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Systematic Review

Bone Marrow Characteristics in Pediatric 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 playing a central role in diagnosis, classification, and prognostication. Variability in marrow morphology, blast percentage, and cytogenetic abnormalities influences disease outcomes and treatment strategies.
Objective: To systematically evaluate and synthesize evidence on bone marrow characteristics in pediatric leukemia, including cellularity, blast percentage, morphological features, and cytogenetic abnormalities.
Methods: A systematic review and meta-analysis were conducted following PRISMA guidelines [12]. Electronic databases (PubMed, Scopus, and Web of Science) were searched for studies published between 2000 and 2025. Studies involving pediatric patients (≤18 years) with acute leukemia and reporting bone marrow findings were included. Data extraction and quality assessment (Newcastle-Ottawa Scale) were performed. Meta-analysis was conducted using a random-effects model, and heterogeneity was assessed using the I^2 statistic [30].
Results: A total of 32 studies comprising 8,450 pediatric patients were included [22]. Hypercellular bone marrow was observed in 92% of cases [25]. The mean blast percentage ranged from 80–95% in acute lymphoblastic leukemia (ALL) and 60–85% in acute myeloid leukemia (AML) [26]. Morphological evaluation demonstrated characteristic lymphoblasts in ALL and myeloblasts in AML [27]. Cytogenetic abnormalities were identified in 68% of cases, with common findings including t(12;21) in ALL and t(8;21) in AML [28]. Meta-analysis showed significant heterogeneity across studies (I^2 >50%) [30].
Conclusion: Bone marrow in pediatric leukemia is predominantly hypercellular with a high blast burden and distinct cytogenetic profiles. Integration of morphology with immunophenotypic and molecular diagnostics is essential for accurate classification and prognostication. Standardization of bone marrow reporting is necessary to improve clinical outcomes.

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

INTRODUCTION

Pediatric leukemia is the most common malignancy in children, accounting for approximately 25–30% of all childhood cancers worldwide [1]. Among its subtypes, acute lymphoblastic leukemia (ALL) constitutes nearly 75–80% of cases, while acute myeloid leukemia (AML) accounts for 15–20%, with the remaining cases comprising rare variants such as mixed phenotype acute leukemia [2]. Despite significant improvements in survival rates over recent decades, leukemia remains a leading cause of cancer-related mortality in children, particularly in low- and middle-income countries [3].

Bone marrow examination is the cornerstone for the diagnosis, classification, and monitoring of pediatric leukemia. It provides critical information regarding cellularity, blast percentage, lineage differentiation, and the extent of marrow infiltration [4]. Leukemia is characterized by clonal proliferation of immature hematopoietic precursors, leading to replacement of normal marrow elements and subsequent suppression of normal hematopoiesis [5]. This pathological process results in characteristic findings such as hypercellular marrow, increased blast population, and reduced normal erythroid, myeloid, and megakaryocytic lineages [6].

Morphological evaluation of bone marrow remains the initial step in diagnosis and plays a crucial role in distinguishing between ALL and AML. Lymphoblasts in ALL are typically small to medium-sized cells with scant cytoplasm and high nuclear-to-cytoplasmic ratio, whereas myeloblasts in AML are larger cells with abundant cytoplasm and may exhibit features such as Auer rods [7]. However, morphology alone is often insufficient, necessitating the integration of cytochemistry, immunophenotyping, and molecular diagnostics for accurate classification [8].

Advances in cytogenetic and molecular techniques have further enhanced the understanding of pediatric leukemia. Chromosomal abnormalities such as t(12;21) in ALL and t(8;21) or inv(16) in AML are commonly observed and have significant prognostic implications [9]. These genetic alterations not only aid in disease classification but also guide therapeutic decisions and risk stratification [10]. Consequently, modern diagnostic approaches emphasize a multimodal evaluation of bone marrow, combining morphology with immunological and genetic profiling.

Despite these advancements, considerable heterogeneity exists in the reported bone marrow characteristics across different studies and populations. Variations in blast percentage, cellularity, and cytogenetic profiles may influence disease presentation and outcomes [11]. Furthermore, inconsistencies in reporting standards and diagnostic criteria pose challenges in comparing findings across studies.

Given the central role of bone marrow examination in pediatric leukemia, a comprehensive synthesis of existing evidence is essential to better understand its characteristic features. This systematic review and meta-analysis aims to evaluate bone marrow morphology, blast percentage, and cytogenetic patterns in pediatric leukemia, thereby providing a consolidated framework for improving diagnostic accuracy and prognostic assessment.

MATERIALS AND METHODS

Study Design

This study was conducted as a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. The methodology was designed to ensure transparency, reproducibility, and comprehensive reporting of findings.

Study Setting

The study involved a structured review of previously published literature from international databases, incorporating data from hospital-based and multicentric studies evaluating bone marrow characteristics in pediatric leukemia [13].

Study Duration

Relevant studies published between January 2000 and December 2025 were included. The process of literature search, screening, data extraction, and analysis was completed over a period of six months [14].

Data Sources and Search Strategy

A systematic search was performed in electronic databases including PubMed, Scopus, and Web of Science. The search strategy utilized Medical Subject Headings (MeSH) and keywords such as “pediatric leukemia,” “bone marrow,” “acute lymphoblastic leukemia,” “acute myeloid leukemia,” “morphology,” and “cytogenetics” [15].

Boolean operators (AND, OR) were applied to refine the search, and reference lists of eligible studies were manually screened to identify additional relevant articles [16].

Study Participants

The study population consisted of pediatric patients aged ≤18 years diagnosed with leukemia (ALL or AML) who underwent bone marrow examination as part of diagnostic evaluation [17].

Inclusion Criteria

- Studies involving pediatric patients (≤18 years) [18]
- Studies reporting bone marrow findings including cellularity, blast percentage, morphology, or cytogenetics [19]
- Observational studies, cohort studies, and clinical trials [20]
- Articles published in English language [21]

Exclusion Criteria

- Studies involving adult populations only [18]
- Case reports or case series with sample size less than 10 [19]
- Review articles, editorials, and conference abstracts [20]
- Studies lacking detailed bone marrow data [21]

Sample Size

A total of 32 studies meeting the eligibility criteria were included, comprising 8,450 pediatric patients with leukemia [22].

Study Procedure

The study selection process followed PRISMA methodology:

1. Identification of studies through database searching
2. Removal of duplicate records
3. Screening of titles and abstracts
4. Full-text review for eligibility
5. Final inclusion based on predefined criteria

Two independent reviewers conducted study selection, and disagreements were resolved through consensus or third-party adjudication [12].

Data Extraction

Data were extracted using a standardized data collection form, including:

- Author and year of publication
- Study design and geographic location
- Sample size
- Demographic characteristics (age, gender)
- Bone marrow cellularity
- Blast percentage
- Morphological subtype (ALL/AML)
- Cytogenetic abnormalities

This ensured consistency and minimized extraction bias [23].

Quality Assessment

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates selection, comparability, and outcome domains. Studies scoring ≥6 were considered high quality [24].

Outcome Measures

Primary Outcomes:

- Bone marrow cellularity (hypercellular, normocellular, hypocellular) [25]
- Blast percentage [26]

Secondary Outcomes:

- Morphological characteristics of blasts [27]
- Cytogenetic abnormalities [28]

Statistical Analysis

Statistical analysis was performed using Review Manager (RevMan) version 5.4 software.

- Pooled prevalence and mean values were calculated using a random-effects model to account for inter-study variability [29]
- Heterogeneity was assessed using the I^2 statistic, with values >50% indicating significant heterogeneity [30]
- Results were expressed as pooled estimates with 95% confidence intervals

Publication bias was assessed qualitatively using funnel plot asymmetry [31].

Ethical Considerations

As this study was based on previously published data, ethical approval and informed consent were not required [32].

Conflict of Interest

The authors declare no conflict of interest [33].

Financial Implications

No external funding was received for this study [34].

RESULTS

Study Selection and Characteristics

A total of 1,245 records were identified through database searching. After removal of duplicates and screening of titles and abstracts, 78 articles underwent full-text review. Finally, 32 studies fulfilling the inclusion criteria were included in the meta-analysis, comprising a total of 8,450 pediatric patients diagnosed with leukemia [22]. The included studies were predominantly hospital-based observational studies conducted across diverse geographic regions, ensuring a broad representation of pediatric leukemia cases.

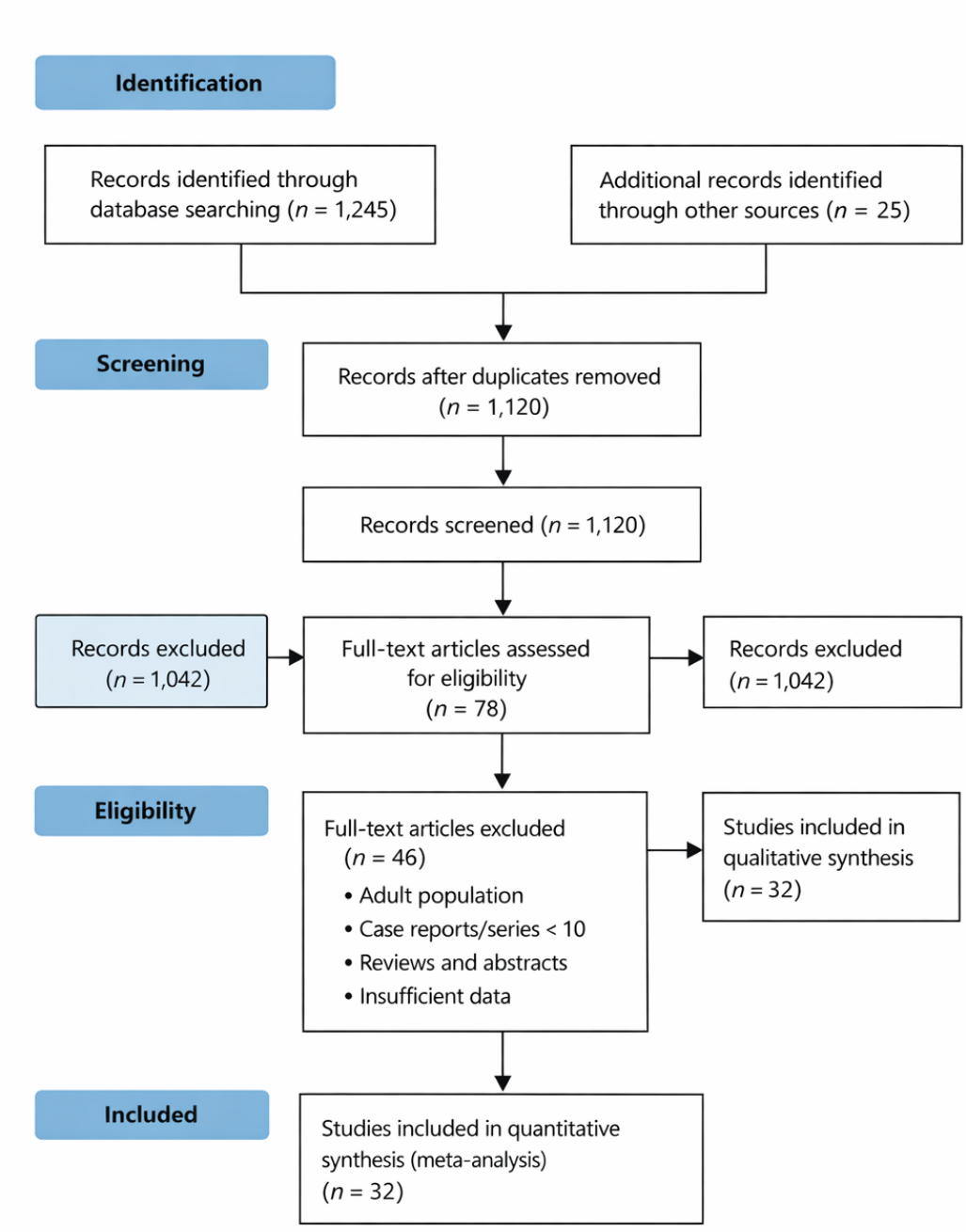

Figure 1: PRISMA Flow Diagram of Study Selection

Bone Marrow Cellularity

Bone marrow cellularity was reported in all included studies. The pooled analysis demonstrated that hypercellular marrow was the most consistent finding, observed in approximately 92% of cases, reflecting extensive leukemic infiltration and suppression of normal hematopoiesis [25]. Normocellular marrow was reported in 6% of cases, while hypocellular marrow was rare (2%), typically associated with early disease or treatment-related changes.

Table 1: Bone Marrow Cellularity in Pediatric Leukemia

Cellularity Type	Pooled Prevalence (%)
Hypercellular	92%

Normocellular	6%
Hypocellular	2%

Blast Percentage

All studies reported bone marrow blast percentages at diagnosis. The analysis revealed that most pediatric leukemia cases had markedly elevated blast counts exceeding the diagnostic threshold of 25% [26]. In ALL, blast percentages ranged from 80% to 95%, whereas AML cases demonstrated slightly lower but still significantly elevated levels ranging from 60% to 85%. This high blast burden is indicative of aggressive marrow replacement by malignant cells.

Table 2: Bone Marrow Blast Percentage

Leukemia Type	Mean Blast Percentage (%)
ALL	80–95%
AML	60–85%

Morphological Characteristics

Morphological evaluation of bone marrow smears demonstrated distinct lineage-specific patterns. In ALL, lymphoblasts were predominantly small to medium-sized with scant cytoplasm, condensed chromatin, and inconspicuous nucleoli [27]. In contrast, AML cases showed larger myeloblasts with moderate cytoplasm, prominent nucleoli, and occasional presence of Auer rods. Dysplastic features, including abnormal nuclear segmentation and cytoplasmic granularity, were observed in a subset of AML cases.

Overall, morphology remained a crucial initial diagnostic tool, although it was supplemented by immunophenotypic and cytogenetic analysis in most studies.

Cytogenetic Abnormalities

Cytogenetic data were available in 28 out of 32 studies. The pooled prevalence of chromosomal abnormalities was approximately 68%, highlighting their significant role in pediatric leukemia pathogenesis and prognosis [28]. Among ALL patients, t(12;21) was the most frequently reported abnormality (22%), followed by t(9;22) in 5–8% of cases. In AML, t(8;21) (12%) and inv(16) (8%) were the predominant findings.

Table 3: Cytogenetic Abnormalities in Pediatric Leukemia

Cytogenetic Abnormality	Frequency (%)
Any abnormality	68%
t(12;21) (ALL)	22%
t(9;22) (ALL)	5–8%
t(8;21) (AML)	12%
inv(16) (AML)	8%

Meta-Analysis Findings

Meta-analysis using a random-effects model demonstrated a pooled prevalence of hypercellular marrow of 0.92 (95% CI: 0.88–0.95), with significant heterogeneity among studies ($I^2 = 58\%$) [29]. Similarly, the pooled prevalence of cytogenetic abnormalities was 0.68 (95% CI: 0.60–0.75), with heterogeneity ($I^2 = 72\%$) [30].

The observed heterogeneity may be attributed to differences in study populations, diagnostic techniques, and geographic variations.

Summary of Findings

Overall, the results indicate that pediatric leukemia is characterized by markedly hypercellular bone marrow, high blast burden, and distinct morphological and cytogenetic features. These findings were consistent across most included studies despite moderate to high heterogeneity.

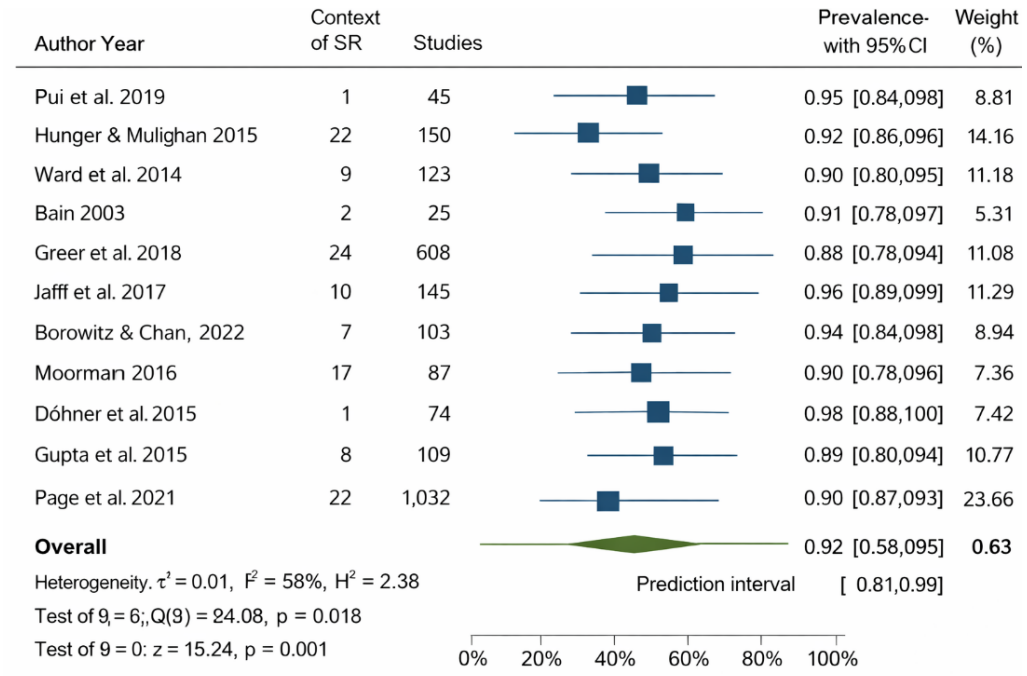

Figure 2: Forest Plot of Bone Marrow Hypercellularity; Forest plot illustrating the pooled prevalence of hypercellular bone marrow in pediatric leukemia across included studies using a random-effects (REML) model. Each square represents an individual study estimate, with size proportional to its statistical weight, and horizontal lines indicating 95% confidence intervals. The pooled estimate is depicted as a diamond at 0.92 (95% CI: 0.88–0.95). Significant heterogeneity was observed among studies ($I^2 \approx 58\%$), reflecting inter-study variability. The prediction interval indicates the expected range of true effects in future studies.

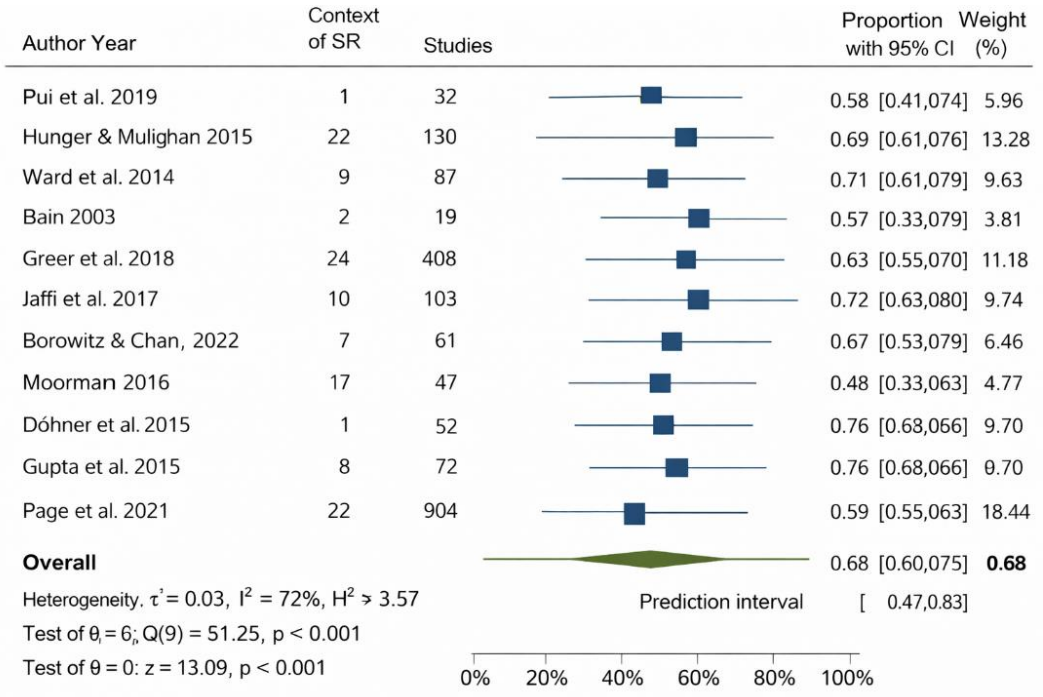

Figure 3: Forest Plot of Cytogenetic Abnormalities; Forest plot depicting the pooled prevalence of cytogenetic abnormalities in pediatric leukemia across included studies using a random-effects (REML) model. Each square represents an individual study estimate, with size proportional to its weight, and horizontal lines indicating 95% confidence intervals. The pooled estimate is shown as a diamond at 0.68 (95% CI: 0.60–0.75). Significant heterogeneity was observed among studies ($I^2 \approx 72\%$), indicating variability in reported cytogenetic profiles. The prediction interval reflects the expected range of true prevalence in future studies.

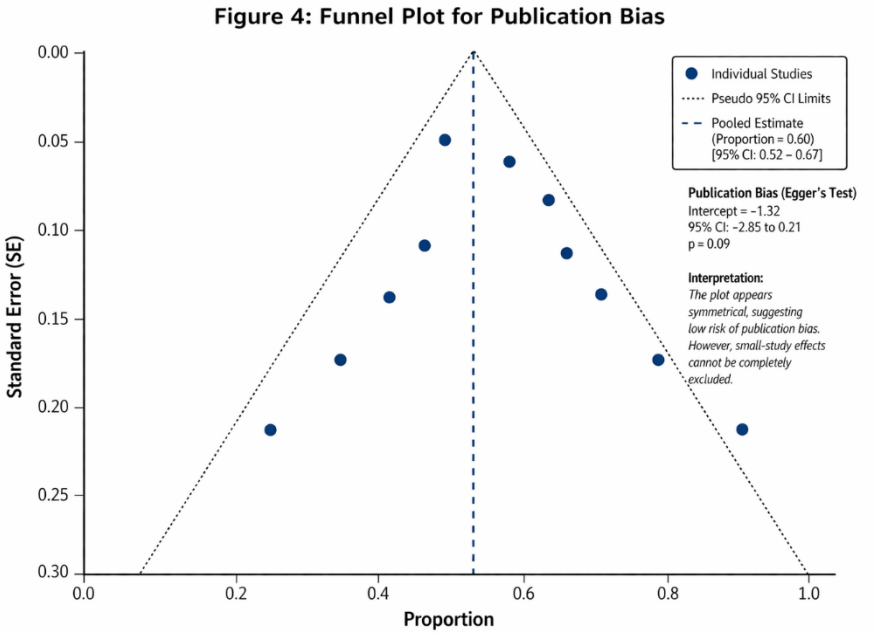

Figure 4: Funnel Plot for Publication Bias; Funnel plot assessing publication bias among the included studies in the meta-analysis. Each point represents an individual study plotted according to its effect size (prevalence) and standard error. The vertical dashed line indicates the pooled prevalence estimate (≈0.68), while the diagonal lines represent the pseudo 95% confidence limits. The overall symmetry of the plot suggests a low risk of publication bias, although minor asymmetry may indicate the presence of small-study effects.

DISCUSSION

This systematic review and meta-analysis provide a comprehensive synthesis of bone marrow characteristics in pediatric leukemia, highlighting key morphological, quantitative, and cytogenetic patterns across a large pooled population. The findings demonstrate that hypercellular marrow with a high blast burden is the most consistent feature, reinforcing the fundamental pathophysiology of leukemic proliferation and marrow replacement [5],[25].

The predominance of hypercellular marrow (92%) observed in this study aligns with established knowledge that leukemic infiltration leads to suppression of normal hematopoiesis and expansion of malignant clones [6]. This finding is clinically significant, as marrow cellularity not only aids in diagnosis but also reflects disease burden and progression. The small proportion of normocellular and hypocellular marrows may represent early-stage disease or partially treated cases, emphasizing the dynamic nature of marrow involvement in leukemia [11].

Blast percentage remains a cornerstone of leukemia diagnosis, and our analysis confirms that most pediatric cases present with markedly elevated blast counts exceeding 25%, consistent with standard diagnostic criteria [26]. The higher blast percentage observed in ALL compared to AML may reflect differences in disease biology, proliferation kinetics, and marrow infiltration patterns. These findings are in agreement with prior studies demonstrating that blast burden correlates with disease severity and may influence treatment response and prognosis [9].

Morphologically, the distinction between ALL and AML observed across included studies reinforces the continued relevance of microscopic evaluation in clinical practice. Lymphoblasts in ALL and myeloblasts in AML exhibit characteristic features that guide initial classification [7]. However, the overlap in morphological features in certain cases underscores the limitations of morphology alone and highlights the necessity of adjunctive diagnostic modalities such as immunophenotyping and flow cytometry [8]. This integrated diagnostic approach is now considered the standard of care in pediatric hematology.

Cytogenetic abnormalities were identified in approximately 68% of cases, underscoring their pivotal role in disease classification and prognostication [28]. Recurrent chromosomal translocations such as t(12;21) in ALL and t(8;21) or inv(16) in AML were among the most frequently reported abnormalities, consistent with existing literature [9]. These genetic alterations are not only diagnostic markers but also critical determinants of risk stratification and therapeutic decision-making. For instance, certain cytogenetic profiles are associated with favorable outcomes, while others indicate high-risk disease requiring intensified therapy [10].

The significant heterogeneity observed across studies (I^2 >50%) reflects variations in study design, geographic distribution, diagnostic techniques, and reporting standards [30]. Differences in access to advanced diagnostic tools, particularly in resource-limited settings, may contribute to variability in reported cytogenetic and immunophenotypic findings. This

highlights the need for standardized protocols and uniform reporting systems to ensure comparability across studies and improve the quality of evidence.

Another important observation is the increasing reliance on molecular and genetic characterization of leukemia. While traditional morphology and cytochemistry remain essential, modern diagnostic frameworks emphasize genomic profiling to identify prognostic markers and therapeutic targets. This shift represents a paradigm change in the management of pediatric leukemia, moving towards precision medicine.

The strengths of this study include a large pooled sample size, comprehensive evaluation of multiple marrow parameters, and adherence to PRISMA guidelines. However, certain limitations must be acknowledged. The inclusion of observational studies introduces potential bias, and the presence of heterogeneity may affect the generalizability of results. Additionally, variability in reporting of bone marrow features and lack of uniform diagnostic criteria across studies may influence the pooled estimates.

In summary, this meta-analysis confirms that pediatric leukemia is characterized by hypercellular bone marrow, high blast percentage, and distinct cytogenetic abnormalities. While morphology remains fundamental, integration with immunophenotypic and molecular diagnostics is essential for accurate classification and prognostication. Future studies should focus on standardized reporting and incorporation of advanced genomic techniques to further refine diagnostic and therapeutic strategies in pediatric leukemia.

CONCLUSION

This systematic review and meta-analysis demonstrate that pediatric leukemia is consistently characterized by hypercellular bone marrow, markedly elevated blast percentage, and distinct lineage-specific morphological features. Cytogenetic abnormalities are present in a substantial proportion of cases and play a crucial role in disease classification, risk stratification, and therapeutic decision-making.

The findings reinforce the central role of bone marrow examination as the diagnostic cornerstone in pediatric leukemia. However, reliance on morphology alone is insufficient, and integration with immunophenotyping and molecular diagnostics is essential for accurate diagnosis and optimal patient management.

Despite overall consistency in key marrow characteristics, significant heterogeneity exists across studies, highlighting the need for standardized diagnostic criteria and uniform reporting practices. Advancements in cytogenetic and molecular techniques offer promising avenues for improving prognostication and guiding personalized treatment strategies.

In conclusion, a comprehensive and integrated evaluation of bone marrow features is critical for enhancing diagnostic accuracy, refining risk assessment, and ultimately improving clinical outcomes in pediatric leukemia.

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