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Meta-Analysis

Comparison of Cytochemistry and Flow Cytometry for Leukemia Immunophenotyping: A Systematic Review and Meta-Analysis

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Abstract

Background: Accurate diagnosis and classification of leukemia are essential for effective treatment planning. Traditional cytochemistry relies on enzyme-based staining for morphological evaluation, while flow cytometry (FCM) employs monoclonal antibodies to detect multiple surface and intracellular markers. This systematic review and meta-analysis compared the diagnostic accuracy of cytochemistry and FCM in leukemia immunophenotyping.

Methods: A systematic search of PubMed and Google Scholar was conducted according to PRISMA guidelines. Studies evaluating sensitivity, specificity, and accuracy of cytochemistry and FCM in diagnosing acute and chronic leukemia were included. Data extraction covered study characteristics, diagnostic markers, and performance outcomes. Meta-analysis was performed to compare diagnostic values across methods.

Results: Eleven eligible studies comprising pediatric and adult leukemia cases were analyzed. Cytochemical stains such as Myeloperoxidase (MPO) and Sudan Black B (SBB) showed high specificity (91–100%) and moderate-to-high sensitivity (60–97%), while Periodic Acid–Schiff (PAS) and Nonspecific Esterase (NSE) had lower reliability. FCM demonstrated superior diagnostic performance with average sensitivity of 87.7% and specificity of 85.6%, achieving >95% accuracy in several studies. Marker panels including CD3, CD45, CD79a, and MPO enabled precise subtype differentiation and minimal residual disease (MRD) detection.

Conclusion: Cytochemistry remains useful as an affordable screening tool in resource-limited settings, but FCM provides greater sensitivity, specificity, and comprehensive immunophenotypic data, making it the preferred method for leukemia diagnosis and monitoring. Combining both approaches can enhance diagnostic performance across diverse clinical contexts.

Keywords:

Leukemia
Cytochemistry
Flow Cytometry
Immunophenotyping

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1. INTRODUCTION

Leukemia consists of a group of hematologic carcinoma that initiates in the bone marrow, leading to the uncontrolled proliferation of abnormal blood cells.[1,2] It is classified into various subtypes, acute and chronic leukemia, with acute leukemia being the most aggressive form. Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML) represent the two distinct forms of Acute leukemia. Similarly, chronic leukemia is further subclassified into Chronic Lymphocytic Leukemia (CLL) and Chronic Myeloid Leukemia (CML)[3–5] Differentiating between these subtypes is crucial for determining appropriate treatment strategies, as each type responds differently to chemotherapy and targeted therapies. The procedure of immunophenotyping serves as a vital diagnostic method for proper leukemia classification, which helps medical professionals make decisions about both prognosis and treatment[6–9]

The diagnosis of leukemia has heavily depended on cytochemical tests, which stain cellular enzymes to identify myeloid versus lymphoid cell types throughout history. Myeloperoxidase (MPO) for myeloid cells[6,10], Sudan Black B (SBB) for granulocytes[11,12], and non-specific esterase (NSE) stand as the top choices for cytochemical analysis that functions well in resource-limited areas.[13] Cytochemical staining has been particularly valuable in resource-limited settings due to its affordability and accessibility. The subjective nature of test results constitutes the main disadvantage as it leads to inconsistent diagnoses. The diagnostics value of this method decreases because it detects some leukemia subtypes with reduced effectiveness and does not analyze multiple markers simultaneously.

In contrast, flow cytometry (FCM) has revolutionized leukemia diagnosis because it provides automated high-speed screening and multiple parameter cellular analysis. This technique uses the combination of monoclonal antibodies labeled with fluorochromes, enabling FCM to detect various antigens, which enables the distinction of different leukemic populations across multiple subtypes.[14–16] FCM provides superior advantages over cytochemistry in leukemia screening because it assesses many markers through a single testing process. The increased accuracy and specificity of leukemia classification become possible through this capability because it provides advanced characterization of leukemic cells.[17–22] FCM plays a pivotal role in the detection of minimal residual disease (MRD), a critical aspect of managing leukemia and monitoring treatment response. [23–25] Despite its advantages, FCM is based on technical expertise and specialized equipment and is expensive, which may limit its widespread use in some healthcare settings. However, FCM provides quick, impartial, and extremely thorough immunophenotypic analysis, which makes it especially useful for MRD identification and therapy tracking.

The shift from cytochemistry to FCM in leukemia diagnosis has posed significant questions of cost-effectiveness, clinical usefulness, and relative diagnostic precision..[26–29] Cytochemistry is still used in practice despite FCM is considered the gold standard especially in developing countries with limited access to modern laboratory facilities. The differences in sensitivity, specificity, and reliability between these two techniques highlight the need for a systematic review and meta-analysis to synthesize existing evidence and provide a clear, evidence-based comparison.

In a study the efficacy of FCM and cytochemistry in leukemia immunophenotyping was assessed in a clinical hematology lab. The results showed that FCM outperformed cytochemistry with regard to total accuracy, specificity (>95%), and sensitivity (>90%), based on findings. FCM offers accurate single-cell analysis of surface and intracellular markers, whereas cytochemistry is more subjective and has intermediate sensitivity (60–80%) and specificity (70–85%) because to its reliance on morphological evaluation and enzyme stains. This makes it possible to distinguish leukemia subtypes more clearly, especially when mixed-lineage leukemia is involved. While cytochemistry is still more widely available but less dependable, FCM necessitates specialized equipment and technical know-how despite having a greater diagnosis accuracy. In light of these findings, FCM ought to be the go-to diagnostic method for leukemia immunophenotyping in clinical settings. [30]

Although both cytochemistry and FCM are employed in leukemia immunophenotyping, their relative accuracy, sensitivity, and clinical utility remain a topic of ongoing debate. Studies conducted in the past have shown different results about the agreement levels, yet their outcomes remain inconclusive. Additional research must be conducted to detect the exact levels of accuracy, sensitivity, and clinical usefulness between these methods because current findings show conflicting results. Healthcare providers gain better decision-making capacity on diagnostic tool selection when they examine the benefits and constraints of available evaluation methods which leads to enhanced patient outcomes. Standardized diagnosis practices can be achieved through systematic review combined with meta-analysis because this approach enables the selection of appropriate techniques that match individual healthcare requirements.

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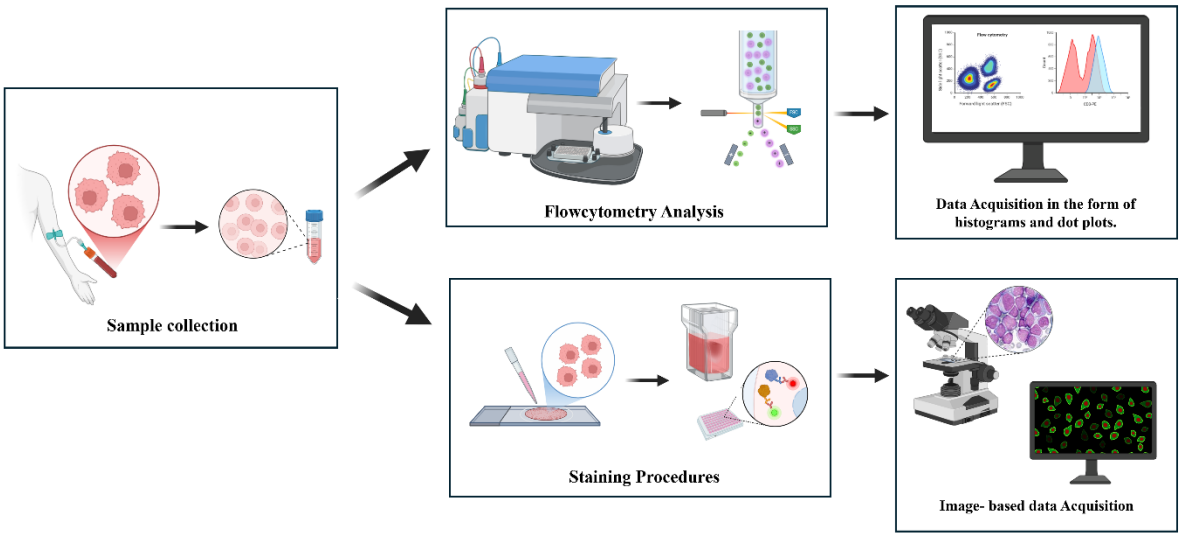

Figure 1. Workflow of Sample Processing and Data Acquisition in Leukemia Immunophenotyping. The process begins with blood sample collection from the patient and is processed for further analysis. Following collection, the sample is then introduced to flow cytometer. Here, the isolated cells are passed through a laser-based system that detects their fluorescence signals based on surface markers. The data is obtained in the form of histograms and dot plots, allowing for quantitative as well as qualitative assessment of cell populations via forward and side scattering. This technique helps in distinguishing between normal and malignant cells based on their immunophenotypic characteristics. Immunophenotypic profiling differentiates normal cells from those which are malignant. Cell microscopic examination requires staining procedures which serve to prepare cells in cytochemistry analyses. Scientific markers and staining tests are deployed to discover both cellular features and molecular components. After staining the samples microscopy is used to perform image-based data acquisition. The microscope captures high-resolution images of stained cells in order to examine their morphology while identifying marker expression. Flow cytometry quantitative data can be enhanced through qualitative results obtained via this approach which delivers a complete evaluation of leukemia phenotypic features. The illustration created with Biorender.

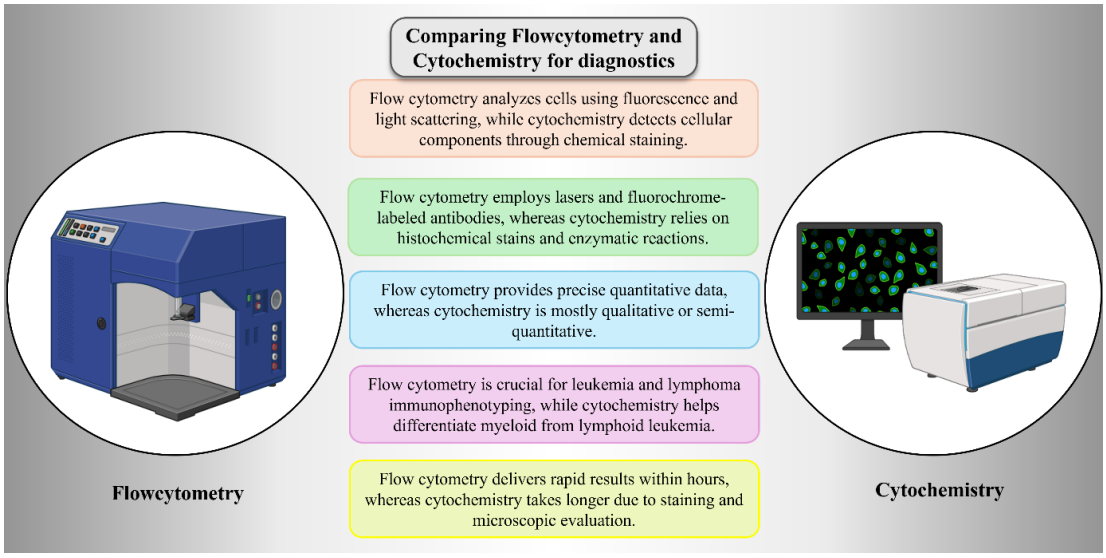

Figure 2. Understanding Flow Cytometry and Cytochemistry: A Side-by-Side Comparison. The illustration is created using Biorender.

This work examines a thorough assessment between the diagnostic abilities of FCM and cytochemistry approaches when performing leukemia immunophenotyping tests. Accurate assessment of these proposed two techniques remains essential because proper leukemia classification directly influences both treatment plans along with prognosis predictions for patients. The project seeks to conduct an exact comparison of the complete diagnostic

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performance and detection rates as well as identification performance between these two methods for different leukemia types. The statistical analysis through this systematic review process reveals the diagnostic method with the highest accuracy levels.

A meta-analysis, combined with literature review, will determine the performance of these diagnostic methods in identifying different leukemia types. The research identifies both benefits and drawbacks that come with cytochemical analysis and flow cytometry diagnosis methods. This paper provides an impartial review of the testing approaches through an analysis of research studies to reveal their clinical strengths and weaknesses. The systematic research will lead to improved understanding about appropriate methods for leukemia immunophenotyping diagnosis which will guide future clinical procedures.

METHODOLOGY

2.1. Literature Search

We have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to conduct this systematic review, guaranteeing a methodical and transparent approach for analysis. Our goal was to locate pertinent research that used FCM and cytochemistry to diagnose leukemia in a variety of subtypes. Boolean search operators and Medical Subject Headings (MeSH) phrases were used to conduct a thorough literature search across scholarly databases, PubMed and Google Scholar.

In PubMed search, we used two search strategies: [("Leukemia" OR "Acute Leukemia" OR "AML" OR "ALL" OR "CLL") AND ("Cytochemistry" OR "Cytochemical Staining" OR "Myeloperoxidase" OR "Sudan Black B" OR "Esterase") AND ("Sensitivity" OR "Specificity" OR "Diagnostic Accuracy" OR "Comparison Study")] and [("Leukemia" OR "Acute Leukemia" OR "AML" OR "ALL" OR "CLL") AND ("Flow Cytometry" OR "Immunophenotyping" OR "CD Markers") AND ("Sensitivity" OR "Specificity" OR "Diagnostic Accuracy" OR "Comparison Study")]. This approach has been essential to identify studies that assessed the diagnostic capabilities of cytochemistry and FCM for leukemia detection and to find data relevant to the topic. The search for scholarly material on Google Scholar relied on using MeSH terms that included leukemia, cytochemical staining, and FCM. Adjusting our keyword combinations enabled us to collect a wide range of studies which discussed diagnostic sensitivity and specificity and accuracy. The research selection process concentrated on written works that showed diagnostic measurement sensitivities and specificities to produce a diverse overview of relevant findings.

2.2. Study Selection

A set of inclusion and exclusion criteria helped us identify proper studies and ensure a methodologically strong analytical approach. The current analysis only included studies that specifically examined leukemia diagnosis through accuracy measurement of both methods together with their sensitivity and specificity evaluation. All analyses included various leukemia subtypes encompassing acute and chronic cases when researchers presented valid quantitative performance data for diagnosis. The analysis needed complete assessment of methods and outcomes which is why only full-text articles published in English were used for evaluation. Review papers, conference abstracts, case reports, editorials and non-original diagnostic research papers were excluded through defined criteria. The analysis excluded research studies which did not provide specific information regarding sensitivity and specificity. The software Zotero detected duplicated studies which were then removed from the dataset to maintain a clear and non-repetitive database. The systematic selection process confirmed the inclusion of only high-quality data-driven research which directly contributed to the comparison between cytochemistry and FCM in leukemia diagnosis.

2.3. Extracting outcome data

The data extraction followed a standardized procedure to maintain accuracy and consistency throughout the process. Relevant studies underwent full-text examination for final assessment after the reviews of study abstracts and titles. Whenever we had discrepancies regarding selection the reviewers met to resolve them.

A strict procedure was used to acquire necessary information from selected studies that involved obtaining participant statistics along with age breakdowns while noting publication dates and authors' names and total number of participants. Lymphoma and leukemia subtypes together with their diagnostic techniques (cytochemistry or flow cytometry and other subtypes) formed part of the recorded information. Important diagnostic performance metrics such as sensitivity and specificity and accuracy percentages were recorded with myeloperoxidase, Sudan Black B as well as CD markers and other pertinent biomarkers and stains. The evaluation of diagnostic reliability was enhanced through positive predictive value (PPV) and negative predictive value (NPV) assessment whenever they were reported.

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The systematic organization of collected data allowed for an analysis of FCM and cytochemical marker and stain effectiveness in leukemia detection. The applied systematic structure allowed researchers to obtain dependable results which served as valuable indicators for comparing different diagnostic procedures.

3. RESULTS

3.1. Literature Search and Screening

Initially, 7,105 records were found via database searches that contained 2,675 entries from PubMed and 4,430 from Google Scholar. After filtering out 3,721 irrelevant records, we further flagged 3,275 as ineligible based on unsuitable statistical data and contrasting study designs before screening. Hence, 109 articles were left for evaluation. During the screening phase, 56 articles were discarded, leading to the retrieval of 53 articles. However, only 29 papers were evaluated for eligibility because 24 publications could not be downloaded. Eleven articles that satisfied all inclusion criteria were ultimately included in the systematic review after 18 publications were eliminated during the eligibility evaluation.

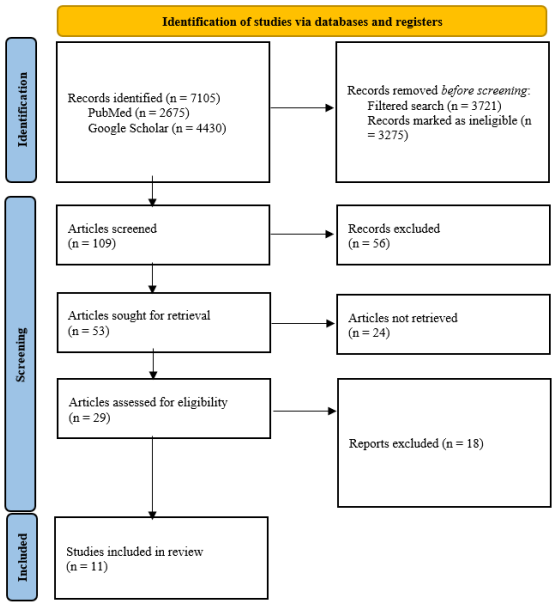

Figure 3. PRISMA Flow Diagram: Screening and Tracking Study Inclusion and Exclusion

3.2. Study Characteristics

The dataset's cytochemistry research used cytochemical staining techniques to investigate different kinds of leukemia, mainly AML, ALL, and CMML. A wide demographic representation was indicated by the sample sizes, which varied from 30 to 81 individuals, and the age distributions, which spanned from 0.3 to 89 years. MPO (Myeloperoxidase), CD68R IHC+, CD14 IHC+, CD123, and MPO-/CD33+ were among the frequently used cytochemical stains that were utilized to distinguish various leukemia subtypes according to their staining properties. For various stains, the reported average sensitivity was 67.46%, values ranged from 28% to 86.67%, average specificity was 94.09%, values ranged from 91% to 100%, and average accuracy of 82.99% values ranged from 72% to 93.33%. Some studies also reported the negative predictive value (NPV) and positive predictive value (PPV), with NPV of 88.24% and PPV as high as 100%. The FCM studies used a variety of immunophenotyping markers to evaluate the diagnosis accuracy of leukemia cases, specifically focusing on ALL, AML, and B-ALL. Although age data was inconsistent, the sample sizes ranged between 74 to 94 participants and included both adult and pediatric groups ranging from 0 to 93 years of ge. CD79a, CD22, CD66c, CD3, and MPO were the primary FCM markers utilized to distinguish between leukemia subtypes. Reports indicate average sensitivity of 87.71%, values ranging from 82% to 100%, and average specificity of 85.62%, values ranging from 69% to 98% demonstrate the efficacy of FCM in the diagnosis of leukemia.

3.3. Meta-analysis

The meta-analysis output of FCM diagnosis highlights the diagnostic values, sensitivity, and specificity of immunophenotypic markers used across various leukemia subtypes. In Zhang et al.'s investigation, CD14, CD68, and CD163 markers showed moderate sensitivity (65.4–74.2%) and relatively high specificity (74.2–90.6%), indicating their potential but limited accuracy as the only diagnostics. The notable diagnostic performance of CD45 in ALL was confirmed by the largest investigation by Lam et al., involving 383 pediatric ALL cases and reported 99.7% sensitivity and 98.5% specificity. To an abounding degree, the study of Lui et al. involving 1668 AML cases indicated remarkable diagnostic performance with 99% sensitivity and 99.2 % specificity.

From a broader perspective, CD79a, CD3, and MPO stand out as highly sensitive and specific indicators. However, rather than depending solely on individual markers, differences in specificity among them underscore the necessity of a panel-based diagnostic approach. When distinguishing between related leukemia subtypes, the accuracy and dependability of leukemia diagnosis are

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Table 1. Summary of Flow Cytometry Markers in Leukemia Diagnosis – Meta-Analysis Findings.

Sr. No.	Author-Year-Ref	Sample Size	Age (years)	Leukemia Type	Flow Cytometry Markers	Sensitivity (%)	Specificity (%)
1	Paredes-Aguilera et al (2001) (31)	74	-	ALL, AML	CD79a	100	88
					CD22	90	88
2	Guillaume et al. (2011) (32)	94	2-86	B-ALL	CD66c	82	69
					CD3	100	98
					MPO	100	97.5
3	Liu et al. (2017) (33)	73	14-80	APL	CD34	87.5	88.3
		1668	15-88	AML	CD117+	99	99.2
4	Lam et al. (2017) (34)	383	0-18	ALL	CD45	99.7	98.5
5	Raskovalova et al. (2019) (35)	44	>50	CMML	MPO	95.9	36.4
6	Zhang et al. (2021) (36)	114	-	AML, CMML, ALL, BPDCN	IBA1	93.7	97.1
					CD14	65.4	88.2
					CD68	74.4	74.2
					CD163	52.6	90.6

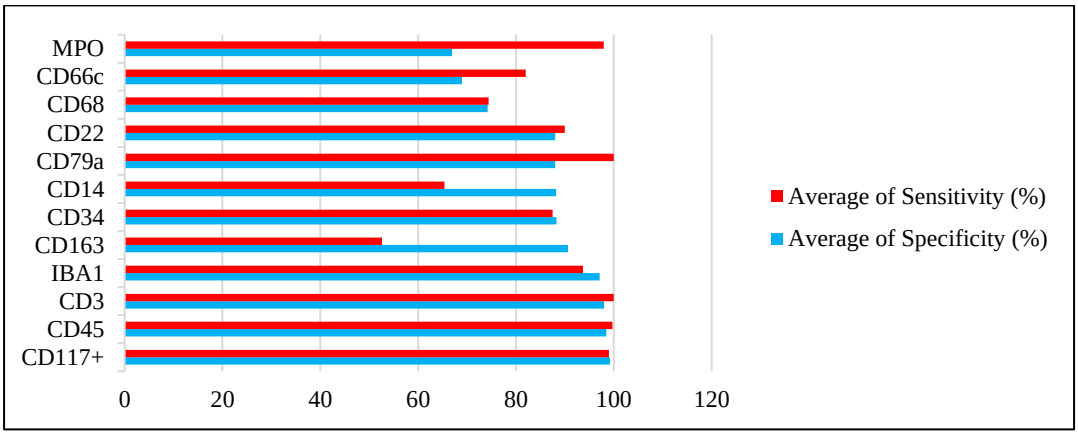

Figure 4. Sensitivity and Specificity of Flow Cytometry Markers in Leukemia Diagnosis. CD3, CD79a, and MPO demonstrate high sensitivity and specificity, indicating their notable diagnostic value, while other markers like CD14 and CD163 show moderate sensitivity.

improved by combining numerous markers in an FCM panel.

A brief comparison of the sensitivity and specificity of assorted FCM markers used in leukemia diagnosis is shown in the graph in **Figure 3**. The y-axis lists the markers that were used, and the x-axis shows the percentage values of both the diagnostic values. Bars represent the average sensitivity and specificity of each marker. Across most of the markers the specificity value has a broadly wide range and CD3, CD45 and MPO retain specificity >90%. Thus, this means that although they have very high power in distinguishing leukemia cases from other hematological diseases, CD14 and CD68 suggest medium specificity. In terms of the leukemia identification, the graph demonstrates the very good diagnostic reliability of CD79a and CD3 markers. Moreover, it suggests that MPO should also be specific due to its lower sensitivity, therefore confirming the necessity of the panel-based method for accurate leukemia diagnosis.

The forest plots in **Figure 4** display point estimates of sensitivity for each marker, along with their corresponding 95% confidence intervals (CIs) evaluated. Section A visualizes the sensitivity of different flow cytometry markers across multiple studies, and Section B visualizes specificity. In sensitivity analysis, the narrow CIs of CD3, MPO, and CD79a indicate their high precision, while that of CD163, CD66c, and CD14 display a great variability. In specificity analysis, MPO indicates higher precision while CD117 and CD45 indicate greater variability.

The diagnostic accuracy of several cytochemical stains, such as Myeloperoxidase (MPO), Sudan Black B(SBB), Periodic Acid-Schiff (PAS), Nonspecific Esterase (NSE), and

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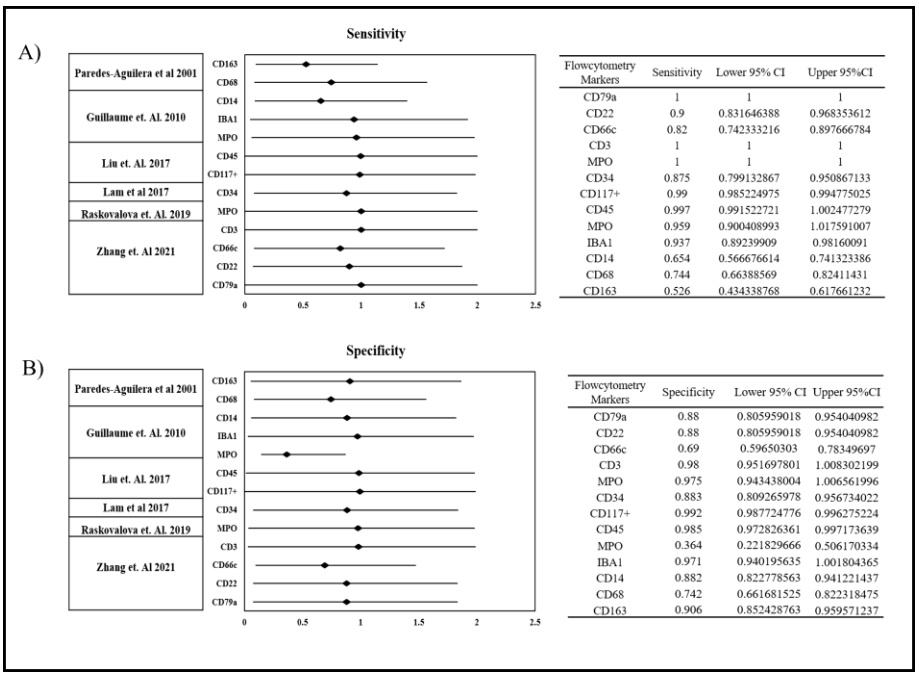

Flowcytometry Markers	Sensitivity	Lower 95% CI	Upper 95%CI
CD79a	1	1	1
CD22	0.9	0.831646388	0.968353612
CD66c	0.82	0.742333216	0.897666784
CD3	1	1	1
MPO	1	1	1
CD34	0.875	0.799132867	0.950867133
CD117+	0.99	0.985224975	0.994775025
CD45	0.997	0.991522721	1.002477279
MPO	0.959	0.900408993	1.017591007
IBA1	0.937	0.89239909	0.98160091
CD14	0.654	0.566676614	0.741323386
CD68	0.744	0.66388569	0.82411431
CD163	0.526	0.434338768	0.617661232

Flowcytometry Markers	Specificity	Lower 95% CI	Upper 95%CI
CD79a	0.88	0.805959018	0.954040982
CD22	0.88	0.805959018	0.954040982
CD66c	0.69	0.59650303	0.78349697
CD3	0.98	0.951697801	1.008302199
MPO	0.975	0.943438004	1.006561996
CD34	0.883	0.809265978	0.956734022
CD117+	0.992	0.987724776	0.996275224
CD45	0.985	0.972826361	0.997173639
MPO	0.364	0.221829666	0.506170334
IBA1	0.971	0.940195635	1.001804365
CD14	0.882	0.822778563	0.941221437
CD68	0.742	0.661681525	0.822318475
CD163	0.906	0.852428763	0.959571237

Figure 5. **Forest Plot depicting Sensitivity and Specificity of Various Flow Cytometry Markers for Leukemia Immunophenotyping. The** forest plot depicts the sensitivity (A) and specificity (B) of various flow cytometry markers used for leukemia immunophenotyping across several studies. The horizontal lines show the respective confidence intervals, and the black diamonds are point estimates. While CD163 and CD68 show poor specificity, markers like CD79a and MPO show great sensitivity. The studies that are cited demonstrate the differences in the diagnostic performance of several markers and encompass findings from Paredes-Aguilera et al. (2001) to Zhang et al. (2021).

immunohistochemical (IHC) markers (CD123, CD68R, CD14, and MPO-/CD33+), is assessed in the meta-analysis of cytochemistry studies for the diagnosis of leukemia. The investigation covered both pediatric as well as adult populations, with sample sizes ranging from 30 to 129 patients and participant ages ranging from 0 to 93 years.

The sensitivity of cytochemical stains differed significantly between investigations. Sudan Black B continuously demonstrated great sensitivity, ranging from 83.33% to 100% indicating more reliability. MPO's importance in differentiating myeloid leukemia was further supported by its excellent sensitivity (varying from 83.8% to 100%) and specificity (81.82% to 100%). The diagnostic performance of PAS staining, which is frequently utilized in lymphoid leukemia, varies depending on the leukemia subtype, as seen by sensitivity values that range from 40.3% to 82.9%. NSE's inadequate solo diagnostic accuracy was indicated by one study's findings of 50% sensitivity and 81.82% specificity.

Overall, specificity values ranged from 70 to 100% for both generally high values in the capacity to demonstrate great selective ability in leukemia diagnosis. As an example, we observed some of the highest values of specificity of some of the highest specificity (100% and 98.8%) for leukemia identification by some of MPO and Sudan Black B. Non reliable as the only diagnostic method only with test specificity of 91–98% and test sensitivity of 20–60%, IHC markers CD68R, CD14, CD123, and MPO/CD33+ are not. The results of the cytochemical stains SBB and MPO were considered the most accurate, displaying percentages of 72-98.8%. To further confirm MPO and SBB efficacy as diagnostic tools, they had high reported Positive Predictive Value (PPV) and Negative Predictive Value (NPV).

The study gives a summary of MPO and SSB as two of the best cytochemical stains for leukemia diagnosis, with excellent sensitivity, specificity, and a wide accuracy. Although NSE provides less dependable staining, PAS is moderately sensitive and specific and useful in some leukemia subtypes. Results indicate that cytochemistry is of value in the diagnosis of leukemia, particularly in resource-limited environments where FCM might not be readily available.

The average sensitivity, specificity, and accuracy of several cytochemical stains used for leukemia diagnosis are compared in the bar chart given in **Figure 2**. The y-axis lists all the cytochemical stains and IHC markers, while the x-axis shows the percentage values of diagnostic parameters. Significant variance in diagnostic performance between various stains are revealed by the data. The maximum

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Table 2. **Meta-Analysis of Cytochemical Stains in Leukemia Diagnosis – Summary of Diagnostic Performance.**

Sr. No.	Author & Year	Sample Size	Age (years)	Leukemia Type	Cyto-chemistry	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
1	Rollins-Raval et al. (2012)37	81	0.3-89	AML, CMML	CD68R IHC+	60	98	86	-	-
					CD14 IHC+	20	98	74	-	-
					CD123	28	91	72	-	-
					MPO-/CD33+	28	96	75	-	-
2	Deghady et al. (2016) 38	30	4-60	ALL and AML	MPO	86.67	100	93.33	100	88.24
					SBB	100	86.67	93.33	88.24	100
					NSE	50	81.82	73.33	50	81.82
					PAS	40.3	70	50	72.73	36.84
3	Resende et al. (2017) 39	67	2-93	AML and ALL	MPO	83.8	100	91	100	83.8
					PAS	82.9	100	90.9	100	83.8
					SBB	96.9	100	98.4	100	96.9
4	Hamid et al. (2018) 40	53	1.5-76	ALL (58.5%), AML (37.7%), Undifferentiated (3.8%)	MPO	95	100	-	100	-
					PAS	80.6	85	-	89.28	-
5	Venkatesan et al. (2023) 41	129	2-70	AML (82.22%), ALL (59.45% in children)	MPO	84.44	100	88.97	-	-
					PAS	59.45	98.88	87.4	-	-
					SB B	83.33	100	88.18	-	-

low sensitivity, close to 100%, is shown by Sudan Black B and MPO, demonstrating their potent capacity to accurately detect leukemia-positive cases. This aligns with their proven function in detecting myeloid leukemia. The reduced sensitivity of PAS, NSE, and immunohistochemical markers (CD14 IHC+, CD68R IHC+, CD123, and MPO/CD33+) ranges from about 20% to 82%, indicating their limited applicability as major diagnostic techniques.

The majority of cytochemical markers have good specificity values, usually exceeding 80%, with some (such as CD14 IHC+ and MPO) approaching 98%. This shows how well they can rule out patients who aren't affected by leukemia. Their diagnostic robustness is further supported by the fact that Sudan Black B and MPO have some of the highest accuracy rates. On the other hand, NSE and PAS exhibit modest accuracy, which is indicative of their variation in diagnostic efficacy among distinct leukemia subtypes. Broadly, the graph demonstrates that MPO and Sudan Black B are the most dependable cytochemical stains, whereas markers such as NSE and other IHC markers have performance and need to be used in combination with other methods.

The forest plots in **Figure 5** display point estimates of sensitivity for cytochemical stain, along with their corresponding calculated 95% CI. Section A visualizes the sensitivity of different stains used across multiple studies, and Section B visualizes its specificity. In sensitivity analysis, the narrow CIs of SBB indicate their high precision, while that of NSE, and IHC marker CD68R, display a great variability. In specificity analysis, MPO and SBB indicates higher precision while NSE and PAS indicate greater variability.

4. DISCUSSION

The strengths and limitations of each technique in the detection of all the leukemia subtypes are highlighted by the comparison of cytochemistry and FCM in leukemia diagnosis. MPO and SBB demonstrated good sensitivity and specificity across investigations and are two examples of the conventional yet popular cytochemistry approach that

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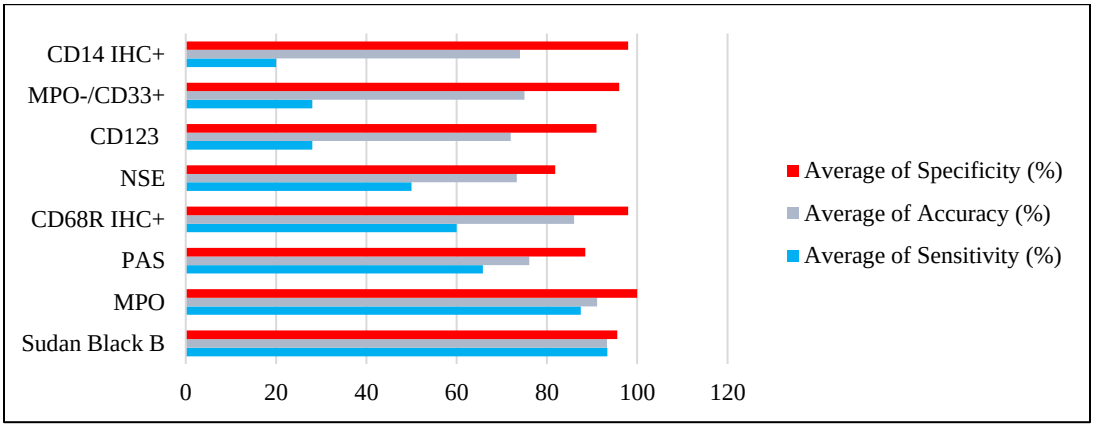
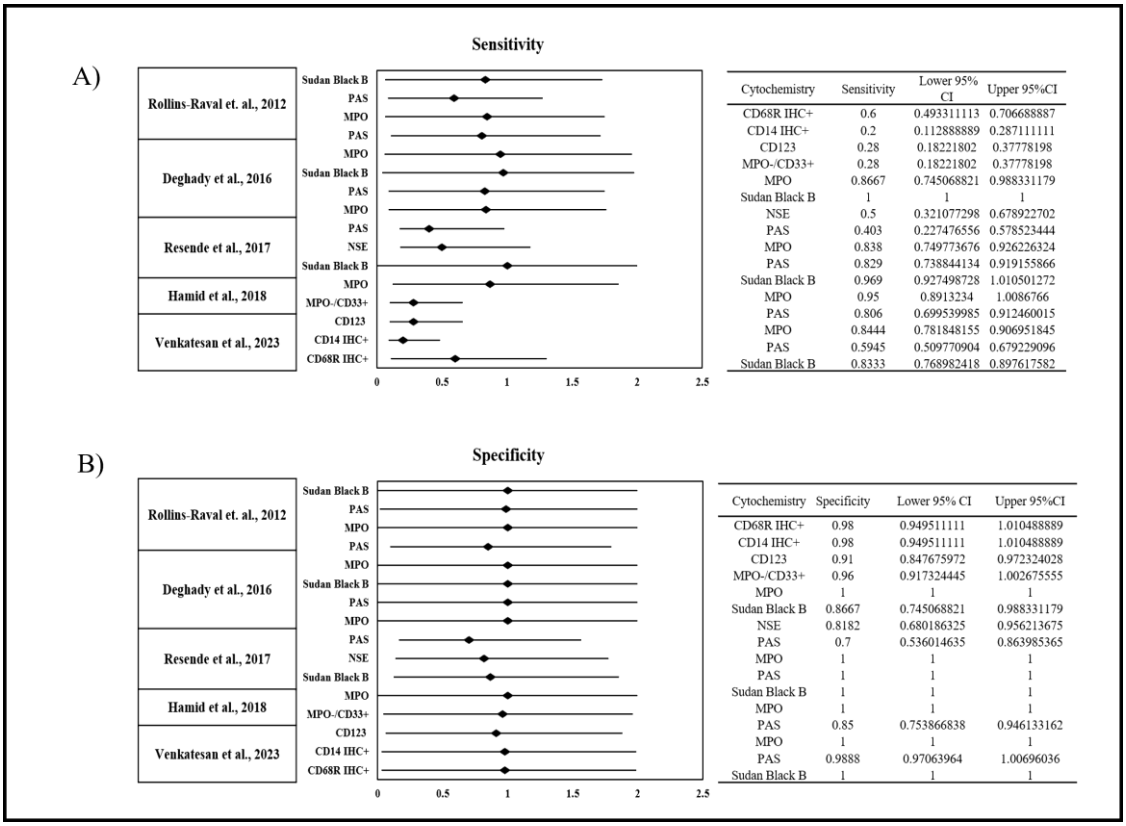


Figure 6. **Comparative Analysis of Sensitivity, Specificity, and Accuracy of Cytochemical Stains in Leukemia Diagnosis.** Sudan Black B and MPO indicates the highest diagnostic performance based on the sensitivity and specificity data, while NSE and PAS show moderate diagnostic performance.



Cytochemistry	Sensitivity	Lower 95% CI	Upper 95%CI
CD68R IHC+	0.6	0.493311113	0.706688887
CD14 IHC+	0.2	0.112888889	0.287111111
CD123	0.28	0.18221802	0.37778198
MPO-/CD33+	0.28	0.18221802	0.37778198
MPO	0.8667	0.745068821	0.988331179
Sudan Black B	1	1	1
NSE	0.5	0.321077298	0.678922702
PAS	0.403	0.227476556	0.578523444
MPO	0.838	0.749773676	0.926226324
PAS	0.829	0.738844134	0.919155866
Sudan Black B	0.969	0.927498728	1.010501272
MPO	0.95	0.8913234	1.0086766
PAS	0.806	0.699539985	0.912460015
MPO	0.8444	0.781848155	0.906951845
PAS	0.5945	0.509770904	0.679229096
Sudan Black B	0.8333	0.768982418	0.897617582

Cytochemistry	Specificity	Lower 95% CI	Upper 95%CI
CD68R IHC+	0.98	0.949511111	1.010488889
CD14 IHC+	0.98	0.949511111	1.010488889
CD123	0.91	0.847675972	0.972324028
MPO-/CD33+	0.96	0.917324445	1.002675555
MPO	1	1	1
Sudan Black B	0.8667	0.745068821	0.988331179
NSE	0.8182	0.680186325	0.956213675
PAS	0.7	0.536014635	0.863985365
MPO	1	1	1
PAS	1	1	1
Sudan Black B	1	1	1
MPO	1	1	1
PAS	0.85	0.753866838	0.946133162
MPO	1	1	1
PAS	0.9888	0.97063964	1.00696036
Sudan Black B	1	1	1

Figure 4. **Forest Plot of Sensitivity and Specificity of Cytochemical assays for Leukemia Immunophenotyping.** The forest plot depicts sensitivity (A) and specificity (B) of several cytochemical markers employed in leukemia immunophenotyping across several studies. The horizontal lines show the confidence intervals, and the black diamonds show the point estimates. While the diagnostic efficacy of NSE and PAS varies, markers like MPO and Sudan Black B demonstrate good sensitivity and specificity across investigations. A comparative review of the efficacy of cytochemical markers in leukemia diagnosis is provided by the data, which includes findings from Rollins-Raval et al. (2012) to Venkatesan et al. (2023).

exhibits high specificity. The ability of these stains to differentiate between AML and ALL further supports their use as quick and affordable diagnostic methods. However, the range of PAS staining sensitivity (40.3-82.9%) indicates that its reliability for diagnosing ALL is limited, requiring the use of further confirmatory techniques. Comparably, NSE showed poor sensitivity, limiting its use to particular

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leukemia subtypes as acute monocytic leukemia (AMoL) instead of more general uses.

The immunophenotypic information from FCM provides detailed analysis that leads to exact leukemia subclassification results. Diagnosis markers CD79a demonstrated 100% sensitivity and 88% specificity while CD3 showed 100% sensitivity together with 98% specificity when used to differentiate between B- and T-cell ALL. Additionally, the strong potential of FCM in lineage assignment is demonstrated by CD45 (99.7% sensitivity, 98.5% specificity) and MPO (95.9% sensitivity, 36.4% specificity in CMML). The need to use a panel of markers rather than a single marker is highlighted by the reduced specificity of some markers, such as MPO in CMML (36.4%), which suggests the possibility of false-positive diagnosis.

In general, the specificity values found in FCM and cytochemistry are comparable, especially for MPO and Sudan Black B, which showed specificities higher than 80%. Despite their high specificity, immunohistochemical markers have a limited sensitivity, which suggests that they work best when combined with other diagnostic methods. However, FCM offers a comprehensive immunophenotypic characterization that is crucial for distinguishing unique leukemia lineages and subpopulations, whereas cytochemistry is less accurate in differentiating between leukemia subtypes. Lab tests with monocyte-associated markers CD14, CD68 and CD163 enable FCM to distinguish AMoL from CMML which cytochemistry fails to achieve independently.

The fast and cost-effective method of cytochemistry continues to prove valuable but requires combining it with FCM precision diagnosis due to its challenges in lineage differentiation and sensitivity sensitivity adjustments in leukemia testing. FCM's capacity to examine many markers simultaneously provides precise detection of leukemia along with therapeutic stratification therefore becoming essential for the diagnostic process. Medical professionals should integrate the low-cost benefits of cytochemical analysis with the precise immunophenotypic capabilities of FCM for accurate and timely leukemia diagnosis in diverse medical settings.

5. CONCLUSION

Results from studying cytochemical methods and FCM in leukemia diagnosis establish FCM as the preferred method because it provides better sensitivity and accuracy for subtype detection together with extensive immunophenotypic data. FCM provides the most advantageous solution for diagnostic applications because it enhances both sensitivity and accuracy for discriminating various leukemia subtypes. The laboratory method enables distinction between different leukemia types through its ability to collect significant immunophenotypic data sets.FCM proves more reliable due to its ability to perform complex marker assessments simultaneously after cytochemical testing produces uncertain outcomes. Cytochemical tests remain important for clinical practice but especially benefit healthcare locations with limited funding which restricts FCM implementation because of budget constraints and limited access to resources. The combined application of MPO and Sudan Black B staining permits fast screening procedures which lead to sophisticated confirmatory testing. The ability of cytochemistry to diagnose diseases stands limited because interpretation requires human input and it fails to identify certain leukemia types, such as ALL. Future advancements in machine learning technology for cytochemical tests together with automated digital image processing systems will make cytochemical stain readings more objective and reliable and thereby reduce the differences between laboratory approaches. Multiparametric FCM and MRD detection systems will advance leukemia diagnosis along with prognosis evaluation and therapy monitoring until the time when automated methods become available. The best diagnostic approach for effective analysis will unite rapid cytochemistry assessments while using FMC's precise evaluation techniques. The classification process for leukemia combined with directed therapeutic approaches will be assured through this speedy and accurate diagnostic methodology.

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Conflict of interest

The authors declare that they have no conflicts of interest regarding this study. All authors have completed the ICMJE Disclosure Form for Potential Conflicts of Interest.

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Ethical statement

This article is a systematic review and meta-analysis of previously published studies. No new patients were

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enrolled, and therefore, ethical approval and informed consent were not required. The review was conducted in accordance with the principles of the Declaration of Helsinki.

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