such as rib penciling and vertebral scalloping. In the review of the literature, the musculoskeletal manifestations of other types of malignancy in children had not been studied.

The overall prevalence of musculoskeletal manifestations in childhood leukemia

The overall pooled prevalence of musculoskeletal manifestations in children suffering hematopoietic tumors (ALL and AML) was 32.1% (95%CI: 24.0–41.3%). To determine the rate of these manifestations, our assessment found a significant heterogeneity across the studied groups ($I^2 = 94.569$, $p < 0.001$. However, publication bias was not revealed based on the funnel plot analysis (Fig. 3).

The overall prevalence of musculoskeletal manifestations in childhood neuroblastoma

In summarizing studies related to neuroblastoma in children, the overall prevalence of musculoskeletal manifestations was 30.5% (95%CI: 19.2–44.9%).Heterogeneity between studies was significant in the aforementioned evaluation ($I^2 = 79.494$, $p = 0.002$). The publication bias across the studies remained insignificant (Fig. 4).

The overall prevalence of musculoskeletal manifestations in other malignancies.

Due to the limitation in the number of studies, it was not possible to perform a meta-analysis on other types of malignancies. In evaluating studies on other types of malignancies, the prevalence of musculoskeletal manifestations in bone cancers was 80.3%, in soft-tissue sarcomas was 23.5%, in langerhans histiocytosis was 47.0%, in spinal tumors was 56.9%, and in other CNS tumors was 25.2%.

Discussion

Apart from the specific manifestations of each malignancy, the occurrence of musculoskeletal symptoms is a common finding among all types of malignancies, both in children and adults. This matter is of double importance in children. First, it is difficult to evaluate clinical manifestations in children because sometimes it is not possible to establish a complete and reliable speech relationship with the child due to their age. Secondly, in many cases, due to the rarer nature of malignancies in children, less attention is paid to the diagnosis of malignancy and therefore to its clinical manifestations, and therefore sometimes misdiagnosis of benign disorders is considered more by experts. Two important points should be noted here. First, many children diagnosed with cancer in the early stages of the disease do not present with musculoskeletal manifestations, and in other

Author, year	Selection				Comparability		Outcome			Total
	❶	❷	❸	❹	❺	❻	❼	❽	❾	
Roser et al, 2024	★	★	★		★	★	★	★	★	8
Dybedokken et al, 2024	★	★	★	★	★	★	★	★		8
Civino et al, 2021	★	★	★	★	★	★	★	★		8
Kang et al, 2017	★	★	★	★	★	★	★	★	★	9
Riccio et al, 2013	★	★	★		★	★	★	★	★	9
Sinigaglia et al, 2008	★	★	★	★	★	★	★	★		8
Campos et al, 2008	★	★	★	★		★	★	★		7
Robazzi et al, 2007	★	★	★	★	★	★	★	★	★	9
Murthi et al, 2001	★	★	★	★	★	★	★	★	★	9
Mehlman et al, 1999	★	★	★	★	★	★	★	★	★	9
Kai et al, 1996	★	★	★	★	★	★	★	★		8
Rogalsky et al, 1986	★	★	★	★	★	★	★	★	★	9
Costello et al, 1983	★	★	★	★	★	★	★	★	★	9

Fig. 2 The quality assessment of the studies according to the nine-star Newcastle-Ottawa Scale (NOS) scoring system

words, the occurrence of these manifestations and complaints can be a profile of the advanced stages of cancer. Secondly, it is very difficult to distinguish between primary bone, metabolic and rheumatologic disorders and cancer in children, and therefore, it seems that periodic tracking of musculoskeletal manifestations is very necessary in children with a definite diagnosis of cancer.

What our study emphasizes is the significant prevalence of musculoskeletal manifestations in children with various types of malignancies, especially hematological malignancies. Based on the findings of this study, about one-third of leukemia patients are faced with multiple bone and rheumatologic manifestations, and the occurrence of these manifestations is basically associated with the inability of children's motor and functional functions and therefore, disruption of their quality of life. According to the results of some studies, this manifestation sometimes affects more than 80% of children. In the context of childhood hematopoietic malignancies, bone pain is a common manifestation usually localized in long bones along with spinal vertebral bodies and this pain usually occurs due to different bone pathological lesions such as pathological fractures, bone compression, osteoporosis, bone structural deviation, bone swelling and referral pain from joints. In most cases, the pain is severe, sharp, localized and sudden in onset. In many cases, these manifestations may mimic inflammatory joint and rheumatic diseases. It is sometimes very difficult to distinguish between musculoskeletal manifestations caused by malignancy and primary rheumatic diseases. The occurrence of arthritis or arthralgia is a common finding in children suffering from malignancies, especially hematological cancers.

The most of pediatric rheumatic diseases are associated with musculoskeletal manifestations, including bone pain, arthritis, arthralgia, and myalgia. Systemic juvenile rheumatoid arthritis, systemic lupus erythematosus, juvenile dermatomyositis and some types of vasculitis are the most common of this group of diseases. For the differential diagnosis of these diseases, the presence of signs and symptoms of involvement of other organs and paraclinical findings are helpful, but in some cases, it is

Table 2 The prevalence of musculoskeletal manifestations of childhood malignancies

Author, year	Prevalence of musculoskeletal manifestation	Types of manifestations
Roser et al., 2024	192/756 (Leukemia) 124/577 (Lymphoma) 105/417 (CNS tumor) 25/87 (Neuroblastoma)	Osteoporosis (2.4%), Arm- or leg-length discrepancy (4.3%), Limited joint mobility (6.8%), Persistent pain in bones or joints (7.5%), Scoliosis (8.2%), Changes to chest/ribs (1.6%)
Dybedokken et al., 2024	33/58	Back pain (64%), Gait abnormalities (52%), Leg pain (49%), Nocturnal pain (33%), Neck pain (15%), Arthritis (3%), Unspecified (21%)
Civino et al., 2021	Total: 324/1277 Bone cancer: 53/66 Langerhans histiocytosis: 16/34 Leukemia: 189/582 Soft-tissue sarcomas: 16/68 Neuroblastoma: 21/109	Joint pain (hip, knee) Limb bone pain
Kang et al., 2017	Total: 24/125	---
Riccio et al., 2013	73/328	Clinical: pain, septic arthritis-type symptoms, and five osteomyelitis-type symptoms. Joint compression in the tibia-tarsus, knee, coxofemoral, and elbow, vertebral collapses, limited flexor and extensor muscle capacity Radiological: osteoporosis, pathological fractures, osteolysis, osteosclerosis, periosteal reactions, metaphyseal bands, avascular necrosis (75.3%)
Sinigaglia et al., 2008	Total: 46/122	Clinical: pain (34.4%), functional impairment (22.9%), limping (12.3%), swelling (10.6%), and joint effusion (5.7%) Radiological: osteolysis (13.1%), metaphyseal bands (9.8%), osteopenia (9%), osteosclerosis (7.4%), permeative pattern (5.7%), pathological fractures (5.7%), periosteal reactions (4.1%), and mixed lysis-sclerosis lesions (2.5%)
Campos et al., 2008	10/13 10/12	Arthritis and/or arthralgia
Robazzi et al., 2007	222/406	Joint tenderness (16.2% in ALL, 5.4% in AML), arthritis (26.6% in ALL, 9.7 in AML), bone tenderness (26.1% in ALL, 16.1% in AML), limb tenderness (49.5% in ALL, 25.8% in AML), and antalgic gait (32.8% in ALL, 9.7% in AML)
Murthi et al., 2001	33/128	Multiple joint pains (21.8%), paraplegia (two patients), dislocation of a left hip (one patient), and swollen mandible (one patient).
Mehlman et al., 1999	24/52	Spinal deformity (46%)
Kai et al., 1996	36/168 (ALL) 6/57 (AML)	Locomotor disability (69%), bone/joint pain (92%), bone/joint swelling (62%)
Rogalsky et al., 1986	Total: 22/107	Clinical: pain in the extremities, back pain, osteomyelitis, septic arthritis, or fracture Radiological: osteopenia, lytic lesions, metaphyseal bands, periosteal new bone, and sclerotic lesions (43.9%)
Costello et al., 1983	14/28	Knee arthritis

necessary to rule out malignancy with appropriate tests such as bone marrow aspiration [5, 8–11].

Benign musculoskeletal pains such as growing pains are common in children. Red flags for differentiating pathological pain from benign pain including unilateral limb pain, upper limbs pain, pain that wakes up the child and does not respond to analgesics. Also, the presence of arthritis, fever, weight loss and systemic symptoms are red flags. In these cases, examination for pathological causes including malignancy is necessary [5, 12].

In the case of other childhood cancers, it seems that more than a third of affected children face musculoskeletal complications. Of course, it should be kept in mind that in cancers related to the skeletal system, it is obvious that a significant part of affected children have musculoskeletal manifestations. As the prevalence of musculoskeletal manifestations in patients with bone malignancies, spine cancers and central nervous system malignancies, the prevalence of musculoskeletal involvement will be much higher. Of course, there are very few studies on the mentioned manifestations among non-hematological malignancies and it is not possible to evaluate them systematically at the moment. The limitation of this study is that we investigated common malignancies and meta-analysis was not possible.

Conclusion

Musculoskeletal manifestations occur in many cases of childhood malignancies. Therefore, clinicians should consider malignancies when dealing with any child with musculoskeletal manifestations, especially in the presence of red flags.

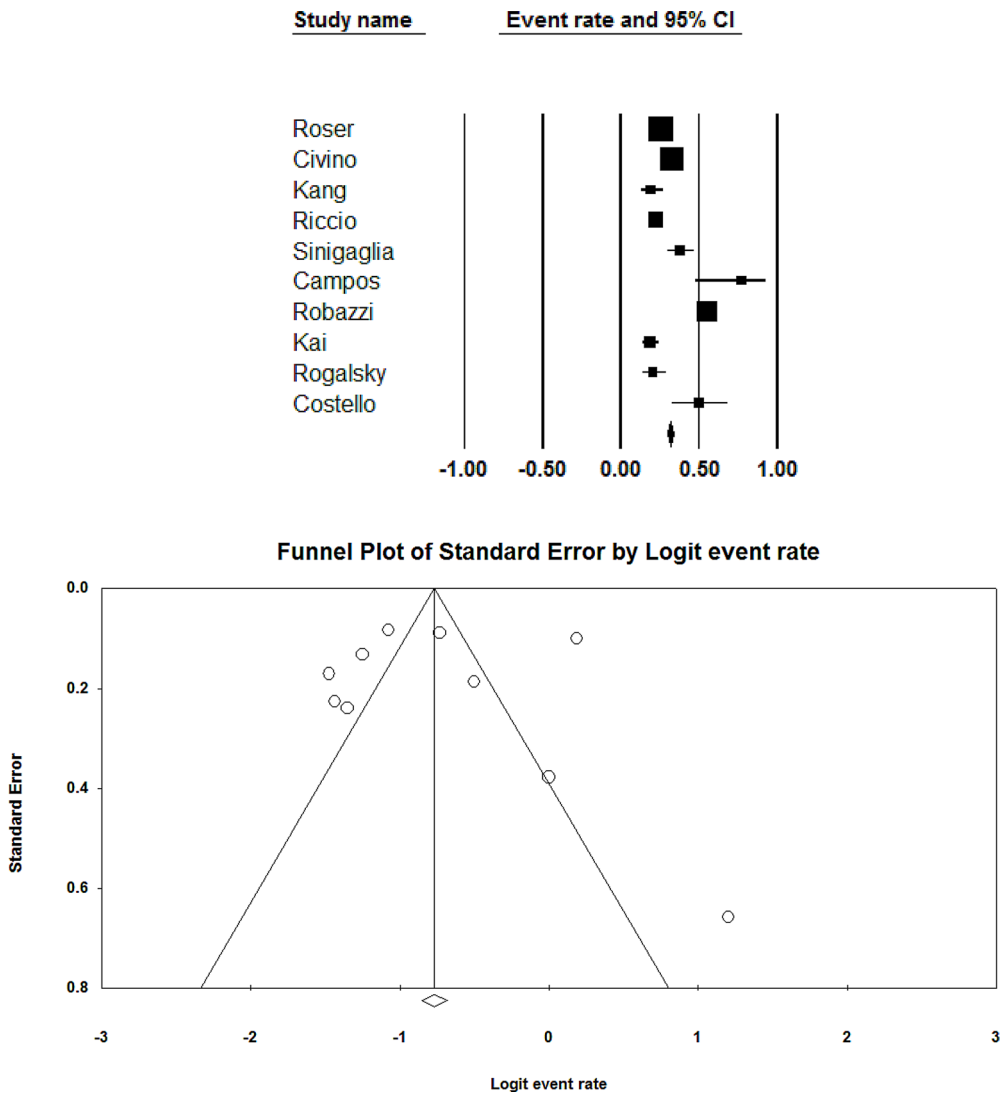

Fig. 3 The overall prevalence of musculoskeletal manifestations in children with leukemia, The funnel plot indicating publication bias across the studies

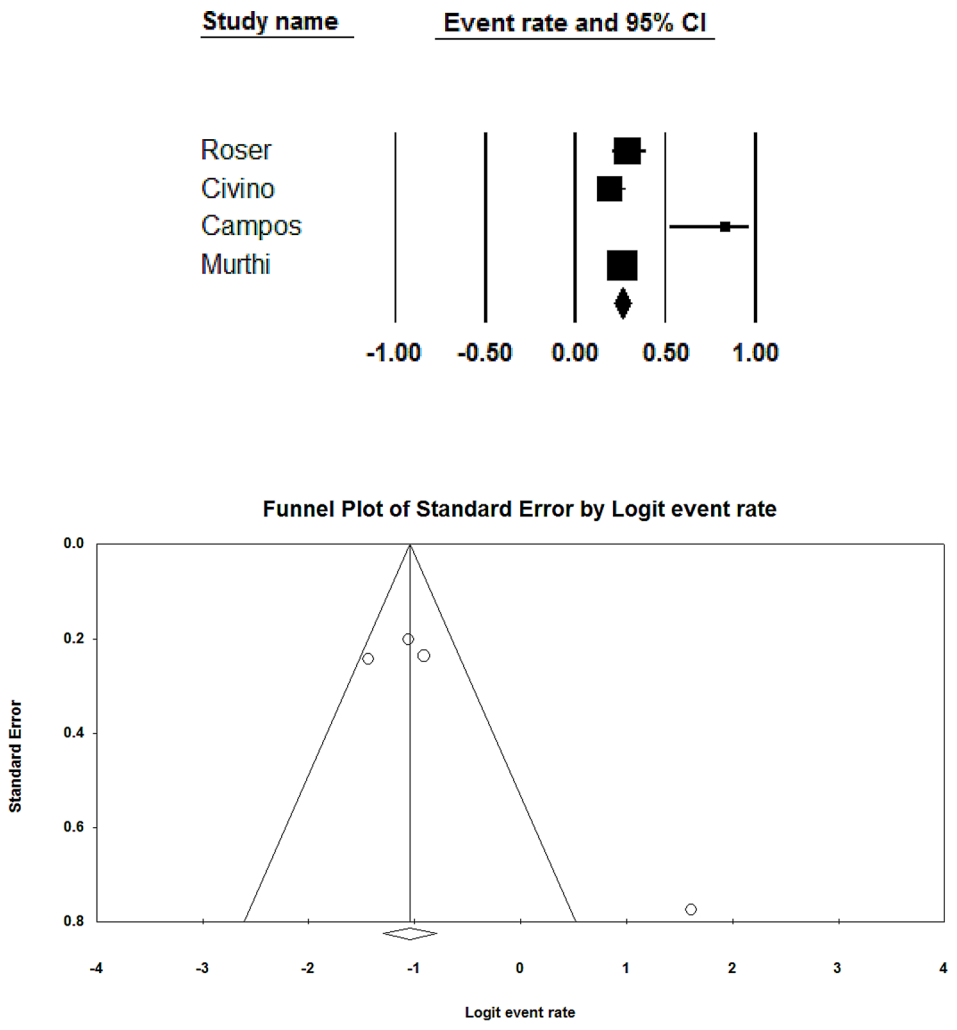

Fig. 4 The overall prevalence of musculoskeletal manifestations in children with neuroblastoma, The funnel plot indicating publication bias across the studies

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-05556-1.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
This work was supported by the Isfahan University of Medical Sciences and the authors are sincerely grateful.

Author contributions
M. J: Substantial contributions to the conception, Design of the work, Final approval of the work. F. Kh: Analysis and interpretation of data for the work, Drafting the work. All authors read and approved the final manuscript.

Funding
Isfahan University of Medical Sciences, Thesis code: 340312.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The ethical approval code was: Isfahan University of Medical Sciences, IR.MUI.REC1403.035.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 25 October 2024 / Accepted: 27 February 2025
Published online: 17 March 2025

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