

miR-140 and miR-196a as Potential Biomarkers in Breast Cancer Patients

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Abstract

Objective: *miR-140* and *miR-196a* were known to be correlated with cancer diagnosis and prognosis. The current study aimed at the analysis of *miR-140* and *miR-196a* expression patterns and their clinical significance for breast cancer (BC) patients. **Methods:** Differentially expressed *miR-140* and *miR-196a* were examined via quantitative PCR in 110 cases of BC and their adjacent non-tumor (ANT) tissues. **Results:** The results indicated that *miR-140* and *miR-196a*, respectively, notably decreased and increased expression in BC samples in comparison with ANT ($p < 0.001$). Reduced *miR-140* expression was also related to Lymph node metastasis (LNM, $P = 0.023$) and stage ($P = 0.009$). Additionally, Receiver Operating Characteristics (ROC) analysis illustrated that *miR-140* had a significant diagnostic accuracy for stage and LNM of BC patients. We also discovered a strong negative correlation between *miR-196a* expression with histological grade ($P = 0.038$), LNM ($P = 0.012$) and stage ($P = 0.001$). **Conclusion:** Overall, exploring the *miR-140* and *miR-196a* profiles not only can statistically different among BC and ANT samples, but it is also expected to become potential BC biomarkers.

Keywords: Biomarkers- *miR-140*- *miR-196a*- quantitative PCR- breast cancer

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Introduction

As the most predominant malignancies in females, breast cancer (BC) accounts for the number one cause of cancer mortality worldwide among women (Jafari-Gharabaghlu et al., 2018; Javidfar et al., 2018). The relationship between genes and environmental risk factors associated with the etiopathology of various tumors (Rudolph et al., 2016). Recently, many studies have been made aiming to identify the connection between genetic alterations of protein-coding genes and mechanisms of carcinogenesis (Chakravarthi et al., 2016). But latest studies have supported the potential role of noncoding RNAs in tumorigenesis, in which miRNAs recognized as new players in cancer pathobiology (Sheervalilou et al., 2016; Mohammadian et al., 2017a). microRNAs (miRNAs/miRs) are short (about 18–23 nucleotides), conserved, noncoding regulatory RNAs that negatively regulate gene expression based on targeting of the mRNA 3'-untranslated regions (3'-UTR) (Mohammadian et al., 2016b; Norouzi et al., 2019). Computational approaches report that miRNA-mediated the activity of about 30% of all human genomes, in which each miRNA on average potentially

interact with >100 of mRNA targets (Mohammadian et al., 2016a; Sheervalilou et al., 2020). The biological function of miRNAs as either tumor suppressors or oncogenes related to their target mRNA (Bertoli et al., 2015; Shahabi et al., 2019). Given that the particular miRNA signatures reported in many tumor types, so, logically, the alterations of miRNA profiles would be promising diagnostics and prognostic cancer biomarkers (Mohammadian et al., 2017b; Rupaimoole and Slack, 2017). The dysregulation of miRNA profiles may contribute to the malignant transformation such as cancer initiation, progression, and therapeutic resistance (O'Bryan et al., 2017). At the moment, numerous investigations have illustrated that *miR-140* and *miR-196a* expression frequently are altered in human cancers tissues, which proposes that they play key roles in tumorigenesis (Schimanski et al., 2009; Green et al., 2015).

Recent studies have demonstrated that *miR-140* expression mediated phenotypic alterations of tumor cells (Fang et al., 2017). As an example, *miR-140* expression significantly represses the growth and BC stem cell self-renewal potential (Li et al., 2013) and effectively prevents tumorigenicity of glioblastoma, osteosarcoma

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and non-small cell lung carcinoma (NSCLC) (Liu et al., 2016; Ji et al., 2018; Yang et al., 2018). Indeed, numerous published studies have displayed that the *miR-140* may serve as tumor suppressor miRNA and its replacement has been indicated as a novel therapeutic strategy among different cancer types (Fang et al., 2017; Li et al., 2018). *miR-196a* belongs to the homeotic genes (HOX) family which has different function in various types of cell lines and tissues (Chen et al., 2011). Several recent profiling studies of miRNAs reported that upregulated *miR-196a* expression was significantly linked to tumor progression (Sun et al., 2012; Jin et al., 2016). Besides, numerous studies illustrated that *miR-196a* has significant effects on the growth, differentiation, and metastasis of tumor cells based on the regulation of specific genes (Papaconstantinou et al., 2012; Jiang et al., 2018). These investigations permit us to simultaneously evaluate the *miR-196a* and *miR-140* expression profiles in BC tissues and their matched adjacent non-tumor (ANT) tissues, and to demonstrate their clinicopathological significance. Our results support the interpretation that upregulation of tumor suppressor *miR-140* and downregulation of oncogene *miR-196a* may be an intriguing possibility for future BC treatment.

Materials and Methods

Patient and clinical specimens

All specimens (BC and ANT tissues) were acquired from 110 patients admitted in Noor Nejat Hospital (Tabriz, Iran) and then transferred to -80°C before further analysis. Current research underwent ethical review and was applied through the ethics committee of Tabriz University of Medical Sciences.

Real-time qRT-PCR for miRNAs

The relative levels of *miR-140* and *miR-196a* in both BC and ANT samples were analyzed by Real-time quantitative PCR (qPCR) method (Jeddi et al., 2019). The tissues were homogenized using a tissue homogenizer and total RNA was isolated from the homogenized tissue following the Exiqon's miRCURYTM RNA Isolation Kit (Exiqon, Denmark) and Phenol/Chloroform methods. Total RNA concentrations were investigated by using

NanoDrop 2000 (Thermo Scientific, Waltham, MA). Also, the integrity of total RNA was investigated by agarose gel electrophoresis on 1.5% agarose gel containing GelRedTM (Biotium). PCR reactions for quantifying *miR-140* and *miR-196a* were performed in triplicate by LNA Universal RT miRNA PCR kit (Exiqon, Denmark). qPCR protocol was: 95°C pre-denaturation step for 10 min, 95°C 40 cycles of denaturation step for 15 seconds, annealing, and synthesis steps at 60°C for 1 min. The relative expression levels of *miR-140* and *miR-196a* were normalized by U6 and the results were calculated based on the $2^{-\Delta\Delta\text{Ct}}$ method (Livak and Schmittgen, 2001). The sequence and details of PCR primer for mature *miR-140*, *miR-196a*, and U6 are shown in Table 1.

Data analysis

Mann-Whitney U test was applied for the evaluation of statistical differences in tissue miRNAs expression between BC and ANT groups. Chi-square test (χ^2) was to measure the relationship among both *miR-140* and *miR-196a* expression levels and clinical parameters. Receiver operating characteristic curves (ROC curves) were considered for investigation mentioned miRNAs as two biomarkers. Statistical analyses were investigated by the SPSS[®] software (SPSS, Version 16.0; SPSS Inc, Chicago, IL) or GraphPad Prism Software (version 6, GraphPad software, Inc., San Diego, CA, USA).

Results

Patient characteristics

From April 2016 to July 2018, 110 female BC patients were recruited for the present study. The clinicopathological information of all participants is indicated in Table 2. The mean age was 46 years and the range of 27–65 years.

Differential *miR-140* and *miR-196a* expression levels in BC and ANT tissues

Using the RT-qPCR method, the relative level of *miR-140* and *miR-196a* expression was assessed in BC and ANT tissues. Our findings illustrated that the relative level of *miR-140* in BC tissues significantly was significantly downregulated than that of the ANT tissues (BC vs. ANT:

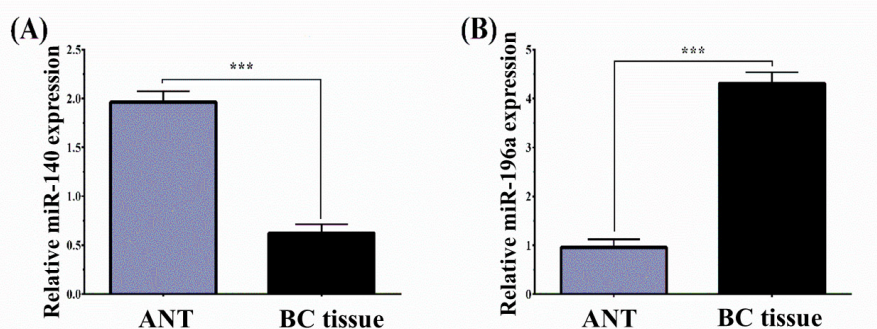


Figure 1. MiR-140 and miR-196a Expression Levels of 110 BC and ANT Tissues Normalized to U6 Analyzed by Using qRT-PCR. The results represent that (A) *miR-140* was downregulated in BC compared to that in ANT group (BC vs. ANT: 0.623 ± 1.07 vs 1.74 ± 1.393 , $P < 0.001$) and (B) *miR-196a* was upregulated in BC compared to that in ANT group (BC vs ANT: 4.31 ± 2.55 vs 2.77 ± 2.45 , $***P < 0.001$). BC, Breast cancer; ANT, Adjacent non-tumor; qRT-PCR, Real-Time Quantitative Reverse Transcription PCR.

0.623 ± 1.07 vs 1.74 ± 1.393, P < 0.001) (Figure 1A). However, the expression of miR-196a was higher in BC patients than that in ANT (BC vs ANT: 4.31 ± 2.55 vs 2.77 ± 2.45, P < 0.001) (Figure 1B). To investigate the correlation of these miRNAs with clinicopathologic features, we classified BC patients into *miR-140*-low/high and *miR-196a*-low/high expression groups according to the median value of *miR-140* and *miR-196a* expression.

Correlation between downregulated miR-140 expression and clinical characteristics

Correlation of *miR-140* relative expression level with clinical criteria is presented in Table 2. Low *miR-140* expression was positively associated with Lymph node metastasis (LNM, P = 0.023) and stage (P = 0.009) in BC patients. But, correlations between *miR-140* expression and age, histological grade, estrogen receptor (ER) expression, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) were not statistically significant. Additionally, the ROC curve was

plotted to investigate the miRNA diagnostic power cancer detection. According to the ROC curve, *miR-140* had the ability only to predict stage and LNM occurrence in BC patients (Table 3). At an appropriate cut-off value, *miR-140* superior performance in predicting the LNM occurrence (AUC=0.765, P=0.001) and stage (AUC=0.847, P<0.001). The specificity and sensitivity values, respectively, were 77% and %, 68, and 95%, and 87% (Figure 2A, B).

Correlation between upregulated miR-196a expression and clinical characteristics

As showing in Table 2, high *miR-196a* expression was closely linked with histological grade (P = 0.038), LNM (P = 0.012) and stage (P = 0.001) in BC patients. However, no remarkable associations between the *miR-196a* expression and age, ER/PR, and Her2 status were evident. Based on the ROC findings, *miR-196a* was an important predictor of histological grade, LNM, and stage in BC patients (Table 3). At an appropriate cut-off value, *miR-196a* superior performance in predicting the histological grade (AUC=0.718, P=0.017), LNM (AUC=0.758, P=0.010) and stage (AUC=0.820, P<0.001). The specificity and sensitivity values, respectively, were 72% and 65%, 74% and 70%, and 88% and 81% (Figures 2C, D, E).

Table 1. Primer Sequences

| Objective genes | Primer sequence |
|-----------------|--|
| <i>miR-140</i> | Forward: 5'-GAGTGTCAGTGGTT TTACCCT-3' Reverse: 5'-GCAGGGTCCGAGGTATTC-3' |
| <i>miR-196a</i> | Forward: 5'-CGTCAGAAGGAATGATGCACAG-3' Reverse: 5'-ACCTGCGTAGGTAGTTTCATGT-3' |
| <i>U6</i> | Forward: 5'-CTCGCTTCGGCAGCACATATACT-3' Reverse: 5'-ACGCTTCACGAATTTGCGTGTGC-3' |

Discussion

Tumor markers are highly important for early detection, outcome prediction, and selection of effective treatment strategies (Mehta et al., 2010). As involved

Table 2. Relationship between *miR-140* and *miR-196a* Expression with Clinicopathological Parameters of BC Patients. (n = 110). BC, Breast cancer

| Clinical pathological criteria | | miR-140 Expression | | | miR-196a Expression | | | |
|--------------------------------|----------|--------------------|-------------|---------|---------------------|-------------|---------|-------|
| | | Low 53 (%) | High 57 (%) | P-value | Low 49 (%) | High 61 (%) | P-value | |
| Age | <50 | 75 | 32 | 43 | NS | 29 | 46 | NS |
| | >50 | 35 | 21 | 14 | | 20 | 15 | |
| histological grade | I | 21 | 9 | 12 | NS | 8 | 13 | 0.038 |
| | II | 79 | 38 | 41 | | 35 | 44 | |
| | III | 10 | 6 | 4 | | 6 | 4 | |
| Progesterone receptor | negative | 34 | 20 | 14 | NS | 18 | 16 | NS |
| | positive | 76 | 33 | 43 | | 31 | 45 | |
| Estrogen receptors | negative | 27 | 12 | 15 | NS | 9 | 18 | NS |
| | positive | 83 | 41 | 42 | | 40 | 43 | |
| HER2 | negative | 99 | 50 | 49 | NS | 45 | 54 | NS |
| | positive | 11 | 3 | 8 | | 4 | 7 | |
| lymph node metastasis | negative | 46 | 21 | 25 | 0.023 | 18 | 28 | 0.012 |
| | positive | 64 | 32 | 32 | | 31 | 33 | |
| Stage | I | 16 | 7 | 9 | 0.009 | 7 | 9 | 0.001 |
| | II | 72 | 37 | 35 | | 35 | 37 | |
| | III | 18 | 8 | 10 | | 7 | 11 | |
| | IV | 4 | 1 | 3 | | 0 | 4 | |
| Tumor size | <20mm | 39 | 16 | 23 | NS | 14 | 25 | NS |
| | 20-49mm | 61 | 32 | 29 | | 31 | 30 | |
| | >50mm | 10 | 5 | 5 | | 4 | 6 | |

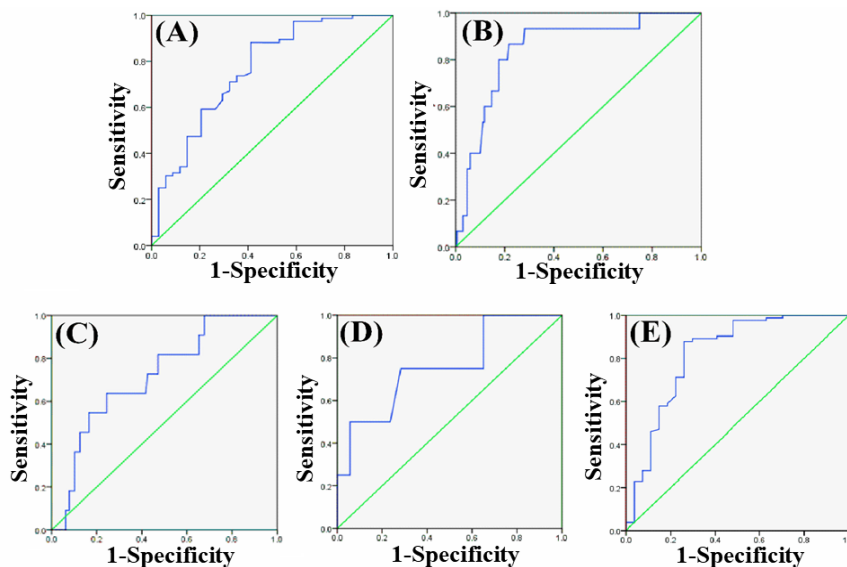


Figure 2. ROC Curve Analysis of the Expression *miR-140* and *miR-196a* to Detect BC. Expression of *miR-140* was an applicable biomarker for prediction of occurrence of LNM (A), and stage (B). Moreover, ROC curve analysis revealed the potential of the *miR-196a* level to predict histological grade (C), the occurrence of LNM (D) and stage (E), and in BC. BC, Breast cancer; LNM, Lymph node metastasis; ROC, Receiver operating characteristics.

Table 3. AUC of ROC Curve Corresponding to the Diagnostic *miR-140* and *miR-196a* Values in BC. AUC, Area under the curve; ROC, Receiver operating characteristics; BC, Breast cancer.

| Parameter | <i>miR-140</i> Expression | | | | <i>miR-196a</i> Expression | | | |
|-----------------------|---------------------------|----------------|-------------|---------|----------------------------|----------------|-------------|---------|
| | AUC | Standard Error | 95 % C.I | P-value | AUC | Standard Error | 95 % C.I | P-value |
| Histological grade | 0.635 | 0.09 | 0.458–0.812 | 0.143 | 0.718 | 0.072 | 0.576–0.859 | 0.017 |
| lymph node metastasis | 0.765 | 0.051 | 0.665–0.866 | 0.001 | 0.758 | 0.061 | 0.671–0.845 | 0.01 |
| Stage | 0.847 | 0.049 | 0.751–0.942 | <0.001 | 0.82 | 0.054 | 0.714–0.927 | <0.001 |

in different cancer biological processes, miRNA studies have become imperative for the detection of miRNA profiles-based prognosis, diagnosis, and theranostics biomarkers (Sheervalilou et al., 2020; Wang et al., 2018). Altered expression of miRNAs provides crucial information about molecular signatures of disease status without the performance of biopsy (Lu et al., 2005; Ayub et al., 2015). The objective of our research was to clarify the prognostic significance of *miR-140* and *miR-196a* in 110 Iranian women with BC and to describe their possible relationship with clinicopathological criteria. Our data exhibited that the *miR-140* and *miR-196a* levels in BC samples were notably lower and higher than those in corresponding ANT tissues. The reduced level of miR-140 was significantly relevant to LNM and stage. Besides, ROC results illustrated that the expression of miR-140 was an applicable molecular biomarker for the prediction of LNM occurrence and stage in BC patients. Based on prior studies results, *miR-140* considered being one of the importantly reduced miRNAs in human cancers such as BC. For instance, Zhou et al., (2019) found that high levels of *miR-140* expression could significantly suppress BC cell growth and migration. In another study, Lu et al., (2017) also found similar results that the level of miR-140 was negatively related to the patient's clinical-grade and tumor metastasis. Furthermore, both gain and loss of function studies by Yuan et al., (2013) revealed that *miR-140* represses the NSCLC metastasis.

Also, the high expression of *miR-145* significantly reduced lung cancer growth in nude mice models. Other studies also reported that *miR-140* was downregulated in cell lines and human tumor tissues (Liu et al., 2016; Yan et al., 2017). According to our study, an inverse association also found between the *miR-196a* expression profile and histological grade, LNM, and stage. Besides, ROC curve analysis indicated the potential of *miR-196a* level to predict histological grade, LNM occurrence, and stage in the BC. Based on the tumor tissue and the cell type, *miR-196a* has oncogenic or tumor-suppressor functions. Few reports have revealed the *miR-196* family function as a tumor suppressor through negatively regulating the expression of oncogenes. For instance, Cao et al., (2018) indicated that *miR-196a* level was considerably lower in clinical osteosarcoma tissues than normal controls, and the osteosarcoma cell progression and migration abilities were inhibited by *miR-196* overexpression. Likewise, in melanoma, *miR-196a* inhibits the processes of proliferation and metastasis through the negative regulation of transcription factor HOXC8 (Mueller and Bosserhoff, 2011). However, several other studies (e.g. Liu et al. (Liu et al., 2012); Hou et al., (2014); Yang et al., (2016); Milevskiy et al., (2019) have examined and reported the significant roles of *miR-196a* in promoting proliferation, migration and invasion of NSCLC, cervical, epithelial ovarian and ER+ BC cell lines and malignant tissues in comparison with healthy tissues.

Our findings recommend that both *miR-140* and *miR-196a* are promising biomarkers for the diagnosis and management of BC patients. Nevertheless, the shortcomings of the present study were that we could not investigate the correlation between miRNA expression and the survival status because it needs a 5-year follow-up of BC patients.

In conclusion, briefly, the results exhibited that both *miR-140* and *miR-196a* may be potential biomarkers for determining the BC diagnosis and prognosis, which may serve, respectively, as a tumor-suppressing and -promoting gene. However, more research is required to determine the *miR-140* and *miR-196a* molecular mechanisms in the BC progression.

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Ethical approval

All procedures performed in studies involving human participants were under the ethical standards of the Ethics Committee of Tabriz University of Medical Science (NO. IR.TBZMED.REC.1396.55) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author's contribution

NZ and BN designed and directed the project; AS and VM processed the experimental data and performed the analysis, drafted the manuscript, and designed the figures; NZ, BN, and KA contributed to the final version of the manuscript. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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