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The Diagnostic Value and Clinical Significance of lncRNA ITGB8-AS1 in Colorectal Cancer Patients

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ABSTRACT

Background: One of the most prevalent gastrointestinal diseases is colorectal cancer (CRC). In CRC tissues and plasma, the long noncoding RNA (lncRNA) ITGB8-AS1 is abundantly expressed and can promote migration, colony formation, and proliferation of cancer cells.

Objective: This study aimed to evaluate the clinical correlations of lncRNA ITGB8-AS1 and its potential as a diagnostic marker for colorectal cancer.

Patients and methods: Twenty patients with benign colorectal lesions, twenty patients with colorectal cancer, and twenty healthy volunteers were enrolled in total. The lncRNA ITGB8-AS1 was assessed using a quantitative real-time polymerase chain reaction.

Results: Compared to patients with benign lesions or the control group, patients with colorectal cancer showed higher levels of carcinoembryonic antigen (CEA), CA19-9, and lncRNA ITGB8-AS1. The combined use of lncRNA ITGB8-AS1, CA19-9, and CEA achieved high accuracy (97.5%), with 100% specificity and 95% sensitivity. Logistic regression identified lncRNA ITGB8-AS1 as a significant independent predictor with an adjusted odds ratio of 32, outperforming other markers. Furthermore, lncRNA ITGB8-AS1 showed significant correlations with parameters such as platelet count, PT, INR, CEA, and CA19-9, and a negative association with hemoglobin. Its levels increased with higher tumor stages and grades

Conclusions: This study supported the promise of lncRNA ITGB8-AS1 as a novel biomarker by highlighting its strong diagnostic potential in colorectal cancer. It does this by showing that it is significantly upregulated, performed exceptionally well as an independent predictor, and had meaningful correlations with tumor markers and laboratory parameters, particularly when combined with CEA and CA19-9.

Keywords: Colorectal cancer; Biomarker; Diagnostic; lncRNA ITGB8-AS1.

INTRODUCTION

Colorectal cancer (CRC) is the most common cause of cancer-related death and one of the most prevalent gastrointestinal cancers. It is the second leading cause of cancer-related deaths globally and the third most prevalent type of cancer to be diagnosed. The incidence of CRC has almost doubled in younger adults since the early 1990s, despite declining incidence in older groups [1].

Although estimates of CRC's prevalence in Egypt are inconsistent, some publications place it as the seventh most prevalent cancer diagnosis [2].

It is yet unknown what causes colorectal cancer. CRC patients frequently have no conventional clinical manifestations or only show non-specific indicators in the early stage, which results in a low early diagnosis rate, despite the fact that early diagnosis can greatly improve prognosis [3].

Although early detection rates have increased due to the implementation of CRC screening programs, many CRC patients continue to receive their diagnoses at an advanced stage, sometimes losing their prospects of a curative resection [4]. Even with the significant progress made, there are still few therapy options and survival improvements for advanced colorectal cancer. Therefore, research into new biomarkers and targets is desperately needed to enhance CRC outcomes. Despite their widespread use in CRC diagnosis, staging, and screening, the tumor markers carcinoembryonic antigen (CEA) and CA 19-9 have poor diagnostic sensitivity [5].

A family of non-coding transcripts longer than 200 nucleotides is known as long noncoding RNAs, or lncRNAs. There is mounting evidence that lncRNA dysregulation occurs in a variety of cancer types, including colorectal cancer, and that it plays a crucial role in all cancer hallmarks [6–9]. The majority of lncRNAs' roles and processes in CRC are still unknown, nevertheless. It is crucial to use transcriptomics to identify CRC-related lncRNAs for additional functional validation [10]. The lncRNAs provide information on their possible clinical uses by contributing to immune modulation, tumor heterogeneity, and the progression of colorectal cancer [11].

In order to stimulate focal adhesion signaling and integrin α3 and β3 transcription, which were necessary for CRC development and migration, LncRNA ITGB8-AS1 sponged different microRNAs (miRNAs). Additionally, CRC tissues and plasma have elevated levels of lncRNA ITGB8-AS1, which can promote migration, colony formation, and proliferation of cancer cells. ITGB8-AS1 regulates integrin-mediated focal adhesion signaling, a competing endogenous RNA (ceRNA) that is essential for the development and spread of colorectal cancer [12].

Given the critical role lncRNAs play as essential biomarkers in cancer, the current study was carried out

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to evaluate the potential of lncRNA ITGB8-AS1 as a diagnostic marker for CRC and to evaluate its clinical correlations.

SUBJECTS AND METHODS

Study design and subjects: A case-control study was conducted at the Internal Medicine, Surgery and Clinical Pathology Departments of Zagazig University Hospitals from April 2024 to March 2025. Assuming that the average lncRNA ITGB8-AS1 delta cycle threshold (CT) in CRC patients is 0.3 ± 0.24 and that of the control group is 0.1 ± 0.2, the sample size was calculated. Therefore, the sample size established by the open EPI program was 60 individuals, 20 in each group, with a 95% confidence level and 80% test power.
Twenty patients with benign colorectal lesions, twenty patients with colorectal cancer, and twenty healthy volunteers were enrolled in total. Upon approval of their participation, patients who had recently been diagnosed with colorectal cancer were included in the study.

Exclusion criteria: Those who received radiation therapy or chemotherapy before the sample was collected. Furthermore, patients with any further inflammatory disorders or other cancers were prohibited.

Methods: A clinical examination will be performed on each patient. The tumor was staged TNM and graded histologically [13, 14]. Both routine and special tests were carried out in labs. A volume of approximately 5 milliliters of venous blood was drawn and immediately divided into three vacutainer tubes, which were purchased from Becton, Dickinson Company, Franklin Lakes, New Jersey, USA. The complete blood count (CBC) was carried out on one milliliter (mL) of blood that was taken in an EDTA vacutainer. CBC was carried out using an automatic cell counter, model XN 2000 (**Sysmex, Japan**). 1.8 mL of blood was drawn into the citrate vacutainer and after centrifuging to separate the plasma. The plasma was used on the Sysmex CS2100i (**Siemens, Munich, Germany**) to measure the coagulation profile. The serum was separated by centrifuging two milliliters of blood. The RNA was extracted using an aliquot of serum. Measurements of CEA and CA 19-9 were performed using a second serum aliquot on a Roche/Hitachi Cobas 6000-e601 instrument (**Roche, Germany).**

The lncRNA ITGB8-AS1 was assessed using a quantitative real-time polymerase chain reaction. RNA was extracted from serum using the miRNeasy Serum/Plasma kit (Catalogue no. 217184; **Qiagen, Hilden, Germany**). The procedures were carried out in accordance with the manufacturer's guidelines. Gel electrophoresis and a spectrophotometer (Nano Drop 1000, **Wilmington, DE, USA**) were used to assess the RNA. One microgram of isolated RNA is utilized in the miScript RT II kit (Catalogue No. 218160) from QIAGEN GmbH in Hilden, Germany), to perform the reverse transcription process. The cDNA was amplified using the StepOne™ System (**Applied Biosystems, USA**) and the miScript SYBR Green PCR Kit with a catalogue number of 218073 (**Qiagen, Germany**). Every step was conducted in compliance with the manufacturer's recommendations. The real-time cycler is programmed as follows: The initial denaturation was scheduled to last for 15 minutes at 95 °C. The thermal process was set up to run for 40 cycles, with 15 seconds of denaturation at 95 °C, 30 seconds of annealing at 58 °C, and 30 seconds of extension at 70 °C throughout each cycle.

The forward primer for the lncRNA ITGB8-AS1 was 5'-AAGCCGTGATCCCAACCTTA-3', whereas the reverse primer was 5'-TGGCACCTGACATATATTTGCA-3'. The primers for beta-actin were 5'-CTCTTCCAGCCTTCCTTCCT-3' for the forward primer and 5'-AGCACTGTGTTGGCGTACAG-3' for the reverse primer. The amplification curves were used to calculate the CT of each sample. Melting curve analysis was employed to assess the specificity of the amplified product. The fold change was computed using the negative result of the delta-delta CT subtraction, which produces the exponent of 2.

Ethical approval: This study was approved by The Institutional Review Board (IRB) (IRB No # 156/5-March-2024). In compliance with the Declaration of Helsinki. Informed written consent was obtained before using any participant's clinical data or sample in this study. The study followed Helsinki Declaration through its execution.

Statistical analysis

The data analysis was done using SPSS version 20 (Chicago, IL, USA). For quantitative data, Mann-Whitney, or Kruskal-Wallis followed by Hoc Dunn's test was used for data comparison. The Fisher's exact test, or Chi square test was applied appropriately for qualitative data. To investigate the relationship between the marker and clinical factors, a Spearman correlation analysis was performed. The diagnostic performance was evaluated using the study of the receiver operating characteristic (ROC) curve. Both univariate and multivariate analysis were used to identify the predicted variables. Values ≤ 0.05 showed statistical significance.

RESULTS

Table (1) displayed the primary research variables in rows. Sixty percent of the patients were in stages 3 and 4. The grade that occurred the most commonly was grade 2.

Table (1): Study subjects characteristics

Parameter	Control (No. = 20)	Benign (No.=20)	Colorectal cancer (No. = 20)	p
Age (years)	54 [32-65]	56 [37-62]	55 [34-66]	0.39
Sex: Male/ Female	8/12 (40/60)	8/12 (40/60)	9/11 (45/55)	0.9
Smoking	5 (25)	9 (45)	7 (35)	0.42
Family history of carcinoma	2 (10)	5 (25)	5 (25)	0.39
Co-morbidity	0	3 (15)	4 (20)	0.12
Clinical symptoms				
• Abdominal pain	—	10 (50)	11 (55)	
• Change in bowel habit	—	8 (40)	6 (30)	0.53
• Bleeding	—	2 (10)	3 (15)	
Site of cancer				
• Rectal	—	—	8 (40)	
• Colon	—	—	12 (60)	
Size of cancer				
• < 5 cm	—	—	15 (75)	
• ≥ 5 cm	—	—	5 (25)	
Tumor grade (G)**:**				
• G1	—	—	4 (20)	
• G2	—	—	9 (45)	
• G3	—	—	7 (35)	
TNM Staging:				
• Stage 1	—	—	3 (15)	
• Stage 2	—	—	5 (25)	
• Stage 3	—	—	6 (30)	
• Stage 4	—	—	6 (30)	

No.: number of subjects; **TNM:** Tumor, node, and metastasis, Co-morbidity represents hypertension or diabetes mellitus, Data are presented as No. (%) or median [range], ***** Significant.

Table (2) displayed the lab data for each group. When comparing the hemoglobin and platelets of patients with colorectal cancer to other groups, table (2) demonstrated significant variations between the studied groups. Compared to other groups, patients with colorectal cancer had considerably greater PT and INR. Compared to patients with benign lesions or the control group, patients with colorectal cancer showed higher levels of CEA, CA19-9, and lncRNA ITGB8-AS1.

Table (2): Routine laboratory tests results in the studied groups

Parameter	Controls (No. = 20)	Benign (No.=20)	Colorectal cancer (No. = 20)	p
WBCs (10^3/µL)	5.2 [4-10.5]	4.9 [4.7-9.2]	5.1 [4.3-10.5]	0.31
Hemoglobin (g/dL)	12.9 [11.2-14.3]	12.3 [10.9-14.9]	11.2 [10.1-13.9][a,b]	<0.001*
Platelet (10^3/µL)	220 [150-374]	222 [149-374]	344 [150-420] [a,b]	0.43
PT (Seconds)	12.7 [11.7-13.1]	12.1 [11.6-13][a]	13.1 [11.6-14.2] [a,b]	0.001
INR	1.07 [1-1.1]	1.02 [1-1.1]	1.19 [1.1-1.3] [a,b]	0.57
PTT (Seconds)	27.2 [255.6-31]	26.9 [25.6-30]	26.9 [24.2-32]	<0.001*
CEA (ng/mL)	2 [0.7-11.2]	8.95 [1.9-16.9] [a]	25.5 [5-70.3] [a,b]	<0.001*
CA 19-9 (U/mL)	8.4 [1.2-25.9]	21 [1.5-30.7] [a]	31.1 [2.5-61.3] [a,b]	<0.001*
lncRNA ITGB8-AS1 (Fold change)	1.07 [1-1.3]	1.45 [1-2.1] [a]	3.9 [1.1-5.1] [a,b]	<0.001*

WBCs: White blood cells; **PT:** prothrombin time; **PTT:** partial thromboplastin time; **INR:** International normalized ratio, **CEA:** Carcinoembryonic antigen; **CA:** Cancer antigen; **lncRNA:** long non-coding RNA; **HIF1A-AS1:** Hypoxia Inducible Factor 1-α antisense 1, Data are presented as median [range], p= Kruskal-Wallis followed by Hoc Dunn's test ***** Significant, **a:** difference in comparison to control, **b:** difference in comparison to benign.

The effectiveness of tumor markers as a diagnostic tool was assessed using ROC curve analysis. Figure (1) showed the ROC curves for lncRNA ITGB8-AS1, CA19-9, and CEA in the prediction of colorectal cancer. The combination of the three markers performed best at the chosen cutoff points where it had a total accuracy of 97.5%, 100% specificity, and 95% sensitivity. The performance characteristics of every marker are displayed in table (3).

Table (3): Diagnostic performance of different tumor markers

Marker	Cutoff	Youden's index	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
CEA (ng/mL)	≥ 9.1	0.63	85	77.5	79.1	83.8	81.3
CA 19-9 (U/mL)	≥ 13.3	0.43	80	62.5	68.1	75.8	71.3
lncRNA ITGB8-AS1 (Fold change)	≥1.95	0.88	95	97.5	97.4	95.1	96.3
Combined CEA, CA19-9, and lncRNA ITGB8-AS1	Same cutoffs	0.93	95	100	100	95.2	97.5

AUC: Area under the ROC curve; **CI:** Confidence interval; **PPV:** Positive predictive value; **NPV:** Negative predictive value.

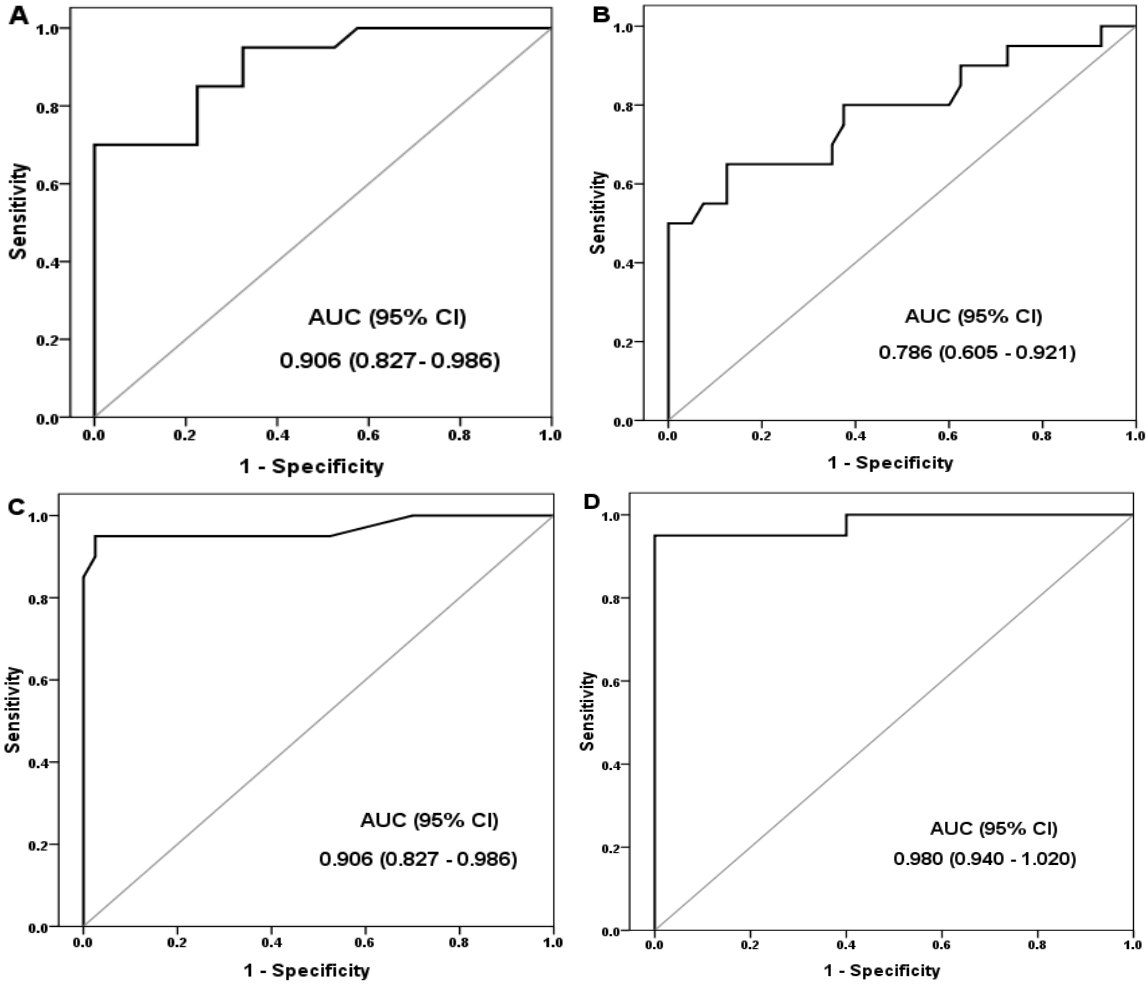

Figure (1): ROC curves of markers in colorectal prediction (A) CEA, (B) CA19-9, (C) lncRNA ITGB8-AS1, and (D) Combined three markers.

Table (4) evaluated the predictive efficacy of the LncRNA ITGB8-AS1 expression cutoff in the diagnosis of colorectal cancer. The purpose of the logistic regression study was to find any possible CRC predictors. HIF1A-AS1, CEA, and CA19-9 were found to be univariate predictors of CRC. lncRNA ITGB8-AS1 was a significant independent predictor of CRC on multivariate analysis involving all characteristics listed in table (4). lncRNA ITGB8-AS1 had an adjusted odds ratio of 32 (95% CI: 2.6-413) (p = 0.007).

Table (4): Logistic regression analysis of colorectal cancer prediction

Parameters	Univariate		Multivariate	
	OR (95%CI)	p	AOR (95%CI)	p
Age	0.99 (0.91-1.07)	0.86	0.91 (0.71-1.16)	0.40
Sex	0.81 (0.28-2.4)	0.71	0.29 (0.02-35.6)	0.61
Smoking	1 (0.34-3.08)	0.99	0.18 (0.01-26.2)	0.50
Family history of carcinoma	1.5 (0.4-5.8)	0.49	0.14 (0-138)	0.58
CEA	1.23 (1.1-1.4)	<0.001*	1.2 (0.87-1.65)	0.26
CA19-9	1.09 (1.04-1.15)	0.001*	1.06 (0.85-1.33)	0.59
LncRNA ITGB8-AS1	133 (6.8-263)	0.001*	32 (2.6-413)	0.007*

OR: Odds ratio; **CI:** Confidence interval; **AOR:** Adjusted OR; **lncRNA:** long non-coding RNA; **HIF1A-AS1:** Hypoxia Inducible Factor 1-α antisense 1; **CEA:** Carcinoembryonic antigen; **CA:** Cancer antigen, ***:** Significant .

Among the groups under investigation, the relationship between LncRNA ITGB8-AS1 and several parameters was assessed. Between platelet count, PT, INR, CEA, and CA19-9, there was a significant correlation (r = 0.39, 0.37, 0.58, 0.73, and 0.52, respectively) (p<0.01)

. On the other hand, lncRNA ITGB8-AS1 and hemoglobin showed a strong negative association (r = -0.55) (p<0.001). The tumor's grade and stage had a significant association with the LncRNA HIF1A-AS1. It was found that when the stage and grade increase, so does the marker level. Figure (2A) showed that LncRNA ITGB8-AS1 was able to distinguish between early and late cancer grades. With an increase in CRC stages, lncRNA ITGB8-AS1 showed an increasing tendency (Figure 2B).

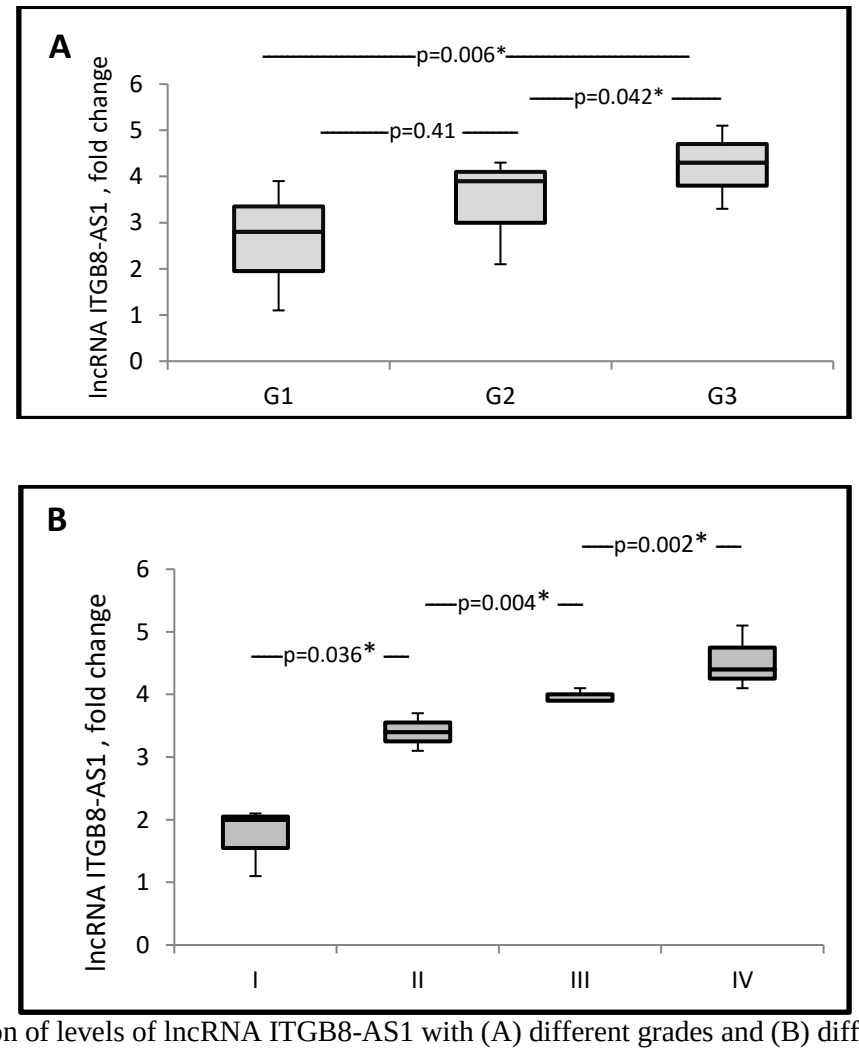

Figure (2): Association of levels of lncRNA ITGB8-AS1 with (A) different grades and (B) different stages of CRC.

DISCUSSION

Colorectal cancer (CRC) remains a significant global health challenge, characterized by high morbidity and mortality rates, underscoring the critical need for the identification of novel, highly sensitive, and specific biomarkers for early detection, accurate prognosis, and effective therapeutic monitoring [15].

This study was undertaken to investigate the diagnostic value and clinical significance of long non-coding RNA ITGB8-AS1 (lncRNA ITGB8-AS1) in patients with CRC, by evaluating its expression levels and correlating them with various clinical and laboratory parameters across distinct cohorts: Healthy controls, patients with benign colorectal lesions, and patients diagnosed with colorectal cancer. The baseline characteristics of our study participants demonstrated a notable homogeneity across the control, benign, and colorectal cancer groups with respect to key demographic and lifestyle factors. Specifically, no statistically significant differences were observed in age, sex, smoking status, family history of carcinoma, or co-morbidity. This careful matching of baseline parameters is crucial for strengthening the internal validity of our findings, effectively mitigating potential confounding effects that could otherwise obscure the true associations between the studied variables and disease status.

The clinical symptomatology observed in CRC patients, particularly the high prevalence of abdominal pain (55%) and changes in bowel habit (30%), is consistent with the established clinical presentation of colorectal malignancies [16]. Furthermore, our analysis of disease staging revealed that a substantial proportion of CRC patients (60%) presented with advanced disease (Stages 3 and 4), with grade 2 being the most frequently observed tumor grade (45%). This finding underscored the persistent challenge of late-stage diagnosis in CRC [17], highlighting the urgent necessity for the development and implementation of more effective early detection strategies to improve patient outcomes [18].

Regarding routine laboratory test results across the studied groups offering critical insights into the systemic physiological alterations associated with CRC, we observed statistically significant variations in hemoglobin levels among the groups. Patients with CRC exhibited markedly lower hemoglobin concentrations compared to both the benign lesion group and the healthy control group. This observation is a common clinical manifestation in CRC, often attributed to chronic gastrointestinal blood loss from the tumor, cancer-related anemia, or nutritional deficiencies [19].

Regarding platelet counts, there was a trend towards higher platelet counts in CRC patients. This could be indicative of cancer-associated thrombocytosis, a well-recognized paraneoplastic phenomenon that is frequently linked to a pro-coagulant state and may be associated with a poorer prognosis in various malignancies [20]. Moreover, our data revealed significantly elevated Prothrombin Time (PT) in CRC patients compared to the other cohorts. This is consistent with **Zhang *et al.*** [21] who revealed that elevated levels of preoperative PT were predictors of poor outcomes in CRC patients.

In line with their well-established roles as conventional tumor markers in gastrointestinal malignancies, our study demonstrated significantly higher levels of CEA and CA19-9 in patients diagnosed with colorectal cancer when compared to individuals with benign colorectal lesions and the healthy control group. These results corroborate numerous previous studies and reaffirm the clinical utility of CEA and CA19-9 in the diagnosis, staging, and post-treatment surveillance of CRC, particularly in advanced disease stages [22]. However, it is important to acknowledge the inherent limitations of these markers, including their suboptimal sensitivity for early-stage disease and their lack of absolute specificity, which necessitates the exploration and validation of novel, more precise complementary biomarkers.

A pivotal finding of our study is the elucidation of the promising diagnostic value of lncRNA ITGB8-AS1 in colorectal cancer. Our results unequivocally demonstrated significantly elevated expression levels of lncRNA ITGB8-AS1 (Fold change: 3.9 [1.1-5.1]) in colorectal cancer patients. This upregulation was markedly higher compared to patients with benign lesions (1.45 [1-2.1]) and healthy controls (1.07 [1-1.3]), with a highly significant statistical difference. This substantial and statistically significant upregulation of lncRNA ITGB8-AS1 in CRC suggests its potential as a novel and highly sensitive biomarker for the disease. This aligns with prior literature indicating that lncRNAs are involved in tumorigenesis and metastasis, often exhibiting altered expressions in various cancers [23]. Specifically, ITGB8-AS1 has been implicated in promoting cell proliferation and invasion through modulation of integrin pathways, which are crucial in CRC [12].

The assessment of tumor markers for colorectal cancer (CRC) diagnosis using ROC curve analysis revealed significant insights into their diagnostic performance. The combined use of lncRNA ITGB8-AS1, CA19-9, and CEA demonstrated superior accuracy, with an area under the curve (AUC) of 0.93, achieving 97.5% sensitivity and 100% specificity. This combined approach underscored the potential of integrating multiple biomarkers to enhance diagnostic precision, aligning with previous studies emphasizing multi-marker panels for cancer detection [24].

LncRNA ITGB8-AS1 emerged as a strong independent predictor of CRC, with a multivariate adjusted odds ratio (AOR) of 32 (95% CI: 2.6–413, p=0.007). Its high performance suggests that it could serve as a reliable biomarker, which is consistent with findings by **Wu *et al.*** [25] who reported the utility of specific lncRNAs in cancer progression.

Correlation analyses revealed significant associations between lncRNA ITGB8-AS1 and several clinical parameters, including platelet count, PT, INR, CEA, and CA19-9. Conversely, there was a strong negative correlation with hemoglobin. These relationships are consistent with prior research demonstrating the interplay between tumor biomarkers and systemic inflammatory or hematological parameters [26].

In our current study, lncRNA ITGB8-AS1 levels progressively increased from grade 1 to grade 3 tumors, indicating its ability to distinguish between varying degrees of tumor differentiation and aggressiveness. Similarly, there was a clear increasing tendency of lncRNA ITGB8-AS1 expression with advancing CRC stages (from Stage 1 to Stage 4), suggesting its potential as a marker for disease progression and severity. These stage- and grade-dependent expression patterns further highlighted the clinical utility of lncRNA ITGB8-AS1 as a potential biomarker for assessing disease severity and progression, which is echoing the findings by **Lin *et al.*** [12] on lncRNA's role in cancer progression.

LIMITATIONS

Our study's limitations include a relatively small sample size and lack of longitudinal follow-up to assess the prognostic implications of ITGB8-AS1 levels. Additionally, correlation analysis between lncRNA expression and clinical outcomes would strengthen the clinical relevance. Lastly, the study focused solely on lncRNA ITGB8-AS1 in combination with CEA and CA19-9.

RECOMMENDATIONS

To further solidify these findings and translate them into clinical practice, future studies are warranted. These should include larger, multicenter cohorts to validate the observed expression patterns, to assess the sensitivity and specificity of lncRNA ITGB8-AS1 across diverse patient populations, and to elucidate the precise molecular mechanisms by which it influences CRC initiation, progression, and metastasis. Furthermore, investigating its utility in different stages of CRC development, its potential as a non-invasive screening tool, and its role as a predictive or prognostic biomarker would significantly enhance our understanding of its overall clinical utility and therapeutic implications. Moreover, its association with tumor progression implies a role in prognosis and possibly in guiding therapeutic interventions. Further studies should focus on assessing its predictive value for treatment response and survival outcomes.

CONCLUSIONS

This study found compelling evidence for the significant diagnostic value and clinical relevance of lncRNA ITGB8-AS1 in the context of colorectal cancer. The observed substantial upregulation of this lncRNA in CRC patients, its superior diagnostic performance, its independent predictive power, and its correlations with characteristic alterations in routine laboratory parameters and established tumor markers, strongly reinforces its potential as a novel and effective biomarker. Especially when it combined with established tumor markers like CEA and CA19-9. LncRNA ITGB8-AS1 had potential as a marker for disease staging.

Conflict of interest: None.
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