RESEARCH ARTICLE

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Clinical Analysis of Pyroptosis-Related Long Non-Coding RNAs MIAT and Gm15441 in Colorectal Cancer Patients with a History of Ulcerative Colitis

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Abstract

Background: Pyroptosis can play a significant role in the development of inflammatory bowel diseases such as ulcerative colitis (UC) and colorectal cancer (CRC). The expression pattern of two pyroptosis related-lncRNAs MIAT and Gm15441 was investigated in clinical samples of CRC with and without a history of UC. **Methods:** In this case-control study, 48 tumor samples from patients with CRC and 48 healthy adjacent tissue samples were studied. A quantitative PCR was completed to analyze the relative expression of lncRNAs GM15441 and MIAT. Quantitative expression levels of the lncRNAs in tumor and healthy tissues were compared. The potential relationship with clinicopathological features and diagnostic values of the lncRNAs were evaluated. **Results:** The expression levels of both lncRNAs MIAT and Gm15441 were significantly increased in CRC tissues in comparison with healthy tissues (P=0.038 and 0.012, respectively). Also, there was a significant relationship between the expression levels of lncRNA MIAT and lymph node metastasis, but not other clinicopathological characterizations. An AUC of 0.65 for lncRNA MIAT with a sensitivity of 62% and specificity of 54%, with a cut-off value of 2.9 (P= 0.025), and an AUC of 0.66 for lncRNA Gm15441, with a sensitivity of 68% and specificity of 52%, with a cut-off value 1.7 (P= 0.005) were detected. **Conclusion:** Dysregulated lncRNAs MIAT and Gm15441 in CRC can be more clinically important in cases of cancer related to UC due to their biological function in regulating the inflammation process, providing new ideas about the diagnosis and management of pyroptosis-related diseases.

Keywords: Pyroptosis- Long non-coding RNA MIAT- Long non-coding RNA Gm15441- Colorectal cancer

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Introduction

Pyroptosis is one type of inflammatory-related cell death. In general, gasdermins mediate pyroptosis, a necrotic process that increases inflammatory activity and ultimately triggers a severe inflammatory response [1]. A growing body of scientific data has shown that pyroptosis may have a dual effect on carcinogenesis and cancer progression. Pyroptosis results in cell death, but in some cellular microenvironments, it may also promote the formation and development of tumors [2]. Because of the inflammatory conditions and activated inflammatory mechanisms linked to inflammatory bowel disorders (IBD) and colorectal cancer (CRC), pyroptosis may play a role in the development of inflammation. Conversely, it may control cell development by preventing inflammatory reactions [3]. Oncology researchers have been looking into the biological signaling pathways and clinical importance of this cell death process because it plays such complex biological roles and is controlled by many factors [4, 5]. An increasing amount of research indicates that non-coding RNAs (ncRNAs) can start or control pyroptosis in pathological conditions, such as cancer. Researchers have examined the regulatory function and molecular processes of ncRNAs in tumor cell pyroptosis using cutting-edge sequencing technology [6, 7].

Recent research has demonstrated the role of ncRNAs in the onset and spread of colorectal cancer. Despite

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their essential role in various cellular and physiological functions, ncRNAs do not primarily translate into proteins [8]. Long non-coding RNAs (lncRNAs), which are non-coding RNAs longer than 200 nucleotides, play a role in many cell-specific processes, such as metastasis, apoptosis, differentiation, and proliferation [9]. LncRNAs may bind to proteins, DNA, or RNA. They frequently work as competing endogenous RNAs (ceRNA) to control the amounts of certain microRNAs (miRNAs) and the molecules that they target. Many human malignancies, including CRC, which is the second-leading cause of cancer death worldwide as well as the third-most common cancer in both men and women [10], have linked LncRNAs to their growth and spread. Long noncoding RNAs play a part in cell processes like cell death, cell division, and metastasis [11]. They are also important for cancer stem cells (CSCs). Furthermore, studies have connected these molecules to the clinicopathological characteristics of CRC patients, highlighting their clinical significance as markers for diagnosis and prognosis [12-14].

The findings about how lncRNAs affect pyroptosis in UC-associated CRC and how they work in cell signaling suggest that more biological and clinical research into their possible roles in cell signaling and diagnosis could be helpful. The purpose of this study was to assess the expression pattern and clinical analysis of pyroptosis-related lncRNAs, MIAT, and *Gm15441* in CRC patients with a history of UC.

Materials and Methods

Sampling from patients and sample processing

In this study, the test group was patients with CRC referred to Rasool Akram and Firozgar hospitals of Tehran, Iran, who were approved as tumor patients based on colonoscopy and clinical symptoms. The inclusion criteria included the presence of gastrointestinal symptoms indicating the presence of malignancy (blood in the stool, pain, and constipation), confirmation of the presence of colorectal tumor tissue by a specialist doctor and surgeon during the colonoscopy process, and pathological confirmation of the stages of the disease. Exclusion criteria included the diagnosis of benign polyps in the intestine, the history of taking certain drugs and chemotherapy up to two months before sampling, and the presence of any type of metabolic disease and other malignancies. After obtaining the consent of the subjects under study, 48 colorectal tumor tissue and 48 corresponding healthy adjacent tissue samples were collected in tubes containing RNA later and after being transferred to the laboratory, they were stored in appropriate conditions. To prevent RNA degradation, the samples were saved at -80°C until extraction.

The study was approved by the Ethical Committee of Iran University of Medical Sciences (Ethical Code: IR.IUMS.REC.1401.167) and completed according to the ethical guidelines.

RNA extraction

Total RNA was extracted from the tissue samples using the TRIzol (Invitrogen) protocol based on the manufacturer's instructions [15]. To investigate gene expression (those with a weight higher than 200 bp), the isolated RNAs were purified and concentrated using the RNeasy MinElute Cleanup Kit (Qiagen). The quantity and quality of isolated RNA was evaluated using nanodrop and gel electrophoresis. The RNA was saved at -80°C for next use.

cDNA Synthesis from RNA and real-time PCR reaction

Reverse transcription reaction for cDNA synthesis was done by PrimeScript First Strand cDNA Synthesis Kit (Takara, Japan) according to the manufacturer protocol.

A quantitative real-time PCR (qPCR) method was used to quantitatively analyse the expression of target lncRNAs *MIAT* and *Gm15441*. The used primer sequences are presented in Table 1. PCR reactions were performed using specific primers of the β-Actin housekeeping gene as a normalizer and the studied lncRNAs with a real-time PCR kit (Takara, Japan). All the real-time PCR tests were completed as duplicated. Threshold cycle (Ct) of the target lncRNAs and β-Actin, was attained from thermocycler analyses. The Pfaffl method was applied to evaluate the expression levels of the studied lncRNAs using the data obtained from qPCR. In this method, based on the ΔΔCt formula, the ratio of changes in the expression level of the target gene compared to the control gene is calculated. Based on the set of samples, data analysis was conducted by the Rotor-Gene AssayManager software.

Statistical analysis

For the statistical analysis of qPCR data, SPSS software version 19.0 was used. Kolmogorov Smirnov test was used to check normality. By using t test, ANOVA and Mann–Whitney U test, the average expression data in different groups were compared. P values less than 0.05 were reported as statistically significant.

Results

Expression levels of lncRNAs MIAT and Gm15441 in CRC patients

The Kolmogorov-Smirnov normality test showed that variables are not normally distributed ($p<0.05$). Therefore, non-parametric tests were completed to analyze the data between the two groups of tumor and healthy tissues.

The results of data analysis to compare the expression of lncRNA *MIAT* in tumor tissues and healthy adjacent tissues showed that the mean expression levels of the lncRNA were meaningfully increased in tumor tissues than in healthy tissues ($p=0.038$). Also, expression analysis of GM15441 showed a significant difference in the tumor

Table 1. Primer Sequences Used for qPCR in This Study

LncRNA/Gene	Primer sequence (5' to 3')
MIAT	Forward: GAGGGAAGTTCTGAGCTTGG
	Reverse: CCTTTCTTCTGGGCTGAGAC
Gm15441	Forward: AGAGTTGTGAGCTGCCGTTT
	Reverse: AGGGGAGGTCAGAGTTGGTT
β-Actin	Forward: AGAGCTACGAGCTGCCTGAC
	Reverse: AGCACTGTGTTGGCGTACAG

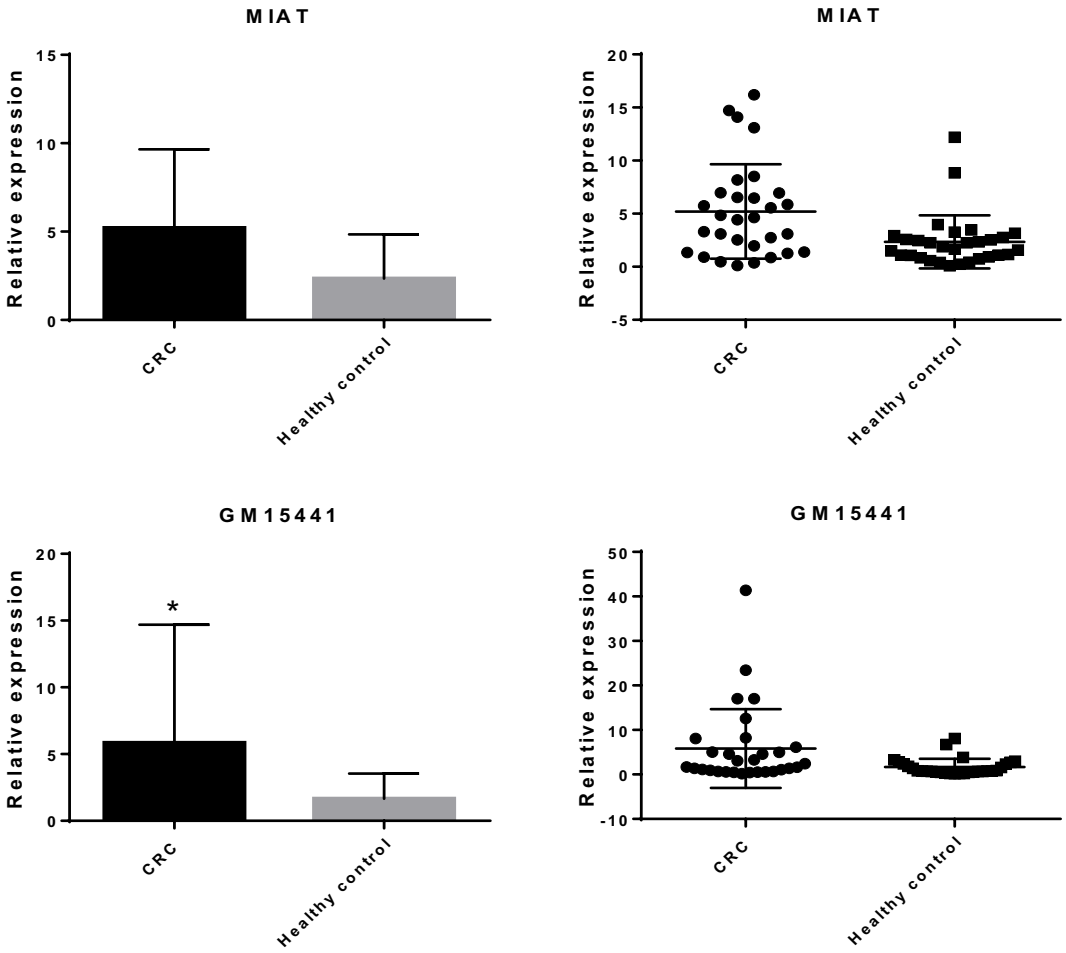

Figure 1. Evaluation of the Expression Levels of lncRNAs in the Tumor Tissues Compared to the Healthy Adjacent Tissues. The results showed a significant difference in the expression levels of *MIAT* in tumor tissues in comparison with the healthy tissues (P=0.038). Also, a significant difference in the regulation of lncRNA *Gm15441* expression in tumor tissues in comparison with healthy tissues was detected (P<0.012).

and healthy groups (p=0.012) (Figure 1).

Correlation of lncRNAs expression levels with clinical characterization of CRC patients

The clinicopathological characterizations of studied CRC patients are presented in Table 2. Further analysis revealed that the high expression of lncRNA *MIAT* was positively associated with lymph node metastasis (p=0.044). Also, data analysis between the two groups of tumor and healthy tissue documented that there was no significant relationship between the expression levels of these two lncRNAs and other clinicopathological features such as tumor differentiation, disease stage and tumor size (p>0.05). Also, the mean expression levels of these two

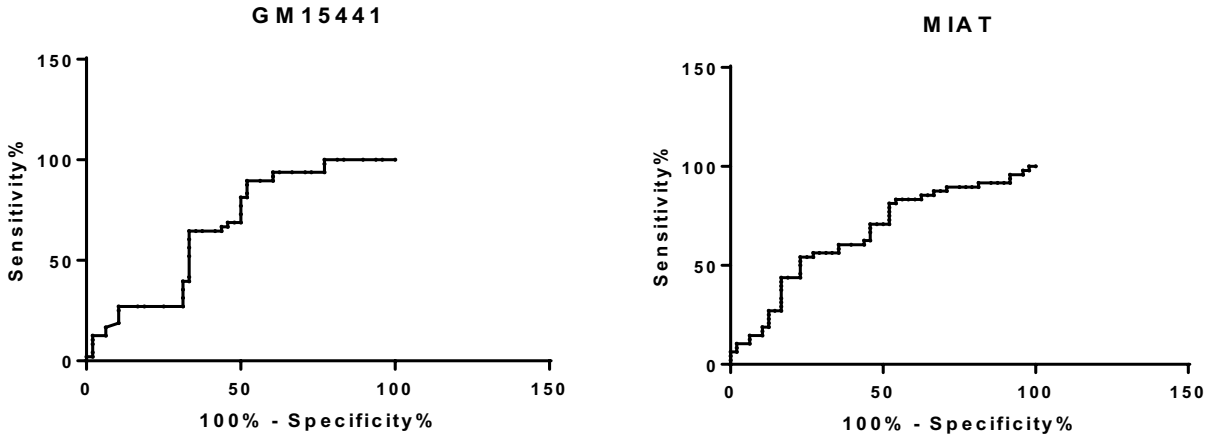

Figure 2. Evaluation of Diagnostic Value of lncRNAs for CRC Patients. The ROC analysis showed the specificity and sensitivity of lncRNAs *MIAT* and *Gm15441* for CRC patients.

Table 2. Clinical and Pathological characteristics of CRC Patients

Features		Frequency	Percentage
Age	<60	21	43.7
	≥60	27	56.3
Sex	Male	33	68.7
	Female	15	31.3
Tumor location	Colon	18	37.5
	Rectum	30	62.5
Polyp	Positive	11	23.3
	Negative	31	76.7
Ulcerative colitis	Positive	27	56.3
	Negative	21	43.7
Lymph node metastasis	Positive	13	27
	Negative	35	73
Pathological tissue differentiation	Well	32	66.7
	Moderate	13	27
	Poor	3	6.3
Family history	Positive	6	12.5
	Negative	42	87.5
Tumor size	<2 cm	10	20.1
	2 - 3.99 cm	31	64.5
	≥ 4 cm	7	15.4
Tumor stage	T2	31	64.5
	T3	13	27
	T4	4	9.5

lncRNAs in patients with polyps and a history of ulcerative colitis did not show significant differences with other patients ($p>0.05$). In other words, the expression level of these pyroptosis-related lncRNAs was not related to polyps and UC in CRC patients.

ROC analysis was done to evaluate the clinical potential of lncRNAs as diagnostic markers for CRC patients. The findings indicated that the area under the ROC curve (AUC) of lncRNA *MIAT* was 0.65 with a sensitivity of 62% (47.35% to 76.05%) and specificity of 54% (39.17% to 68.63%), with a cut-off value 2.9 (P= 0.025, CI: 95%; 0.5499 to 0.7696, Std. Error 0.05604). ROC analysis also showed an AUC 0.66 for lncRNA *Gm15441*, with a sensitivity of 68% (53.75% to 81.34%) and specificity of 52% (37.19% to 66.71%), with a cut-off value of 1.7 (P= 0.005, CI: 95%; 0.5540 to 0.7750, Std. Error 0.05635) (Figure 2).

Discussion

Numerous studies have examined the biological and therapeutic functions of lncRNAs in cancer cells and clinical tissues, including tissues, blood, plasma, and serum [16, 14]. Several investigation also revealed that lncRNAs, among other non-coding RNAs, can control cell pyroptosis. Recent studies have demonstrated that lncRNAs can influence proteins associated with pyroptosis-related signaling pathways, thereby contributing to the pathological processes of various illnesses [7, 17]. In this sense, it has become more and more clear how the carcinogenesis pyroptosis signaling pathway and lncRNA-mediated underlying regulatory mechanisms. Researchers have linked the lncRNA-pyroptosis axis, associated regulatory pathways, and clinical implications to several malignancies [18, 1]. Despite extensive research on the biology and therapeutic relevance of lncRNA, few clinical studies have determined the diagnostic and prognostic usefulness of lncRNAs associated with pyroptosis in colorectal cancer (CRC). This case-control investigation assessed the relative expression of lncRNAs GM15441 and MIAT, as well as their potential clinical significance. In this study, it was found that the mean expression level of both pyroptosis-related lncRNAs, *MIAT* and *Gm15441*, was much higher in colorectal tumor tissues compared to nearby healthy tissues.

Nevertheless, there was no discernible relationship between lncRNA expression levels and UC history or comorbidities in CRC patients with a history of UC, according to data analysis. Additional analysis revealed that these lncRNAs associated with pyroptosis may serve as clinical indicators for CRC patients, whether or not they have a history of UC. Biomedical and bioinformatic investigations have identified the myocardial infarction-associated transcript, or lncRNA MIAT, as a pyroptosis-related lncRNA [19, 20]. Therefore, by investigating the potential molecular pathways of lncRNA-mediated pyroptosis, we may obtain a more precise functional understanding of the pathophysiology

of the resulting disorders and a more effective treatment approach.

Some researchers have been shown that lncRNA *MIAT* plays a mechanistic role in controlling pyroptosis by focusing on miR-214-3p [19]. Additionally, this lncRNA may help cells die from lack of oxygen by attaching to SF1 and stopping CGRP transcription [20]. LncRNA MIAT, a carcinogenic regulator in several malignant tumors, controls the cell cycle, proliferation, invasion, and metastasis. Numerous studies point to MIAT's diverse biological roles, molecular regulatory processes, and clinical significance in several malignancies. *MIAT* overexpression is a useful clinical tool in cancer, as demonstrated by its correlation with the clinicopathological features of some malignancies [21-23]. Recent reports have revealed the biological functions and clinical importance of lncRNA *MIAT* in the formation and progression of common gastrointestinal malignancies, including CRC [24, 21]. Functional research revealed that *MIAT* expression is elevated in clinical samples and may encourage GC cell motility and invasion.

Additionally, cell-free liquid biopsies have demonstrated the clinical use of lncRNA as a possible non-invasive biomarker [25, 26]. According to research, lncRNA *MIAT* may control the growth of colorectal cancer cells by facilitating the DNA damage-responsive pathway [27]. Researchers have found that *MIAT* levels are higher in the later stages of many types of cancer, such as thyroid, ovarian, breast, and prostate cancer [23, 28-30].

This is consistent with our findings when they were clinically significant. Researchers have identified *Gm15441*, a distinct pyroptosis-related long noncoding RNA, as a critical metabolic regulator in the liver and a potent transcriptional inhibitor of thioredoxin-interacting protein [31]. We have not yet studied the altered expression of lncRNA *Gm15441* and its potential clinical significance in CRC clinical samples. Thus, we examined the expression levels of lncRNA-*Gm15441* in CRC patients. The study's findings revealed an enhanced expression of this lncRNA in tumor tissues compared to nearby healthy tissues.

Additionally, we found a significant connection ($p = 0.011$) between the advanced illness stage of CRC patients and the expression levels of GM15441. Since more data is currently unavailable, further research is necessary to validate these results. Numerous studies' findings have shown that the *Gm15441* mRNA may have a functional role in carcinogenesis via several signaling pathways connected to pyroptosis. Scientists have studied how PPARα affects lncRNA *Gm15441* and found that it lowers the level of inflammation in the liver caused by metabolic stress. Because of these findings, fatty acids turn on PPARα. This reduces inflammation by strongly activating *Gm15441* and controlling TXNIP and NLRP3 [32]. As a result, lncRNA Gm15441 contributes to the inhibition of metabolic stress. [32, 33].

An increasing body of research suggests that different lncRNAs may influence cell pyroptosis to control carcinogenesis and may serve as clinical indicators for cancer. Researchers found a substantial elevation of the lncRNA MYOSLID in cancer tissues, which was associated with a poor prognosis. Researches employing loss- and gain-of-function techniques revealed that miR-29c-3p binds to MCL target proteins to produce lncRNA MYOSLID, which then functions as miR-29c-3p ceRNA, stimulating the growth of gastric cancer cells and inhibiting apoptosis. It has been showed that MYOSLID has a biological effect by controlling the pyroptosis pathway, which helps colorectal cancer grow and spread. In cancer, it is unclear how this lncRNA functions clinically or biologically [34].

According to lung cancer microarray data, there was a significant decrease in SFTA1P expression in lung cancer tissues as compared to normal tissues. Furthermore, we found a negative correlation between reduced expression of SFTA1P and a poor prognosis for individuals with lung adenocarcinoma. Studies using gain-of-function and in vivo models validated SFTA1P's tumor-suppressive effect in lung cancer. A previous research reveals a complex relationship between the formation of tumors and this lncRNA's control of pyroptosis. Therefore, the scientists can assert that lncRNA SFTA1P, by regulating the pyroptosis pathway, could significantly contribute to the start and progression of malignancies. It is unclear what function this lncRNA plays in tumor biology and therapeutic settings [35, 36]. Additionally, researchers have studied LncRNA HOTAIR in CRC patient blood and tissue samples. Consequently, researchers presented HOTAIR expression levels in the blood as a potential biomarker for CRC prognosis. They identified the lncRNA as pyroptosis-related and completed the CRC prognostic signature [17, 37].

For the first time, researchers constructed a recently created ceRNA regulatory network associated with pyroptosis, which includes 5 mRNAs, 7 miRNAs, and 11 lncRNAs, to investigate the potential molecular mechanism of carcinogenesis [38]. Furthermore, GO and KEGG enrichment analyses demonstrated the frequent enrichment of these genes in the TNF and IL-17 signaling pathways. These findings suggested that the pyroptosis-related ceRNA network might predict the clinical outcomes of CRC [39].

Prior studies have shown that pyroptosis induction in conjunction with PD-1 enhances anticancer efficacy. The researchers has been suggested a novel PR lncRNA risk model to predict patients' responses to immunotherapy and investigate the relationship between pyroptosis and cancer-related genes. These kinds of research's conclusions suggest that lncRNAs may be crucial in promoting pyroptosis [40]. For instance, lncRNA MEG3 may enhance pyroptosis in endothelial cells [41] .

LncRNA-H19 promotes NLRP3/6 inflammasome imbalance and produces microgliocyte pyroptosis [41], whereas lncRNA HOTTIP may target the miR-148a-3p/AKT2 axis and suppress ovarian cancer cells' activity [42]. LncRNA XIST induces pyroptosis via the XIST/miR-150-5p/c-Fos axis. However, research on pyroptosis-related lncRNAs in CRC and their potential therapeutic use remains limited. According to our and other studies, pyroptosis may play a role in colorectal cancer initiation and spread. Because they are parts of cellular homeostasis factors, LncRNAs may play a role in CRC by controlling

the pyroptosis process. Changes in the expression of these components in patient samples may have therapeutic implications, given their biological function in cell development. It is crucial to assess these variations in expression in clinical patient samples by their clinical significance for diagnosis and prognosis. We, along with other researchers, have determined that lncRNAs linked to the pyroptosis process serve as a crucial biological resource for evaluating and pinpointing valuable clinical and biomarker outcomes. The study's findings show that lncRNAs GM15441 and *MIAT* are expressed more highly in the tumor tissue of people with colon cancer compared to healthy tissue samples. The study's findings suggest that these variables' expression may be useful for diagnosing this illness. However, the results were based on a very small number of clinical samples of patients, and such data may include some inaccuracies, particularly when assessing the diagnostic capability. Examining these molecules in other clinical samples, such as blood, might be useful in assessing their function and significance, especially considering the expression dysregulation. We recommend conducting larger-scale clinical and functional research to determine the biological and clinical significance of these lncRNAs. This will enable the introduction and validation of the biomarker as a diagnostic tool, as well as its application in clinical settings, particularly alongside other dependable and standard markers.

Conclusion: The expression pattern of lncRNAs regulating the pyroptosis process (*MIAT* and *Gm15441*) may be changed in CRC. It was concluded that some lncRNAs can be more clinically important in cases of ulcerative colitis and cancer due to their biological function in regulating the inflammation process. These kinds of investigations are crucial for therapeutic purposes in order to better understand the relationship between non-coding RNAs, and the process of cancer development, and provide new thoughts around the diagnosis and management of pyroptosis-related diseases. By designing more extensive clinical and functional studies, the role and relevance of the lncRNAs in cancer development through the regulation of the pyroptosis process will be revealed.

Author Contribution Statement

A.K.N and A.A. and SP.T. contributed to study conceptualization, data curation and project administration. A.A. and SP.T. completed funding acquisition and resources. A.A. and Z.SE. contributed to methodology, data curation and formal data analysis. B.S. and S.A. and M.M. and M.A. and A.BA. contributed to clinical investigation, supervision, validation and visualization. A.N. and Z.SE. prepared the original draft or critical revision for important intellectual content. All authors approved the final version of the draft.

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Conflict of interest statement

The authors report no declarations of interest.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of Iran University of Medical Sciences (Ethical Code: IR.IUMS.REC.1401.167). Written informed consent to participate in this study was provided by the participants. All the methods were carried out following the guidelines of the Declaration of Helsinki.

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