Iraqi journal of Bioscience and Biomedical
Published Online First: 31/December/2025
p-ISSN: 3007-5491 / e-ISSN:3007-5505

Gene Expression of microRNA-34a and microRNA-28 as Biomarkers in Iraqi Patients with Acute Myeloid leukemia

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Received :12/10/2025 , Accepted: 16/12/2025, Published: 31/12/2025.

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Abstract

Acute myeloid leukemia (AML) is a disease which results from the uncontrolled expansion of immature myeloid cells that have different chromosomal defects. There is a family of micro-RNAs that control the development of the disease. These comprise cellular proliferation, survival, and differentiation. The aim of this study is to determine the diagnostic value of miRNA-34a and miRNA-28 by comparing the relative expression of healthy controls with newly diagnosed acute myeloid leukemia cases and investigate if the expression level of the miRNA is different depending on sub-type and new diagnosis cases.

In a retrospective case-control study, 40 AML newly diagnosed patients and 20 age and sex matched healthy controls were enrolled. The peripheral blood samples were taken, and total miRNA was extracted and the levels of miR-34a and miR-28 were measured through qRT-PCR by using U6 as the endogenous control. The $2^{-\Delta\Delta ct}$ method was used to determine relative expression. Diagnostic performance was measured by receiver operating characteristic (ROC) curve analysis and statistical significance was taken as $p < 0.05$.

There were strong down-regulations in MiR-34a in patients with AML compared to controls (mean fold-change 0.052 vs 1.0, $p < 0.0001$) and there were no significant differences in each French American-British (FAB) subtype (M0-M5, $p > 0.05$). MiR-28 was found to be expressed numerically higher in AML (mean fold-change 1.57 vs 1.0) but not statistically significantly folded-changed ($p = 0.535$) and no subtype specific pattern. ROC analysis revealed that miR-34a fold-change has a high diagnostic accuracy on AML with sensitivity of 90.32% and specificity of 89.66%, $p = 0.0001$, but miR-28 had moderate diagnostic accuracy with sensitivity of 58.28% and specificity of 90.32%, $p = 0008$.

Iraqi journal of Bioscience and Biomedical
Published Online First: 31/December/2025
p-ISSN: 3007-5491 / e-ISSN:3007-5505

MiR-34a is greatly downregulated in AML and has good diagnostic characteristics as a non-invasive biomarker, regardless of FAB subtype. The expression of MiR-28 is more heterogeneous and can be complementary, but not an independent marker. The results indicate the additional confirmation of miR-34a-based assays in larger, multi-centered cohorts to perfect the diagnostics of AML and risk assessment.

Keywords: acute myeloid leukemia (AML), MiR-34a, MiR-28, biomarkers, qRT-PCR, Gene expression.

Introduction

Leukemia is a disease of blood which refers to the abnormal proliferation of the white blood cells and their precursors in the bone marrow and peripheral blood. In cancer, the level of unripe blasts increases but their final development never occurs leading to faulty hematopoiesis and progressive marrow failure[1]. Acute myeloid leukemia, or AML, is the most frequently encountered acute leukemia in adults[2]. This arises from myeloid progenitor cells that undergo changes over time that specifically grant them advantages in proliferation, self-renewal and inhibit further differentiation. Cytogenetic mutations (NPM1, FLT3, IDH1/2, TP53) of core-binding factors comprise these lesions and underpin the biological heterogeneity of the disease, its clinical course and outcomes[3,4,5]. This categorization of AML was developed by clinical advisory committees (CACS) and World Health Organization (WHO) of hematologists, pathologists, oncologists, geneticists, and bioinformaticians[6,7].

The global burden of AML has been progressively increasing for the last 30 years. Disease incidence and death rates are higher among older adults and males. Demographic and socio-developmental indicators influence the pattern and result of diseases in regions[8,9]. Studies show clinical and epidemiological features have effects on comprehending incidence and disease development which led to observance in the rise number of leukemia cases that were reported in Iraq. Successful biomarker programs need relevant risk stratification and care pathways (and clinical ingestion)[10,11]. MiR-34a is a highly studied tumor-suppressor microRNA, and a direct transcriptional target of the p53 pathway. MiR-34a downregulates major regulators including SIRT1 and BCL2 and cyclin dependent kinases, which cause cell-cycle arrest, cell-apoptosis and restrict self-renewal of leukemic cells. It also can reverse immune evasion by inhibiting programmed death-ligand 1 (PD-L1), especially in the AML pathogenesis. MiR-28, conversely, has not been so well characterized in AML, but there is growing evidence indicating that it is able to regulate oncogenic and immune-related pathways, such as T-cell exhaustion and inhibitory receptor pathways, and can act as an oncogene or tumor suppressor depending on context[12,13].

MicroRNAs, or MiRNAs, are tiny non-coding RNAs which regulate the expression of gene(s) after transcription. In AML, MiRNA networks are dysregulated. Which is how leukemia develops and responds to chemotherapy[14]. MiRNAs would be good diagnostic and prognostic markers. They also promise therapeutic targets[15,16]. MiR-34a is a type of tumor-suppressing miRNA that affects the transcription of p53. It restricts the cell cycle and promotes apoptosis by targeting SIRT1, BCL2, the CDKs and other pro-survival and cell cycle genes. It can also prevent immune evasion by PD-L1 repression which is directly relevant in AML models and patient material[15,17,18]. Analyses of AML specifically have afforded MiR-28 a less extensive profiling. Despite this, mechanistic work in immune system can function as an oncogene or tumor suppressor in many malignancies, and it does this by modulating the expression of several genes and the downstream signaling network[19]. Although there is increasing evidence that miRNA-34a and

Iraqi journal of Bioscience and Biomedical
Published Online First: 31/December/2025
p-ISSN: 3007-5491 / e-ISSN:3007-5505

miRNA-28 have a role to play in hematologic malignancies, there are limited data regarding the dynamics of their expression and their diagnostic value in Iraqi AML patients. Moreover, their expression according to French-American-British (FAB) subtypes is not clear. Consequently, the current research designed to examine the gene expression in miR-34a and miR-28 peripheral blood in newly diagnosed Iraqi AML

patients in contrast to the healthy controls and to determine their connection with FAB subtypes. We hypothesized that miR-34a would be extensively downregulated in AML and would be diagnostic, with miR-28 being more variably expressed with the possible lower diagnostic performance.

Materials and Methods

Subject:

A case-control retrospective study was done during the period from September 2024 to May 2025. The total number of participants were sixty reflected all eligible cases during the study period which is consist of forty Iraqi patient samples diagnosed with acute myeloid leukemia and twenty samples of apparently healthy individuals collected from Baghdad teaching hospital and hematology and bone marrow transplant center were enrolled in this study, while controls were volunteers with no history of hematologic malignancy. with age ranged of Participants (15-43) years. The study protocol was approved by the Ethics Committee and written informed consent was obtained from all participants before entering the study. The Ethics Committee of the Iraqi Ministry of Health approved the study.

Ethical approval

Al-Nahrain University, College of Biotechnology Ethics Committee and Iraqi Ministry of Health had approved this study with the (Approval ID: REC.COB/0429/07). Written informed consent was obtained from all participants.

RNA Extraction

Total miRNA was extracted and purified from whole blood using the (*EasyPure*®) miRNA Purification Kit (TransGen Biotech, China), according to the manufacturer's instructions. RNA concentration and purity were assessed using a NanoDrop™ 1000 spectrophotometer (Thermo Fisher Scientific, USA). Samples with A260/280 ratios between 1.8 and 2.1 and A260/230 ratios > 1.8 were considered acceptable for downstream qRT-PCR analysis. Extracted RNA was stored at −80°C for future use.

MiRNA amplification by q RT-PCR

Reverse transcription (TransGen Biotech, China) was done as per the manufacturer instructions and 125ng total RNA was used in reaction. Endogenous control primers miR-34a (F: AACACGCTGGCAGTGTCTTA,R:GTCGTATCCAGTGCAGGGT),miR-28(F: AACAGTGAAGGAGCTCACAGT, R: GTCGTATCCAGTGCAGGGT), and U6 mall nuclear RNA as the endogenous control, RNA was converted to cDNA by reverse transcription kit (transgenbiotech kit/China). Then Real-time qPCR quantification was performed using (transgenbiotech/China). The rection total volume is 20 µL consist of 2 µL cDNA, 10 µL master mix, 1 µL primer, and complete the volume with nuclease-free water. The reaction was carried out by Real-Time PCR System, Applied Biosystems, according to the following protocol: Enzyme activation was at 94 C° for 5 min, then 40 cycles repeat:

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Published Online First: 31/December/2025
p-ISSN: 3007-5491 / e-ISSN:3007-5505

Denaturation at 94 C° for 20 sec, Annealing at 60 C° for 1 min and Extension at 72 C° for 30 sec.After every run a melt-curve was run to check specificity of the amplification and the lack of primer-dimers. Each of the samples was run in duplicate (or triplicate).

Statistical analysis

GraphPad Prism version 10.0 (GraphPad Software, USA) was used in analyzing the data. Mean ± standard deviation (SD) is used to represent continuous variables. The Shapiro-Wilk test used for normality, while unpaired t-test was used to compare differences of AML patients and controls.one-way ANOVA (or Kruskal–Wallis test), followed by appropriate post-hoc analyses. Relative miRNA expression levels were calculated using the 2^−ΔΔCt method, where ΔCt = Ct(target) − Ct(U6) and ΔΔCt = ΔCt(patients) − ΔCt(controls). Diagnostic performance was assessed using receiver operating characteristic (ROC) curve analysis to evaluate sensitivity, specificity, and overall classification performance. A two-sided p-value < 0.05 was considered statistically significant.

Results

Results in table (1) show that MiR-34a expression is significantly downregulated in AML patients (0.052±0.068) compared to healthy controls (1) p< (0.05).

Table 1: Folding Change expression of miRNA-34a in AML patients

Group	miRNA 34a Mean ± SD			
	CT	ΔCT	ΔΔCT	Folding
Control	24.49±2.864	4.410±3.562	-0.009±3.56	1.00 ± 0.00
Patients	29.16±3.052	8.968±3.946	4.548±3.946	0.052±0.068
p-value	<0.0001**	<0.0001**	<0.0001**	<0.0001**
*p < 0.05; **p < 0.001; NS, not statistically significant.				

Across all AML subtypes, miR-34a expression is significantly down-regulated compared with normal samples, indicating a general loss of this tumor-suppressor miRNA in AML. Although M2 shows the lowest fold expression and M3 appears relatively less suppressed, no statistically significant differences were detected among the subtypes (p > 0.05), suggesting that miR-34a down-regulation is a broad feature of AML rather than subtype-specific as illustrated in table (2).

Table 2: Folding Change expression of miRNA-34a in AML patients according to subtypes

Subtype Group	miRNA 34a (Mean ± SD)		
	ΔCT	ΔΔCT	Folding
M0	8.90±0.0	4.480 ± 0.0	0.044 ± 0.0
M1	10.63±0.850	6.213 ± 0.85	0.015 ± 0.00837
M2	13.00 ±0.0	8.580 ± 0.0	0.003 ± 0.0

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M3	7.438 ± 4.87	3.018 ± 4.87	0.08 ± 0.0835
M4	11.13 ±1.42	6.713 ± 1.42	0.013 ± 0.01041
M5	9.600 ±1.57	5.180 ± 1.575	0.038 ± 0.02853
P-value	**0.327 NS**	**0.327 NS**	**0.279 NS**
** p < 0.05; *$p < 0.001$; NS: not statistically significant*			
***M0–M5: French–American–British (FAB) morphological subtypes of AML**			

Results in table (3) revealed an elevation in the miRNA-28 expression levels (1.57±*5.06*) in AML compared with controls with no significant differences.

Table 3: Folding Change expression of miRNA-28 in AML patients

Group	**miRNA 28 (Mean ± SD)**			
	CT	**ΔCT**	**ΔΔCT**	**Folding**
Control	26.99 ± 2.884	6.910 ± 3.858	0.100 ± 3.858	1.00 ± 0.00
Patients	30.21 ± 2.949	10.01 ± 4.509	3.203 ± 4.509	1.57 ± 5.06
p-value	<0.0001**	0.0057**	0.0056**	0.535 NS
*p < 0.05; **p < 0.001; NS, not statistically significant.				

Although there was an increase in gene expression in of mir-28 in M3 (1.44±3.78) and M5(6.17±12.2), but these were not significant differences. These findings indicate that miR-28 expression is not significantly associated with AML morphological subtypes regulation table (4)

Table 4: Fold-change expression of miRNA-28 in AML patients according to FAB subtypes.

Subtype Group	**miRNA 28 (Mean ± SD)**		
	ΔCT	**ΔΔCT**	**Folding**
M0	15.10 ± 0.000	8.29 ± 0.00	0.003 ± 0.00
M1	10.03 ± 1.804	3.22 ±1.80	0.168 ± 0.169
M2	16.00 ± 0.000	9.19 ± 0.00	0.002 ± 0.00
M3	9.138 ± 5.383	2.33 ± 5.38	1.44 ± 3.78
M4	11.48 ± 1.776	4.67 ± 1.78	0.065 ± 0.0613
M5	8.525 ± 4.365	1.72 ± 4.36	6.17 ± 12.2
P-value	0.4772 NS	0.4772 NS	0.539 NS
NS: non-significant differences			
*M0–M5: French–American–British (FAB) morphological subtypes of AML			

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ROC results showed miR-34a expression analysis particularly using fold change offers the strongest sensitivity (90.32%) and specificity (89.66%) for AML detection, while miR-28 may serve as a complementary marker with good specificity (90.32%) but lower sensitivity (58.28%) table (5).

Table 5: Sensitivity, Specificity, and Statistical Significance of miRNA-34a and miRNA-28 in AML

Parameters	Sensitivity%	Specificity%	P-value
miRNA-34a Folding	90.32	89.66	<0.0001**
miRNA 28 Folding	58.28	90.32	0.0008**

The variability of miRNA-34a and miRNA-28 expression is depicted in Figure 1, highlighting the wide dispersion and high SD observed in AML patients.

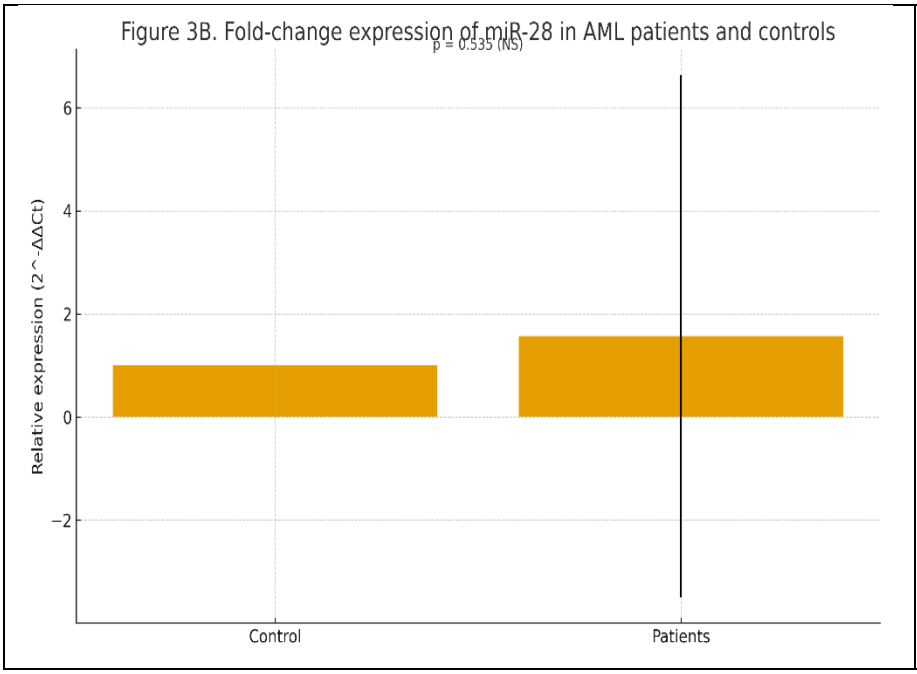

Figure1: miRNA-34a and miRNA-28 expression in patients and controls in AML.

(A) Fold change (2^−ΔΔCt) of miR-28 normalized to U6 in AML patients and controls.

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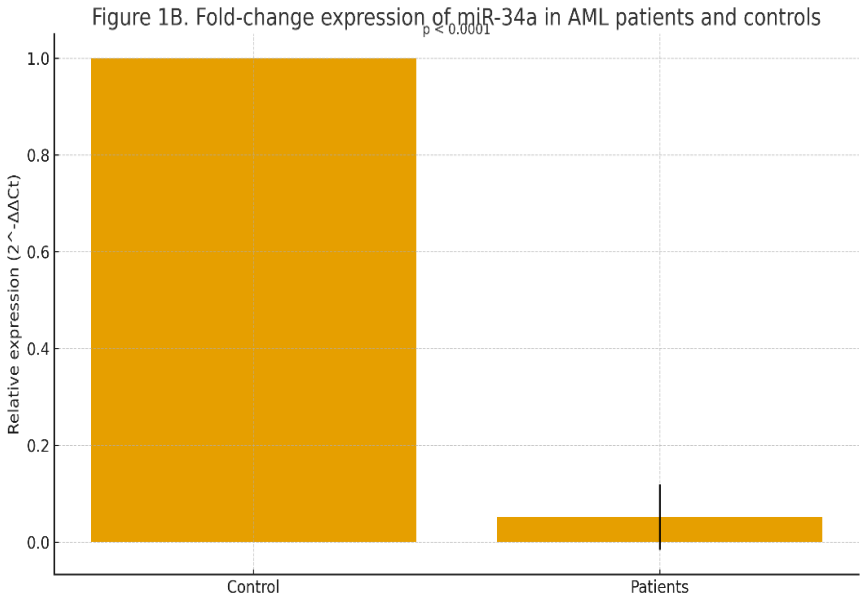
p-ISSN: 3007-5491 / e-ISSN:3007-5505



(B) Fold change (2^−ΔΔCt) of miR-34a in AML patients versus controls, demonstrating significant downregulation in the patient group ($p < 0.0001$). Bars represent mean ± standard deviation (SD).

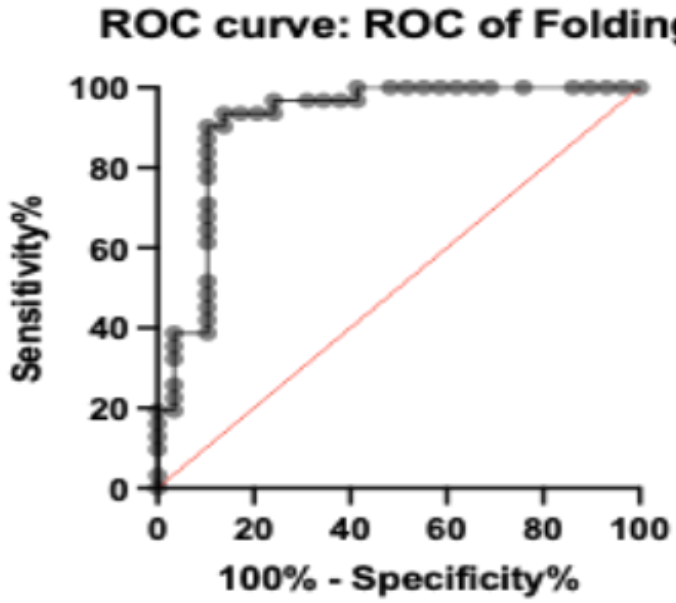


Figure2: Receiver operating characteristic (ROC) curve evaluation of miR-34a performance in AML.

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Published Online First: 31/December/2025
p-ISSN: 3007-5491 / e-ISSN:3007-5505

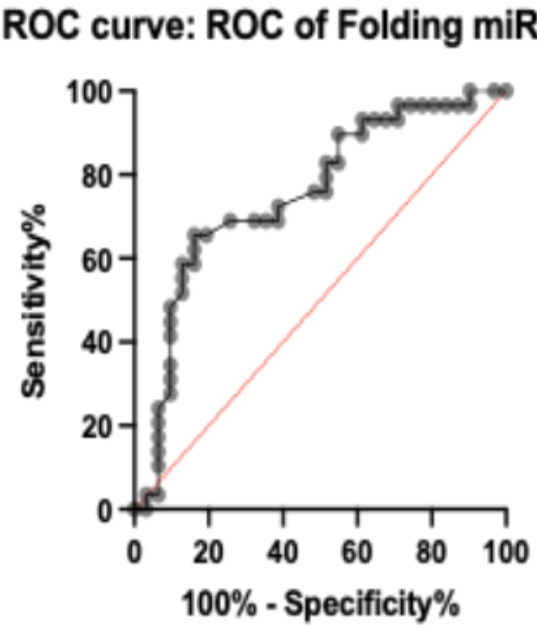

Figure3: Receiver operating characteristic (ROC) curve evaluation of miR-28 performance in AML.

Discussion

In the current research, the expression of miR-34a and miR-28 in the acute myeloid leukemia of the Iraqi patients was researched. The overall results were that miR-34a was highly suppressed in AML in comparison to healthy controls and was highly diagnostic with little heterogeneity but high potential to discriminate[20]. On the other hand, miR-28 exhibited more heterogeneous expression and low diagnostic power. There was no statistically significant difference between miRNA between FAB subtypes (M0-M5). The downregulation of miR-34a in AML agrees with the known functions of this microRNA as a tumor-suppressor and a major effector of the p53 pathway[21,22], and regulates key genes involved in cell-cycle control, apoptosis, and senescence, including SIRT1, BCL2 and several cyclin-dependent kinases[23]. Decrease or loss of miR-34a has been linked to increased leukemic cell survival, chemoresistance and disease progression, whereas miR-34a replacement expression can trigger apoptosis and block proliferation of the blast. Moreover, miR-34a directly responds to PD-L1, connecting the downregulation of this gene to immune evasion in AML. These mechanistic observations are further reinforced by our findings, as well as the idea that decreased miR-34a levels are a shared molecular pathology of AML. The present RNA analysis demonstrated that miR-34a fold-change had high specificity and sensitivity in identifying AML cases vs controls, as reported before that found that circulating miR-34a or bone marrow miR-34a is a good diagnostic and response-to-treatment biomarker. The fact that no substantial differences were found between FAB subtypes indicates that down-regulation of miR-34a is not unique to a specific morphological type and instead represents more global leukemogenic processes common to the various AML subtypes[24,25].

In contrast, MiR-28 expression showed significant differences in CT, ΔCT, and ΔΔCT between AML and controls but fold-change differences were not statistically significant. ROC analysis suggests MiR-28 has

Iraqi journal of Bioscience and Biomedical
Published Online First: 31/December/2025
p-ISSN: 3007-5491 / e-ISSN:3007-5505

moderate diagnostic power but lower sensitivity than MiR-34a, supporting its potential as a secondary or adjunct marker rather than a standalone diagnostic tool. This trend can indicate a high degree of biological heterogeneity in the miR-28 regulation of AML patients, which can be determined by cytogenetic and molecular subgroups, immune microenvironment, or pre-existing inflammatory conditions. Increased variance can also be caused by technical reasons like the fluctuating integrity of RNA or low expression levels[26]. Importantly, there is no significant difference in MiR-34a or MiR-28 expression among FAB subtypes. This finding supports prior reports showing that many miRNAs are dysregulated broadly in AML without strict subtype specificity, except for a few with known cytogenetic associations. The uniform reduction of MiR-34a across subtypes suggests it may be a molecular hallmark of AML, independent of morphology or classical karyotypic groups. From a clinical perspective, our results reinforce the promise of MiR-34a as a simple, minimally invasive biomarker for AML diagnosis and potentially for disease monitoring. MiR-28 is critical for modulating exhausted Tregs, namely $TIM3^{+}Foxp3^{+}$ and $PD1^{+}Foxp3^{+}$ phenotypes in vitro. This substance helps fix exhausted T cells that cannot produce cytokine anymore. It can help recover signaling of T cells, for example, it can help recover IL-2 and TNF-α signaling. Overall, the studies suggest that miR-28 impacts T-cell exhaustion and the expression of inhibitory receptors, mainly PD-1, and potentially offers a therapeutic target for cancer immunotherapy[27,28].

This study has limitations, which is the sample size limits the applicability of the results and the ability to be able to analyze individual cytogenetic or molecular subsets in detail. Cross-sectional nature and absence of follow up also imply this study did not measure the prognostic role of miR-34a and miR-28 on the response to treatment and survival. The single endogenous control (U6) could have been a source of variation, and more reference genes would reinforce the findings. In addition, there is no extensive molecular profiling (e.g., NPM1, FLT3, IDH1/2, TP53) which could help to explain genotype-miRNA interactions. These results should be confirmed in studies of larger, multi-center cohorts with integrated molecular data to the future, the prognostic utility of miR-34a in the context of therapy, and miR-34a, miR-28 and other AML-related miRNA multi-phenotype panels with clinical and genetic outcome should be tested to further validate these findings and enhance risk stratification and personalized treatment in the future.

Conclusions

Overall, the current results support MiR-34a as a robust, non-invasive biomarker with potential clinical utility for early AML detection and risk refinement, while also identifying MiR-28 as a candidate component of multi-marker diagnostic panels. Validation of these findings in larger, genetically annotated patient cohorts and prospective studies could facilitate the integration of microRNA profiling into routine AML diagnostics and precision medicine approaches.

Acknowledgments

The authors would like to express our deepest gratitude to all those who contributed to the completion of this study. Our sincere thanks go to the healthcare providers and staff at Baghdad Teaching Hospital and hematology and bone marrow transplant center for their invaluable assistance in sample collection and

patient care. We are also grateful to the participants for their cooperation and willingness to be part of this study. extend our heartfelt appreciation to the faculty and staff of the College of Biotechnology, Al-Nahrain University, for their support and guidance throughout this research.

Author's Declaration

- We hereby confirm that all the Figures and Tables in the manuscript are original and have been created by us.
- We have obtained ethical clearance for our study from the local ethical committee at [Al-Nahrain University/College of Biotechnology]. This approval underscores our commitment to ethical research practices and the well-being of our participants.
- Ethical Clearance: The project was approved by the local ethical committee at [Al-Nahrain University/College of Biotechnology], ensuring adherence to ethical standards and the protection of participants' rights and welfare.

Author's Contribution Statement

[***Dania omar***]: Played a critical role in the statistical analysis of the data and interpretation of the results.

[***Shahlaa M. Salih***]: Played a critical role in supervising the research, providing guidance, and designing the study

[***Tareq abdullah saleh***]: Played a critical role in supervising the research and collecting the sample.

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