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RESEARCH ARTICLE

Clinical Implications of Circulating miRNA-200a and Mucin 16 in Late-Stage Colorectal Cancer: A Study in Iraqi Patients

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ABSTRACT

Background: Colorectal cancer, the most common gastrointestinal cancer, is a significant health issue globally. Mucin 16 plays a critical role in cancer signal transduction pathways and is a potential glycoprotein target for cancer therapy. The miRNA-200 family also regulates the expression of numerous genes that play vital roles in cancer cells. This study aimed to investigate the changes in mucin 16 and miRNA-200a in patients with colorectal cancer (CRC). Subjects and Methods: Fifty-six patients with CRC, including 26 in stage 3 and 30 in stage 4, were included in this study, along with 38 healthy volunteers as a control group. Parameters such as mucin 16, miRNA-200a, total protein, albumin, globulin, and the albumin/globulin ratio were estimated in serum samples from participants. Results: The results indicated that mucin 16 concentration and miRNA-200a levels were significantly elevated ($P \leq 0.05$) in the stage 4 group compared to the stage 3 and control groups. A significant increase was also observed in stage 3 compared to the control group for these two parameters. The concentrations of total protein, globulin, albumin, and the albumin/globulin ratio exhibited no significant differences between patients with stage 3 or stage 4 and the control group. The receiver operating characteristic analysis demonstrated that mucin 16 is a good diagnostic marker for CRC in late stages. Conclusions: These results identify mucin 16 as a promising marker for CRC diagnosis.

Keywords: Biomarkers, Cancer antigen 125, Colorectal cancer, MiRNA-200a, Mucin 16

Introduction

Cancer is characterized by uncontrolled cell division and aberrant cell survival. When such abnormal growth occurs in the colon or rectum, it is referred to as colorectal cancer (CRC).[1] Colorectal cancer, the most prevalent gastrointestinal malignancy, constitutes a major global health concern. It is the third most common malignancy after lung and breast cancer.[2] Clinical trial findings indicate that screening tests aid in diagnosing CRC at earlier stages, thereby reducing deaths from this disease. Typically, a noncancerous growth leads to dysplastic tissue (tumor), which may develop into CRC after multiple DNA changes. A benign soft tissue tumor does not metastasize. A benign polyp or adenoma (stage 0) forms from hyperproliferation. Adenocarcinoma, which invades the muscularis propria (stage I), develops in approximately 10% of adenomatous lesions that become malignant. The tumor expands further, penetrating the serosa (stage II) and the visceral peritoneum (stage III). At stage IV, lymphatic or blood vessel metastasis may occur. Disease severity and treatment options are determined by the stage. While surgery is preferred for stages 0–II, stage III requires surgery with adjuvant chemotherapy, and stage IV or recurrent CRC necessitates surgery, chemotherapy, and targeted therapy. Regrettably, there is no known cure at this time.[3,4] The epidemiology of CRC varies markedly between countries; it is more common in

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developed nations than in low- and middle-income countries.[5] In Iraq, CRC is also the third most common cancer, with 2,328 new cases detected in 2022.[6]

Glycoproteins are well-defined biomarkers for inflammatory and cancer diseases.[7–9] They are the most widely used markers for cancer diagnosis in clinical settings. The main ones include CA15-3, CA19-9, mucin 16 (CA125), CEA, and PSA.[10] Several studies have verified that the mucin family represents potential glycoprotein targets for cancer therapy. Because of their roles in cancer signal transduction pathways, transmembrane mucin networks have been strongly studied for anti-tumor therapy. Antibody-mediated treatments, including neutralizing antibodies, chimeric antigen receptors (CARs), bispecific T-cell engagers (BiTEs), and antibody–drug conjugates (ADCs), can target the extracellular domain of membrane-bound mucins. Likewise, mucin protein expression in cancer offers potential for vaccine development.[11–13]

The largest membrane-bound mucin identified to date is believed to be mucin 16. Mucin 16's amino acid sequence indicates that it is analogous to other membrane-bound mucins, with a molecular weight of less than 2 MDa and a high content of serine, threonine, and proline. The three main domains of this glycoprotein include an N-terminal domain, a large multiple repeat domain (comprising up to 60 tandem repeats of 156 amino acids each), and a C-terminal domain.[14] Both O- and N-linked oligosaccharides significantly glycosylate the repeat domain and the N-terminal domain. Mucin 16[15] has been associated with increased levels in various cancers.[16] Molecular cloning of the cancer antigen 125 (CA125) led to the discovery of mucin 16 in 2001.[17] Mutations of mucin 16 may be linked to a higher tumor mutation burden, improved survival, enhanced immune response, and altered cell cycle pathways. Over the last 15 years, it has become clear that this marker is present not only in ovarian cancer but also in gastric, pancreatic, and other adenocarcinomas.[18]

Small RNA molecules known as microRNAs (miRNAs) regulate gene expression by inhibiting translation or triggering the degradation of specific gene transcripts. These small, naturally occurring RNA molecules do not code for proteins and decrease gene expression, thereby modulating protein levels.[19] The miRNA-200 family controls the expression of numerous genes that play vital roles in cancer cells. The miRNA-200 family consists of five members: miRNA-200a, miRNA-200b, miRNA-200c, miRNA-141, and miRNA-429. They can serve as potential diagnostic and prognostic aids for cancer patients because they are associated with cell transformation and carcinogenesis, tumor development, cancer metastasis, angiogenesis, migration, invasion, and tumor cell survival in circulation (intravasation and extravasation).[20]

This study aimed to investigate the concentration of mucin 16 and the potential use of this protein for monitoring the development of CRC in late stages (i.e., stages 3 and 4 of CRC). Additionally, this work examines the relationship between variations in miRNA-200a and mucin 16 expression.

Materials and methods

Study design

The present study comprised 56 patients with CRC who were enrolled at the Tumor Teaching Center at the Medical City of Baghdad, Iraq, including 26 patients with stage 3 and 30 patients with stage 4 CRC diagnosed by the consultancy of the Tumor Teaching Center. This work was controlled with 38 individuals (control group) who were considered healthy based on their medical history, without prior CRC, and matched for age and body mass index (BMI) with CRC patients. The age range for both patients and control groups was 24–79 years. Sample collections were conducted from January 2024 to April 2024. The study was approved by the scientific board at the Chemistry Department, University of Baghdad College of Science. Patients who consumed alcohol, smoked, or had a history of other cancers or diseases prior to admission were excluded.

Evaluation of serum total proteins, albumin, and globulins

The serum total protein concentration was assessed using Agappe kits. Color intensity was determined using a spectrophotometer (Lasany, China, model 721) at a wavelength of 546 nm, and the total protein concentration was calculated in g/dL. Serum albumin levels were estimated using the Agappe kit at a wavelength of 630 nm, and the albumin concentration was calculated in g/dL. Globulin levels were calculated by subtracting albumin from total protein concentration.[21]

Evaluation of Mucin 16

Mucin 16 concentration in the serum was determined based on electrochemiluminescence immunoassays (ECLIA), a sandwich principle, using the Cobas kit and Cobas™ e411 (Roche Diagnostics GmbH, Mannheim, Germany). Immune complexes formed during the reaction were detected at 680 nm,

Table 1. The amplification conditions of miRNA-200a gene expression.

Cycle Steps	Temperature	Time	Cycles
Initial Denaturation	95 °C	60 s	1
Denaturation	95 °C	15 s	40–45
Extension	60 °C	30 s (+plate read)	
Melt Curve	60–95 °C	40 min	1

and the mucin 16 concentration was expressed in U/mL.[22]

Evaluation of miRNA-200a

RNA isolation was performed using chloroform by adding 0.15 mL of TRIzol™ reagent for lysis. The quantification of miRNA was determined using Qubit 4.0.

Complementary DNA synthesis for miRNA-200a

Total RNA was reverse-transcribed using the TransScript®miRNA First-strand Complementary DNA (cDNA) Synthesis SuperMix kit. Twenty microliters of RNA were subjected to reverse transcription. To ensure effective RT for subsequent qPCR steps, cDNA concentration was assessed for yield.

Primers

The study's primers were acquired from Macrogen®(South Korea) and stored in lyophilized form until needed.[23]

miRNA-200a Reverse Transcription (RT) (GTCGTATCCAGTGCGTCGAGTGACACGAGAGC-CACCTGGGCAATTTGCACTGGATACGACACATCG)

miRNA-200a-F (AGTAACACTGTCTGGTAACGA)

miRNA-200a-R (TCGTATCCAGTGCGTCGAGT)

Quantitative reverse transcriptase PCR (qRT-PCR)

The quantitative real-time polymerase chain reaction (RT-qPCR) system, which relies on the measurement of fluorescent light, was used to ascertain the quantity of cDNA specific to a particular gene using Luna Universal qPCR Master Mix (M3003S). The cycling protocol for the qPCR reaction was configured according to the designated thermal profile in Table 1.

Housekeeping gene for miRNA-200a

The RNAU6 small nuclear housekeeping gene was used as an internal control for the ΔCt calculation.[24] This choice ensures robust normalization in the quantitative analysis of miRNA-200a expression, facilitating accurate interpretation of the RT-qPCR results.

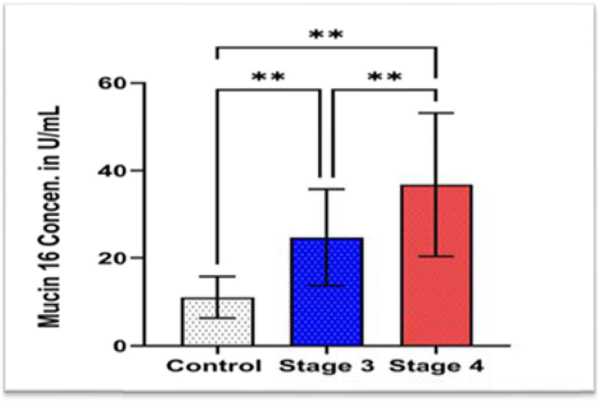

Fig. 1. The mucin 16 level in control and patients with stage 3 and stage 4 of CRC (** = $P < 0.01$).

Statistics

The data were analyzed using the Statistical Package for Social Sciences (SPSS version 26.0). The mean and standard deviation were computed and presented as mean ± SD. For mean comparisons between two groups, a T-test followed by the post-hoc least significant difference (LSD) was applied. Statistical significance was considered at $P \leq 0.05$ to explain the differences between groups.

Results

Demographic details and protein concentrations

The demographic details and protein levels of participants are listed in Table 2.

No significant differences ($P > 0.05$) were found among the groups studied regarding age, BMI, total protein, albumin, globulin, and the albumin/globulin ratio. Fig. 1 shows the variation in mucin 16 levels in stages 3 and 4 of CRC and control group.

Mucin 16 levels were highly increased ($P < 0.01$) in stage 4 compared to stage 3 and the controls. A significant increase ($P \leq 0.01$) was also observed in stage 3 compared to the controls.

miRNA-200a expression analysis

Normalization via the U6 gene was crucial in miRNA-200a expression analysis. Amplification plots for the target miRNA-200a and a U6 were created, enabling the computation of the cycle threshold (Ct) value for each gene. Fig. 2 presents the fold change

Table 2. Comparison of demographic details and protein levels in stage 3, stage 4 of CRC, and control groups.

Parameter	Control	Stage 3	Stage 4	*P* Value
Sex (Male/Female) %	20/18	16/10	19/11	——
Age (Years)	48.47 ± 15.13	52.96 ± 16.96	55.27 ± 13.91	0.5002a 0.1845b 0.8404c
BMI (Kg/m^2)	28.00 ± 4.986	26.50 ± 5.334	26.35 ± 5.462	0.5224a 0.4249b 0.9931c
Total Protein (g/dL)	6.468 ± 0.5097	6.804 ± 1.068	6.640 ± 0.8114	0.2485a 0.6691b 0.7277c
Albumin (g/dL)	3.433 ± 0.4176	3.504 ± 0.50	3.333 ± 0.4420	0.8195a 0.6536b 0.3451c
Globulin (g/dL)	3.035 ± 0.6739	3.184 ± 0.9384	3.373 ± 0.8354	0.7649a 0.2232b 0.6645c
Albumin/Globulin Ratio	1.209 ± 0.3965	1.212 ± 0.4362	1.039 ± 0.3597	0.9997a 0.2047b 0.2462c

The data are presented as Mean ± SD. $P \leq 0.05$ indicates significance between stage 3 groups and control **(a)**, between stage 4 group and control **(b)**, and between stage 3 and stage 4 groups **(c)**.

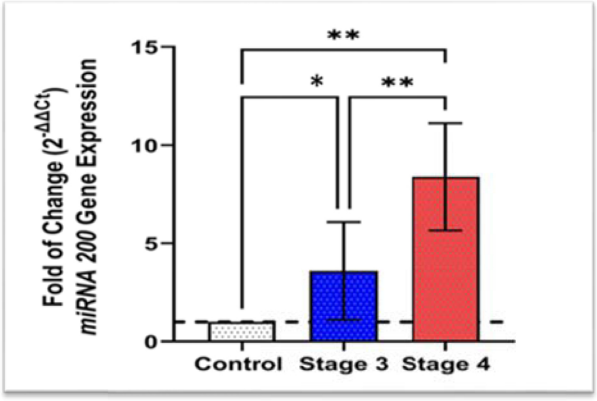

Fig. 2. Fold change of miRNA-200a in studied groups (** $P < 0.01$, * $P < 0.05$).

of miRNA-200a in the control, stage 3, and stage 4 groups.

In stage 3 CRC patients, the mean fold change of miRNA-200a showed a significant increase ($P < 0.05$) compared to the controls. A highly significant increase ($P < 0.01$) was also observed in stage 4 compared to both stage 3 and the controls.

Correlations between mucin 16, total protein, and albumin in stage 4 are shown in Fig. 3.

It was observed that there were no significant differences between the studied parameters in all groups. However, Pearson's correlations between mucin 16 levels and albumin ($r = -0.5353$, $P = 0.0023$) as well as between mucin 16 levels and total protein ($r = -0.4181$, $P = 0.0215$) showed a significant negative correlation in the stage 4 group.

The receiver operating characteristic (ROC) analysis was used to evaluate the possibility of using mucin 16 for monitoring CRC in late stages. Fig. 4 illustrates the ROC analysis, indicating that mucin 16 has good sensitivity and specificity in differentiating between stage 4 and the control (AUC 0.9804, cut-off value > 13.77 U/mL, 93% sensitivity and 97% specificity), as well as between stage 3 and control (AUC 0.9106, cut-off value > 13.77 U/mL, 88% sensitivity and 71% specificity) and between stage 3 and stage 4 (AUC 0.7744, cut-off value > 27.22 U/mL, 77% sensitivity and 69% specificity).

Discussion

Mucins are high molecular-weight epithelial glycoproteins involved in many physiological activities, including signal transduction, epithelial cell protection, and tissue homeostasis. They provide a protective environment against hypoxia, acidity, and other biological factors that accelerate cancer.[25,26] Mucin 16 is a membrane-linked molecule that exhibits abnormal expression or mutations in various diseases, including cancers, while also being present in normal epithelial tissues.[27]

The outcomes of this study showed a significant increase in mucin 16 levels in CRC patients with stages 3 and 4 compared to the control group, with mucin 16 levels significantly rising throughout the stages of CRC development. Therefore, our findings suggest that mucin 16 might be involved in CRC progression. Based on the available data, the involvement of

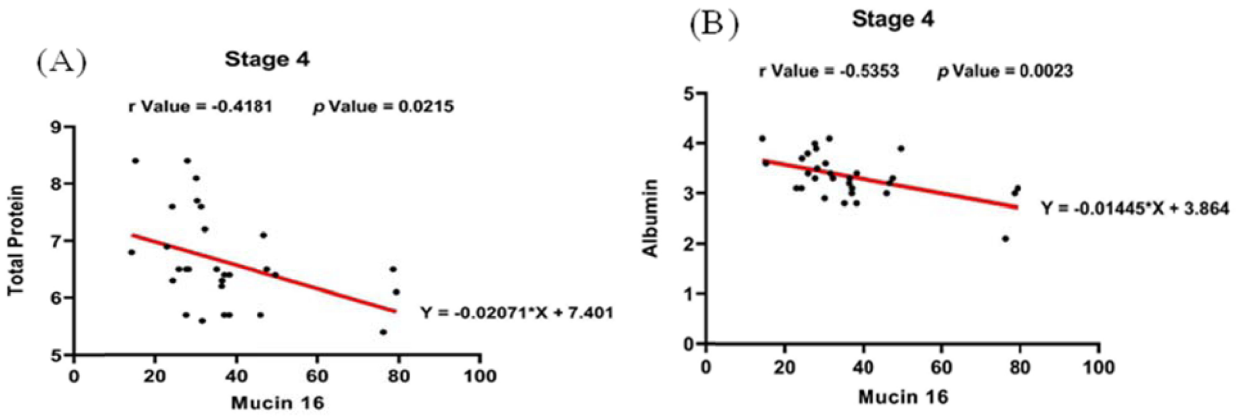

Fig. 3. Pearson's correlation of A) Mucin 16 with total protein concentration, B) Mucin 16 with albumin concentration.

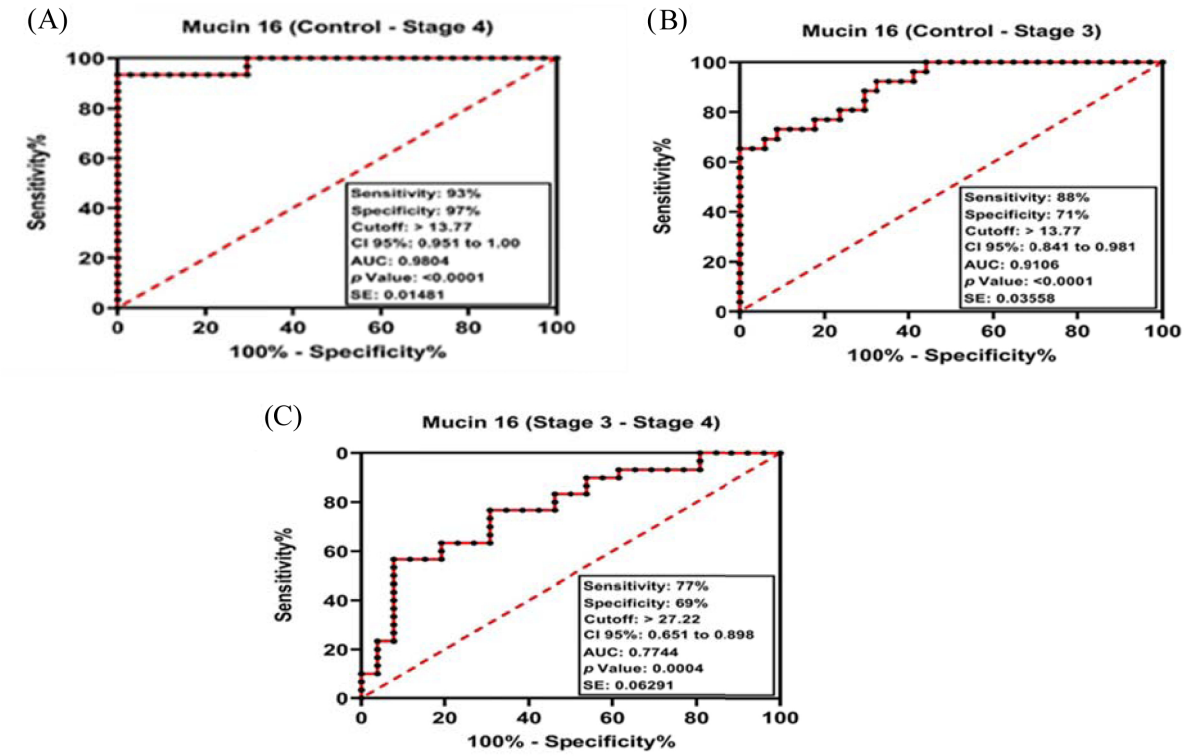

Fig. 4. ROC curve of mucin 16, A) stage 3 vs. control, B) stage 4 vs. control, and C) stage 3 vs. stage 4.

mucin 16 in various cancers has been highlighted as a potential prognostic biomarker owing to its unique expression in cancers and its association with tumor advancement.[28] It has been reported that mucin 16 may contribute to tumor biology, presumably in the context of tumor development, metastasis, or immune escape mechanisms, given that it is elevated in the terminal stages of CRC. In addition, a strong correlation of mucin 16 with disease stage positions mucin 16 as a potentially valuable biomarker for tracking the course of the illness and ultimately guiding therapy choices.[29,30]

A higher level of mucin 16 in metastatic gastric cancer has also been noticed, and similar mechanisms might be acting in colorectal cancer, validating the notion that mucin 16 can function as a marker for late-stage disease.[31] A previous meta-analysis examining the significance of various mucins in the carcinogenesis process across multiple cancer types unequivocally demonstrated that mucin expression contributes to CRC biology. Consistent with the results of this work, a marked increase in mucin expression was detected in CRC tissue compared to healthy mucosa.[32] The substantial increase in mucin

16 expression in late tumor stages emphasizes the potential importance of mucin 16 in neoplastic transformation and reveals an essential function for this protein in the carcinogenesis or metastatic process.[33]

The genetic aspect of this study includes the assessment of miRNA-200a in CRC patients. A significant increase in miRNA-200a was found in the stage 3 group compared to the control group. Moreover, CRC patients in stage 4 exhibited a significant increase in miRNA-200a compared to controls, indicating a robust overexpression of mucin 16 associated with more advanced disease. Additionally, a high degree of significance was observed when comparing patients in stages 3 and 4, suggesting that miRNA-200a may serve as an invaluable biomarker for tracking CRC progression. Similar to the findings of this study, which emphasized the prognostic and diagnostic utility of miRNA-200a, a team of investigators observed that CRC patients had a significantly higher fold expression of this miRNA compared to controls. Furthermore,[34,35] low expression of miR-200a correlated with poor survival outcomes in CRC patients, mediated by the regulatory role of miRNA-200a in epithelial-to-mesenchymal transition and cancer stem cell properties.[36] Earlier studies reported that among twenty-five cancer types in body fluids, including saliva, serum, and urine, miRNA-200a enhances the progression of five cancer types and impedes the proliferation of thirteen cancer types, with varying results regarding colorectal cancer, non-small cell lung cancer, and renal cell carcinoma in comparison to corresponding healthy tissue using RT-qPCR. The target genes of miR-200a, miR-200b, and miR-200c have been reported to significantly regulate essential processes at the biological process level, show enrichment in key cellular structures at the cellular component level, and are involved in binding functions at the molecular level. This highlights the role of miR-200s in the initiation and progression of CRC.[37] To our knowledge, there were no data available regarding the detection of circulating miRNA-200a in the serum of CRC patients. Our results show that both miRNA-200a and mucin 16 levels increased throughout CRC stages, suggesting that miRNA-200a might positively regulate the expression of mucin 16 throughout CRC stages. Further genetic studies are required to confirm the role of miRNA-200a in the regulation of mucin 16 expression.

The study findings also indicated no significant correlations between mucin 16 levels and other studied parameters. However, total protein and albumin showed negative correlations in stage 4 of CRC. These results align with previous studies reporting a negative correlation between mucin 16 and albumin. It has been suggested that an increase in mucin 16 is associated with a decrease in albumin, potentially reflecting a worsening nutritional state or heightened inflammation.[38] Likewise, the association with total protein supports the hypothesis that mucin 16 may be connected to systemic modifications in protein metabolism in later stages of cancer.[39] However, malnutrition or liver disease may also inhibit the production of proteins like albumin, which may arise from cancer cachexia, a state marked by weight loss and muscular atrophy.[40]

The ROC analysis indicated that mucin 16 has good specificity and sensitivity in differentiating between stage 3 and control, stage 4 and control, and between stage 3 and stage 4. Accordingly, mucin 16 may be clinically utilized as a valuable tool for monitoring CRC progression.

Conclusion

Mucin 16, a cell surface-associated mucin, has been implicated in being upregulated in a wide range of malignancies. The results of this study demonstrated a similar increase in mucin 16 and miRNA-200a throughout the CRC stages compared to healthy individuals. Therefore, we conclude that miRNA-200a may positively regulate mucin 16 in CRC. Additionally, the ROC analysis presents promising results for using mucin 16 as a useful tool for monitoring CRC progression.

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Author's declaration

- Conflicts of Interest: None.
- We hereby confirm all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- No animal studies are present in the manuscript.
- Authors signed on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at University of Baghdad.

Authors' contributions statement

This work was a collaborative effort among all authors E.S.A was responsible for sample collection, experimental and writing of manuscript while A.W.A author contributed to the research supervision and modifications. The final manuscript was revised and approved by all authors.

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التأثيرات السريرية لـ miRNA-200a المتداول والميوسين 16 في سرطان القولون والمستقيم في المرحلة المتأخرة: دراسة أجريت على المرضى العراقيين

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الخلاصة

يُعد سرطان القولون والمستقيم أكثر أنواع سرطانات الجهاز الهضمي شيوعًا، ويمثل مشكلة صحية كبيرة على مستوى العالم. يلعب البروتين المخاطي 16 (Mucin 16) دورًا حاسمًا في مسارات نقل الإشارات المرتبطة بالسرطان، كما يُعد هدفًا جلايكوبروتينيًا واعدًا في استراتيجيات علاج السرطان. كما أن عائلة الميكرو (miRNA-200)تتحكم في التعبير عن العديد من الجينات الحيوية التي تؤدي أدوارًا مهمة في خلايا السرطان. تهدف هذه الدراسة إلى التحقق من التغيرات في بروتين mucin16 وmiRNA-200a لدى مرضى سرطان القولون والمستقيم (CRC). المواضيع والطرق: شملت الدراسة 56 مريضًا بسرطان القولون والمستقيم، منهم 26 في المرحلة الثالثة و30 في المرحلة الرابعة، بالإضافة إلى 38 شخصًا سليمًا كمجموعة ضابطة. تم تقدير عدد من المؤشرات في عينات مصل الدم للمشاركين، بما في ذلك: بروتين mucin16، وmiRNA-200a، والبروتين الكلي، والألبومين، والغلوبيولين، ونسبة الألبومين إلى الغلوبيولين (A/G). النتائج: أظهرت النتائج ارتفاعًا معنويًا ($p\leq0.05$) في تركيز بروتين mucin16 ومستوى miRNA-200a في مجموعة المرضى في المرحلة الرابعة مقارنةً بمجموعتي المرحلة الثالثة والأشخاص الأصحاء. كما لوحظت زيادة معنوية في مجموعة المرحلة الثالثة مقارنةً بالمجموعة الضابطة لنفس المؤشرين. أما تركيزات البروتين الكلي، والغلوبيولين، والألبومين، ونسبة A/G فلم تُظهر فروقًا معنوية بين المرضى في المرحلتين الثالثة والرابعة مقارنةً بالمجموعة الضابطة. وقد أظهر تحليل منحنى الخصائص التشغيلية للمستقبِل (ROC) أن بروتين mucin16 يُعد مؤشرًا تشخيصيًا جيدًا لسرطان القولون والمستقيم في مراحله المتأخرة. الأستنتاج: تشير هذه النتائج إلى أن بروتين mucin16 يُعد مؤشرًا واعدًا لتشخيص سرطان القولون والمستقيم.

الكلمات المفتاحية: المؤشرات الحيوية ، مستضد السرطان 125، سرطان القولون والمستقيم، مايكرو رنا200a، المخاط 16.