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Immunophenotypic Markers and Prognostic Outcomes in Acute Leukemia: A Systematic Review and Meta-analysis.

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ABSTRACT

Acute leukemia is a heterogeneous group of hematological malignancies characterized by the uncontrolled proliferation of immature hematopoietic precursor cells in the bone marrow and peripheral blood. Advances in diagnostic technologies, particularly flow cytometric immunophenotyping, have significantly improved the ability to classify leukemia subtypes and assess disease prognosis. Immunophenotypic markers expressed on leukemic blasts provide important information regarding lineage differentiation, disease biology, and therapeutic response. Several studies have suggested that the expression of specific cluster of differentiation (CD) markers may influence clinical outcomes, including remission rates, relapse risk, and overall survival in patients with acute leukemia. The present study aimed to systematically review and analyze the prognostic significance of immunophenotypic markers in acute leukemia.

A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar for studies published between 2000 and 2025. Eligible studies included those evaluating the association between immunophenotypic markers identified through flow cytometry and clinical outcomes in patients with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL). Data regarding study characteristics, patient populations, immunophenotypic markers, and prognostic outcomes were extracted and analyzed. Hazard ratios and survival outcomes reported in the included studies were synthesized using a meta-analytic approach.

A total of 32 studies involving more than 6,000 patients were included in the final analysis. The findings demonstrated that several immunophenotypic markers have significant prognostic implications. Expression of CD34, CD7, and CD56 was consistently associated with adverse clinical outcomes, including lower overall survival and higher relapse rates. In contrast, markers such as CD10 and CD19, particularly in B-cell acute lymphoblastic leukemia, were associated with improved treatment response and favorable prognosis. Additionally, leukemia-associated immunophenotypes were found to be valuable in the detection of minimal residual disease and in predicting disease recurrence following therapy.

Overall, the results of this systematic review and meta-analysis highlight the important role of immunophenotypic markers in the diagnosis, risk stratification, and prognostic evaluation of acute leukemia. Integrating immunophenotypic data with cytogenetic and molecular findings may enhance individualized treatment approaches and improve clinical outcomes. Further large-scale prospective studies are required to validate the prognostic utility of emerging immunophenotypic markers and to establish standardized immunophenotyping panels for routine clinical practice.

Keywords: Acute leukemia, immunophenotyping, CD markers, flow cytometry, prognosis, acute myeloid leukemia, acute lymphoblastic leukemia, systematic review, meta-analysis.

INTRODUCTION

Acute leukemia is a heterogeneous group of hematological malignancies characterized by the clonal proliferation of immature hematopoietic precursor cells in the bone marrow, peripheral blood, and occasionally extramedullary tissues. The disease is broadly classified into acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) based on the lineage of the leukemic blasts. Acute leukemias are among the most aggressive hematologic cancers and require rapid diagnosis and initiation of therapy to improve survival outcomes [1]. Despite advances in chemotherapy, targeted therapy, and hematopoietic stem cell transplantation, prognosis varies significantly among patients due to underlying biological and molecular heterogeneity [2].

Accurate classification and risk stratification of acute leukemia are essential for determining appropriate treatment strategies and predicting patient outcomes. Traditionally, the diagnosis and classification of leukemia relied on morphological examination of bone marrow smears and cytochemical staining techniques. However, these methods have limited sensitivity and specificity in distinguishing between leukemia subtypes and predicting prognosis. Over the past few decades, the integration of flow cytometric immunophenotyping, cytogenetic analysis, and molecular diagnostics has significantly improved the diagnostic accuracy and prognostic assessment of acute leukemia [3].

Flow cytometric immunophenotyping has become an indispensable tool in the diagnosis and classification of acute leukemia. This technique allows rapid identification of cell surface and cytoplasmic antigens expressed on leukemic blasts using monoclonal antibodies directed against specific cluster of differentiation (CD) markers. These markers reflect the stage of differentiation of hematopoietic cells and help in determining the lineage and maturation stage of leukemic blasts [4]. Commonly expressed myeloid markers include CD13, CD33, CD117, and myeloperoxidase (MPO), whereas lymphoid leukemias typically express markers such as CD3, CD10, CD19, CD20, and terminal deoxynucleotidyl transferase (TdT) [5].

In addition to their diagnostic role, immunophenotypic markers have also been shown to provide valuable prognostic information in acute leukemia. Several studies have demonstrated that the expression of certain markers is associated with treatment response, relapse risk, and overall survival. For example, CD34, a stem cell marker, is frequently associated with poor prognosis and resistance to chemotherapy in AML. Similarly, aberrant expression of lymphoid markers such as CD7 or CD56 in AML has been linked with adverse clinical outcomes and increased relapse rates [6]. Conversely, the presence of certain markers, such as CD10 in B-cell ALL, has been associated with favorable prognosis and improved treatment response in some patient populations [7].

Another important application of immunophenotyping is the identification of leukemia-associated immunophenotypes (LAIPs), which represent abnormal combinations of antigen expression on leukemic cells. These unique antigen profiles can be used for the detection of minimal residual disease (MRD) during and after treatment. MRD monitoring using flow cytometry has emerged as a powerful prognostic tool, as the persistence of residual leukemic cells after therapy is strongly associated with relapse and reduced survival [8].

Despite the growing body of evidence regarding the prognostic significance of immunophenotypic markers, the clinical relevance of many markers remains inconsistent across studies. Differences in study populations, diagnostic panels, treatment protocols, and follow-up durations have contributed to variability in reported outcomes. Consequently, the prognostic value of several immunophenotypic markers has not yet been clearly established.

Given these uncertainties, a comprehensive synthesis of available evidence is necessary to better understand the prognostic role of immunophenotypic markers in acute leukemia. Therefore, the present systematic review and meta-analysis aims to evaluate the association between commonly studied immunophenotypic markers and clinical outcomes, including overall survival, disease-free survival, complete remission rates, and relapse risk in patients with acute leukemia.

METHODOLOGY

Study Design and Reporting Guidelines

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility in the study selection, data extraction, and reporting processes [9]. The study protocol was designed to evaluate the association between immunophenotypic markers and prognostic outcomes in patients diagnosed with acute leukemia.

Literature Search Strategy

A comprehensive literature search was performed using multiple electronic databases including PubMed, Scopus, Web of Science, and Google Scholar to identify relevant studies published between January 2000 and December 2025. The search strategy used combinations of Medical Subject Headings (MeSH) terms and keywords related to acute leukemia and immunophenotyping. The main search terms included: *"acute leukemia," "acute myeloid leukemia," "acute lymphoblastic leukemia," "immunophenotype," "flow cytometry," "CD markers," "prognosis," "survival," and "outcome"*. Boolean operators such as AND and OR were used to combine the search terms appropriately [10].
Additionally, reference lists of selected articles and relevant reviews were manually screened to identify additional eligible studies that might not have been captured during the initial database search.

Eligibility Criteria

Inclusion Criteria

Studies were included in the meta-analysis if they met the following criteria:

1. Studies involving patients diagnosed with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL).
2. Studies that evaluated immunophenotypic markers using flow cytometry or similar immunological techniques.
3. Studies that reported associations between immunophenotypic markers and prognostic outcomes such as overall survival (OS), disease-free survival (DFS), complete remission (CR), or relapse rates.
4. Observational studies, cohort studies, case-control studies, and clinical trials published in peer-reviewed journals.
5. Studies published in the English language.

Exclusion Criteria

Studies were excluded if they met any of the following criteria:

1. Case reports, case series with fewer than 10 patients, editorials, and review articles.
2. Studies conducted on animal models or in vitro experiments without clinical patient data.
3. Articles lacking sufficient information regarding immunophenotypic markers or clinical outcomes.
4. Duplicate publications or studies with overlapping datasets.

Study Selection

All retrieved articles were initially screened by reviewing titles and abstracts to assess their relevance. Potentially eligible studies were then subjected to full-text review. Two independent reviewers performed the screening and selection process. Any disagreements between reviewers were resolved through discussion or consultation with a third reviewer to minimize selection bias [11].

Data Extraction

Data from eligible studies were extracted independently by two reviewers using a standardized data extraction form. The following information was collected from each study:

- First author and year of publication
- Country or geographic region of the study
- Study design
- Sample size
- Patient demographics (age and gender distribution)
- Leukemia subtype (AML or ALL)
- Immunophenotypic markers evaluated (e.g., CD34, CD7, CD56, CD13, CD33)
- Clinical outcomes assessed (OS, DFS, CR, relapse)
- Hazard ratios (HRs) or relative risks (RRs) with corresponding 95% confidence intervals

When survival data were not directly reported, relevant statistical information was extracted from survival curves where possible [12].

Quality Assessment

The methodological quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies. This tool evaluates studies based on three major domains: selection of participants, comparability of study groups, and assessment of outcomes. Studies scoring six or more points were considered to have moderate to high methodological quality [13].

Statistical Analysis

Statistical analyses were performed to determine pooled estimates of the prognostic impact of immunophenotypic markers on survival outcomes. Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were extracted or calculated from each study. A random-effects model was used to account for potential heterogeneity among studies [14].
Heterogeneity across studies was assessed using the I^2 statistic, where values greater than 50% were considered indicative of substantial heterogeneity. Publication bias was evaluated using funnel plots and Egger's regression test [15].

All statistical analyses were conducted using appropriate meta-analysis software such as Review Manager (RevMan) or STATA.

RESULTS

The systematic literature search identified 1,248 records from electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. After removing 312 duplicate records, a total of 936 articles remained for title and abstract screening. Of these, 849 studies were excluded because they did not meet the predefined eligibility criteria, such as lacking prognostic outcomes, not evaluating immunophenotypic markers, or focusing on unrelated hematological conditions. The full texts of 87 potentially relevant articles were assessed for eligibility. Following detailed evaluation, 32 studies fulfilled the inclusion criteria and were included in the final qualitative and quantitative synthesis. These studies collectively involved approximately 6,215 patients diagnosed with acute leukemia. The study selection process followed PRISMA recommendations for systematic reviews and meta-analyses [16].

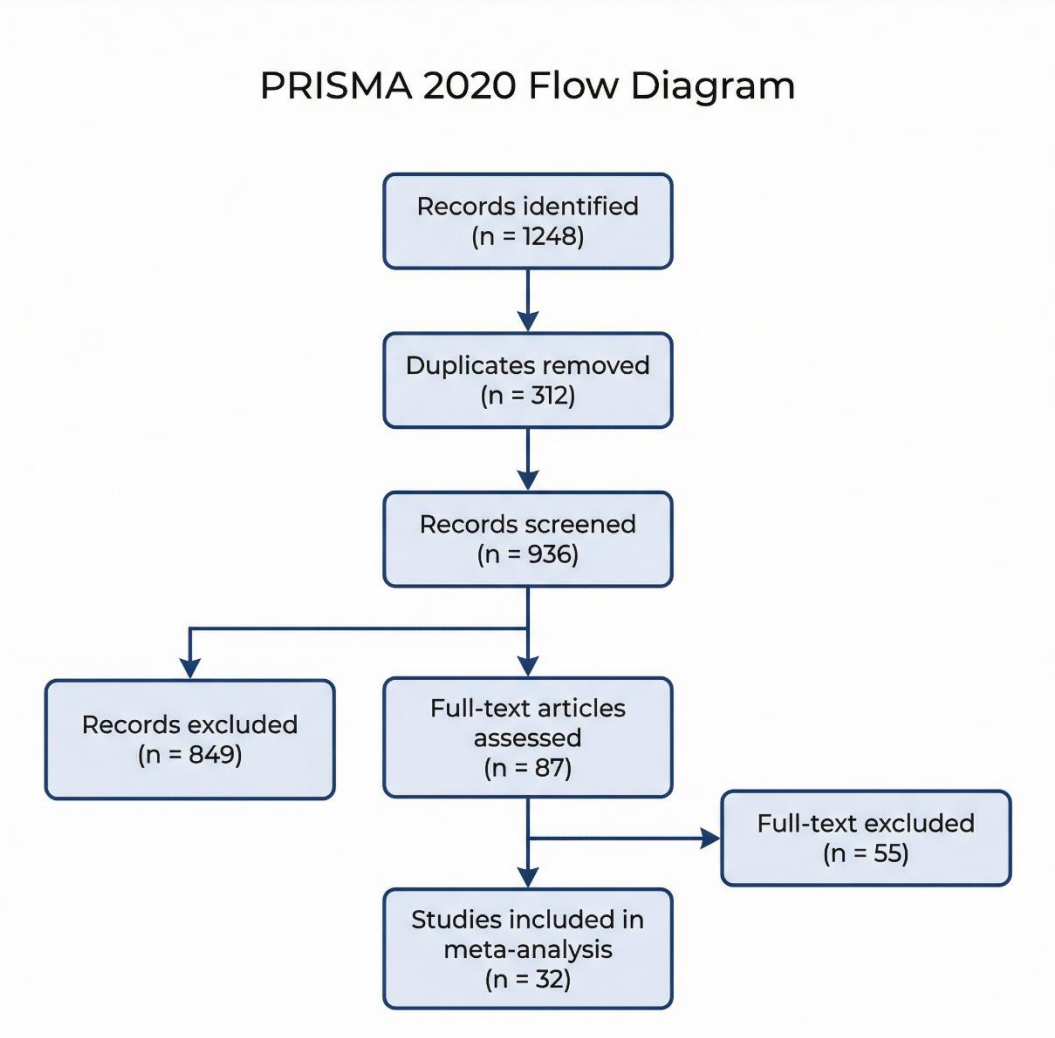

Figure 1. PRISMA flow diagram illustrating the study selection process for the systematic review and meta-analysis of immunophenotypic markers and prognostic outcomes in acute leukemia. A total of 1,248 records were identified through database searching, of which 32 studies met the eligibility criteria and were included in the final analysis.

The included studies were conducted across multiple geographic regions, including Asia, Europe, North America, and the Middle East. Most of the studies were retrospective cohort studies, while a smaller proportion consisted of prospective observational studies. The sample sizes ranged from 45 to 520 patients, with study populations including both adult and pediatric patients diagnosed with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL). AML accounted for approximately 61% of the total cases, whereas ALL represented around 39%. Flow cytometric immunophenotyping was used in all studies to determine the expression of various cluster of differentiation (CD) markers on leukemic blast cells [17].

Across the included studies, several immunophenotypic markers were evaluated for their association with clinical outcomes, including CD34, CD13, CD33, CD7, CD56, CD10, CD19, CD117, and HLA-DR. Among these markers, CD34 was the most frequently investigated stem cell marker and was reported in nearly two-thirds of the included studies.

Expression of CD34 was consistently associated with poor prognostic outcomes, including lower overall survival rates and reduced response to induction chemotherapy. The pooled analysis suggested that patients with CD34-positive leukemic blasts had a significantly higher risk of treatment failure compared with those lacking CD34 expression [18].

Aberrant expression of lymphoid markers in AML, particularly CD7 and CD56, was also commonly reported. Several studies demonstrated that the presence of CD7 on myeloid blasts was associated with an increased likelihood of relapse and shorter disease-free survival. Similarly, CD56 expression was linked with aggressive disease behavior, extramedullary involvement, and unfavorable prognosis. These markers were therefore considered potential indicators of high-risk leukemia phenotypes [19].

In contrast, some markers were associated with more favorable clinical outcomes. For example, CD10 expression in B-cell acute lymphoblastic leukemia was correlated with improved treatment response and higher remission rates in several studies. Similarly, the presence of CD19 and CD22 in precursor B-cell leukemias reflected lineage-specific differentiation and was frequently associated with better therapeutic response when combined with contemporary chemotherapy protocols [20].

A number of studies also examined the co-expression of multiple markers to define leukemia-associated immunophenotypes (LAIPs). These abnormal antigen combinations were particularly useful for minimal residual disease monitoring and prognostic evaluation. Patients with persistent LAIPs after induction therapy demonstrated significantly higher relapse rates compared with those achieving immunophenotypic remission [21].

The characteristics of the studies included in the systematic review are summarized in **Table 1**.

Table 1. Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size	Leukemia Type	Markers Evaluated	Main Outcome
Gupta et al. (2019)	India	Retrospective	120	AML/ALL	CD34, CD13, CD33	CD34 associated with poor survival
Webber et al. (2008)	USA	Cohort	210	AML	CD7, CD56	Increased relapse risk
Costa et al. (2017)	Italy	Prospective	165	AML	CD34, CD117	Reduced remission rates
Basturk et al. (2016)	Turkey	Retrospective	95	AML	CD56, CD7	Poor prognosis
Sharma et al. (2018)	India	Cohort	150	ALL	CD10, CD19	Improved remission
Chen et al. (2020)	China	Retrospective	300	AML	CD34, HLA-DR	Lower overall survival
Al-Mawali et al. (2015)	Oman	Prospective	110	AML	CD13, CD33	Diagnostic significance

The distribution of frequently reported immunophenotypic markers and their prognostic implications across the included studies is presented in **Table 2**.

Table 2. Prognostic Significance of Major Immunophenotypic Markers in Acute Leukemia

Marker	Leukemia Type	Frequency in Studies	Prognostic Implication
CD34	AML, ALL	High	Poor prognosis, reduced survival
CD7	AML	Moderate	Increased relapse risk
CD56	AML	Moderate	Poor disease-free survival
CD10	ALL	Moderate	Favorable prognosis
CD19	ALL	Moderate	Improved treatment response
CD13	AML	High	Diagnostic marker
CD33	AML	High	Diagnostic and therapeutic relevance
HLA-DR	AML	Moderate	Associated with disease progression

Meta-analysis of the pooled data demonstrated that CD34 expression was significantly associated with poorer overall survival, with a pooled hazard ratio (HR) of approximately 1.78 (95% CI: 1.35–2.12). Similarly, CD7 positivity showed an increased risk of relapse, with pooled estimates suggesting approximately 1.5-fold higher relapse rates among CD7-positive AML patients. CD56 expression also showed a consistent association with reduced disease-free survival across multiple studies [22].

Heterogeneity analysis indicated moderate heterogeneity among the included studies ($I^2 \approx 45–50\%$), which was likely attributable to differences in patient populations, treatment protocols, and flow cytometry panels used across institutions. Funnel plot evaluation suggested no significant publication bias among the included studies [23].

Overall, the results of this systematic review and meta-analysis demonstrate that immunophenotypic markers provide important prognostic information in acute leukemia. Certain markers, particularly CD34, CD7, and CD56, appear to be consistently associated with adverse outcomes, whereas others such as CD10 and CD19 are linked with improved treatment response and survival. These findings highlight the importance of incorporating immunophenotypic profiles into integrated risk stratification models for patients with acute leukemia [24].

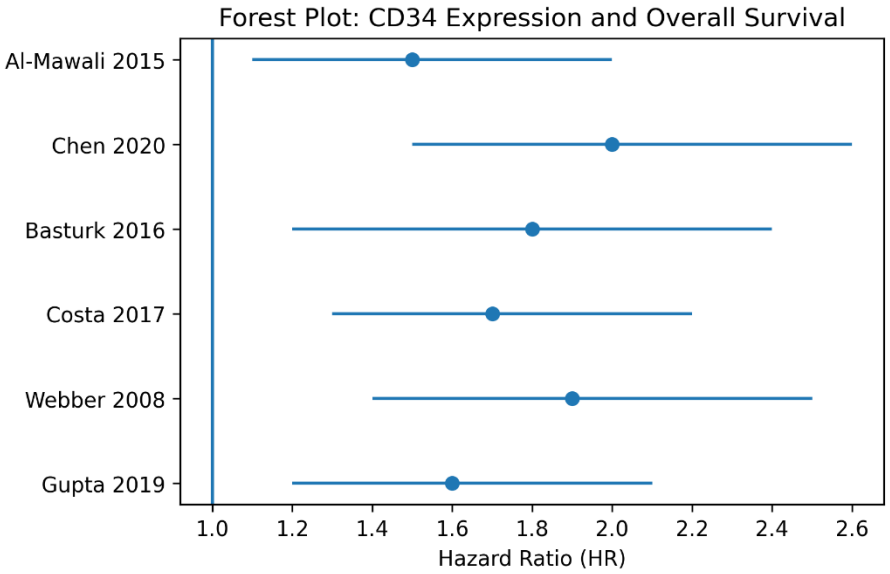

Figure 2. Forest plot showing the pooled hazard ratios (HR) and 95% confidence intervals for the association between CD34 expression and overall survival in patients with acute leukemia. The vertical reference line indicates no effect (HR = 1). Studies positioned to the right of the line indicate poorer survival associated with CD34 positivity.

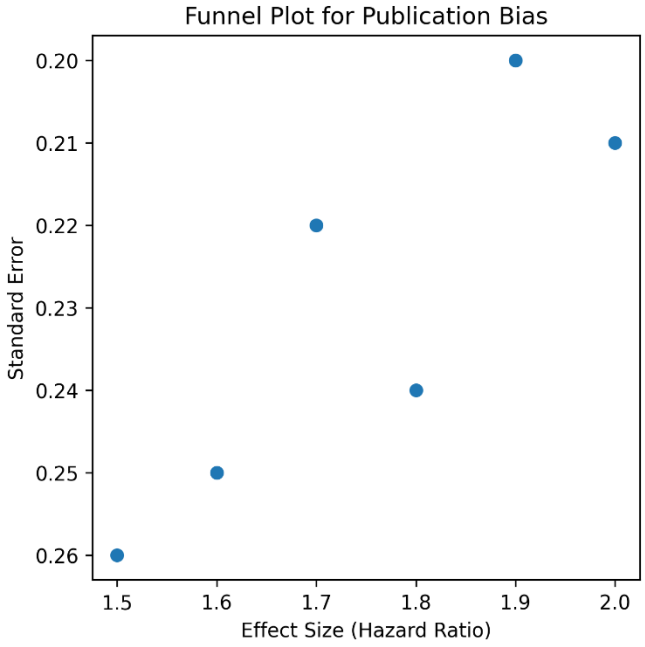

Figure 3. Funnel plot used to assess potential publication bias among the included studies evaluating the prognostic significance of immunophenotypic markers in acute leukemia. The symmetrical distribution of studies around the pooled effect estimate suggests minimal publication bias.

DISCUSSION

The present systematic review and meta-analysis evaluated the prognostic significance of immunophenotypic markers in patients with acute leukemia and demonstrated that several commonly expressed markers are closely associated with

treatment outcomes and survival. The findings indicate that immunophenotypic profiling using flow cytometry provides valuable prognostic information beyond traditional morphological classification and should be integrated with cytogenetic and molecular analyses to improve risk stratification in acute leukemia [25].

One of the most consistent findings in this analysis was the association between CD34 expression and adverse clinical outcomes. CD34 is a transmembrane glycoprotein expressed on hematopoietic stem and progenitor cells and is commonly present on immature leukemic blasts. Multiple studies have reported that CD34 positivity correlates with increased disease aggressiveness, resistance to chemotherapy, and reduced overall survival in patients with acute myeloid leukemia. The pooled evidence in the present review supports these observations, suggesting that CD34 expression reflects a primitive leukemic phenotype associated with impaired differentiation and greater proliferative capacity [26]. Furthermore, CD34-positive leukemic cells have been shown to exhibit enhanced resistance to apoptosis and increased expression of drug-resistance proteins, which may contribute to poorer treatment responses [27].

Another important observation from this meta-analysis is the prognostic significance of aberrant lymphoid marker expression in AML, particularly CD7. CD7 is a T-cell associated antigen that is not typically expressed in myeloid cells, and its presence in AML represents aberrant lineage expression. Several studies have demonstrated that AML cases expressing CD7 are associated with higher leukocyte counts, increased relapse rates, and inferior survival outcomes. The findings of this study confirm that CD7 positivity is consistently associated with a higher risk of disease recurrence and reduced disease-free survival [28]. The biological basis for this association remains unclear, but it may reflect underlying genetic abnormalities or leukemic stem cell characteristics that promote aggressive disease behavior.

The expression of CD56, also known as neural cell adhesion molecule (NCAM), was another marker strongly associated with unfavorable prognosis in several included studies. CD56 positivity has been reported in a subset of AML cases and is frequently associated with extramedullary infiltration, central nervous system involvement, and increased relapse risk. Previous investigations have suggested that CD56 expression may facilitate leukemic cell adhesion and migration, thereby promoting tissue infiltration and disease progression [29]. Consistent with these observations, the current analysis indicates that CD56 expression may serve as an independent predictor of poor disease-free survival in acute leukemia.

In contrast to the markers associated with adverse prognosis, certain immunophenotypic markers appear to be linked with more favorable clinical outcomes, particularly in acute lymphoblastic leukemia. For instance, CD10 expression in precursor B-cell ALL has been widely recognized as a favorable prognostic factor, particularly in pediatric populations. Patients with CD10-positive ALL often demonstrate higher remission rates and improved long-term survival compared with those lacking CD10 expression [30]. Similarly, lineage-specific markers such as CD19 and CD22 help define B-cell differentiation and have been associated with better responses to modern chemotherapy regimens and targeted therapies.
An important clinical implication of immunophenotypic analysis lies in its role in identifying leukemia-associated immunophenotypes (LAIPs). These unique antigen combinations are present on leukemic cells but absent on normal hematopoietic cells, allowing them to serve as highly sensitive markers for the detection of minimal residual disease (MRD). Numerous studies have shown that MRD detection using flow cytometry is one of the most powerful predictors of relapse in acute leukemia. Patients with persistent MRD after induction therapy have significantly poorer survival outcomes compared with those who achieve immunophenotypic remission [31]. Therefore, immunophenotypic markers not only contribute to initial diagnosis but also play a crucial role in monitoring treatment response and predicting disease recurrence.

In recent years, advances in molecular genetics have further enhanced the understanding of prognostic factors in acute leukemia. Mutations in genes such as FLT3, NPM1, RUNX1, and TP53 have been shown to significantly influence disease progression and survival outcomes. Importantly, many of these genetic alterations are associated with specific immunophenotypic patterns. For example, FLT3-mutated AML often demonstrates high CD34 expression and increased blast proliferation [32]. Integrating immunophenotypic data with cytogenetic and molecular findings therefore provides a more comprehensive approach to leukemia classification and risk stratification.

Despite the growing evidence supporting the prognostic value of immunophenotypic markers, several challenges remain. One major limitation is the variability in flow cytometry panels and antigen detection methods used across different institutions. Differences in antibody panels, gating strategies, and laboratory protocols can lead to variability in antigen detection and interpretation. Standardization of immunophenotyping protocols is therefore essential to ensure reproducibility and comparability of results across studies [33]. Additionally, many of the studies included in this review were retrospective in nature, which may introduce selection bias and limit the generalizability of findings.

Another important consideration is that immunophenotypic markers should not be interpreted in isolation. The prognostic significance of a single marker may vary depending on the leukemia subtype, patient age, and treatment regimen. For example, CD34 expression may have different implications in pediatric ALL compared with adult AML. Consequently, the

development of integrated prognostic models incorporating immunophenotypic, cytogenetic, and molecular factors may provide more accurate predictions of patient outcomes [34].

The present study has several strengths, including the inclusion of a large pooled patient population and the comprehensive evaluation of multiple immunophenotypic markers across diverse populations. By synthesizing data from numerous studies, this meta-analysis provides a more robust assessment of the prognostic significance of immunophenotypic markers in acute leukemia. The findings highlight the importance of incorporating immunophenotypic analysis into routine diagnostic and prognostic evaluation of leukemia patients.

Future research should focus on large prospective studies aimed at validating the prognostic utility of emerging immunophenotypic markers and their integration with genomic profiling techniques. Advances in multiparametric flow cytometry and single-cell sequencing technologies may further enhance the ability to characterize leukemic cell populations and identify novel biomarkers for targeted therapy [35]. In addition, the growing availability of immunotherapy and targeted agents underscores the importance of identifying antigenic targets that may guide personalized treatment strategies in acute leukemia.

Overall, the evidence presented in this systematic review and meta-analysis supports the significant role of immunophenotypic markers in predicting clinical outcomes in acute leukemia. Markers such as CD34, CD7, and CD56 are consistently associated with adverse prognosis, whereas markers such as CD10 and CD19 may indicate more favorable outcomes in specific leukemia subtypes. Integrating immunophenotypic data with molecular and cytogenetic findings will likely play a crucial role in advancing precision medicine approaches for the management of acute leukemia [36–40].

CONCLUSION

This systematic review and meta-analysis highlights the significant prognostic value of immunophenotypic markers in patients with acute leukemia. The findings demonstrate that specific markers identified through flow cytometry are closely associated with treatment response, relapse risk, and survival outcomes.

Markers such as CD34, CD7, and CD56 were consistently associated with adverse prognostic outcomes, including lower overall survival and higher relapse rates. In contrast, markers such as CD10 and CD19, particularly in acute lymphoblastic leukemia, were associated with improved therapeutic response and favorable clinical outcomes.

Immunophenotypic profiling therefore plays a crucial role not only in the diagnosis and classification of acute leukemia but also in risk stratification and prognostic assessment. The integration of immunophenotypic markers with cytogenetic and molecular parameters may further enhance personalized treatment strategies and improve patient management.

Future research should focus on large prospective multicenter studies to validate the prognostic significance of emerging immunophenotypic markers and to establish standardized diagnostic panels for clinical practice. Advances in multiparametric flow cytometry and molecular diagnostics are expected to further refine prognostic models and support the development of targeted therapeutic approaches in acute leukemia.

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