RESEARCH ARTICLE

Editorial Process: Submission:27/02/2026 Acceptance:22/09/2026 Published:28/09/2026

Circulating miR-181a-3p, ATR, and HMGB-1 as Integrated Predictors of Induction Blast Clearance in Adults with Acute Myeloid Leukemia

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Abstract

Methods: This study included 71 adult patients with newly diagnosed AML who received standard "7+3" induction chemotherapy. Baseline circulating *miR-181a-3p* and miR-181b-5p levels were quantified using quantitative real-time polymerase chain reaction, while ATM, ATR, and *HMGB-1* protein levels were measured using enzyme-linked immunosorbent assay. Induction blast clearance was defined as a post-induction bone marrow blast count of <5%. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cut-off values. Associations were evaluated using Spearman correlation and relative risk (RR) with 95% confidence intervals. **Results:** Circulating *miR-181a-3p* demonstrated limited discriminatory performance (AUC = 0.564), while *HMGB-1* showed modest performance (AUC = 0.615). Using ROC-derived cut-off values, low baseline *miR-181a-3p* expression was associated with a significantly higher likelihood of achieving induction blast clearance in monocytic AML (FAB M4–M5) (RR = 2.33, 95% CI: 1.18–4.63, p = 0.015), but not in non-monocytic subtypes. Higher ATR (RR = 1.53, 95% CI: 0.99–2.38, p = 0.047) and *HMGB-1* levels (RR = 1.61, 95% CI: 1.04–2.50, p = 0.031) were also associated with improved induction response. Circulating *miR-181a-3p* correlated with baseline bone marrow blast percentage, suggesting its potential as a surrogate marker for leukemic burden. **Conclusion:** Circulating *miR-181a-3p*, ATR, and *HMGB-1* are associated with induction blast clearance in AML, with lineage-specific effects observed for *miR-181a-3p*. Although the individual biomarkers demonstrated limited discriminatory performance, their integration may provide clinically relevant insights into early treatment response.

Keywords: microRNA profiling, replication stress signaling, monocytic subtype, treatment response, leukemic burden

Asian Pac J Cancer Prev, **27 (9)**, 3479-3485

Introduction

Acute myeloid leukemia (AML) is a biologically heterogeneous hematologic malignancy characterized by clonal proliferation of immature myeloid precursors and impaired differentiation [1, 2]. Despite advances in molecular classification and risk stratification, induction chemotherapy remains the cornerstone of treatment for most patients [3, 4]. However, response to induction therapy varies considerably, reflecting differences in underlying disease biology and cellular response to chemotherapy-induced DNA damage [5].

The cytotoxic effects of induction chemotherapy are mediated primarily through the induction of DNA damage, which activates the cellular DNA damage response (DDR) pathway [6, 7]. Key regulators of this pathway include ataxia-telangiectasia mutated (ATM) and ATM- and Rad3-related (*ATR*), which coordinate DNA repair, cell cycle arrest, and apoptosis [8 , 9]. *ATR*, in particular, plays a central role in responding to replication stress, a hallmark of rapidly proliferating leukemic cells [10]. High-mobility group box-1 (*HMGB-1*), a chromatin-associated protein, has also been implicated in modulating DNA repair and chemotherapy response [11, 12].

In parallel, microRNAs have emerged as important regulators of gene expression in AML. The miR-181

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family has been shown to influence hematopoietic differentiation and leukemia biology [13-15]. Altered miR-181 expression has been associated with clinical outcomes and treatment response in AML, although findings have been inconsistent and appear to depend on disease subtype and biological context [16-18]. MicroRNAs may also interact with DDR-related pathways, influencing cellular response to genotoxic stress [19, 20].

Circulating microRNAs are particularly attractive as minimally invasive biomarkers due to their stability in peripheral blood [21-23]. Circulating *miR-181a-3p* may reflect leukemic burden and provide clinically useful information regarding disease status and treatment response.

Despite increasing interest in DDR-related proteins and circulating microRNAs, their integrated role in predicting induction response remains incompletely defined. Therefore, this study aimed to evaluate the relationship between circulating miR-181 family members and DDR-related proteins with induction blast clearance in AML.

Materials and Methods

Study design and patient population

This study was conducted using a prospectively collected cohort of adult patients diagnosed with acute myeloid leukemia (AML) who underwent standard induction chemotherapy at a tertiary national referral cancer center. Patients were diagnosed based on morphologic and immunophenotypic criteria in accordance with established AML diagnostic standards with WHO criteria 2001 [4, 24].

Patients were eligible for inclusion if they were >18 years of age, had newly diagnosed AML, and received standard induction chemotherapy. Patients with M3 classification and history of Myelodysplastic Syndrome were excluded and if baseline biomarker data were incomplete or if post-induction bone marrow evaluation was not available. Initially, 109 adult patients with newly diagnosed AML were identified and assessed for eligibility. Of these, 7 patients were excluded prior to induction therapy due to early mortality (n = 4) or loss to follow-up before treatment initiation (n = 3). The remaining 102 patients proceeded to receive standard induction chemotherapy.

During treatment and early post-treatment follow-up, 27 additional patients were excluded from the final evaluable cohort due to death during induction therapy or early recovery (n = 25), primarily related to treatment-associated complications, and loss to follow-up after discharge (n = 2). Among the remaining patients who completed induction therapy and post-treatment bone marrow evaluation (n = 75), 4 patients were further excluded due to incomplete or non-evaluable biomarker laboratory results.

Ultimately, a total of 71 patients met all inclusion criteria and had complete clinical, laboratory, and biomarker data, and were therefore included in the final analysis. This secondary analysis specifically evaluated the relationship between circulating microRNAs, DNA damage response–related proteins, and induction blast clearance. The detailed patient selection process is illustrated in Figure 1.

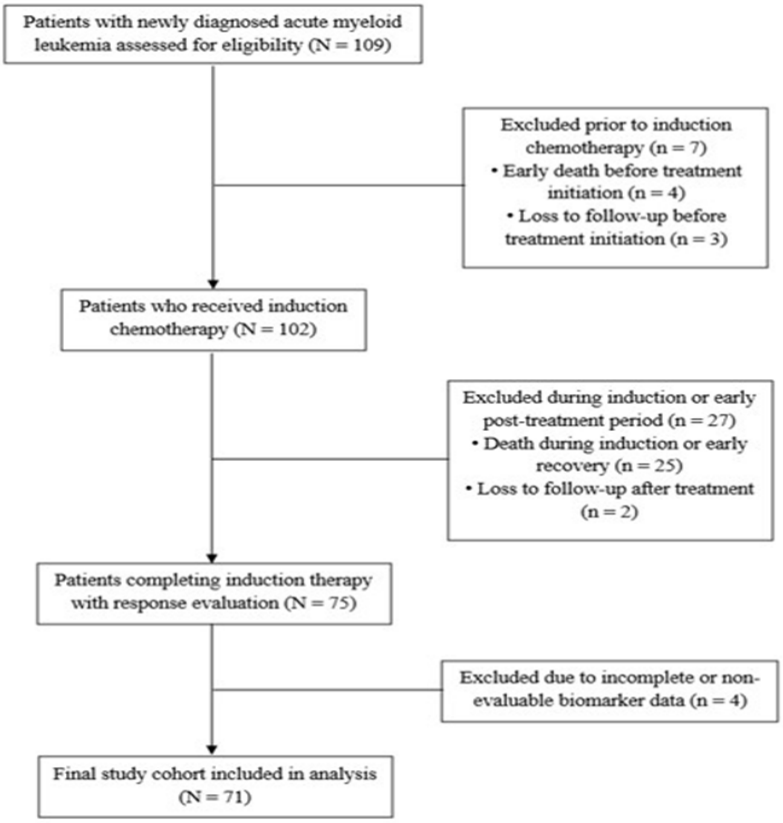

Figure 1. Flow Diagram of Patient Selection and Study Cohort

Sample collection and biomarker measurement

Peripheral blood samples were collected at baseline prior to initiation of induction chemotherapy. Plasma was separated by centrifugation and stored at −80°C until analysis. Circulating microRNAs were isolated from plasma using a silica membrane–based small RNA extraction protocol. The extracted RNA was reverse-transcribed into complementary DNA (cDNA), and expression levels of *miR-181a-3p* and miR-181b-5p were quantified using quantitative real-time polymerase chain reaction (qRT-PCR) with sequence-specific primers. MicroRNA expression levels were calculated based on amplification signals and reported as copies per microliter, consistent with established circulating microRNA quantification methods [21-23].

Baseline protein levels of key DDR biomarkers, including ataxia-telangiectasia mutated (ATM), ATM- and Rad3-related (*ATR*), and high-mobility group box-1 (*HMGB-1*), were measured using quantitative enzyme-linked immunosorbent assay (ELISA) according to standardized laboratory protocols. Protein concentrations were determined using calibration curves generated from known standards [6, 9, 11].

All biomarker measurements were performed using baseline samples obtained prior to treatment initiation to ensure that values reflected intrinsic disease biology rather than treatment-related effects.

Induction chemotherapy protocol

All patients received standard induction chemotherapy consisting of a combination of cytarabine and an anthracycline (D3A7 protocol), in accordance with established AML treatment guidelines and institutional protocols. Cytarabine was administered at a dose of 100–200 mg/m² per day as a continuous intravenous infusion for seven consecutive days. This was combined with daunorubicin administered intravenously at a dose of 60 mg/m² per day during the first three days of treatment. This regimen represents the standard "7+3" induction protocol and was delivered according to institutional treatment protocols and individual patient clinical condition.

Clinical and morphologic assessment

Baseline bone marrow blast percentage was determined using standard morphologic evaluation of bone marrow aspirate specimens. Post-induction bone marrow assessment was performed following completion of induction chemotherapy to evaluate treatment response [4, 24].

Induction blast clearance was defined as post-induction bone marrow blast percentage <5%, consistent with established morphologic response criteria. This endpoint was selected as an early indicator of treatment effectiveness and leukemic cell sensitivity to induction chemotherapy [4].

Patients were also classified according to the French-American-British (FAB) subtype. For subgroup analyses, patients were categorized as monocytic AML (FAB M4–M5) or non-monocytic AML, given the known biological and clinical differences between these subtypes [1, 5].

Statistical analysis

Continuous variables were summarized using median and interquartile range (IQR), reflecting the non-normal distribution of biomarker levels. Categorical variables were summarized using frequencies and percentages. Associations between continuous biomarker levels and post-induction bone marrow blast percentage were evaluated using Spearman's rank correlation coefficient. This non-parametric approach was selected due to the skewed distribution of biomarker measurements [21, 23].

For categorical analyses, biomarker levels were classified into low and high expression groups based on predefined cut-off values. The association between biomarker expression and induction blast clearance was evaluated using relative risk (RR) or odds ratio (OR), as appropriate [4, 5].

Subgroup analyses were performed according to FAB classification to assess potential lineage-specific effects, given known biological heterogeneity across AML subtypes [1, 5]. In addition, the relationship between circulating *miR-181a-3p* levels and baseline bone marrow blast percentage was evaluated to explore its potential role as a surrogate indicator of leukemic burden, consistent with previous studies evaluating circulating microRNAs as biomarkers [21-23].

All statistical analyses were performed using standard statistical software. A two-sided p-value <0.05 was considered statistically significant.

Ethical Approval

The original study protocol was approved by the Institutional Ethics Committee of Dharmais National Cancer Center, Jakarta, Indonesia. Written informed consent was obtained from all participants prior to inclusion in the study. This secondary analysis utilized de-identified data and was conducted in accordance with institutional guidelines and the Declaration of Helsinki. Approval number: DP.04.03/11.7/076/2025.

Results

Patient characteristics and baseline biomarker profile

A total of 71 adult patients with newly diagnosed AML were included in the analysis. The median age at diagnosis was 39 years (interquartile range [IQR], 27.5–45.5). Based on FAB classification, 24 patients (33.8%) were classified as monocytic AML (FAB M4–M5), while 47 patients (66.2%) had non-monocytic subtypes.

At baseline, patients demonstrated a substantial leukemic burden, with a median bone marrow blast percentage of 53.0% (IQR, 38.5–68.5). Circulating biomarker levels varied widely across individuals. Median baseline expression of *miR-181a-3p* was 5.17 copies/μL (IQR, 0.97–20.92), while miR-181b-5p levels were higher overall, with a median of 26.31 copies/μL (IQR, 7.65–134.95). Among DDR-related proteins, median baseline levels were 1.16 ng/mL (IQR, 0.78–1.90) for ATM, 44.12 pg/mL (IQR, 29.60–94.99) for *ATR*, and 29.21 pg/mL (IQR, 19.84–43.30) for *HMGB-1*. These findings reflect considerable heterogeneity in both microRNA and DDR-related biomarker expression at diagnosis (Table 1).

Table 1. Baseline Characteristics Relevant to Induction Response Analysis

Variable	Overall (n = 71)
Age at diagnosis, years, median (IQR)	39 (27.5–45.5)
FAB category, n (%)	
Monocytic AML (M4–M5)	24 (33.8%)
Non-monocytic AML (non M4–M5)	47 (66.2%)
Baseline marrow blast, %, median (IQR)	53.0 (38.5–68.5)
Circulating miR-181a-3p, copies/µL, median (IQR)	5.17 (0.97–20.92)
Circulating miR-181b-5p, copies/µL, median (IQR)	26.31 (7.65–134.95)
ATM, ng/mL, median (IQR)	1.16 (0.78–1.90)
ATR, pg/mL, median (IQR)*	44.12 (29.60–94.99)
HMGB-1, pg/mL, median (IQR)	29.21 (19.84–43.30)

Association between circulating microRNAs and induction blast clearance

We first examined the relationship between circulating microRNA levels and post-induction bone marrow blast percentage. In continuous analyses, baseline *miR-181a-3p* showed a weak positive correlation with post-induction blast percentage (r = 0.197, p = 0.099), indicating a trend toward lower residual blast burden among patients with lower *miR-181a-3p* expression, although this association did not reach statistical significance. In contrast, miR-181b-5p showed no meaningful correlation with post-induction blast percentage (r = −0.041, p = 0.733).

When stratified according to predefined expression categories, a more pronounced association emerged within specific AML subtypes. Among patients with monocytic AML (FAB M4–M5), low baseline *miR-181a-3p* expression was associated with a significantly higher likelihood of achieving induction blast clearance (RR = 2.33, p = 0.015). However, this association was not observed in non-monocytic AML subtypes, suggesting a lineage-dependent predictive effect (Table 2 and Table 3).

Association between DNA damage response biomarkers and induction blast clearance

We next evaluated DDR-related proteins in relation to induction response. In continuous analyses, *ATR* levels showed a modest inverse correlation with post-induction blast percentage (r = −0.181, p = 0.148), while ATM showed no significant association (r = −0.029, p = 0.807). *HMGB-1* demonstrated a trend toward inverse correlation with residual blast burden (r = −0.227, p = 0.057), suggesting a potential relationship with treatment sensitivity.

When analyzed categorically, higher *ATR* levels were associated with a significantly greater likelihood of induction blast clearance (OR ≈ 3.76, p = 0.038). Similarly, elevated *HMGB-1* expression was associated with improved induction response (OR ≈ 2.47, p = 0.033). In contrast, ATM levels did not demonstrate a significant association with induction blast clearance (Table 2).

Table 2. Association of Baseline Molecular Biomarkers with Induction Blast Clearance

A. Continuous biomarker analysis

Biomarker	Effect size (r)	p-value
miR-181a-3p	0.197	0.099
miR-181b-5p	−0.041	0.733
ATM	−0.029	0.807
ATR	−0.181	0.148
HMGB-1	−0.227	0.057

B. Categorical biomarker analysis (predefined cut-off values)

Biomarker	Comparison	RR (95% CI)	p-value
miR-181a-3p	Low vs high (FAB M4–M5)	2.33 (1.18 – 4.63)	0.015
ATR	High vs low	1.53 (0.99–2.38)	0.047
HMGB-1	High vs low	1.61 (1.04–2.50)	0.031

Relationship between circulating miR-181a-3p and baseline leukemic burden

Given the potential clinical utility of circulating biomarkers, we further evaluated whether circulating *miR-181a-3p* levels reflected baseline leukemic burden. Circulating *miR-181a-3p* expression demonstrated a significant correlation with baseline bone marrow blast percentage, suggesting that peripheral *miR-181a-3p* levels may serve as a surrogate indicator of disease burden at diagnosis. This finding supports the potential role of circulating *miR-181a-3p* as a minimally invasive biomarker.

Exploratory analysis of miR-181b-5p and HMGB-1

We also explored the potential relationship between miR-181b-5p and *HMGB-1* expression. No significant correlation was observed between circulating miR-181b-5p and *HMGB-1* levels (r = −0.068, p = 0.576). These findings suggest that the observed association between *HMGB-1* and induction response is unlikely to be directly mediated by miR-181b-5p in this cohort (Table 4).

Discussion

In this study, we evaluated the relationship between circulating miR-181 family members and key DNA

Table 3. FAB-Stratified Association between Baseline *miR-181a-3p* and Induction Response Outcome: Induction blast clearance (post-induction marrow blast <5%)

FAB subgroup	Induction response in low miR-181a-3p	Induction response in high miR-181a-3p	RR (95% CI)	p-value
M4–M5 (monocytic AML)	Higher	Lower	2.333 (1.177–4.627)	0.015
Non–M4–M5	Similar	Similar	1.108 (0.680–1.815)	0.62

Table 4. Exploratory Analysis of *HMGB-1* as an Additional Biomarker of Induction Response Outcome: Induction blast clearance (post-induction marrow blast <5%)

Analysis	Effect size	p-value
HMGB-1 (high vs low) vs induction response	OR ≈ 2.47	0.033
HMGB-1 vs post-induction blast (%)	r = −0.227	0.057
miR-181b-5p vs *HMGB-1*	r = −0.068	0.576

damage response (DDR)–related proteins in relation to induction blast clearance in adult AML. Our findings demonstrate that circulating *miR-181a-3p*, *ATR*, and *HMGB-1* provide clinically relevant information regarding induction response, although their predictive value appears to be context-dependent. In particular, low circulating *miR-181a-3p* expression was associated with improved induction blast clearance in monocytic AML, while higher *ATR* and *HMGB-1* levels were independently associated with treatment response. In contrast, miR-181b-5p and ATM did not demonstrate significant predictive associations in this cohort.

One of the most notable findings of this study is the lineage-dependent predictive value of *miR-181a-3p*. The association between low *miR-181a-3p* expression and improved induction response was observed specifically in monocytic AML (FAB M4–M5), but not in other subtypes. This observation is consistent with previous studies demonstrating biological heterogeneity across AML subtypes and differential treatment responses [1, 3, 5]. MicroRNAs have been shown to regulate hematopoietic differentiation and leukemia biology, and miR-181 family members have been implicated in AML pathogenesis and treatment sensitivity [15-20].

In addition to its predictive association with induction response, circulating *miR-181a-3p* was also correlated with baseline bone marrow blast burden. This finding suggests that circulating *miR-181a-3p* may reflect underlying disease burden and supports its potential role as a minimally invasive biomarker. Circulating microRNAs have been increasingly recognized as stable and clinically accessible indicators of disease activity, and our findings add to growing evidence supporting their translational relevance in AML. The ability to assess disease burden through peripheral blood biomarkers could have practical clinical implications, particularly in situations where bone marrow sampling is limited or cannot be performed frequently [21-23].

Our results also highlight the importance of DDR-related proteins, particularly *ATR* and *HMGB-1*, in determining induction response. *ATR* plays a central role in coordinating cellular responses to replication stress and DNA damage, which are key mechanisms through which cytotoxic chemotherapy exerts its effects. Higher baseline *ATR* levels may reflect a cellular state that is more capable of appropriately sensing and responding to DNA damage, thereby facilitating effective apoptotic signaling following chemotherapy exposure. Similarly, *HMGB-1* has been implicated in modulating chromatin structure, DNA repair, and chemotherapy-induced cell death. The association between higher *HMGB-1* levels and improved induction response observed in this study suggests that *HMGB-1* may contribute to treatment sensitivity through mechanisms related to DNA damage signaling or apoptotic regulation [6, 7].

In contrast, ATM did not demonstrate a significant association with induction blast clearance in our cohort. Although ATM is a well-established DDR regulator, its functional role may differ from that of *ATR* in the context of replication stress induced by chemotherapy. *ATR* is more directly involved in responding to replication-associated DNA damage, whereas ATM primarily responds to double-strand breaks. These differences in functional specialization may partly explain why *ATR*, but not ATM, demonstrated predictive relevance in this setting [8, 9].

We also explored the potential interaction between miR-181b-5p and *HMGB-1*, given prior evidence suggesting possible regulatory relationships between microRNAs and DDR-related proteins. However, no significant correlation was observed between miR-181b-5p and *HMGB-1* expression in this cohort. This suggests that the observed association between *HMGB-1* and induction response is unlikely to be mediated through miR-181b-5p alone and may instead reflect independent biological mechanisms.

Taken together, our findings underscore the importance of considering both microRNA and DDR-related biomarkers in understanding variability in treatment response. Rather than functioning as isolated predictors, these biomarkers likely reflect interconnected biological processes that influence leukemic cell sensitivity to chemotherapy-induced DNA damage. The lineage-dependent effect of *miR-181a-3p* further highlights the need to interpret biomarker findings within the appropriate biological and clinical context.

Several limitations should be acknowledged. First, this study was conducted as a secondary analysis of a single cohort, and the sample size, particularly within specific FAB subgroups, was relatively modest. Second, although circulating biomarker levels were measured prior to treatment initiation, functional studies were not performed to directly elucidate the mechanistic relationship between miR-181 expression and DDR activity. Third, while blast clearance represents an important early indicator of treatment response, longer-term outcomes such as survival were not evaluated in this analysis. These limitations underscore the need for further validation in larger and independent cohorts.

Despite these limitations, this study provides novel translational insights into the integrated role of circulating microRNAs and DDR-related proteins in AML. Our findings suggest that circulating *miR-181a-3p*, *ATR*, and *HMGB-1* may serve as clinically relevant biomarkers

for predicting induction response, particularly when interpreted in the context of AML subtype. Future studies incorporating larger patient populations and mechanistic investigations will be important to further clarify the biological pathways underlying these associations and to determine their potential clinical utility [13, 14, 21].

This study has several limitations. First, it was conducted in a single-center cohort, which may limit generalizability to broader AML populations. Second, subgroup analyses involved relatively small numbers, particularly within specific FAB subtypes, and therefore require validation in larger independent cohorts.

In addition, biomarker measurements were performed only at baseline prior to induction chemotherapy. While this allows assessment of pretreatment predictive value, longitudinal biomarker evaluation during and after treatment was not performed. Serial measurements may provide further insight into treatment-related molecular dynamics and their clinical significance.

Finally, this study focused on early treatment response as reflected by induction blast clearance, and longer-term outcomes such as survival were not evaluated. Future studies incorporating longitudinal follow-up may further clarify the prognostic relevance of these biomarkers.

In conclusion, this study demonstrates that circulating *miR-181a-3p*, *ATR*, and *HMGB-1* are associated with induction blast clearance in adult AML, although their predictive value appears to depend on biological context. Low circulating *miR-181a-3p* expression was associated with improved induction response specifically in monocytic AML, highlighting the importance of lineage-specific biomarker interpretation. In addition, higher *ATR* and *HMGB-1* levels were independently associated with blast clearance, supporting the relevance of DNA damage response–related pathways in determining treatment sensitivity.

Our findings also suggest that circulating *miR-181a-3p* may reflect baseline leukemic burden, underscoring its potential role as a minimally invasive biomarker. The integration of circulating microRNA and DDR-related protein profiling may therefore provide clinically meaningful insights into early treatment response.

Further validation in larger and independent cohorts will be necessary to confirm these findings and to clarify the potential role of these biomarkers in clinical risk stratification. Nonetheless, this study highlights the translational relevance of circulating molecular biomarkers in improving our understanding of treatment response variability in AML.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

The authors would like to acknowledge the clinical staff and laboratory personnel of the Hematology and Medical Oncology Division at Dharmais National Cancer Center for their assistance in patient management and sample processing. We also thank the Clinical Pathology and Molecular Biology teams for their technical support in biomarker analysis. The authors are grateful to all patients who participated in this study.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest Statement

The authors declare no conflict of interest.

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