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Original Article

Categorized Serum miRNAs as Potential Biomarkers for Predicting the Progression and Prognosis of Colorectal Cancer

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Abstract

Background: Colorectal cancer (CRC), a common and aggressive gastrointestinal cancer, presents significant challenges in diagnosis and prognosis prediction despite available detection and treatment options. Many studies emphasized the crucial link between abnormal microRNA regulation and their potential role in cancer development and progression. These miRNAs are recognized as important non-invasive biomarkers for prognosis and overall survival prediction in various cancers, including CRC.

Materials and Methods: In this study, we compared the expression patterns of eight miRNAs in the serum of 36 CRC patients with those of 37 healthy controls. The matching criteria included clinicodemographic factors and CRC susceptibility, and the analysis was performed using quantitative real-time PCR (qRT-PCR).

Results: The serum miRNA levels of these eight miRNAs (miR-19a, miR-92a, miR-103, miR-106a, miR-107a, miR-150, miR-221, and miR-720) in the study groups are significantly higher compared to the control group. This analysis revealed eight specific miRNAs with varying expression levels in CRC patients. Furthermore, bioinformatic analysis using data collection and analytical tools has shown that these miRNAs may be associated with important aspects of colorectal cancer development and progression through the PI3K/AKT/PTEN, WNT/CATENIN, and EMT signaling pathways.

Conclusion: Our analysis has identified a group of 8 overexpressed miRNAs (miR-19a, miR-92a, miR-103, miR-106a, miR-107a, miR-150, miR-221, and miR-720.) in serum samples of CRC patients. **:** Although further validation in larger and more diverse groups is necessary, these findings support a potential mechanism of action for these miRNAs in CRC and their association with essential signaling pathways, including PI3K/AKT/PTEN, WNT/CATENIN, and EMT.

Keywords:
Colorectal cancer (CRC)
microRNAs (miRNAs)
biomarkers
prognosis
PI3K/AKT/PTEN
WNT/CATENIN
EMT

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1. INTRODUCTION

Advanced colorectal cancers (CRC), commonly found within communities, typically undergo late diagnosis, leading to increased mortality and morbidity rates. Despite the transdisciplinary treatments, the patient's prognosis remains poor (1). Sporadic CRC involves most cases of this cancer, which has an obvious relationship with individual lifestyle factors such as physical activity and alcohol consumption (2). Colorectal Carcinoma is generally categorized into two distinct groups; the first type of CRC is characterized by microsatellite instability and the other is related to microsatellite stability but chromosomal instability (1). Advances in molecular genetics have elucidated key mutations responsible for both sporadic and familial colorectal cancer. Many oncogenes and tumor suppressor genes, such as APC, KRAS, and p53, are frequently involved in these mutations in CRC. These genetic alterations dysregulate well-conserved signaling pathways (MAPK, PI3K, WNT, and EMT) critical for diverse cellular functions, tumor hallmarks development, and undesirable patient outcomes (1), as demonstrated in **Figure 1**.

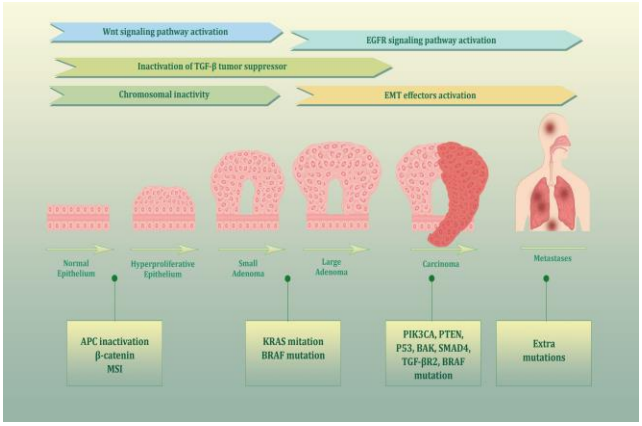

Figure 1. Pathophysiology and molecular perspective of colorectal cancer.

The molecular underlying pathways and the location of colorectal tumors are crucial and defining criteria for predicting the patient's prognosis and treatment response (2, 3, 4). A large body of literature reveals diverse levels of mortality reduction at CRC related to these tests such as (gFOBT) with a mortality reduction of 8-16%, flexible sigmoidoscopy with a mortality reduction of 20-30%, and fecal immunochemical test (FIT) and follow-up colonoscopy with a mortality reduction of 41% (4, 5, 6). All this data addressing worldwide challenges in colorectal cancer (CRC) screening and diagnosis programs remain a critical public health concern. MiRNAs, these short single-stranded RNA molecules, have emerged as key players in the complex landscape of many cancers' biology. MiRNAs have attracted significant research attention for their potential as oncogenes or tumor suppressors through critical signaling network manipulation. Utilizing these miRNAs promises early detection, monitoring, and personalized treatment strategies for CRC. Numerous studies have highlighted the diagnostic roles of miRNAs in CRC. Despite this body of research, developing CRC-specific functional miRNA panel of biomarkers as an informative predicting prognosis and treatment response criteria remains an obstacle. The present study aims to scrutinize the regulation patterns of microRNAs in colorectal cancer patients' serum to identify CRC-specific miRNAs and categorize them in terms of their mechanisms of action at the molecular level according to the bioinformatic analysis. A panel of categorized serum CRC-miRNAs could provide an invaluable prediction marker table for prognostic prediction and clinical assessment of colorectal cancer patients in the future.

2. MATERIAL AND METHOD

2.1. Sample collection

Samples were collected from the Department of Medical Oncology, Faculty of Medicine, Pamukkale University, from May 2018 to December 2019. These included 36 patients diagnosed histopathologically with colorectal cancer (who had not received preoperative radiotherapy or chemotherapy) and 37 healthy controls matched by demographic criteria. Experimental studies were conducted in the Cancer Biology laboratories within the Advanced Technology Application and Research Center at Pamukkale University. All patients had provided written informed consent. The study was granted ethical approval by the Pamukkale University Faculty of Medicine Ethics Committee. All participants provided written informed consent, and their samples were collected and subsequently stored at -80°C for further analysis.

2.2. Isolation and quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted from the samples using TRIzol reagent (Invitrogen, Waltham, MA, USA) following the manufacturer's protocol. The quality and quantity of the isolated RNA were subsequently evaluated using a NanoDrop 2000c spectrophotometer (Thermo Scientific,

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Waltham, MA, USA). cDNA synthesis was performed using the High-Capacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific) to generate first-strand cDNA from 1 µg of total RNA. Quantitative real-time PCR (qRT-PCR) was then performed using EvaGreen miRNA qPCR MasterMix (ABM, Canada) on a Rotor-Gene 6000 PCR system (Corbett Life Science, Australia). Relative miRNA expression levels were determined using the ΔΔCt method (Livak method) (7) with normalization to GAPDH as a reference gene.

2.3. Statistical analysis

All quantitative information was reported as mean ± standard deviation (SD) from three separate trials. The comparisons between the two groups were evaluated through Student's t-test P:0.05, signifying statistical significance.

3. RESULTS

3.1. Data collection and analysis workflow

A literature review and dataset analysis have been done to identify the CRC-specific miRNAs of interest. The Reactome (https://reactome.org/)(8) and KEGG (https://pubmed.ncbi.nlm.nih.gov/10592173/)(9) provided invaluable insights about pathways and member genes. Also for the analysis of these relationships, tools like miRbase (https://www.mirbase.org/)(10), (https://mirtarbase.cuhk.edu.cn/)(11), and In silico target prediction of miRNAs was performed using the TargetScan database (https://www.targetscan.org/)(12) for our specific miRNAs. These tools use various algorithms to predict interactions between miRNAs and mRNA transcripts. Afterward, perform pathway enrichment analysis and survey if miRNA target genes are statistically enriched in specific pathways utilized from tools like Enrichr (https://maayanlab.cloud/Enrichr/)(13) and DAVID (https://pubmed.ncbi.nlm.nih.gov/35325185/)(14)(15). Tools like Cytoscape (https://cytoscape.org/)(16) and STRING (https://academic.oup.com/nar/article/47/D1/D607/5198476)(17) were used to visualize the network of interactions between miRNAs, their target genes, and pathway components.

3.2 various associations between patients' clinicodemographic factors and their susceptibility to CRC

The study enrolled 35 patients with colorectal cancer and 37 healthy controls. The patient group involved 10 males (27.8%) and 26 females (72.2%), while the control group had 12 males (32.4%) and 25 females (67.6%). Both groups had similar age distributions within a range of 42-80 years (median age: 58 years for patients and 56 years for controls; $p > 0.05$). While the patient group had a slightly higher smoking rate (50%) compared to the control group (40.5%), this difference wasn't statistically significant ($p > 0.05$). Similarly, the groups did not exhibit any significant differences in alcohol consumption (40.5% in patients vs. 39.3% in controls; $p > 0.05$) or type 2 diabetes prevalence (38.9% in patients vs. 43.2% in controls; $p > 0.05$). These findings suggest that the patient and control groups were matched in terms of demographics (age, gender) due to the similar distribution observed (**Table 1**).

Table 1. Clinicodemographic factors and their association with CRC.

Clinicodemographic factors		CRC patient group	Healthy control group
Age(median)		58	56
Sex	Female	26 (%72.2)	25 (%67.6)
	Male	10 (%27.8)	12 (%32.4)
Cigarette	Yes	18 (%50)	15 (%40.5)
	No	18 (%50)	22 (%59.5)
Alcohol	Yes	15 (%37.8)	12(%32.7)
	No	26 (%72.2)	28(%77.3)
Type 2 DM	Yes	14 (%38.9)	16(%43.2)
	No	22(%61.1)	21 (%56.8)

3.3 The different expression levels of microRNAs in CRC serums

The candidate miRNAs (miR-19a, miR-92a, miR-103, miR-106a, miR-107, miR-150, miR-221, and miR-720,) were selected according to the previous experimental findings suggesting potential functions of these miRNAs in CRC pathogenesis. These miRNA expression levels were examined in 36 colorectal cancer patient groups and 37 individuals in the control group. As **Figure 2** displays, the serum miRNA expression levels in the patient group exhibit significantly higher levels of expression related to the healthy control group.

Examining the expression levels of chosen miRNAs showed a significant increase ($p<0.001$) within CRC patients compared to healthy individuals. This suggests that there might be varying levels of miRNA dysregulation linked to CRC. The sensitivity and specificity of these miRNAs for CRC diagnosis were evaluated using Receiver Operating Characteristic (ROC) analysis. Our analysis yielded an area under the ROC curve (AUC) ranging from 0.83 to 0.99,

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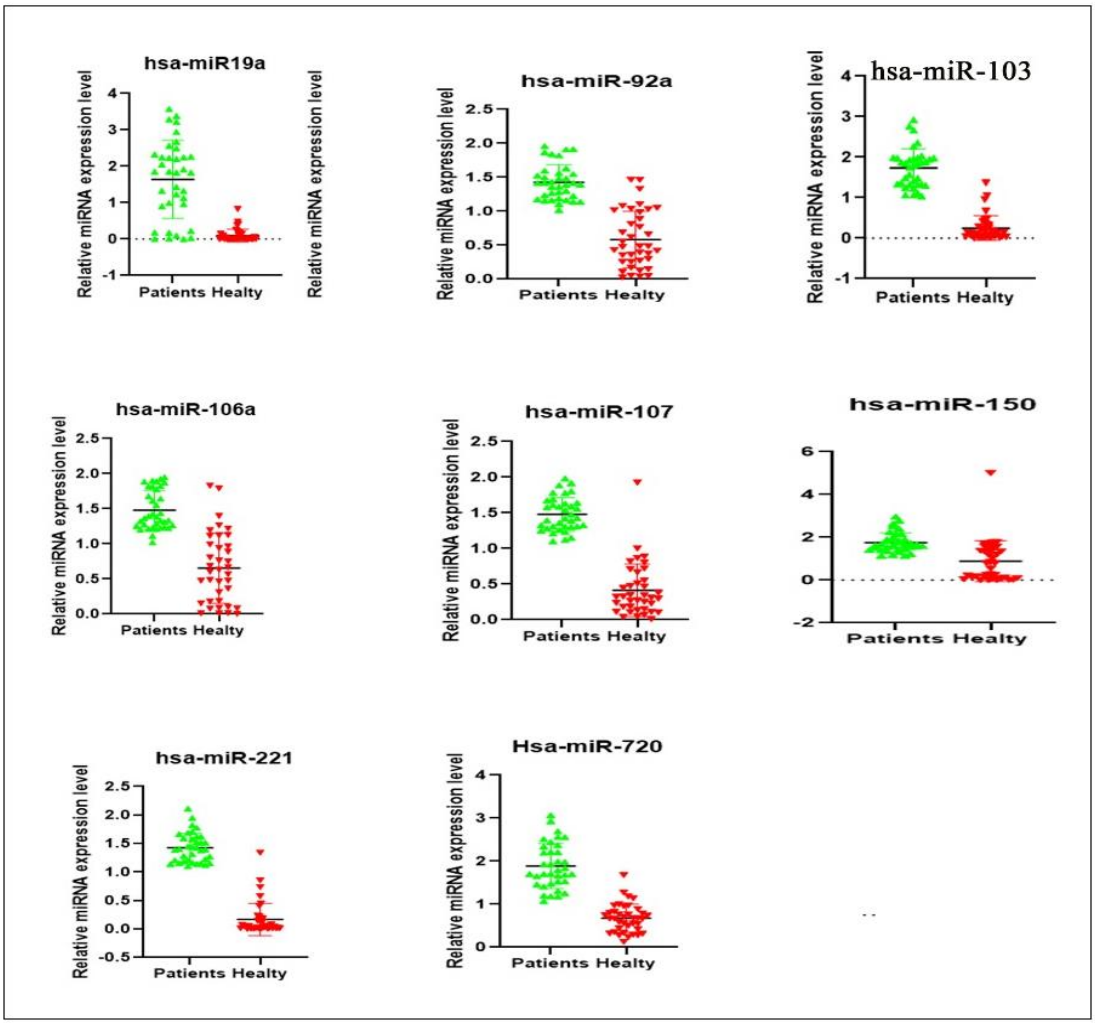

Figure 2. Fold changes in targeted miRNAs' expression in CRC.

indicating excellent diagnostic potential (AUC > 0.9). These results are presented in **Figure 3**.

4. DISCUSSION

This study examined a panel of CRC-miRNAs in a Turkish population with colorectal cancer, focusing on their molecular mechanisms and potential for non-invasive early detection, monitoring, and personalized treatment. Initially, an in silico approach, TCGA transcriptome survey, and several experiments using CRC cells were employed to determine significantly dysregulated miRNAs in CRC, where the expression of specific miRNAs was modulated. Logistic regression, ROC curve, and survival analyses indicated the most crucial miRNAs with potential clinical applications. Through a comprehensive examination of healthy controls and CRC patients at each stage, specific candidates (miR-19a, miR-92a, miR-103, miR-106a, miR-107, miR-150, miR-221, miR-720) emerged for evaluating their potential as predictive and prognostic factors. Our analysis offers 3 groups of special serum-miRNAs that are substantially prominent for their role in colorectal cancer cell initiation and development. These miRNAs are categorized based on their molecular functions, contributing to the dysregulation of basic cellular and molecular processes. The intersection of goal miRNAs with the relative signal transductions is schematically depicted in **Figure 4**.

The first miRNA from the PTEN dysregulated categorization is miRNA-19a. This miRNA is involved in critical cellular processes such as cell proliferation and apoptosis, and the development of tumor cells. In the current study, the average level of serum miRNA-19a in the

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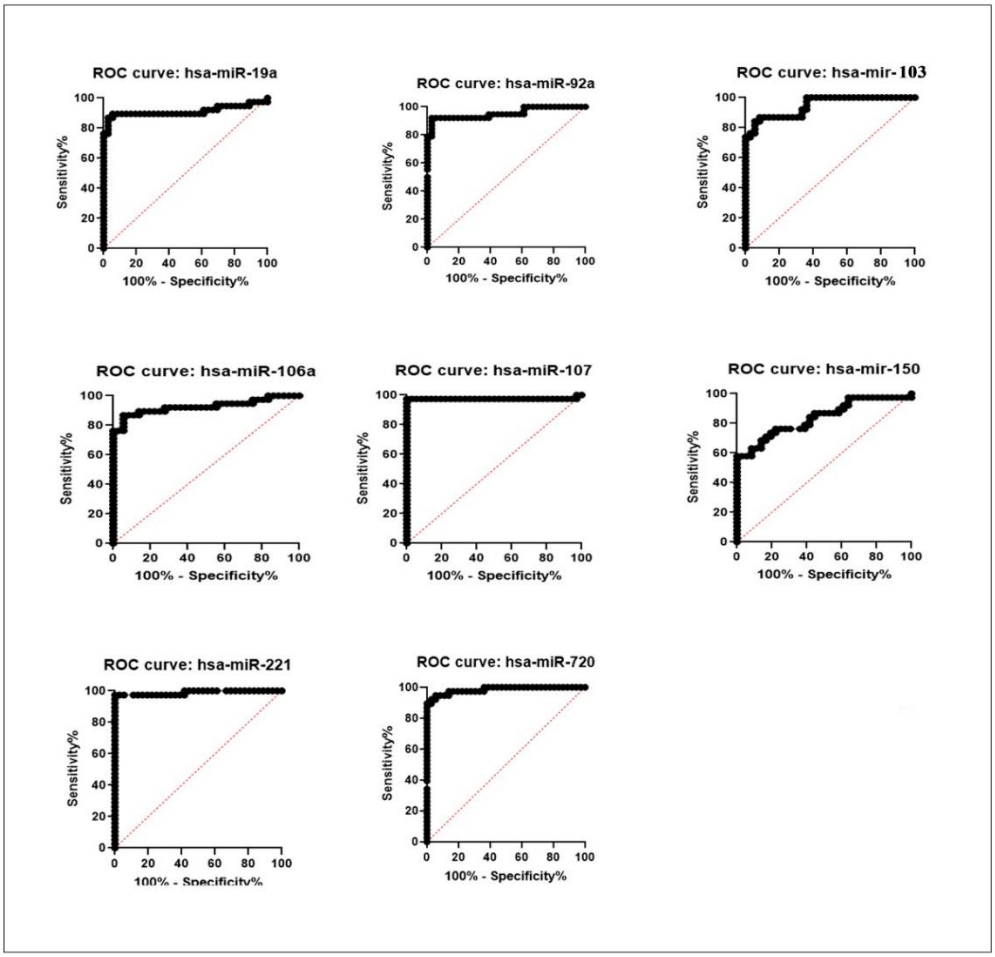

Figure 3. Diagnostic performance of selected miRNAs in CRC using ROC analysis.

patient group was 2.45 ± 1.16, compared to 0.03 ± 0.08 in the control group. The data indicated a difference with a high statistical significance rate in the two groups ($p<0.001$), indicating a high expression of this miRNA in the serum of colorectal cancer patients. Zhang et al. 2020 provided data supporting the substantial function of miRNA-19a through a negative feedback regulatory mechanism with PTEN down-expression in CRC patients (18). Based on existing evidence (19, 20), the miR-19a/ PTEN pathway is remarkably an executive role player in colorectal cancer and aligns with our results. MiR-92a is the other candidate miRNA identified to take part in this context. MiRNA-92a has an exponential expression level in the patient group with 2.77 ± 1.03 compared to the control group with 0.47 ± 0.47 which is statistically considerable ($p<0.001$). MiR-92a functions as an oncogene in the facilitation of tumor cell invasion and migration by regulating E-cadherin, PTEN, RECK, and C13orf125 (21, 13). In a meta-analysis directed by Peng et al. miRNA-92a has a sensitivity of 76% and specificity of 75% in detecting colorectal cancer from healthy controls (22). However, in our study, miRNA-92a has a sensitivity of 97% and specificity of 97% in distinguishing colorectal cancer from healthy controls. This indicates that miRNA-92a has a high potential as a screening biomarker for colorectal cancer. The ongoing work revealed the average serum level of miRNA-103 as 1.19 ± 0.47 in the patient group and 0.78 ± 0.52 in the control group demonstrating a significant difference between them ($p<0.001$). Taking into account studies demonstrating the downregulation of LATS2 (22), Dicer, and PTEN (24) by miR-103 overexpression, leading to enhanced CRC cells' hallmarks, it can be assumed that miR-103 plays its oncogenic role through inhibition of key tumor suppressors in PTEN transduction network (25). MiRNA-106a is one of the biomarkers that demonstrated statistically remarkable variation ($p<0.001$) in the serum expression level of the two groups. While the expression level in the CRC group was 1.57 ± 0.83; in the non-patient

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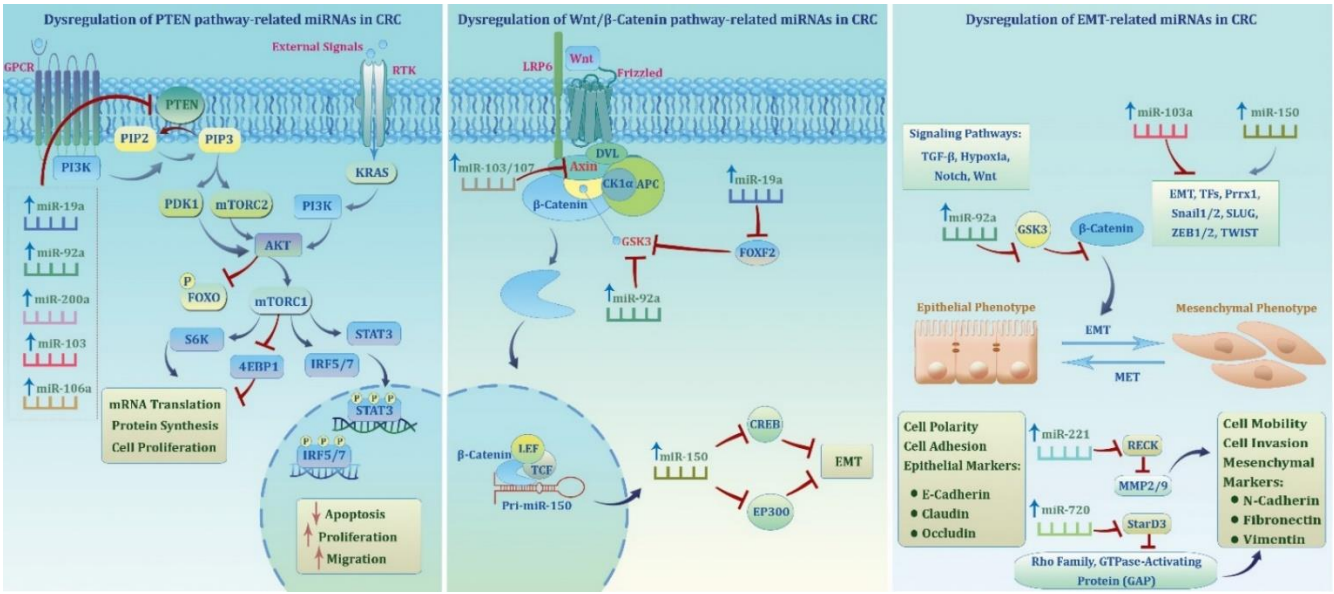

Figure 4. The functional overlap between candidate miRNAs and signal transduction pathways.

group, it was 0.62 ± 0.69. Hao et al 2017, found that the apoptosis resistance and cell proliferation in the CRC cells resulted from the suppressive effect of miR-106a on the autophagy-related gene 7 ATG7, confirming the miRNA-106a over-expression correlation and its effective role in colorectal cancer (26), (27). The serum miRNA 200a levels were found with an average of 2.49 ± 0.52 in the CRC group and 0.4 ± 0.64 in the healthy control group in our experiment, with a dramatic differentiation between the two groups ($p<0.001$). Expression of this miRNA is positively correlated with the degree of tumorigenesis and differentiation of CRC cells, suggesting the miR-200a involvement in this concept (26). Li et al reported that miR-200a overexpression remarkably decreased the activity of the PTEN by targeting the 3′-UTR region of this tumor suppressor (26). This finding suggests a potential role for miR-200a as a negative regulator of PTEN, possibly justifying its categorization among CRC-related miRNAs that influence PTEN function.

Upregulation of miR-19a acts through a negative feedback loop with Forkhead box F2 (FOXF2)-dependent on the canonical Wnt signaling cascade in colorectal cancer. It could be considered an effective factor in lymph node metastasis (28) which supports miR-19a's potential role in promoting CRC progression. In the study by Zhang and colleagues, the transcript abundance of miR-92a was recorded at a high rate in colorectal cancerous cells and tumor tissues. This is consistent with our results related to the high expression of this biomarker in the serum. Moreover, targeting GSK3β, negative regulators of this pathway by miR-92a probably resulted in CRC stem cell-like phenotype in this type of cells (18). The miR-107 transcription level was on average 1.54 in the patient group and 0.41 ± 0.48 in the control group ($p<0.001$). In line with the oncogenic function of this biomarker, an increase in miR-103/miR-107 expression in advanced colon cancer has been illustrated (29). Additionally, it was shown that miR-103/107 targets Axin2, a negative regulator of this pathway resulting in a continuous induction of β-catenin signaling, consequently probably contributing to the cell stemness, recurrence, and poor prognosis (30). The current exploration revealed a substantially elevated amount of miRNA-150 within the group of patients (1.38 ± 0.59) in contrast to the other one (0.49 ± 0.64), ($p<0.001$). Guo et al. study confirmed that miR-150 could potentially act as a novel Wnt effector, enhancing EMT in CRC cells by targeting the CREB1 and EP300 (31). As mentioned above, our serum analysis revealed overexpression of miR-92a in the trial group compared to the control group ($p<0.001$). There is overwhelming evidence that. the upregulation of miR-92a in CRC samples is linked to the aggressive phenotype of human colorectal cancer cells. It could affect the Epithelial to Mesenchymal Transition process (EMT) by regulating the GSK-Wnt/β-catenin pathway in CRC cells (32).

Similar to our findings, a study by Hong et al. (2014) demonstrates a strong correlation between miR-103a accumulation levels and a more aggressive cancer phenotype, as well as poorer overall survival rates in colorectal cancer (CRC) patients (33). Additionally, the

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existing data are consistent with a negative feedback loop between miR-103-induced expression and a decreased amount of LATS2 a key component of the Hippo signaling cascade that could potentially interact with EMT-activating transcription factors (23, 34). The role of miR-150 and its cross-talk with EMT in CRC progression have been delineated in various above-mentioned studies (35). A 2016 study by Guo et al. provided evidence suggesting that miR-150 might play a remarkable role in colorectal cancer (CRC). Aligns with our findings, they demonstrated that miR-150 is specifically upregulated in CRC tissues. This upregulation seems to be linked to CRC invasion and metastasis with the elevated expression of Gli1 (glioma-associated oncogene homolog 1), a factor potentially involved in the epithelial-to-mesenchymal transition (EMT) process (31). Additionally, molecular elements such as ZEB1, HMGA2, and FOXO4 are destined to be targets of miR-150 to promote EMT in CRC (36). The expression level of miR-221 was observed to be an average of 2.37 ± 0.6 in the patient group and 0.41 ± 0.74 in the control group with a prominent differentiation ($p < 0.001$). In the study conducted by Qin in 2014, it was demonstrated that there is a reverse association between the overexpression of miR-221 and RECK (MMP inhibitor) in CRC cells' progression (32). Given the data presented, it is reasonable to posit a potential oncogenic role for miR-221 in CRC through its facilitation of epithelial-to-mesenchymal transition (EMT). In our ongoing study, the serum miRNA-720 level in the CRC group was significantly higher 1.32 ± 0.7 compared to the control group 0.63 ± 0.69, ($p < 0.001$). Similar to the other findings related to this miRNA (37), our analysis demonstrated the over-expression of miR-720 in CRC. In addition, Wang et al. identified miR-720 as a specific regulator of the StarD13 3′-UTR, which exerts its control by targeting the Rho GAP activity of StarD13 (37). So, it could be considered a potential role player in colorectal cancer.

5. Conclusion

To summarize, this research has uncovered a panel of eight effective miRNAs including, miR-19a, miR-92a, miR-103, miR-106a, miR-107a, miR-150, miR-221, miR-720 with substantial expression variations in serum colorectal cancer patients. Our data provide valuable comprehensive insights into the mechanistic categorization of these miRNAs and their connection with progressive factors in colorectal cancer, which are related to critical cellular signal transductions such as PI3K/AKT/PTEN, WNT/CATENIN, and EMT. Despite these promising results, additional studies are needed to validate these observations in a bigger group of participants and different ethnicities. Nonetheless, the identification of these special dysregulated miRNAs with their signaling mechanism of action associated with colorectal cancer is pivotal to improving accurate diagnosis, monitoring, and treatment of this disease, either in the wet lab or in the clinic.

Ethical statement

The study was approved by the Institutional Review Board (IRB) of Pamukkale University of Turkey (approval number: [60116787-020/25606]). Written informed consent was obtained from all participants in the Department of Medical Oncology of Pamukkale University Faculty of Medicine according to the Declaration of Helsinki.

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Conflict of interest

None.

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