RESEARCH ARTICLE

Editorial Process: Submission:04/01/2026 Acceptance:01/09/2026 Published:28/09/2026

Expression of *miR-214* in Pediatric Acute Leukemia: Correlations with Leukemia Subtypes, Familial Predisposition, and Hepatitis B Virus Infection

Maysaa N Ibrahim[1], Ruqaia Sabbar Salman[2], Anfal M. Khudhair[2]*, Dunya Jawad Ridha[3], Rasha Tariq Jawad[4], Muhammed Munim Radwan[5], Aya Ali Mohammed[6], Jaafar Alsadiq Arkan Farhan Ali[6], Hayder Rafid Abduljalil[6]

Abstract

Background: miR-214 dysregulation has been implicated in various cancers, yet its role in pediatric acute lymphoblastic leukemia (ALL) is not fully understood. This study evaluated *miR-214* expression in newly diagnosed pediatric ALL patients and explored associations with leukemia subtypes, family history, and hepatitis B virus (HBV) infection. **Methods:** Bone marrow aspirates were collected from 44 pediatric ALL patients (26 B-ALL, 18 T-ALL) and five non-leukemic controls. qRT-PCR quantified *miR-214* expression. Clinical data included HBV status and family history of hematologic malignancy. Relative expression levels were analyzed using $2^{-\Delta\Delta Ct}$ and $\log_{10}$ transformed for statistical analyses, including correlation and logistic regression models with interaction terms. **Aim of the Study:** The present study aimed to quantitatively evaluate the expression pattern of *miR-214* in newly diagnosed pediatric acute lymphoblastic leukemia (ALL) patients compared with non-leukemic controls. In addition, the study sought to investigate whether *miR-214* expression differs according to immunophenotypic subtype (B-ALL versus T-ALL) and to explore its potential associations with clinical and host-related factors, specifically family history of hematologic malignancy and hepatitis B virus (HBV) infection status. Furthermore, this study aimed to assess whether these variables exert interaction effects that may reflect context-dependent regulation of *miR-214* in pediatric leukemogenesis. **Results:** *miR-214* expression was generally downregulated in ALL compared to controls, though differences were not statistically significant. B-ALL patients showed lower median expression than T-ALL, with the lowest levels observed in those with a positive family history. T-ALL patients exhibited broader expression variability, including marked upregulation in some cases. Exploratory regression models suggested differential effects of *miR-214* based on HBV status and family history, but interaction terms did not reach statistical significance ($p > 0.05$). **Conclusions:** *miR-214* expression in pediatric ALL appears to vary according to leukemia subtype and selected clinical factors, including family history and HBV infection. However, no statistically significant interaction effects were observed. These findings should be considered preliminary and warrant validation in larger, adequately powered cohorts to clarify the potential clinical relevance of *miR-214* in leukemogenesis.

Keywords: *miR-214*, pediatric leukemia, B-ALL, T-ALL, HBV, family history, gene–environment interaction

Asian Pac J Cancer Prev, **27 (9)**, 3325-3332

Introduction

Acute lymphoblastic leukemia (ALL) represents the most common pediatric malignancy in Iraq, accounting for the majority of childhood leukemia cases reported in national oncology centers. Local epidemiological data indicate that leukemia constitutes a substantial proportion of pediatric cancers in Iraq, with ALL being the predominant subtype among children. A molecular and serological study conducted on Iraqi pediatric patients with acute lymphoid leukemia confirmed the high frequency of ALL in the pediatric population and emphasized its clinical and hematological burden within the country [1]. These findings align with regional cancer registry data highlighting leukemia as one of the leading malignancies affecting Iraqi children.

Acute lymphoblastic leukemia (ALL) is the most prevalent pediatric malignancy and a leading cause of cancer-related mortality in children worldwide [2]. It is characterized by clonal proliferation of immature

*[1]Department of Pediatrics, College of Medicine, Al-Iraqi University, Baghdad, Iraq. [2]Department of Microbiology, College of Medicine, Al-Iraqi University, Baghdad, Iraq. [3]Dijlah Unversity Collage, Iraq. [4]Central Child Teaching Hospital, Baghdad, Iraq. [5]Medical Student, Al-Nahrain College of Medicine, Iraq. [6]Medical student, Al-Iraqia College of Medicine, Iraq. *For Correspondence: anfal_khudhair@aliraqia.edu.iq*

lymphoid progenitors and classified into two major immunophenotypic subtypes: B-cell lineage ALL (B-ALL), accounting for approximately 80–85% of cases, and T-cell lineage ALL (T-ALL), comprising 15–25% [3]. T-ALL is associated with poorer outcomes compared to B-ALL, mainly due to greater chemoresistance, limited targeted therapies, and lower incidence of favorable cytogenetic alterations [2, 4]. Conversely, B-ALL more frequently harbors genetic abnormalities associated with a favorable prognosis, resulting in better clinical outcomes [2, 4]. ALL is thought to result from a combination of genetic predisposition and environmental influences. The prevailing model, particularly in B-ALL, involves a prenatal initiation through somatic mutations, followed by secondary postnatal events that drive leukemic progression. This two-step mechanism is supported by molecular and epidemiological studies identifying preleukemic clones in neonatal blood spots [5]. While definitive environmental causes remain elusive, several exposures have been associated with increased risk, including ionizing radiation, specific chemotherapeutic agents, undefined viral infectious agents, and older parental age. These associations underscore the importance of timing and the nature of environmental insults in children with latent preleukemic clones [4]. Several case-control studies and reports of familial clusters support the hypothesis that a family history of cancer increases the risk of childhood acute leukemia [5, 6]. In particular, having a sibling with leukemia is associated with a higher relative risk of ALL. However, the absolute risk for siblings remains low and is only slightly higher than that of the general population [7].

MicroRNAs (miRNAs) are crucial regulators in leukemia, influencing gene expression and playing dual roles as oncogenes or tumor suppressors depending on context. They are recognized for their ability to shape distinct expression profiles that help differentiate leukemia subtypes and correlate with clinical prognosis [8]. *miR-214* is encoded within the long non-coding RNA (lncRNA) transcript DNM3OS, situated in intron 14 of the Dynamin-3 (DNM3) gene on chromosome 1q24.3. The DNM3OS precursor itself is about 7.9–8 kb long and harbors both *miR-214* and *miR-199a-2* [9]. *miR-214* is implicated in various developmental and immune processes, as well as cancer progression. Its function appears highly context-dependent, acting as a tumor suppressor in some tissues and as an oncogene in others. In leukemia, *miR-214*-3p (one of the mature forms) mainly has tumor suppressor activity [10]. Altered *miR-214* expression profiles are associated with specific leukemia subtypes and may serve as diagnostic or prognostic biomarkers. Combinations of miRNA signatures, including *miR-214*, can distinguish between leukemia types, such as ALL and AML, with high accuracy [11].

Chronic hepatitis B virus (HBV) infection is a well-established etiological factor for hepatocellular carcinoma (HCC), a malignancy arising from hepatocytes. HBV modulates the expression of liver-enriched host microRNAs, including miR-122, miR-125, and miR-199 family members, which regulate viral replication, immune responses, and hepatocyte proliferation. Dysregulation of these miRNAs contributes to chronic inflammation, genomic instability, and hepatocarcinogenesis. These miRNA-mediated pathways represent potential biomarkers and therapeutic targets in HBV-associated liver malignancies [12].

Although HBV is known to alter the expression of several host miRNAs, direct evidence linking HBV infection to changes in *miR-214* expression is currently lacking.To date, no studies have systematically evaluated the relationship between HBV infection and *miR-214* expression in pediatric acute lymphoblastic leukemia (ALL), representing a vital knowledge gap addressed in the present study. Therefore, this study aims to investigate *miR-214* expression in pediatric ALL patients and explore its potential associations with leukemia subtype (B-ALL vs. T-ALL), family history of leukemia, and HBV infection status. We hypothesize that *miR-214* expression differs according to leukemic subtype and is modulated by host-related variables, such as hereditary predisposition or viral co-infection, reflecting context-dependent roles for this miRNA in leukemogenesis.

Materials and Methods

Sample Collection

Bone marrow aspirate samples were obtained from 44 pediatric patients newly diagnosed with acute lymphoblastic leukemia (ALL) at the Central Child Teaching Hospital, Baghdad, Iraq. Patients' ages ranged from 1 to 18 years (mean =7.5 years), with no prior treatment administered. Immunophenotyping classified cases into B-ALL (n=26) and T-ALL (n=18), and no acute myeloid leukemia (AML) cases were detected. Demographic and clinical data, including age, sex, and family history of hematologic malignancies, were extracted from medical records. A positive family history was defined as having a first-degree relative diagnosed with leukemia; 3 patients (6.8%) met this criterion, all related to chronic lymphocytic leukemia (CLL) in parents or siblings.

Control samples (n = 5) were collected from age-matched children undergoing orthopedic surgery without hematologic malignancy, serving as non-leukemic controls. Ethical approval was obtained, and informed consent was obtained from the legal guardians of the participants.

Inclusion Criteria

Patients were eligible for inclusion if they met the following criteria:

1. Newly diagnosed pediatric acute lymphoblastic leukemia (ALL) confirmed by bone marrow examination and immunophenotyping.
2. Age between 1 and 18 years.
3. No prior chemotherapy, radiotherapy, or immunomodulatory treatment before sample collection.
4. Availability of adequate bone marrow aspirate sample for RNA extraction and molecular analysis.
5. Complete clinical and demographic data, including leukemia subtype and HBV serological status.
6. Written informed consent obtained from legal guardians.

Control subjects were included if they

1. Were age-matched children without hematologic malignancy.
2. Underwent elective orthopedic procedures.
3. Had no history of malignancy, chronic liver disease, or immunodeficiency.

Exclusion Criteria

Participants were excluded if they met any of the following conditions:

1. Prior initiation of anti-leukemic therapy before sample collection.
2. Diagnosis of acute myeloid leukemia (AML) or other hematologic malignancies.
3. Inadequate or hemolyzed bone marrow samples unsuitable for RNA analysis.
4. Known chronic systemic diseases that could affect miRNA expression (e.g., autoimmune disorders, chronic inflammatory diseases).
5. Refusal or withdrawal of informed consent.

Isolation of Mononuclear Cells and RNA Extraction

Bone marrow aspirates (2–3 mL) were collected in sterile EDTA-treated tubes and processed within 2 hours of collection to preserve RNA integrity. Mononuclear cells (MNCs) were isolated using Ficoll-Paque PLUS density gradient centrifugation (GE Healthcare, Sweden) following a standardized protocol.

Briefly, bone marrow samples were diluted 1:1 with sterile phosphate-buffered saline (PBS, pH 7.4) at room temperature. The diluted suspension was carefully layered over Ficoll-Paque solution (density 1.077 g/mL) in a 15 mL sterile conical centrifuge tube, maintaining a ratio of 2:1 (sample to Ficoll) to ensure optimal phase separation. Samples were centrifuged at 400 × g for 30 minutes at 20°C without brake to preserve layer integrity.

Following centrifugation, four distinct layers were observed:

1. Plasma (upper layer)
2. Mononuclear cell layer (opaque buffy coat interface)
3. Ficoll layer
4. Erythrocytes and granulocytes (pellet)

The mononuclear cell layer was carefully aspirated using a sterile Pasteur pipette and transferred into a new tube. Cells were washed twice with PBS by centrifugation at 300 × g for 10 minutes to remove residual Ficoll and platelets. After the final wash, the cell pellet was resuspended and counted using a hemocytometer to assess cell yield and viability.

The purified mononuclear cell pellet was immediately lysed in TRIzol reagent (Invitrogen, USA) at a ratio of 1 mL TRIzol per 1×10^6 cells to ensure efficient RNA stabilization. Total RNA extraction was performed according to the manufacturer's protocol, including phase separation with chloroform, RNA precipitation with isopropanol, and ethanol washing steps. To enhance RNA purity and remove residual contaminants, the extracted RNA was further purified using silica-based spin columns.

RNA concentration and purity were measured using a NanoDrop spectrophotometer (Thermo Scientific), and samples with A260/A280 ratios between 1.8 and 2.1 were considered acceptable for downstream qRT-PCR analysis.

MicroRNA Expression Analysis

For quantification of *miR-214* expression, 10 ng of total RNA was reverse-transcribed using the TaqMan MicroRNA Reverse Transcription Kit with sequence-specific stem-loop primers for hsa-*miR-214*. Quantitative real-time PCR (qRT-PCR) was performed on the StepOnePlus platform using TaqMan miRNA assays. U6 small nuclear RNA was used as an endogenous control. All reactions were run in triplicate. Relative *miR-214* expression was calculated by the $2^{-\Delta\Delta Ct}$ method, normalizing to non-leukemic controls as calibrators. Samples with no detectable amplification after 40 cycles were assigned a Ct value of 40, and the detection threshold was set at approximately Ct = 35.

HBV Serology and Additional Laboratory Assessments

HBV infection status was determined using clinical virology reports of serological screening for hepatitis B surface antigen (HBsAg) and core antibody (anti-HBc). patients with HBVsAg and anti HBc IgG antibody were classified as having chronic HBV infection. None of the HBV-positive patients showed clinical hepatitis symptoms, and liver function tests were within normal limits. Other oncogenic viruses, such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV), were not routinely screened; hence, co-infections beyond HBV were not systematically evaluated. Cytogenetic and molecular analyses, including screening for common ALL-associated fusion genes, were performed as part of standard diagnostic work-up but were excluded from this study due to a lack of association with *miR-214* expression in preliminary analyses.

Statistical Analysis

Statistical analyses were conducted using SPSS v25. Due to non-normal distribution, *miR-214* fold-change values were summarized as medians and ranges and log-transformed ($\log_{10}$) before parametric testing. Pearson correlation was used to assess associations between continuous variables, including Ct and expression levels of *miR-214*. Binary clinical variables (leukemia subtype, HBV status, and family history) were coded as dichotomous indicators and correlated with *miR-214* expression using point-biserial Pearson correlation. Statistical significance was set at $p < 0.05$.

To examine potential effect modification, binary logistic regression models were fitted with leukemia subtype (B-ALL vs. T-ALL) as the dependent variable. Independent variables included log-transformed *miR-214* expression, HBV status, family history, and their respective interaction terms. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported, and model performance was evaluated using Nagelkerke's R^2. Given the limited number of HBV-positive and family history–positive cases, interaction analyses were considered exploratory.

Data visualization was performed using GraphPad Prism (version 9.5.1) and Python (matplotlib, version

3.11). Interaction effects were further illustrated using scatter and probability plots stratified by HBV status and family history.

Ethical Approval

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB) of the College of Medicine, Al-Iraqia University, Baghdad, Iraq (Approval No.: FM.SA.194; Date of approval: 1 June 2025). Written informed consent was obtained from the legal guardians of all participating children prior to enrollment. Patient confidentiality and data anonymity were strictly maintained throughout the study.

Results

Expression Patterns of miR-214 in Pediatric ALL

miR-214 expression tended to be downregulated in pediatric ALL patients compared to non-leukemic controls, although the difference was not statistically significant due to overlapping distributions (Figure 1A). Individual analysis revealed substantial heterogeneity: a subset of ALL cases exhibited profound *miR-214* suppression (log_2 fold-change ≤ –20), while a few samples showed upregulation (Figure 1B). This variability suggests a context-dependent role for *miR-214* in leukemogenesis. A significant inverse correlation between Ct values and fold-change data (r = – 0.303, p = 0.045) confirmed technical reliability.

miR-214 Expression by Leukemia Subtype: B-ALL vs. T-ALL

Among 42 patients, 26 were B-ALL and 16 T-ALL. Median *miR-214* expression was slightly lower in B-ALL (0.0508) than T-ALL (0.0605), but the difference was not significant (p = 0.45). The differences in *miR-214* expression between B-ALL and T-ALL did not achieve statistical significance, and thus no firm conclusions can be drawn regarding subtype-specific regulation based on the present dataset.Expression variability was greater in T-ALL (log_{10} fold-change –2.3 to +1.7) than in B-ALL (–3 to –0.5), suggesting heterogeneity in T-cell

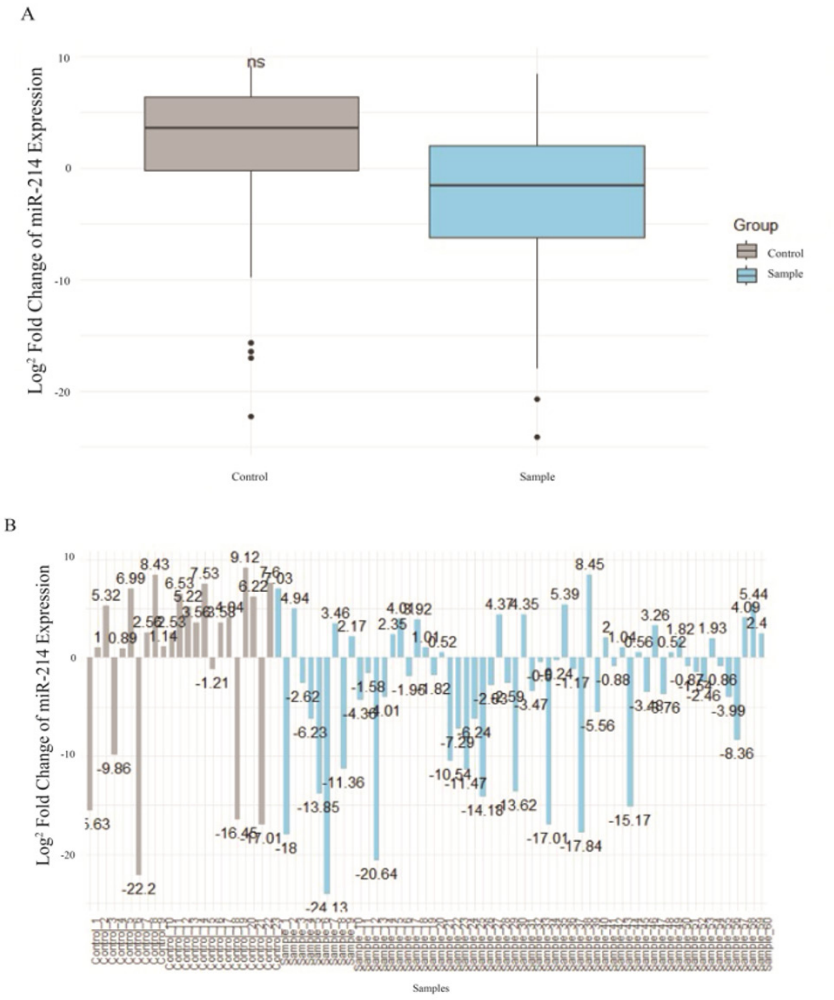

Figure 1. Expression Patterns of *miR-214* in Pediatric ALL. (A) Boxplot comparing log_2-transformed *miR-214* expression levels between pediatric ALL cases (blue) and non-leukemic controls (gray). Although ALL samples exhibited a general downward trend, the distribution overlap rendered the difference statistically non-significant. (B) Bar chart showing individual log_2 fold-change values for *miR-214* expression. Control samples cluster around zero, whereas a subset of ALL cases shows substantial repression, with some samples exhibiting greater than 24-fold (log_2) downregulation ALL; acute lymphoblastic leukemia.

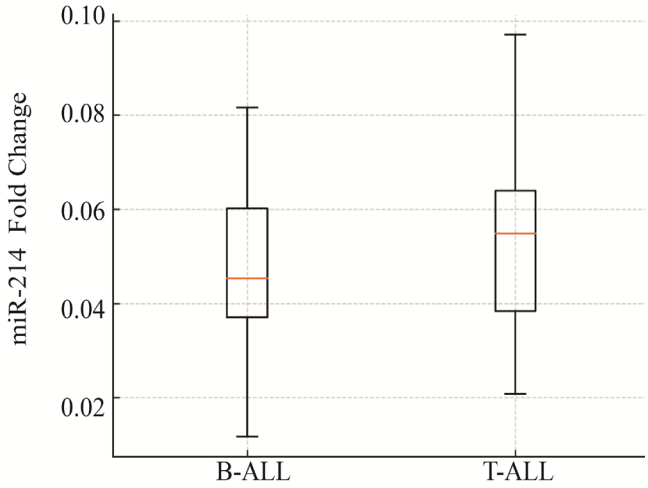

Figure 2. *miR-214* Expression Levels in B-ALL vs. T-ALL.

leukemogenesis (Figure 2).

miR-214 Expression and Family History

Three B-ALL patients (6.8%) had a first-degree relative with hematologic malignancy. These familial cases showed the most profound *miR-214* downregulation (median $\log_2$ fold-change ≈ −10), whereas non-familial B-ALL patients exhibited milder suppression (median ≈ –6). T-ALL patients demonstrated broader expression patterns, including substantial upregulation in some non-familial cases. Although statistical significance was not achieved (p = 0.15), these observations suggest a potential contribution of hereditary predisposition to *miR-214* silencing in B-ALL (Figure 3).

Association of miR-214 with Hepatitis B Virus Infection

Three patients were chronic HBV carriers (1 B-ALL, 2 T-ALL). The HBV-positive B-ALL case had extremely low *miR-214* expression (~0.0008-fold), whereas HBV-positive T-ALL cases had relatively high expression (~3.0-fold). Overall correlation between HBV status and *miR-214* expression was negligible (r = –0.022, p = 0.885). Logistic regression of leukemia subtype, including *miR-214*, HBV status, and their interaction, suggested an exploratory pattern: in HBV-positive patients, low *miR-214* was associated with B-ALL, whereas high *miR-214* was associated with T-ALL (Figure 4). However, the interaction was not statistically significant (Wald p = 0.20), likely due to the small number of HBV-positive cases (n = 3) and sparse data (pseudo-R^2 = 0.024).

Discussion

In this study, we analyzed *miR-214* expression in pediatric ALL patients, examining its association with leukemia subtype (B-ALL vs. T-ALL), family history, and hepatitis B virus (HBV) infection status. Consistent with previous findings [13-15], *miR-214* was generally

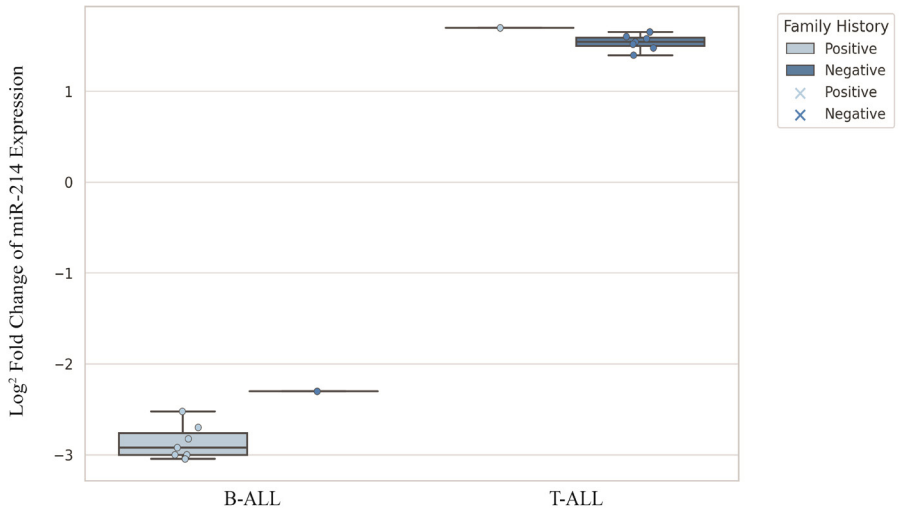

Figure 3. Log_{10}-Transformed Fold Change in *miR-214* Expression Stratified by Leukemia Subtype (B-ALL vs. T-ALL) and Family History. Each point represents a patient: blue circles = B-ALL; red circles = T-ALL; triangle markers = positive family history. B-ALL patients with a positive family history cluster on the far left ($\log_{10}$ FC ≈ –3), indicating profound downregulation (~0.001-fold). T-ALL patients exhibit broader expression patterns, including strong upregulation in some non-familial cases ($\log_{10}$ FC > 1.5). The figure highlights potential subtype- and context-specific regulation of *miR-214*.

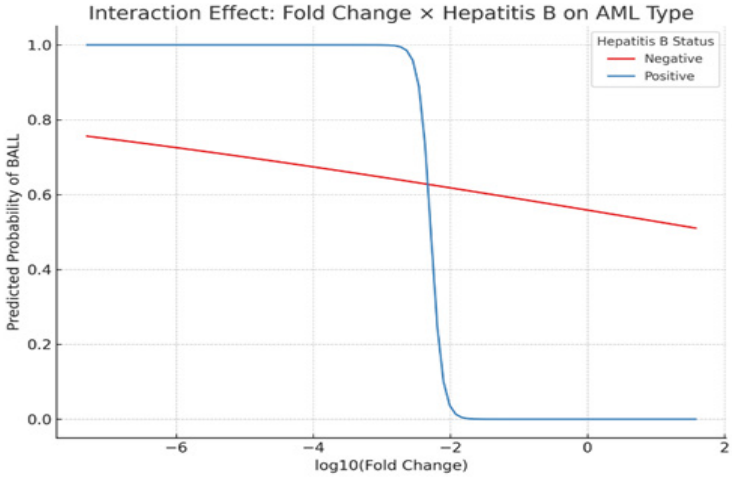

Figure 4. Interaction Plot Illustrating the Predicted Probability of B-Cell Acute Lymphoblastic Leukemia (B-ALL) based on $\log_{10}$-Transformed *miR-214* Fold Change and Hepatitis B Virus (HBV) Infection Status. In HBV-positive patients, higher *miR-214* expression sharply decreases the probability of B-ALL, suggesting a strong association with T-ALL phenotype. In contrast, among HBV-negative patients, the relationship between *miR-214* levels and leukemia subtype is modest and linear. This pattern suggests that HBV infection may amplify the biological impact of *miR-214* on leukemic lineage differentiation.

downregulated in ALL patients compared to healthy controls, supporting its proposed tumor-suppressive role in leukemogenesis. Although median *miR-214* levels appeared lower in B-ALL relative to T-ALL, this difference did not reach statistical significance, likely due to interpatient variability and the limited sample size. Notably, a subset of T-ALL patients exhibited markedly elevated *miR-214* levels, which increased the mean expression for the group. This pattern suggests the existence of a biologically distinct T-ALL subset, potentially characterized by unique cytogenetic features and compensatory miRNA regulatory networks. Moreover, previous studies identified *miR-214* as an independent marker for favorable prognosis in pediatric ALL, potentially through its pro-apoptotic and anti-proliferative functions [16].

Family history appeared to influence *miR-214* expression, particularly in B-ALL. Patients with a first-degree relative affected by leukemia demonstrated pronounced *miR-214* downregulation compared to sporadic cases. Although our findings were limited by sample size and did not reach statistical significance, this observation suggests a potential gene–environment interplay in which germline susceptibility may modulate *miR-214* function in leukemogenesis. In this context, no direct studies have yet investigated the impact of family history on *miR-214* expression in B-ALL. However, inherited germline mutations in genes such as PAX5 or ETV6 are known to increase susceptibility to B-ALL and could potentially synergize with *miR-214* downregulation, promoting the expansion of leukemic clones in the B-cell lineage [17, 18].

HBV infection also showed a context-dependent relationship with *miR-214* expression. Among HBV-positive T-ALL patients, *miR-214* levels were relatively high, whereas the single HBV-positive B-ALL case exhibited virtually undetectable *miR-214*. Although HBV is not considered a direct cause of leukemia, previous studies indicate that chronic HBV infection can modulate systemic miRNA expression and immune responses [18]. *miR-214* has been reported to target genes involved in regulatory T cell formation, potentially enhancing immune suppression and supporting leukemic clone survival in chronically infected hosts [19]. These observations suggest a speculative feedback loop in which HBV-mediated immune modulation may create a permissive environment for leukemic expansion, though further studies are required to validate this mechanism.

Consistent with these studies, aberrant regulation of miRNAs has been noted to contribute to the pathogenesis of cancer. A systematic review, for instance, described the involvement of miRNAs in the pathogenesis of Kaposi's sarcoma, reinforcing the value of these molecules as biomarkers and therapeutic targets [20]. This suggests that the expression patterns of *miR-214* in pediatric ALL could reflect more generalized oncogenic and tumor-suppressive influences across other hematologic malignancies and tumors of viral association.

This study incorporates the two additional components of RNA interactivity described in the case of pediatric acute lymphoblastic leukemia (ALL). First, the analysis of lncRNA SNHG16 documents its varied collaboration with both the WNT and the PI3K signaling axes through the modulation of TCF7, further consolidating proliferative and anti-apoptotic drives in de novo ALL patients [21]. This illustrates the role of noncoding RNAs as integrative nodes, bridging disparate oncogenic pathways, and suggests the need to incorporate dual-pathway targeting in therapeutic approaches instead of unidirectional control of a single pathway.

Viral seroprevalence studies in other disorders, such as exposure to the herpes simplex virus (HSV) in autism spectrum disorder, have similarly emphasized virus-host-miRNA interactions as modifiers of disease susceptibility and/or phenotype [22]. These patterns support the idea that as hidden cofactors, viral childhood infections

could influence non-coding RNA regulatory patterns, thus predisposing a range of disorders. In this scenario, ongoing and/or recurrent viral infections may increase the burden of pediatric disorders, such as neurodevelopmental disorders and hematological cancers, through chronic immune dysregulation and the mechanisms of immune evasion and/or dysregulated expression of disease- and disorder-associated miRNAs.

In summary, *miR-214* expression in pediatric ALL demonstrates variability across patients and may differ according to leukemia subtype and selected clinical characteristics. However, no statistically significant differences or interaction effects were observed in the present study. Therefore, these findings should be interpreted as descriptive and exploratory. Further investigations in larger, adequately powered cohorts are required to clarify the potential biological and clinical relevance of *miR-214* in pediatric leukemogenesis.

Limitations and Future Directions

The small sample size, particularly in subgroups with HBV infection or positive family history, is a significant limitation of this study. Additionally, *miR-214* was evaluated only once at diagnosis, preventing assessment of treatment response or prognostic significance. Only a single miRNA was analyzed; future studies with comprehensive miRNA profiling could clarify the associations of *miR-214* with other regulatory molecules. The functional role of *miR-214* in ALL warrants further investigation, including overexpression in B-ALL cell lines and inhibition in T-ALL lines to elucidate its mechanisms of action.

Author Contribution Statement

Maysaa Ibrahim: Data curation, formal analysis, statistical interpretation, and writing – review & editing. Ruqaia Sabbar Salman: Laboratory investigation, sample processing, and validation of experimental procedures. Anfal M. Khudhair: Conceptualization, study design, methodology, supervision, project administration, and writing – original draft. Dunya Jawad Ridha: Investigation, data validation, and visualization of results. Rasha Tariq Jawad: Patient recruitment, clinical data acquisition, and sample collection. Muhammed Munim Radwan: Writing – review, editing & visualization of results. Jaafar Alsadiq Arkan Farhan Ali: Laboratory assistance and data acquisition. Aya Ali Mohammed: Laboratory assistance and preliminary data organization. Hayder Rafid Abduljalil[5]: Technical support, data entry, and assistance in sample handling.

Acknowledgements

The authors would like to express their sincere gratitude to the College of Medicine, Al-Iraqia University, Baghdad, Dijlah University College, and the Central Child Teaching Hospital for their support in this study. The authors also would like to express their truthful appreciation to all individuals who contributed directly or indirectly to the completion of this project.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical Approval

The study was performed in compliance with the Declaration of Helsinki and was granted ethical approval by the IRB of the College of Medicine, Al-Iraqia University, Baghdad, Iraq (Approval Code: FM.SA.194, Date: 1 June 2025). All subjects' legal guardians provided documented informed consent before enrollment.

Conflicts of Interest

Anfal M. Khudhair: Declares no conflicts of interest.

References

1. Rahema MAH, Al-Shuwaikh AM, Al-Tameemi WF. Molecular and serological detection of human parvovirus b19 in a sample of iraqi patients with acute lymphoid leukemia in relation to hematological parameters. Asian Pac J Cancer Prev. 2025;26(4):1285-92. https://doi.org/10.31557/apjcp.2025.26.4.1285.
2. Ivanov AV, Alecsa MS, Popescu R, Starcea MI, Mocanu AM, Rusu C, et al. Pediatric acute lymphoblastic leukemia emerging therapies-from pathway to target. Int J Mol Sci. 2023;24(5):4661. https://doi.org/10.3390/ijms24054661.
3. Ahmad I, Ghafoor T, Ullah A, Naz S, Tahir M, Ahmed S, et al. Pediatric acute lymphoblastic leukemia: Clinical characteristics, treatment outcomes, and prognostic factors: 10 years' experience from a low- and middle-income country. JCO Glob Oncol. 2023;9:e2200288. https://doi.org/10.1200/go.22.00288.
4. Li X, Sundquist K, Sundquist J, Försti A, Hemminki K. Family history of any cancer for childhood leukemia patients in sweden. EJHaem. 2021;2(3):421-7. https://doi.org/10.1002/jha2.166.
5. Tebbi CK. Etiology of acute leukemia: A review. Cancers (Basel). 2021;13(9):2256. https://doi.org/10.3390/cancers13092256.
6. Ripert M, Menegaux F, Perel Y, Méchinaud F, Plouvier E, Gandemer V, et al. Familial history of cancer and childhood acute leukemia: A french population-based case-control study. Eur J Cancer Prev. 2007;16(5):466-70. https://doi.org/10.1097/01.cej.0000243849.82232.cb.
7. Schmiegelow K, Hjalgrim H. Is the risk of acute lymphoblastic leukemia reduced in siblings to children with the disease? A novel hypothesis explored by international collaboration. Leukemia. 2006;20(7):1206-8. https://doi.org/10.1038/sj.leu.2404250.
8. Tari K, Valizadeh Ardalan P, Ghasemi Mehr N, Daraei A, Abroun Sa. MicroRNAs in t-cell acute lymphoblastic leukemia: Roles and contributions to treatment response. Int J Med Lab. 2024;11(2):101-16. https://doi.org/10.18502/ijml.v11i2.18137.
9. Amin MMJ, Trevelyan CJ, Turner NA. Microrna-214 in health and disease. Cells. 2021;10(12):3274. https://doi.org/10.3390/cells10123274.
10. Chen Z, Deng X, Lu Y, Lu L, Qin Y, Qu H, et al. Role of mirna-214-3p in cancer (review). Oncol Rep. 2025;54(4):123. https://doi.org/10.3892/or.2025.8957.
11. Szczepanek J. Role of MicroRNAs dysregulation in childhood acute leukemias: Diagnostics, monitoring and therapeutics: A comprehensive review. World J Clin Oncol.

2020;11(6):348-69. https://doi.org/10.5306/wjco.v11.i6.348.
12. Lamontagne J, Steel LF, Bouchard MJ. Hepatitis b virus and micrornas: Complex interactions affecting Hepatitis B Virus replication and Hepatitis B Virus-associated diseases. World J Gastroenterol. 2015;21(24):7375-99. https://doi.org/10.3748/wjg.v21.i24.7375.
13. Organista-Nava J, Gómez-Gómez Y, Illades-Aguiar B, Leyva-Vázquez MA. Regulation of the miRNA expression by TEL/AML1, BCR/ABL, MLL/AF4 and TCF3/PBX1 oncoproteins in acute lymphoblastic leukemia (review). Oncol Rep. 2016;36(3):1226-32. https://doi.org/10.3892/or.2016.4948.
14. He Z, Liao Z, Chen S, Li B, Yu Z, Luo G, et al. Downregulated mir-17, mir-29c, mir-92a and *miR-214* may be related to BCL11B overexpression in T-Cell Acute Lymphoblastic Leukemia. Asia Pac J Clin Oncol. 2018;14(5):e259-e65. https://doi.org/10.1111/ajco.12979.
15. Yin Y, Cai X, Chen X, Liang H, Zhang Y, Li J, et al. Tumor-secreted *miR-214* induces regulatory T Cells: A major link between immune evasion and tumor growth. Cell Res. 2014;24(10):1164-80. https://doi.org/10.1038/cr.2014.121.
16. Schotte D, De Menezes RX, Akbari Moqadam F, Khankahdani LM, Lange-Turenhout E, Chen C, et al. Microrna characterize genetic diversity and drug resistance in pediatric acute lymphoblastic leukemia. Haematologica. 2011;96(5):703-11. https://doi.org/10.3324/haematol.2010.026138.
17. Shah S, Schrader KA, Waanders E, Timms AE, Vijai J, Miething C, et al. A recurrent germline PAX5 mutation confers susceptibility to pre-B Cell Acute Lymphoblastic Leukemia. Nat Genet. 2013;45(10):1226-31. https://doi.org/10.1038/ng.2754.
18. Zhang MY, Churpek JE, Keel SB, Walsh T, Lee MK, Loeb KR, et al. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. Nat Genet. 2015;47(2):180-5. https://doi.org/10.1038/ng.3177.
19. Jiang X, Kanda T, Wu S, Nakamura M, Miyamura T, Nakamoto S, et al. Regulation of microRNA by Hepatitis B Virus infection and their possible association with control of innate immunity. World J Gastroenterol. 2014;20(23):7197-206. https://doi.org/10.3748/wjg.v20.i23.7197.
20. Nabavi SE, Soltan Mohseni A, Ghahari SA, Zavvar M. Role of mirnas in the pathogenesis of Kaposi's Sarcoma: A systematic review. Iran Biomed J. 2024;28(7):296-. https://doi.org/10.61186/ibj.25th-11th-IACRTIMSS.
21. Khani M, Latifi A, Sayyadi M. Multifaceted cooperation between WNT and PI3k signaling axis through the long noncoding RNA SNHG16 and TCF7 in de novo acute lymphoblastic leukemia patients. Iran Biomed J. 2025;29(3):104-13. https://doi.org/10.61882/ibj.5031.
22. Shather Radhi L, Khudhair A, Khalil N. Herpes Simplex Virus seroprevalence in children with autism spectrum disorder: A cross-sectional study. J Biosci Appl Res. 2024;10:201-7. https://doi.org/10.21608/jbaar.2024.360953.