https://doi.org/10.34883/PI.2026.15.2.008

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MicroRNA Expression in Platelet Microvesicles of Patients with Different Forms of Oncological Pathology: A Pilot Study

Conflict of interest: nothing to declare.
Authors' contribution: Dremuk I. – conducting experiments and data analysis, writing the manuscript; Shliakhtunou Y., Pashinskaya E. – collection of clinical data; Usova V., Staroselets A. – assistance in conducting the experiment; Lukyanenko L. – reviewing and editing the manuscript; Sveshnikova A., Shamova E. – concept and design, data analysis, reviewing, editing and supervision.
Data availability statement. The data that support the findings of this study are openly available at: https://figshare.com/s/4d0ce9db3131beb005f0
Funding: this work was supported by Belarusian Foundation for Fundamental Research grant (B23-RSF162) and Russian Science Foundation grant (23-45-10039).
The article is published in author's edition.

Submitted: 22.09.2025
Accepted: 17.02.2026
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Abstract

Introduction. MicroRNAs are a class of small non-coding RNAs that play crucial role in gene expression control. Numerous studies indicate that abnormal expression of microRNAs contributes to the development and progression of various malignancies. In recent years, microRNAs found in platelets and platelet-derived microvesicles have attracted considerable attention. Increased circulating platelet microvesicles and modified expression of their microRNAs have been reported in individuals with solid tumors.
Purpose. To study the expression state of microRNA-103a, microRNA-223a, microRNA-27a and microRNA-24 in platelet microvesicles in patients with breast cancer, lung cancer, renal cell carcinoma and skin melanoma.
Materials and methods. The study involved 70 patients, including 20 with breast cancer, 20 – lung cancer, 20 – renal cell carcinoma, 10 – melanoma and 10 clinically healthy individuals were involved in the study. PMVs were isolated from washed thrombin-stimulated platelets by sequential centrifugation. MicroRNA expression was studied using PCR analysis. Differences were considered statistically significant at $p<0.05$ and were assessed using the Mann – Whitney U test. The optimal cutoff value of miRNA-103a, miRNA-27a and miRNA-24 expression was determined using Receiver Operating Characteristic (ROC) analysis.
Results. A significant reduction in the expression levels of platelet-derived microRNA-103a (2.2- and 4.1-fold, respectively), microRNA-27a (2.6- and 7.9-fold, respectively),

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and microRNA-24 (4-fold in both pathologies) was observed in patients with renal cell carcinoma and melanoma. Moreover, reduced levels of platelet-derived microRNA-27a were identified in patients with breast (6.9-fold) and lung cancers (3.3-fold).
Conclusion. The obtained results indicate the potential use of the test for determining the expression of microRNA in platelet microvesicles as biomarkers for a number of oncological diseases: renal cell carcinoma, melanoma, breast cancer and lung cancer.
Keywords: platelet-derived microvesicles, microRNA, breast cancer, lung cancer, renal cell carcinoma, skin melanoma

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Экспрессия микроРНК в микровезикулах тромбоцитов пациентов с различными формами онкологической патологии: пилотное исследование

Конфликт интересов: не заявлен.
Вклад авторов: Дремук И.А. – проведение экспериментов, анализ данных, написание рукописи; Шляхтунов Ю.А., Пашинская Е.С. – сбор клинических данных; Усова В.А., Староселец А.В. – помощь в проведении эксперимента; Лукьяненко Л.М. – рецензирование и редактирование рукописи; Свешникова А.Н., Шамова Е.В. – концепция и дизайн, анализ данных, рецензирование, редактирование и руководство.
Заявление о доступности данных: данные, подтверждающие выводы данного исследования, находятся в открытом доступе (https://figshare.com/s/4d0ce9db3131beb005f0).
Финансирование: работа поддержана Белорусским республиканским фондом фундаментальных исследований (грант № Б23РНФ-162) и Российским научным фондом (грант РНФ23-45-10039).
Статья опубликована в авторской редакции.

Подана: 22.09.2025
Принята: 17.02.2026
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Резюме

Введение. МикроРНК – класс малых некодирующих РНК, играющих ключевую роль в регуляции экспрессии генов. Многочисленные исследования показывают, что аномальная экспрессия микроРНК способствует развитию и прогрессированию различных злокачественных новообразований. В последние годы микроРНК, обнаруженные в тромбоцитах и тромбоцитарных микровезикулах, привлекают значительное внимание. У пациентов с солидными опухолями отмечено увеличение количества циркулирующих тромбоцитарных микровезикул и изменение экспрессии их микроРНК.

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Цель. Изучить состояние экспрессии микроРНК-103a, микроРНК-223a, микроРНК-27a и микроРНК-24 в тромбоцитарных микровезикулах у пациентов с раком молочной железы, раком легкого, почечно-клеточным раком и меланомой кожи.

Материалы и методы. В исследовании приняли участие 70 пациентов, из них 20 страдают раком молочной железы, 20 – раком легкого, 20 – почечно-клеточным раком, 10 – меланомой, и 10 клинически здоровых лиц. PMV были выделены из отмытых тромбин-стимулированных тромбоцитов методом последовательного центрифугирования. Экспрессию микроРНК изучали с помощью ПЦР-анализа. Различия считались статистически значимыми при $p<0,05$ и оценивались с помощью U-критерия Манна – Уитни. Оптимальное пороговое значение экспрессии miRNA-103a, miRNA-27a и miRNA-24 определяли с помощью ROC-анализа.

Результаты. У пациентов с почечно-клеточным раком и меланомой наблюдалось значительное снижение уровня экспрессии микроРНК-103a (в 2,2 и 4,1 раза соответственно), микроРНК-27a (в 2,6 и 7,9 раза соответственно) и микроРНК-24 (в 4 раза при обеих патологиях). Кроме того, снижение уровня тромбоцитарной микроРНК-27a было выявлено у пациентов с раком молочной железы (в 6,9 раза) и раком легкого (в 3,3 раза).

Заключение. Полученные результаты указывают на потенциальную возможность использования теста определения экспрессии микроРНК в микровезикулах тромбоцитов в качестве биомаркеров ряда онкологических заболеваний: почечно-клеточного рака, меланомы, рака молочной железы и рака легкого.

Ключевые слова: микровезикулы тромбоцитарного происхождения, микроРНК, рак молочной железы, рак легкого, почечно-клеточный рак, меланома кожи

■ INTRODUCTION

Platelets are anuclear blood cells of 2–3 μm in diameter, derived from megakaryocytes in the bone marrow [1]. For many years, platelets were considered only as key participants in hemostasis, facilitating primary blood clotting and stopping bleeding [2], however accumulated research data over the past decade have demonstrated the pivotal role of platelets in modulating immune responses, that includes involvement in inflammation, regulation of innate and adaptive immunity, and interactions with immune cells and endothelium [2, 3]. Platelets play an active role in the development, progression and metastasis of oncological diseases by regulating proliferative activity and epithelial-mesenchymal transition [4], stimulating of angiogenesis and vascular remodeling, and protecting circulating tumor cells from immune surveillance [2, 5].

Platelets constitute the main source of microvesicles in the peripheral bloodstream [6]. The number of circulating platelet microvesicles (PMVs) increases in numerous diseases, such as thrombocytopenia [7], arterial thrombosis [8], sepsis [9], malignant neoplasms [10]. It has been shown that PMVs facilitate the delivery of RNA into tumor cells and that platelet-associated microRNAs play a crucial role in cancer progression [11]. MicroRNAs are short sequences of 18–25 nucleotides which influence various aspects of cellular function by regulating gene expression, interfering with protein translation, or facilitating mRNA degradation through binding to the untranslated regions (UTRs) of target mRNA

[12]. TMBs may promote angiogenesis and enhance vascular permeability by transferring microRNAs to endothelial cells, thereby fostering a vascular microenvironment favorable to tumor growth and metastasis [13, 14]. Conversely, TMBs can directly transfer microRNAs into tumor cells, thereby regulating gene expression and tumor progression [13].

MicroRNAs are classified as tumor suppressors or oncogenes based on their role in tumor development. Suppressor microRNAs inhibit the expression of oncogenes or pro-apoptotic genes, while oncogenic microRNAs promote carcinogenesis or downregulate tumor suppressor genes [15]. Several platelet-derived microRNAs, including microRNA-27a, microRNA-24, microRNA-155, microRNA-195, let-7a/b, and microRNA-223, target both tumor suppressor genes and oncogenes across various cancer types, and are currently being considered as diagnostic and prognostic markers for malignancies [16–19]. Specifically, miR-24 and miR-223 are linked to several types of cancer and target both tumor suppressors and oncogenes, with ongoing identification of new targets and mechanisms of action [16, 19]. It is obvious that platelet microRNAs play an important role in cancer, however, the mechanisms underlying their involvement in this pathological process are far from being fully understood.

■ PURPOSE OF THE STUDY

To study the expression state of microRNA-103a, microRNA-223a, microRNA-27a and microRNA-24 in platelet microvesicles in patients with breast cancer, lung cancer, renal cell carcinoma and skin melanoma.

■ MATERIALS AND METHODS

Research Subjects

The study was carried out on PMVs from 70 individuals with resectable stages of malignant neoplasms. The control group consisted of 10 conditionally healthy individuals (without oncological diseases). The characteristics of the study participants are presented in Table 1.

Preparation of PMVs

Peripheral venous blood stabilized with sodium citrate (3.8%, in a ratio of 9 : 1 by volume) was centrifuged for 10 min at 190×g at room temperature. Subsequently, the platelet-rich plasma (PRP) was carefully collected, ensuring that the mononuclear cell

Table 1
Characteristics of study participants and pathomorphological features of the tumor

Localization	n	Average age, years	Pathomorphological features of the tumor, TNM							
			T (%)			N (%)		Stage (%)		
			T1	T2	T3	N0	N+	I	II	III
Lung cancer	20	58.0±12.7	50	40	10	55	45	30	35	35
Breast cancer	20	61.4±7.2	70	30	0	45	55	40	50	10
Renal cell carcinoma	20	62.2±6.7	70	25	5	65	35	60	5	35
Melanoma of the skin	10	43.4±11.3	50	40	10	70	30	50	20	30

Notes: T (Tumor): Describes the size of the primary tumor and the extent of its spread into nearby tissue. Numbers from 1 to 3 indicate increasing tumor size and spread. N (Nodus): Indicates how much cancer has spread to nearby lymph nodes. N0 means no cancer cells are found in the lymph nodes. N+ means the number of affected lymph nodes is unknown.

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and erythrocyte layers remained undisturbed. PRP was then mixed with sodium citrate (pH 5.5) and Tyrode's buffer (TB, 137 mmol/L NaCl, 2.7 mmol/L KCl, 11.9 mmol/L NaHCO3, 0.43 mmol/L NaH2PO4, 5 mmol/L HEPES, 5.5 mmol/L D-glucose, 1 mmol/L MgCl2, 3.5 g/L BSA, pH 7.35) in a 1 : 1 : 2 volume ratio and centrifuged at 400×g for 5 min at room temperature. The supernatant was removed and the pellet was resuspended in TB to a final concentration of 3×108 platelets/mL CaCl2 (1.5 mM) and thrombin (0.1 U/ml) were added to the washed platelet suspension, followed by incubation at 37 °C for 90 minutes. The activated platelet suspension was centrifuged at 3160×g for 15 minutes at 4 °C to pellet the cells. The resulting supernatant was collected and centrifuged again at 2500×g for 15 minutes at 4 °C to ensure complete sedimentation of residual cells. The supernatant was transferred to 1 mL Eppendorf tubes and centrifuged at 20 000×g for 90 minutes at 4 °C. The final supernatant was discarded, and the resulting pellet was washed with TB at one-tenth of the original volume, transferred to clean Eppendorf tubes, and stored at –80 °C. In this way, platelet-derived microvesicles were isolated from washed platelets at a concentration of 3×10^8 platelets/mL and concentrated into a volume reduced tenfold compared to the original suspension of washed platelets.

RNA Extraction and Quantitative RT-PCR of microRNA

Total RNA was extracted from platelet microvesicle samples using the phenol-chloroform method [20]. For this purpose, 1 ml of RNA extraction reagent was added to 200 µl of microvesicles. The resulting mixture was incubated at room temperature for 5 minutes and then centrifuged at 12 000×g for 10 minutes, after which the supernatant was transferred to new tubes. To remove proteins, DNA and other contaminants, 0.2 ml of chloroform was added, mixed thoroughly, and centrifuged at 12000 × g for 15 minutes. The RNA-containing upper aqueous phase was collected. Subsequently, 0.5 ml of isopropanol was added, centrifuged at 12 000 g for 10 minutes, after which the supernatant was carefully discarded. The RNA pellet was washed with 1 mL of 75% ethanol and centrifuged at 8000×g for 5 minutes. The ethanol was carefully removed, and the RNA pellet was air-dried before being dissolved in 50 µL of nuclease-free water. RNA concentration and purity were determined spectrophotometrically. Complementary DNA (cDNA) synthesis and PCR analysis were performed using the miRCURY LNA miRNA PCR Starter Kit (Qiagen) according to the manufacturer's protocol. For cDNA synthesis (Table 2), the RNA concentration was adjusted to 20 ng/µl in all samples.

For PCR analysis (Table 3), commercial primers optimized using LNA technology were used, which provide sensitive and specific quantification of the studied microRNAs [21].

Melting curve analysis was performed in the temperature range of 60–95 °C. Detection of PCR products and initial data processing were carried out using Bio-Rad CFX Maestro software. Further data processing and statistical analysis were performed using MS Excel and Origin 2021.

Table 2
Reverse transcription temperature cycling protocol

Stage	Time	Temperature
Reverse transcription	60 min	42 °C
Inactivation reaction	5 min	95 °C
Cooling	Continuous	4 °C

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Table 3
PCR cycling conditions (40 cycles in total)

Stage	Time	Temperature	Rate of change
Initial heat activation	2 min	95 °C	Maximum / fast mode
Denaturation	10 sec	95 °C	Maximum / fast mode
Annealing	60 sec	56 °C	Maximum / fast mode

For each sample, the threshold cycle (Cq) value was determined, reflecting the point at which the amplification curve intersects the baseline. To eliminate the normalization issue for microRNA expression in the platelet microvesicles, depending on the absence of stable microRNA, we used the means normalization method [22]. The relative expression level (R) of microRNA was calculated using the equation: $R=2^{\Delta Cq}$, where $\Delta Cq = Cq_{average} - Cq_{sample}$; $Cq_{average}$ refers to the average Cq value of the control group (donors), and Cq_{sample} is the Cq value of the individual sample. Differences were considered statistically significant at $p<0.05$ and were assessed using the Mann – Whitney U test. The optimal cutoff value of miRNA-103a, miRNA-27a and miRNA-24 expression was determined using Receiver Operating Characteristic (ROC) analysis.

■ RESULTS

In our preliminary study, we examined those microRNAs that are highly expressed in platelet microvesicles. Using PCR analysis, we examined the expression levels of microRNA-103a, microRNA-223a, microRNA-27a, and microRNA-24 in platelet microvesicles from patients with BC, LC, RCC, and melanoma. Our results revealed a significant decrease in the median expression level of microRNA-103a compared to the control group in RCC (2.2-fold, p=0.0019) and melanoma (4.1-fold, p=0.002). In addition, we observed a trend toward increased expression in BC (1.5-fold) and decreased expression in LC (1.3-fold), although these changes did not reach statistical significance (Fig. 1).

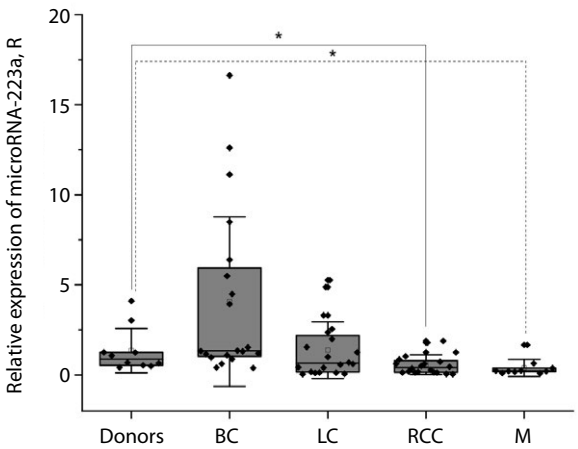

Fig. 1. Relative expression (R) of microRNA-103a in platelet microvesicles from donors and patients with breast cancer (BC), lung cancer (LC), renal cell carcinoma (RCC), and melanoma (M). Data are presented as median values with interquartile ranges [25th percentile; 75th percentile] and standard deviation. * p<0.05 (Mann – Whitney test)

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One of the most abundant platelet microRNAs is microRNA-223a [23, 24], whose expression is also deregulated in many types of cancer [6, 23]. Our results showed that in all the malignancies we examined, the expression of microRNA-223a did not differ significantly from that in the control group (Fig. 2).

In our study, we found a significant decrease in the median expression levels of platelet-derived microRNA-27a compared to the control group across all cancer types examined: in BC by 6.9-fold (p=0.0003), in LC by 3.3-fold (p=0.0006), in RCC by 2.6-fold (p=0.0022), in melanoma by 7.9-fold (p=0.0013) (Fig. 3).

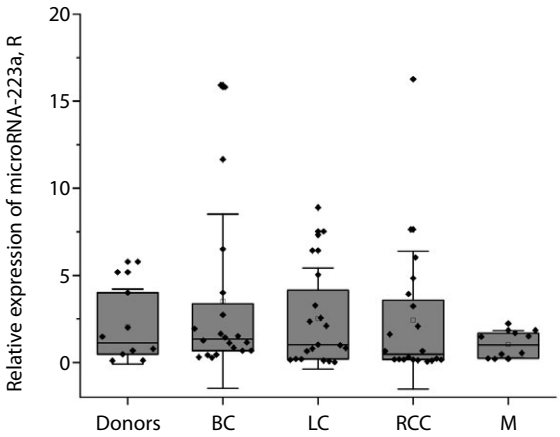

Fig. 2. Relative expression (R) of microRNA-223a in platelet microvesicles from donors and patients with breast cancer (BC), lung cancer (LC), renal cell carcinoma (RCC), and melanoma (M). Data are presented as median values with interquartile ranges [25th percentile; 75th percentile] and standard deviation. * p<0.05 (Mann – Whitney test)

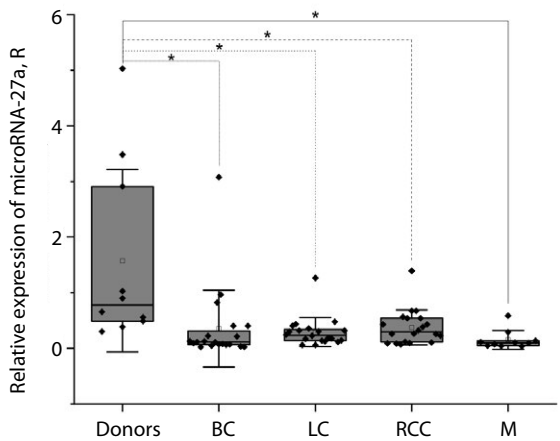

Fig. 3. Relative expression (R) of microRNA-27a in platelet microvesicles from donors and patients with breast cancer (BC), lung cancer (LC), renal cell carcinoma (RCC), and melanoma (M). Data are presented as median values with interquartile ranges [25th percentile; 75th percentile] and standard deviation. * p<0.05 (Mann – Whitney test)

Another important member of the microRNA family is microRNA-24. The results of our study demonstrated a significant decrease in the median expression levels of platelet microRNA-24 compared to the control group in RCC (4-fold, p=0.032) and in melanoma (4-fold, p=0.0035). A trend towards decreased expression of microRNA-24 was also observed in BC (1.7-fold) and in LC (2.3-fold) (Fig. 4).

Table 4 summerizes data we obtained in our study.

We conducted receiver operating characteristic (ROC) curve analysis to determine the optimal threshold (cutoff) expression levels of miRNA-103a and miRNA-24 for RCC and melanoma, as well as miRNA-27a for the entire group of malignancies analyzed. These cutoff values were selected based on the maximal Youden index, providing the greatest discrimination between pathological and non-pathological conditions. The corresponding ROC curves and performance metrics are shown in Fig. 5 and summarized in Table 5.

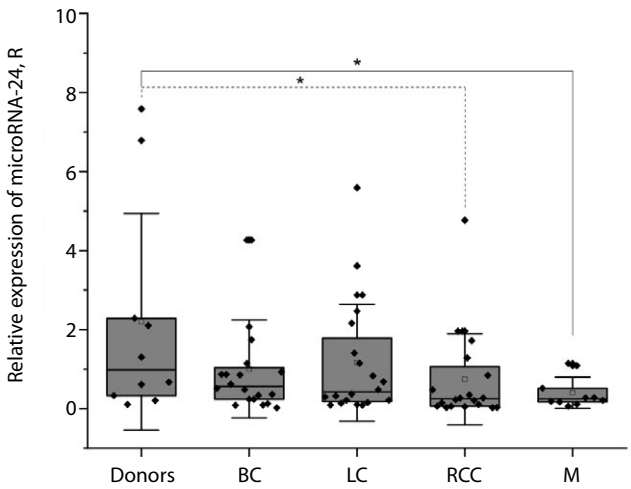

Fig. 4. Relative expression (R) of microRNA-24 in platelet microvesicles from donors and patients with breast cancer (BC), lung cancer (LC), renal cell carcinoma (RCC), and melanoma (M). Data are presented as median values with interquartile ranges [25th percentile; 75th percentile] and standard deviation. * p<0.05 (Mann – Whitney test)

Table 4
Changes in microRNA expression in PMVs of cancer patients

	microRNA-103a	microRNA-223a	microRNA-27a	microRNA-24
BC	–	–	↓6.9-fold, p=0.0003	–
LC	–	–	↓3.3-fold, p=0.0006	–
RCC	↓2.2-fold, p=0.0019	–	↓2.6-fold, p=0.0022	↓4.0-fold, p=0.0032
Melanoma	↓4.1-fold, p=0.0020	–	↓7.9-fold, p=0.0013	↓4.0-fold, p=0.0035

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Table 5
Results of ROC curve analysis of microRNA-103a, microRNA-27a, and microRNA-24 expression in patients with various types of cancer

Study groups	microRNA	AUC	p	Sensitivity	Specificity	Optimal cutoff point
RCC and donors	103a	0.76	0.020	50%	100%	0.39
	24	0.74	0.003	70%	70%	0.54
	27a	0.96	0.0005	90%	100%	0.29
Melanoma and donors	103a	0.89	0.003	80%	100%	0.40
	24	0.78	0.03	70%	80%	0.30
	27a	0.84	0.03	80%	70%	0.55
BC and donors	27a	0.89	0.0007	75%	100%	0.26
LC and donors	27a	0.92	0.0002	95%	80%	0.49

Notes: area under the curve (AUC) values: 0.9–1 – excellent model performance; 0.8–0.9 – very good; 0.7–0.8 – good; 0.6–0.7 – fair (average); 0.5–0.6 – poor.

■ DISCUSSION

MicroRNA-103a has been shown to act as both an oncogene and a tumor suppressor in cancer development. In particular, Hu X. et al. [25] demonstrated that overexpression of microRNA-103a caused stimulation of cell proliferation in gastric cancer. Xia W. et al. [26] found that microRNA-103a promoted the growth of hepatocellular carcinoma by targeting AKAP12 (A-kinase anchoring protein 12). In addition, microRNA-103a has been shown to promote cell proliferation and migration in colorectal cancer cells by targeting the tumor suppressor genes DICER and PTEN [27].

However, some studies have reported that microRNA-103a functions as a tumor suppressor in several human cancers. In prostate cancer (PC) cells, elevated microRNA-103a expression was shown to inhibit cell migration and invasion through regulation of the oncogenic protein TPD52 [28]. Moreover, microRNA-103a inhibited the malignant progression of glioma by binding to FEZF1 at the 3′-UTR [29]. These conflicting findings indicate that microRNA-103a expression is tissue specific and may serve as a potential diagnostic and prognostic marker in various human cancers.

Our study showed that the expression of platelet microRNA-103a was significantly reduced in RCC and melanoma compared to the donor group, suggesting a possible tumor-suppressive role of microRNA-103a in these cancer types. However, the mechanisms underlying its function remain to be elucidated.

Increased expression of microRNA-223a has been associated with poor prognosis and drug resistance in non-small cell LC [30] and stomach cancer [31]. In contrast, microRNA-223a plays a tumor suppressor role in human PC [32], bladder cancer [33], cervical cancer [34] и hepatocellular carcinoma [35]. Liang H. et al. showed that miR-223a expression in platelet-derived microvesicles from patients with metastatic lung cancer was significantly elevated compared to that in donors and may promote lung cancer cell invasion via targeting the tumor suppressor EPB41L3 [6]. However, we did not observe such an increase in our results. A possible explanation is that the patients enrolled in our study were at early, resectable stages of malignancy.

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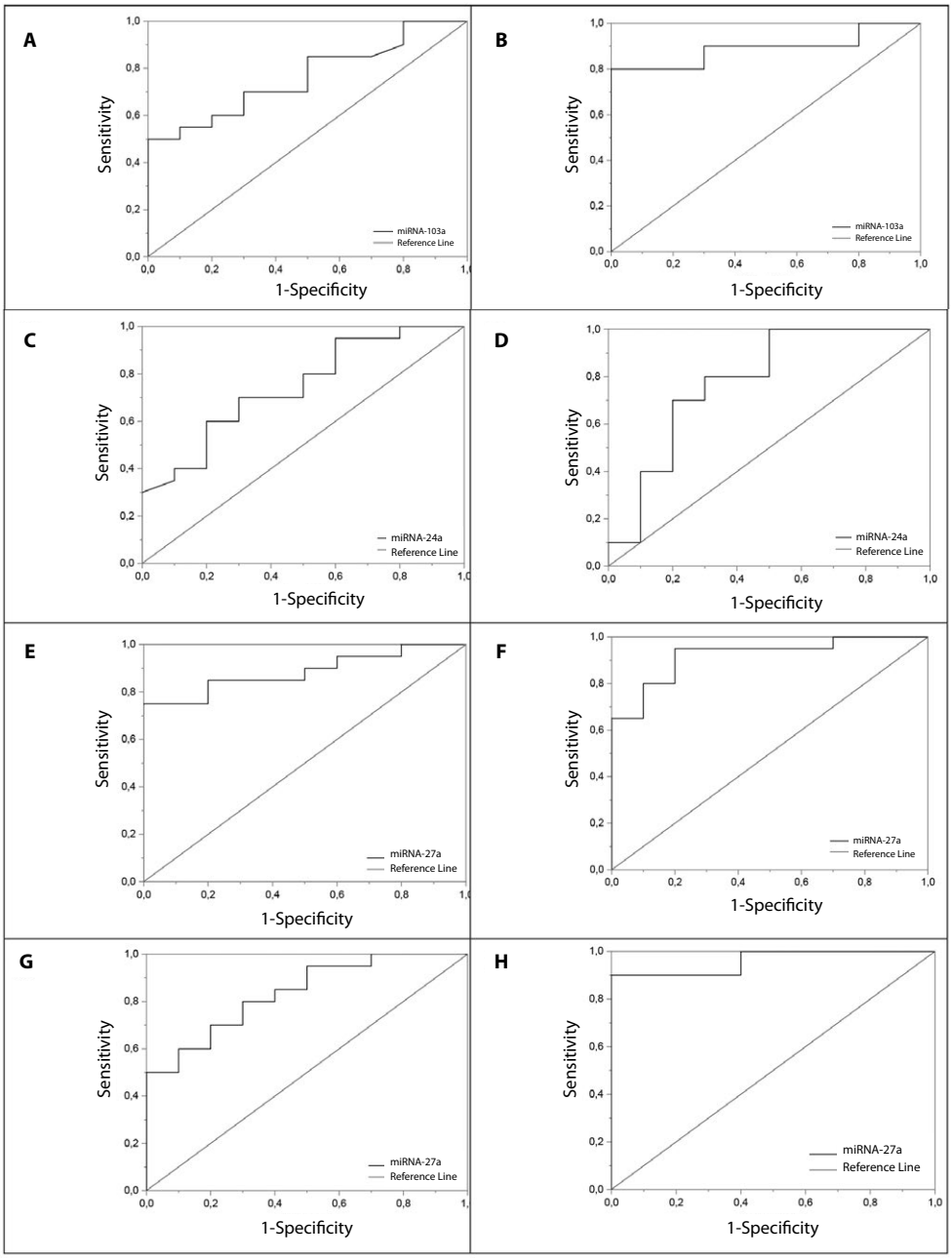

Fig. 5. ROC curves based on the expression levels of microRNA-103a, microRNA-24, and microRNA-27a in patients with RCC (A, C, G) and melanoma (B, D, H), as well as microRNA-27a expression in patients with BC (E) and LC (F)

MicroRNA-27a also plays a dual role in cancer development. This microRNA is upregulated and promotes proliferation and invasion, while inhibiting apoptosis in osteosarcoma cells through TET1 regulation, indicating an oncogenic role for microRNA-27a [36].

In contrast, microRNA-27a has been found to be downregulated in hepatocellular carcinoma, where it suppresses tumor metastasis and vasculogenic mimicry by targeting Twist-1 [37]. In recent years, circulating microRNA-27a has emerged as a predictive and prognostic biomarker in gastrointestinal tumors, as it can be secreted by exosomes into the serum circulation in gastric cancer [38]. Circulating exosomal microRNA-27a has also been reported as a novel diagnostic and prognostic biomarker in colorectal cancer [39]. In our study, we found a significant reduction in median miRNA-27a expression levels compared to the control group in all cancer types studied, which allows us to consider this miRNA as a potential biomarker.

Studies have shown that microRNA-24 is involved in tumor cell proliferation, differentiation, invasion, and metastasis by regulating numerous genes, including PTEN, TRIM11, SOX7, PRKCH, and P16 [40]. Platelet-derived microRNA-24 has also been shown to target mitochondrial mt-Nd2 and Snora75 in tumor cells [14]. Circulating microRNA-24 has been identified as a promising prognostic marker in various types of cancer, including gastric, lung, and colorectal cancers, as well as acute lymphoblastic leukemia and others [40, 41]. However, microRNA-24 exhibits variable expression across different cancers and may function as either an oncogene or a tumor suppressor. In particular, increased microRNA-24 expression has been reported in lung, breast, bladder and gastric cancers, as well as in acute leukemia, and Hodgkin's lymphoma [42]. On the other hand, microRNA-24 has been shown to be downregulated in nasopharyngeal and colorectal cancers, laryngeal squamous cell carcinoma, and lung adenocarcinoma compared to normal tissues [42]. The results of our study demonstrated a significant decrease in the median expression levels of platelet microRNA-24 compared to the control group in RCC and in melanoma, which also allows us to consider microRNA-24 as a potential biomarker for these types of cancer.

The ROC analysis enabled an objective evaluation of the diagnostic performance of the studied microRNAs and facilitated the identification of threshold expression levels distinguishing between the presence and absence of pathology. Expression values equal to or exceeding the determined cutoff points were associated with a higher probability of malignancy in the respective comparisons.

Consequently, our results allowed us to identify three microRNAs (microRNA-103a, microRNA-27a, and microRNA-24) whose expression is suppressed in patients PMVs, suggesting their potential function as tumor suppressors. These microRNAs may serve as possible cancer biomarkers in patients with solid tumors: microRNA-27a in BC and LC, and microRNA-103a, microRNA-27a, and microRNA-24 in RCC and melanoma.

It's also worth noting that the wide variation in the obtained microRNA expression levels is primarily due to the fact that the sample included patients with different cancer subtypes within a single pathology. Future studies should take this into account and conduct a similar study disaggregated by subtype.

■ CONCLUSION

Accumulating evidence suggests that numerous microRNAs are abnormally expressed in tumor tissues, blood, and cells, and that dysregulation of these microRNAs is associated with tumor initiation, progression, and prognosis. Some microRNAs have oncogenic functions and their expression increases in cancer patients; while others are downregulated and act as tumor suppressors. In addition, the same microRNA can act as both an oncogene and an oncosuppressor, depending on the tumor type and location.

In recent years, platelet microRNAs have attracted considerable attention, as they may offer higher sensitivity and specificity in tumor diagnosis compared to circulating microRNAs. In this study, we found decreased expression levels of platelet microRNA-103a, microRNA-27a, and microRNA-24 in patients with RCC and melanoma, as well as decreased expression of platelet-derived microRNA-27a in patients with BC and LC, suggesting that these microRNAs may serve as potential biomarkers.

However, several limitations should be considered in the present study. First, our results are based on a relatively small sample size of donors and patients with different types of cancer, which may limit statistical power. Second, the underlying mechanisms by which these microRNAs contribute to the development of the studied malignancies remain unclear and require further investigation. Nevertheless, our results may serve as a basis for the development of a diagnostic panel of microRNA-based biomarkers, at least for patients with RCC and melanoma.

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