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Malignancy-associated hypercalcemia in children: A Systematic Review

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Abstract

Purpose
Malignancy-associated hypercalcemia (MAH) is a rare but potentially life-threatening oncologic emergency in pediatric patients. Although extensively described in adults, evidence regarding the epidemiology, pathophysiology, clinical presentation, management, and outcomes in children remains limited. This systematic review aimed to summarize the current evidence on pediatric MAH.

Methods
A systematic literature search was conducted in PubMed/MEDLINE, Embase, and the Cochrane Library following PRISMA guidelines. Studies reporting hypercalcemia in patients aged 0-18 years with an underlying malignancy were eligible for inclusion. Data regarding incidence, malignancy subtype, clinical presentation, pathophysiology, treatment, and outcomes were extracted. Risk of bias was assessed using the Joanna Briggs Institute tool.

Results
A total of 123 studies were included, comprising 16 cohort studies and 107 case reports. The reported prevalence of MAH was generally below 1%. MAH occurred in hematological malignancies (49%), predominantly acute lymphoblastic leukemia (ALL, 75%), and solid tumors (51%). Hypercalcemia was reported at initial diagnosis (44%) and disease relapse (36%). The most reported underlying mechanisms were parathyroid hormone-related peptide (PTHrP)-mediated hypercalcemia (11.6%) and osteolytic bone destruction (9.9%). Management strategies were relatively consistent and typically included intravenous hydration, bisphosphonate therapy, and treatment of the underlying malignancy.

Conclusion
MAH is an uncommon yet clinically significant complication in pediatric oncology, occurring across hematologic and solid malignancies. The principal underlying mechanisms are PTHrP-mediated hypercalcemia and osteolytic bone destruction. Current treatment approaches primarily consist of supportive care, antiresorptive therapy, and malignancy-directed treatment. These findings may contribute to standardized international guidelines for the diagnosis and management of pediatric MAH.

Keywords: malignancy-associated hypercalcemia; pediatric oncology; hypercalcemia; childhood cancer; systematic review.

Introduction

Malignancy-associated hypercalcemia (MAH) is a well-recognized complication in adults, occurring in up to 30% of patients with cancer [1]. In pediatric oncology, however, MAH is rare (0.4-1.3% in leukemia) [2]. Despite this, MAH may result in severe and potentially life-threatening complications, including gastrointestinal symptoms (constipation, anorexia, nausea, vomiting), acute kidney injury, pancreatitis, and altered consciousness [3].

Traditionally, MAH has been classified into four pathophysiological subtypes: (1) paraneoplastic secretion of parathyroid hormone-related peptide (PTHrP), referred to as humoral hypercalcemia of malignancy (HHM); (2) local osteolytic hypercalcemia mediated by cytokine-induced bone resorption; (3) tumor-associated production of 1,25-dihydroxyvitamin D by the tumor; and (4) ectopic secretion of parathyroid hormone (PTH) [1, 4]. In adults, HHM is the predominant mechanism and is most associated with solid malignancies, including squamous cell carcinomas and breast cancer [1]. However, the spectrum of malignancies in pediatric oncology differs substantially from that in adults, and it remains unclear whether the pathophysiological distribution applies to children.

Management of severe hypercalcemia may consist of intravenous (re)hydration, with or without loop diuretics, antiresorptive therapy, including bisphosphonates or calcitonin, and denosumab may be considered in refractory cases [5–7]. A recent narrative review by Korkmaz et al. provided an important overview of the incidence, clinical characteristics, pathophysiology, treatment strategies, and outcomes of pediatric MAH [8]. However, the literature has not been systematically evaluated, and the rarity of MAH has left the evidence fragmented across small cohort studies and numerous case reports. Therefore, we conducted the first comprehensive systematic review to synthesize the evidence on the epidemiology, underlying mechanisms, clinical presentation, management, and outcomes of MAH in children with cancer. By consolidating the current evidence, this review provides a foundation for the development of evidence-based practical clinical guidelines for the diagnosis and management of pediatric MAH.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

Search strategy

A comprehensive literature search was performed in the following databases: PubMed/MEDLINE, Embase, and the Cochrane Library. Search terms used a combination of MeSH terms and keywords. Key search criteria included terms related to “children” and “adolescents”, “malignancy”, and “hypercalcemia.”
The full PubMed search can be found in Supplementary Table S1. The search strategy was adapted for all databases, replacing MeSH terms with the appropriate keywords. The initial search took place on February 3, 2026. No restrictions were applied regarding publication date.

The search strategy was developed based on the PICO (Patient or Population covered, Intervention, Comparator, Outcome) framework, as follows: *Population:* children and adolescents (0-18 years) with malignancy-associated hypercalcemia. *Intervention:* all aspects related to this condition, including diagnostic strategies and management approaches. As this review aimed to provide an overview of existing knowledge, no comparison group was defined. *Outcomes:* included incidence, risk factors, underlying pathophysiological mechanisms, clinical presentation, diagnostic strategies, management, and prognosis of malignancy-associated hypercalcemia in the pediatric population.

Inclusion and exclusion criteria

Studies were included with the following criteria: 1) pediatric patients aged 0-18 (<19) years at the time of hypercalcemia; 2) a confirmed diagnosis of a malignant disease (all cancer types); 3) hypercalcemia occurring at initial cancer diagnosis, during the disease course, or at relapse; 4) reporting on at least one of the following aspects of cancer-associated hypercalcemia: incidence, risk factors, clinical presentation, underlying pathophysiological mechanisms, management or prognosis; 5) study design comprising randomized controlled trials, cohort studies, case-control studies, or case reports. Studies were excluded with the following criteria: 1) studies not reporting pediatric separately; 2) studies focusing on benign tumors; 3) hypercalcemia due to non-malignant etiologies (e.g., congenital disorders, vitamin D intoxication); 4) studies without relevant outcome measures about hypercalcemia; 5) hypercalcemia exclusively related to cancer treatment (e.g. use of all-trans retinoic acid); 6) studies in which parathyroid tumors were the cause of hypercalcemia; 7) articles published in languages other than English.

Study selection

All identified records were imported into Rayyan, an online platform designed for systematic literature review. Duplicate records were removed using the built-in duplicate detection function. The titles and abstracts were assessed by two independent reviewers (JT, GB) based on the before mentioned inclusion and exclusion criteria. Any discrepancies were resolved through discussion until a consensus was reached. The remaining articles were then imported into the EndNote library for full-text screening and for reference organization.

Data extraction

Data from each included study were systematically extracted using a standardized data extraction form. Data extracted from the studies included the first author, year of publication, study design, number of patients, sex, age, malignancy, serum calcium level (in mg/dL), clinical symptoms, management strategies, resolution of hypercalcemia, and outcomes. Reports with fewer than three patients were considered case reports and are presented separately in a table.

Risk of Bias

The methodological quality of the included studies was assessed using the Joanna Briggs Institute tool [10]. Each study was given an overall quality rating.

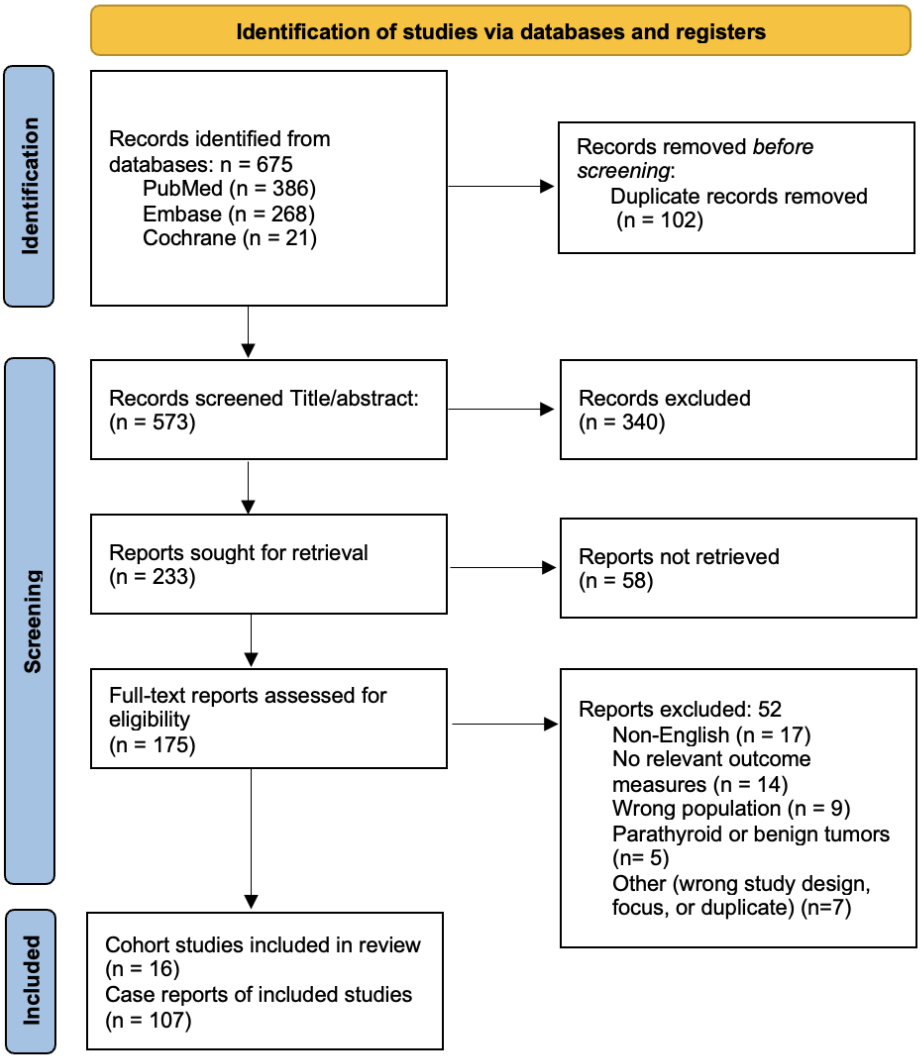


Fig. 1 PRISMA flow diagram [9]

Results

Of the 233 articles identified, 175 full-text papers were assessed for eligibility after 58 were excluded due to unavailable full text. A total of 52 articles were excluded, mainly due to non-English language (n = 17), lack of relevant outcome of hypercalcemia (n = 14), and incorrect study population (n = 9). Consequently, 123 studies met the inclusion criteria, consisting of 16 cohort studies and 107 case reports. In total, data on 289 patients could be included. The study selection process is illustrated in Figure 1.

Study characteristics

The included studies were published between 1964 and 2026, with the age of patients ranging from 0-18 years of age. Cohort studies were retrospective in design and included patient populations ranging from 4 to 39 patients. The included studies reported hypercalcemia in association with a wide range of pediatric malignancies (Table 1, Supplementary Tables S2-S3, and Figure 3).

Risk of bias assessment

The risk of bias of the 16 cohort studies included in this systematic review was illustrated using the Risk of Bias Visualization platform (Figure 2). The risk of bias was rated as 'low' in two studies, 'high' in one study, and 'some concerns' in 13 studies.

Incidence and prevalence

In retrospective cohort studies, MAH was reported in 25 of 6,055 pediatric cancer patients (0.4%) over a 29-year period [11]. A population-based study reported a prevalence ranging from 0.24% to 0.81% [12]. Two retrospective cohort studies reported MAH in 17 of 2,400 patients with solid tumors (0.7%) and in 16 of 1,231 patients (1.3%), respectively [13, 14]. Higher rates were reported in small or tumor-specific cohorts, including 8 of 148 children (5.4%) in a cross-sectional study [15], and 6 of 93 patients (6.5%) in a rhabdomyosarcoma cohort [16]. Across all six cohort studies, MAH occurred in 72 out of 10,410 pediatric cancer patients (0.7%).

Clinical symptoms

Clinical symptoms in patients with hypercalcemia ranged from asymptomatic to severe presentations (Figure 3). Reported manifestations included *gastrointestinal symptoms* (vomiting (n = 33/93 patients), nausea (n = 25/93), anorexia (n = 15/93), weight loss (n = 8/93), abdominal pain (n = 7/93), constipation (n = 7/93)), *musculoskeletal symptoms* (bone pain (n = 49/93), weakness (n = 13/93)), *renal manifestations* (polyuria (n = 8/57), polydipsia (n = 5/57), acute kidney failure (n = 22/57), nephrocalcinosis (n = 11/57)) and *neurological symptoms* (irritability (n = 12/51), lethargy (n = 2/51)). Twenty patients were asymptomatic.

In case reports, a similar distribution of symptom categories was observed, although presentations were often more severe, including marked neurological status (n = 28/117), characterized by reduced consciousness, somnolence, lethargy, and irritability, as well as occasional cardiac manifestations (n = 6/117), including shortened QT interval, electrocardiographic abnormalities, and bradycardia.

Underlying malignancies

In total, 172 patients with hypercalcemia were reported in all included cohort studies. Of these, 71/172 (41%) had hematological malignancies, 99/172 (58%) had solid tumors, and 2/172 (1%) were treated for a brain tumor. Among hematological malignancies, acute lymphoblastic leukemia (ALL) was the most frequently reported diagnosis (n = 49 (69%)), followed by non-Hodgkin lymphoma (n = 10 (14%)). Among solid tumors, hypercalcemia was most reported in rhabdomyosarcoma (n = 24 (24%)), rhabdoid tumors (n = 19 (19%)), neuroblastoma (n = 19 (19%)), and hepatoblastoma (n = 6 (6%)).

Case reports showed a similar distribution, with ALL (n = 58/71 (82%)) and solid tumors (n = 46).

Timing of hypercalcemia

In the included cohort studies, the timing of hypercalcemia was reported in 126 patients, occurring in 56 patients at diagnosis (44%), 45 patients at relapse of the disease (36%), and 25 patients during treatment (20%). Similar findings were reported in case reports, with hypercalcemia most commonly occurring at the time of initial diagnosis (n = 108/117) and sometimes during relapse or disease progression (n = 9/117).

Pathophysiology

The underlying mechanisms of MAH were reported in 12 studies. Humoral hypercalcemia of malignancy (HHM) was described in 20 patients with ALL [17]. In solid tumors, hypercalcemia was associated with osteolytic bone destruction due to tumor infiltration or bone metastases (n = 17).

In case reports, HHM was the most frequently reported mechanism (n = 23), followed by osteolytic bone destruction (n = 11). Less frequently reported mechanisms included ectopic PTH secretion (n = 8) and calcitriol-mediated hypercalcemia (n = 6).

Treatment

Treatment strategies for MAH varied across the different cohort studies. Initial management consisted of intravenous hydration (n = 85/166 (51%) patients), which was combined with loop diuretics in 62 cases. In more severe or persistent hypercalcemia, bisphosphonates (n = 36), calcitonin (n = 34), or corticosteroids (n = 26) were administered as adjunctive therapies. Bisphosphonates were reported to reduce serum calcium levels over the following several days, with pamidronate being the most used agent. Transient hypocalcemia was reported as a treatment-related adverse effect (n = 16). Treatment approaches reported in case reports were comparable to those observed in cohort studies. In n = 7 selected severe cases, additional interventions, including hemodialysis or denosumab, a RANK ligand monoclonal antibody that inhibits osteoclasts, were described (Supplementary Tables S2 and S3).

Prognosis and outcomes

Reported outcomes varied depending on the underlying malignancy. In three studies, hypercalcemia resolved following supportive treatment and/or tumor-directed therapy in both hematological and solid tumors [13, 18, 19]. One study reporting the long-term outcome of children with ALL and hypercalcemia suggested that the survival was comparable to that of other children with ALL [17]. Three studies reported poorer outcomes in patients with MAH in solid tumors, where hypercalcemia was more frequently observed with advanced disease or relapse [11, 19, 20]. Mortality was generally related to the progression of the underlying malignancy rather than hypercalcemia itself [13, 14, 16, 19].

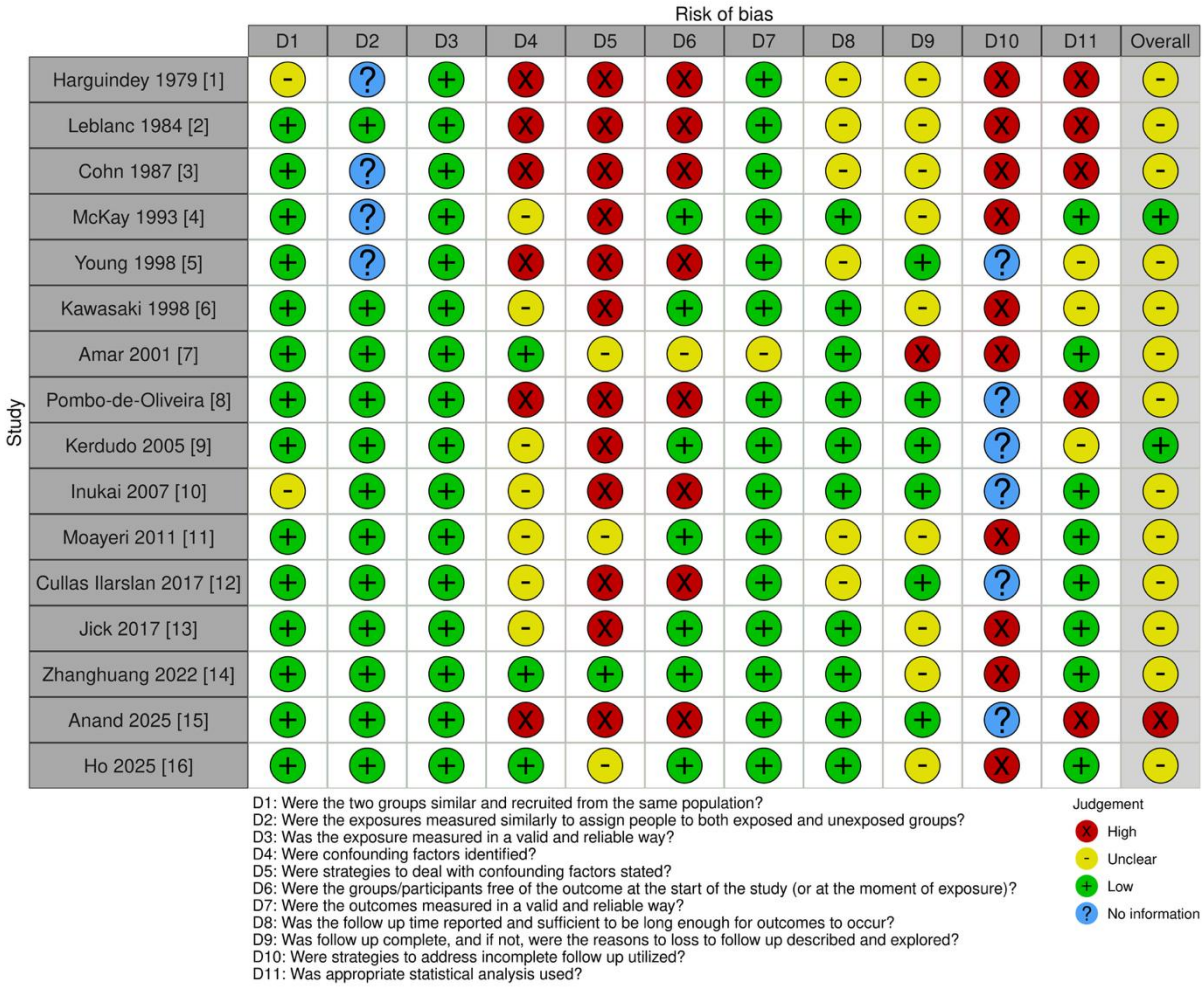


Fig. 2 Summary of the risk of bias for individual studies [12–27]

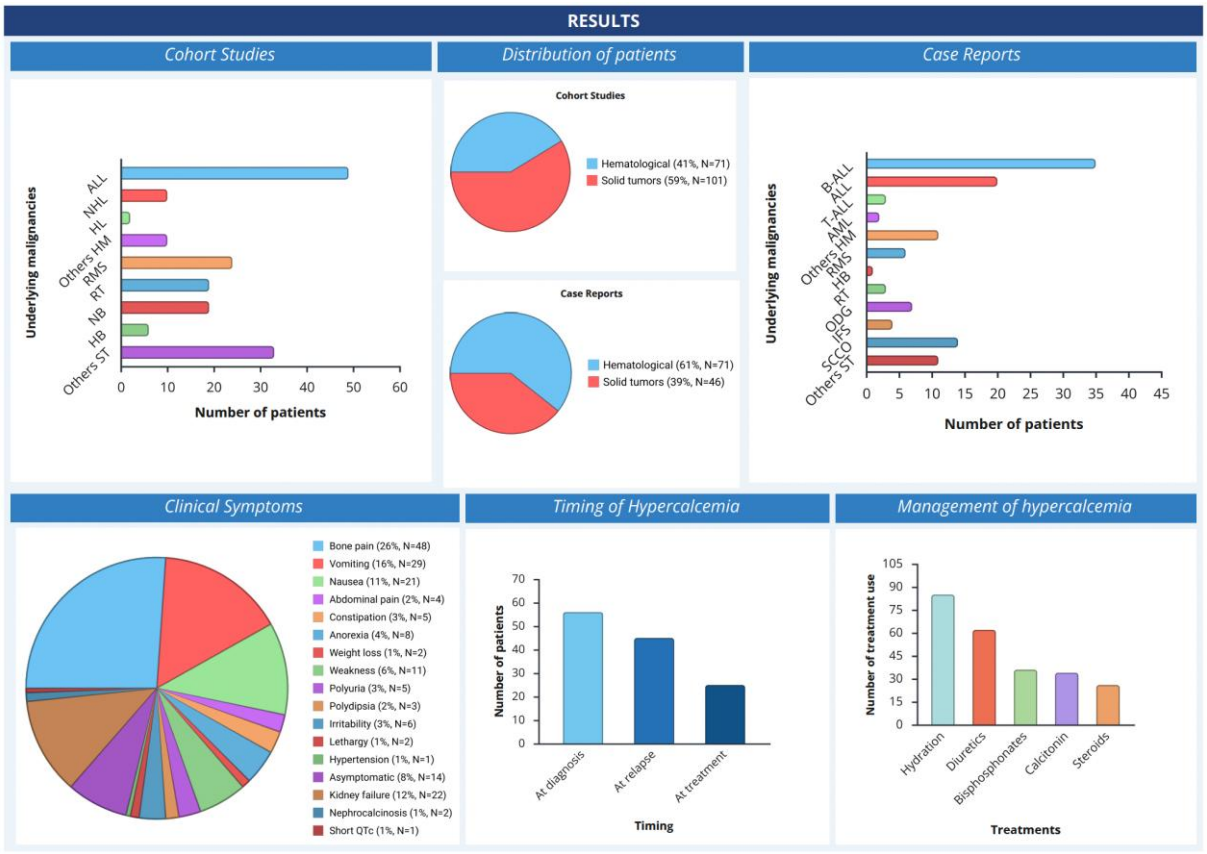


Fig. 3 Summary of findings on malignancy-associated hypercalcemia in children. Distribution of patients by the underlying malignancies, clinical symptoms, timing, and management of hypercalcemia
Abbreviations: ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; HM, hematological malignancies; RMS, rhabdomyosarcoma; RT, rhabdoid tumor; NB, neuroblastoma; HB, hepatoblastoma; ST, solid tumors; AML, acute myeloid leukemia; ODG, ovarian dysgerminoma; IFS, infantile fibrosarcoma; SCCO, small cell carcinoma of the ova

Discussion

In this systematic review, we provide a comprehensive overview of epidemiology, underlying mechanisms, clinical presentation, management, and outcomes of MAH. The available evidence suggests that hypercalcemia is a rare complication in pediatric oncology, with reported prevalence rates generally below 1%. Hypercalcemia has been reported in both children with hematological and solid malignancies, most frequently in ALL, and occurs predominantly at time of diagnosis. The main reported mechanisms were PTHrP-mediated humoral hypercalcemia and osteolytic bone destruction. Management strategies were largely consistent across studies and included intravenous (re)hydration (with or without diuretics), antiresorptive therapy, and tumor-directed treatment. Clinical outcomes appeared to be determined primarily by the underlying malignancy rather than by the hypercalcemia itself.

These findings confirm that MAH is considerably less common in pediatric oncology than in adults with cancer, where prevalence rates of up to 30% have been reported [1]. This difference likely reflects age-related differences in tumor biology and malignancy distribution [21]. Among children with cancer-related hypercalcemia, hematological malignancies predominate. Hence, this differs from adults, where it is more often observed in solid tumors [22]. This may, however, be in line with this distribution of pediatric malignancies, as ALL is the most frequently reported malignancy in children. Several case reports have described hypercalcemia in ALL occurring together with osteolytic lesions, despite the absence of circulating blasts in the peripheral blood, the so-called '*aleukemic leukemia'* situation. In the cohort study by Inukai et al., leukemic blasts were undetectable in the peripheral blood in eight patients [17]. Similarly, Trehan et al. reported that some children with ALL and hypercalcemia presented with normal or even low peripheral blood cell counts and no circulating blasts [23]. Consequently, hypercalcemia and/or osteolytic lesions may represent the only initial manifestations of ALL. This atypical presentation may complicate the diagnostic process. Although these observations are primarily based on case reports, they emphasize the importance of including ALL in the differential diagnosis of children presenting with hypercalcemia. In addition, in children with leukemia, other causes of hypercalcemia must be outweighed in the absence of osteolytic lesions, such as vitamin D intoxication, kidney failure or dehydration.

Our observations raise questions regarding the underlying mechanism of MAH in children. In adults, approximately 80% of cases are attributed to PTHrP-mediated HHM, while the remaining 20% results from osteolytic bone destruction [4]. Although the same two mechanisms appear to predominate in children, their relative distribution appears to differ. In adults, PTHrP-mediated hypercalcemia occurs primarily in association with solid tumors [1], whereas in children, it has been suggested to be present particularly in ALL. Conversely, our findings indicate that local osteolytic-mediated hypercalcemia appeared to be more common among children with solid tumors. These findings differ from the recent report by Korkmaz, which identified local osteolytic-mediated hypercalcemia as the predominant mechanism underlying pediatric HCM, particularly in ALL [8]. In our systematic review, PTHrP-mediated HHM was commonly reported in ALL, whereas osteolytic-mediated hypercalcemia predominated in solid tumors. This discrepancy may reflect the limited and inconsistent biochemical characterization of HCM in the available pediatric literature.

As may be expected, the severity of symptoms of hypercalcemia correlates with serum calcium concentrations. While mild hypercalcemia is often asymptomatic, more severe elevations are associated with gastrointestinal, musculoskeletal, kidney, cardiac, or neurological symptoms [8, 24]. This underscores the importance of routine biochemical screening, as the absence of early symptoms may delay diagnosis.

Management recommendations for MAH in children are largely extrapolated from adult practice and focus on correction of volume depletion, inhibition of osteoclastic bone resorption, and treatment of the underlying malignancy [1]. Although loop diuretics were reported in the literature included in this review, their routine use has become increasingly controversial. Current recommendations discourage routine administration owing to the potential for exacerbating dehydration and electrolyte disturbances, reserving loop diuretics primarily for patients with, or at risk of, fluid overload following adequate rehydration [8].

Although bisphosphonates are increasingly used in childhood, evidence regarding their efficacy and safety in children with cancer remains limited. Current practice is largely informed by adult data, while preclinical studies have raised concerns about potential interactions with chemotherapy, highlighting the need for further pediatric oncology-specific research [25–27]. In addition, because bisphosphonates undergo renal clearance, their use requires caution in the setting of kidney dysfunction, which may accompany hypercalcemia. In this context, denosumab may represent a potential therapeutic alternative. Denosumab is a monoclonal antibody with affinity for receptor activator of NF- κB (RANKL), which decreases bone resorption independently of renal clearance. While recent adult guidelines increasingly support denosumab as a first-line option for MAH, evidence in the

pediatric population remains scarce [28]. The few cases included in the present review suggest that denosumab was generally well tolerated in children. However, adverse effects, including hypocalcemia and rebound hypercalcemia upon discontinuation, have been reported [8]. Reports of dialysis, calcitonin, and steroid use are limited to a few cases.

Prognostic outcomes related to MAH appear to differ between children and adults. In adults, hypercalcemia is typically considered a manifestation of advanced cancer and is associated with poor outcomes, with a reported median survival of 25-52 days following onset [1]. In contrast, findings from the present review suggest that hypercalcemia in children does not invariably indicate an adverse prognosis. Although Korkmaz recently described pediatric HCM as a marker of advanced or aggressive malignancy [8], our systematic findings suggest that this association warrants cautious interpretation. Poorer outcomes were predominantly observed in children with advanced or relapsed solid tumors, whereas hypercalcemia was not consistently associated with an adverse prognosis in ALL. Rather, clinical outcomes appear to be primarily driven by the characteristics and progression of the underlying malignancy. Although mortality was frequently reported among the included cases, deaths were mostly attributed to progression of the underlying cancer rather than to the hypercalcemia itself. These findings highlight potential differences in the clinical significance of MAH between children and adults and underscore the need for pediatric-specific data to better inform prognostic assessment and management strategies.

This review has several limitations that should be considered when interpreting the findings. First, the available evidence consisted predominantly of small retrospective cohort studies and case reports, resulting in an overall low level of evidence. Second, substantial heterogeneity existed in the definition of hypercalcemia across studies, with varying cutoff values used to define the disease severity, thereby limiting direct comparison between reports. Third, biochemical evaluation was inconsistent, as many studies did not systematically assess markers such as PTHrP, PTH, or 1,25-dihydroxyvitamin D (calcitriol). This limited the ability to fully characterize the relative contribution of the different underlying pathophysiological mechanisms. Despite these limitations, the present review provides the most comprehensive synthesis to date of the available evidence regarding MAH in children and adolescents. The findings highlight important gaps in the current literature and may serve as a foundation for future pediatric-specific recommendations and guideline development. Larger prospective studies with standardized diagnostic and biochemical evaluation are needed to better define the epidemiology, pathophysiology, optimal management strategies, and long-term outcomes of this condition.

Conclusion

MAH is a rare but clinically significant complication in children and adolescents with cancer occurring across a broad spectrum of malignancies and most frequently reported in ALL. In childhood, it does not seem to be associated with worse prognosis. The predominant underlying mechanisms are PTHrP-mediated and osteolytic hypercalcemia. Current management strategies are relatively extrapolated from adult practice and generally consist of and include hydration, antiresorptive therapy, and treatment of the underlying malignancy. This review highlights important gaps in the literature and may serve as a foundation for future pediatric-specific guideline development.

Table 1 – Clinical characteristics of cohort studies on pediatric malignancy-associated hypercalcemia

Study	Underlying malignancies	HCM n	Calcium (mg/dL)	Mechanism/ involvement	Timing	Clinical symptoms	Management	Outcomes and resolution
1 [13]	NHL (7), RMS (4), MRT (3), NB (1), Others	17	12.8-19.8	ePTH (2)	RMS: Dx (4)	NR	Chemo/Surg	MRT: res post-surg; Rel; DOD
2 [11]	ALL (10), RMS (4), MRT (2), HB (2), HL (1), NHL (1), Others	25	≥11.5 (40% ≥15.0)	Bone met (8)[a]	Dx: 11 Rel: 14	GI, MSK, Renal, Neuro	Hydr+Diu CTN(8)± Ster(5)	Res (most); high mortality
3 [29]	ALL (3), RMS (1), HCT (2), Car (1)	7	11.8-15.4	Bone met (5)	NR	GI, MSK, Renal, Neuro, A (2)	Hydr, Diu, Ster + Mith	DOD (5)
4 [30]	ALL (4)	4	12.2-20.0	ePTH (1); Bone met (3)	Dx: 2, Rel: 2	NR	Hydr (1)	Res; DOD (2)
5 [16]	RMS (6)	6	>12.0 (67% >14.0)	PTHrP (3)	Dx: 2 Rel: 4	GI, Renal, Neuro	Hydr+Diu(6), CTN+plm (3)	Res; DOD (all)
6 [18]	ALL (2), RMS (1), DCRT (1), ACS (1)	5	12.1-16.4	PTHrP (1)	Rel: 4	GI, MSK, Neuro, A(2)	Hydr+Diu +pam	Res; HypoCa
7 [31]	RTK	6/23	>10.5	PTH?	NR	NR	NR	NR
8 [32]	T-cell ALL/lymp	5/8	10.6-18.8	NR	NR	NR	Chemo	DOD (All)
9 [14]	NB (4), RMS (3), HM (2), OGT (1), Others	16	12.6 (11.6-24)	PTHrP (1); BM (4)	Dx: 8, Tr: 5 Rel: 3	GI, Renal, MSK, A(4)	Hydr(2), Ster(8), CTN(1), Pam(8)	Res; HypoCa (4)
10 [17]	B-ALL	22	>12.0 (73% >15.0)	PTHrP (11); ePTH (1)	Dx: 18 Rel: 4	MSK, GI, Renal	Hydr+Diu(22), CTN(15)±BP(11) (±chemo)	Res; HypoCa (9)
11 [15]	ALL (4), NHL (2), RMS (1), ES (1)	8	>10.8	NR	NR	Renal	Ster(3), Ah(1)	NR
12 [33]	ALL (1), RMS (1), HB (1), CML (1)	4	12.6 (11-16.5)	PTHrP (3), Cyt (1)	NR	GI, Renal, MSK, Neuro, A	Hydr + BP	Res (7-22d); Rec
13 [20]	RTK	4/42	>11.2	NR	NR	NR	Surg, chemo	DOD (All)
14 [34]	HL (1), B-ALL (2), APML (1)	4	14.85-16.0	Bone les (1)	Dx: 3 Rel: 1	GI, MSK, Renal	Hydr+Diu±CTN ±BP	Res; HypoCa (1): DOD (1)
15 [19]	NB (13), RT (4), RMS (3), HB (3), FB (2), MB (2), CMN (2), Others	39	13.1 (11.5-19.1)	PTHrP (1)	Dx: 8,Tr: 20 Rel: 13	GI, MSK, Neuro, A(6)	Hydr, Diu, Ster, CTN, BP	Res (84%); high mortality
Tot: 15 studies	*Solid tumors: 101* *Hemato-oncology: 71*	*172*		*PTHrP: 20* *Bone les: 17*	*Dx: 56, Tr: 25, Rel: 45*	MSK (~59), GI (*~69), Renal (~32), Neuro (~8), A (~14)*	*Hydr: ~85, Diur: ~62, BP: ~36, CTN: ~34, Ster: ~26*	

[a] Solid tumors.

Abbreviations: NR, not reported; HCM, hypercalcemia; ALL, acute lymphoblastic leukemia; RMS, rhabdomyosarcoma; DRCT, desmoplastic round cell tumor; RTK, rhabdoid tumor of the kidney; NB, neuroblastoma; HM, hematological malignancies; HB: hepatoblastoma; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; APML, acute promyelocytic leukemia; RT, rhabdoid tumor; FB, fibrosarcoma; MB, medulloblastoma; CMN, congenital mesoblastic nephroma; OGT, ovarian granulosa tumor; HCT, histiocytosis; Car, carcinoma; ASC, astrocytoma; ES, Ewing sarcoma; MRT, malignant rhabdoid tumor; bone met, bone metastases; ePTH, ectopic PTH; PTHrP, PTHrP-mediated; PTH, PTH-mediated; BM, bone marrow; Cyt, cytokine-mediated; GI, gastrointestinal; MSK, musculoskeletal; Neuro, neurological; A, asymptomatic; chemo, chemotherapy; res post-surg, resolution after surgery; Hydr, hydration; Diu, diuretics; CTN, calcitonin; BP, bisphosphonate; Ster, corticosteroid; Mith, mithramycin; plm, plicamycin; pam, pamidronate; Ah, aluminumhydroxide; DOD, died of disease; HypoCa, hypocalcemia

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Author contributions

Julíe Tamis performed the literature search, study selection, data collection, and analysis and wrote the first draft of the manuscript. Gerrit van den Berg contributed to the study design, acted as a second reviewer for the study selection and data extraction, supervised the research, and critically revised the manuscript. All authors contributed to the interpretation of the findings and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability statement

All data supporting the findings of this systematic review are available within the review and its Supplementary Material.

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