



Significance of LINC00641 and miR-378 as a potential biomarker for colorectal cancer

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Abstract

In colorectal cancer (CRC), dysregulation of noncoding RNA expression is a distinguishing factor. Owing to the conflicting results and the insufficient studies on serum microRNA-378 (miR-378) and long intragenic noncoding RNA00641 (LINC00641) expression patterns, we aimed to explore their expression profiles and diagnostic ability in colorectal cancer. Blood samples were collected from 30 healthy controls and 70 CRC patients. miR-378 and LINC00641 expression levels were determined using quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR), carcinoembryonic antigen (CEA) levels assessed by the enzyme-linked immunosorbent assay (ELISA) method. The expression levels of the studied miR-378 and LINC00641 correlated with patients' CEA levels. LINC00641 expression was dramatically upregulated, and miR-378 expression was significantly downregulated in colorectal cancer compared to the healthy controls. The differential expression of miR-378 and LINC00641 was inversely correlated, whereas the expression folds of both LINC00641 and CEA directly correlated with the advanced stages of colorectal cancer. Receiver operator characteristic (ROC) curve analysis disclosed the highest diagnostic potential for LINC00641 to discriminate colorectal cancer patients from the control and the highest diagnostic potential for discrimination between colorectal cancer stages.

Keywords Colorectal cancer · microRNA-378 · Long intragenic noncoding RNA00641 · Polymerase chain reaction · Carcinoembryonic antigen

Introduction

Colorectal cancer (CRC) has been reported as the most prevalent malignancy worldwide. Many studies have shown that the incidence of CRC has been increasing significantly in recent years (Stoffel and Murphy 2020; Ibrahim et al. 2014). In Egypt, the sixth cancer was CRC. The most important risk factors were metabolic disorders, precancerous bowel injury, and a family history of CRC (Siegel et al. 2019). As a result,

there is a pressing need to improve the early molecular diagnosis of colorectal cancer.

In recent years, the underlying molecular mechanisms of the occurrence and progression of CRC have not been fully understood. Previous studies have reported that CRC develops through the accumulation of genetic mutants and epigenetic modifications (Picard et al. 2020).

Noncoding RNAs (ncRNAs) can be classified as long ncRNAs (lncRNAs) and small ncRNAs (sncRNA), depending on the length of nucleotides. Noncoding RNA over 200 nucleotides losing the ability of biological function in the protein translation pathway is known as lncRNA. Positive associations between lncRNA expression and cell growth and differentiation indicate their impact on various diseases (Kanduri 2016; Jarroux et al. 2017). Schmitt and Chang (2016) and Tang et al. (2017) indicated the significant potential of lncRNAs as new tumor-related biomarkers for the early detection of tumors and the prediction of clinical outcomes in patients with tumors.

Recent research has revealed that regulatory sncRNAs (miRNA, piRNA, tRF, and snoRNA) can act as significant

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gene regulators and play a role in a variety of physiological and pathological processes (Catela et al. 2017). Also, the abnormal expression of sncRNAs is implicated in various human disorders, including cancers (Romano et al. 2017; Elshafei et al. 2017).

The long intragenic noncoding RNA00641 (LINC00641) is a new noncoding RNA located at 14q11.2 on the chromosome. Recent studies have shown that LINC00641 regulates autophagy and disc degeneration under nutritional stress (Wang et al. 2018).

This lncRNA has been suggested as a potential prognostic biomarker for patients with glioblastoma. Recently, Wang et al. (2019) demonstrated that LINC00641 modulates autophagy and is implicated in the pathogenesis of degenerative intervertebral disc. LINC00641 is abnormally expressed in bladder tumor tissues and cell lines and is considered a cancer suppressor in bladder cancer (Li et al. 2018a).

MicroRNA-378a (miR-378a, formerly called miR-378) is a small noncoding RNA molecule that can guide gene expression post-transcriptionally. The two mature strands, miR-378a3p and miR-378a5p, are derived from the first intron of the coactivator-1-beta gene, a peroxisome growth factor-activated gamma that encodes PGC1 β . The embedding of this transcriptional regulator in the sequence of oxidative energy metabolism implies the involvement of miR-378a in the metabolic pathway, the expression of miR-378 improves cell survival by altering caspase-3 activity and enhancing angiogenesis and the growth of the tumor (Li et al. 2018b).

Because of the incoherence of the findings and the inadequacy of the studies on the differential expression schemes of miR-378 and LINC00641, we aimed to explore the biochemical contribution of LINC00641 and miR-378 expression in CRC subjects and correlate these data with clinical-pathological characteristics to clarify their role in the early diagnosis of CRC.

Subjects and methods

This study was a pilot retrospective observational study carried out on 100 participants; 70 of them were CRC patients recruited from the Gastrointestinal Endoscopy Unit in Al-Kasr Al-Ainy Hospital, Cairo University, who attended the colonoscopy unit for general colorectal screening and patients suffering from variable colonic symptoms, including CRC alarming symptoms.

The patient's diagnosis and cancer staging are based on the colonoscopic findings, abdominal radio-imaging, pathological findings, and clinical decisions in three stages:

1. Stage I/II: local cancer.
2. Stage III: involvement of lymph nodes.
3. Stage IV: distant metastasis.

In addition, 30 control subjects were selected as apparently healthy volunteers without gastrointestinal symptoms, chronic disease history, cancer, or family history of CRC. All enrolled subjects' demographics, such as age, gender, and family history, were gathered. Body mass index (BMI) was calculated for all subjects as an index of the weight in kilograms divided by the square of the height in meters. The Helsinki Declaration was followed in the current research. All study participants provided their knowledge of consent.

Venous blood samples (10 ml) were withdrawn from enrolled participants by trained laboratory technicians. Each sample was divided into three portions for processing, total RNA extraction, determination of biochemical markers, and cell blood count (CBC).

The following biochemical tests were done for all involved subjects: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (T. bilirubin), albumin, urea, and creatinine were assayed using the routine biochemical technique. The level of CEA in the blood was tested using ELISA with a kit for CEA (Pointe Scientific, Inc., 4559 Research Drive, Canton, MI 48,188, USA).

Purification of total RNA from serum, which includes small RNAs such as miRs, was performed using the miRNeasy Kit and the reverse transcription of the total RNA was conducted using the MicroRNA easy kit as previously described (Khalil et al. 2022). For real-time polymerase chain reaction (RT-PCR), 5 μ l of diluted RT products (cDNA template) was combined with SYBR Green Master Mix (Qiagen) and primer specific for miR-378 and LINC00641 following the settings for the real-time PCR technique. The melting curve analysis revealed a single peak, confirming the specificity of the target PCR product. qRT-PCR data analysis is accomplished by the $2^{-\Delta\Delta ct}$ comparative expression method (Livak and Schmittgen 2001).

Statistical analysis

Data analysis was performed using the statistical software SPSS 18.0 (SPSS Inc., Chicago, IL, USA). The data was reported as a mean \pm standard error mean. Statistical analyses were performed using one-way ANOVA. When the ANOVA was significant, the Duncan method was used to assess the specific differences between the groups. The analysis of the ROC was used to determine the optimum cut-off value for miR-378 and LINC00641. The correlation coefficient (r) was calculated to determine the relationship between LINC00641, miR-378, and the CEA level of the patients using Pearson product-moment correlation. $P < 0.001$ was considered statistically significant.

Table 1 Demographic characteristics of the studied groups

Variables	Healthy participants (n = 30)	All CRC Patients (n = 70)	Stage I/II (n = 30)	Stage III (n = 17)	Stage IV (n = 23)
Age (mean ± SD, year)	37.83 ± 4.71 ^a	51.79 ± 7.72 ^b	49.71 ± 8.74 ^b	50.37 ± 7.99 ^b	55.17 ± 5.38 ^c
Gender					
Female (n,%)	12 (40%)	34 (48.57%)	14 (46.67%)	10 (58.82%)	10 (43.48%)
Male (n, %)	18 (60%)	36 (51.43%)	16 (53.33%)	7 (41.18%)	13 (56.52%)
BMI (< 25)	24 (80%)	28 (40%)	7 (23.33%)	9 (52.94%)	12 (52.17%)
BMI (> 25)	6 (20%)	42 (60%)	23 (76.67%)	8 (47.06%)	11 (47.83%)
Location					
Recto-sigmoid		15 (21.4%)			
Hepatic flexure		12 (17.1%)			
Ascending colon		9 (12.9%)			
Rectal		9 (12.9%)			
Transverse colon		8 (11.4%)			
Sigmoid		7 (10%)			
Splenic flexure		3 (4.3%)			
Cecal		7 (10%)			

According to the Duncan multiple range test, the different letters indicate statistical significance different means
 CRC colorectal cancer, BMI body mass index, SD standard deviation

Results

This study was carried out on 70 CRC patients aged 34–65 years. Male patients were 36 (51.43%), while female patients were 34 (48.57%). Based on the colonoscopy and radio-imaging findings, the most common CRC locations detected were recto-sigmoid (21.4%), hepatic flexure (17.1%), rectal (12.9%), ascending colon (12.9%), transverse (11.4%), and less commonly sigmoid (10%), cecal (10%), and splenic flexure (4.3%). The recruited CRC patients were grouped into three stages: stage I/II (30), stage III (17), and stage IV (23). Table 1 shows the demographics and clinical findings.

Tables 2, 3, and 4 show a remarkable, statistically significant difference between CRC and healthy control groups regarding hemoglobin, leukocytes, INR, albumin, ALT,

AST, total bilirubin, creatinine, and CEA levels with higher levels of ALT, AST, total bilirubin, creatinine, and CEA. There was also a decline in hemoglobin and albumin levels among CRC patients.

LINC00641 is upregulated in CRC patients compared to healthy participants. Here, LINC00641 shows a highly significant fold elevation in its expression level in CRC patients compared to healthy subjects, confirming that it can be used for early detection of colorectal cancer, as shown in Table 5. A notable and statistically significant elevation in the differential expression folds of LINC00641 was observed among CRC patients along with stages. The highest expression pattern was in stage IV patients (8.89 ± 0.62) with remarkable significance from stages I/II and III, as shown in Table 5.

Table 2 Comparison between CRC participants regarding hematological investigations

Variables	Hb (g/dl)	Platelets (× 10 ³ /mm ³)	Leukocytes (× 10 ³ /mm ³)	INR
Healthy control	12.09 ± 0.23 ^d	265.03 ± 8.06 ^a	5.10 ± 0.27 ^a	1.00 ^a ± 0.01
Stage I/II	10.43 ± 0.25 ^c	304.83 ± 4.37 ^b	8.10 ± 0.57 ^b	1.04 ^b ± 0.01
Stage III	8.22 ± 0.16 ^b	330.71 ± 5.94 ^c	8.18 ± 0.42 ^b	1.06 ^{bc} ± 0.01
Stage IV	6.81 ± 0.28 ^a	351.83 ± 5.48 ^d	8.25 ± 0.45 ^b	1.09 ^c ± 0.02
F-ratio	93.34	35.52	15.53	7.89
P- value	< 0.001	< 0.001	< 0.001	< 0.001

Data were expressed as mean ± SE; according to the Duncan multiple range test, the different letters indicate statistical significance different means

Hb hemoglobin, INR international normalized ratio

Table 3 Comparison between CRC participants regarding liver function investigations

Variables	Albumin (g/dl)	ALT (IU/l)	AST (IU/l)	T. bilirubin (mg/dl)
Healthy control	4.52 ± 0.05 ^c	14.30 ± 0.89 ^a	18.33 ± 1.19 ^a	0.48 ± 0.02 ^a
Stage I/II	3.58 ± 0.07 ^b	22.43 ± 1.19 ^b	29 ± 1.12 ^b	0.78 ± 0.06 ^b
Stage III	3.41 ± 0.06 ^{ab}	27.35 ± 1.27 ^c	31.06 ± 1.51 ^b	0.83 ± 0.09 ^{bc}
Stage IV	3.36 ± 0.07 ^a	28.09 ± 1.12 ^c	32.26 ± 1.23 ^b	1.02 ± 0.13 ^c
F-ratio	78.14	33.51	28.43	9.24
P-value	<0.001	<0.001	<0.001	<0.001

Data were expressed as mean ± SE; according to the Duncan multiple range test, the different letters indicate statistical significance different means

ALT alanine aminotransferase, AST aspartate aminotransferase, T. bilirubin total bilirubin

Our study shows a remarkable statistically significant fold decrease in miR-378 levels in CRC patients compared to healthy subjects, confirming that it can be used as LINC00641 for early detection of CRC, as shown in Table 5. Regarding the gradual decrease in the expression pattern of miR-378 among CRC stages, there was a statistical difference in the expression between stages I/II and III, while stage IV was the most downregulated group (0.34 ± 0.05) with great statistical significance from stage I/II ($p < 0.001$) and no statistical significance from the stage III group, as shown in Table 5.

The diagnostic validities of the targeted miR-378 and LINC00641 to differentiate between CRC patients and normal subjects were calculated using ROC curve analysis; ROC analysis revealed that serum LINC00641 discriminated CRC from healthy controls with a best cutoff value = 1.09, area under curve (AUC) = 0.996, 95% confidence interval (CI) = 0.988–1.005, and $P < 0.001$, with sensitivity = 98.57% and specificity = 100% (Fig. 1b). LINC00641 also distinguished late

Table 4 Comparison between CRC participants regarding renal and CEA investigations

Variables	Urea (mg/dl)	Creatinine (mg/dl)	CEA (ng/ml)
Healthy control	20.90 ± 0.95 ^a	0.63 ± 0.02 ^a	0.99 ± 0.10 ^a
Stage I/II	26.20 ± 0.92 ^b	0.76 ± 0.02 ^b	13.25 ± 0.99 ^b
Stage III	36.94 ± 0.70 ^c	0.85 ± 0.03 ^c	31.40 ± 3.05 ^c
Stage IV	41.87 ± 0.85 ^d	0.91 ± 0.03 ^c	36.32 ± 3.85 ^c
F-ratio	109.92	27.99	59.04
P-value	<0.001	<0.001	<0.001

Data were expressed as mean ± SE; according to the Duncan multiple range test, the different letters indicate statistical significance different means

CEA carcinoembryonic antigen

Table 5 Expression fold of miR-378 and LINC00641 regarding CRC patients

Variables	miR-378	LINC00641
Healthy control	0.99 ± 0.01 ^d	0.98 ± 0.01 ^a
Stage I/II	0.73 ± 0.03 ^c	2.74 ± 0.20 ^b
Stage III	0.50 ± 0.06 ^b	4.29 ± 0.35 ^c
Stage IV	0.34 ± 0.05 ^a	8.89 ± 0.62 ^d
F-ratio	66.58	106.44
P-value	<0.001	<0.001

Data were expressed as mean ± SE; according to the Duncan multiple range test, the different letters indicate statistical significance different means

miR-378 microRNA-378, LINC00641 long intragenic noncoding RNA00641

stage of CRC patients with best cutoff = 5.125, AUC = 0.956, 95% CI = 0.900–1.011, and $P < 0.001$, with sensitivity = 91.3% and specificity = 94.80% (Fig. 1d). ROC analysis revealed that serum miR-378 discriminated CRC from healthy controls with a best cutoff value = 0.90, an AUC = 0.957, 95% CI = 0.915–0.999, and $P < 0.001$, with sensitivity = 90% and specificity = 100% (Fig. 1a). miR-378 also distinguished the late stage of CRC with a best cutoff = 0.375, an AUC = 0.894, a 95% CI = 0.819–0.969, and $P < 0.001$, with sensitivity = 73.91% and specificity = 90.90% (Fig. 1c).

miR-378 expression was negatively correlated with the expression of LINC00641 ($r = -0.689$, $P < 0.001$), and serum CEA level ($r = -0.747$, $P < 0.001$) in CRC patients. However, serum expression of LINC00641 was positively correlated with serum CEA level ($r = 0.719$, $P < 0.001$), as shown in Table 6 and Fig. 2.

Discussion

Inadequate management and control of colorectal cancer is the most common gastrointestinal malignancy and is considered third cancer in mortality rates viewed as a life-threatening disorder worldwide (Ferlay et al. 2021). In Egypt, CRC has a high incidence among patients > 50 years after colonoscopic screening (Elkeleny et al. 2021). The high prevalence of early-onset colorectal cancer is due to a lack of awareness of contributing factors. So, in the current study, we aimed to explore the expression behavior of LINC00641 and miR-378, their association with cancer progression, and their diagnostic power in CRC early identification and staging. To the best of our knowledge, this is the first serum-based study to investigate the expression level of both LINC00641 and miR-378 in the serum of 70 CRC (grades I/II, III, and IV) Egyptian patients and 30 healthy participants.

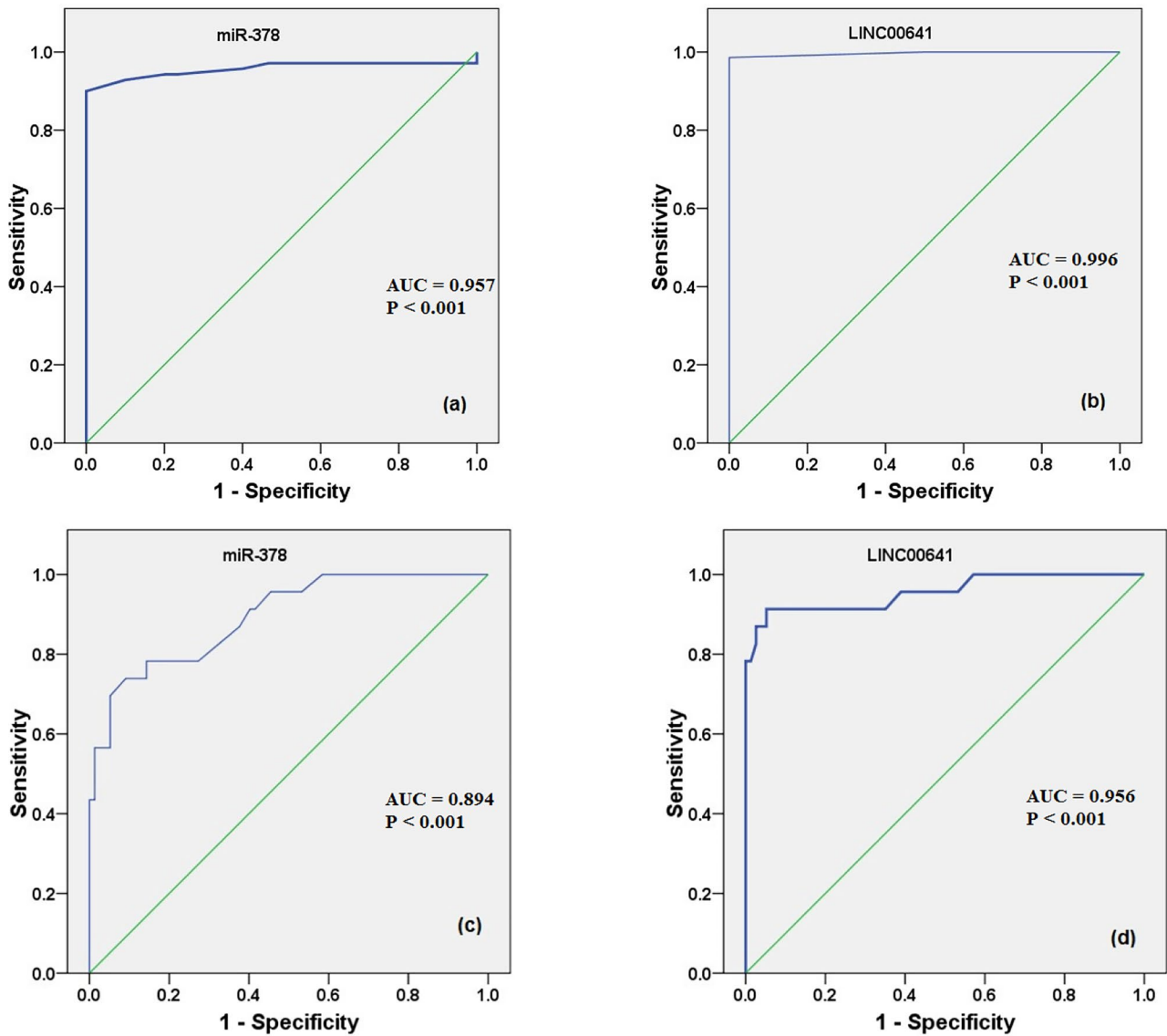


Fig. 1 **a, b** ROC analysis regarding miR-378 and LINC00641 between CRC and healthy participants. **c, d** ROC analysis regarding serum miR-378 and LINC00641 for stage IV CRC. miR-378, microRNA-378; LINC00641, long intragenic noncoding RNA00641; AUC, area under curve

The mean age of CRC enrolled patients were 51.79 years, and the major location for the diagnosed cases was colonic, but regarding the colorectal anatomy, most of the cases were

recto-sigmoid and hepatic flexure carcinomas, which is consistent with other Egyptian studies (Ramzy et al. 2015; Elkeleny et al. 2021).

Table 6 Pearson correlation coefficient between mir-378, LINC00641, and CEA in study participants

Parameter	miR-378		LINC00641		CEA	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
miR-378	—	—	−0.689**	<0.001	−0.747**	<0.001
LINC00641	−0.689**	<0.001	—	—	0.719**	<0.001
CEA	−0.747**	<0.001	0.719**	<0.001	—	—

**Significant linear correlation at *P* < 0.001 (2-tailed)

miR-378 microRNA-378, *LINC00641* long intragenic noncoding RNA00641, *CEA* carcinoembryonic antigen, *r* Pearson correlation coefficient

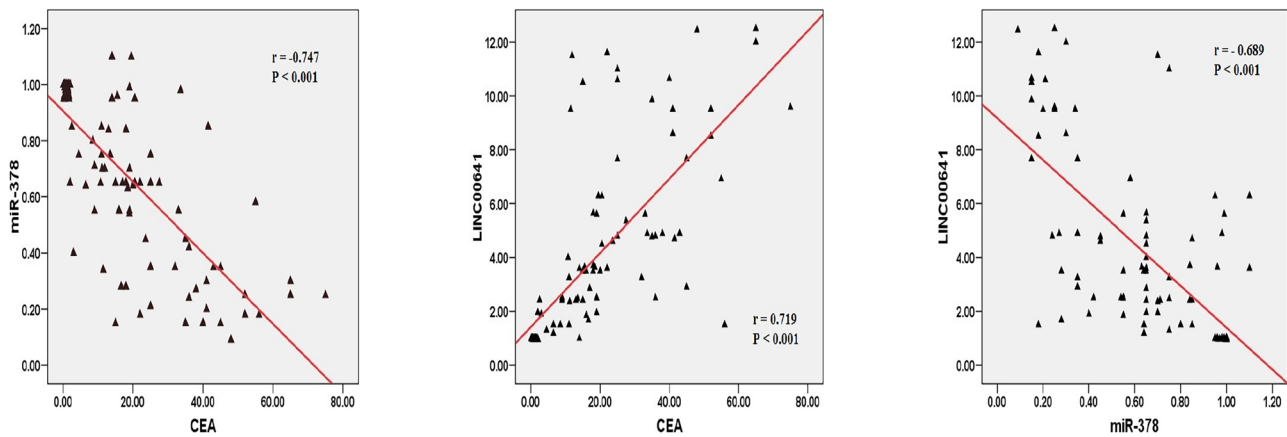


Fig. 2 Correlations between miR-378, LINC00641, and CEA of study participants. miR-378, microRNA-378; LINC00641, long intragenic non-coding RNA00641; CEA, carcinoembryonic antigen; *r*, Pearson correlation coefficient

Non-coding RNA possesses a remarkable role in cell processes such as proliferation, differentiation, and metastasis. lncRNA and miRNA have emerged as gene expression regulators that target more than 30% of the human genome (Wallace et al. 2016; Parikh et al. 2014), opening up new avenues for therapeutic and detectable biomarkers.

LINC00641 has shown to serve as an important regulator in several cancers, including bladder cancer (Li et al. 2018a), glioblastoma (Liang et al. 2019), lung cancer (Li et al. 2019), prostate cancer (Sajjadi et al. 2021), and nasopharyngeal carcinoma (Ren et al. 2021).

Herein, our results revealed a remarkable, significant upregulation of the LINC00641 expression level in CRC patients compared to healthy controls. The LINC00641 expression levels were elevated and associated with TNM stage and metastasis. Our results are consistent with the previous studies of Zhang et al. (2021) and Hu et al. (2020), who reported that LINC00641 expression is upregulated in various cancers and pointed to LINC00641 as a novel prognostic oncogenic biomarker.

Our study revealed that the LINC00641 expression was elevated significantly in CRC patients with stage IV, which is compatible with the findings of Xue et al. (2021), who reported that elevated LINC00641 expression positively correlated with lymph node metastasis and other clinical-pathological variables of CRC patients. Remarkably, our results showed a positive correlation between CEA and LINC00641 expression.

miR-378 have implicated in the development of a variety of cancers. Reduced miR-378 expression level in gliomas implies significant tumor invasiveness and a poor prognosis (Li et al. 2015). In hepatocellular carcinoma, miR-378 suppresses tumor cell growth and proliferation (Niu et al. 2015).

However, there are limited investigations on the link between miR-378 and colon cancer development.

Our study found that the expression fold of miRNA-378 was lower in CRC patients than in healthy control groups. The relative expression of miR-378 in serum could effectively distinguish CRC patients and normal populations, which is consistent with Faltejskova et al. (2012) and Peng et al. (2015). Additionally, Zeng et al. (2017) demonstrated that blocking the Wnt/catenin pathway with miR-378 expression reduced the malignant behaviors of colon cancer cells. Furthermore, Li et al. (2013) stated that miRNA-378 suppresses the growth features of HBV-related HCC by directly targeting the down expression of IGF 1R 3'-UTR.

Finally, the data obtained from the ROC analysis shows that LINC00641 and miR-378 can successfully discriminate between CRC patients and healthy controls. LINC00641 presented the best diagnostic potential because it showed the highest diagnostic accuracy for CRC patients from control subjects (AUC = 0.996, 98.57% sensitivity) and the highest ability to discriminate late-stage (IV) colorectal cancer (AUC = 0.956, 91.30% sensitivity, and 94.8% specificity). However, serum miR-378 discriminated CRC from healthy controls with an AUC of 0.957, 90% sensitivity, and 100% specificity. Moreover, miR-378 distinguished the late stage of CRC with an AUC of 0.894, with 73.91% sensitivity, and 90.90% specificity. Hence, LINC00641 and miR-378 may be promising circulating biomarkers for early CRC diagnosis and disease prognosis, respectively. However, some limitations exist, such as the study's small sample size and the evaluation of inflammatory biomarkers. As a result, more large-scale studies and clinical trials are required, as well as an assessment of their functional impacts on putative genes and target pathways.

Conclusion

Our findings suggest that LINC00641 and miR-378 can be used as simple and promising biological biomarkers for the diagnosis of CRC and for predicting the progression of complications. Overall, our results suggested that LINC00641/miR-378 axis might serve as a novel therapeutic target for CRC.

Author contribution N.H. and O.G. conceived and designed the research study; N.A. and O.G. contributed reagents/materials/analysis tools; N.A. and N.H. analyzed the data; N.H. and N.A. wrote the manuscript. Finally, all authors reviewed the manuscript.

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Declarations

Ethical approval The study was performed with the approval of the ethics committee of Al-Kasr Al-Ainy Hospital, Cairo University, Egypt, and The Helsinki Declaration was followed in the current research. All of the participants in this study gave their informed consent.

Conflict of interest The authors declare no conflicts of interest.

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