MicroRNA Analysis as Accurate Biomarkers for Diagnosis and Treatment of Cancer

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Abstract: MicroRNAs (miRNAs) are naturally occurring non-coding RNA (~22 nucleotides) molecules that function as post-transcriptional regulators of gene expression. Their dysregulation is implicated in carcinogenesis and thus they are potential non-invasive biomarkers. We evaluated the diagnostic utility of a 3-miRNA panel (miR-21, miR-155 and let-7) in distinguishing cancer patients from healthy controls in this study. In this case-control study, plasma samples were obtained from 100 newly diagnosed cancer patients (mixed malignancies) and 75 healthy controls in Baghdad, Iraq. The extraction of total RNA was performed using the Qiagen miRNeasy Serum/Plasma Kit Based on the leaflet included with the kit.

Expression of miR-21, miR-155 and let-7 was measured by reverse transcription and quantitative PCR (TaqMan assays) and normalized to U6 small nuclear RNA.

Examination of receiver operating characteristic (ROC) curves with leave-one-out cross-validation was employed to evaluate the diagnostic effectiveness. Compared to controls, cancer patients had considerably increased levels of miR-21 and miR-155($P < 0.001$ for both), while let-7 was significantly lower ($P < 0.01$). Differences in miRNA expression levels were observed across tumor stages and treatment response groups.

ROC analysis demonstrated AUC values of 0.89 (miR-21), 0.79 (miR-155), and 0.68 (let-7). A combination panel was able to an AUC of 0.88 (95% CI: 0.82–0.94), with 85% diagnostic sensitivity and 79% diagnostic specificity. Cross-validation confirmed robust performance (AUC = 0.86). The findings of this exploratory study suggest that miR-21, miR-155, and let-7 may have potential as circulating biomarkers for cancer detection in this heterogeneous cohort. However, further multicentre validation studies with cancer-specific subgroup analyses are needed to establish their diagnostic utility.

Keywords: MicroRNAs (miRNAs), Biomarkers, Cancer diagnosis, miR-21, miR-155, Gene expression analysis.

1. INTRODUCTION

Cancer claims millions of lives every year and represents a massive global health threat. Early detection and precise diagnosis are important factors for increasing treatment effectiveness and patient survival. Conventional diagnostic methods, such as imaging and histopathology, may have limited sensitivity and specificity, which can hinder the early detection of cancer.

There have been several promising reports of molecular markers in the development of bioassays for cancer diagnosis [1].

MicroRNAs (miRNAs), which are endogenous ~22-nucleotide noncoding RNAs, are crucial for the posttranscriptional regulation of gene expression. It regulates several biological processes, including cell division, cell proliferation and death [2,3]. The dysregulation of certain miRNAs has been linked to carcinogenesis, progression and metastasis [4].

Consequently, miRNAs molecules have come to be regarded as promising biomarkers for cancer detection and the prediction of clinical outcomes.[5]. miRNAs have been investigated as potential biomarkers in various cancers [6, 7].

MicroRNA molecules that promote tumorigenesis—such as miR-21 and miR-155—exhibit elevated levels in many types of cancer and contribute to the growth and spread of tumors [8-10]. In contrast, tumor-suppressive miRNAs, such as let-7, are often downregulated in cancer [11, 12].

These findings suggest that miRNAs may serve as potential biomarkers for cancer classification and treatment response [13].

Although accumulating evidence implicates miRNAs in oncogenesis, their therapeutic application in cancer remains under investigation [14, 15].

Validation of standard methods for the detection and quantification of miRNAs in cell subpopulations is needed [16]. Furthermore, understanding the regulatory roles of miRNA expression and biogenesis is likely also critical for the development of therapeutic approaches involving miRNA delivery or targeting

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[17,18]. However, evidence on circulating miRNA biomarkers in Iraqi cancer patients remains limited.

Therefore, research focuses on exploring the diagnostic potential of circulating miR-21, miR-155, and let-7 in a heterogeneous cohort of patients with eight different malignancies in Baghdad, Iraq. Given the diversity of malignancies and the small number of patients in some cancer subgroups, this study was designed as an exploratory investigation of the overall expression patterns rather than a definitive evaluation of cancer-specific diagnostic performance. The findings may provide a basis for further studies involving larger, cancer-specific cohorts.

2. MATERIALS AND METHODS

2.1. Study Population and Setting

This case-control study was conducted in Baghdad, Iraq and enrolled 100 newly diagnosed cancer patients and 75 healthy controls (total N = 175). To ensure representation across cancer types and stages, participants were recruited from oncology centers and hospitals in Baghdad. Inclusion criteria for cancer patients were as follows: (i) newly diagnosed with histologically confirmed malignancy, (ii) no previous chemotherapy or radiotherapy, and (iii) age ≥ 18 years. The types of cancers were breast (n=28), colorectal (n=18), lung (n=15), gastric (n=12), hepatocellular (n=10), prostate (n=8), ovarian (n=5) and pancreatic (n=4) cancers (Table **1**). Healthy controls were defined as those without a personal history of malignancy, chronic disease or known predisposition to cancer. All participants underwent extensive assessment for eligibility and identification of potential confounders in terms of clinical status.

Baseline blood samples were collected at the time of diagnosis, before the initiation of any treatment. Therapy response was assessed at 3–6 months following treatment initiation using RECIST criteria (version 1.1). The patients were classified into two groups: those who achieved a complete or partial therapeutic response to treatment, and those who showed no response—with their condition either remaining stable or continuing to progress. Regarding treatment modalities, approximately 75 patients received chemotherapy alone, while the remaining 25 patients received combined chemotherapy and radiotherapy.

2.2. Sample Collection and Processing

Samples of blood were taken from all the participants following sterile venipuncture to avoid any culture contamination. The samples were subsequently centrifuged in EDTA-lined tubes to prevent clotting and degradation of nucleic acids. Whole blood was centrifuged at 3000 rpm for 10 min to obtain plasma to eliminate cellular contamination and obtain a clean plasma fraction enriched with circulating miRNAs, which is necessary [19,20]. The separated plasma was aliquoted into sterile tubes and stored at −80°C until RNA extraction to preserve RNA integrity and prevent degradation.

RNA, including miRNA, was extracted using the Qiagen miRNeasy Serum/Plasma Kit according to the manufacturer's instructions.

RNA concentration and purity were assessed using a NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, USA) by measuring absorbance at 260 and 280 nm (A260/A280).

2.3. miRNA Expression Analysis

Complementary DNA (cDNA) was synthesized from the extracted RNA using the conventional TaqMan MicroRNA reverse transcription protocol. The reverse transcription reaction was performed under the following thermal conditions: 16°C for 30 min, 42°C for 30 min, and 85°C for 5 min, followed by a hold at 4°C [21].

Real-time quantitative polymerase chain reaction (qRT-PCR) was subsequently conducted using TaqMan miRNA assays specific for miR-21, miR-155, and let-7 on an Applied Biosystems 7500 Fast Real-Time PCR System.

Each assay was performed in triplicate to ensure reproducibility, and a no-template control (NTC) was included in each run to monitor potential contamination [22]. The amplification protocol consisted of an initial denaturation step at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15 sec and annealing/extension at 60°C for 1 min.

The miRNA expression levels were normalized to U6 snRNA, which was used as an internal reference control to account for variations in RNA input and reverse transcription efficiency.

The $^{2}\Delta\Delta Ct$ method was used to calculate the relative expression levels of miRNAs between cancer patients and healthy controls [23].

2.4. Ethical Considerations

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical

approval was obtained from the Scientific Research Ethics Committee at the College of Education for Pure Science (Ibn Al-Haitham), University of Baghdad, Baghdad, Iraq - the institutional review body responsible for overseeing research involving human participants.

2.5. Statistical Analysis

Data were analyzed using SPSS v26.0 (IBM Corp.). The Shapiro-Wilk test assessed normality. Continuous variables were expressed as mean ± standard deviation or median (interquartile range). Group comparisons utilized the Mann-Whitney U test (non-parametric data) or independent t-test (parametric data). Categorical variables were compared using Fisher's exact or chi-square tests. ROC curve analysis determined diagnostic accuracy (AUC), with 95% confidence intervals calculated using the DeLong method. Optimal cutoffs were determined by the Youden index (maximum [sensitivity + specificity−1]). Group comparisons of miRNA expression levels across disease-stage and treatment-response categories were performed using the appropriate statistical tests. P-values < 0.05 were considered statistically significant.

P-values < 0.05 were considered significant. Post-hoc power analysis was performed using G*Power software [24,25].

3. RESULTS

3.1. Patient Characteristics

Demographic and clinical characteristics are summarized in Table **1**. No significant differences were observed between groups regarding age, gender distribution, or smoking history. However, family history of cancer was significantly higher in the patient group (46% vs. 13.3%, P < 0.001).

3.2. Differential miRNA Expression

Plasma levels of miR-21 and miR-155 were significantly elevated in cancer patients compared to controls (P < 0.001 for both), while let-7 expression was significantly reduced (P = 0.002) (Figure **1**). Individual values showed overlap between groups, suggesting that a panel approach may improve diagnostic discrimination.

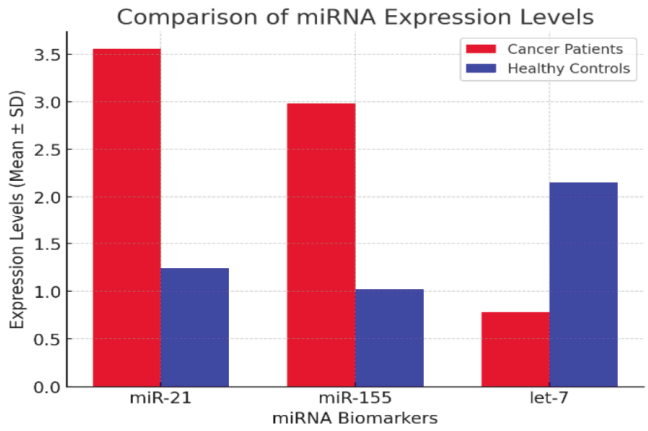

Figure 1: Differential expression of miRNAs in cancer patients and healthy controls.

3.3. Diagnostic Performance

ROC analysis was performed to evaluate the diagnostic performance of the three miRNAs. Individual miRNA performance was as follows: miR-21 achieved an AUC of 0.89 (95% CI: 0.83–0.94), indicating excellent discriminatory ability. miR-155 demonstrated moderate-to-good performance with an AUC of 0.79 (95% CI: 0.72–0.86). let-7 showed modest discriminatory ability with an AUC of 0.68 (95% CI: 0.60–0.76).

A combined logistic regression model incorporating all three miRNAs achieved an AUC of 0.88 (95% CI: 0.82–0.94), with 85% sensitivity and 79% specificity at the optimal cutoff determined by the Youden index. To address potential overfitting, leave-one-out cross-validation (LOOCV) was performed, yielding a cross-validated AUC of 0.86 (95% CI: 0.80–0.92). Calibration of the logistic regression model was assessed using the Hosmer-Lemeshow goodness-of-fit test (χ^2 = 8.24, df = 8, P = 0.41), indicating good model calibration.

Table 1: Demographic Characteristics of the Participants Studied

Characteristic	Cancer Patients (n=100)	Healthy Controls (n=75)
Age (years)	45.6 ± 8.9	42.3 ± 7.2
Gender (Male/Female)	58/42	40/35
Smoking History	32 (32%)	20 (26.7%)
Family History of Cancer	46 (46%)	10 (13.3%)

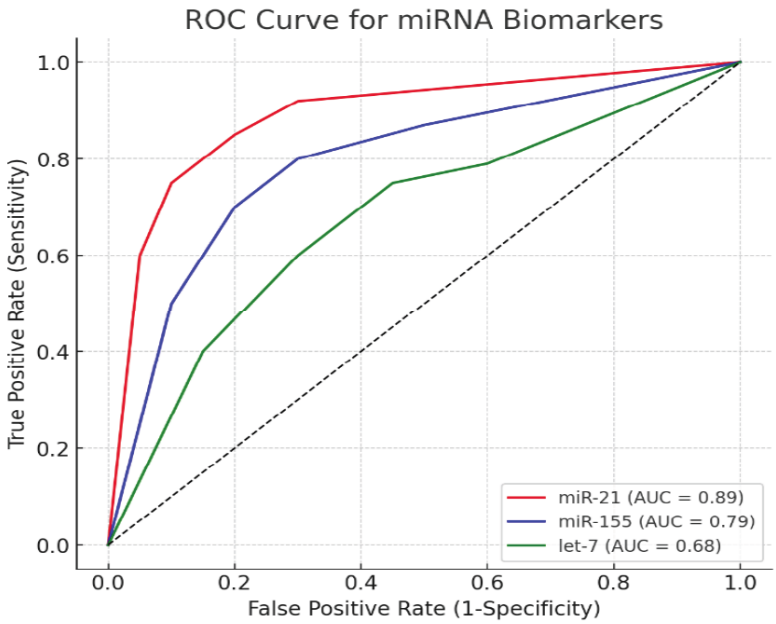

Figure 2: ROC curve analysis of miRNA biomarkers for cancer diagnosis.

Table 2: Comparison of miRNA Expression Levels According to Disease Stage and Treatment Response

Variable	miR-21 (Mean ± SD)	P Value	miR-155 (Mean ± SD)	P Value	let-7 (Mean ± SD)	P Value
Early-stage cancer	2.85 ± 0.94	<0.001*	2.30 ± 0.73	0.004*	1.12 ± 0.42	0.002*
Advanced-stage cancer	4.10 ± 1.05	<0.001*	3.45 ± 1.01	0.002*	0.65 ± 0.30	0.003*
Responding to therapy	2.95 ± 0.91	0.01*	2.20 ± 0.80	0.03*	1.05 ± 0.50	0.02*
Nonresponding to therapy	4.20 ± 1.20	0.001*	3.60 ± 0.95	0.002*	0.50 ± 0.28	0.004*

(Statistically significant at P ≤ 0.05).

3.4. Clinical Correlations

miRNA expression levels were compared across disease-stage and treatment-response groups (Table **2**).

Advanced-stage (III/IV) patients exhibited higher miR-21 and miR-155 levels and lower let-7 levels compared to early-stage (I/II) patients ($P < 0.01$). Non-responding patients showed significantly higher miR-21 and miR-155 expression than responders ($P < 0.05$), suggesting potential utility for treatment monitoring.

4. DISCUSSION

In this exploratory study, miR-21 and miR-155 expression levels were higher, whereas let-7 expression was lower, in cancer patients than in healthy controls. These findings indicate differences in circulating miRNA expression but do not establish their clinical utility or therapeutic effects.[26,27]

The most striking finding is the 3.5-fold upregulation of miR-21 in cancer patients compared to controls (mean ~3.5 vs. ~1.2, $P < 0.001$). This marked elevation of miR-21 is consistent with previous reports describing its frequent upregulation in different cancer types. Although miR-21 has been reported to regulate several tumor-suppressor genes, including PTEN and PDCD4 [1], the expression of these target genes and the activity of related signaling pathways were not assessed in the present study. Therefore, the observed increase in miR-21 expression should be interpreted as an expression finding rather than direct evidence of pathway activation.

The observed upregulation of miR-155 is consistent with its reported involvement in cancer-related inflammatory and regulatory processes. However, the present study focused on miR-155 expression levels and did not investigate its molecular targets or related signaling pathways. Therefore, its potential biological and clinical significance should be interpreted cautiously and requires further investigation.

The observed downregulation of let-7 in cancer patients is consistent with previous reports describing

its tumor-suppressive role. In the present study, let-7 expression was significantly lower in patients than in healthy controls. However, its molecular targets and potential therapeutic implications were not experimentally investigated and should be addressed in future studies.

The AUC of 0.89 observed for miR-21 indicates promising diagnostic performance within the present study cohort. However, given the heterogeneous cancer population and the exploratory nature of this analysis, this finding should not be interpreted as evidence of equivalence to established clinical diagnostic assays. Independent validation in larger, cancer-specific cohorts is required.

Our findings align with and extend previous meta-analytic evidence. Peng *et al*. (2017) reported pooled sensitivity of 81% and specificity of 78% for miR-21 in colorectal cancer across 36 studies [28, 29]. The AUC of 0.79 observed for miR-155 indicates moderate diagnostic discrimination in the present study. However, its performance should be interpreted cautiously because of the heterogeneous cancer cohort [30].

The AUC of 0.68 observed for let 7 indicates limited discriminatory performance in the present study. This result should be interpreted cautiously, particularly given the heterogeneous cancer cohort, and requires further evaluation in larger, cancer-specific studies.

The differential ROC profiles suggest opportunities for biomarker combination. In the present study, the combined logistic regression model achieved an AUC of 0.88 (95% CI: 0.82–0.94), with 85% sensitivity and 79% specificity. This value was slightly lower than the AUC obtained for miR-21 alone (0.89), indicating that the combined panel did not demonstrate improved discrimination over the individual marker in this cohort.

Further studies may evaluate whether incorporating additional clinical variables improves the diagnostic performance of miRNA-based models.

However, several contextual factors warrant consideration. First, our case-control design comparing established cancer patients with healthy controls may overestimate real-world performance due to spectrum bias; screening scenarios involving indeterminate nodules or high-risk surveillance populations typically yield lower AUC values [31]. Second, the heterogeneous cancer types included in our cohort (Table **1**), with small subgroup sizes, represent an important limitation. Since miRNA expression may vary across tumor types, these findings should be considered exploratory rather than universally applicable. Larger cancer-specific studies are needed for validation [32].

The diagnostic performance of miR-21 observed in this study requires further evaluation in cancer-specific cohorts before comparison with established tumor biomarkers can be justified.[33,34]

Our ROC analysis benefits from rigorous methodological execution. The study used TaqMan miRNA assays, triplicate technical measurements, and U6 snRNA normalization for miRNA expression analysis.

However, limitations must be acknowledged. The cross-sectional design precludes assessment of temporal stability and dynamic changes in miRNA levels during treatment or follow-up. The single-center Baghdad cohort may limit generalizability to populations with different genetic backgrounds, environmental exposures, or healthcare access patterns. Additionally, the absence of benign disease controls precludes assessment of differential diagnosis performance, a critical requirement for biomarkers in symptomatic patient populations [35].

5. LIMITATIONS

The study faced several limitations, including a small sample size, the inclusion of various types of cancer, and a focus on only three types of miRNAs. Furthermore, the absence of a control group consisting of individuals with benign conditions—along with the potential impact of hemolysis on miRNA levels—may affect the accuracy and reliability of the findings.

6. CONCLUSION

This exploratory study investigated the diagnostic potential of miR-21, miR-155, and let-7 in a heterogeneous cohort of cancer patients.

The marked difference in their expression levels between patients with and without disease as well as the observed differences in expression across disease stages and treatment-response groups reinforce their potential utility as cancer biomarkers. Larger cohorts and multicenter validation studies are warranted to confirm their clinical potential for tumor diagnosis and treatment monitoring.

CONFLICT OF INTEREST DECLARATION

None.

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