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RESEARCH ARTICLE
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CORRELATION BETWEEN THREE LO NG NON-CODING RNA GENE EXPRESSION AND PATHOLOGICAL RESPONSE IN BREAST CANCER PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY IN EGYPT

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Abstract

Background: Breast cancer (BC) is the second cancer in global cancer incidence with an estimated 2.3 million new cases compromising 11.6% of all cancer cases, and the fourth leading cause of cancer mortality worldwide (6.9% of all cancer deaths). Numerous studies have reported the relationship between long non-coding RNAs (lncRNAs) and multi drug resistance (MDR) in BC, whether this therapy was chemotherapy, targeted therapy or endocrine treatment, where each has a specific lncRNA that is responsible for the resistance mechanism.

Aim: This study aimed at improving the plan of management of breast cancer patients receiving neoadjuvant chemotherapy by better understanding the factors that may affect the pathological response via studying the possible role of the three lncRNAs (BC032585, AK291479, and U79293) as predictive biomarkers and/or therapeutic targets.

Patients and methods: This retrospective comparative study was conducted on 120 BC patients recruited from both clinical oncology departments at Faculty of Medicine Suez Canal University and Dar el Salam cancer hospital (Harmel) in the period between October 2020 to October 2021. Molecular analysis was done to assess the gene expression levels of the three lncRNAs AK291479, U79293 and BC032585 via comparative real time PCR technique using the paraffin blocks of the BC patients receiving neoadjuvant chemotherapy (NACTH) at two different stages of treatment (paraffin blocks of the biopsy before receiving neoadjuvant chemotherapy and those of surgery; after receiving NACTH).

Results: The lncRNA BC0332585 showed overexpression in both groups under study with median and interquartile (IQR) values equivalent to 6.12 (4.16 – 7.18) among the pathologic complete response (pCR) group and 6.38 (4.82 – 7.72) among partial pathological response (pPR) group and

both were statistically significant. The lncRNA AK291479 showed under expression among both groups under study, with pCR expression levels equivalent to -4.33 (-6.90 – 0.02) and pPR -6.26 (-9.45– -3.53), and both were statistically significant. Finally, the lncRNA U79293 showed under expression among the pCR group where expression levels ranged between -1.45 (-3.12 – 0.16) and those with pPR expression ranged from -0.83 (-3.36 – 0.70) and both were statistically significant.
Conclusion: Although there is a statistically significant correlation between the expression levels of the three lncRNAs understudy; AK291479, U79293 and BC032585 in both pCR and pPR groups, the three tested lncRNAs showed the same pattern of expression in both pCR and pPR groups suggesting that they cannot be utilized as predictive markers for pathological response after NACTH. Meanwhile many lncRNAs showed to be key regulators in BC drug resistance via modulating its pathways at epigenetic, transcriptional, and post-transcriptional levels in many studies, our study didn't prove the significance of the three lncRNAs; AK291479, U79293 and BC032585 as promising biomarkers in BC management as predictive and or prognostic biomarkers, however they showed a possible potential for being used as therapeutic biomarkers.

Keywords: long non-coding RNA, breast cancer, neoadjuvant chemotherapy

Introduction

Breast cancer (BC) is the second most common cause of cancer in terms of incidence, accounting for an estimated 2.3 million new cases, or 11.6% of all cancer cases. It also ranks the fourth globally in terms of cancer mortality (6.9% of all cancer deaths) In women, breast cancer accounts for the majority of cancer-related fatalities (15.5% of deaths) and is the most common disease diagnosed (24% of cases) (1).

In Egypt, BC accounts for 38.8% of all cancer diagnoses in females. In 2020, there were roughly 22,700 instances of BC, and by 2050, there would likely be around 46,000 cases. An estimated 11% of people die from BC, making it the second leading cause of cancer-related death after hepatocellular carcinoma (2).

Neoadjuvant chemotherapy (NACTH) trials have shown the occurrence of pathologic complete response (pCR), which is characterized by the absence of any remaining invasive component in the tumor or local lymph nodes upon pathologic evaluation after treatment. Improved overall survival (OS) and disease-free survival (DFS) were also shown to be substantially correlated with pCR (3).

Unfortunately, only 30–50% of patients typically achieve pCR, and about 5% of patients experience disease progression while receiving NACTH. For this reason, it is critical to accurately assess the response to NACTH in order to plan subsequent surgeries. Additionally, early tumor response prediction is important in order to tailor treatment regimens by escalation or de-escalation, thereby avoiding overtreatment of patients who only experience physiological side effects and psychological implications (4).

According to Derouane et al. (5), imaging, clinicopathology, and plasma biomarkers are being used to predict response to NACTH. With a length ranging from 200 nt (?) to more than 100 kb, long non-coding RNAs (lncRNAs) are a class of non-coding transcripts that lack the ability to code for proteins. They have been discovered to be present in serum, plasma, and tissues, and they have been implicated at both the transcriptional and posttranscriptional levels in the processes of tumor genesis, invasion, metastasis, and drug resistance in BC (6).

Numerous studies have shown the connection between lncRNAs and multi-drug resistance (MDR) in BC. Whether the therapy was endocrine, targeted, or chemotherapy, each has a unique lncRNA that is in charge of the resistance mechanism. In BC cells and tissues, the majority of lncRNAs are elevated. They target traditional signaling pathways, induce the Epithelial Mesenchymal Transition (EMT) process, and modify cell death to enhance MDR (7).

Anti-miRNAs and miRNA mimics are also used to imitate natural tumor suppressor miRNAs and deplete oncogenic miRNAs, which has been shown to effectively overcome BC drug resistance in many experimental settings. In order to address the problem of medication resistance in BC, it may

be possible to combine systemic therapy with the delivery of specific RNA-based formulations (8). In this study, we investigated the role of three lncRNAs; AK291479, BC032585, and U79293 as possible predictive and/or therapeutic biomarkers and how they relate to the pathological response after NACTH in Egyptian BC patients.

Aim of the work

This study aimed at improving the plan of management of BC patients receiving neoadjuvant chemotherapy by better understanding the factors that may affect the pathological response and the possible role of the three lncRNAs (BC032585, AK291479, and U79293) understudy as predictive biomarkers and/or therapeutic targets.

Patients and methods

Patients understudy:

This retrospective, comparative study was conducted on BC patients recruited to both Clinical Oncology Departments in Faculty of Medicine Suez Canal University and Dar el Salam cancer hospital (Harmel) in the period between October 2020 October 2021 and fulfilling the inclusion criteria: Adult patients (aged between 18-70 years old), pathologically proven BC patients eligible for NACTH, patients who are not metastatic at diagnosis, patients with paraffin blocks for both the biopsy and surgery available at the pathology lab and eligible for the criteria of testing: 5-6 slices after 2-3 microtomes, each of 4-8 micrometer thickness. Patients younger than 18 or older than 70, patients who have metastatic BC at diagnosis, bilateral BC, patients with double pathology, or patients with non-available paraffin blocks or blocks not fitting the criteria were excluded from the study.

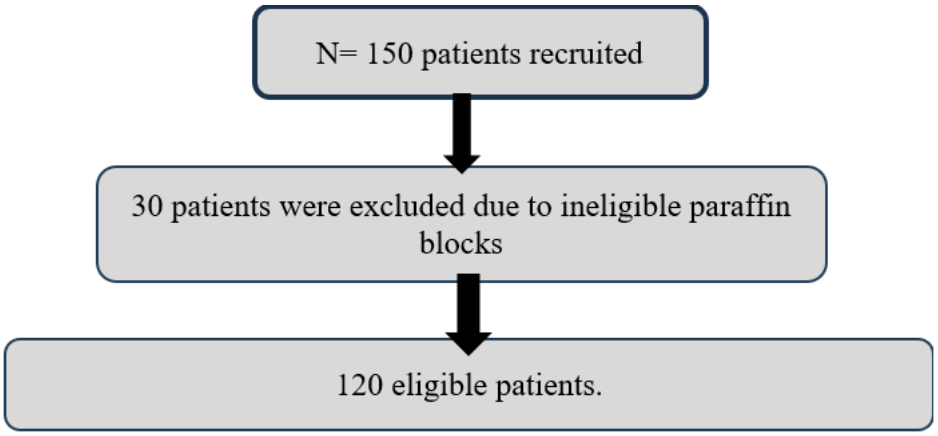

Figure 1: Consort diagram for the included sample size in the study

The initial number of patients recruited was 150 BC patients, then 30 BC patients were excluded due to ineligible paraffin blocks (necrosis, hemorrhage, not enough tissue), so n = 120 patients.

The study included the 240 specimens from paraffin blocks of the 120 BC patients receiving NACTH at two different stages of treatment (paraffin blocks of the biopsy before and after receiving NACTH). Clinical data was extracted from the BC patients' files as following: clinicopathological features: age, laterality, pre-operative clinical staging & hormonal profile. NACTH protocol (type of chemotherapy and number of cycles) varied as follows:

- Luminal disease: 4 cycles of Anthracyclines, Cyclophosmaide (AC) followed by four cycles of Taxenes.
- Triple negative disease: AC for 4 cycles (+\- Dose Dense) followed by Paclitaxel Carboplatin weekly for 12 weeks.

- Her-2 positive disease: (TCHP) protocol; Taxenes (Docetaxel every 3 weeks \Paclitaxel weekly) Carboplatin area under curve (AUC 5 \ AUC 2) for 6 cycles in addition to double Her-2 blockades: Trastzumab-Pertzumab for 6 cycles.

The pathological response was assessed post-operatively, where the pCR was defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/Tis ypN0 in the current AJCC staging system).

B. Molecular Analysis

Lab work was executed in Genetics Unit Lab and Center of Excellence in Molecular and Cellular Medicine (CEMCM), Faculty of Medicine, Suez Canal University. The study was conducted in accordance with the guidelines in the Declaration of Helsinki. In summary, we first isolated RNA, transcribed it to complementary DNA, then the expression levels of the three lncRNAs under study were quantified using RT-PCR technique.

1.Isolation of total RNA:

Total RNA was isolated from FFPE tissue sections using the Qiagen miRNeasy FFPE Kit (Qiagen, 217504) following the protocol supplied by the manufacturer. RNA concentration and purity at the absorbance ratio 260/280 nm was determined using the NanoDrop 2000 1C spectrophotometer with wavelength-dependent extinction coefficient '33' for small RNA (NanoDrop Tech., Inc. Wilmington, DE, USA).

2.Reverse Transcription (RT):

The miScript II RT Kit (Qiagen, Catalog no. 218161), in which noncoding RNAs (ncRNAs) are polyadenylated by poly(A) polymerase and converted into cDNA by reverse transcriptase with oligo-dT priming. RT was carried out in a Veriti™ 96-Well Thermal Cycler (Applied Biosystems, USA) at 37 °C for 1 hour, followed by inactivation of the reaction by briefly incubating at 95 °C.

3.Quantitative expression analysis of the three lncRNAs understudy:

Relative quantification of the three lncRNAs understudy (BC032585, AK291479, and U79293) was done using quantitative real time PCR (qRT-PCR) conducted according to the MIQE (minimum information for publication of quantitative real-time PCR experiments) guidelines.

The premix of cDNA was used as a template for qRT-PCR of the three lncRNAs. Primers for the lncRNAs understudy are described in Table 1 and miScript SYBR Green PCR Kit (Qiagen, cat. no 218076) was used to measure the expression levels. GAPDH was used as endogenous controls to enable data analysis using the ΔΔCT method of relative quantification. A "No-template" and a "No-Reverse Transcribed" controls were included in each run and all reactions run in duplicate. The PCR runs initially at 95 °C for 5 min, followed by 40 cycles at 95 °C (15 s), then at 55 °C (1 min), finally at 72 °C (1 min) for denaturation, annealing and elongation respectively.

Table 1: Primer sequences of the three lncRNAs understudy.

LncRNA	Sequence
BC032585_Forward	GCTCTGACAATGTTGTGCTGG
BC032585_Reverse	GAGTGCTCAAAGTCACACGC
AK291479_ Forward	TGACT CTGTGGTTCATTCTGGT
AK291479_ Reverse	CCATCCCCAAGTCAG GAACC
U79293_ Forward	CTTCTGCTGCTGCTTGGAGT
U79293_ Reverse	AAGCTCGCCACTCATGACAG

Data analysis

Quantification of the lncRNAs BC032585, AK291479, and U79293 was estimated using the relative quantification method to quantify differences in the expression level of lncRNA gene relative to a reference sample (pre and post adjuvant therapy). The expression levels of BC032585, AK291479, and U79293 were normalized by the expression levels of GAPDH to correct any possible differences among samples. The result of this method is presented as the fold change of target gene expression in a target sample relative to a reference sample, normalized to a reference gene.

The relative quantity (RQ) of BC032585, AK291479, and U79293 in BC patients, normalized to GAPDH and relative to the expression of the samples of pre-neoadjuvant therapy and were calculated using the equation $RQ = 2^{-\Delta\Delta CT}$ method The result of this method is presented as the fold change of target gene expression in a target sample relative to a reference sample, normalized to a reference gene.

Data management:

Data was collected and coded then was entered as a spread sheet using Microsoft excel for windows office 2019. Data analysis using Statistical Package of Social Science (SPSS) software program version 21.0 for analysis. Data was presented as tables and graphs; t-test was used to compare quantitative data expressed as mean and standard deviation. Chi-square test was used to compare the qualitative data expressed as number and percent. ANOVA test was used for parametric data. The Kruskal Wallis test was used for non-parametric data. P value is considered significant when $p < 0.05$.

Results

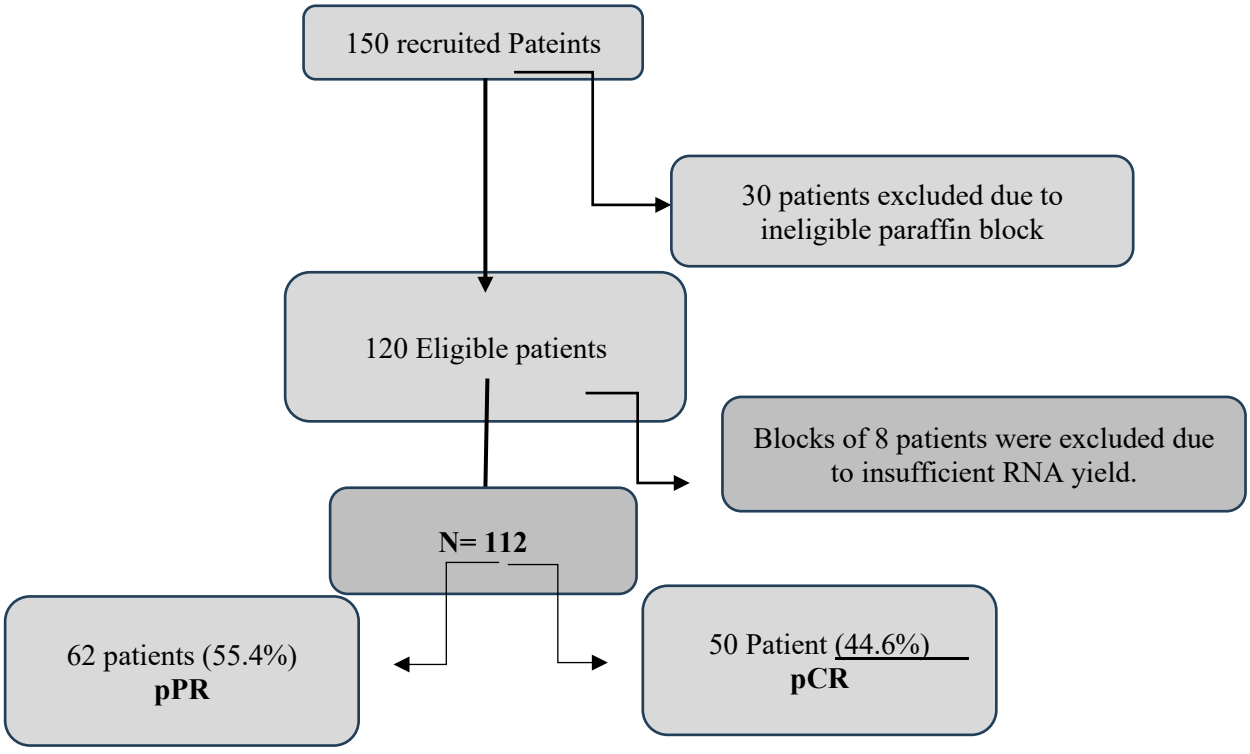

Fig 2: Summarizes the pathological responses of 112 patients with breast cancer (BC), who received neoadjuvant chemotherapy. The findings indicate that more than two-fifths of cases (44.6%) achieved a complete pathological response (pCR) compared to more than half of patients (55.4%) exhibited a partial response (pPR).

Table 2: Expression of LncRNA BC0332585 in BC patients receiving neoadjuvant chemotherapy and its correlation with pathological response.

	Total (n = 112)	**Pathological response**		**Control (n = 112)**	**p1**	**p2**
		Complete (n = 50)	**Partial (n = 62)**			
BC03 LOGFC						
Min. – Max.	-0.69 – 10.91	0.75 – 10.72	-0.69 – 10.91	0.0 – 0.0	<0.001*	<0.001*
Mean ± SD.	6.02 ± 2.25	5.72 ± 2.14	6.27 ± 2.33	0.0 ± 0.0		
Median (IQR)	6.32 (4.82 – 7.51)	6.12 (4.16 – 7.18)	6.38 (4.82 – 7.72)	0.0 (0.0 – 0.0)		

IQR: Inter quartile range SD: Standard deviation

Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Dunn's for multiple comparisons test) for Kruskal Wallis test

p1: p value for comparing between Complete Pathological response and Control

p2: p value for comparing between Partial Pathological response and Control

*: Statistically significant at $p \leq 0.05$

Table 5 presents data on the expression of LncRNA BC0332585 in BC patients undergoing neoadjuvant chemotherapy, showing overexpression of LncRNA BC0332585 among those with complete pathological response showing an expression that ranged from 0.75 to 10.72, with a mean of 5.72 ± 2.14 (±SD) , and those with partial response where the expression levels were between -0.69 to 10.91, with an average of 6.27 ± 2.33 (±SD). The p-values for comparisons between the complete and partial response groups versus the control group were both less than 0.001, indicating statistically significant differences in LncRNA BC0332585 expression levels among the studied groups vs the control group. However, there is no difference between the pattern of expression of the lncRNA BC0332585 between the two groups (; BC0332585 was overexpressed in both patients achieving pCR and those achieving pPR).

Table 1: Expression of LncRNA AK291479 in BC patients receiving neoadjuvant chemotherapy and its correlation with pathological response.

	Total (n = 112)	**Pathological response**		**Control (n = 112)**	**p1**	**p2**
		Complete (n = 50)	**Partial (n = 62)**			
AK29 LOGFC						
Min. – Max.	-13.81 – 5.71	-13.81 – 5.71	-13.62 – -1.04	0.0 – 0.0	<0.001*	<0.001*
Mean ± SD.	-5.63 ± 4.42	-4.25 ± 4.89	-6.75 ± 3.68	0.0 ± 0.0		
Median (IQR)	-5.04 (-9.22 – -2.75)	-4.33 (-6.90 – 0.02)	-6.26 (-9.45 – -3.53)	0.0 (0.0 – 0.0)		

IQR: Inter quartile range SD: Standard deviation

Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Dunn's for multiple comparisons test) for Kruskal Wallis test

p1: p value for comparing between Complete Pathological response and Control

p2: p value for comparing between Partial Pathological response and Control

*: Statistically significant at $p \leq 0.05$

Table 6 presents the expression of LncRNA AK291479 in BC patients undergoing neoadjuvant chemotherapy, showing Under expression of lncRNA AK291479 among both those with pCR, where the expression was between -13.81 and 5.71, with a mean of -4.25 ± 4.89 (±SD) and those with pPR, where the levels of expression ranged from -13.62 to -1.04, with an average of -6.75 ± 3.68 (±SD).

Based on these outcomes, there was a statistically significant difference (p=<0.001) in LncRNA AK291479 expression measures between the complete and partial response groups versus the control group. However, there is no difference between the pattern of expression of the lncRNA AK291479 between the two groups (; AK291479 was under expressed in both patients achieving pCR and those achieving pPR).

Table 2: Expression of LncRNA U79293 in BC patients receiving neoadjuvant chemotherapy and its correlation with pathological response.

	Total (n = 112)	**Pathological response**		**Control (n = 112)**	**p_1**	**p_2**
		Complete (n = 50)	**Partial (n = 62)**			
U79 LOGFC						
Min. – Max.	-9.92 – 4.75	-9.92 – 2.72	-6.06 – 4.75	0.0 – 0.0	<0.001*	0.020*
Mean ± SD.	-1.47 ± 2.58	-1.81 ± 2.74	-1.19 ± 2.43	0.0 ± 0.0		
Median (IQR)	-1.26(-3.36– 0.68)	-1.45(-3.12 – 0.16)	-0.83(-3.36 – 0.70)	0.0 (0.0 – 0.0)		

IQR: Inter quartile range SD: Standard deviation

Pairwise comparison bet. each 2 groups were done using Post Hoc Test (Dunn's for multiple comparisons test) for Kruskal Wallis test

p1: p value for comparing between Complete Pathological response and Control

p2: p value for comparing between Partial Pathological response and Control

*: Statistically significant at $p \leq 0.05$

Table 7 presents data on the expression of LncRNA U79293 in BC patients undergoing neoadjuvant chemotherapy, showing under expression of lncRNA U79293 among both those with pCR where expression was between -9.92 to 2.72 with Mean ± SD. -1.81 ± 2.74 and those with pPR, where the expression ranged from -6.06 to 4.75 with Mean ± SD -1.19 ± 2.43. The p-values for comparisons between the control group with the pCR group and the pPR were (p1<0.001), (p2 = 0.020), respectively, indicate statistically significant differences in LncRNA U79293 expression levels in both groups' vs control. However, there is no difference between the pattern of expression of the lncRNA U79293 between the two groups (; U79293 was under expressed in both patients achieving pCR and those achieving pPR.

Discussion

It has been suggested that a number of lncRNAs that have been shown to have either an oncogenic or tumor-suppressive role in BC may potentially function as predictive biomarkers because they interact with treatment resistance processes (9). Three lncRNAs (BC032585, AK291479, and U79293) and the pathological response in BC patients are the subjects of our retrospective investigation being treated with neoadjuvant chemotherapy. By focusing on these lncRNAs in the treatment of breast cancer or incorporating them into prediction models to more accurately choose patients for neoadjuvant chemotherapy, this discovery may open the door for future diagnostic and therapeutic approaches.

This field of study is regarded as a top new area. Furthermore, although the idea of linking lncRNA to pathological response to neoadjuvant in patients with breast cancer has been studied, not all studies have used the same methodology or evaluated the same lncRNAs. Importantly, the research was either on American, European, or Asian people (the bulk of the studies were on Asian populations). Therefore, identifying our unique pattern of genetic expression via such study on our Egyptian people is essential.

Regarding the lncRNA BC0332585, it was overexpressed in our study in both patients who achieved pCR, with expression levels ranging from 0.75 to 10.72, with a mean of 5.72 ± 2.14 (±SD), and in patients who had pPR, with expression levels ranging from -0.69 to 10.91, with an average of 6.27 ± 2.33 (±SD) showing that there was no difference in the two groups' levels of this lncRNA expression.

This was in contrast to Zeng et al.'s findings, which said that a high chance of pCR is linked to high expression of the lncRNA BC032585. Moreover, Zeng et al. conducted an in vitro investigation to ascertain the sensitivity of breast cancer cells with or without BC032585 alteration to the chemotherapeutic agent: doxorubicin and paclitaxel. They discovered that BC032585 knockdown demonstrated a notable resistance to chemotherapy and anthracyclines, but not to paclitaxel, which may be interfering with the pathological response in breast cancer (10).

Additionally, underexpression of the lncRNA BC0332585 was linked to multidrug resistance, but to both doxorubicin and paclitaxel, according to Du et al. By targeting ABC (ATP Binding Cassette) transporters in BC, drug efflux pumps are activated, and the EMT epithelial mesenchymal transition is promoted (7).

The expression of the lncRNA AK291479 was underexpressed in both the pCR group (expression ranged from -13.81 to 5.71, mean -4.25 ± 4.89 (±SD)) and the pPR group (expression levels ranged from -13.62 to -1.04, mean -6.75 ± 3.68 (±SD), indicating no difference in expression between the two groups.

This was at odds with the findings of Zeng et al., who indicated that a high likelihood of pCR is linked to increased expression of the lncRNA AK291479 (10).

With respect to LncRNA U79293 expression in BC patients receiving neoadjuvant chemotherapy, our analysis reveals that both those with pCR, whose expression ranged from -9.92 to 2.72 with Mean ± SD -1.81 ± 2.74, and those with pPR, whose expression ranged from -6.06 to 4.75 with Mean ± SD -1.19 ± 2.43.

This was at odds with the findings of Zeng et al., who indicated that a low likelihood of pCR is linked to high expression of the lncRNA U79293(10).

Interestingly, our study's three lncRNAs' patterns of expression differed from Zang et al.'s studies. This might be ascribed to the population under investigation difference; Zang et al.'s work included Chinese patients, while our research had Egyptian patients. The sample size was different (112 patients were included in our research vs 488 individuals).

Conclusion

There is a statistically significant correlation between the expression of three tested lncRNAs AK291479, U79293 and BC032585 in both pCR and pPR groups versus Control groups. The three tested lncRNAs showed the same pattern of expression in pCR and pPR groups, where the lncRNA BC032585 showed over expression and the other two lncRNAs AK291479 and U79293 showed under expression, this suggests that they cannot be utilized as predictive markers for pCR. LncRNAs are emerging as key regulators in BC drug resistance via modulating its pathways at epigenetic, transcriptional, and post-transcriptional levels and they might be regarded as promising biomarkers in BC management as predictive and or prognostic biomarkers as well as potential therapeutic targets

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