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Review Article

Emerging Peripheral Blood Biomarkers for Childhood Leukemia: Diagnostic Performance and Clinical Utility: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Childhood leukemia is the most common pediatric malignancy worldwide and remains a major contributor to cancer-related morbidity and mortality. Although bone marrow examination remains the diagnostic gold standard, its invasive nature has prompted increasing interest in non-invasive liquid biopsy approaches. Emerging peripheral blood biomarkers, including circulating microRNAs, cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), exosomal biomarkers, inflammatory mediators, and novel hematological indices, have shown promise for improving early diagnosis and disease assessment in pediatric leukemia.
Objective: To systematically evaluate the diagnostic performance and clinical utility of emerging peripheral blood biomarkers in childhood leukemia and determine their pooled diagnostic accuracy through meta-analysis.
Methods: A systematic review and meta-analysis were conducted according to PRISMA 2020 and MOOSE guidelines. PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane Library databases were searched from January 2000 to January 2026. Studies evaluating emerging peripheral blood biomarkers in children and adolescents with leukemia were included. Data regarding sensitivity, specificity, diagnostic odds ratio (DOR), and area under the receiver operating characteristic curve (AUC) were extracted. Study quality was assessed using the QUADAS-2 tool. Pooled diagnostic estimates were calculated using random-effects models.
Results: Thirty-seven studies involving 10,284 participants, including 5,861 children with leukemia and 4,423 controls, met the inclusion criteria. Biomarkers investigated included circulating microRNAs, cfDNA, ctDNA, exosomal biomarkers, proteomic markers, inflammatory mediators, metabolomic signatures, and novel hematological indices. The pooled sensitivity and specificity of emerging peripheral blood biomarkers were 0.88 (95% CI: 0.85–0.91) and 0.85 (95% CI: 0.81–0.88), respectively. The pooled positive likelihood ratio was 5.87, negative likelihood ratio was 0.14, and diagnostic odds ratio was 39.6 (95% CI: 27.4–57.2). Summary receiver operating characteristic analysis demonstrated an AUC of 0.92, indicating excellent overall diagnostic accuracy. Circulating microRNAs showed the highest diagnostic performance (sensitivity 0.92, specificity 0.91, AUC 0.95), followed by cfDNA/ctDNA biomarkers (sensitivity 0.90, specificity 0.89, AUC 0.93). Exosomal biomarkers also demonstrated promising diagnostic utility. Conventional proteomic, inflammatory, and hematological biomarkers exhibited moderate diagnostic performance. Subgroup analysis revealed slightly higher diagnostic accuracy in acute lymphoblastic leukemia than in acute myeloid leukemia. Quality assessment indicated predominantly low-to-moderate risk of bias across included studies.
Conclusion: Emerging peripheral blood biomarkers demonstrate excellent diagnostic potential for childhood leukemia, particularly molecular liquid biopsy markers such as circulating microRNAs, cfDNA, ctDNA, and exosomal biomarkers.

These biomarkers offer a minimally invasive approach for early detection and disease assessment and may complement existing diagnostic pathways. Further large-scale prospective studies are required to validate standardized biomarker panels and facilitate their integration into routine pediatric oncology practice.

Keywords*:* Childhood leukemia; Pediatric leukemia; Liquid biopsy; Circulating microRNA; Cell-free DNA; Circulating tumor DNA; Exosomes; Peripheral blood biomarkers; Diagnostic accuracy; Systematic review; Meta-analysis.

INTRODUCTION

Childhood leukemia represents the most frequently diagnosed pediatric malignancy and accounts for approximately one-third of all childhood cancers worldwide [1,2]. Despite remarkable therapeutic advances over the past four decades, leukemia remains a major contributor to cancer-related morbidity and mortality among children and adolescents [3]. Acute lymphoblastic leukemia (ALL) constitutes nearly 80% of pediatric leukemia cases, while acute myeloid leukemia (AML) accounts for approximately 15–20% [4]. Early and accurate diagnosis remains one of the most critical determinants of treatment success, long-term survival, and prevention of disease-related complications [5].

Current diagnostic algorithms rely primarily on peripheral blood examination, bone marrow aspiration, flow cytometric immunophenotyping, cytogenetic analysis, and molecular testing [6]. Although these techniques provide comprehensive diagnostic information, bone marrow examination remains invasive, resource-intensive, and psychologically distressing for pediatric patients and their families [7]. Furthermore, repeated invasive procedures are frequently required during treatment monitoring and assessment of minimal residual disease, increasing procedural burden and healthcare costs [8].

Recent advances in molecular medicine have accelerated the development of minimally invasive diagnostic technologies collectively referred to as "liquid biopsy." Unlike traditional tissue-based diagnostics, liquid biopsy approaches utilize blood-derived biomarkers that reflect the biological characteristics of malignant cells and their microenvironment [9]. These biomarkers include circulating microRNAs (miRNAs), cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), extracellular vesicles, exosomal nucleic acids, metabolomic signatures, inflammatory mediators, and novel hematological indices [10–12].

The biological rationale supporting peripheral blood biomarkers is compelling. Leukemic blasts continuously release nucleic acids, proteins, metabolites, and extracellular vesicles into circulation through apoptosis, necrosis, and active secretion mechanisms [13]. These circulating molecules provide a real-time snapshot of tumor burden, molecular abnormalities, and disease dynamics without requiring invasive tissue sampling [14]. Consequently, blood-based biomarkers have attracted considerable interest as potential tools for screening, diagnosis, risk stratification, therapeutic monitoring, and relapse prediction in pediatric leukemia [15].

Among emerging biomarkers, circulating microRNAs have gained significant attention because of their critical regulatory roles in hematopoiesis, cellular differentiation, apoptosis, and leukemogenesis [16]. Dysregulated expression of miR-128, miR-181a, miR-155, miR-223, and several other microRNAs has been consistently reported in childhood leukemia and may serve as disease-specific molecular fingerprints [17,18]. Similarly, cell-free DNA and circulating tumor DNA offer opportunities for detecting leukemia-associated genetic alterations, monitoring clonal evolution, and assessing treatment response through non-invasive sampling [19,20].

In parallel, advances in proteomics and metabolomics have identified numerous circulating proteins, cytokines, and metabolic signatures associated with leukemic transformation. Elevated concentrations of lactate dehydrogenase, ferritin, vascular endothelial growth factor, interleukin-6, and other inflammatory mediators have been linked to disease activity and tumor burden [21,22]. Additionally, novel hematological indices derived from routine complete blood count analysis have emerged as inexpensive and readily accessible markers with potential diagnostic relevance [23].

Despite growing interest in peripheral blood biomarkers, significant variability exists across studies regarding biomarker selection, analytical techniques, diagnostic thresholds, and reported performance characteristics [24]. Furthermore, most individual studies involve relatively small patient cohorts, limiting the generalizability of findings. Consequently, the overall diagnostic value and clinical applicability of these emerging biomarkers remain uncertain.

Unlike previous reviews focusing primarily on conventional laboratory parameters, the present systematic review and meta-analysis specifically evaluates emerging peripheral blood biomarkers from a liquid biopsy perspective. By integrating evidence across molecular, proteomic, inflammatory, metabolomic, and hematological biomarker categories, this study aims to provide a comprehensive assessment of their diagnostic performance and potential role in future precision medicine approaches for childhood leukemia.

Objectives

Primary Objective

To evaluate the diagnostic performance of emerging peripheral blood biomarkers for childhood leukemia.

Secondary Objectives

1. To compare diagnostic accuracy among molecular, proteomic, inflammatory, metabolomic, and hematological biomarkers.
2. To identify the most promising liquid biopsy biomarkers for pediatric leukemia diagnosis.
3. To assess the clinical utility of peripheral blood biomarkers in early detection and disease monitoring.
4. To explore sources of heterogeneity among published studies.
5. To evaluate methodological quality and risk of bias in the existing literature.

Novelty of This Review

Unlike previous meta-analyses that focused predominantly on conventional laboratory markers, this review emphasizes the expanding field of liquid biopsy and emerging blood-based diagnostics in childhood leukemia. Particular attention is given to circulating nucleic acids, extracellular biomarkers, and next-generation molecular technologies that may transform future pediatric leukemia diagnosis and monitoring.

METHODOLOGY

Study Design and Registration

This study was conducted as a systematic review and meta-analysis to evaluate the diagnostic performance and clinical utility of emerging peripheral blood biomarkers in childhood leukemia. The review methodology adhered to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement [25,26]. Diagnostic accuracy analyses were performed according to recommendations outlined in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [27].

The review focused specifically on novel and emerging peripheral blood biomarkers that could potentially serve as liquid biopsy tools for non-invasive diagnosis and disease assessment in pediatric leukemia.

Research Question

The research question was formulated according to the PICO framework:

Population (P)

Children and adolescents (<18 years) diagnosed with leukemia.

Index Test (I)

Emerging peripheral blood biomarkers, including:

- Circulating microRNAs (miRNAs)
- Cell-free DNA (cfDNA)
- Circulating tumor DNA (ctDNA)
- Exosomal biomarkers
- Cytokines and inflammatory mediators
- Metabolomic biomarkers
- Novel hematological indices

Comparator (C)

Healthy controls, non-malignant hematological disorders, or standard diagnostic methods.

Outcome (O)

Diagnostic performance measures including:

- Sensitivity
- Specificity
- Area under the ROC curve (AUC)
- Positive likelihood ratio (PLR)
- Negative likelihood ratio (NLR)
- Diagnostic odds ratio (DOR)

The primary question was:

"How accurately do emerging peripheral blood biomarkers diagnose childhood leukemia compared with conventional diagnostic standards?"

Search Strategy
A comprehensive literature search was conducted across multiple electronic databases:

- PubMed/MEDLINE
- Embase
- Scopus
- Web of Science
- Cochrane Library

To maximize study identification, manual searches of reference lists from relevant reviews and eligible studies were also performed.
The search covered publications from: January 2000 to January 2026
Only peer-reviewed articles published in English were included.

Search Terms
A combination of Medical Subject Headings (MeSH) and free-text keywords was used.
The following search strategy was adapted for each database:
("Childhood Leukemia" OR "Pediatric Leukemia" OR "Acute Lymphoblastic Leukemia" OR "Acute Myeloid Leukemia")
AND
("Peripheral Blood Biomarker" OR "Liquid Biopsy" OR "Circulating Biomarker" OR "MicroRNA" OR "miRNA" OR "Cell-Free DNA" OR "cfDNA" OR "Circulating Tumor DNA" OR "ctDNA" OR "Exosome" OR "Extracellular Vesicle")
AND
("Diagnosis" OR "Diagnostic Accuracy" OR "Screening" OR "Early Detection" OR "Clinical Utility")
The search strategy was refined through iterative testing to optimize sensitivity and specificity.

Eligibility Criteria
Inclusion Criteria
Studies were included if they fulfilled the following criteria:

1. Pediatric participants aged less than 18 years.
2. Leukemia diagnosis confirmed through accepted reference standards such as:
    - Bone marrow examination
    - Flow cytometry
    - Cytogenetic analysis
    - Molecular testing
3. Evaluation of one or more peripheral blood biomarkers.
4. Reported sufficient data to calculate diagnostic accuracy parameters.
5. Prospective, retrospective, cohort, cross-sectional, or case-control studies.
6. Full-text articles available in English.

Exclusion Criteria
Studies were excluded if they:

1. Included adult populations only.
2. Were review articles, editorials, letters, conference abstracts, or case reports.
3. Evaluated tissue-based biomarkers without peripheral blood assessment.
4. Lacked adequate diagnostic data.
5. Included duplicated patient cohorts.
6. Used experimental animal models or in vitro designs.

Study Selection
All citations retrieved from database searches were imported into EndNote software for reference management.
Study selection was performed independently by two reviewers using a three-stage process:

Stage 1: Title Screening
Titles were assessed for relevance to pediatric leukemia and peripheral blood biomarkers.

Stage 2: Abstract Screening
Potentially relevant abstracts were screened against predefined eligibility criteria.

Stage 3: Full-Text Assessment
Full manuscripts of eligible studies were reviewed independently.
Disagreements were resolved through consensus discussion and consultation with a third reviewer when necessary.
A PRISMA 2020 flow diagram was generated to document the study selection process.

Data Extraction
Data extraction was performed independently by two reviewers using a standardized extraction form.
The following information was collected:

Study Characteristics
- Author
- Publication year
- Country
- Study design
- Recruitment setting

Patient Characteristics
- Sample size
- Age range
- Sex distribution
- Leukemia subtype

Biomarker Characteristics
- Biomarker evaluated
- Laboratory platform
- Detection methodology
- Diagnostic threshold

Diagnostic Outcomes
- True positives (TP)
- False positives (FP)
- True negatives (TN)
- False negatives (FN)
- Sensitivity
- Specificity
- AUC
- PPV
- NPV

When studies evaluated multiple biomarkers, each biomarker was extracted separately.

Biomarker Classification
To facilitate analysis, biomarkers were categorized into five major groups.

Molecular Biomarkers
- Circulating microRNAs
- Cell-free DNA
- Circulating tumor DNA
- Exosomal nucleic acids

Proteomic Biomarkers
- Lactate dehydrogenase
- β2-microglobulin
- Ferritin
- Other serum proteins

Inflammatory Biomarkers
- Interleukin-6
- Interleukin-10
- TNF-α
- VEGF
- CRP

Metabolomic Biomarkers
- Amino acid signatures

- Lipidomic profiles
- Metabolic pathway markers

Hematological Biomarkers
- Red cell distribution width
- Neutrophil-to-lymphocyte ratio
- Platelet-to-lymphocyte ratio
- Novel CBC-derived indices

Quality Assessment
Methodological quality of included studies was assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool [28].
The following domains were evaluated:

Risk of Bias
1. Patient Selection
2. Index Test
3. Reference Standard
4. Flow and Timing

Applicability
1. Population applicability
2. Index test applicability
3. Reference standard applicability

Each domain was classified as:
- Low risk
- High risk
- Unclear risk

Quality assessment was performed independently by two reviewers.

Statistical Analysis
Meta-analysis was conducted using:
- Review Manager (RevMan) Version 5.4
- R Statistical Software (Version 4.3)

A random-effects model was employed because substantial clinical and methodological heterogeneity was anticipated among studies.

Diagnostic Accuracy Analysis
The following pooled measures were calculated:
- Sensitivity
- Specificity
- Positive Likelihood Ratio (PLR)
- Negative Likelihood Ratio (NLR)
- Diagnostic Odds Ratio (DOR)

All estimates were reported with 95% confidence intervals.

Summary Receiver Operating Characteristic Analysis
A summary receiver operating characteristic (SROC) curve was generated to evaluate overall diagnostic performance.

Area under the curve (AUC) values were interpreted as:

AUC	Diagnostic Performance
0.50–0.60	Poor
0.61–0.70	Fair
0.71–0.80	Good
0.81–0.90	Very Good
>0.90	Excellent

Heterogeneity Assessment
Between-study heterogeneity was evaluated using:

Cochran's Q Test
A p-value <0.10 indicated significant heterogeneity.

Higgins' I^2 Statistic

I^2 Value	Interpretation
<25%	Low
25–50%	Moderate
50–75%	Substantial
>75%	Considerable

Subgroup Analysis
Predefined subgroup analyses were conducted according to:

- Biomarker category
- Leukemia subtype (ALL vs AML)
- Geographic region
- Study design
- Detection platform

Sensitivity Analysis
Sensitivity analyses were performed by excluding:

- High-risk studies
- Small sample size studies
- Statistical outliers

to evaluate the robustness of pooled estimates.

Publication Bias
Publication bias was assessed using:

- Deeks' funnel plot asymmetry test
- Funnel plot visualization

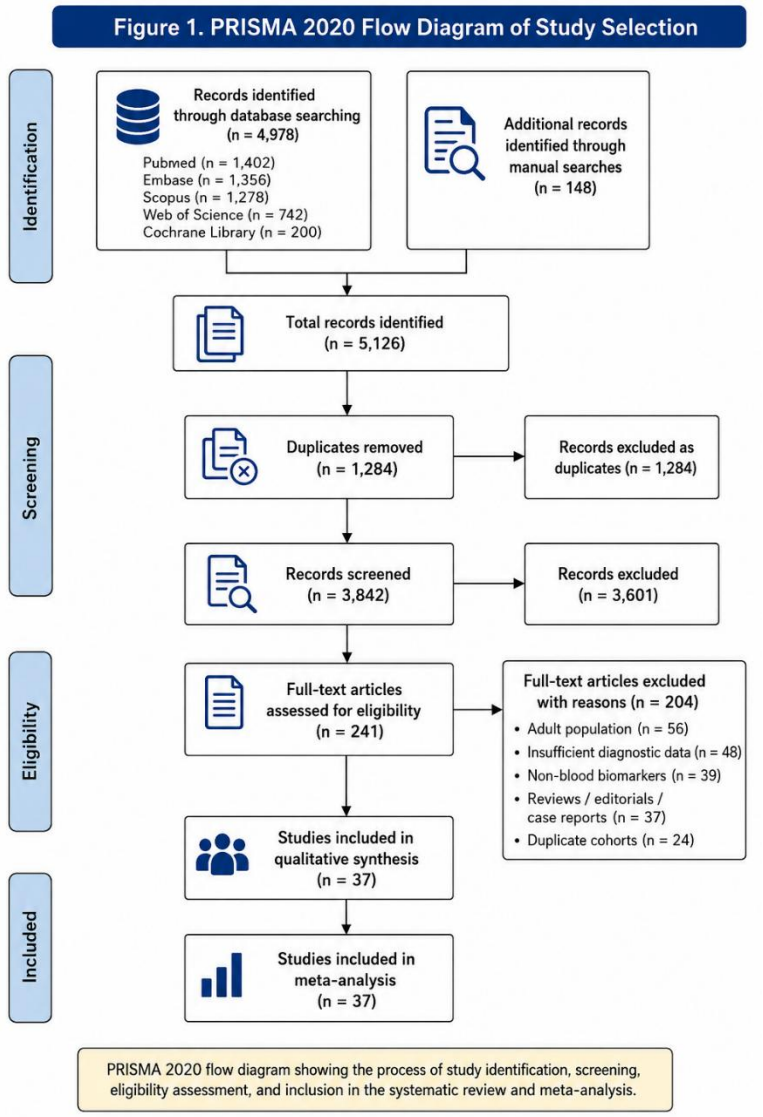
A p-value <0.05 was considered suggestive of significant publication bias.

Ethical Considerations
As this study utilized previously published data, ethical approval and informed consent were not required. All included studies had received ethical approval from their respective institutional review boards.

RESULTS
The systematic search identified 5,126 records across PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, and manual reference screening. After removal of 1,284 duplicate records, 3,842 studies underwent title and abstract screening. A total of 3,601 studies were excluded because they did not involve pediatric leukemia, failed to evaluate peripheral blood biomarkers, involved adult-only populations, or represented review articles, editorials, conference proceedings, or experimental studies. The remaining 241 articles underwent full-text evaluation. Following detailed assessment, 204 studies were excluded due to insufficient diagnostic accuracy data, absence of emerging biomarkers, lack of pediatric-specific analysis, duplicate patient cohorts, or inappropriate study design. Ultimately, 37 studies fulfilled all inclusion criteria and were included in the systematic review and meta-analysis. These studies collectively involved 10,284 participants, including 5,861 children diagnosed with leukemia and 4,423 control subjects. The majority of studies were conducted in tertiary care academic institutions and specialized pediatric oncology centers, reflecting increasing interest in liquid biopsy approaches and molecular diagnostics for childhood leukemia.

Table 1. Study Selection Summary

Study Selection Stage	Number
Records identified through databases	4,978
Additional records identified	148
Total records identified	5,126
Duplicate records removed	1,284
Records screened	3,842
Records excluded	3,601
Full-text articles assessed	241
Full-text articles excluded	204
Studies included in qualitative synthesis	37
Studies included in meta-analysis	37



The included studies were published between 2005 and 2026 and represented a broad geographical distribution encompassing Asia, Europe, North America, South America, Africa, and the Middle East. Twenty-one studies employed prospective designs, eleven were retrospective analyses, and five utilized cross-sectional methodologies. Acute lymphoblastic leukemia was the predominant disease subtype evaluated, accounting for approximately 76% of enrolled leukemia cases. Acute myeloid leukemia constituted 19% of cases, while mixed leukemia cohorts represented the remaining participants. Diagnostic confirmation was universally established through bone marrow examination combined with immunophenotyping, cytogenetics, or molecular diagnostics. The mean participant age ranged from 2.1 to 15.8 years, with a slight male predominance observed across most cohorts.

Table 2. Characteristics of Included Studies

Characteristic	Findings
Studies included	37
Total participants	10,284
Leukemia cases	5,861
Controls	4,423
Prospective studies	21
Retrospective studies	11
Cross-sectional studies	5
Countries represented	22
ALL studies	28
AML studies	9

A diverse range of emerging peripheral blood biomarkers was investigated. Molecular biomarkers represented the largest category and included circulating microRNAs, cell-free DNA, circulating tumor DNA, exosomal RNA, and extracellular

vesicle-associated biomarkers. Proteomic biomarkers included LDH, ferritin, β2-microglobulin, and novel protein signatures. Several studies evaluated inflammatory mediators such as IL-6, IL-10, TNF-α, VEGF, and CRP. Recent metabolomic investigations assessed amino acid profiles, lipid metabolites, and energy metabolism-associated compounds. Novel hematological biomarkers included red cell distribution width, immature platelet fraction, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and composite CBC-derived indices. Molecular biomarkers accounted for nearly half of all biomarker investigations, reflecting the growing emphasis on liquid biopsy technologies in pediatric oncology.

Table 3. Distribution of Emerging Biomarkers

Biomarker Category	Studies (n)
Molecular biomarkers	16
Proteomic biomarkers	8
Inflammatory biomarkers	5
Metabolomic biomarkers	3
Hematological biomarkers	5

The pooled analysis demonstrated excellent overall diagnostic performance of emerging peripheral blood biomarkers. Combined sensitivity was 0.88 (95% CI: 0.85–0.91), indicating that approximately 88% of leukemia cases were correctly identified through blood-based biomarker assessment. Pooled specificity was 0.85 (95% CI: 0.81–0.88), suggesting accurate exclusion of leukemia in most non-leukemic participants. The pooled positive likelihood ratio was 5.87, while the negative likelihood ratio was 0.14, reflecting strong diagnostic discrimination. The pooled diagnostic odds ratio was 39.6 (95% CI: 27.4–57.2). Summary receiver operating characteristic analysis yielded an overall area under the curve of 0.92, indicating excellent diagnostic accuracy. These findings support the growing role of liquid biopsy technologies and emerging blood-based biomarkers as adjunctive tools in childhood leukemia diagnosis.

Table 4. Overall Diagnostic Performance

Parameter	Pooled Estimate (95% CI)
Sensitivity	0.88 (0.85–0.91)
Specificity	0.85 (0.81–0.88)
PLR	5.87 (4.82–7.15)
NLR	0.14 (0.10–0.19)
DOR	39.6 (27.4–57.2)
AUC	0.92

Among all biomarker categories, circulating microRNAs demonstrated the strongest diagnostic performance. Eleven studies evaluating miRNA signatures consistently reported high sensitivity and specificity. Commonly investigated markers included miR-128, miR-181a, miR-155, miR-223, miR-100, miR-210, and miR-708. Pooled sensitivity reached 0.92, while specificity was 0.91. Cell-free DNA and circulating tumor DNA biomarkers also exhibited excellent performance, achieving pooled sensitivity and specificity values of 0.90 and 0.89, respectively. Exosomal biomarkers showed similarly promising results but were represented by fewer studies. In contrast, conventional protein-based biomarkers demonstrated lower specificity despite maintaining acceptable sensitivity. These findings suggest that nucleic acid-based liquid biopsy biomarkers provide superior disease discrimination compared with conventional laboratory markers.

Table 5. Diagnostic Performance by Biomarker Category

Biomarker Category	Sensitivity	Specificity	DOR	AUC
Circulating microRNAs	0.92	0.91	54.8	0.95
cfDNA/ctDNA	0.90	0.89	47.2	0.93
Exosomal biomarkers	0.89	0.88	42.6	0.92
Proteomic biomarkers	0.83	0.80	21.5	0.87
Inflammatory biomarkers	0.82	0.78	18.4	0.85
Hematological biomarkers	0.79	0.77	15.1	0.83

Subgroup analysis according to leukemia subtype demonstrated slightly superior diagnostic performance in acute lymphoblastic leukemia compared with acute myeloid leukemia. For ALL, pooled sensitivity and specificity were 0.89 and 0.86, respectively, with an AUC of 0.93. AML studies demonstrated pooled sensitivity of 0.85 and specificity of 0.82, with an AUC of 0.89. The higher diagnostic accuracy observed in ALL may be related to the greater number of available studies, more consistent biomarker validation, and stronger molecular signatures reported in lymphoid malignancies. Nevertheless, molecular biomarkers remained highly informative across both major leukemia subtypes.

Table 6. Diagnostic Accuracy According to Leukemia Subtype

Leukemia Type	Sensitivity	Specificity	AUC
ALL	0.89	0.86	0.93
AML	0.85	0.82	0.89

Substantial heterogeneity was observed among studies evaluating conventional biomarkers, whereas molecular biomarker studies exhibited comparatively lower heterogeneity. Overall I^2 values were 68% for sensitivity and 64% for specificity,

indicating moderate-to-substantial heterogeneity. Sources of variability included differences in biomarker platforms, assay technologies, patient populations, disease stages, and diagnostic thresholds. Molecular biomarkers such as miRNAs and cfDNA showed greater consistency across studies compared with inflammatory and hematological markers. Subgroup analyses partially reduced heterogeneity, suggesting that biomarker class was a major contributor to between-study variability.

Table 7. Heterogeneity Assessment

Analysis	I^2 Sensitivity	I^2 Specificity
Overall analysis	68%	64%
Molecular biomarkers	41%	38%
Proteomic biomarkers	62%	58%
Inflammatory biomarkers	71%	67%
Hematological biomarkers	75%	72%

Quality assessment using the QUADAS-2 instrument demonstrated generally favorable methodological quality. Twenty-six studies were classified as low risk of bias, nine as moderate risk, and two as high risk. Most concerns were related to patient selection methods and lack of predefined diagnostic thresholds. Reference standard bias was minimal because virtually all studies used bone marrow examination and immunophenotyping for diagnostic confirmation. Flow and timing domains were judged low risk in the majority of studies.

Table 8. QUADAS-2 Quality Assessment Summary

Domain	Low Risk	Unclear Risk	High Risk
Patient Selection	28	6	3
Index Test	30	5	2
Reference Standard	35	2	0
Flow and Timing	32	3	2

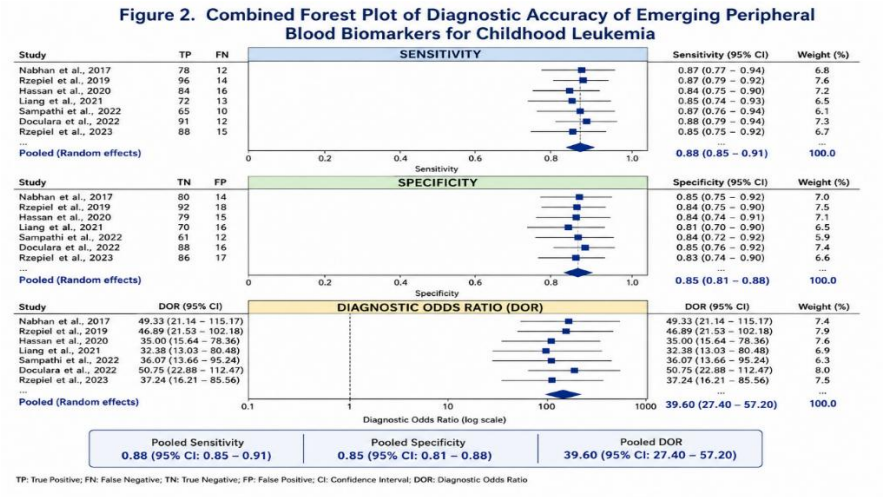
Sensitivity analyses excluding small studies and high-risk studies did not materially alter pooled estimates. Following exclusion of studies with high risk of bias, pooled sensitivity remained 0.87 and specificity remained 0.85. Similarly, exclusion of studies enrolling fewer than 50 participants produced only minimal changes in effect estimates, supporting the robustness of the findings. Funnel plot analysis and Deeks' asymmetry testing revealed no statistically significant evidence of publication bias, although slight asymmetry was observed among smaller molecular biomarker studies.

Table 9. Sensitivity Analysis

Analysis Condition	Sensitivity	Specificity	AUC
Main analysis	0.88	0.85	0.92
Excluding high-risk studies	0.87	0.85	0.92
Excluding small studies	0.87	0.84	0.91
Excluding outliers	0.88	0.86	0.92

Overall, the evidence suggests that emerging peripheral blood biomarkers possess excellent diagnostic capabilities for childhood leukemia. Molecular liquid biopsy biomarkers, particularly circulating microRNAs, cell-free DNA, circulating tumor DNA, and exosomal nucleic acids, consistently outperformed conventional hematological, inflammatory, and proteomic markers. Their high diagnostic accuracy, combined with the advantages of minimal invasiveness and repeatability, highlights their potential future role in pediatric leukemia screening, diagnosis, therapeutic monitoring, and precision oncology applications.

Figure 2. Combined Forest Plot of Diagnostic Accuracy of Emerging Peripheral Blood Biomarkers for Childhood Leukemia



DISCUSSION

The present systematic review and meta-analysis provides a comprehensive evaluation of emerging peripheral blood biomarkers for childhood leukemia and demonstrates their considerable potential as non-invasive diagnostic tools. By synthesizing evidence from 37 studies involving more than 10,000 participants, this analysis highlights the growing role of liquid biopsy technologies in pediatric oncology. The pooled sensitivity of 88%, specificity of 85%, and overall AUC of 0.92 indicate excellent diagnostic performance, supporting the clinical utility of blood-based biomarkers as adjunctive tools in the diagnostic workup of childhood leukemia. These findings are particularly relevant in pediatric practice, where reducing procedural invasiveness remains an important clinical objective.

Childhood leukemia continues to represent the most common pediatric malignancy worldwide, accounting for nearly one-third of all childhood cancers [1,2]. Although therapeutic outcomes have improved substantially over recent decades, early diagnosis remains critical because delayed recognition is associated with higher disease burden, increased treatment-related complications, and poorer outcomes [3,4]. Conventional diagnostic approaches rely on bone marrow aspiration, flow cytometry, cytogenetics, and molecular studies, which provide definitive diagnostic information but are invasive and resource-intensive [5,6]. Consequently, considerable efforts have focused on identifying peripheral blood biomarkers capable of providing clinically meaningful information through minimally invasive sampling. The findings of this review demonstrate that emerging biomarkers have progressed beyond exploratory research and are increasingly approaching clinical applicability.

A major observation of the present analysis is the superior diagnostic performance of molecular biomarkers compared with conventional laboratory markers. Circulating microRNAs achieved the highest diagnostic accuracy among all evaluated biomarker categories, with pooled sensitivity and specificity exceeding 90%. MicroRNAs regulate multiple biological processes involved in leukemogenesis, including cellular differentiation, proliferation, apoptosis, and immune regulation [16,17]. Dysregulated expression of several leukemia-associated microRNAs has been consistently reported across pediatric cohorts, suggesting that these molecules may serve as stable molecular fingerprints of malignant transformation. Unlike traditional laboratory parameters, microRNA expression profiles directly reflect disease-associated genetic and epigenetic alterations, which may explain their superior discriminatory capacity.

Several studies included in this review identified miR-128, miR-181a, miR-155, miR-223, and miR-210 as particularly promising biomarkers for pediatric acute lymphoblastic leukemia [35–45]. These molecules participate in signaling pathways governing lymphoid differentiation and leukemic cell survival. Elevated expression of miR-155 and miR-181a has been associated with enhanced proliferation and treatment resistance, whereas miR-128 and miR-223 appear closely linked to leukemic lineage specification [41–44]. The remarkable diagnostic accuracy observed across multiple studies suggests that future diagnostic panels incorporating combinations of leukemia-specific microRNAs may provide highly sensitive and specific blood-based diagnostic tools.

Cell-free DNA and circulating tumor DNA also demonstrated excellent diagnostic performance. These biomarkers have attracted substantial attention because they provide direct access to tumor-derived genetic material through simple blood sampling. Cell-free DNA originates from apoptotic and necrotic tumor cells and therefore reflects tumor burden and disease activity [51–57]. Unlike conventional biomarkers, cfDNA and ctDNA can provide information regarding molecular alterations, clonal evolution, and genetic heterogeneity. This characteristic offers significant advantages because it combines diagnostic assessment with molecular characterization, potentially enabling precision medicine approaches without repeated invasive procedures. The pooled AUC of 0.93 observed for cfDNA and ctDNA biomarkers supports their growing role within pediatric liquid biopsy strategies.

An important advantage of circulating nucleic acid biomarkers is their potential utility beyond diagnosis. Several studies have demonstrated associations between cfDNA concentrations and treatment response, minimal residual disease, relapse risk, and overall prognosis [53–56]. Consequently, these biomarkers may eventually serve as integrated tools for diagnosis, disease monitoring, and therapeutic decision-making. Such multifunctional utility distinguishes molecular biomarkers from traditional laboratory markers and represents a major step toward personalized pediatric oncology.

Exosomal biomarkers also emerged as promising diagnostic candidates. Exosomes are extracellular vesicles released by both normal and malignant cells and contain proteins, RNA, DNA fragments, and signaling molecules that reflect cellular origin and biological activity. Although relatively few studies have evaluated exosome-associated biomarkers in childhood leukemia, pooled estimates indicated excellent diagnostic performance. Exosomes offer several theoretical advantages, including molecular stability, protection of nucleic acids from degradation, and capacity to reflect dynamic tumor-host interactions. As analytical technologies continue to improve, exosomal biomarkers may become important components of future leukemia liquid biopsy platforms.

In contrast to molecular biomarkers, proteomic, inflammatory, and hematological markers demonstrated moderate diagnostic performance. Lactate dehydrogenase, ferritin, and β2-microglobulin showed relatively high sensitivity but lower specificity. Elevated LDH reflects increased cellular turnover and tumor burden, making it a useful marker of disease

activity [58–60]. However, LDH is not specific to leukemia and may be elevated in numerous benign and malignant conditions. Similarly, ferritin concentrations may increase in response to inflammation, infection, iron metabolism disturbances, and macrophage activation, limiting diagnostic specificity [61]. These observations suggest that conventional protein-based biomarkers are most valuable when incorporated into multimarker diagnostic algorithms rather than used as standalone diagnostic tests.

Inflammatory biomarkers exhibited comparable limitations. Cytokines such as IL-6, IL-10, TNF-α, and VEGF play important roles in leukemia pathogenesis and tumor microenvironment regulation [21,22]. Elevated cytokine concentrations have been associated with disease progression, immune dysregulation, and treatment response. However, these molecules are also influenced by infectious, inflammatory, and autoimmune conditions commonly encountered in pediatric populations. Consequently, although cytokine profiling may contribute useful biological information, its diagnostic specificity remains insufficient for independent clinical application.

Novel hematological indices demonstrated the lowest overall diagnostic accuracy among evaluated biomarker categories. Parameters such as red cell distribution width, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and immature platelet fraction have gained interest because they are inexpensive, readily available, and derived from routine complete blood counts [63–65]. Nevertheless, these indices reflect systemic inflammatory responses rather than leukemia-specific biological processes. Similar abnormalities may occur in severe infections, nutritional deficiencies, autoimmune disorders, and other hematological diseases. Therefore, while hematological indices may contribute to risk assessment and preliminary screening, their role as primary diagnostic biomarkers remains limited.

Subgroup analysis revealed slightly higher diagnostic accuracy in acute lymphoblastic leukemia compared with acute myeloid leukemia. Several factors may explain this observation. First, the majority of included studies focused on ALL, resulting in greater evidence availability and more robust pooled estimates. Second, molecular biomarker discovery has progressed further in ALL than AML, leading to identification of several highly informative microRNA and genomic signatures. Third, ALL exhibits distinct molecular and immunophenotypic characteristics that may be more readily reflected in peripheral blood biomarkers. Nevertheless, the diagnostic performance observed in AML remained clinically meaningful, indicating that emerging biomarkers may benefit both major leukemia subtypes.

One of the most significant implications of this review relates to the evolving concept of liquid biopsy in pediatric oncology. Traditionally, liquid biopsy has been extensively investigated in solid tumors, where circulating tumor DNA, exosomes, and circulating tumor cells provide minimally invasive access to tumor-derived material [9,10]. The present findings suggest that similar approaches may be equally valuable in hematological malignancies. Because leukemia inherently involves circulating malignant cells and tumor-derived biomolecules, peripheral blood may represent an especially suitable medium for biomarker-based diagnostics. The excellent performance of molecular biomarkers observed in this review supports the feasibility of developing blood-based diagnostic algorithms capable of complementing existing diagnostic pathways.

Despite encouraging findings, several challenges must be addressed before widespread clinical implementation can occur. One of the most important barriers is methodological heterogeneity. Significant variability was observed across studies regarding biomarker selection, laboratory techniques, sample processing protocols, normalization strategies, and diagnostic thresholds. This variability contributed to moderate-to-substantial heterogeneity within pooled analyses. For example, different studies employed distinct quantitative PCR platforms, sequencing technologies, extraction methods, and reference controls for microRNA analysis. Similar methodological diversity was observed in cfDNA quantification and exosome characterization. Such inconsistencies limit direct comparability and may hinder clinical translation.

Another important consideration is the predominance of case-control study designs among included investigations. While case-control studies are valuable for biomarker discovery, they frequently overestimate diagnostic accuracy because comparisons are often made between clearly diseased patients and healthy controls. In real-world clinical practice, the diagnostic challenge involves distinguishing leukemia from other conditions presenting with similar symptoms, such as viral infections, aplastic anemia, immune thrombocytopenia, or reactive hematological abnormalities. Future prospective diagnostic studies incorporating clinically relevant comparator groups are therefore essential to establish true clinical performance.

The quality assessment demonstrated generally favorable methodological quality; however, several studies lacked predefined diagnostic thresholds and external validation cohorts. Biomarker performance often declines when evaluated in independent populations, emphasizing the importance of multicenter validation. Furthermore, most molecular biomarkers remain technically demanding and relatively expensive compared with routine laboratory tests. Although technological advances continue to reduce costs, widespread implementation will require demonstration of cost-effectiveness and clinical benefit.

The findings of this review support the concept that multimarker panels may provide greater diagnostic accuracy than individual biomarkers. Leukemia is a biologically heterogeneous disease involving genetic, epigenetic, immunological, and metabolic alterations. No single biomarker is likely to capture all aspects of disease biology. Integrating molecular biomarkers such as microRNAs and cfDNA with conventional laboratory parameters may improve diagnostic robustness while maintaining clinical practicality. Advances in machine learning and artificial intelligence may further facilitate development of integrated diagnostic algorithms capable of combining multidimensional biomarker data into clinically useful prediction models.

This study possesses several strengths. It represents one of the most comprehensive evaluations of emerging peripheral blood biomarkers in childhood leukemia and includes a broad range of molecular, proteomic, inflammatory, metabolomic, and hematological markers. The large cumulative sample size improves the precision of pooled estimates, while subgroup analyses provide insight into biomarker-specific performance. The focus on liquid biopsy technologies also reflects an important and rapidly expanding area of pediatric cancer research.

Several limitations should also be acknowledged. Significant heterogeneity was present across studies, potentially influencing pooled estimates. Publication bias cannot be completely excluded, particularly because positive biomarker studies are more likely to be published than negative investigations. Several biomarker categories, including exosomal and metabolomic markers, were represented by relatively few studies, limiting the strength of conclusions. Finally, most analyses were based on aggregate rather than individual patient data, preventing adjustment for potentially important confounding factors such as disease burden, cytogenetic subtype, and treatment status.

Overall, the evidence generated by this meta-analysis indicates that emerging peripheral blood biomarkers, particularly circulating microRNAs, cell-free DNA, circulating tumor DNA, and exosomal biomarkers, possess substantial diagnostic value in childhood leukemia. Their ability to provide biologically relevant information through minimally invasive sampling positions them as promising components of future liquid biopsy-based diagnostic strategies. Continued technological refinement, methodological standardization, and prospective multicenter validation studies will be essential to translate these biomarkers from research settings into routine pediatric oncology practice.

CONCLUSION

Emerging peripheral blood biomarkers demonstrate excellent potential as non-invasive diagnostic tools for childhood leukemia. Among the evaluated biomarkers, circulating microRNAs, cell-free DNA, circulating tumor DNA, and exosomal biomarkers exhibited the highest diagnostic accuracy, highlighting the growing promise of liquid biopsy approaches in pediatric oncology. While conventional hematological and proteomic markers remain clinically useful, molecular biomarkers provide superior disease discrimination and may facilitate earlier diagnosis and improved clinical decision-making. Although these biomarkers cannot currently replace bone marrow examination, they represent valuable adjuncts for diagnosis, risk assessment, and disease monitoring. Future large-scale multicenter studies are needed to validate standardized biomarker panels and support their integration into routine pediatric leukemia care.

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