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## **INTEGRATED ANALYSIS OF hsa-miR-26b-5P AND hsa-miR-186-5p IN BLOOD SERUM AND TUMOR TISSUE REVEALS THEIR PROGNOSTIC AND PREDICTIVE SIGNIFICANCE IN BREAST CANCER**

**Background.** Breast cancer (BC) heterogeneity significantly complicates diagnosis, prognosis, and prediction of treatment response. MicroRNAs (miRNAs) have emerged as promising biomarkers due to their involvement in tumor progression and in regulating therapy sensitivity. However, the combined clinical significance of circulating and tumor-associated miRNAs, such as hsa-miR-26b-5p and hsa-miR-186-5p, remains insufficiently elucidated. **Materials and Methods.** Expression levels of hsa-miR-26b-5p and hsa-miR-186-5p were analyzed in serum and tumor tissue of 124 BC patients. Associations with clinicopathological parameters were assessed. The prognostic significance was evaluated based on disease progression and recurrence within 3 years. The predictive value was determined in patients receiving neoadjuvant chemotherapy (4AC regimen) using response assessment and ROC analysis. **Results.** Young BC patients ( $\leq 45$  years) demonstrated significantly lower circulating levels of both miRNAs. Serum hsa-miR-186-5p expression was associated with early-stage disease, tumor size, lymph node status, and molecular subtype. Increased circulating hsa-miR-26b-5p levels were linked to disease progression, whereas decreased hsa-miR-186-5p levels were observed in patients with unfavorable outcomes. In tumor tissue, hsa-miR-26b-5p expression correlated with tumor grade, size, and metastatic status, showing elevated levels in poorly differentiated tumors and reduced expression in metastatic disease. In contrast, hsa-miR-186-5p was associated with the molecular subtype and lymph node involvement, with the highest expression observed in HER2-positive tumors and in patients with recurrence. Elevated levels of hsa-miR-186-5p in both serum and tumor tissue were associated with reduced sensitivity to doxorubicin-based neoadjuvant chemotherapy. ROC analysis confirmed its predictive value (AUC = 0.750 for serum and 0.818 for tumor tissue). No significant association between hsa-miR-26b-5p and chemotherapy response was observed. **Conclusions.** hsa-miR-26b-5p and hsa-miR-186-5p demonstrate complementary roles in BC biology. hsa-miR-26b-5p is primarily associated with tumor aggressiveness and cancer progression, whereas hsa-miR-186-5p reflects its molecular characteristics and response to chemotherapy. Their combined assessment in serum and tumor tissue represents a promising approach for improving prognostic stratification and predicting treatment efficacy in BC patients.

**Keywords:** breast cancer, hsa-miR-26b-5p, hsa-miR-186-5p, doxorubicin.

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Breast cancer (BC) is a clinically heterogeneous disease characterized by substantial variability in therapeutic response, even within the same molecular subtype [1]. Despite the widespread use of anthracycline-based regimens, including doxorubicin, intrinsic and acquired resistance remain major limitations

#### Clinicopathological characteristics of the BC patients

Characteristics	<i>n</i>	%
Number of patients	124	100
Average age	49.44 ± 12.32	
Age range	20–77	
Reproductive status		
Perimenopause	33	73.4
Menopause	91	26.6
BC stage		
I	25	20.2
II	66	53.2
III	19	15.3
IV	14	11.3
Category N according to TNM		
N0	83	66.9
N1-3	41	33.1
Category M according to TNM		
M0	111	89.5
M1	13	10.5
Tumor grade		
G1	11	8.9
G2	94	75.8
G3	19	15.3
3-year progression		
No progression	113	91.1
Progression	11	8.9
Molecular subtype		
Luminal A	20	16.1
Luminal B	73	58.9
Her2/neu-positive	17	13.7
Basal	14	11.3
Miller—Payne pathological complete response grade		
V	14	18.4
IV	17	22.3
III	19	25.0
II	22	28.9
I	4	5.4

affecting treatment efficacy and patient outcomes [2]. This highlights the need for robust molecular markers that not only reflect tumor biology but also predict individual response to systemic therapy.

Recent advances in molecular oncology have emphasized the importance of the regulatory RNA networks in shaping tumor behavior and drug sensitivity. Among these, microRNAs (miRNAs) act as fine-tuners of gene expression and are involved in multiple oncogenic pathways, including epithelial–mesenchymal transition, apoptosis, and modulation of the tumor microenvironment [3]. Importantly, certain miRNAs have been shown to simultaneously influence tumor progression and response to chemotherapy, suggesting their potential as dual-function biomarkers [4].

In this context, hsa-miR-26b-5p and hsa-miR-186-5p are promising candidates due to their reported tumor-suppressive properties and involvement in key signaling pathways associated with proliferation, invasion, and chemoresistance in BC [5–7]. However, their integrated clinical relevance, particularly in relation to neoadjuvant chemotherapy response, remains insufficiently explored.

Our previous studies indicate that using miRNAs as diagnostic and prognostic cancer markers is a promising approach, particularly as medical oncology actively moves toward a personalized model [8–10]. Given the great potential of miRNAs as marker molecules, the aim of our study was to validate the use of hsa-miR-26b-5p and hsa-miR-186-5p for diagnosis, prognosis of disease course, and prediction of the effectiveness of neoadjuvant chemotherapy of BC patients.

#### Materials and Methods

Malignant tissue samples were obtained from BC patients (*n* = 124) who were treated at the National Cancer Institute of the Ministry of Health of Ukraine between 2019 and 2022. The blood samples and tumor biopsies were collected from all patients before therapy initiation. A subset of patients received neoadjuvant therapy according to the 4AC regimen, and in these cases, the material was used to assess the relationship between miRNA expression levels and doxorubicin sensitivity (Table). All patients subsequently underwent standard therapeutic interventions, and disease recurrence was monitored over a 3-year follow-up period. The comparison group was

composed of 10 fibroadenoma samples and 5 conditionally normal breast tissue samples. The study was approved by the Institutional Review Board and Research Ethics Committee of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the National Academy of Sciences of Ukraine and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent for the use of clinical data for research purposes. Clinical and pathological characteristics of the studied BC cases are detailed in the Table. The therapeutic response in BC cases was evaluated using the Miller—Payne grading system, which provides a standardized morphological measure of treatment efficacy.

miRNA expression was analyzed using real-time PCR. Formalin-fixed paraffin-embedded (FFPE) tumor biopsy samples and blood serum samples were used for the assessment. Total RNA was extracted from the FFPE tissue sections using an RNeasy FFPE Kit (QIAGEN, Germany) and from blood samples using a NucleoSpin kit (MACHEREY-NAGEL, Germany) according to the manufacturer's instructions. RNA concentration was measured with a NanoDrop 1000 Spectrophotometer (Thermo Scientific, USA), and the purity was assessed by the 260/280 nm absorbance ratio. Isolated RNA was dissolved in Tris-EDTA buffer and stored at  $-20^{\circ}\text{C}$  until further use.

Complementary DNA was synthesized from 100 ng of total RNA using the LunaScript® RT Super-Mix Kit (New England Biolabs, USA). RNU48 small nucleolar RNA was employed as an endogenous control to normalize miRNA expression levels. Primers for the target RNAs were synthesized by YP Biotech (Ukraine) according to the sequences: RNU48 forward 5'-AGT GAT GAT GAC CCC AGG TAA CTC-3' and reverse 5'-CTG CGG TGA TGG CAT CAG-3'; hsa-miR-26b-5p forward 5'-GTT TGG GTT CAA GTA ATT CAG G-3' and universal reverse; hsa-miR-186-5p forward 5'-GTT TGG GTT CAA GTA ATT CAG G-3' and universal reverse.

Quantitative real-time PCR was performed using a QuantStudio 5 Dx Real-Time PCR System (Thermo Fisher Scientific, USA) and a LunaScript® MasterMix Kit (New England Biolabs, USA). Each sample was analyzed in triplicate, and the threshold cycle (Ct) values were averaged. Relative miRNA expression was calculated using the  $2^{-\Delta\text{Ct}}$  method, as previously described [11].

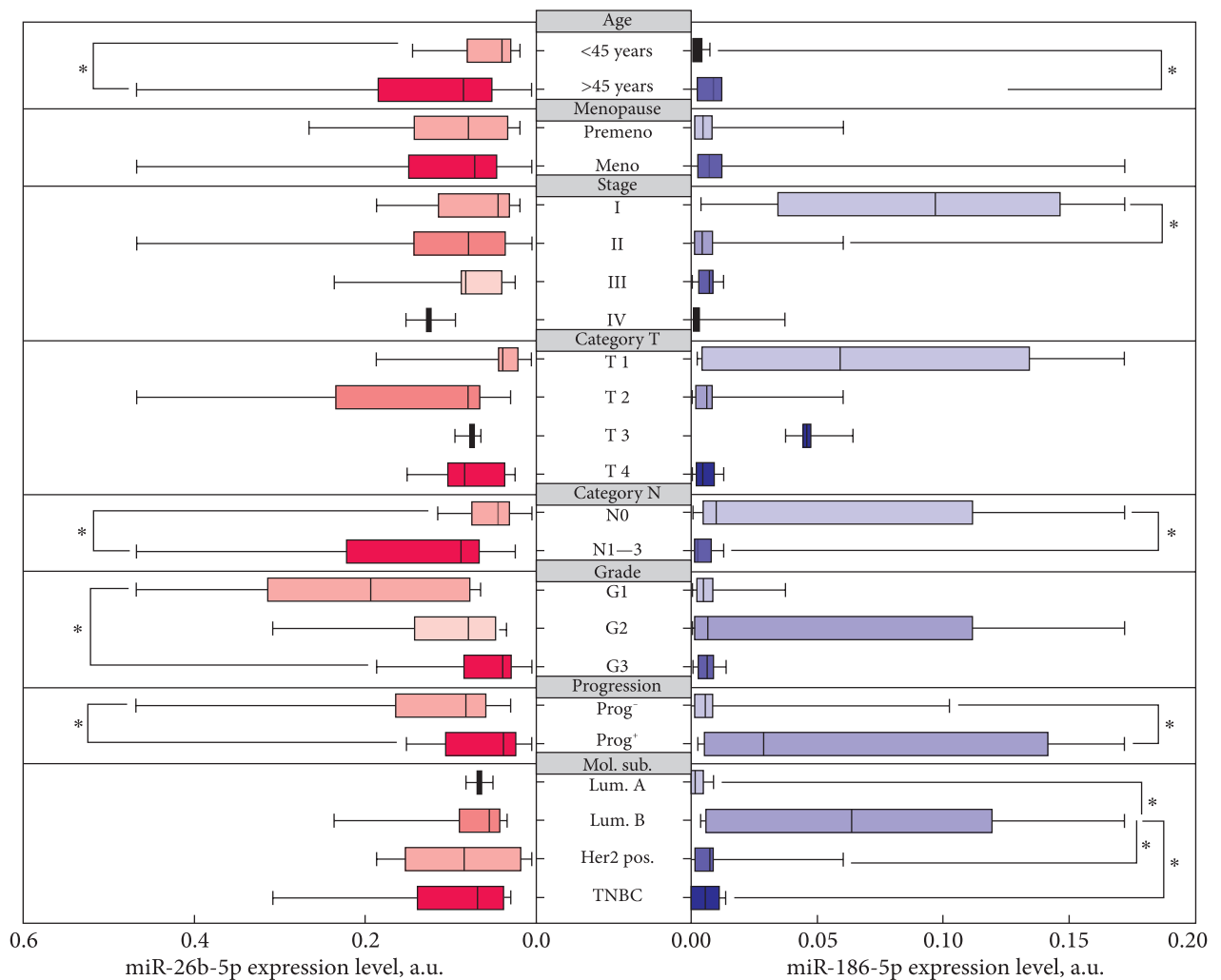
Comparisons between two groups were performed using the Mann—Whitney U test, while comparisons among three or more groups were conducted using the Kruskal—Wallis test followed by post hoc analysis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance of selected markers according to neoadjuvant chemotherapy (NAC) effectiveness. Statistical analyses were conducted using GraphPad Prism 10 (GraphPad Software, USA), and  $p$ -values  $< 0.05$  were considered statistically significant.

## Results

**Prognostic and predictive value of circulating hsa-miR-26b-5p and hsa-miR-186-5p expression in serum of breast cancer patients.** At the first stage, we investigated the expression of circulating hsa-miR-26b-5p and hsa-miR-186-5p in the serum of BC patients to verify their prognostic significance (Fig. 1). We revealed that young BC patients ( $\leq 45$  years) were characterized by significantly lower levels of hsa-miR-26b-5p and hsa-miR-186-5p by 2.15-fold ( $p = 0.0274$ ) and 37.5-fold ( $p = 0.0241$ ), respectively. At the same time, the expression of hsa-miR-186-5p in the serum of patients with stage I BC was significantly higher by 8.32-fold ( $p = 0.0456$ ) compared to the corresponding values in patients with stage II BC. No association between circulating hsa-miR-26b-5p levels and disease stage was found. We established that the highest expression levels of hsa-miR-186-5p in serum were characteristic of BC patients with the T1 and T3 categories ( $p = 0.0475$ ).

An association between the levels of the studied miRNAs and the regional lymph node involvement was demonstrated. In patients with the N0 category, the expression levels of hsa-miR-26b-5p were significantly decreased by 1.96-fold ( $p = 0.0113$ ), and those of hsa-miR-186-5p increased by 3.93-fold ( $p = 0.0109$ ), compared to the cohort of patients with the diagnosed regional lymph node involvement (N1—3 category).

The relationship between circulating hsa-miR-26b-5p levels and the BC grade is worth noting. We observed significantly higher levels of this miRNA (3.53-fold,  $p = 0.02$ ) in the serum of patients with well-differentiated BC compared to the blood samples from patients with poorly differentiated breast tumors. In addition, the relationship



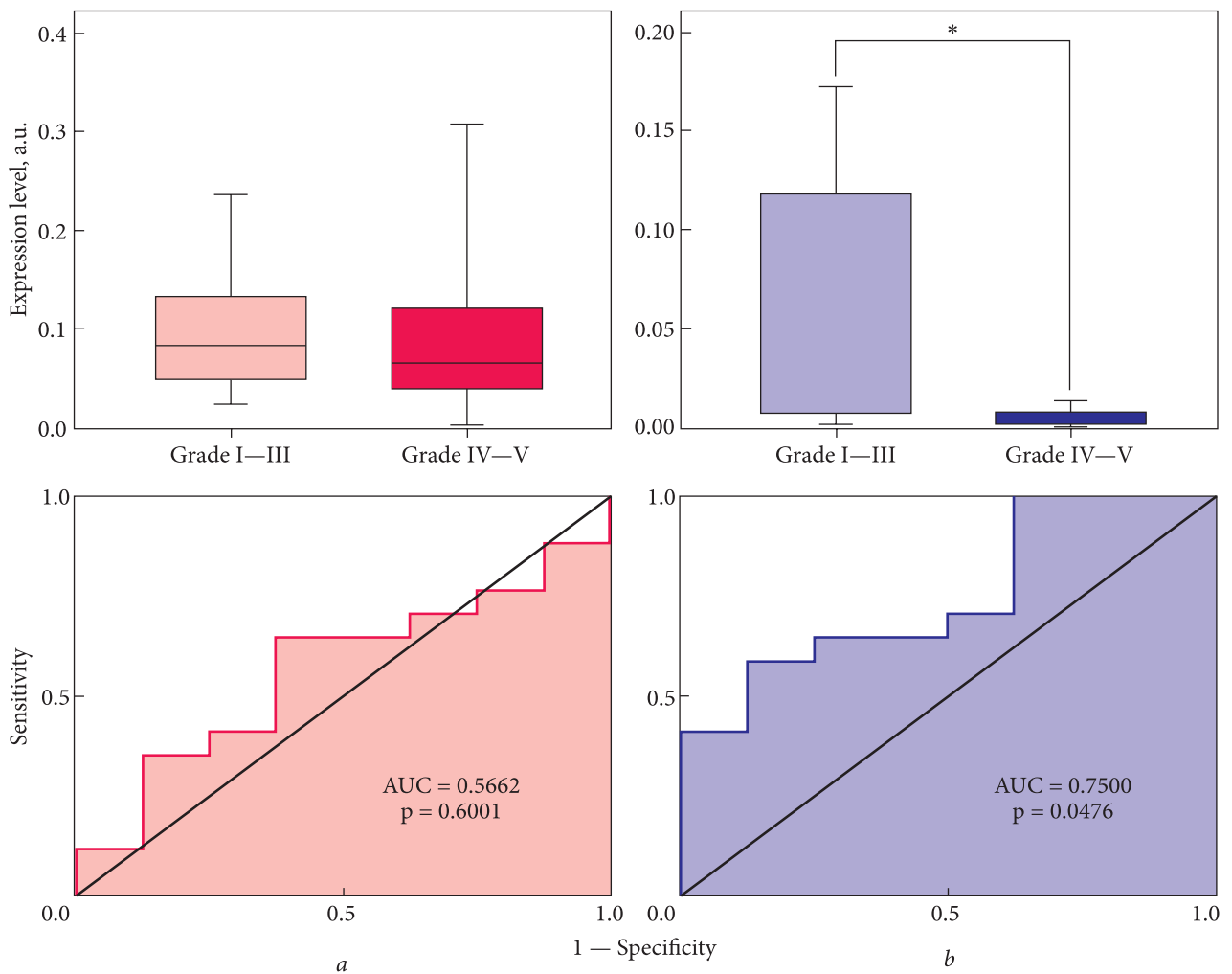
**Fig. 1.** Relationship between circulating serum levels of hsa-miR-26b-5p or hsa-miR-186-5p and clinical status of BC patients. \*  $p < 0.05$

between hsa-miR-186-5p expression levels and molecular subtype was shown. In patients with luminal B BC, the expression of this miRNA was higher by 22.9-fold ( $p = 0.0178$ ), 5.74-fold ( $p = 0.0199$ ), and 11.84-fold ( $p = 0.0089$ ) compared to patients with the luminal A, HER2/neu-positive, and triple-negative subtypes, respectively.

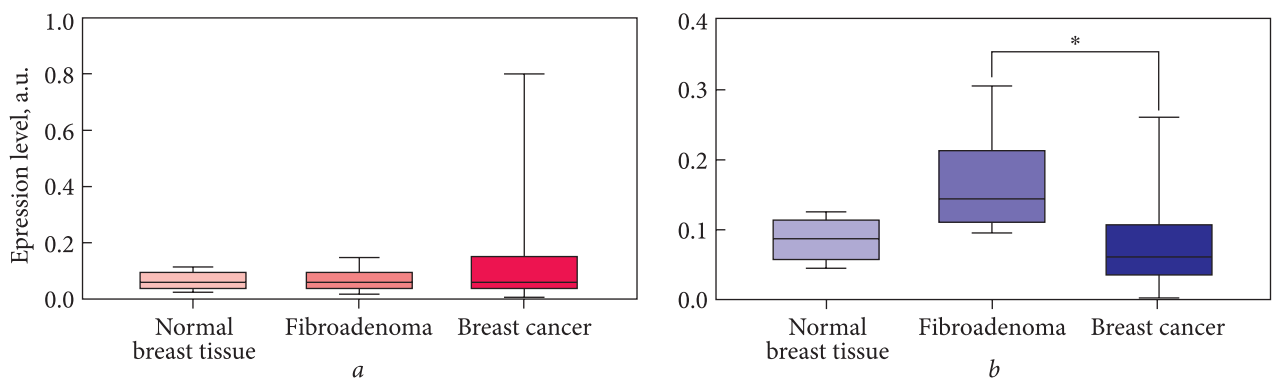
The prognostic value of the studied miRNAs for assessing the risk of disease progression was also demonstrated. In the serum of BC patients who experienced disease progression within 3 years after primary diagnosis, the levels of hsa-miR-26b-5p significantly increased by 2.15-fold ( $p = 0.0246$ ), while circulating hsa-miR-186-5p levels decreased by 5.19-fold ( $p = 0.0438$ ), compared to patients without documented progression. No associations were found in BC patients between circulating hsa-miR-26b-5p and hsa-miR-186-5p levels and reproductive status, tumor size, or clinical stage.

We further assessed the predictive value of the studied circulating serum miRNAs in BC patients undergoing 4AC therapy. It was shown that patients with significantly higher levels of circulating hsa-miR-186-5p (11.29-fold,  $p = 0.0495$ ) were characterized by a significant decrease in sensitivity to doxorubicin. Meanwhile, the area under the ROC curve (AUC) for this miRNA was 0.750 (SE = 0.102), indicating high discriminative ability of the biomarker. The 95% confidence interval (0.5508 to 0.9492) confirmed a stable trend toward discrimination between sensitive and resistant tumors, and the observed differences were significant ( $p = 0.0476$ ). At the same time, no relationship between serum hsa-miR-26b-5p level and sensitivity to doxorubicin was revealed (Fig. 2).

**Diagnostic, prognostic, and predictive value of the expression of tumor-associated hsa-miR-26b-5p and hsa-miR-186-5p in breast tumor tissue.** At the next stage of the study, we evaluated the expression



**Fig. 2.** Serum levels of hsa-miR-26b-5p (a) and hsa-miR-186-5p (b) depending on the response to NAC with doxorubicin (upper panels), and the corresponding ROC curves (lower panels) reflecting the predictive ability of these miRNAs for BC sensitivity to treatment. \*  $p < 0.05$

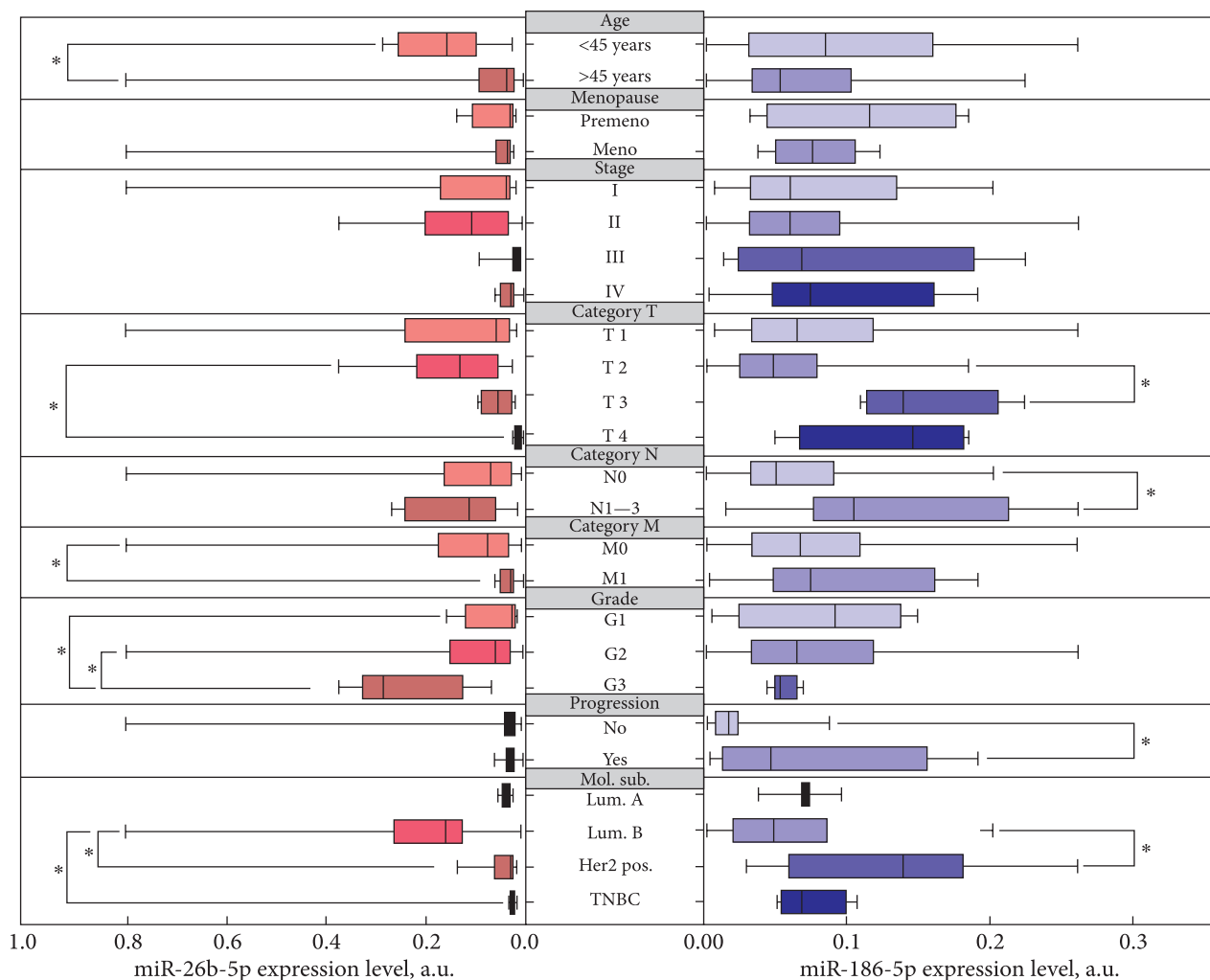


**Fig. 3.** Expression of hsa-miR-26b-5p (a) and hsa-miR-186-5p (b) in conditionally normal breast tissue, fibroadenoma, and BC tissue. \*  $p < 0.05$

levels of tumor-associated miRNAs to determine their diagnostic, prognostic, and predictive potential in BC. A characteristic feature of fibroadenoma tissue was significantly higher expression levels of hsa-miR-186-5p (2.05-fold,  $p = 0.0223$ ) compared to BC sam-

ples. The differences in hsa-miR-26b-5p expression depending on the type of breast tissue were insignificant (Fig. 3).

We also demonstrated that BC tissue samples from young patients were characterized by increased ex-



**Fig. 4.** Relationship between expression levels of tumor-associated hsa-miR-26b-5p or hsa-miR-186-5p and clinical status of BC patients. \*  $p < 0.05$

pression levels of hsa-miR-26b-5p (1.76-fold,  $p = 0.0005$ ) compared to those from patients older than 45 years. In addition, a tendency toward decreased expression of tumor-associated hsa-miR-26b-5p ( $p = 0.030$ ) with increasing tumor stage was observed.

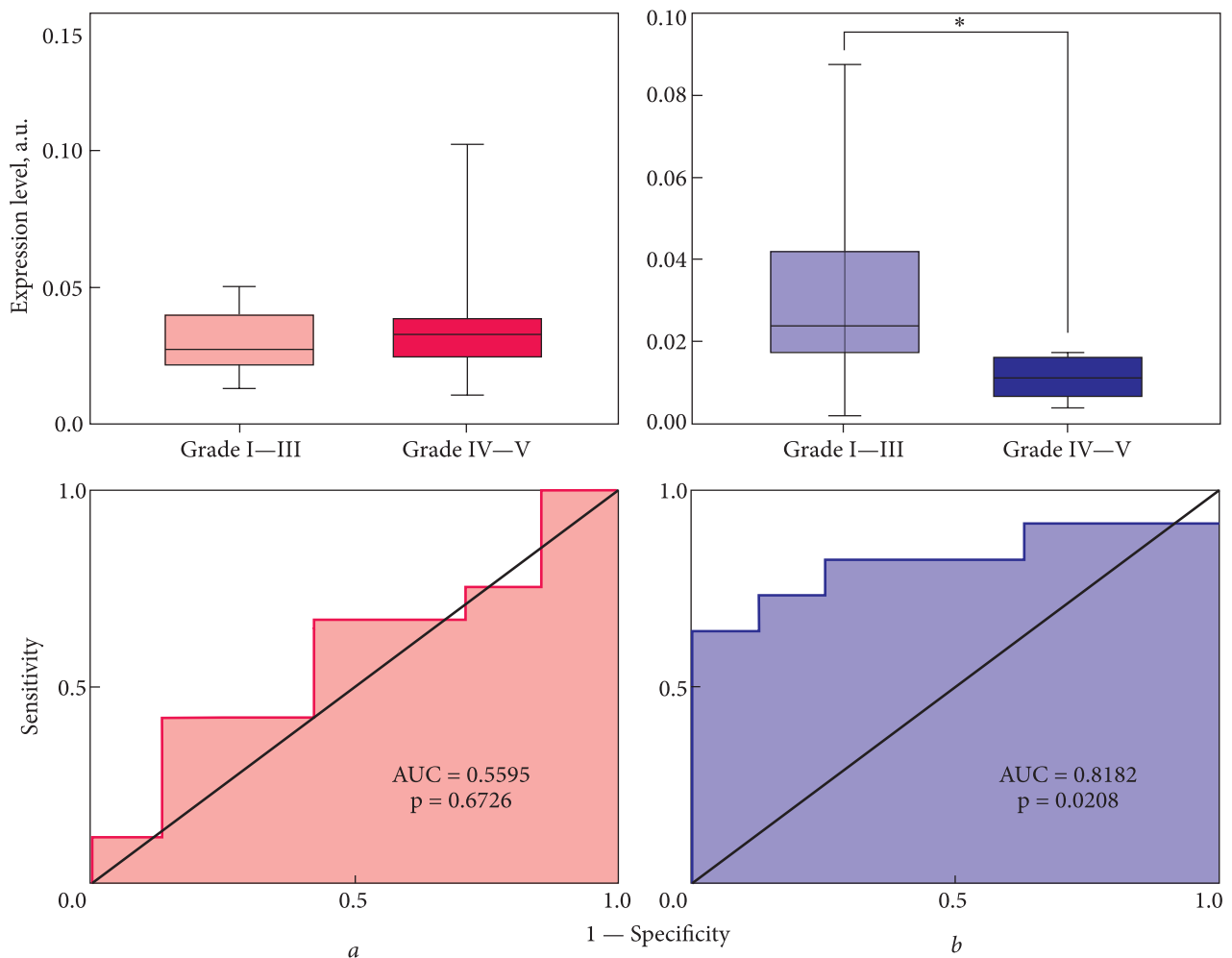
An association between the expression of the studied miRNAs in tumor tissue and tumor size was established (Fig. 4). In particular, BC tissue of the T2 category was characterized by significantly higher levels of hsa-miR-26b-5p (9.06-fold,  $p = 0.0036$ ), accompanied by a decrease in hsa-miR-186-5p levels (2.4-fold,  $p = 0.0216$ ) compared to those of tumors of the T4 and T3 categories, respectively. It is worth noting a general trend toward an increased hsa-miR-186-5p expression along with decreased hsa-miR-26b-5p levels with increasing tumor size.

We found that BC with diagnosed regional lymph node involvement is characterized by significantly higher hsa-miR-186-5p expression levels in tumor

tissue (1.92-fold,  $p = 0.0262$ ) compared to BC of the N0 category. At the same time, the decreased expression of hsa-miR-26b-5p was associated with the presence of distant metastases. In the M1 category cases, the expression of this miRNA was 3.79-fold lower ( $p = 0.0216$ ) compared to the M0 category.

A significant increase in hsa-miR-26b-5p levels (4.25-fold,  $p = 0.0202$  and 2.14-fold,  $p = 0.0471$ ) was observed in poorly differentiated BC tissue compared to tumor samples of highly and moderately differentiated tumors, respectively. The highest levels of this miRNA (4.01-fold,  $p = 0.0069$  and 7.18-fold,  $p = 0.0118$ ) were detected in luminal B BC tissue compared to HER2/neu-positive and triple-negative molecular subtypes, respectively.

An increase in tumor-associated hsa-miR-186-5p expression was shown in HER2/neu-positive BC (2.23-fold,  $p = 0.0450$ ) compared to the luminal B subtype. No significant association between the ex-



**Fig. 5.** Levels of hsa-miR-26b-5p (a) and hsa-miR-186-5p (b) in BC tissues depending on the response to NAC with doxorubicin (upper panels), and the corresponding ROC curves (lower panels) reflecting the predictive ability of these miRNAs for the BC sensitivity to the treatment. \*  $p < 0.05$

pression levels of the studied miRNAs and the histological type of BC was found.

In addition, the prognostic role of hsa-miR-186-5p expression levels in BC tissues was demonstrated. The patients with recurrence within 3 years after primary diagnosis were characterized by significantly higher expression levels of this miRNA in tumor tissue (3.29-fold,  $p = 0.0262$ ).

No association was found between the expression levels of the studied miRNAs in tumor tissue and menopausal status or tumor stage.

At the final stage, we evaluated the relationship between the levels of the studied miRNAs in tumor tissues and the effectiveness of NAC in BC patients treated with doxorubicin (Fig. 5). The patients who exhibited nonresponse or partial response to 4AC therapy (Miller–Payne grade I–III) were characterized by significantly higher expression levels of hsa-miR-186-5p in BC tissues (2.09-fold,  $p = 0.0203$ )

compared to the patients who responded to chemotherapy (Miller–Payne grade IV–V). No association between NAC effectiveness and hsa-miR-26b-5p expression levels was observed.

Finally, ROC analysis was performed to evaluate the predictive value of the studied miRNAs for sensitivity to 4AC therapy. AUC was 0.818 (SE = 0.103), indicating high discriminative ability of the biomarker. The 95% CI (0.616–1.000) confirmed a stable trend toward discrimination between sensitive and resistant tumors. The observed differences were significant ( $p = 0.0208$ ), indicating the potential of hsa-miR-186-5p as a predictive marker of NAC response.

The results of the study demonstrated the coordinated changes in the levels of hsa-miR-26b-5p and hsa-miR-186-5p in both serum and tumor tissues of BC patients, reflecting clinicopathological characteristics and tumor behavior. The young patients and those with poorly differentiated tumors exhibited in-

creased levels of hsa-miR-26b-5p in both serum and tumor tissue, whereas hsa-miR-186-5p showed the highest expression in HER2/neu-positive tumor tissue and in the serum of patients with early-stage BC, indicating its specific association with the tumor molecular profile and local activity.

The elevated serum levels of hsa-miR-26b-5p were associated with BC progression, while the high levels of hsa-miR-186-5p in peripheral blood and tumor tissue correlated with recurrence and resistance to NAC.

The results obtained are consistent with current evidence of the involvement of the studied miRNAs in the regulation of the tumor microenvironment and carcinogenesis. In particular, hsa-miR-26b-5p is considered an important regulator of extracellular matrix genes and metabolic cascades, as demonstrated in pancreatic cancer [12], hepatocellular carcinoma [13], and non-small cell lung cancer [14], as well as in malignant tumors of the uterus [15]. Moreover, its increased expression after prolonged radiation exposure is associated with enhanced DNA repair and increased migratory and invasive potential of tumor cells, highlighting its link with adaptive tumor stress responses [7]. Meanwhile, hsa-miR-186-5p has been described as a key regulator of the TGF $\beta$  signaling pathway through suppression of SMAD6/SMAD7 and is involved in the pathogenesis of colorectal [16], hepatocellular [17], endometrial and ovarian [18], lung [19], and esophageal [20] cancers,

indicating its broad involvement in tumor progression signaling networks. Despite accumulating evidence regarding the functional roles of both miRNAs in multiple tumor types, their prognostic and diagnostic value remains insufficiently characterized, underscoring the need for further research into their potential as biomarkers.

The combined analysis of these miRNAs suggested that hsa-miR-26b-5p could be involved in tumor aggressiveness and systemic response, whereas hsa-miR-186-5p expression is related to the molecular characteristics and NAC sensitivity. This integrated pattern highlights the potential of both miRNAs as biomarkers for the simultaneous assessment of progression risk, molecular subtype, and the prediction of treatment response, making them promising candidates for comprehensive prognostic and predictive evaluation in BC.

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#### ПРОГНОСТИЧНЕ ТА ПРЕДИКТИВНЕ ЗНАЧЕННЯ ЦИРКУЛЮЮЧИХ ТА ПУХЛИНО-АСОЦІЙОВАНИХ hsa-miR-26b-5p ТА hsa-miR-186-5p ПРИ РАКУ МОЛОЧНОЇ ЗАЛОЗИ

**Стан питання.** Гетерогенність раку молочної залози (РМЗ) суттєво ускладнює діагностику, прогнозування перебігу захворювання та передбачення ефективності лікування. МікроРНК розглядаються як перспективні біомаркери завдяки їхній участі в регуляції пухлинної прогресії та чутливості до терапії. Водночас комбіноване клінічне значення циркулюючих і пухлиноасоційованих hsa-miR-26b-5p та hsa-miR-186-5p залишається недостатньо вивченим. **Матеріали та методи.** Досліджено рівні експресії hsa-miR-26b-5p та hsa-miR-186-5p у сироватці крові та пухлинній тканині 124 пацієнтів із РМЗ. Проаналізовано їх зв'язок із клініко-патологічними характеристиками. Прогностичну значущість оцінювали за розвитком прогресії та рецидиву протягом 3 років. Предиктивну цінність визначали в пацієнтів, які отримували неоад'ювантну хіміотерапію (схема 4AC), із використанням оцінки відповіді та ROC-аналізу. **Результати.** У пацієнтів молодого віку ( $\leq 45$  років) виявлено достовірне зниження рівнів обох мікроРНК у сироватці крові. Експресія hsa-miR-186-5p у сироватці асоціювалася зі стадією захворювання, розміром пухлини, статусом лімфатичних вузлів та молекулярним підтипом. Підвищені рівні циркулюючої hsa-miR-26b-5p були пов'язані з прогресією захворювання, тоді як зниження hsa-miR-186-5p спостерігалось в пацієнтів із несприятливим перебігом. У пухлинній тканині експресія hsa-miR-26b-5p корелювала зі ступенем диференціювання, розміром пухлини та наявністю метастазів: її рівні були підвищені у низькодиференційованих пухлинах та знижені при метастатичному процесі. Натомість hsa-miR-186-5p була пов'язана з молекулярним підтипом та ураженням лімфатичних вузлів, із найвищими рівнями при HER2-позитивному РМЗ та в пацієнтів із рецидивом. Підвищені рівні hsa-miR-186-5p у сироватці та пухлинній тканині асоціювалися зі зниженням чутливості до неоад'ювантної хіміотерапії на основі доксорубіцину. ROC-аналіз підтвердив її високу предиктивну цінність (AUC = 0,750 для сироватки та 0,818 для тканини). Для hsa-miR-26b-5p такого зв'язку не встановлено. **Висновки.** hsa-miR-26b-5p та hsa-miR-186-5p відіграють взаємодоповнюючі ролі у біології РМЗ. hsa-miR-26b-5p переважно відображає агресивність пухлини та системну прогресію, тоді як hsa-miR-186-5p характеризує молекулярні особливості пухлини та чутливість до хіміотерапії. Їх комбіноване визначення у сироватці крові та пухлинній тканині є перспективним підходом для покращення прогнозування перебігу захворювання та ефективності лікування.

**Ключові слова:** рак молочної залози, hsa-miR-26b-5p, hsa-miR-186-5p, доксорубіцин.