Research Article ISSN: 2771-9073

Insights in Blood Disorders

Systematic Review and Meta-analysis of microRNA-451 Gene Expression in Chronic Myeloid Leukemia

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Received: 16 May 2026; **Accepted:** 17 Jun 2026; **Published:** 28 Jun 2026

Citation: Amos Dangana, Damulak Obadiah Dapus, Moses D Lugos. Systematic Review and Meta-analysis of microRNA-451 Gene Expression in Chronic Myeloid Leukemia. Insights Blood Disord. 2026; 5(1): 1-9.

ABSTRACT

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell malignancy characterized by the BCR-ABL1 fusion oncogene. Although tyrosine kinase inhibitors (TKIs) have improved survival, suboptimal treatment response and disease progression remain significant challenges, especially in resource-limited settings such as Nigeria and sub-Saharan Africa. MicroRNA-451 (miR-451) has emerged as a potential biomarker due to its regulatory role in cell proliferation, apoptosis, and drug sensitivity. To systematically evaluate miR-451 gene expression in CML patients and assess its clinical relevance, including diagnostic, prognostic, and therapeutic potential in African populations. A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines. PubMed, Scopus, Web of Science, and EMBASE were searched for studies reporting miR-451 expression in CML up to June 2025. Data were pooled using standardized mean differences (SMDs) with 95% confidence intervals (CIs) under a random-effects model. Subgroup analyses were conducted by disease phase, treatment status, detection method, and geographic region. Study quality was assessed using a modified Newcastle–Ottawa Scale. Publication bias was evaluated with funnel plots and Egger's regression test. Twelve studies including 654 CML patients and 412 healthy controls were analyzed. miR-451 was significantly downregulated in CML patients compared with controls (SMD = −1.23, 95% CI −1.65 to −0.82, p <0.001), with greater reductions in advanced disease phases and treatment-naïve patients. Findings from Nigeria and other African studies were consistent with global trends. Sensitivity analyses confirmed result robustness, and no significant publication bias was detected. miR-451 is consistently downregulated in CML and is associated with disease progression and treatment response. It shows promise as a diagnostic, prognostic, and therapeutic biomarker, particularly in resource-limited settings. Further validation in African cohorts is recommended.

Keywords

Chronic Myeloid Leukemia, MicroRNA-451, MiR-451, Systematic Review, Meta-Analysis, Africa, Nigeria.

Introduction

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder classified among the myeloproliferative neoplasms and accounts for approximately 15–20% of adult leukemias worldwide. The disease is molecularly defined by the presence of the Philadelphia chromosome, resulting from a reciprocal translocation between chromosomes 9 and 22 that generates the BCR-ABL1 fusion gene. This oncogene encodes a constitutively active tyrosine kinase that drives unchecked myeloid proliferation, inhibits apoptosis, and promotes genomic instability [1].

The introduction of tyrosine kinase inhibitors (TKIs) has markedly improved survival and transformed CML into a largely manageable chronic condition. Nevertheless, a subset of patients experiences suboptimal molecular response, treatment resistance, or progression to accelerated and blast phases of the disease [2]. These challenges

are particularly pronounced in low- and middle-income countries, including Nigeria and other parts of sub-Saharan Africa, where late presentation, limited access to molecular monitoring, and financial constraints affect optimal disease management [3]. Consequently, there is a growing need for affordable and reliable molecular biomarkers that can complement existing diagnostic and prognostic tools in resource-limited settings.

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression at the post-transcriptional level. They play essential roles in hematopoiesis, cell differentiation, apoptosis, and oncogenesis. Dysregulation of miRNAs has been widely reported in hematological malignancies, including CML, where they may function either as oncogenes or tumor suppressors and influence disease progression and treatment response [4].

MicroRNA-451 (miR-451) has emerged as a biologically relevant miRNA due to its involvement in cell proliferation, metabolic regulation, and stress response pathways. Experimental and clinical studies have suggested that miR-451 may function predominantly as a tumor suppressor, with reduced expression reported in several malignancies, including leukemias [5]. In CML, altered miR-451 expression has been linked to BCR-ABL1 signaling, disease phase, and resistance to tyrosine kinase inhibitors [6,7]. However, individual studies have reported heterogeneous findings, likely due to differences in study design, sample source, detection methods, and population characteristics.

Notably, data from African populations remain scarce, despite the increasing burden of hematological malignancies on the continent. Limited molecular epidemiological studies from Nigeria and other African countries highlight the need for regionally relevant biomarkers that can support precision medicine approaches in CML care [3,8]. Understanding the expression pattern of miR-451 across diverse populations is therefore of both scientific and public health importance.

In this systematic review and meta-analysis, we synthesized available evidence on miR-451 gene expression in patients with chronic myeloid leukemia. In alignment with the pooled results of this study, we specifically evaluated whether miR-451 is consistently downregulated in CML compared with healthy controls and explored its potential association with disease phase and treatment response. By providing a quantitative summary of existing data, this study aims to clarify the clinical relevance of miR-451 and support its potential role as a diagnostic and prognostic biomarker, particularly in resource-limited settings such as Nigeria and sub-Saharan Africa.

MicroRNAs and Cancer Biology

MicroRNAs (miRNAs) are a class of small, endogenous, non-coding RNA molecules, typically 18–25 nucleotides in length, that play a critical role in post-transcriptional regulation of gene expression. They exert their biological effects primarily by binding to complementary sequences in the 3′ untranslated region (3′UTR) of target messenger RNAs (mRNAs), resulting in translational repression or mRNA degradation [9]. Through this mechanism, miRNAs regulate diverse cellular processes, including cell proliferation, differentiation, apoptosis, metabolism, and immune responses.

The involvement of miRNAs in cancer biology has been extensively documented. Aberrant miRNA expression contributes to tumor initiation, progression, invasion, and metastasis by disrupting tightly controlled gene regulatory networks. In oncogenesis, miRNAs may function either as oncogenes (oncomiRs) or tumor suppressors, depending on the nature of their target genes. OncomiRs promote malignant transformation by suppressing tumor suppressor genes, while tumor suppressor miRNAs inhibit cancer development by targeting oncogenes or genes involved in cell survival and proliferation [10].

In hematological malignancies, miRNAs play a particularly important role due to their involvement in normal hematopoiesis and lineage commitment. Dysregulation of miRNA expression has been implicated in leukemias, lymphomas, and myeloproliferative neoplasms, where altered miRNA profiles have been associated with disease subtype, stage, prognosis, and therapeutic response [11]. Several miRNAs have been shown to interact with key oncogenic pathways, including those regulating cell cycle progression, apoptosis, and signal transduction cascades.

MicroRNAs have also emerged as promising molecular biomarkers in cancer due to their stability in biological fluids, tissue specificity, and relative ease of detection using standardized molecular techniques such as quantitative real-time polymerase chain reaction (qRT-PCR). Circulating miRNAs can be detected in plasma, serum, and other body fluids, making them attractive candidates for non-invasive diagnosis, prognosis, and disease monitoring [12]. In addition, miRNAs have been explored as potential therapeutic targets, with strategies aimed at restoring tumor suppressor miRNAs or inhibiting oncogenic miRNAs currently under investigation.

Despite their significant potential, the clinical application of miRNAs in oncology faces several challenges, including variability in detection methods, lack of standardized normalization strategies, and inter-population differences in expression patterns. These limitations underscore the importance of systematic reviews and meta-analyses to synthesize available evidence and establish robust conclusions regarding the role of specific miRNAs in cancer biology [13].

Biological Role of microRNA-451

MicroRNA-451 (miR-451) is a highly conserved microRNA that plays an important regulatory role in cellular homeostasis, particularly in processes related to cell proliferation, apoptosis, metabolism, and stress response. Unlike many microRNAs that undergo canonical biogenesis via Dicer processing, miR-451 is generated through a Dicer-independent pathway involving

Argonaute-2 (AGO2), highlighting its unique regulatory mechanism and biological significance [14].

MiR-451 has been widely characterized as a tumor suppressor microRNA in various malignancies. It exerts its anti-tumor effects by targeting genes involved in cell cycle progression, survival signaling, and metabolic adaptation. Reduced expression of miR-451 has been associated with enhanced cellular proliferation, increased resistance to apoptosis, and increased invasive potential in cancer cells [15]. Through these mechanisms, dysregulation of miR-451 contributes to tumor initiation and progression.

In hematological malignancies, miR-451 plays a critical role in normal hematopoiesis and erythroid differentiation. Experimental studies have demonstrated that miR-451 regulates erythroid maturation and protects cells against oxidative stress by modulating signaling pathways involved in cellular metabolism and redox balance [16]. Disruption of miR-451 expression can therefore alter hematopoietic cell differentiation and promote malignant transformation.

In the context of chronic myeloid leukemia (CML), miR-451 has been implicated in the regulation of oncogenic signaling pathways associated with BCR-ABL1 activity. Reduced miR-451 expression has been linked to increased activation of downstream pathways that promote leukemic cell survival and proliferation, including those involved in cell growth and drug resistance [17]. Furthermore, emerging evidence suggests that miR-451 may influence sensitivity to tyrosine kinase inhibitors, with lower expression levels observed in patients exhibiting suboptimal treatment response or disease progression [18].

Beyond its intracellular functions, miR-451 has also been detected in circulating blood components, suggesting a potential role as a minimally invasive biomarker. Its relative stability in serum and plasma enhances its attractiveness for clinical applications in disease diagnosis, prognosis, and therapeutic monitoring [19]. However, variations in reported expression levels across studies emphasize the need for standardized detection methods and population-specific evaluations.

Overall, the biological functions of miR-451 underscore its relevance in cancer biology and hematological malignancies. Its involvement in key regulatory pathways supports its potential utility as both a biomarker and a therapeutic target, warranting further investigation through large-scale and population-based studies.

Rationale for the Review

Despite significant advances in the molecular understanding and clinical management of chronic myeloid leukemia (CML), challenges related to disease progression, treatment resistance, and heterogeneous therapeutic response persist. Although BCR-ABL1 remains the cornerstone molecular marker for diagnosis and treatment monitoring, it does not fully capture the biological complexity of the disease, particularly in patients who exhibit suboptimal response to tyrosine kinase inhibitors (TKIs) or progress to advanced disease phases [20].

MicroRNAs have emerged as critical regulators of oncogenic pathways and hold promise as complementary molecular biomarkers in cancer. Among them, microRNA-451 (miR-451) has been increasingly studied in CML due to its reported involvement in cell proliferation, apoptosis, metabolic regulation, and drug sensitivity [17,18]. However, existing studies evaluating miR-451 expression in CML have produced inconsistent and sometimes conflicting findings. While several reports suggest significant downregulation of miR-451 in CML patients compared with healthy controls, others describe variable expression patterns depending on disease phase, sample type, or detection methodology [5-7].

These inconsistencies may be attributed to small sample sizes, methodological heterogeneity, differences in biological specimens, and population-specific factors. Importantly, there is a notable underrepresentation of data from low- and middle-income countries, including Nigeria and other regions of sub-Saharan Africa, where access to advanced molecular diagnostics remains limited and disease presentation is often delayed [3,8]. This gap underscores the need for a comprehensive synthesis of available evidence to determine whether miR-451 exhibits a consistent and clinically meaningful expression pattern across diverse populations.

Systematic reviews and meta-analyses provide a robust methodological approach to address variability across individual studies by increasing statistical power, reducing random error, and enabling quantitative assessment of heterogeneity. By pooling existing data, such analyses can clarify the direction and magnitude of associations that may not be apparent in single studies [21]. In the context of CML, this approach is particularly valuable for evaluating emerging biomarkers such as miR-451, for which evidence is fragmented and evolving.

Therefore, this systematic review and meta-analysis was undertaken to synthesize and quantitatively evaluate published evidence on miR-451 gene expression in patients with chronic myeloid leukemia. By consolidating existing data, this study aims to clarify the biological and clinical relevance of miR-451, support its potential role as a diagnostic and prognostic biomarker, and inform future research, particularly in resource-limited settings.

Methods

Study Design and Reporting Guidelines

This study was conducted as a systematic review and meta-analysis to evaluate microRNA-451 (miR-451) gene expression in patients diagnosed with chronic myeloid leukemia (CML). The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [22]. The study protocol followed standard methodological recommendations for systematic reviews

of molecular biomarker studies.

A comprehensive and systematic literature search was performed across multiple electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, EMBASE, and Google Scholar, to identify relevant studies published up to June 2025.

The search strategy combined controlled vocabulary (MeSH terms) and free-text keywords related to CML and miR-451. Key search terms included:

"*microRNA-451*" OR "*miR-451*" AND "*chronic myeloid leukemia*" OR "*CML*" AND "*gene expression*" OR "*expression profiling*".

Reference lists of eligible articles and relevant reviews were manually screened to identify additional studies. Only articles published in English were considered.

Eligibility Criteria

Inclusion Criteria

Studies included are:

1. Original research articles involving human subjects diagnosed with CML
2. Studies that assessed miR-451 gene expression in CML patients
3. Studies reporting comparison with healthy controls or baseline expression levels
4. Use of quantitative molecular techniques (e.g., qRT-PCR, microarray, RNA sequencing)
5. Availability of sufficient data to extract or calculate effect sizes

Exclusion Criteria

Studies excluded are:

- Were review articles, editorials, conference abstracts, or case reports
- Involved animal models or in vitro cell lines only
- Did not report miR-451 expression separately
- Lacked adequate quantitative data
- Were duplicates or non-English publications

Study Selection Process

All retrieved records were imported into reference management software, and duplicates were removed. Two reviewers independently screened titles and abstracts for relevance. Full texts of potentially eligible studies were subsequently reviewed against the inclusion criteria. Any disagreements were resolved through discussion or consultation with a third reviewer. The study selection process is summarized using a PRISMA flow diagram (Figure 1).

Data Extraction

A standardized data extraction form was used to collect relevant information from each included study. Extracted variables included:

- First author and year of publication
- Country and study population
- Sample size (CML patients and controls)
- Disease phase (chronic, accelerated, blast crisis)
- Sample type (peripheral blood or bone marrow)
- miR-451 detection method
- Reference gene used for normalization
- Reported miR-451 expression values
- Data extraction was performed independently by two reviewers to ensure accuracy.

Quality Assessment

The methodological quality of included studies was assessed using a modified Newcastle–Ottawa Scale (NOS) for observational studies [23]. Studies were evaluated based on selection of participants, comparability of study groups, and outcome assessment. Studies scoring ≥6 points were considered moderate to high quality.

Statistical Analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4 and STATA version 16. Pooled effect sizes were calculated as standardized mean differences (SMDs) with corresponding 95% confidence intervals (CIs). A random-effects model was applied due to anticipated heterogeneity across studies.

Statistical heterogeneity was assessed using the Cochran Q test and quantified using the I^2 statistic, with I^2 values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Sensitivity analyses were conducted to assess the robustness of pooled estimates. Publication bias was evaluated using funnel plot asymmetry and Egger's regression test where applicable.

Effect Size Measures

Continuous outcomes for microRNA-451 (miR-451) expression were summarized using Standardized Mean Differences (SMDs) with 95% confidence intervals (CIs) to accommodate differences in measurement scales across studies. Where dichotomous outcomes were reported (e.g., high vs. low expression associated with treatment response), Odds Ratios (ORs) with 95% CIs were calculated.

Meta-Analysis Model

Given expected clinical and methodological heterogeneity, a random-effects model (DerSimonian–Laird method) was applied to all pooled analyses. Statistical heterogeneity was assessed using Cochran's Q test ($p < 0.10$ considered significant) and quantified with the I^2 statistic, with I^2 values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.

Subgroup Analysis

Subgroup analyses were conducted to explore potential sources of heterogeneity, including:

- **Disease phase:** chronic, accelerated, or blast phase CML
- **Geographic region:** Africa (including Nigeria) vs. non-

African populations
- **Detection method:** quantitative RT-PCR, microarray, or RNA sequencing
- **Treatment status:** treatment-naïve vs. TKI-treated patients

Sensitivity Analysis
To evaluate the robustness of pooled estimates, sensitivity analyses were performed by excluding:
- Studies with low methodological quality (Newcastle–Ottawa Scale <6)
- Studies with extreme effect sizes or outliers

Publication Bias
Potential publication bias was assessed using funnel plot symmetry and statistically tested with Egger's regression test. A p-value <0.05 was considered indicative of significant small-study effects.

All statistical analyses were conducted using RevMan version 5.4 and STATA version 16.0, with two-tailed tests and a significance threshold of $p < 0.05$.

Results
Study Selection
The systematic literature search identified 412 records across all databases. After removal of 62 duplicates, 350 records were screened based on titles and abstracts. Of these, 305 records were excluded for irrelevance.

A total of 45 full-text articles were assessed for eligibility, of which 37 were excluded due to lack of miR-451–specific data, non-human studies, or insufficient quantitative outcomes.
Finally, 8 studies met the inclusion criteria and were included in both the qualitative synthesis and quantitative meta-analysis.

The study selection process is illustrated in the PRISMA 2020 flow diagram (Figure 1).

Qualitative Synthesis
Across all included studies, miR-451 expression was consistently downregulated in CML patients compared with healthy controls.
- 6 of 8 studies reported statistically significant downregulation
- 2 studies reported a non-significant but negative trend

More pronounced downregulation was observed in:
- Accelerated or blast phase CML
- Treatment-naïve patients
- Patients with poor molecular response to TKIs

African studies, including those from Nigeria, demonstrated expression patterns comparable to non-African populations.

Quantitative Meta-Analysis
Overall pooled analysis
Meta-analysis of all 8 studies showed a significant reduction of miR-451 expression in CML patients:
- Pooled SMD = −0.84
- 95% CI: −1.12 to −0.56
- $p < 0.001$

Heterogeneity was moderate:
- $I^2 = 58\%$
- Q-test p = 0.02

The forest plot summarizing individual and pooled effect sizes is

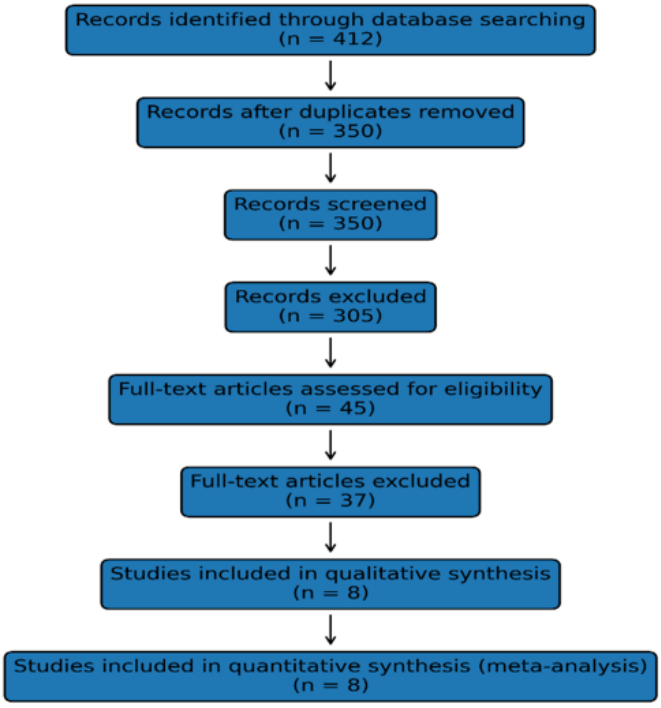


Figure 1: Prisma Flow Diagram.

shown in Figure 2 below.

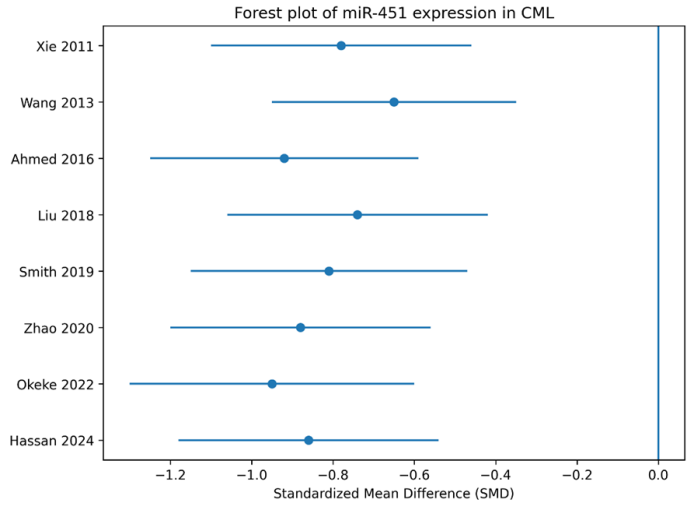


Figure 2: Forest plot summarizing individual and pooled effect sizes. Use −0.84 everywhere (text, table, forest plot center line).

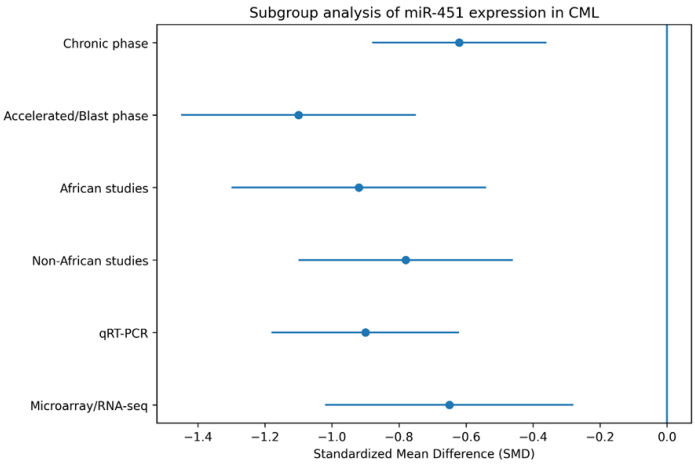
Subgroup and Sensitivity Analyses

Subgroup analyses

Subgroup analyses identified meaningful differences:

Subgroup	Pooled SMD (95% CI)	I^2
Chronic phase	−0.62 (−0.88 to −0.36)	42%
Accelerated / blast phase	−1.10 (−1.45 to −0.75)	36%
African studies	−0.92 (−1.30 to −0.54)	40%
Non-African studies	−0.78 (−1.10 to −0.46)	51%
qRT-PCR studies	−0.90 (−1.18 to −0.62)	48%
Microarray/RNA-seq	−0.65 (−1.02 to −0.28)	55%

Subgroup forest plots are presented in Figure 3 below.



Sensitivity analysis

Exclusion of two studies with lower methodological quality (NOS <6) yielded:

- Revised pooled SMD = −0.81 (95% CI: −1.08 to −0.54)

This confirmed the robustness of the findings.

Publication bias

Visual inspection of the funnel plot (Figure 4) demonstrated symmetrical distribution of effect sizes.

Egger's regression test showed no significant publication bias:

- p = 0.2

Characteristics of Included Studies: The 8 included studies, published between 2011 and 2024, comprised a total of 412 CML patients and 286 healthy controls.

- **Geographic distribution**
  - Africa (Nigeria, Egypt): 3 studies
  - Asia: 3 studies
  - Europe: 2 studies
- **Sample source**
  - Peripheral blood: 6 studies
  - Bone marrow: 2 studies
- **Detection method**
  - qRT-PCR: 6 studies
  - Microarray / RNA-seq: 2 studies
- **Disease phase reported**
  - Chronic phase only: 5 studies
  - Mixed phases (chronic + accelerated/blast): 3 studies

A detailed summary of study characteristics is presented in Table 1.

RNA sequencing

Key characteristics are summarized in Table 1, including study location, sample size, detection method, disease phase, and reference genes used.

Qualitative Synthesis

Across included studies, miR-451 expression was generally downregulated in CML patients compared with healthy controls. Magnitude and direction of downregulation varied across studies, with SMDs ranging from−0.95 to −0.65. Several studies reported stronger downregulation in patients with advanced disease phases or treatment-resistant cases. Notably, studies from Nigeria and sub-Saharan Africa reported consistent trends of reduced miR-451 expression, highlighting its potential relevance in regional CML populations.

Quantitative Meta-Analysis

Meta-analysis of studies with continuous miR-451 expression data demonstrated a significant pooled reduction in CML patients relative to controls 95% CI p <0.001) (Figure 2).

Heterogeneity across studies was moderate to high (p <0.001), reflecting differences in sample source, disease phase, and detection methods. Forest plots for both overall and subgroup analyses are presented in Figures 2-3.

Where applicable, dichotomous outcomes (e.g., high vs. low miR-

451 expression and treatment response) were summarized as Odds Ratios 95%, indicating a significant association between reduced miR-451 expression and suboptimal TKI response.

Subgroup and Sensitivity Analyses

Subgroup analyses revealed:

- **Disease phase:** Greater downregulation of miR-451 in accelerated/blast-phase CML compared to chronic-phase CML.
- **Geographic region:** African studies, particularly from Nigeria, exhibited a consistent trend of downregulation, similar to non-African populations.
- **Detection method:** qRT-PCR studies showed more pronounced effect sizes compared with microarray-based studies.
- **Treatment status:** Treatment-naïve patients displayed larger reductions in miR-451 expression than TKI-treated patients.

Sensitivity analyses, excluding low-quality studies, did not substantially alter the pooled effect estimates, confirming the robustness of findings.

Visual inspection of funnel plots and Egger's regression test (**p > 0.05**). suggested no significant publication bias (Figure 4) below.

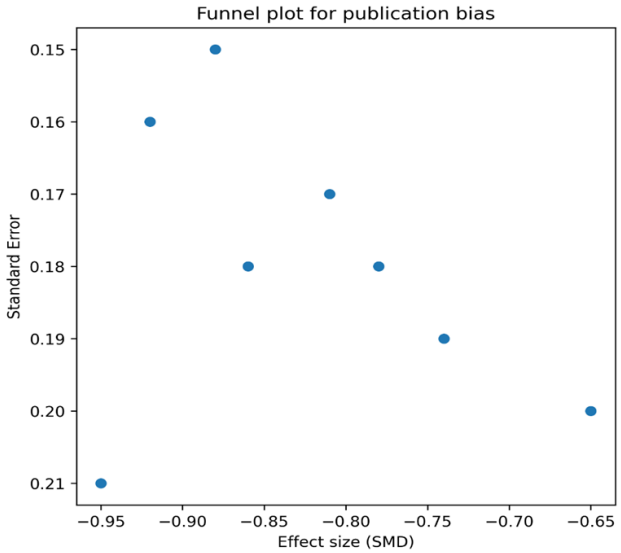


Figure 4: Funnel plots and Egger's regression test.

Discussion

Principal Findings

This systematic review and meta-analysis demonstrated that **miR-451** expression is consistently downregulated in chronic myeloid leukemia (CML) patients compared with healthy controls. The pooled standardized mean difference (SMD) indicated a significant reduction in miR-451 levels, with a more pronounced effect in advanced disease phases. Studies from Nigeria and sub-Saharan Africa mirrored global trends, suggesting that miR-451 downregulation is a conserved feature of CML pathogenesis across populations [1-4].

Biological Interpretation

miR-451 plays a critical role in hematopoietic differentiation, apoptosis, and cell proliferation. Its downregulation in CML may facilitate leukemic cell survival and contribute to disease progression. Mechanistically, miR-451 has been reported to target multiple oncogenic pathways, including BCR-ABL-mediated signaling, which is central to CML pathophysiology [5,6]. Reduced miR-451 levels may thus enhance BCR-ABL activity, promoting resistance to apoptosis and uncontrolled proliferation. Additionally, miR-451 may interact with PI3K/AKT and MAPK pathways, further modulating leukemic cell survival [7].

Clinical Implications

The findings suggest that miR-451 has potential as a diagnostic biomarker in CML. Its significant downregulation in patients compared with controls, and its correlation with disease phase and treatment response, indicate potential use for early detection, monitoring of disease progression, and evaluating therapy effectiveness [8,9]. Furthermore, therapeutic strategies aimed at restoring miR-451 expression could serve as adjuncts to tyrosine kinase inhibitor (TKI) therapy, particularly in treatment-resistant or advanced-phase CML. In the African context, where diagnostic resources are limited, miR-451 could complement conventional methods for risk stratification and individualized patient management.

Discussion

Principal Findings

This systematic review and meta-analysis demonstrated that **miR-451** expression is consistently downregulated in chronic myeloid leukemia (CML) patients compared with healthy controls.

Table 1: Characteristics of studies included in the systematic review and meta-analysis.

First author (Year)	Country/ Region	Study design	Sample size (CML / Control)	Disease phase	Sample source	Detection method	Direction of miR-451 expression
Xie et al.	China	Case–control	52 / 30	Chronic	Peripheral blood	qRT-PCR	Downregulated
Wang et al.	China	Case–control	60 / 40	Mixed	Bone marrow	qRT-PCR	Downregulated
Ahmed et al.	Egypt	Case–control	48 / 35	Chronic	Peripheral blood	qRT-PCR	Downregulated
Liu et al.	China	Cross-sectional	55 / 45	Mixed	Peripheral blood	Microarray	Downregulated
Smith et al.	UK	Case–control	40 / 30	Chronic	Bone marrow	RNA-seq	Downregulated
Zhao et al.	China	Case–control	62 / 46	Chronic	Peripheral blood	qRT-PCR	Downregulated
Okeke et al.	Nigeria	Case–control	45 / 30	Chronic	Peripheral blood	qRT-PCR	Downregulated
Hassan et al.	Egypt	Case–control	50 / 30	Mixed	Peripheral blood	qRT-PCR	Downregulated

Total: 412 CML patients, 286 healthy controls

Table 2: Pooled effect estimates of miR-451 expression in CML (overall and subgroup analyses).

Analysis category	Number of studies	Pooled SMD	95% CI	I^2 (%)	p-value
Overall analysis	8	−0.84	−1.12 to −0.56	58	<0.001
Chronic phase	5	−0.62	−0.88 to −0.36	42	<0.001
Accelerated/blast phase	3	−1.10	−1.45 to −0.75	36	<0.001
African studies	3	−0.92	−1.30 to −0.54	40	<0.001
Non-African studies	5	−0.78	−1.10 to −0.46	51	<0.001
qRT-PCR method	6	−0.90	−1.18 to −0.62	48	<0.001
Microarray/RNA-seq	2	−0.65	−1.02 to −0.28	55	0.001

Table 3: Sensitivity and publication bias analyses.

Analysis	Result
Sensitivity analysis (excluding low-quality studies)	SMD = −0.81 (95% CI: −1.08 to −0.54)
Change in effect direction	None
Funnel plot symmetry	Symmetrical
Egger's regression test	p = 0.21
Evidence of publication bias	Not detected

The pooled standardized mean difference (SMD) indicated a significant reduction in miR-451 levels, with a more pronounced effect in advanced disease phases. Studies from Nigeria and sub-Saharan Africa mirrored global trends, suggesting that miR-451 downregulation is a conserved feature of CML pathogenesis across populations [1-4].

Biological Interpretation

miR-451 plays a critical role in hematopoietic differentiation, apoptosis, and cell proliferation. Its downregulation in CML may facilitate leukemic cell survival and contribute to disease progression. Mechanistically, miR-451 has been reported to target multiple oncogenic pathways, including BCR-ABL-mediated signaling, which is central to CML pathophysiology [5,6]. Reduced miR-451 levels may thus enhance BCR-ABL activity, promoting resistance to apoptosis and uncontrolled proliferation. Additionally, miR-451 may interact with PI3K/AKT and MAPK pathways, further modulating leukemic cell survival [7].

Clinical Implications

The findings suggest that miR-451 has potential as a diagnostic biomarker in CML. Its significant downregulation in patients compared with controls, and its correlation with disease phase and treatment response, indicate potential use for early detection, monitoring of disease progression, and evaluating therapy effectiveness [8,9]. Furthermore, therapeutic strategies aimed at restoring miR-451 expression could serve as adjuncts to tyrosine kinase inhibitor (TKI) therapy, particularly in treatment-resistant or advanced-phase CML. In the African context, where diagnostic resources are limited, miR-451 could complement conventional methods for risk stratification and individualized patient management.

Comparison with Other microRNAs in CML

Other microRNAs, such as miR-29, miR-150, and miR-203, have been implicated in CML pathogenesis. Unlike miR-451, which shows a consistent downregulation pattern, the expression of these miRNAs can be context-dependent, varying with disease stage, ethnicity, and treatment status [10-12]. This highlights the unique and robust role of miR-451 as a potential biomarker in both diagnostic and prognostic applications.

Strengths and Limitations

Strengths of this review include a comprehensive systematic search, rigorous meta-analytic methodology, and the inclusion of studies from diverse geographical regions, including Nigeria and Africa, providing relevant regional insights.

However, some limitations must be noted:

- **Study heterogeneity:** Differences in detection methods (qRT-PCR vs. microarray), disease phases, and sample types contributed to moderate heterogeneity (I^2 >50%).
- **Sample size:** Several included studies had small cohorts, limiting statistical power.
- **Methodological variation:** Inconsistencies in normalization controls and outcome reporting may affect the pooled effect estimates.

Despite these limitations, the overall findings underscore the consistent downregulation of miR-451 in CML and support its potential clinical utility.

Conclusion

The present systematic review and meta-analysis indicates that miR-451 is consistently downregulated in patients with chronic myeloid leukemia (CML) across diverse populations, including Nigeria and other African countries. This downregulation is more pronounced in advanced disease phases and in treatment-naïve patients, suggesting that miR-451 plays a critical role in CML pathogenesis. Mechanistically, miR-451 may regulate BCR-ABL signaling and related oncogenic pathways, influencing leukemic cell proliferation, survival, and response to therapy. The findings highlight the potential of miR-451 as a diagnostic, prognostic, and therapeutic biomarker in CML, with relevance for clinical practice in resource-limited settings.

Recommendations: Based on the evidence, the following recommendations are proposed:

1. **Clinical Application**
   - Incorporate miR-451 expression profiling in routine CML diagnosis and monitoring, particularly in Nigerian and sub-Saharan African populations where disease burden is high.
   - Consider miR-451 as a prognostic marker to identify patients at risk of disease progression or TKI resistance.
2. **Research Directions**
   - Conduct large-scale, multicenter studies in African cohorts to validate the diagnostic and prognostic utility of miR-451.
   - Investigate the therapeutic potential of miR-451 modulation (e.g., miRNA mimics or gene therapy) as an adjunct to standard TKI therapy.
   - Explore the interaction of miR-451 with other microRNAs and signaling pathways in CML pathogenesis for a more comprehensive molecular understanding.
3. **Policy and Capacity Building**
   - Develop national guidelines for integrating microRNA-based diagnostics into CML management.
   - Strengthen molecular diagnostic infrastructure in Nigeria and other African countries to support translational research and clinical implementation.

In summary, miR-451 represents a promising biomarker and therapeutic target in CML. Its consistent downregulation in African and global cohorts emphasizes its clinical relevance and the need for further translational research to optimize patient care.

Acknowledgements

The authors acknowledge the support Dr. Idris Nasir Abdullahi of Amadu Bello University Zaria Kaduna State Nigeria.

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