

Integrated analysis of non-coding RNAs (HOTAIR and miR-130a) and their cross-talk with TGF- β 1, SIRT1 and E-cadherin as potential biomarkers in colorectal cancer

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Abstract. Molecular changes have a substantial impact on the onset of colorectal cancer (CRC). Complexes of HOTAIR and miRNAs disrupt several cellular functions during carcinogenesis, primarily by disrupting several carcinogenic signaling pathways. In the present study, the relationships between the serum levels of transforming growth factor- β 1 (TGF- β 1), sirtuin-1 (SIRT1) and E-cadherin and those of HOX transcript antisense intergenic RNA (HOTAIR) and microRNA-130a (miR-130a) in individuals with CRC were analyzed, including their correlations and diagnostic potential. Patients with colon cancer and healthy volunteers were enrolled in the study. Blood samples were collected from 70 patients with CRC and 30 age-matched healthy control volunteers and reverse transcription-quantitative polymerase chain reaction (RT-qPCR) was used to determine the serum levels of HOTAIR and miR-130a. In addition, the levels of TGF- β 1, SIRT1 and E-cadherin were determined utilizing enzyme-linked immunosorbent assays. Patients with CRC were found to have significantly higher TGF- β 1, SIRT1, HOTAIR and miR-130a serum levels than those of healthy participants. In addition, patients with high-grade CRC had significantly higher levels

of TGF- β 1, SIRT1, HOTAIR and miR-130a compared with those of patients with low-grade CRC. A significant reduction in the serum levels of E-cadherin was observed in participants with CRC compared with healthy participants, but no significant difference was detected according to the grade of CRC. Positive correlations were found between HOTAIR and miR-130a, as well as TGF- β 1 and SIRT1. By contrast, negative correlations were noted between E-cadherin and HOTAIR, miR-130a, TGF- β 1 and SIRT1. Therefore, it may be concluded that the miR-130a/HOTAIR and TGF- β 1/SIRT1/E-cadherin axes may serve as novel biomarkers for the early diagnosis of CRC.

Introduction

Colorectal cancer (CRC) is a major threat to life, and is a prevalent disease, with eating habits and lifestyle patterns contributing to its high incidence rate, which stands at 9.8 cases per 100,000 individuals (1). The onset of CRC is a complex biological process characterized by various genomic and epigenomic alterations. The increasing occurrence and poor outcomes of CRC have prompted extensive scientific research and ongoing trials to uncover the underlying pathological processes of CRC progression, halt these processes and prevent further progression (2-4).

Transforming growth factor- β (TGF- β) and E-cadherin are biomarkers associated with epithelial-mesenchymal transition (EMT), a process that plays a crucial role in driving cellular events, resulting in the loss of cell-cell contact and increased cell motility (5). The TGF- β superfamily regulates multiple cellular processes, including migration, apoptosis, proliferation and EMT (6). Paradoxically, TGF- β exhibits both tumor-suppressive and tumor-promoting effects in cancer,

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depending on the molecular and cellular pathways that it influences (7). Although TGF- β signaling pathways can contribute to tumor progression, their role in carcinogenesis remains unclear. Cadherins are a key group of adhesion proteins that are crucial in facilitating cellular interactions by binding to calcium ions (8). Abnormalities in E-cadherin molecules have been shown to contribute to the progression of neoplastic disease in the stomach, pancreas and large intestine (9).

Sirtuin 1 (SIRT1) is one of the seven isoforms of the SIRT family, which bind to various histone and non-histone proteins. The functions of SIRT proteins differ according to their substrates, with some acting as lysine deacetylases (SIRT1-3, 5, 6 and 7), ADP ribosyl transferases (SIRT4 and 6) and deacetylases (SIRT5) (10). SIRT1s are crucial in the maintenance of normal cellular balance as they participate in the regulation of metabolism, autophagy and preservation of genetic stability (10). SIRT1s are involved in various age-related illnesses, including metabolic syndrome, cardiovascular disease, neurodegeneration and cancer (11). It is imperative to note that SIRT1 is a multifaceted protein with a pivotal function in multiple pathways (12). Nevertheless, its involvement in cancer is yet to be decisively established.

The identification of reliable and non-invasive biomarkers, such as long chain noncoding ribonucleic acids (lncRNAs) and microRNAs (miRNAs/miRs) for CRC should facilitate the early detection of this cancer, and thereby enable prompt intervention to prevent its progression. miRNAs contribute to the regulation of gene expression by binding to target mRNA (13). miRNAs regulate the transcripts of intestinal barrier proteins, which contributes to gastrointestinal pathologies, and these regulatory roles are associated with inflammation and colon cancer (14). Regulation of the hypoxia response, immune cell performance and mesenchymal differentiation have all been shown to be associated with the expression of miR-130 in CRC (15). However, knowledge of the involvement of miR-130 in carcinogenesis is limited.

lncRNAs are noncoding RNA transcripts. They are a key area of research, as they have been shown to be associated with carcinogenesis and metastasis in various human cancers, including breast (16), liver (17) and gastric (18) cancer. Numerous studies have linked the prognosis of patients with cancer to the expression of specific lncRNAs. One notable example is HOX transcript antisense intergenic RNA (HOTAIR), which has been shown to be highly oncogenic in various malignancies, including breast (16), colon (19) and gastric (20) cancer. HOTAIR is a 2,158-nucleotide lncRNA located on chromosome 12q13.13 within the homeobox C gene locus (19). To the best of our knowledge, the difference in the serum levels of HOTAIR and miR-130a according to the grade of CRC (low and high) and their correlation with TGF- β 1, SIRT1 and cadherin levels are unclear. Therefore, the present study was undertaken to evaluate the correlations between the serum levels of TGF- β 1, SIRT1 and E-cadherin and those of HOTAIR and miR-130a in individuals with CRC in order to explore their associations and diagnostic potential for CRC.

Materials and methods

Characteristics of participants. In the present retrospective cross-sectional study, 70 patients with pathologically

diagnosed CRC and complete clinical records during the period from October 2023 to May 2024 were recruited from Fayoum University Hospital (Fayoum, Egypt). The protocol was approved by the Medical Ethics and Human Clinical Trial Committee of the Faculty of Medicine, Fayoum University (approval no. R492; date of approval, September 17, 2023), following the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to participation in the study; all subjects signed a consent form after being briefed on the objectives of the study. The range age of the patients was 37-61 years (mean age, 49.65 $\pm$ 11.98 years) and 38.4% of participants were female, while 61.6% were male. The CRC was present in a variety of locations, including the sigmoid, ascending, transverse and rectosigmoid colon. All patients were newly diagnosed with CRC by colonoscopy and confirmed by pathology. A colonoscopy was recommended for individuals with a positive fecal occult blood test, hemorrhoids, unexplained abdominal pain or visible bleeding. After surgery, a definitive pathology diagnosis and tumor grade were obtained. The CRC was precisely classified using the World Health Organization classification system (21) into low-grade (well-differentiated to moderately differentiated) and high-grade (poorly differentiated to undifferentiated) categories. None of the patients had received chemotherapy or radiotherapy before the collection of blood samples. Patients who had a history of secondary or recurring tumors were excluded from the study. A total of 30 healthy control participants (mean age, 46.97 $\pm$ 9.50 years; 40.4% female and 59.6% male) who had negative colonoscopy results for malignancy or inflammatory bowel disease and had no history of familial adenomatous polyposis or hereditary non-polyposis CRC were also recruited.

Data and sample collection. Relevant medical history data were collected from all subjects, including age and body mass index. A 10-ml venous blood sample was taken from each participant. After allowing the blood sample to coagulate, serum was extracted by centrifugation at 1,000-2,000 x g for 10 min in a refrigerated centrifuge and frozen at -70°C for subsequent biochemical and molecular analysis.

Enzyme-linked immunosorbent assays. Serum E-cadherin (cat. no. DCAE0B), SIRT1 (cat. no. 201-12-2558) and TGF- β 1 (cat. no. MBS2501101) were determined using quantitative sandwich enzyme immunoassay kits from R&D Systems Europe, Ltd., Shanghai Sun Red Biological Technology Co., Ltd. and BioSource Europe SA, respectively. The assays were performed according to the manufacturers' instructions.

Reverse transcription-quantitative PCR (RT-qPCR). The circulating RNA levels of miRNA-130a and HOTAIR in the study participants were determined using RT-qPCR. Briefly, RNA was isolated from the serum samples using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.). The isolated RNA was then reverse transcribed using the miScript II RT kit (Qiagen, Inc.), according to the manufacturer's instructions. The miScript SYBR® Green PCR Kit (cat. no. 218073; Qiagen GmbH) was used for qPCR, along with the target-specific miScript primer assay for miRNA-130a (cat. no. MS00003444) compared with the reference gene

RUN U6B (cat. no. MS00033740). In addition, GAPDH was used as the reference gene for HOTAIR. The primer sequences were as follows: miRNA-130a forward, 5'-GTC AGTGCTAAAAGGGCAT-3' and reverse, 5'-CAGTGC GTGTCGTGGAGT-3'; and U6 forward, 5'-GCTTCGGCAGCA CTATAAT-3' and reverse, 5'-CGCTTCACGAATTGCTGT CAT-3'; HOTAIR forward, 5'-GGTAGAAAAAGCAACCAC GAAGC-3', and reverse, 5'-ACATAAACCTCTGTCTGTGAG TGCC-3'; GAPDH forward, 5'-GAAGGTCCGAGTCAACGG ATT-3', and reverse, 5'-CGCTCCTGGAAGATGGTGAT-3'. The Rotor-Gene Q System (Qiagen, Inc.) was programmed as follows: Heating at 95°C for 10 min, followed by 45 cycles of denaturation at 95°C for 15 sec, and annealing and extension at 60°C for 60 sec. The data were analyzed using the $2^{-\Delta\Delta C_q}$ method (22).

Statistical analysis. Data are presented as the mean $\pm$ standard error or standard deviation. Differences between two groups were analyzed using unpaired Student's t-test for continuous data and Chi-square test for categorical data. One-way ANOVA was used to examine the differences among multiple groups. When the ANOVA indicated a significant difference, Tukey's multiple range test was utilized to conduct pairwise analysis of the groups. The normality assumptions for each variable were verified using the Shapiro test. The correlations between variables were evaluated using Pearson's correlation analysis. The diagnostic value of miR-130a and HOTAIR was assessed using receiver operating characteristic (ROC) curve analysis. The analyses were performed using SPSS version 22 software (IBM Corp). $P < 0.05$ was considered to indicate a statistically significant result.

Results

Patient characteristics. The study included 70 patients with CRC, with an average age of 49.65 ± 11.98 years. Of these, 40 (57.14%) were non-obese and the remaining 30 (42.86%) were obese. The most common presenting symptoms were weight loss, which was exhibited by 40 patients (57.14%), and constipation, which affected 45 patients (64.30%). Based on colonoscopic findings, the most common locations of CRC were the sigmoid colon ($n=20$; 28.57%), rectum ($n=15$; 21.43%), rectosigmoid region ($n=14$; 20%) and transverse colon ($n=10$; 14.29%). Less commonly, CRC was found in the cecum ($n=4$; 5.71%) and ascending colon ($n=7$; 10%) (Table I).

Comparison of serum analyte levels. Regarding the serum levels of TGF- β 1 and SIRT1, all patients with CRC had significantly higher levels than the healthy individuals ($P < 0.05$). Moreover, patients with high-grade CRC had significantly higher levels of TGF- β 1 than those with low-grade CRC ($P < 0.05$). Additionally, a notable difference in SIRT1 levels was observed between the low-grade and high-grade CRC groups (Table II; Fig. 1A and B).

A clear and significant reduction in the serum levels of E-cadherin was observed in patients with CRC compared with those in healthy individuals ($P < 0.05$). However, no significant difference in serum E-cadherin levels was detected between patients with low-grade and high-grade CRC (Table II; Fig. 1C).

Table I. Demographic characteristics of the study groups.

Variables	Healthy participants (n=30)	Patients with CRC (n=70)	P-value
Mean age $\pm$ SD, years	46.97 $\pm$ 9.65	49.65 $\pm$ 11.98	>0.05
BMI, n (%)			0.141
Non-obese	22 (73.33)	40 (57.14)	
Obese	8 (26.67)	30 (42.86)	
Weight loss, n (%)			
Yes		40 (57.14)	
No		30 (42.86)	
Constipation, n (%)			
Yes		45 (64.30)	
No		25 (35.70)	
Location, n (%)			
Sigmoid colon		20 (28.57)	
Ascending colon		7 (10)	
Transverse colon		10 (14.29)	
Rectosigmoid region		14 (20)	
Rectum		15 (21.43)	
Cecum		4 (5.71)	

Unpaired Student's t-test was used to analyze the difference in age between the two groups and χ^2 test was employed to assess the difference in BMI. CRC, colorectal cancer; BMI, body mass index; SD, standard deviation.

To determine whether the serum levels of HOTAIR and miR-130a differ between patients with CRC and control individuals, RT-qPCR analysis was performed. The serum levels of HOTAIR and miR-130a in patients with CRC were significantly higher than those in healthy controls ($P < 0.05$). Furthermore, patients with high-grade CRC had significantly higher serum HOTAIR and miR-130a levels compared with those of patients with low-grade CRC ($P < 0.05$; Table II; Fig. 1D and E).

Association of serum analyte with lesion location and inter-analyte correlations. No significant association was detected between the serum levels of TGF- β 1, SIRT1, E-cadherin and HOTAIR and the lesion location. However, a significant association between lesion site and the serum level of miR-130a was detected. In this regard, a statistically significant increase in the expression level of miR-130a was observed in patients with CRC located in the sigmoid, ascending colon, rectum and cecum compared with that in the patients with colon tumors located in the transverse colon and rectosigmoid ($P < 0.05$; Table III).

The correlations among the serum levels of HOTAIR, miR-130a, TGF- β 1, SIRT1 and E-cadherin were evaluated using Pearson's correlation analysis. Positive correlations were identified between HOTAIR and miR-130a, TGF- β 1

Table II. Comparisons of serum levels of TGF- β 1, SIRT1, E-cadherin, HOTAIR and miR-130a among the study participants.

Variables	TGF- β 1, ng/ml	SIRT1, ng/ml	E-cadherin, ng/ml	HOTAIR	miR-130a
Healthy control	2.10 $\pm$ 0.10	4.43 $\pm$ 0.23	4.75 $\pm$ 0.11	0.98 $\pm$ 0.01	0.97 $\pm$ 0.01
Low-grade CRC	15.11 $\pm$ 0.42 ^a	7.39 $\pm$ 0.40 ^a	2.77 $\pm$ 0.08 ^a	6.38 $\pm$ 0.82 ^a	4.14 $\pm$ 0.38 ^a
High-grade CRC	16.30 $\pm$ 0.36 ^{a,b}	7.87 $\pm$ 0.47 ^{a,b}	2.65 $\pm$ 0.07 ^a	7.06 $\pm$ 0.53 ^{a,b}	4.54 $\pm$ 0.34 ^{a,b}
F-ratio	528.47	20.80	182.546	52.136	38.99
P-value	<0.05	<0.05	<0.05	<0.05	<0.05

Data are expressed as the mean $\pm$ standard error. Analysis was performed using one-way ANOVA followed by Tukey's multiple range test. ^aP<0.05 vs. healthy controls; ^bP<0.05 vs. patients with low-grade CRC. TGF- β 1, transforming growth factor- β 1; SIRT1, sirtuin 1; HOTAIR, HOX transcript antisense intergenic RNA; miR, microRNA; CRC, colorectal cancer.

Table III. Associations between lesion location and serum levels of TGF- β 1, SIRT1, E-cadherin, HOTAIR and miR-130a in patients with colorectal cancer.

Lesion location	TGF- β 1, ng/ml	SIRT1, ng/ml	E-cadherin, ng/ml	HOTAIR	miR-130a
Sigmoid colon	16.137 $\pm$ 0.536	7.493 $\pm$ 0.797	2.585 $\pm$ 0.100	5.967 $\pm$ 0.521	4.39 $\pm$ 0.411 ^{a,b}
Ascending colon	14.922 $\pm$ 0.804	7.262 $\pm$ 0.694	2.652 $\pm$ 0.087	6.585 $\pm$ 1.134	6.158 $\pm$ 0.984 ^b
Transverse colon	15.137 $\pm$ 0.650	7.059 $\pm$ 0.536	2.866 $\pm$ 0.131	6.374 $\pm$ 0.688	3.596 $\pm$ 0.534 ^a
Rectosigmoid region	16.105 $\pm$ 0.415	7.941 $\pm$ 0.773	2.798 $\pm$ 0.142	7.145 $\pm$ 1.151	3.789 $\pm$ 0.767 ^a
Rectum	16.033 $\pm$ 0.736	8.625 $\pm$ 0.588	2.676 $\pm$ 0.110	7.788 $\pm$ 1.031	4.603 $\pm$ 0.534 ^{a,b}
Cecum	15.557 $\pm$ 1.512	6.750 $\pm$ 0.664	2.582 $\pm$ 0.162	7.480 $\pm$ 1.790	4.827 $\pm$ 0.568 ^{a,b}

Data are expressed as the mean $\pm$ standard error. Analysis was performed using one-way ANOVA followed by Tukey's multiple range test. Different letters indicate statistically significantly different means. TGF- β 1, transforming growth factor- β 1; SIRT1, sirtuin 1; HOTAIR, HOX transcript antisense intergenic RNA; miR, microRNA.

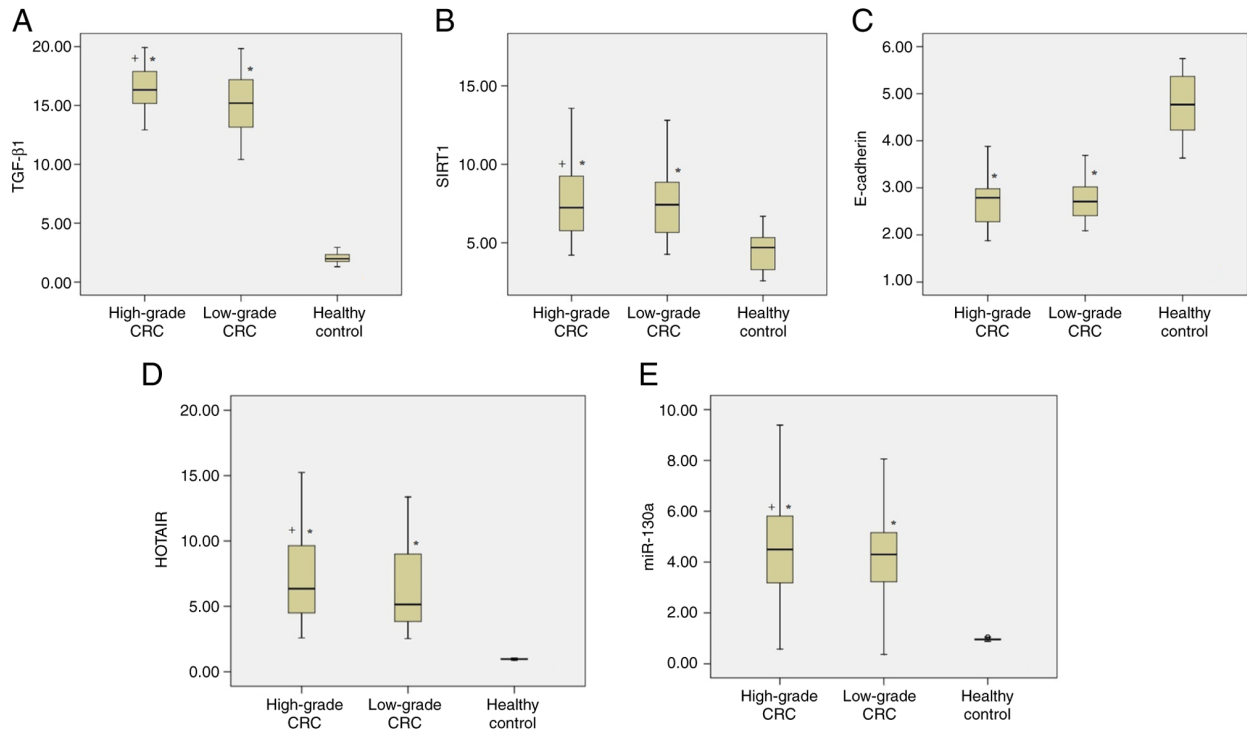


Figure 1. Comparison of serum levels of TGF- β 1, SIRT1, E-cadherin, HOTAIR and miR-130a among the study participants. Serum levels of (A) TGF- β 1, (B) SIRT1, (C) E-cadherin, (D) HOTAIR and (E) miR-130a in patients with high-grade and low-grade CRC and healthy controls. *P<0.05 vs. healthy controls; ^aP<0.05 vs. low-grade CRC. TGF- β 1, transforming growth factor- β 1; SIRT1, sirtuin 1; HOTAIR, HOX transcript antisense intergenic RNA; miR, microRNA; CRC, colorectal cancer.

Table IV. Pearson's correlation coefficients between miR-130a, HOTAIR, TGF- β 1, SIRT1 and E-cadherin among CRC participants.

Parameters	miR-130a	HOTAIR	TGF- β 1	SIRT1	E-cadherin
miR-130a	-	0.478	0.662	0.366	-0.592
HOTAIR	0.478	-	0.738	0.455	-0.621
TGF- β 1	0.662	0.738	-	0.529	-0.838
SIRT1	0.366	0.455	0.529	-	-0.515
E-cadherin	-0.592	-0.621	-0.838	-0.515	-

All linear correlations were statistically significant with $P < 0.05$ (2-tailed). miR, microRNA; HOTAIR, HOX transcript antisense intergenic RNA; TGF- β 1, transforming growth factor- β 1; SIRT1, sirtuin 1.

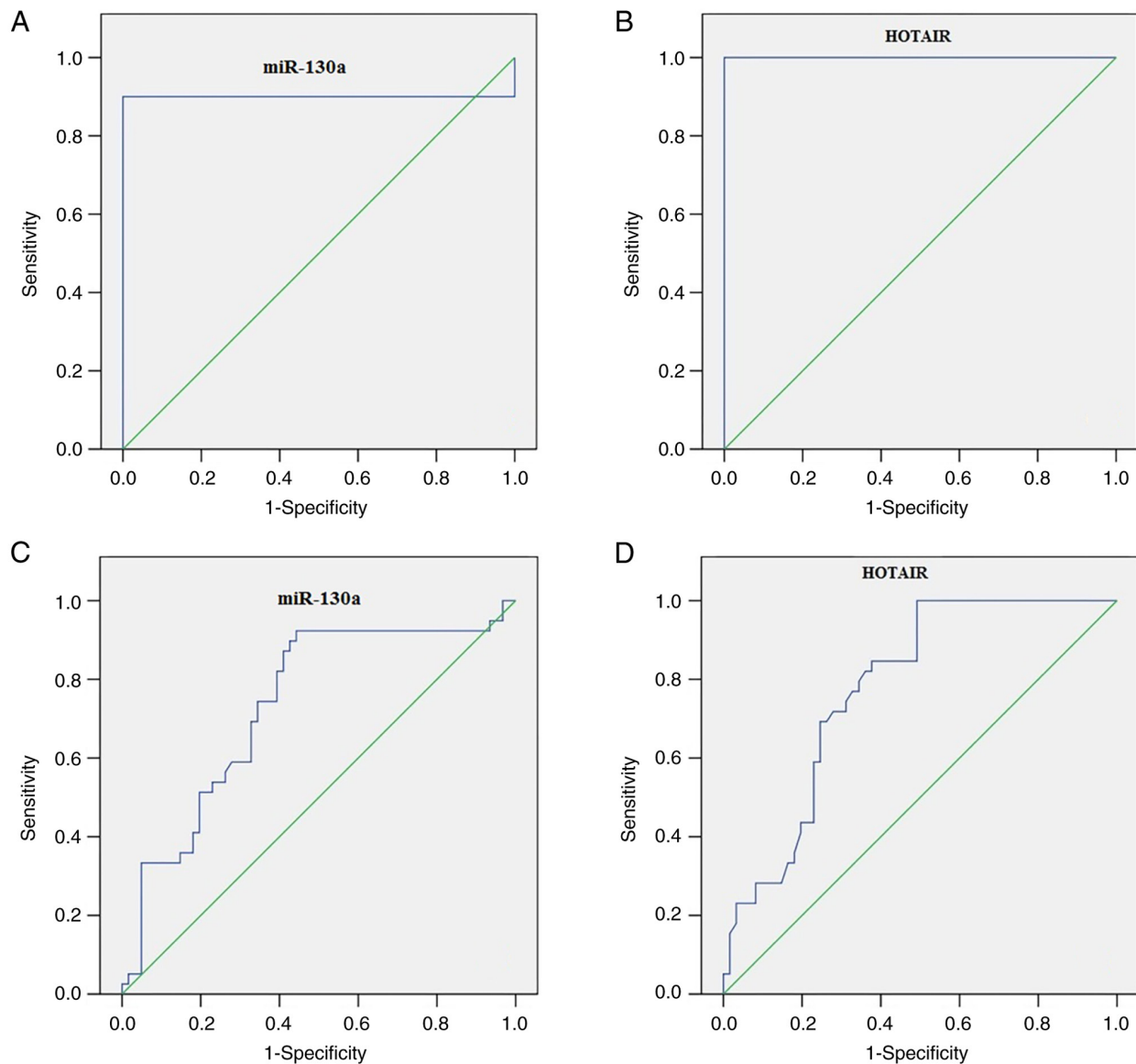


Figure 2. ROC curve analyses for miR-130a and HOTAIR in the study participants. ROC analysis of serum (A) miR-130a between all patients with CRC and healthy controls, (B) HOTAIR between all patients with CRC and healthy controls, (C) miR-130a between patients with high-grade CRC and all other participants and (D) HOTAIR between patients with high-grade CRC and all other participants. ROC, receiver operating characteristic; miR, microRNA; HOTAIR, HOX transcript antisense intergenic RNA; CRC, colorectal cancer.

and SIRT1 ($r=0.478, 0.738$ and 0.455 , respectively). However, negative correlations were observed between E-cadherin and

HOTAIR, miR-130a, TGF- β 1 and SIRT1 ($r=-0.621, -0.592, -0.838$ and -0.515 , respectively). In addition, miR-130a was

positively correlated with TGF- β 1 and SIRT1 ($r=0.662$ and 0.366 , respectively) (Table IV; Figs. S1-S3).

Diagnostic performance. ROC curve analysis revealed that serum miR-130a differentiated patients with CRC from healthy controls with an optimum cutoff value of 1.195 [area under the ROC curve (AUC), 0.90 ; 95% confidence interval (CI), $0.830-0.970$; $P<0.001$], 90% sensitivity and 100% specificity (Fig. 2A). Furthermore, serum HOTAIR differentiated patients with CRC from healthy controls with an optimum cutoff value of 1.79 (AUC, 1.00 ; $P<0.001$), sensitivity of 100% and specificity of 100% (Fig. 2B). Serum miR-130a distinguished patients with high-grade CRC from all other participants with an optimum cutoff value of 2.41 (AUC, 0.735 ; $P<0.001$), sensitivity of 89.74% and specificity of 57.38% (Fig. 2C). In addition, serum HOTAIR distinguished patients with high-grade CRC from all other participants, with an optimum cutoff value of 2.56 (AUC, 0.682 ; $P<0.004$), sensitivity of 90.77% and specificity of 53.08% (Fig. 2D).

Discussion

Numerous biological factors have been shown to contribute to the growth and progression of CRC, both directly and indirectly (13,23). In our previous study, the potential of miR-146a and miR-215 as reliable biological markers for detecting CRC and predicting associated complications was identified, suggesting that using these miRNAs to target TGF- β and IL-6 could provide a promising approach for the treatment of CRC (23).

An intricate mRNA-miRNA-lncRNA network critically regulates various biological processes and molecular mechanisms in tumors, with lncRNAs acting as sponges that sequester miRNAs, thereby modulating miRNA levels and affecting mRNA modulation (24,25). An intricate mechanism, involving dysregulation of the mRNA-miRNA-lncRNA network, plays a crucial role in the regulation of gene transcription and post-transcriptional translation. This network has prognostic utility and can be used to identify therapeutic targets (26,27).

The present study aimed to explore the levels of HOTAIR and miR-130a in the serum of patients with CRC and evaluate their correlation with the serum levels of TGF- β 1, SIRT1 and E-cadherin. Using RT-qPCR, it was identified that patients with CRC had significantly increased serum levels of HOTAIR and miR-130a, in addition to significantly elevated serum levels of TGF- β 1 and SIRT1, and significantly reduced serum levels of E-cadherin compared with those of healthy individuals. Additionally, the levels of miR-130a and HOTAIR increased with the grade of CRC. These findings suggest that miR-130a and HOTAIR could potentially serve as reliable biomarkers for detecting and predicting the outcomes of CRC. Previous studies have consistently reported that miR-130 and HOTAIR have oncogenic effects in CRC (26-30).

Zhang *et al* (31) detected a substantial association between the prognosis of patients with breast cancer after systemic treatment and the differential expression of miR-130a/HOTAIR in these patients. Furthermore, the oncogenic nature of HOTAIR promotes cell migration and invasion while suppressing apoptosis; HOTAIR has also been identified as a strong predictor

of metastasis and mortality for numerous types of cancers, including prostate cancer (32), lung cancer (33) and breast cancer (16).

Regarding miR-130, a number of studies have shown that it is involved in the pathogenesis of various tumors, including ovarian (34), esophageal (35), liver (36) and stomach (37) cancer. Additionally, Wang *et al* (38) demonstrated that circulating miR-130a levels are upregulated in patients with high-grade bladder cancer and significantly correlated with tumor stage.

In CRC, persistent TGF- β expression is primarily associated with the advanced stages of the disease (39). The present research revealed that the plasma levels of SIRT1 and TGF- β 1 were increased in patients with higher grades of CRC compared with those with lower grades. This increase in plasma level is likely to be related to tumor progression and the associated oncogenic activity. The upregulation of SIRT1 and TGF- β accelerates tumor growth and metastasis while preventing immune surveillance (40,41). Previous studies have shown that the expression of SIRT1 and TGF- β is significantly increased in CRC, suggesting the oncogenic roles of these factors in CRC progression (23,42).

The present study revealed that the serum levels of E-cadherin are lower in patients with CRC than in healthy individuals. This finding aligns with a study by Hydrú and Das (43), who reported a downregulation in cadherin expression levels in the tumor tissues of patients with CRC, and suggested that this reduction could be used as a diagnostic biomarker to track the progression of the disease and predict the invasiveness and migration the tumor cells. The downregulation of E-cadherin is a key factor in EMT, which has been linked to invasiveness in various types of cancer, such as pancreatic cancer (44).

In the present study, the relationships between the serum levels of TGF- β 1, SIRT1 and E-cadherin and those of the HOTAIR/miR-130a were investigated. Pearson's correlation analysis revealed significant positive correlations between serum HOTAIR levels and those of miR-130a and TGF- β 1. Notable positive correlations were also observed among the serum levels of TGF- β 1, SIRT and miR-130. Therefore, it is hypothesized that TGF- β upregulates SIRT1, which then induces changes in E-cadherin expression. This is supported by previous studies by Carafa *et al* (45) and Palmirotta *et al* (46) in which it is reported that TGF- β upregulates SIRT1, which interacts with other transcription factors, thereby leading to the downregulation of E-cadherin, and promoting the migration, invasion and death resistance of cancer cells. In addition, the present study found a negative correlation between HOTAIR and E-cadherin levels, suggesting a potential contribution of HOTAIR to EMT, due to the downregulation of E-cadherin and associated promotion of CRC cell migration and invasiveness.

The ROC curve analysis performed in the present study indicate that miR-130a and HOTAIR have good sensitivity and specificity as biomarkers for the discrimination of patients with CRC from healthy study participants. Notably, these results are consistent with a previous study by Wang *et al* (38), in which serum levels of miR-130 were identified as a potential biomarker for distinguishing patients with bladder cancer from healthy individuals.

To the best of our knowledge, the present study is the first to suggest correlations of HOTAIR/miR-130 with

TGF- β 1, SIRT1 and E-cadherin. The miR-130a/HOTAIR and TGF- β 1/SIRT1/E-cadherin axis may serve as a novel biomarker for the early diagnosis of CRC. However, the main limitation of the study is the small sample size, which is due to the lack of financial support and funding. Therefore, future large-scale studies and clinical trials are necessary to establish the relationships of HOTAIR, miR-130a, TGF- β 1, SIRT1 and E-cadherin with their therapeutic effects in clinical settings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

OGS, GA and NAH contributed to the conception and design of the study. Material preparation, data collection and analysis were performed by BMB, KD, TIA, EAH, RAN, SG and NAH. OGS and NAH confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was conducted in compliance with the Declaration of Helsinki, and was approved by Medical Ethics and Human Clinical Trial Committee of the Faculty of Medicine, Fayoum University (approval no. R492; date of approval, September 17, 2023), following the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to participation in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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