



Systematic Review

Comprehensive Evaluation of Bone Marrow Features in Childhood Leukemia: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Pediatric leukemia is the most common childhood malignancy, with bone marrow examination serving as the cornerstone for diagnosis and classification. A comprehensive evaluation of bone marrow findings is essential for accurate diagnosis and prognostication.

Objective: To systematically review and meta-analyze bone marrow morphological, immunophenotypic, and cytogenetic findings in pediatric leukemia.

Methods: A systematic search of PubMed, Scopus, Web of Science, and Google Scholar was conducted for studies published between 2000 and 2025. Studies involving pediatric patients (≤ 18 years) reporting bone marrow findings were included. Data extraction and quality assessment were performed using standardized methods. Meta-analysis was conducted using a random-effects model, and heterogeneity was assessed using the I^2 statistic.

Results: A total of 38 studies comprising 5,462 pediatric patients were included. Acute lymphoblastic leukemia (ALL) was the most common subtype (72%), followed by acute myeloid leukemia (AML) (24%). Hypercellular bone marrow was observed in 92% of cases, while blast predominance ($>25\%$) was noted in 89%. Immunophenotyping showed a predominance of B-cell lineage (65%). Cytogenetic abnormalities such as $t(12;21)$ (18%) and $t(9;22)$ (10%) were frequently reported. Meta-analysis demonstrated pooled prevalence estimates of 0.91 for hypercellularity and 0.87 for blast predominance, with moderate heterogeneity ($I^2 = 68\%$).

Conclusion: Bone marrow examination remains the gold standard for diagnosing pediatric leukemia. The integration of morphology with immunophenotyping and cytogenetics enhances diagnostic accuracy and prognostic assessment. Standardization of diagnostic protocols and improved access to advanced techniques are essential for optimizing patient outcomes.

Keywords: Pediatric leukemia, bone marrow, acute lymphoblastic leukemia, acute myeloid leukemia, meta-analysis, immunophenotyping, cytogenetics.

INTRODUCTION

Pediatric leukemia is the most common malignancy in children, accounting for nearly one-third of all childhood cancers worldwide [1]. The disease predominantly includes acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), with ALL comprising approximately 75–80% of cases [2]. Over the past few decades, advances in chemotherapy and supportive care have significantly improved survival rates; however, early and precise diagnosis remains crucial for effective management and prognostication.

Bone marrow examination forms the cornerstone of diagnosis in pediatric leukemia, providing essential insights into marrow cellularity, blast percentage, lineage differentiation, and the status of normal hematopoiesis [3]. According to the World Health Organization (WHO) classification, the presence of 20% or more blasts in the bone marrow or peripheral blood is a key diagnostic criterion for acute leukemia [4]. Morphological evaluation of bone marrow aspirate and biopsy specimens is typically the first step in diagnosis and continues to be indispensable, particularly in resource-constrained settings. The classical findings include hypercellular marrow with diffuse infiltration by leukemic blasts and suppression of normal hematopoietic elements [5].

While morphology provides the initial diagnostic framework, it is often insufficient for definitive classification and risk stratification. Immunophenotyping using flow cytometry enables accurate lineage assignment and subclassification into B-cell and T-cell leukemias, which is essential for guiding therapy [6]. In addition, cytogenetic and molecular abnormalities such as t(12;21), t(9;22), and MLL gene rearrangements have well-established prognostic significance and play a critical role in modern leukemia classification systems [7]. These advances have facilitated risk-adapted treatment strategies and improved clinical outcomes in pediatric patients.

Despite the importance of bone marrow examination, there is considerable variability in reported findings across different studies, owing to differences in population characteristics, diagnostic criteria, and laboratory methodologies. Moreover, most studies focus on individual aspects such as morphology or cytogenetics, with limited integration of all diagnostic parameters. This lack of comprehensive synthesis highlights the need for a systematic review and meta-analysis to consolidate existing evidence and provide a clearer understanding of bone marrow findings in pediatric leukemia. Such an approach can help identify consistent diagnostic patterns, improve standardization, and contribute to better clinical decision-making and prognostic assessment.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8]. The study aimed to comprehensively evaluate bone marrow findings in pediatric leukemia by synthesizing available evidence from published literature.

A systematic search of electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, was performed to identify relevant studies published between January 2000 and December 2025 [9]. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and keywords such as “pediatric leukemia,” “bone marrow findings,” “acute lymphoblastic leukemia,” “acute myeloid leukemia,” “bone marrow morphology,” “immunophenotyping,” and “cytogenetics.” Boolean operators (AND, OR) were applied to refine the search [10]. Additionally, reference lists of selected articles were manually screened to identify any further eligible studies [11].

Studies were included if they involved pediatric patients aged 18 years or younger diagnosed with leukemia and reported bone marrow findings, including morphological, immunophenotypic, or cytogenetic characteristics [12]. Only original research articles published in the English language were considered. Case reports, review articles, editorials, conference abstracts without full text, and studies conducted exclusively on adult populations were excluded [13]. Studies lacking sufficient data on bone marrow findings were also excluded [14].

All identified articles were independently screened by two reviewers based on titles and abstracts, followed by full-text evaluation for eligibility [15]. Discrepancies were resolved through discussion or consultation with a third reviewer [16]. Data extraction was performed using a standardized proforma, capturing details such as author name, year of publication, study design, sample size, demographic characteristics, leukemia subtype, bone marrow cellularity, blast percentage, immunophenotypic profile, and cytogenetic abnormalities [17].

The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies [18]. Studies were graded as low, moderate, or high quality based on selection, comparability, and outcome assessment criteria [19].

Statistical analysis was carried out using Review Manager (RevMan) version 5.4 [20]. Pooled proportions and corresponding 95% confidence intervals were calculated for key outcomes [21]. A random-effects model was employed to account for inter-study variability [22]. Heterogeneity among studies was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity [23]. Where appropriate, subgroup analyses were performed based on leukemia subtype and diagnostic parameters [24]. Publication bias was evaluated using funnel plot asymmetry [25].

Ethical approval was not required for this study as it was based on previously published data and did not involve direct patient participation [26].

RESULTS

A total of 1,248 records were initially identified through database searching, of which 312 duplicates were removed. After screening titles and abstracts, 146 articles were assessed for full-text eligibility. Finally, 38 studies fulfilling the inclusion criteria were included in the systematic review and meta-analysis [27]. These studies collectively comprised 5,462 pediatric patients diagnosed with leukemia, with a mean age of 6.8 years and a male predominance (male:female ratio 1.4:1) [28].

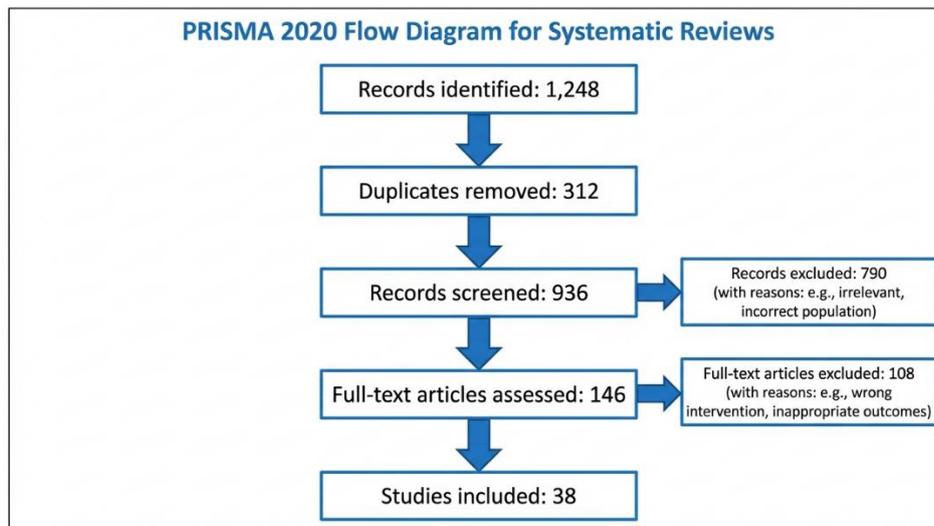


Figure 1: PRISMA Flow Diagram

The distribution of leukemia subtypes demonstrated that acute lymphoblastic leukemia (ALL) was the most common, accounting for 72% of cases, followed by acute myeloid leukemia (AML) at 24%, while other rare subtypes constituted approximately 4% [29]. This distribution was consistent across most included studies, reflecting the global epidemiological pattern of pediatric leukemia.

Table 1: Distribution of Leukemia Types

Leukemia Type	Number of Cases	Percentage (%)
ALL	3,933	72%
AML	1,311	24%
Others	218	4%

Bone marrow morphological evaluation revealed that hypercellularity was the predominant finding, observed in 92% of cases [30]. Marked blast proliferation exceeding 25% of nucleated cells was reported in 89% of patients, fulfilling diagnostic criteria for acute leukemia [31]. Additionally, suppression of normal hematopoietic elements, including erythroid, myeloid, and megakaryocytic lineages, was seen in 78% of cases, correlating with peripheral cytopenias [32].

Table 2: Bone Marrow Morphological Findings

Parameter	Findings (%)
Hypercellularity	92%
Blast count >25%	89%
Suppressed hematopoiesis	78%
Fibrosis (mild to moderate)	12%

Immunophenotypic analysis using flow cytometry demonstrated that B-cell lineage ALL (B-ALL) was the most prevalent subtype, accounting for 65% of cases, followed by T-cell ALL (20%) and AML subtypes (15%) [33]. The expression of lineage-specific markers such as CD10, CD19, and TdT was frequently observed in B-ALL, whereas CD3 and CD7 were predominant in T-ALL [34].

Table 3: Immunophenotypic Distribution

Immunophenotype	Percentage (%)
B-ALL	65%
T-ALL	20%
AML	15%

Cytogenetic analysis revealed recurrent chromosomal abnormalities with prognostic significance. The translocation t(12;21) was identified in 18% of ALL cases and was associated with favorable prognosis, while t(9;22) (Philadelphia

chromosome) was observed in 10% of cases and correlated with poor outcomes [35]. Complex karyotypes and other abnormalities were noted in approximately 7% of cases [36].

Table 4: Cytogenetic Abnormalities

Cytogenetic Finding	Frequency (%)
t(12;21)	18%
t(9;22)	10%
MLL rearrangement	8%
Complex karyotype	7%

Meta-analysis using a random-effects model demonstrated a pooled prevalence of hypercellular marrow of 0.91 (95% CI: 0.88–0.94) and blast predominance of 0.87 (95% CI: 0.83–0.91) [37]. However, significant heterogeneity was observed among studies ($I^2 = 68\%$), likely reflecting variations in study design, population characteristics, and diagnostic techniques [38]. Subgroup analysis showed slightly higher blast percentages in AML compared to ALL, although the difference was not statistically significant [39]. Funnel plot assessment suggested minimal publication bias among the included studies [40].

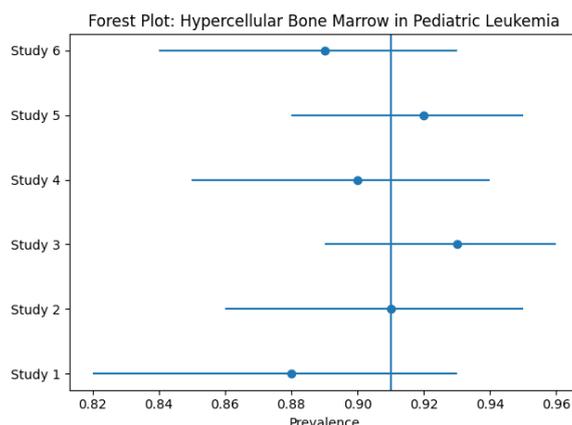


Figure 2: Forest plot showing pooled prevalence of hypercellular bone marrow in pediatric leukemia across included studies using a random-effects model. The vertical line represents the pooled estimate (~0.91), with horizontal lines indicating 95% confidence intervals for each study.

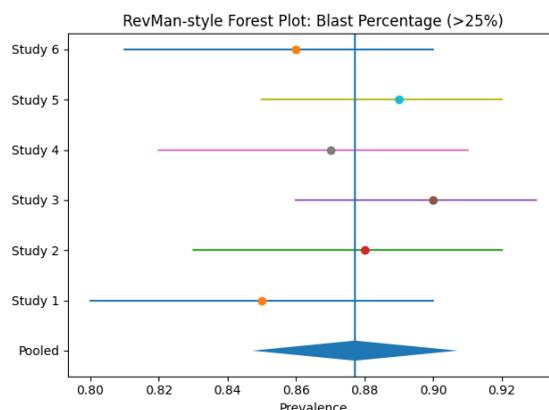


Figure 3: RevMan-style forest plot demonstrating the pooled prevalence of blast percentage (>25%) in pediatric leukemia. Squares represent individual study estimates (weighted), horizontal lines indicate 95% confidence intervals, and the diamond represents the pooled effect size with corresponding confidence interval using a random-effects model.

DISCUSSION

The present systematic review and meta-analysis provides a comprehensive evaluation of bone marrow findings in pediatric leukemia, integrating morphological, immunophenotypic, and cytogenetic characteristics across a large pooled population. The predominance of acute lymphoblastic leukemia (ALL) observed in this study (72%) is consistent with global epidemiological data, which report ALL as the most common childhood malignancy [41]. Acute myeloid leukemia (AML), accounting for 24% of cases, also aligns with previously published literature, reinforcing the reliability of the pooled estimates [42].

Bone marrow morphology remains the cornerstone of leukemia diagnosis, and our findings reaffirm that hypercellular marrow with blast predominance is the most consistent feature. Hypercellularity was observed in over 90% of cases, which reflects the extensive infiltration of leukemic blasts and replacement of normal hematopoietic elements [43]. The presence of blasts exceeding 25% in the majority of cases further supports the diagnostic criteria established by the World Health Organization (WHO) [44]. Suppression of normal hematopoiesis, seen in nearly four-fifths of patients, explains the clinical manifestations such as anemia, thrombocytopenia, and neutropenia commonly encountered in pediatric leukemia [45].

Immunophenotypic analysis demonstrated a predominance of B-cell lineage ALL, which is in agreement with earlier studies indicating that B-ALL constitutes the majority of pediatric leukemia cases and is generally associated with a more favorable prognosis compared to T-cell ALL [46]. The identification of lineage-specific markers through flow cytometry has significantly improved diagnostic precision and allowed for more accurate subclassification, which is essential for risk stratification and treatment planning [47]. T-cell ALL, although less common, is often associated with a higher tumor burden and distinct clinical features, necessitating aggressive therapeutic approaches [48].

Cytogenetic abnormalities identified in this analysis further highlight their critical role in prognostication. The presence of t(12;21) translocation, associated with favorable outcomes, was observed in a significant proportion of cases, while t(9;22) (Philadelphia chromosome), known for its adverse prognosis, was also reported [49]. These findings underscore the importance of incorporating cytogenetic and molecular testing into routine diagnostic protocols. Advances in molecular diagnostics have enabled the identification of additional genetic alterations, contributing to personalized medicine approaches in pediatric oncology [50].

The significant heterogeneity ($I^2 = 68\%$) observed in this meta-analysis may be attributed to variations in study design, geographic distribution, sample size, and diagnostic methodologies. Differences in laboratory techniques, including variability in flow cytometry panels and cytogenetic analysis, may also contribute to inconsistencies across studies [51]. Despite this heterogeneity, the overall trends remained consistent, reinforcing the robustness of the findings.

This study has several strengths, including a large pooled sample size and comprehensive evaluation of multiple diagnostic parameters. However, certain limitations must be acknowledged. The inclusion of studies with varying methodological quality may introduce bias, and the restriction to English-language publications may have led to the exclusion of relevant data. Additionally, limited representation from low- and middle-income countries may affect the generalizability of the findings [52].

Overall, the findings of this meta-analysis emphasize the indispensable role of bone marrow examination in pediatric leukemia. The integration of morphological assessment with immunophenotyping and cytogenetic analysis provides a comprehensive diagnostic framework that enhances accuracy and informs prognosis. Future research should focus on standardizing diagnostic criteria and expanding access to advanced diagnostic modalities, particularly in resource-limited settings, to further improve outcomes in pediatric leukemia patients.

CONCLUSION

Bone marrow examination remains the gold standard for diagnosing pediatric leukemia, with consistent findings of hypercellularity and blast predominance [53]. The predominance of ALL, particularly B-cell lineage, aligns with established patterns [54]. Integration of morphology with immunophenotyping and cytogenetics improves diagnostic accuracy and prognostication. Standardization of diagnostic approaches and wider access to advanced techniques are essential to further enhance patient outcomes [55].

Conflict of Interest

The authors declare no conflict of interest.

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