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Unravelling the Impact of Aberrant Expression of LncRNA-*H19* in Acute Myeloid Leukemia

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Abstract

Acute Myeloid Leukemia (AML) is a highly aggressive hematologic malignancy marked by the proliferation of abnormal myeloid precursors. Despite therapeutic developments, the prognosis for AML patients remains poor, primarily due to high relapse frequencies and resistance to chemotherapy. Molecular alterations are a hallmark of AML pathogenesis and are believed to impact clinical outcomes. The long non-coding RNA *H19* is one of the newly identified molecular biomarkers that has emerged as a crucial regulator of leukemogenesis. In this study, *H19* expression levels were analysed in 60 Iraqi *de novo* AML patients and 30 healthy controls to assess the prognostic significance. *H19* expression levels were assessed using quantitative Real-time Polymerase Chain Reaction and then linked to overall survival, treatment response, and clinical features. Results indicated that *H19* expression increased progressively from responders to non-responders and deceased patients ($p < 0.0001$). Longer survival and optimized response to treatment have been attributed to lower *H19* expression. Kaplan-Meier analysis confirmed that high *H19* expression is significantly associated with lower overall survival ($p < 0.0001$), and Receiver Operating Characteristic (ROC) curve analysis showed attractive diagnostic accuracy (AUC = 0.831). In conclusion, *H19* represents a promising molecular biomarker for predicting prognosis and treatment response in AML. Its clinical integration could enhance patient risk stratification and support the development of personalized therapeutic strategies.

Keywords: Acute myeloid leukemia, lncRNA *H19*, biomarker, RT-qPCR, Iraqi patients

كشف تأثير التعبير الشاذ عن *LncRNA-H19* في ابيضاض الدم النخاعي الحاد

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الخلاصة

يُعد ابيضاض الدم النخاعي الحاد (AML) أحد الأورام الدموية شديدة العدوانية، ويتّسم بالتكاثر غير الطبيعي للخلايا السلفية النخاعية. وعلى الرغم من التطورات العلاجية، لا يزال الإنذار السريري لمرضى AML ضعيفًا، ويُعزى ذلك غالبًا إلى ارتفاع معدلات الانتكاس ومقاومة العلاج الكيميائي. تُعد التغيرات الجزيئية سمة مميزة في التكوين المرضي لـAML ، ويُعتقد أنها تؤثر على النتائج السريرية. وقد برز الحمض النووي الريبوزي الطويل غير المشفّر (lncRNA) المسمى *H19* كواحد من المؤشرات الجزيئية الجديدة، وأصبح يُعتبر من المنظمين الرئيسيين لعملية تكون اللوكيميا. في هذه الدراسة، تم تحليل مستويات التعبير الجيني لـ *H19* لدى 60 مريضًا عراقيًا تم تشخيصهم حديثًا بـAML ، إلى جانب 30 فردًا سليمًا، بهدف تقييم الأهمية التنبؤية لهذا المؤشر الحيوي. جرى قياس مستويات *H19* باستخدام تقنية تفاعل البوليميراز المتسلسل الكمي في الوقت الحقيقي–RT) (qPCR، ثم تم ربط النتائج بالبقاء الكلي، والاستجابة للعلاج، والخصائص السريرية. أظهرت النتائج أن تعبير *H19*ازداد تدريجيًا من المرضى المستجيبين إلى غير المستجيبين ثم المتوفين($p < 0.0001$) .وقد ارتبط انخفاض تعبير *H19* بتحسّن الاستجابة للعلاج وزيادة في معدلات البقاء على قيد الحياة. أكّد تحليل–Kaplan Meierأن ارتفاع تعبير *H19* يرتبط بشكل ملحوظ بانخفاض البقاء الكلي($p < 0.0001$) ، كما أظهر تحليل منحنى ROC دقة تشخيصية متميزة($AUC = 0.831$) . ختامًا، تشير النتائج إلى أن H19 يُعد مؤشرًا جزيئيًا واعدًا يمكن استخدامه في التنبؤ بالتشخيص والاستجابة للعلاج لدى مرضى .AML وقد يُسهم إدماجه في الممارسة السريرية في تعزيز تصنيف المرضى ودعم تطوير استراتيجيات علاجية مخصصة.

الكلمات المفتاحية :ابيضاض الدم النخاعي الحاد، lncRNA H19، المؤشرات الحيوية، RT–qPCR، المرضى العراقيون.

1. Introduction

Acute myeloid leukemia (AML) is an aggressive and heterogeneous hematologic malignancy characterized by the rapid growth of abnormal myeloid precursor cells. Although treatment strategies for AML have improved, the prognosis of AML patients is still poor; besides, relapse and drug resistance are the main causes of treatment failure. AML is a multigene disorder characterized by a complex molecular architecture, in which genetic mutations, chromosomal abnormalities, and altered gene expression profiles act as critical factors in disease progression, treatment response, and ultimate patient survival [1-4]. LncRNAs are one of the regulatory molecules that have emerged as a potential component in the regulation of gene expression and cell function in AML. One example of such an lncRNA, *H19,* has emerged as a key player in various cancers, including AML. *H19* is a maternally imprinted gene encoding a non-coding RNA implicated in regulating crucial cellular processes, including cell growth, apoptosis, and metastasis [5, 6]. It has increasingly been recognised that it plays a role in not only tumorigenesis but also tumor progression in a range of malignancies, though its specific role in AML is not yet comprehensively understood [7]. Recent studies have emerged showing that abnormal expression of *H19* is a potential prognostic biomarker and a regulator of networks primarily in AML patients [8]. Increased *H19* expression is associated with poor clinical outcomes, chemotherapy resistance, and disease recurrence in several cancers, but its mechanistic role in AML is largely unknown [9]. Moreover, signal pathways related to cell survival, differentiation, and angiogenesis are downstream targets of *H19*, providing possible therapeutic targets in AML [10, 11]. To the best of our knowledge, this is the first study to investigate the expression of the long non-coding RNA *H19* in Iraqi patients with AML. The present study aimed to evaluate the role of *H19* expression in AML patients and explore its possible effects on patient prognosis. Additionally, to measure *H19* levels in AML patients and evaluate their correlation with clinical data and clinical outcomes, aiming to explore the diagnostic value and therapeutic target of *H19*. This information could be instructive for the molecular pathogenesis of AML, which may lead to new approaches for better patient stratification and improved treatment outcomes.

2. Materials and Methods

Sample Collection

A sample of 60 newly diagnosed patients with AML was obtained from the Hematology and Bone Marrow Transplant Center, Medical City, Baghdad, in the period between October 2022 and April 2023. Inclusion criteria required patients to be newly diagnosed, over 14 years of age, and not previously treated with chemotherapy. The enrolled patients were aged 14 years or older. Written informed consent was obtained from all participants before enrolment. Exclusion criteria included patients with acute promyelocytic leukemia (FAB subtype M3), central nervous system (CNS) infiltration, secondary AML, prior treatment with hypomethylating agents, HIV infection, severe comorbidities, or pregnancy. In parallel, 30 age- and sex-matched healthy individuals were recruited as the control group. "Healthy" was defined as individuals with no history of hematological disorders, malignancy, chronic inflammatory conditions, autoimmune diseases, or recent infections (within the last four weeks) that might influence *H19* expression. Each controls underwent routine clinical and hematological screening to confirm their eligibility. Each participant provided 3 mL of peripheral blood, collected in EDTA tubes. A single time point blood draw was performed prior to the initiation of chemotherapy to ensure that all measurements reflected baseline (pre-treatment) conditions. AML diagnoses were established by a consultant hematologist based on clinical features, complete blood count, peripheral blood smear, bone marrow aspiration, and confirmed by morphological classification according to the French-American-British (FAB) classification system, which was used to subtype AML cases.

Treatment for patients under 60 years of age typically involves the 7+3 regimen, which includes daunorubicin (60 mg/m²) on days 1 to 3 and cytarabine (100 mg/m²) administered as a continuous infusion on days 1 to 7. In contrast, elderly patients (≥60 years) who are not eligible for intensive chemotherapy are often treated with less aggressive options, such as decitabine (20 mg/m²) on days 1 to 5 combined with venetoclax.

RNA Extraction

Whole blood was used for total RNA isolation using the GENEzol™ TriRNA Pure Kit (Geneaid, Taiwan) according to the manufacturer's instructions. Briefly, 200 µL of whole blood was lysed with 700 µL of GENEzol™ Reagent, followed by phase separation, ethanol precipitation, and column purification. RNA was eluted in 30 µL of RNase-free water. The concentration and purity of RNA were assessed using a NanoDrop spectrophotometer (Thermo Scientific, USA). RNA purity was evaluated based on both the A260/280 and A260/230 absorbance ratios. Samples were considered acceptable when the A260/280 ratio ranged between 1.7 and 2.0 and the A260/230 ratio was greater than or equal to 1.8, indicating low contamination from proteins, phenol, or chaotropic salts. Only RNA samples meeting these quality criteria were used for downstream applications, including cDNA synthesis and quantitative real-time PCR (RT-qPCR) for gene expression analysis.

cDNA Synthesis

cDNA was synthesized with the AccuPower® RocketScript RT PreMix Kit (Bioneer, Korea). Each 20 µL reaction comprised 10 µL total RNA (100 ng/µL), 1 µL oligo(dT) primer, 9 µL DEPC-treated water. Reverse transcription was performed at 50°C for 60 minutes, and the reaction was inactivated at 95°C for 5 minutes.

Quantitative Real-Time PCR (qPCR)

The expression of *H19* lncRNA was quantified by GoTaq qPCR MasterMix (Promega) in a final volume of 10 µL reaction, with 5 µL of qPCR master mix, 0.5 µL each of forward and

reverse primers, 2 µL of cDNA, and 2 µL of nuclease-free water. Primer sequences for *H19* were: forward, `5-ATCGGTGCCTCAGCGTTCGG-3′ and reverse `5-CTGTCCTCGCCGTCACACCG-3′. The reference gene used was *GAPDH,* and the primer sequences were: forward: `5-GTCAACGGATTTGGTCTGTATT-3′, reverse: `5-AGTCTTCTGGGTGGCAGTGAT-3′ [12].
Primer specificity was confirmed by performing melting curve analysis at the end of each qPCR run. A single sharp peak was observed for each primer set, indicating the amplification of a single, specific product without primer-dimer formation or nonspecific products.
Amplification was performed using the Exicycler™ 96 Real-Time PCR System (Bioneer, Korea). Thermal cycling conditions were as follows: an initial denaturation at 95°C for 10 minutes, followed by 40 amplification cycles. Each cycle included 15 seconds of denaturation at 95°C and a combined annealing and extension step at 60°C for 1 minute.

Data Analysis
Relative gene expression was calculated using the 2^–ΔΔCt method [13]. Fold change values >1 was considered indicative of upregulation, and values <1 were considered as downregulation of *H19* expression.
Remission Criteria
Complete Remission (CR) is defined as bone marrow blasts <5%, normal blood counts, no extramedullary disease, and no Auer rods, while no remission indicates ≥5% blasts, persistent symptoms, or detectable minimal residual disease [14].

Statistical analysis
statistical analyses were carried out using GraphPad Prism 7.0 and SPSS 26.0. Data distribution was first examined with the Shapiro–Wilk test to select the suitable method. For variables with normal distribution, parametric approaches such as the t-test and ANOVA were applied, whereas non-parametric alternatives, including the Mann–Whitney U and Kruskal–Wallis tests, were used for skewed data. Categorical parameters were compared using either the chi-square test or Fisher's exact test. Correlations between continuous variables were explored using Spearman's rank test. Diagnostic accuracy of biomarkers was assessed by ROC curve analysis, while survival outcomes were estimated with Kaplan–Meier analysis. Statistical significance was set at $p < 0.05$.

3. Results and Discussion

The study included 60 newly diagnosed adult AML patients and 30 age- and sex-matched healthy controls. The mean age of the control group was 46.97 ± 3.41 years, with an equal male-to-female distribution (15:15). The AML patient group had a mean age of 52.87 ± 2.40 years and a sex distribution of 29 males (48.33%) and 31 females (51.67%). There was no statistically significant difference between the groups in terms of age ($p = 0.1598$) or sex distribution ($p > 0.999$), confirming the appropriateness of the matching.
Clinical characteristics (Table 1) of AML patients stratified by treatment outcome revealed significant differences across several parameters. Responders were significantly younger (mean 44.6 years) than non-responders (59.8 years) and deceased patients (56.6 years) ($p = 0.0207$), consistent with previous studies showing improved outcomes in younger individuals due to better physiological reserve and treatment tolerance [14,15]. Hemoglobin levels were also significantly higher in the response group ($p= 0.0152$), indicating a more robust bone marrow function at baseline.

Although white blood cell (WBC) count, platelet count, and blast percentages did not reach statistical significance across groups, their distribution patterns remain clinically relevant.

Elevated WBC count in the deceased group (median $37.6 \times 10^3/\mu L$) suggests a trend toward higher leukemic burden and an increased risk of complications such as leukostasis or tumor lysis syndrome. Similarly, lower platelet counts in non-responders and deceased patients may reflect extensive marrow infiltration and impaired thrombopoiesis, which could contribute to bleeding risk and reduced chemotherapy tolerance. Higher peripheral and bone marrow blast percentages in the deceased group further indicate a more aggressive disease course and are consistent with recognized adverse prognostic indicators in AML. In contrast, the sex distribution was not statistically significant, but showed a trend with a male predominance among responders and a higher proportion of females among non-responders and deceased individuals. The M5 (monocytic) subtype was more common in poor outcome groups, aligning with prior evidence linking this subtype to aggressive disease biology and resistance to standard chemotherapy regimens [16]. These results are supported by a local Iraqi study, in which Dawood and Mohammed [17] linked older age and lower hemoglobin levels to a poor prognosis through elevated *TP53* expression in AML patients. In contrast, Jebur and Al-Rubaie [18] found no significant association between p53 expression and hematological parameters in relation to treatment response.

Table 1: Comparison between the investigated AML patients according to outcome at time of diagnosis

Characteristics		Groups			P value
		Response (n=24)	No response (n=20)	Deceased (n=16)	
Age (years), mean ± SE		44.58 ± 3.8	59.8 ± 4.41	56.6 ± 3.16	0.0207
Age group (years), n (%)	10-19	1 (4.17)	2 (10)	0 (0)	-
	20-29	5 (20.83)	0 (0)	1 (6.25)	
	30-39	5 (20.83)	1 (5)	1 (6.25)	
	40-49	4 (16.67)	2 (10)	2 (12.5)	
	50-59	3 (12.50)	0 (0)	2 (12.5)	
	60-69	4 (16.67)	9 (45)	9 (56.25)	
	≥ 70	2 (8.33)	6 (30)	1 (6.25)	
Sex, n (%)	Male	16 (66.67)	7 (35)	6 (37.5)	0.067
	Female	8 (33.33)	13 (65)	10 (62.5)	
FAB classification, n (%)	M0	1 (4.17)	2 (10)	1 (6.25)	-
	M2	5 (20.83)	4 (20)	4 (25)	
	M4	6 (25)	4 (20)	3 (18.75)	
	M5	6 (25)	6 (30)	5 (31.25)	
	M7	0 (0)	2 (10)	0 (0)	
	AML unclassified	6 (25)	2 (10)	3 (18.75)	
HGB (g/dl), mean ± SE		8.45 ± 0.46	7.69 ± 0.41	6.63 ± 0.28	0.0152
WBC ($\times 10^3/\mu L$), median (range)		9.5 (0.42-125)	5.15 (0.26-219)	37.6 (0.3–124)	0.1854
PLT ($\times 10^3/\mu L$), median (range)		55 (11-477)	35.5 (11-152)	28.1 (5-270)	0.0657
OS (Days), median (range)		180 (92-180)	180 (31-180)	19 (2-28)	<0.0001
PB blast (%), mean ± SE		46.9 ± 5.77	51.1 ± 6.14	57.4 ± 7.06	0.5159
BM blast (%), mean ± SE		56.8 ± 4.57	59.95 ± 5.74	71.4 ± 5.7	0.1568

FAB (French-American-British), HGB (Hemoglobin), WBC (White blood cells), PLT (Platelet), OS (Overall survival), PB (Peripheral blood), BM (Bone Marrow).

Analysis of *H19* expression across AML patient groups revealed a significant stepwise increase in expression levels corresponding to the severity of clinical outcomes. Median *H19* expression level was the lowest among responders (9.3-fold), increased markedly in non-responders (38.4-fold), and was highest in deceased patients (153.4-fold), with all intergroup differences reaching statistical significance ($p < 0.05$). These results, visually represented in Figure 1, suggest a strong association between elevated *H19* expression and adverse outcomes in AML. Mechanistically, *H19* is known to contribute to leukemogenesis through several pathways. It functions as a competing endogenous RNA (ceRNA), sponging tumor-suppressive miRNAs such as *let-7* and *miR-29*, leading to the derepression of oncogenic targets. Additionally, *H19* activates pro-survival signaling cascades including the *PI3K/AKT, MAPK*, and *Wnt/β*-catenin pathways, thereby promoting leukemic cell proliferation, inhibiting apoptosis, and conferring chemoresistance. These biological effects help explain why *H19* expression is elevated in patients with aggressive disease phenotypes [19, 20]. The obtained results are in agreement with previous reports. Zhang *et al.,* demonstrated that *H19* is significantly upregulated in AML-derived bone marrow cells and is associated with poor response to chemotherapy and reduced overall survival [5]. Zhao *et al.,* and Wang *et al.,* further confirmed *H19*'s involvement in chemoresistance and its ability to modulate apoptotic regulators [19, 20]. While Zhou *et al.,* have demonstrated that *H19* knockdown sensitizes CML cells to imatinib and *in vivo* reduces tumorigenesis [21]. Importantly, Alin *et al.,* reported that *H19* expression was significantly higher in AML patients with complex karyotypes and unfavorable genetic backgrounds, acting as an independent prognostic marker [22]. These findings were further supported by a large meta-analysis conducted by Asadi *et al.*, which highlights *H19* as a potential molecular marker linked to key leukemia well-established prognostic parameters, including age, white blood cell count, cytogenetic risk, and overall survival across multiple datasets, including the cancer genome atlas (TCGA) and gene expression omnibus (GEO) [23]. Together, these results highlight the relevance of *H19* not only as a marker of disease severity in AML but also as a potential target for molecularly guided treatment strategies.

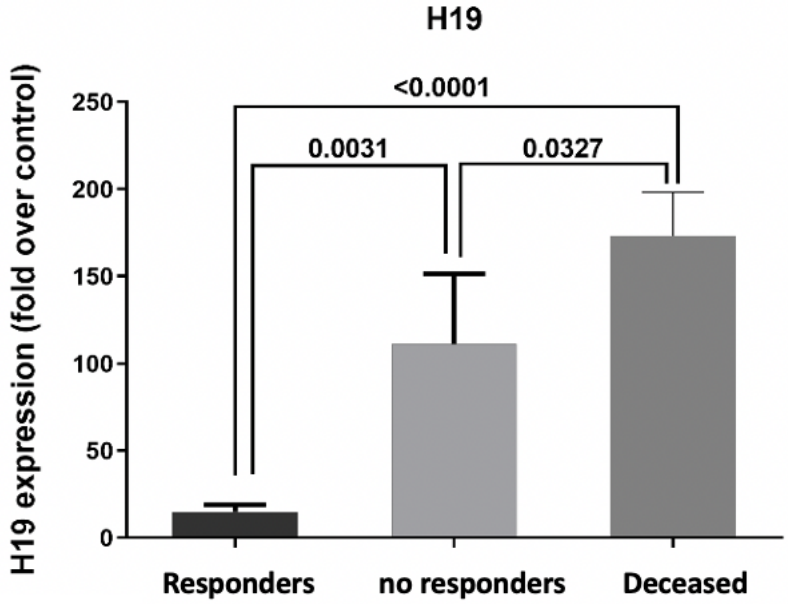

Figure 1: Comparison of lncRNA *H19* expression between AML patients according to their clinical outcome

To evaluate the diagnostic potential of *H19* expression in predicting treatment response in AML, a receiver operating characteristic (ROC) curve analysis was performed. The results in Table 2 demonstrated a strong discriminative performance for *H19* expression, with an area under the curve (AUC) of 0.831 (95% CI: 0.688–0.975, p = 0.0002), placing it in the "very good" classification range. An optimal cutoff point of 12.68-fold over control was identified, yielding a sensitivity of 80% and a specificity of 91.67%. These findings indicate that *H19* expression could serve as a reliable biomarker for distinguishing between AML responders and non-responders. The ROC curve (Figure 2) visually supports these findings, demonstrating robust separation between the groups. The clinical utility of this result is further substantiated by the biological role of *H19* in AML pathophysiology. *H19* has been shown to promote resistance to chemotherapeutic agents by modulating apoptosis-related pathways and altering the expression of genes associated with drug resistance [20]. The high specificity observed suggests that elevated *H19* expression is a strong predictor of treatment resistance, which could aid in early stratification and individualized therapy planning in AML patients.

Table 2: Response *vs.* no response group ROC analysis by *H19* expression

Comparison groups	AUC	95% CI of AUC	P-value	Optimum Cut off value	SN (%)	SP (%)
Response *vs.* No response	0.831	0.688-0.975	0.0002	12.68	80	91.67
(AUC) area under the curve, (CI) confidence interval, (SN) sensitivity, (SP) specificity AUC reference: 0.9-1 (excellent), 0.8-0.9 (very good), 0.7-0.8 (good), 0.6-0.7 (satisfactory), 0.5-0.6 (unsatisfactory)						

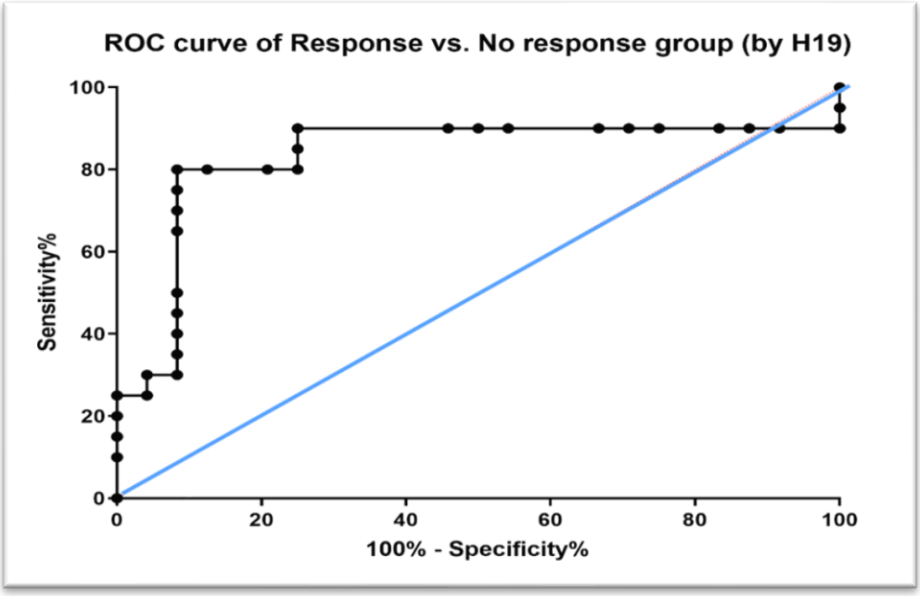

Figure 2: A receiver operating characteristic (response vs. no response group) by *H19* expression

Kaplan–Meier survival analysis was performed to assess the prognostic impact of *H19* expression in AML patients, stratifying them into two groups based on a cutoff value of 38.35-fold. As shown in Figure 3, patients with low *H19* expression (< 38.35-fold) exhibited significantly higher overall survival**,** with most remaining alive throughout the follow-up

period. In contrast, patients with high *H19* expression (≥ 38.35-fold) had a sharp decline in survival, with the majority of deaths occurring within the first 60 days. The survival difference between the two groups was statistically significant (log-rank $p < 0.0001$), confirming that elevated *H19* expression is associated with poor prognosis in AML. This result complements the ROC findings and supports the utility of *H19* as a predictive and prognostic biomarker. The biological plausibility of this association is supported by the oncogenic function of *H19*, which promotes leukemic cell survival through anti-apoptotic signalling, chemoresistance, and proliferation-enhancing pathways [24-26]. Together with previous findings from Zhang *et al.,* [7] and Alin *et al.,* [22], this survival analysis highlights the clinical relevance of *H19* and strengthens its potential as a marker for risk stratification, prognosis, and therapeutic decision-making in AML.

Taken together, these findings underscore the value of integrating clinical features with molecular profiling, particularly *H19* expression, for improving risk stratification and guiding personalized therapy in AML. However, the interpretation of these results should consider certain limitations, including the small sample size and single-center design, which may affect their generalizability. In addition, only baseline *H19* expression was assessed, and dynamic changes over time were not evaluated due to time constraints within the scope of this study.

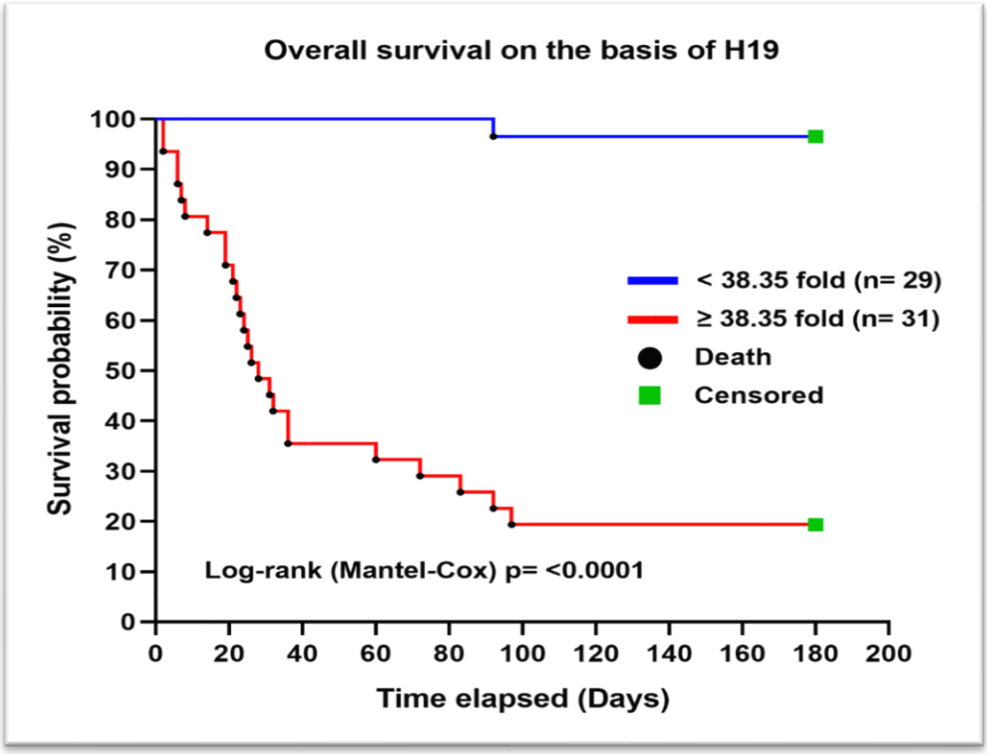

Figure 3: Kaplan–Meier survival curve stratified by *H19* expression in AML patients

Conclusion

In summary, this study highlights the prognostic significance of both clinical and molecular characteristics in AML. Younger age and higher baseline hemoglobin levels were independent predictors of response, highlighting the role of host factors in determining treatment response. Among them, high expression of the long non-coding RNA *H19* was significantly correlated with disease failure, early mortality, and short survival. The expression of *H19* demonstrated promising diagnostic value in distinguishing between responders and non-responders, suggesting its potential as a candidate molecular marker for risk stratification. Collectively, these findings support the integration of clinical features with molecular profiling, particularly

H19 expression, to improve personalized treatment decisions and prognostication in AML patients. Future studies should include larger, multi-center cohorts to validate the role of *H19* in AML. Longitudinal and functional analyses are recommended to assess its dynamic expression and clarify its mechanistic involvement in disease progression and treatment response.

Conflict of Interest Statement

The authors have no conflicts of interest with respect to the publication of this paper.

Ethical Approval

This study was approved by the Research Ethics Committee at the College of Science, University of Baghdad (Approval No. CSEC/0922/0082, dated September 22, 2022). Written informed consent was obtained from all participants, including both AML patients and healthy controls. In cases where participants were under the age of 18, consent was obtained from their legal guardians in accordance with the committee's ethical guidelines.

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