Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Musculoskeletal Manifestations at the Initial Presentation of Acute Leukemia in Children: A Retrospective Study from Southern Iran

Mohammad Bagher

mbrahmati@gmail.com

Hormozgan University of Medical Sciences

Borhan Bafandegan

Hormozgan University of Medical Sciences

Mohammad Ali Molavi

Hormozgan University of Medical Sciences

Marjan Tariverdi

Hormozgan University of Medical Sciences

Shahram Zare

Hormozgan University of Medical Sciences

Research Article

Keywords: Acute leukemia, Childhood leukemia, Musculoskeletal manifestations, Bone pain, Limping

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11562221/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Musculoskeletal symptoms are common in children with acute leukemia and may initially be mistaken for more common orthopedic or rheumatologic conditions. This can make early recognition challenging.

Objective

To describe the frequency and pattern of musculoskeletal manifestations at the time of diagnosis in children with acute leukemia at a tertiary pediatric center in southern Iran.

Methods

We conducted a retrospective cross-sectional study of 40 children aged 1–15 years who were diagnosed with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) at Bandar Abbas Children's Hospital between 2012 and 2022. Demographic and clinical information was collected from medical records. Musculoskeletal manifestations were described, and their relationships with sex and leukemia subtype were explored.

Results

Of the 40 children, 23 (57.5%) were boys. ALL was diagnosed in 31 children (77.5%), while 9 (22.5%) had AML. Limping was the most frequently reported musculoskeletal manifestation (15/40, 37.5%), followed by bone pain (13/40, 32.5%), limb pain (7/40, 17.5%), arthritis (4/40, 10.0%), and joint pain (3/40, 7.5%). No statistically significant associations were reported between individual manifestations and either sex or leukemia subtype. These findings should be interpreted with caution because of the relatively small sample size.

Conclusion

Limping and bone pain were the most frequently documented musculoskeletal manifestations in this group of children with acute leukemia. When these symptoms are persistent or unexplained, clinicians should consider a broader range of possible causes, including malignancy, particularly when other clinical findings raise concern. Further studies involving larger groups of children are needed to better understand the relationship between musculoskeletal symptoms, diagnostic delay, and the early recognition of childhood leukemia.

Introduction

Acute leukemia is one of the most common malignancies in children, accounting for approximately 30% of all pediatric cancers(1). The two main subtypes, Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML), have distinct pathophysiological mechanisms but often present with overlapping clinical symptoms(2). While early diagnosis and treatment significantly improve survival rates, the nonspecific nature of initial symptoms can lead to delayed recognition, impacting prognosis and treatment outcomes(3).

Among the various clinical manifestations of acute leukemia, musculoskeletal symptoms are frequently overlooked as an early presentation. These symptoms, including bone pain, arthritis, and limping, can be mistakenly attributed to benign conditions such as growing pains, juvenile idiopathic arthritis, or viral infections(4). However, studies suggest that a substantial proportion of pediatric leukemia patients initially present with osteoarticular complaints before hematologic abnormalities become apparent(5, 6).

The pathophysiology of these symptoms is multifactorial, involving leukemic infiltration of the bone marrow, periosteal elevation due to expanding blast cells, and cytokine-mediated inflammation. For instance, bone pain in leukemia is often localized to the metaphyseal regions of long bones, such as the tibia or femur, and may mimic orthopedic conditions (7).

The diagnostic challenge is compounded by the variability in symptom severity and duration. A retrospective cohort study found that 20% of children with ALL had musculoskeletal pain as their primary complaint, with a median delay of 4 weeks before leukemia was confirmed(8). In a previous study, musculoskeletal manifestations were observed in 29% of pediatric patients with AML, with 8% initially misdiagnosed with a musculoskeletal disorder, predominantly due to nonspecific pain-related presentations. No substantial differences were noted between patients with and without musculoskeletal involvement regarding clinical features at the time of AML diagnosis, and hematologic parameters were comparably affected in both groups. Nonetheless, patients presenting with musculoskeletal symptoms demonstrated a higher likelihood of elevated lactate dehydrogenase (LDH) and ferritin levels(9). A systematic review identified the principal musculoskeletal manifestations associated with pediatric malignancies as bone pain, swelling, tenderness, fractures, vertebral collapse, joint effusion, and joint tenderness. Additional presentations included symptoms resembling septic arthritis or osteomyelitis, as well as true osteomyelitis. The pooled prevalence of musculoskeletal involvement among children with hematopoietic tumors, including acute lymphoblastic leukemia and acute myeloid leukemia, was 32.1%. Similarly, the prevalence among patients with neuroblastoma was 30.5%. Reported rates for other pediatric cancers varied more widely, ranging from 23.5% to 80.3%(10). These findings underscore the importance of maintaining a high index of suspicion for leukemia in children with persistent or atypical musculoskeletal symptoms, even in the absence of cytopenias or overt laboratory abnormalities.

Delayed diagnosis has significant clinical implications. A study demonstrated that a longer time to diagnosis negatively affected the clinical outcome of childhood ALL(11). Reducing the time to diagnosis could help to improve survival in these patients. This highlights the critical need for integrating

musculoskeletal evaluations into routine diagnostic workflows for pediatric patients with unexplained pain or swelling.

Understanding the prevalence and characteristics of musculoskeletal manifestations in children with acute leukemia is crucial for early detection and timely referral. Given the potential for misdiagnosis, this study aims to investigate the frequency and patterns of osteoarticular symptoms in pediatric leukemia patients, differentiating between ALL and AML, and assessing variations based on age and gender. By highlighting the importance of these early indicators, we seek to improve awareness among pediatricians and general practitioners, ultimately facilitating prompt diagnosis and treatment initiation.

Objective

To determine the types of musculoskeletal manifestations in children with acute leukemia, to examine differences in these manifestations based on gender and age groups, and to analyze the variations of these symptoms between Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML) .

Materials and Methods

Study Design and Setting

This study is a descriptive-analytical, retrospective cross-sectional study conducted at Bandar Abbas Children's Hospital. The study population included pediatric patients diagnosed with Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML) who were hospitalized between 2012 and 2022.

Study Population and Sampling

The study included children aged 1 to 15 years with a confirmed diagnosis of acute leukemia. All eligible patients diagnosed during the study period were included. The inclusion criteria were: A confirmed diagnosis of ALL or AML based on bone marrow aspiration and immunophenotyping, availability of complete medical records, including laboratory findings, imaging reports, and clinical symptoms at the time of admission.

Exclusion criteria included:

The exclusion criteria include pre-existing musculoskeletal disorders, congenital bone diseases, autoimmune conditions, symptoms developing after leukemia treatment, and incomplete medical records.

Data Collection

During the study period, more than 100 children were diagnosed with acute leukemia at Bandar Abbas Children's Hospital. 40 children met the eligibility criteria and were included in the final analysis. Data were collected from patients' medical records, including demographic details (age, gender), clinical presentations, laboratory findings, imaging results, and treatment history. Musculoskeletal manifestations were categorized into bone pain (generalized or localized), arthritis (joint swelling, tenderness, and limited range of motion), limping (gait abnormalities without a clear traumatic cause), and other skeletal complaints (e.g., vertebral or hip pain).

Laboratory and imaging analyses were categorized as follows: Complete Blood Count (CBC), peripheral blood smear, bone marrow aspiration findings, and serum levels of lactate dehydrogenase (LDH), uric acid, calcium, and inflammatory markers. Additionally, X-rays, MRIs, and bone scans (if available) were reviewed to identify any skeletal abnormalities, osteopenia, or lytic lesions.

Statistical Analysis

Data were analyzed using SPSS software version 22. Descriptive statistics, including mean, standard deviation, and frequency distributions, were used to summarize patient characteristics. Comparative analyses were performed using: Chi-square test for categorical variables (e.g., presence vs. absence of musculoskeletal symptoms), Independent t-test for continuous variables (e.g., hemoglobin levels, WBC count), Logistic regression analysis to identify potential predictors of musculoskeletal involvement. A p-value of < 0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1402.071), and written informed consent was obtained from parents or legal guardians in accordance with the Declaration of Helsinki.

Results

This study evaluated the skeletal and articular manifestations that presented initially in children with acute leukemia admitted to Bandar Abbas Children's Hospital. A total of 40 children diagnosed with acute leukemia (either AML or ALL) between 2012 and 2022 were included in the analysis. Among the participants, 57.5% (23/40) were male, and 42.5% (17/40) were female. The mean age for females was 6.8 years (range: 2–14 years), while for males, it was 7.4 years (range: 3–13 years). Acute lymphoblastic leukemia (ALL) was more common, accounting for 77.5% (31/40) of the cases, compared to acute myeloid leukemia (AML), which made up 22.5% (9/40).

The most frequently observed musculoskeletal manifestations included: Limping (37.5%, 15/40), Bone pain (32.5%, 13/40), Limb pain (17.5%, 7/40), Arthritis (10%, 4/40), and Joint pain (7.5%, 3/40) (Table 1). No statistically significant association was found between musculoskeletal manifestations and gender

($p > 0.05$) (Table 2). However, limping was more common in males (47.8%) than in females (23.5%), while arthritis was somewhat more prevalent in females (17.6%) compared to males (4.3%).

Table 1
Prevalence of Osteoarticular Manifestations in Children with Acute Leukemia

Variable	Count (Percentage)
Bone Pain	13 (32.5%)
Limping	15 (37.5%)
Arthritis	4 (10.0%)
Limb Pain	7 (17.5%)
Joint Pain	3 (7.5%)

Table 2
Association Between Osteoarticular Manifestations and Gender

Variable	Total (%)	Female (%)	Male (%)	P-value
Bone Pain	13 (32.5)	7 (41.2)	6 (26.1)	0.25
Limping	15 (37.5)	4 (23.5)	11 (47.8)	0.10
Arthritis	4 (10.0)	3 (17.6)	1 (4.3)	0.19
Limb Pain	7 (17.5)	2 (11.8)	5 (21.7)	0.35
Joint Pain	3 (7.5)	2 (5.0)	1 (2.5)	0.30

No significant association was observed between musculoskeletal manifestations and leukemia subtype ($p > 0.05$) (Table 3). Specifically, limping was reported in 38.7% of ALL patients versus 33.3% of AML patients, and bone pain occurred in 32.3% of ALL patients compared to 33.3% of AML patients. Limping and bone pain were the most frequent initial musculoskeletal manifestations.

Table 3
Association Between Osteoarticular Manifestations and Leukemia Type (AML vs. ALL)

Variable	Total (%)	AML (%)	ALL (%)	P-value
Bone Pain	13 (32.5)	3 (33.3)	10 (32.3)	0.62
Limping	15 (37.5)	3 (33.3)	12 (38.7)	0.54
Arthritis	4 (10.0)	1 (11.1)	3 (9.7)	0.65
Limb Pain	7 (17.5)	1 (11.1)	6 (19.4)	0.49
Joint Pain	3 (7.5)	1 (33.3)	2 (66.7)	-

Discussion

This study adds data from a tertiary pediatric center in Bandar Abbas, Hormozgan Province, in southern Iran, a region where sickle cell disease is relatively prevalent and represents an important part of pediatric clinical practice. In this setting, musculoskeletal complaints, particularly bone pain, may frequently be encountered in children with sickle cell disease and other common pediatric conditions. Consequently, distinguishing leukemia-related musculoskeletal manifestations from symptoms associated with sickle cell disease or other benign conditions can present a particular diagnostic challenge for clinicians. Our findings provide local data on the pattern of musculoskeletal manifestations in children with acute leukemia and highlight the importance of maintaining clinical awareness of leukemia when evaluating persistent or unexplained musculoskeletal complaints, even in regions where other causes of bone pain are common. Although these findings cannot be considered representative of all children in southern Iran, they may be relevant to clinicians working in similar healthcare settings. These results emphasize the importance of recognizing these osteoarticular symptoms as potential warning signs of malignancy, particularly in a pediatric population where early detection is crucial for improving prognosis (12, 13).

Our observations align with existing literature reporting that MSK symptoms are among the most common initial presentations of childhood leukemia, occurring in 30–40% of patients (14). This frequently leads to initial misdiagnoses of juvenile idiopathic arthritis, benign growing pains, or orthopedic conditions, which can delay crucial oncologic evaluation (15). Furthermore, our data support the established finding that these symptoms are more prevalent in acute lymphoblastic leukemia (ALL) than in acute myeloid leukemia (AML) (16, 17), a distinction likely attributable to the higher burden of leukemic infiltration in the bone marrow and subsequent periosteal inflammation in ALL (18).

A significant diagnostic challenge remains the overlap of leukemia-related MSK pain with common pediatric conditions. Several clinical features can help distinguish a malignant etiology: leukemia-related pain is often persistent, worsens over time, is frequently diffuse and non-symmetrical, and is refractory to conventional analgesics. The presence of "red flag" signs such as fever, pallor, unexplained bruising, or

hepatosplenomegaly should raise clinical suspicion. Laboratory and radiographic findings, including abnormal blood counts, elevated lactate dehydrogenase (LDH), osteopenia, or metaphyseal bands, are critical for differentiating leukemia from benign disorders (19, 20, 21).

It is important to note that while we describe these as "early" signs, they often precede formal diagnosis by a median of 3–4 weeks, a window that can contribute to diagnostic delays, especially if initial blood tests are non-revealing (22). Although ALL incidence peaks between ages 2–5, MSK presentations occur across the pediatric age range; future studies should therefore analyze whether osteoarticular patterns differ by age (23).

Finally, it is essential to distinguish these infiltrative symptoms from metabolic complications of advanced disease. Syndromes like tumor lysis syndrome (causing myalgias or weakness) or leukostasis (causing respiratory/neurologic symptoms) typically present with systemic signs and occur later, often post-treatment. In contrast, a child presenting with persistent focal bone pain or isolated limping should prompt an evaluation for marrow-infiltrative processes, including targeted laboratory tests (complete blood count [CBC], LDH, uric acid, electrolytes) and imaging (24).

Conclusion

Musculoskeletal manifestations, particularly limping and bone pain, were common findings at the initial presentation of children with acute leukemia in this study. These symptoms may be attributed to more common musculoskeletal or hematologic conditions, potentially making clinical recognition challenging. In regions such as southern Iran, where sickle cell disease is also encountered in pediatric practice, clinicians should consider acute leukemia in the differential diagnosis of children presenting with persistent or unexplained musculoskeletal complaints. Careful clinical assessment and appropriate investigations may help identify children who require further evaluation for an underlying malignancy. Larger multicenter studies are needed to confirm these findings and to clarify the relationship between musculoskeletal manifestations and the time to leukemia diagnosis.

Limitations and Future Directions

This study has several limitations that should be acknowledged. First, the relatively small sample size (40 patients) limits the statistical power and generalizability of the findings. Second, the retrospective design may have introduced bias due to incomplete documentation in medical records and reliance on symptom reports from patients or caregivers, potentially affecting the accuracy of musculoskeletal symptom characterization. In particular, the anatomical location and severity of bone or joint pain were not consistently documented, limiting a more detailed assessment of these manifestations. Furthermore, we did not examine the association between musculoskeletal manifestations and patient age, although the presentation of osteoarticular symptoms may vary across pediatric age groups.

Future studies should address these limitations through larger, preferably multicenter prospective studies. Systematic documentation of the location, severity, and duration of musculoskeletal symptoms,

together with age-stratified analyses, would provide a more comprehensive understanding of their clinical patterns in childhood acute leukemia. Such studies may also help clarify the potential role of musculoskeletal manifestations in the early recognition of leukemia among children presenting with persistent or unexplained musculoskeletal complaints.

Declarations

Ethics approval and consent to participate: Ethically approved by the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1402.071). Written informed consent was obtained from a legally authorized representative(s) for the anonymized patient.

Clinical trial number: not applicable.

Consent for publication: The authors declare that they have no conflict of interest.

Availability of data and material: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Competing interests: The authors have non-financial competing interests.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements: We gratefully acknowledge the dedicated efforts of the investigators, the coordinators, the volunteer patients who participated in this study, and the Clinical Research Development Unit (CRDU) of BandarAbbass Children's Hospital. During the preparation of this work, the authors used "ChatGPT-4" in order to grammar checking," "to rephrase complex sentences," "to improve readability. After using this tool , the author reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

1. Belson M, Kingsley B, Holmes A. Risk factors for acute leukemia in children: a review. Environ Health Perspect. 2007;115(1):138–45. 10.1289/ehp.9023.
2. Wemyss C, Jones E, Stentz R, Carding SR. Acute Myeloid Leukaemia and Acute Lymphoblastic Leukaemia Classification and Metabolic Characteristics for Informing and Advancing Treatment. Cancers (Basel). 2024;16(24):4136. 10.3390/cancers16244136.
3. Mullen CJR, Barr RD, Franco EL. Timeliness of diagnosis and treatment: the challenge of childhood cancers. Br J Cancer. 2021;125(12):1612–1620. 10.1038/s41416-021-01533-4. Epub 2021 Sep 1. Erratum in: Br J Cancer. 2021;125(8):1178. doi: 10.1038/s41416-021-01548-x.
4. Slouma M, Hannech E, Ghedira H, Dhahri R, Khrifech Y, Doghri R, Gharsallah I. Osteoarticular manifestation of acute lymphoblastic leukemia in adults: a literature review. Clin Rheumatol.

2023;42(2):607–20. 10.1007/s10067-022-06459-7.

5. Kittivisuit S, Sripornsawan P, Songthawee N, Chavananon S, McNeil EB, Chotsampancharoen T. Musculoskeletal involvement in childhood leukemia: Characteristics and survival outcomes. Pediatr Rheumatol Online J. 2022;20(1):34. 10.1186/s12969-022-00692-9.
6. Gkoudina A, Gekas C, Polydorides M, Graikos G, Papakonstantinou E, Saloupis P. Pediatric Leukemia From an Orthopedic Perspective: A Case of Acute Lymphoblastic Leukemia Initially Managed as Septic Hip With Osteomyelitis. Cureus. 2022;14(4):e24103. 10.7759/cureus.24103.
7. Pimenta DB, Varela VA, Datoguia TS, Caraciolo VB, Lopes GH, Pereira WO. The Bone Marrow Microenvironment Mechanisms in Acute Myeloid Leukemia. Front Cell Dev Biol. 2021;9:764698. 10.3389/fcell.2021.764698.
8. Hijiya N, Hudson MM, Lensing S, Zacher M, Onciu M, Behm FG, Razzouk BI, Ribeiro RC, Rubnitz JE, Sandlund JT, Rivera GK, Evans WE, Relling MV, Pui CH. Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. JAMA. 2007;297(11):1207–15. 10.1001/jama.297.11.1207.
9. Jensen ABH, Andersen HRP, Jensen ST, Jensen CF, Amstrup J, Mathiasen R, Henriksen KA, Hasle H, Callesen MT, Brix N. Musculoskeletal Symptoms and Misdiagnoses in Children With Acute Myeloid Leukaemia: A Nationwide Cohort Study. Eur J Haematol. 2025;114(1):57–69. 10.1111/ejh.14303.
10. Jari M, Ana FK. Musculoskeletal manifestations of childhood malignancies: a systematic review and meta-analysis. BMC Pediatr. 2025;25:200. https://doi.org/10.1186/s12887-025-05556-1.
11. Dai Q, Liu R, Wang Y, Ye L, Peng L, Shi R, Guo S, He J, Yang H, Zhang G, Jiang Y. Longer Time Intervals From Symptom Onset to Diagnosis Affect the Overall Survival in Children With Acute Lymphoblastic Leukemia. J Pediatr Hematol Oncol. 2022;44(6):285–92. 10.1097/MPH.0000000000002344.
12. Kittivisuit S, Sripornsawan P, Songthawee N, et al. Musculoskeletal involvement in childhood leukemia: Characteristics and survival outcomes. Pediatr Rheumatol. 2022;20:34. https://doi.org/10.1186/s12969-022-00692-9.
13. Louvigné M, Rakotonjanahary J, Goumy L, et al. Persistent osteoarticular pain in children: early clinical and laboratory findings suggestive of acute lymphoblastic leukemia (a multicenter case-control study of 147 patients). Pediatr Rheumatol. 2020;18:1. https://doi.org/10.1186/s12969-019-0376-8.
14. Torres Jimenez AR, Solis Vallejo E, Cespedes Cruz AI, Ramirez Miramontes JV, Cortina Olvera GDC, Velazquez Cruz A, Sanchez Jara B. Differences between leukemic arthritis and juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2023;21(1):50. 10.1186/s12969-023-00836-5.
15. Ehrenfeld M, Gur H, Shoenfeld Y. Rheumatologic features of hematologic disorders. Curr Opin Rheumatol. 1999;11(1):62–7. https://doi.org/10.1097/00002281-199901000-00011.
16. Civino A, Alighieri G, Prete E, et al. Musculoskeletal Manifestations of Childhood Cancer and Differential Diagnosis With Juvenile Idiopathic Arthritis (ONCOREUM): A Multicentre, Cross-Sectional Study. Lancet Rheumatol. 2021;3:507–16. [DOI] [PubMed] [Google Scholar].

17. Brix N, Amstrup J, Nørgaard M, Hagstrøm S, Hasle H, Herlin T. Musculoskeletal Diagnoses Before Cancer in Children: A Danish Registry-Based Cohort Study. J Pediatr. 2021;242:32–8.
18. Jensen ABH, Andersen HRP, Jensen ST, Jensen CF, Amstrup J, Mathiasen R, Henriksen KA, Hasle H, Callesen MT, Brix N. Musculoskeletal Symptoms and Misdiagnoses in Children With Acute Myeloid Leukaemia: A Nationwide Cohort Study. Eur J Haematol. 2025;114(1):57–69. 10.1111/ejh.14303.
19. Coluzzi F, Rocco M, Green Gladden R, Persiani P, Thur LA, Milano F. Pain Management in Childhood Leukemia: Diagnosis and Available Analgesic Treatments. Cancers (Basel). 2020;12(12):3671. 10.3390/cancers12123671.
20. Sakata H, Nakao A, Matsuda K, Yoshie N, Yamada T, Osako T, Iwano M, Kotani J. Acute leukemia presenting as bone pain with normal white blood cell count. Acute Med Surg. 2014;1(4):249. 10.1002/ams2.46.
21. Owaidhah NA, Khawaji ZY, Alahmadi MA, Badawi AS, Mogharbel GH, Makhdoom ON. Epidemiological Trends and Clinical Characteristics of Childhood Leukemia in Saudi Arabia: A Review. Cureus. 2022;14(8):e28178. 10.7759/cureus.28178.
22. Kittivisuit S, Sripornsawan P, Songthawee N, Chavananon S, McNeil EB, Chotsampancharoen T. Musculoskeletal involvement in childhood leukemia: Characteristics and survival outcomes. Pediatr Rheumatol Online J. 2022;20(1):34. 10.1186/s12969-022-00692-9. Erratum in: Pediatr Rheumatol Online J. 2022;20(1):37. doi: 10.1186/s12969-022-00695-6.
23. Ding F, Deng L, Xiong J, Cheng Z, Xu J. Analysis of global trends in acute lymphoblastic leukemia in children aged 0–5 years from 1990 to 2021. Front Pediatr. 2025;13:1542649. 10.3389/fped.2025.1542649.
24. Adeyinka A, Kaur A, Bashir K. Tumor Lysis Syndrome. [Updated 2024 Oct 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK518985/?utm_source=chatgpt.com