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ORIGINAL ARTICLE

The influence of blood levels of circRNAs and microRNAs on the development of ulcerative colitis

Mai A. H. Abouelenin[1] · Safaa I. Tayel[1,2] · Amany A. Saleh[1,3] · Naglaa S. Elabd[5] · Randa M. Seddik[5] · Eman A. El-Masry[6,7] · Mahmoud Rizk[8] · Osama Elbahr[9] · Huda I. Abd-Elhafiz[10] · Mohammed G. Elhelbawy[11] · Ghada E. Elgarawany[12,13] · Heba F. Khader[1,4]

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Abstract

Background Ulcerative colitis is an inflammatory condition of the colon with an unknown cause. It is the most common form of inflammatory bowel disease worldwide, typically starting in the rectum and extending continuously through the mucosa and submucosa of the colon. A primary genetic component or disturbed gut microbiota may precipitate the disease.

Methods We are investigating the roles of circRNAs and microRNAs in the disease, focusing on their connections to severity and remission. We used real-time PCR to measure the expression levels of selected microRNAs (miR-29a, miR-30c, miR-148a, and miR-410-3p) and the circRNA met oncogene and circ 0084764 in peripheral blood.

Results Fecal calprotectin was elevated in the severe group than in the mild group ($p=0.005$). MicroRNA-29a was significantly upregulated in the severe group compared to the mild group ($p=0.016$). MicroRNA-30c was significantly downregulated in the severe group compared to the mild group ($p=0.004$). MicroRNA-410-3p was downregulated in the severe group compared to both the mild and moderate groups ($p<0.001$ and $p=0.022$), respectively. Conversely, microRNA-148a exhibited no significant alterations among the patient groups ($p=0.318$). CircRNA-0084764 was upregulated in the severe group compared to the mild and moderate groups ($p<0.001$ and $p=0.001$), respectively. The diagnostic performance of markers in distinguishing patients from controls showed that circRNA-met oncogene had the highest sensitivity of 94.83% and a specificity of 100%.

Conclusion We confidently established that the altered expression of circRNAs and microRNAs contributes to UC's pathogenesis and drug therapy's personalization. Notably, circRNA-met oncogene stands out as an independent predictor of disease severity, while microRNA-30c is a proven and reliable independent remission predictor.

Keywords CircRNA-met oncogene · CircRNA-0084764 · MicroRNA-29a · MicroRNA-30c · MicroRNA-410-3p · MicroRNA-148a · Ulcerative colitis

✉ Safaa I. Tayel
drsafaa_tayel@yahoo.com; safaa.tail@med.menofia.edu.eg

[1] Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Menoufia University, Cairo, Egypt

[2] Medical Biochemistry Unit, College of Medicine, Albaha University, Al Baha city, Saudi Arabia

[3] Medical Surgical Nursing Department, College of Nursing, Taibah University, Madinah, KSA, Saudi Arabia

[4] Basic Medical Sciences Department, Unaizah College of Medicine and Medical Sciences, Qassim University, Unaizah, Kingdom of Saudi Arabia

[5] Tropical Medicine Department, Faculty of Medicine, Menoufia University, Cairo, Egypt

[6] Medical Microbiology and Immunology Department, Faculty of Medicine, Menoufia University, Cairo, Egypt

[7] Microbiology and Immunology Unit, Department of Pathology, College of Medicine, Jouf University, Al-Jouf, Sakaka, Saudi Arabia

[8] Internal Medicine Department, Faculty of Medicine, Benha University, Banha, Egypt

[9] Hepatology and Gastroenterology Department, National Liver Institute - Menoufia University, Cairo, Egypt

[10] Clinical Pharmacology Department, Faculty of Medicine, Menoufia University, Cairo, Egypt

[11] Clinical Pathology Department, Faculty of Medicine, Menoufia University, Cairo, Egypt

[12] Medical Physiology Departement, Faculty of Medicine, Menoufia University, Cairo, Egypt

[13] Biomedical Science Department, College of Medicine, Gulf Medical University, Ajman, UAE

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Introduction

Inflammatory bowel diseases (IBD) are autoimmune disorders characterized by chronic inflammation affecting the gastrointestinal tract (GIT) [1]. The main types of IBD are Crohn's disease (CD), ulcerative colitis (UC), indeterminate colitis (IC), and unclassified colitis (IBD-U), each affecting different areas of the GIT tract. Ulcerative colitis constantly targets the colon or rectal mucosa, while CD can affect the GIT, from mouth to anus, often in a discontinuous pattern [2].

Multifactorial agents, including environmental changes, various susceptibility gene variants, and imbalances in gut microbiota and immune responses, are critical for developing IBD [3, 4]. Understanding these factors is essential for effective interventions. Eubiosis of the gut microbiome is crucial for maintaining a healthy intestinal barrier and tight junctions. In contrast, dysbiosis, often seen in IBD, weakens the intestinal barrier, increases permeability to pathogens, and triggers immune and inflammatory responses [5].

Both CD and UC significantly affect young adults, causing malabsorption, abdominal pain, fatigue, bloody diarrhea, and weight loss. Persistent inflammation increases the risk of colorectal cancer (CRC) and raises mortality rates to 10–15% [6]. Prompt action is essential to mitigate these risks.

MicroRNAs play significant roles in the pathophysiology of IBD [7]. These evolutionarily conserved, noncoding RNAs bind to the untranslated regions of target mRNAs, inhibiting their translation and expression [8]. Abnormal microRNA activity has been linked to various diseases, including IBD, suggesting that new management could target specific molecular pathways to correct microRNA expression imbalances [9].

The microRNA-29 family includes three major forms: miR-29a-3p, miR-29b-3p, and miR-29c-3p. Additionally, there are four less-expressed forms: miR-29a-5p, miR-29b1-5p, miR-29b2-5p, and miR-29c-5p. These microRNAs are encoded in two clusters: miR-29a-b1 and miR-29b2-c. They are localized on human chromosomes 7 and 1 [10]. MicroRNA-29a-3p plays a role in UC's pathogenesis by promoting intestinal epithelial cell apoptosis through the downregulation of the myeloid cell leukemia-1 (MCL-1) gene [11].

The microRNA-30 family includes the members miR-30a, miR-30b, miR-30c (which comprises miR-30-c1 and miR-30-c2), miR-30d, and miR-30e [12]. These microRNAs are localized on chromosomes 1, 6, and 8 [13]. An increase in the expression of microRNA-30c-5p in T84 cells, triggered by the activation of nuclear factor-κB, leads to a decrease in the levels of autophagy-related proteins and results in a severe inflammatory response [14]. MicroRNA-148a on chromosome 7 is essential for T and B lymphocyte function. Its modified expression is significantly associated with immune-related disorders, rendering it a potential target for chronic inflammatory therapies [15]. Significantly, reduced levels of miR-148a have been observed in various solid tumors, such as gastric cancer, renal cell carcinoma, hepatocellular, pancreatic, and lung cancers. This reduction is primarily due to the hypermethylation of its promoter, underscoring its tumor-suppressive role, likely mediated through Akt2 targeting [16].

Circular RNAs (circRNAs) are a type of noncoding RNA that lack terminal structures, such as a 5' cap or a 3' poly-(A) tail [17]. CircRNAs act as sponges for various microRNAs, playing a role in chronic inflammation and cancer. Recently, they have also been implicated in the dysregulation of the intestinal epithelial barrier and immune homeostasis, which is a critical factor in the development of IBD [18]. Genome-wide profiling of circRNAs and mRNAs indicates that the circMET-miR-410-3p-MET motif has a role in accelerating cell growth in CRC [19].

We conducted a thorough investigation into the expression levels of specific microRNAs (miR-29a, miR-30c, miR-148a, and miR-410-3p) as well as the circRNA met oncogene and circ 0084764 (EYA1), in relation to clinical parameters in ulcerative colitis (UC). Furthermore, we explored their strong association with the disease's severity and the state of remission.

Subjects and methods

The Departments of Tropical Medicine, Medical Biochemistry and Molecular Biology, Medical Microbiology and Immunology, and Clinical Pharmacology at Menoufia University Hospital collaborated effectively with the Departments of Hepatology and Gastroenterology and Clinical Pathology at the National Liver Institute and the Internal Medicine Department of Banha University to conduct a robust case-control study. From April 2023 to September 2023, we selected fifty-eight newly diagnosed UC patients who were naïve to treatment and closely monitored them for six months after initiating specific treatment protocols. Our exclusion criteria were rigorous: (1) individuals under 18 years; (2) patients previously treated for UC; (3) those who had undergone steroid, immunosuppressive, or biological therapies for any reason; and (4) patients with other comorbidities.

In parallel, we included 40 healthy volunteers, meticulously matched for age and gender with the UC group, to ensure the integrity of our findings. All participants underwent comprehensive socio-demographic data collection, thorough clinical assessments—including bowel motion

frequency, rectal bleeding, fever, fatigue, abdominal pain, extraintestinal manifestations, as well as general and abdominal examinations—and extensive laboratory investigations (including complete blood count (CBC), liver function tests, kidney function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fecal calprotectin). Additionally, each patient underwent colonoscopy and histopathological examinations.

The assessment of UC disease activity was rigorously conducted using the Mayo score, which ranges from 0 to 12, with higher scores indicating increased severity [20]. This comprehensive approach underscores our commitment to generating reliable and meaningful data in the study of UC. The UC group was confidently divided into three subgroups: mild (18 cases), moderate (17 cases), and severe (23 cases). We expertly outlined the treatment for the UC patients based on the established ECCO guidelines. Following this, we ensured regular follow-ups with the patients at the outpatient clinics, fully adhering to the recommendations of the ECCO guidelines [21].

At the initial admission, we effectively treated 18 cases of mild activity with systemic mesalamine, 3 mild cases with local mesalamine, and 2 mild cases with a combination of systemic and local mesalamine. For the moderate cases, we administered a robust oral steroid regimen of 60 mg of prednisolone; however, two patients who did not respond were transitioned to biological therapy utilizing Adalimumab. Severe cases received intravenous (IV) steroids, utilizing either hydrocortisone or methylprednisolone, and three of these patients required biological treatment due to a lack of improvement with IV steroids.

During the follow-up period for UC cases, patients with mild activity continued their mesalamine treatment as a maintenance strategy. Those with moderate and severe cases who responded to steroid therapy were successfully shifted to immunomodulator therapy, while patients responding to biological therapy remained on that effective treatment.

After six months, we conducted a thorough assessment of the UC patients using the Mayo score, revealing that 49 patients achieved remission. Meanwhile, 3 presented with mild activity, 4 with moderate activity, and 2 with severe activity. This demonstrates the effectiveness of our treatment protocols.

Ethical Considerations: Following a thorough clarification of the research objectives and inquiries, each participant received a comprehensive explanation of the study's nature. They confidently provided their written informed consent before the study began. The research received approval from the local ethics committee of Menoufia University's Faculty of Medicine (IRB: 3/2023TROP11) and was conducted in strict compliance with the Declaration of Helsinki.

Molecular biology investigations

Detection of microRNA-410-3p, microRNA-148a, microRNA-30c, and microRNA-29a expression by real-time PCR

We utilized a miRNeasy kit (QIAGEN, United States, Cat. No. 217,004) to efficiently extract total RNAs, including microRNAs, from 100 µl of whole blood. The NanoDrop instrument (ND-1000 spectrophotometer, Thermo Scientific, USA) was then employed to assess the quantity and quality of the RNA in the samples.

For cDNA synthesis, the miRCURY LNA RT Kit (Cat. No./ID: 339340) (QIAGEN, USA) was used in the reaction and included 4 µl of 5X Reaction Buffer, 2 µl of reverse transcriptase, 2 µl of dNTP Mix, 2 µl of nuclease-free H_2O, and 10 µl of the extracted microRNA, resulting in a total volume of 20 µl. The reaction was carried out on ice to effectively inhibit reverse transcriptase activity before using the Applied Biosystems thermal cycler 2720 (Singapore), which was set for one cycle at 37 °C for 60 min, followed by 95 °C for 5 min. The resulting cDNA was stored at −20 °C in preparation for real-time PCR analysis.

Quantitative real-time PCR (qRT-PCR)

We confidently employed a miScript SYBR Green PCR kit (QIAGEN, United States, Cat. No./ID: 339345) for our real-time PCR experiments. The reaction mixture included 4 µl of cDNA, 12.5 µl of SYBR Green Master Mix, 3 µl of the miScript universal primer, 3.5 µl of nuclease-free water, and 2 µl of the miScript primer assay, achieving a precise total volume of 25 µl. 5′-GGATGACACGCAAA TTCGTG AAGC-3′ was the housekeeping gene RNU6b (NC_000015.10). Primers that were used were as follows: mature microRNA-410-3p, 5′- AAUAUAACACAGAUG GCCUGU-3′ (MIMAT0002171); microRNA-148a, 5′-UC AGUGCACUACAGAACUUUGU-3′ (MIMAT0000243); microRNA-30c, 5′-UGUAAACAUCCUCGACUGGAA G −3′ (MIMAT0000087); and microRNA-29a, 5′- UAG CACCAUUUGAAAUCGGUUA-3′ (MIMAT0000681) (miScript primer assay kit, QIAGEN, USA). We analyzed the samples using 7,500 real-time PCR devices (software version 2.0.1). The cycling settings were optimized with an initial denaturation stage of 15 min at 95 °C, followed by 40 cycles consisting of 10 s at 94 °C, 60 s at 56 °C, and 30 s at 70 °C. We confidently measured the expression levels of microRNA-410-3p, microRNA-148a, microRNA-30c, and microRNA-29a using the 2-ΔΔCt method, standardizing RNU6b for precise comparison. The amplification plot was thoroughly analyzed (Supplemental Fig. 1A). In addition, we conducted a detailed melting curve analysis for each microRNA (Supplemental Figs. 1 C, D, E, and F). ΔCt is

calculated first by subtracting the housekeeping gene Ct from the target gene Ct then ΔΔCt is calculated by subtracting ΔCt of control from ΔCt of sample so the final relative expression is 2- ΔΔCt.

Estimation of circrna Met oncogene and circrna0084764 (EYA1) levels

RNA was isolated from 2 ml of whole blood collected in an EDTA tube using kits from Qiagen (Cat. No. 74, 104). The quality and purity of the extracted RNA were assessed using a Nanodrop ND-1000 spectrophotometer (Thermo Scientific, USA). The RNA was then stored at −80 °C until needed. For cDNA synthesis, the miRCURY LNA RT Kit (QIAGEN, USA) was utilized. The reaction mixture contained 4 µl of miRCURY RT enzyme, 4 µl of miRCURY RT buffer, 2 µl of RNase-free H_2O, 2 µl of miRCURY Nucleic Mix, and 8 µl of extracted RNA, resulting in a final volume of 20 µl. This mixture was kept on ice during the process.

For the reverse transcriptase enzyme inhibition, the Applied Bio-systems heat cycler 2720 (Singapore) was utilized and set to 42 °C for 60 min and then 95 °C for 5 min. For the PCR, the resultant cDNA was kept at −20 °C. Maxima SYBR Green Master mix (Thermo Scientific, Lithuania (K0251)) for quantitative real-time PCR was used to detect cDNA amplification using the specially created primers provided by (Thermofisher Scientific, Invitrogen,

USA). CircRNA met oncogene forward primer 5′ -TT GTCACTGCCTATACCTGC- 3′, reverse primer 5′-CCA AAGCCATCCACTTCACT-3′. CircRNA0084764 (EYA1) forward primer 5′ GGGGCGAGGTAGAAACTCTC 3′, reverse primer 5′ TCTGCTGCATCCACCAGTTT 3′ (NM_000503.6). According to NM_001101.5, the reference gene was β-actin, with forward primer 5′ GTGGCCGAGG ACTTTGATTG 3′ and reverse primer 5′ CCTGTAACAAC GCATCTCATATT 3′.

A total of 20 µl of qPCR samples was expertly prepared, containing 10 µl of SYBR Green master mix, 1 µl each of forward and reverse primers for both the reference gene and the target gene, 5 µl of nuclease-free H_2O, and 3 µl of cDNA product. The data analysis was conducted using version 2.0.1 of the Applied BioSystems 7500 software.

The cycling program was precisely structured, beginning with an initial denaturation step at 95 °C for 10 min, followed by 45 cycles of denaturation at 95 °C for 15 s and annealing/extension at 60 °C for 1 min. We employed the 2- ΔΔCt comparative method to robustly assess the relative expression levels of the circRNA met oncogene and circRNA0084764 genes. The reference gene β-actin and control were effectively used to normalize the target circular RNA. To ensure amplification specificity (amplification plot Supplemental Fig. 1 A) and to confirm the absence of primer dimers, we conducted a thorough melting curve analysis (Supplemental Figs. 1G and 1 H).

Statistical analysis

Data was analyzed using IBM SPSS version 20.0 (Armonk, NY: IBM Corp., 2011). Categorical data were presented as numbers and percentages, utilizing the chi-square test for comparisons and the Monte Carlo correction test when over 20% of cells had expected counts below 5. Continuous data underwent normality assessment with the Kolmogorov-Smirnov test. The student's t-test and one-way ANOVA were used for normally distributed data, followed by Tukey's post hoc test for comparisons. Non-normally distributed variables were addressed with the Mann-Whitney test for two groups and the Kruskal-Wallis test for multiple groups, followed by Dunn's post hoc test. The Wilcoxon signed-rank test analyzed abnormally distributed variables across two time periods, with significance set at the 5% level.

Results

This study enrolled 58 patients diagnosed with UC and 40 control subjects. Based on the Mayo score severity index assessed before treatment, the UC patients were classified into three categories: mild ($n=23$), moderate ($n=20$), and severe ($n=15$). After completing the treatment regimen, the patients were reclassified based on their outcomes into two groups: remission ($n=49$) and non-remission ($n=9$).

The demographic, clinical, and laboratory parameters between patients with UC and the control group were statistically demonstrated, as shown in Supplemental Table 1. The patients and controls were matched for age ($p=0.181$) and sex ($p=0.513$). Notably, the frequency of bowel movements was significantly higher in patients compared to the control group ($p<0.001$). Additionally, both systolic ($p=0.045$) and diastolic blood pressure ($p<0.001$) were significantly lower in patients than in controls, which may be attributed to the frequent bleeding associated with their condition. CBC analysis revealed that hemoglobin (Hb) levels were significantly lower in patients compared to the control group ($p<0.001$). Conversely, the platelet count ($p=0.007$), neutrophil count ($p<0.001$), and neutrophil-to-platelet ratio ($p<0.001$) were all higher in patients than in the control group. These findings suggest an inflammatory basis for the disease.

Liver function tests showed slight alterations in patients compared to controls. Specifically, elevated levels of ALT ($p<0.001$) and AST ($p=0.036$) were observed in patients. Additionally, albumin levels were slightly lower in patients than in controls ($p<0.001$). Serum creatinine levels were

Table 1 Comparison between the three UC patient groups studied according to demographic and clinical data

	Mild ($n=23$)	Moderate ($n=20$)	Severe ($n=15$)	Test of Sig.	p
Gender					
Male	13 (56.5%)	9 (45.0%)	8 (53.3%)	$\chi^2=$ 0.590	0.745
Female	10 (43.5%)	11 (55.0%)	7 (46.7%)		
Age					
Min. – Max.	18.0–55.0	18.0–43.0	18.0–60.0	F= 2.673	0.078
Mean ± SD.	28.39 ± 7.79	29.20 ± 8.81	35.67 ± 13.92		
Median (IQR)	27.0 (23.50–31.50)	29.50(20.50–35.50)	32.0 (25.50–46.0)		
Frequency of bowel motion					
Min. – Max.	2.0–5.0	3.0–6.0	6.0–13.0	H= 39.945*	>0.001*
Median (IQR)	3.0 (2.50–4.0)	4.0 (4.0–5.0)	8.0 (7.0–10.0)		
sig.bet.Grps	$p_1=0.012^*, p_2>0.001^*, p_3>0.001^*$				
Abdominal pain					
No	15 (65.2%)	4 (20.0%)	0 (0.0%)	$\chi^2=$ 19.787*	>0.001*
Yes	8 (34.8%)	16 (80.0%)	15 (100.0%)		
Bleeding rectum					
No	10 (43.5%)	0 (0.0%)	0 (0.0%)	$\chi^2=$ 54.172*	MCp >0.001*
Blood streaks	13 (56.5%)	11 (55.0%)	0 (0.0%)		
Obvious with stool	0 (0.0%)	9 (45.0%)	8 (53.3%)		
Blood alone	0 (0.0%)	0 (0.0%)	7 (46.7%)		
Fever					
No	21 (91.3%)	18 (90.0%)	10 (66.7%)	$\chi^2=$ 4.211	MCp= 0.114
Yes	2 (8.7%)	2 (10.0%)	5 (33.3%)		
Fatigue					
No	12 (52.2%)	6 (30.0%)	4 (26.7%)	$\chi^2=$ 3.325	0.190
Yes	11 (47.8%)	14 (70.0%)	11 (73.3%)		
Temperature					
Min. – Max.	36.70–37.90	36.70–38.50	36.80–39.0	F= 6.103*	0.004*
Mean ± SD.	37.08 ± 0.27	37.23 ± 0.46	37.59 ± 0.63		
Median (IQR)	37.0 (36.95–37.20)	37.0 (37.0–37.35)	37.50(37.20–37.95)		
Sig.bet.Grps	$p_1=0.513, p_2=0.003^*, p_3=0.054$				
Pulse					
Min. – Max.	69.0–107.0	67.0–108.0	78.0–125.0	F= 6.555*	0.003*
Median (IQR)	87.0 (81.50–91.0)	91.0 (86.0–102.0)	98.0 (92.0–108.5)		
Sig.bet.Grps	$p_1=0.289, p_2=0.002^*, p_3=0.088$				
Systolic Blood pressure (mmHg)					
Min. – Max.	100.0–130.0	90.0–130.0	90.0–110.0	F= 9.504*	>0.001*
Mean ± SD.	113.5 ± 9.35	108.5 ± 11.82	99.33 ± 7.04		
Median (IQR)	110.0(110.0–120.0)	110.0(100.0–120.0)	100.0 (95.0–100.0)		
Sig.bet.Grps	$p_1=0.228, p_2>0.001^*, p_3=0.022^*$				
Diastolic Blood pressure (mmHg)					
Min. – Max.	60.0–80.0	60.0–90.0	60.0–80.0	F= 4.994*	0.010*
Mean ± SD.	70.0 ± 7.39	70.0 ± 9.18	62.67 ± 5.94		
Median (IQR)	70.0 (65.0–75.0)	70.0 (60.0–80.0)	60.0 (60.0–60.0)		
Sig.bet.Grps	$p_1=1.000, p_2=0.016^*, p_3=0.020^*$				
Pallor					
No	23 (100.0%)	16 (80.0%)	11 (73.3%)	$\chi^2=$ 7.143*	MCp= 0.019*
Yes	0 (0.0%)	4 (20.0%)	4 (26.7%)		
Abdominal tenderness					
No	16 (69.6%)	7 (35.0%)	0 (0.0%)	$\chi^2=$ 18.637*	>0.001*
Yes	7 (30.4%)	13 (65.0%)	15 (100.0%)		
Extra intestinal					
No	23 (100.0%)	17 (85.0%)	10 (66.7%)	$\chi^2=$ 8.460*	MCp= 0.007*
Yes	0 (0.0%)	3 (15.0%)	5 (33.3%)		
Colonoscopy finding					

Table 1 (continued)

	Mild ($n=23$)	Moderate ($n=20$)	Severe ($n=15$)	Test of Sig.	p
I	17 (73.9%)	2 (10.0%)	0 (0.0%)	$\chi^2=$ 61.429*	^{MC}p >0.001*
II	6 (26.1%)	15 (75.0%)	0 (0.0%)		
III	0 (0.0%)	3 (15.0%)	15 (100.0%)		
Pathological finding					
I	11 (47.8%)	2 (10.0%)	0 (0.0%)	$\chi^2=$ 41.089*	^{MC}p >0.001*
II	11 (47.8%)	11 (55.0%)	0 (0.0%)		
III	1 (4.3%)	7 (35.0%)	15 (100.0%)		
Treatment					
- Mesalamine					
Systemic	18(78.3%)	0(0.0%)	0(0.0%)	$\chi^2=39.717$	<0.001*
Local	3(13.0%)	0(0.0%)	0(0.0%)	$\chi^2=3.291$	$^{MC}p=0.107$
Combined	2(8.7%)	0(0.0%)	0(0.0%)	$\chi^2=2.104$	$^{MC}p=0.332$
- Steroids					
Oral	0(0.0%)	20(100.0%)	0(0.0%)	$\chi^2=58.0$*	<0.001*
Intravenous	0(0.0%)	0(0.0%)	15(100.0%)	$\chi^2=58.0$*	<0.001*
Biological therapy (Adalimumab)	0 (0.0%)	3(15.0%)	3 (20.0%)	$\chi^2=5.015$	$^{MC}p=0.074$

IQR: Inter quartile range SD: Standard deviation χ^2: Chi square test

H: H for Kruskal Wallis test, pairwise comparison bet. Each of the 2 groups was done using a Post Hoc Test (Dunn's for multiple comparisons test)

F: F for One-way ANOVA test, pairwise comparison bet. Each of the 2 groups was done using a Post Hoc Test (Tukey)

MC: Monte Carlo

p: p value for comparing between different groups

p_1: p value for comparing between mild and moderate

p_2: p value for comparing between mild and severe

p_3: p value for comparing between moderate and severe

*: Statistically significant at $p<0.05$

also mildly elevated in patients compared to controls ($p<0.001$); however, this increase did not indicate kidney impairment (Supplemental Table 1).

Inflammatory markers were significantly elevated in patients compared to the control group. ESR showed a statistically significant difference ($p<0.001$). Additionally, CRP levels were notably different, with 38 patients testing positive and 20 testing negative, whereas all 40 control subjects tested negative ($p<0.001$). The level of CRP was measured at 24 for patients compared to 2 for controls ($p=0.001$). Furthermore, calprotectin levels were also significantly higher in patients, at 394, compared to 117 in controls ($p<0.001$) (Supplemental Table 1).

The results decisively demonstrate that all studied microRNAs are significantly dysregulated in patients. MicroRNA-29a shows remarkable upregulation, with a median of 2.4 compared to just 0.52 in controls ($p<0.001$) (Supplemental Fig. 2A). In contrast, microRNA-30c (median: 0.19 vs. 0.83, $p<0.001$) (Supplemental Fig. 2B), microRNA-148a (median: 0.04 vs. 0.23, $p=0.001$) (Supplemental Fig. 2C) and microRNA-410-3p (median: 0.07 vs. 0.16, $p=0.025$) (Supplemental Fig. 2D) are downregulated when compared to controls. Regarding circular RNAs, circRNA −0084764 EYA was significantly upregulated in patients compared to controls (median: 2.3 vs. 0.13, $p<0.001$) (Supplemental Fig. 2E). Additionally, circRNA-met oncogene showed a marked increase in patients (median: 10.18 vs. 0.30, $p<0.001$) (Supplemental Fig. 2F). These findings suggest that noncoding RNAs may play a role in the pathogenesis of the disease and in diffrentaiting UC patients from controls (Supplemental Table 1).

The findings related to demographics and clinical data among the groups categorized by disease severity—mild ($n=23$), moderate ($n=20$), and severe ($n=15$)—are summarized in Table 1. Notable symptoms of UC, including the frequency of bowel movements, abdominal pain, and rectal bleeding, were all statistically significant ($p<0.001$). Severe cases exhibited the highest severity, with 100% of patients experiencing abdominal pain. Additionally, approximately 53.3% of severe cases reported having bloody stools, while 46.7% had rectal bleeding without stool. Most patients also experienced frequent bowel movements.

In examining the signs of patients, we found that temperature ($p=0.004$) and pulse ($p=0.003$) were slightly elevated in severe cases compared to mild and moderate cases. In contrast, both systolic ($p<0.001$) and diastolic blood

pressure ($p=0.01$) were lower in severe cases. Additionally, signs such as pallor ($p=0.019$), abdominal tenderness ($p<0.001$), and extraintestinal manifestations ($p=0.007$) were more frequently observed in severe cases than in mild and moderate cases (Table 1).

Colonoscopy findings indicated the following results: for stage I, there were 17 cases of mild, 2 cases of moderate, and 0 cases of severe findings. In stage II, there were 6 cases of mild, 15 cases of moderate, and 0 cases of severe findings. For stage III, there were 0 cases of mild, 3 cases of moderate, and 15 cases of severe findings ($p<0.001$). Regarding pathological staging, the results were as follows: In stage I, there were 11 cases of mild, 2 cases of moderate, and 0 cases of severe. In stage II, there were 11 cases of mild, 11 cases of moderate, and 0 severe cases. For stage III, there was 1 case of mild, 7 cases of moderate, and 15 cases of severe ($p<0.001$) (Table 1).

In terms of pharmacological regimens, 18 mild cases received systemic mesalamine ($p<0.001$), three mild cases received local mesalamine, and two cases received both systemic and local mesalamine. Moderate cases were treated with oral steroids in 20 ($p<0.001$), whereas severe cases were treated with intravenous steroids in 15 ($p<0.001$). Biological treatment was necessary for two intermediate and three severe cases (Table 1).

The laboratory investigations presented in Supplemental Table 2 demonstrate that the severe group exhibits significantly lower Hb levels ($p=0.016$), fasting blood glucose levels ($p<0.001$), and albumin levels ($p<0.001$). This decline is directly linked to the frequent bowel bleeding observed in the severe group. Conversely, the severe group consistently showed higher levels of platelets ($p<0.001$), total leukocyte count (TLC) ($p<0.001$), neutrophils ($p<0.001$), and serum creatinine ($p=0.012$), underscoring the intense inflammatory processes that are characteristic of severe presentations. Neutrophil/platelet ratio ($p=0.096$), liver enzymes ALT ($p=0.19$) and AST ($p=0.949$), and international normalized ratio (INR) ($p=0.635$) showed no significant differences among patient groups.

The inflammatory markers analyzed in this study were compared among different patient groups, as shown in Table 2. ESR was significantly higher in the severe group compared to the mild group (median 55 vs. 20, $p<0.001$) and moderate group (median 55 vs. 40, $p=0.039$). Additionally, the moderate group had a higher ESR than the mild group (median 40 vs. 20, $p<0.001$).

CRP levels were elevated in severe cases compared to mild cases (median 24 vs. 12, $p=0.001$); however, there was no significant difference between severe and moderate cases (median 24 vs. 24, $p=0.463$). The moderate group did show elevated CRP levels compared to mild cases (median 24 vs. 12, $p=0.007$). In terms of fecal calprotectin, the severe group exhibited higher levels than the mild group (median 455 vs. 340, $p=0.005$) and the moderate group (median 455 vs. 355, $p=0.032$). However, there was no significant difference between the mild and moderate groups (median 340 vs. 355, $p=0.509$) (Table 2).

In a comparison of microRNA levels among different patient groups, microRNA-29a was significantly upregulated in the severe group compared to the mild group, with median values of 5.34 and 1.09, respectively ($p=0.016$). However, this difference was insignificant when comparing the severe and moderate groups (median 5.34 vs. 1.90, $p=0.066$). Additionally, the moderate group did not show significant differences compared to the mild group (median 1.90 vs. 1.09, $p=0.577$) (Fig. 1A). MicroRNA-30c was significantly downregulated in the severe group compared to the mild group, with medians of 0.06 and 0.34, respectively ($p=0.004$). However, there was no significant difference when comparing the severe and moderate groups (median 0.06 vs. 0.17, $p=0.069$). Similarly, the moderate group did not differ significantly from the mild group (median 0.17 vs. 0.34, $p=0.260$) (Table 2) (Fig. 1B).

MicroRNA-410-3p showed notable downregulation in the severe group compared to both the mild and moderate groups, with median values of 0.01 vs. 0.35 ($p<0.001$) and 0.01 vs. 0.07 ($p=0.022$), respectively. Notably, the moderate group also showed significant differences from the mild group (median 0.07 vs. 0.35, $p=0.035$) (Fig. 1C). Conversely, microRNA-148a did not exhibit any significant alterations among the patient groups ($p=0.318$) (Table 2) (Fig. 1D).

CircRNA-0084764 EYA demonstrated significant upregulation in the severe group compared to the mild and moderate groups. The median values were 17.34 for the severe group versus 1.39 for the mild group ($p<0.001$) and 17.34 versus 3.15 for the moderate group ($p=0.001$). Additionally, the moderate group showed a significant difference from the mild group, with median values of 3.15 compared to 1.39 ($p=0.018$) (Fig. 1E). Furthermore, circRNA-met oncogene was also upregulated in the severe group when compared to both the mild and moderate groups, with median values of 20.40 versus 3.12 for the mild group ($p<0.001$) and 20.40 versus 11.43 for the moderate group ($p=0.019$). Similarly, the moderate group displayed significant differences from the mild group, with median values of 11.43 compared to 3.12 ($p=0.002$) (Table 2) (Fig. 1F).

Supplemental Table 3 illustrates the effects of the treatment regimen on inflammatory markers by comparing two groups of patients: the remission group ($n=49$) and the non-remission group ($n=9$). MicroRNA-29a showed a significant increase in the remission group compared to the non-remission group, with median values of 1.23 versus 0.17 ($p=0.008$). Additionally, microRNA-30c and

Table 2 Comparison between the three UC-studied patient groups according to different baseline inflammatory markers

	Mild ($n=23$)	Moderate ($n=20$)	Severe ($n=15$)	Test of Sig.	p
ESR					
Min. – Max.	5.0–30.0	8.0–86.60	35.0–78.0	H= 31.288*	>0.001*
Mean ± SD.	19.04 ± 8.46	39.38 ± 19.48	54.27 ± 14.70		
Median (IQR)	20.0 (12.0–26.50)	40.0 (28.50–50.0)	55.0 (42.50–65.0)		
Sig.bet.Grps	$p_1>0.001^*, p_2>0.001^*, p_3=0.039^*$				
CRP					
Negative	16 (69.6%)	3 (15.0%)	1 (6.7%)	χ^2= 21.027*	>0.001*
Positive	7 (30.4%)	17 (85.0%)	14 (93.3%)		
Min. – Max.	6.0–12.0	6.0–36.0	12.0–48.0	H= 10.698*	0.005*
Mean ± SD.	10.29 ± 2.93	21.18 ± 8.37	24.86 ± 11.97		
Median (IQR)	12.0 (9.0–12.0)	24.0 (12.0–24.0)	24.0 (12.0–24.0)		
Sig.bet.Grps	$p_1=0.007^*, p_2=0.001^*, p_3=0.463$				
Fecal calprotectin (µg/g)					
Min. – Max.	96.0–580.0	210.0–720.0	366.0–910.0	8.316*	0.016*
Mean ± SD.	326.0 ± 145.53	382.05 ± 177.26	492.07 ± 155.19		
Median (IQR)	340.0(220.0–425.0)	355.0(230.0–511.0)	455.0(390.0–482.50)		
Sig.bet.Grps	$p_1=0.509, p_2=0.005^*, p_3=0.032^*$				
MicroRNA-29a					
Min. – Max.	0.025–17.67	0.024–25.67	0.030–35.67	H= 6.059*	0.048*
Mean ± SD.	3.74 ± 5.43	4.57 ± 6.90	9.86 ± 11.44		
Median (IQR)	1.09 (0.11–3.88)	1.90 (0.34–5.41)	5.34 (3.51–11.45)		
Sig.bet.Grps	$p_1=0.577, p_2=0.016^*, p_3=0.066$				
MicroRNA- 30c					
Min. – Max.	0.011–1.20	0.016–1.12	0.001–0.99	H= 8.465*	0.015*
Mean ± SD.	0.37 ± 0.30	0.31 ± 0.36	0.16 ± 0.26		
Median (IQR)	0.34 (0.12–0.52)	0.17 (0.06–0.39)	0.06 (0.01–0.20)		
Sig.bet.Grps	$p_1=0.260, p_2=0.004^*, p_3=0.069$				
MicroRNA- 148a					
Min. – Max.	0.003–1.15	0.004–1.28	0.004–0.98	H= 2.289	0.318
Mean ± SD.	0.34 ± 0.41	0.24 ± 0.40	0.11 ± 0.25		
Median (IQR)	0.08 (0.01–0.72)	0.01 (0.01–0.27)	0.02 (0.01–0.09)		
MicroRNA- 410-3P					
Min. – Max.	0.002–0.99	0.001–0.63	0.001–0.30	H= 18.480*	>0.001*
Mean ± SD.	0.39 ± 0.30	0.15 ± 0.17	0.04 ± 0.08		
Median (IQR)	0.35 (0.09–0.62)	0.07 (0.03–0.23)	0.01 (0.0–0.03)		
Sig.bet.Grps	$p_1=0.035^*, p_2>0.001^*, p_3=0.022^*$				
CircRNA − 0084764 EYA					

Table 2 (continued)

	Mild (n=23)	Moderate (n=20)	Severe (n=15)	Test of Sig.	p
Min. – Max.	0.002–8.68	0.23–40.12	1.67–45.21	H=	>0.001*
Mean ± SD.	1.72 ± 1.68	6.04 ± 8.87	18.30 ± 10.73	29.920*	
Median (IQR)	1.39(1.15–2.10)	3.15(1.70–6.72)	17.34(12.04–20.18)		
Sig.bet.Grps	p_1=0.018*,p_2>0.001*,p_3=0.001*				
CircRNA-met oncogene					
Min. – Max.	0.16–24.12	3.67–34.12	1.89–56.12	H=	>0.001*
Mean ± SD.	5.56 ± 5.45	13.47 ± 8.18	25.38 ± 13.19	29.162*	
Median (IQR)	3.12 (1.89–8.73)	11.43 (8.85–18.16)	20.40(20.16–30.90)		
Sig.bet.Grps	p_1=0.002*,p_2>0.001*,p_3=0.019*				

IQR: Inter quartile range SD: Standard deviation χ^2: Chi square test

H: H for Kruskal Wallis test, pairwise comparison bet. Each of the 2 groups was done using a Post Hoc Test (Dunn's for multiple comparisons test), F: F for One-way ANOVA test, pairwise comparison bet. Each of the 2 groups was done using a Post Hoc Test (Tukey). p: p value for comparing between different groups

p_1: p value for comparing between mild and moderate

p_2: p value for comparing between mild and severe

p_3: p value for comparing between **moderate and severe** *: Statistically significant at $p<0.05$

microRNA-148a were also significantly elevated in the remission group, with median values of 0.34 versus 0.03 ($p<0.001$) and 0.22 versus 0.04 ($p=0.01$), respectively. These results support the potential use of these inflammatory markers for predicting remission. Conversely, fecal calprotectin ($p=0.259$), microRNA-410-3p ($p=0.821$), circRNA-0084764 EYA ($p=0.427$), and circRNA-met oncogene ($p=0.667$) did not show significant differences between the groups and are, therefore, not considered valuable markers for predicting remission.

The receiver operating characteristic (ROC) curve is presented in Tables 3, 4 and 5, illustrating the diagnostic and prognostic efficiency of various inflammatory markers. Table 3; Fig. 2A indicate the diagnostic performance of markers in distinguishing patients from controls and show that circRNA-met oncogene demonstrated the highest sensitivity of 94.83% and a specificity of 100% with a cutoff value greater than 1, yielding an area under the curve (AUC) of 0.974 ($p<0.001$). This was followed by circRNA-0084764 EYA, which showed a sensitivity of 93.33% and a specificity of 90.70% at a cutoff of greater than 7.2, resulting in an AUC of 0.930 ($p<0.001$). Additionally, fecal calprotectin demonstrated a sensitivity of 93.10% and a specificity of 90.00% at a cutoff level greater than 130, with an AUC of 0.958 ($p<0.001$). The remaining inflammatory markers exhibited lower sensitivity and specificity, making them unsuitable as diagnostic markers for UC.

The prognostic efficacy of inflammatory markers for predicting severe cases of UC was demonstrated in Table 4. In this study, the performance of various markers was assessed, distinguishing severe cases ($n=15$) from non-severe cases ($n=43$). The marker circRNA-0084764 EYA exhibited the highest sensitivity at 93.33% and a specificity of 90.70% with a cutoff value greater than 7.2, leading to an area under the curve (AUC) of 0.930 ($p<0.001$). This was followed by the circRNA-met oncogene, which presented a sensitivity of 86.67% and a specificity of 83.72% at a cutoff value greater than 12.77, resulting in an AUC of 0.883 ($p<0.001$). Additionally, microRNA-410-3P demonstrated a sensitivity of 80.00% and a specificity of 72.09% with a cutoff value less than or equal to 0.05, yielding an AUC of 0.827 ($p<0.001$). These three markers highlight their prognostic value for predicting the severity of UC (Fig. 2B).

When these top three markers were combined with the current marker in use, fecal calprotectin, the overall predictive efficiency increased. The combination of circRNA-0084764 EYA and fecal calprotectin showed a sensitivity of 93.33% and a specificity of 81.40%, resulting in an AUC of 0.947 ($p<0.001$). The combination of circRNA-met oncogene and fecal calprotectin showed a sensitivity of 86.67% and a specificity of 86.05%, yielding an AUC of 0.902 ($p<0.001$). Lastly, the combination

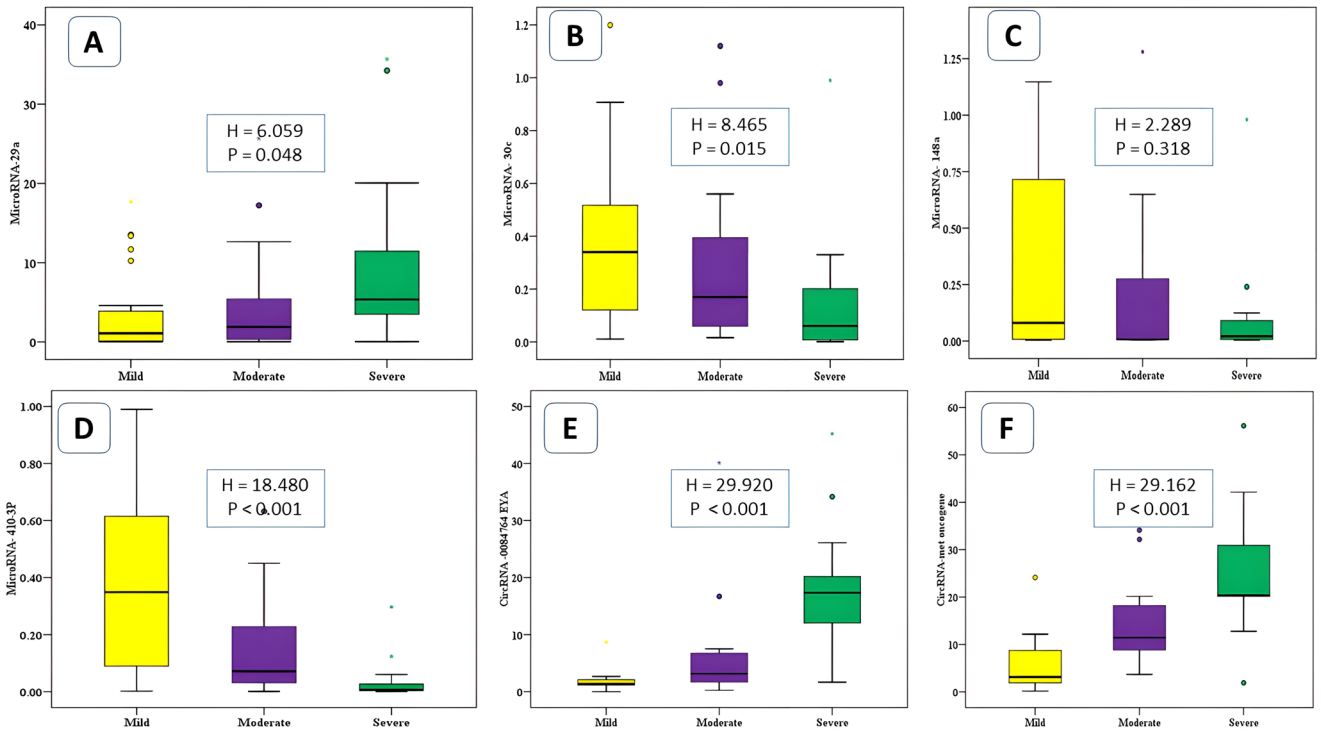

Fig. 1 Comparison of microRNA levels among different patient groups. On the Y axis, the 2-ΔCt value was considered. **A**: Comparison between the three studied groups according to MicroRNA-29a (H = 6.059). **B**: Comparison between the three studied groups according to MicroRNA- 30c (H = 8.465). **C**: Comparison between the three studied groups according to MicroRNA- 148a (H = 2.289). **D**: Comparison between the three studied groups according to MicroRNA-410-3P (H = 18.480). **E**: Comparison between the three studied groups according to CircRNA −0084764 EYA(H = 29.920). **F**: Comparison between the three studied groups according to CircRNA-met oncogene(H = 29.162)

Table 3 Diagnostic performance for different inflammatory markers (pre) to discriminate cases ($n = 58$) from control ($n = 40$)

Pre	AUC	*p*	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Fecal calprotectin (µg/g)	0.958	<0.001*	0.916–1.0	>130	93.10	90.0	93.1	90.0
MicroRNA-29a	0.715	<0.001*	0.611–0.818	>0.488	70.69	50.0	67.2	54.1
MicroRNA- 30c	0.715	<0.001*	0.607–0.822	≤0.377	72.41	62.50	73.7	61.0
MicroRNA- 148a	0.707	0.001*	0.603–0.810	≤0.21	68.97	62.50	72.7	58.1
MicroRNA- 410-3P	0.633	0.026*	0.513–0.753	≤0.124	56.90	55.0	64.7	46.8
CircRNA −0084764 EYA	0.930	<0.001*	0.878–0.982	>7.2	93.33	90.70	77.8	97.5
CircRNA-met oncogene	0.974	<0.001*	0.944–1.0	>1	94.83	100.0	100.0	93.0

AUC: Area Under a Curve p value: Probability value CI: Confidence Intervals

NPV: Negative predictive value PPV: Positive predictive value

*: Statistically significant at $p \leq 0.05$

of microRNA-410-3P and fecal calprotectin demonstrated a sensitivity of 86.67% and a specificity of 83.72%, with an AUC of 0.859 ($p < 0.001$) (Table 4) (Fig. 2C).

The prognostic efficacy of various inflammatory markers in predicting remission following the treatment for UC is illustrated in Table 5, which compares the remission group ($n = 49$) and the non-remission group ($n = 9$). MicroRNA-30c exhibited the highest sensitivity at 89.80% and the highest specificity at 88.89%, with a cutoff value greater than 0.16, resulting in an AUC of 0.900 ($p < 0.001$). Following this, microRNA-148a showed a sensitivity of 75.51% and a specificity of 66.67%, with a cutoff value greater than 0.06, yielding an AUC of 0.772 ($p = 0.01$). Lastly, microRNA-29a demonstrated a sensitivity of 73.47% and a specificity of 55.56%, with a cutoff value greater than 0.22, resulting in an AUC of 0.781 ($p = 0.008$). These findings highlight the value of these three markers in predicting treatment response in UC patients (Fig. 2D).

The relationship between inflammatory markers before treatment, gender, and extraintestinal manifestations in the UC group is comprehensively detailed in Supplemental Table 4. Notably, the circRNA-met oncogene is the only

Table 4 Prognostic performance for different inflammatory markers (pre) to predict severe cases ($n=15$) from non-severe ($n=43$)

	AUC	*p*	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Fecal calprotectin (µg/g)	0.745	0.005*	0.620–0.870	> 398	73.33	60.47	39.3	86.7
MicroRNA-29a	0.709	0.017*	0.554–0.865	> 3.45	73.33	72.09	47.8	88.6
MicroRNA- 30c	0.734	0.007*	0.579–0.889	≤ 0.16	66.67	58.14	35.7	83.3
MicroRNA- 148a	0.564	0.461	0.412–0.717	≤ 0.035	53.33	53.49	28.6	76.7
MicroRNA- 410-3P	0.827	< 0.001*	0.715–0.939	≤ 0.05	80.0	72.09	50.0	91.2
CircRNA −0084764 EYA	0.930	< 0.001*	0.847–1.0	> 7.2	93.33	90.70	77.8	97.5
CircRNA-met oncogene	0.883	< 0.001*	0.767–0.999	> 12.77	86.67	83.72	65.0	94.7
Combination of studied markers with Fecal calprotectin								
MicroRNA-29a + Fecal calprotectin	0.800	0.001*	0.684–0.916	--	86.67	65.12	46.4	93.3
MicroRNA- 30c + Fecal calprotectin	0.784	0.001*	0.651–0.918	--	80.0	67.44	46.2	93.3
MicroRNA- 148a + Fecal calprotectin	0.783	0.001*	0.657–0.909	--	73.33	74.42	50.0	88.9
MicroRNA- 410-3P + Fecal calprotectin	0.859	< 0.001*	0.756–0.962	--	86.67	83.72	65.0	94.7
CircRNA −0084764 EYA + Fecal calprotectin	0.947	< 0.001*	0.889–1.0	--	93.33	81.40	63.6	97.2
CircRNA-met oncogene + Fecal calprotectin	0.902	< 0.001*	0.809–0.996	--	86.67	86.05	68.4	94.9

AUC: Area Under a Curve p value: Probability value CI: Confidence Intervals

NPV: Negative predictive value PPV: Positive predictive value

*: Statistically significant at $p \leq 0.05$

inflammatory biomarker demonstrating a significant association with extraintestinal manifestations. The median value for this biomarker was 20.16 in the positive group ($n=8$), compared to just 8.95 in the negative group ($n=50$), with a p-value of 0.006. This indicates that the high expression of a circRNA-met oncogene is strongly linked to severe cases with extraintestinal manifestations that need biological treatment, establishing its critical role as a prognostic biomarker for the progression of CRC malignancy. In stark contrast, all other inflammatory markers fail to demonstrate any significant relationship with either gender or extraintestinal manifestations.

The logistic regression analysis unequivocally demonstrates the capability of inflammatory biomarkers to predict the severity of UC, as outlined in Table 6. The crude odds ratio (COR) confirms that the inflammatory biomarkers fecal calprotectin (OR = 1.005, $p=0.012$), microRNA-29a (OR = 1.084, $p=0.034$), microRNA-410-3P (OR = 0.0, $p=0.021$), circRNA-0084764 EYA (OR = 1.234, p = < 0.001), and circRNA-met oncogene (OR = 1.167, $p=0.001$) are significant predictors of UC severity. Notably, the adjusted odds ratio (AOR) identifies microRNA-29a (OR = 1.107, $p=0.048$), circRNA-0084764 EYA (OR = 1.280, $p=0.004$), and circRNA-met oncogene (OR = 1.306, $p=0.005$) as independent predictors. These biomarkers should be recognized as essential prognostic markers for assessing the severity of UC.

The logistic regression analysis demonstrates that inflammatory biomarkers can predict the remission of UC, as shown in Supplemental Table 5. The COR indicates that the inflammatory biomarkers microRNA-29a (OR = 3.995, $p=0.044$) and microRNA-30c (OR = 3.693, $p=0.002$) are significant predictors of UC remission. Notably, the AOR identifies microRNA-30c (OR = 3.757, $p=0.002$) as the only independent predictor. Therefore, this biomarker should be recognized as a crucial prognostic marker for evaluating remission in UC.

Supplemental Table 6 displays a correlation between various inflammatory markers and different parameters in the patient group before treatment. Fecal calprotectin was significantly correlated with the frequency of bowel movements ($r=0.289$, $p=0.028$) and colonoscopy results ($r=0.282$, $p=0.032$). MicroRNA-29a also exhibited a significant correlation with the frequency of bowel movements ($r=0.306$, $p=0.020$) and colonoscopy ($r=0.290$, $p=0.027$). Additionally, microRNA-30c showed significant correlations with colonoscopy ($r=0.423$, $p<0.001$), pathology ($r=0.387$, $p=0.003$), platelets ($r=0.306$, $p=0.019$), and fecal calprotectin ($r=0.348$, $p=0.007$). MicroRNA-148a revealed a significant correlation with platelets ($r=0.333$, $p=0.011$). At the same time, microRNA-410-3p was significantly correlated with the frequency of bowel movements ($r=0.367$,

Table 5 Prognostic performance for different parameters (post) to predict remission cases ($n=49$) from non-remission ($n=9$)

post	AUC	*p*	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Fecal calprotectin (µg/g)	0.619	0.260	0.426–0.812	>366	63.27	55.56	88.6	21.7
MicroRNA-29a	0.781	0.008*	0.654–0.908	>0.22	73.47	55.56	90.0	27.8
MicroRNA- 30c	0.900	<0.001*	0.785–1.0	>0.16	89.80	88.89	97.8	61.5
MicroRNA- 148a	0.772	0.010*	0.595–0.949	>0.06	75.51	66.67	92.5	33.3
MicroRNA- 410-3P	0.524	0.822	0.320–0.728	>0.24	48.98	44.44	82.8	13.8
CircRNA −0084764 EYA	0.584	0.621	0.400–0.768	≤2.2	59.18	44.44	85.3	16.7
CircRNA-met oncogene	0.545	0.647	0.319–0.771	≤2.6	53.06	44.44	83.9	14.8

AUC: Area Under a Curve p value: Probability value CI: Confidence Intervals

NPV: Negative predictive value PPV: Positive predictive value

*: Statistically significant at $p \leq 0.05$

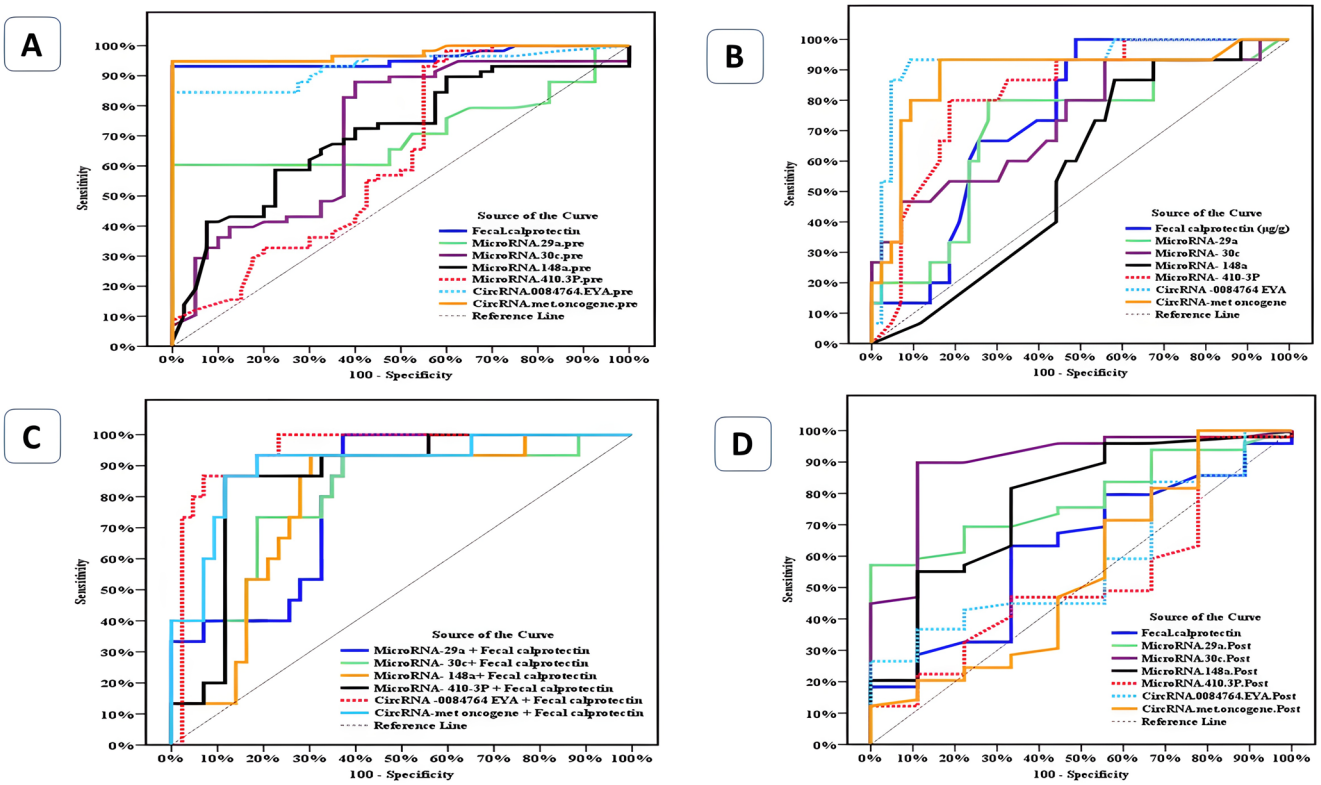

Fig. 2 ROC curve for studied markers. **A**: ROC curve for studied markers (pre) to predict severe cases ($n=15$) from non-severe ($n=43$). **B**: ROC curve for studied markers (pre) to predict severe cases ($n=15$) from non-severe ($n=43$). **C**: ROC curve for studied markers (pre) to discriminate cases ($n=58$) from control ($n=40$). **D**: ROC curve for studied markers (post) to predict remission cases ($n=49$) from non-remission ($n=9$)

$p=0.005$), colonoscopy ($r=0.375$, $p=0.004$), pathology ($r=0.346$, $p=0.008$), platelets ($r=0.328$, $p=0.012$), neutrophils ($r=0.497$, $p<0.001$), and the neutrophil/platelet ratio ($r=0.266$, $p=0.043$).

CircRNA-0084764 EYA demonstrated significant correlations with the frequency of bowel movements ($r=0.689$, $p<0.001$), colonoscopy ($r=0.704$, $p<0.001$), pathology ($r=0.577$, $p<0.001$), platelets ($r=0.300$, $p=0.022$), neutrophils ($r=0.387$, $p=0.003$), and fecal calprotectin ($r=0.374$, $p=0.004$). Finally, circRNA-met oncogene exhibited significant correlations with the frequency of bowel movements ($r=0.612$, $p<0.001$), colonoscopy ($r=0.642$, $p<0.001$), pathology ($r=0.553$, $p<0.001$), platelets ($r=0.318$, $p=0.015$), and neutrophils ($r=0.460$, $p<0.001$) Supplemental Table 6. These diverse correlations suggest that these markers could serve as effective biomarkers for UC's diagnostic and prognostic evaluation after treatment.

Table 6 Logistic regression analysis for the parameters affecting severity of UC (pre)

	COR		AOR	
	p	OR(LL – UL 95%C.I)	*p*	OR(LL – UL 95%C.I)
Fecal calprotectin (µg/g)	**0.012***	1.005(1.001–1.009)	0.135	1.004(0.999–1.010)
MicroRNA-29a	**0.034***	1.084(1.006–1.167)	**0.048***	1.107(1.001–1.224)
MicroRNA-410-3P	**0.021***	0.0(0.0–0.214)	0.147	0.002(0.0–9.283)
MicroRNA- 30c	0.078	0.069(0.004–1.348)	0.221	0.187(0.013–2.744)
MicroRNA- 148a	0.136	0.165(0.015–1.766)	0.263	0.168(0.007–3.827)
CircRNA −0084764 EYA	**<0.001***	1.234(1.100–1.384)	**0.004***	1.280(1.081–1.516)
CircRNA-met oncogene	**0.001***	1.167(1.070–1.274)	**0.005***	1.306(1.084–1.572)

COR: Crude odds ratio AOR: Adjust odds ratio by Gender, Age, ESR, and CRP

C.I.: Confidence interval LL: Lower limit UL: Upper Limit

*: Statistically significant at $p \leq 0.05$

Discussion

Inflammatory bowel disease (IBD) unequivocally increases the risk of cancer progression. IBD is driven by critical factors such as mucosal inflammatory mediators, genetic and epigenetic influences, oxidative stress, intestinal microbiota, and the activation of oncogenic signaling pathways [22]. MicroRNAs are crucial in understanding gastrointestinal disorders since they specifically target molecules regulating the intestinal epithelial barrier, inflammation, and cell migration. Their role in these pathways cannot be overlooked [23]– [24]. CircRNAs are not well characterized in IBD, and their functions are not well understood. Although circRNAs are not widely investigated in IBD, research results have indicated that these molecules play critical roles in this disease [18].

This case-control study included 58 patients with UC and 40 matched controls based on age and sex. The patients were further classified into three categories based on disease severity: mild ($n=23$), moderate ($n=20$), and severe ($n=15$). Our findings indicated that patients experienced a higher bowel movement frequency than controls. Additionally, Hb levels and both systolic and diastolic blood pressure were lower in patients, likely due to the frequent bleeding associated with their condition. In contrast, we observed that platelet counts, neutrophil counts, and the neutrophil-to-platelet ratio were elevated in patients, suggesting an inflammatory component underlying the disease.

Inflammatory markers were significantly elevated in patients compared to the control group, including levels of ESR and CRP. The results demonstrate that all microRNAs studied are significantly dysregulated in patients. Notably, microRNA-29a showed a remarkable upregulation, with a median of 2.4 in patients compared to just 0.52 in controls. In contrast, microRNA-30c had a median of 0.19 versus 0.83, microRNA-148a had a median of 0.04 versus 0.23, and microRNA-410-3p had a median of 0.07 versus 0.16, all showing downregulation compared to controls. MicroRNA-29a was significantly upregulated in the severe group, while microRNA-30c and microRNA-410 were downregulated compared to the mild group. These results indicate that the condition's severity influences microRNA expression and could predict the response to medical treatment.

MicroRNA dysregulation is critically involved in a range of diseases cited by our team, including colorectal cancer [25], diabetic nephropathy [26], psoriasis [27], and chronic hepatitis C [28].

MicroRNA-29 plays a definitive inflammatory role by inhibiting Th1 cell differentiation through its action on the Th1-specific transcription factor T-bet in mice [29]. The interplay between microRNA-29c-3p and leukemia inhibitory factor (LIF) is essential for regulating intestinal inflammation. Overexpression of miR-29c-3p drives inflammation by suppressing LIF in both in vitro and in vivo contexts. The distinct expression patterns of miR-29c-3p and LIF found in inflamed colon lesions are poised to serve as robust biomarkers for UC. Moreover, targeting the miR-29c-3p/LIF axis has the potential to effectively regulate the production of inflammatory cytokines, cell proliferation, and apoptosis, establishing it as a promising therapeutic target for UC treatment [30].

MicroRNA-30a is a significant tumor suppressor in various human cancers. Its levels are notably reduced in multiple tumors [31, 32]. Research by Xie et al. [33] has shown that microRNA-30a is downregulated in CRC, where it inhibits cell proliferation and tumor growth by targeting CD73. Consequently, microRNA-30a may play a role in the onset and progression of CRC by regulating CD73 expression.

MicroRNA-148a is a crucial indirect tumor suppressor that plays a vital role in regulating colitis and colitis-associated tumorigenesis. It effectively suppresses the signaling pathways of NF-κB and STAT3, thereby mitigating their pro-inflammatory effects. The downregulation of miR-148a during the development of CRC results from CpG island hypermethylation, leading to a significant upregulation of NF-κB and STAT3 signaling [34].

Tsai et al. [35] detected that miR-148a effectively downregulates HIF-1α/VEGF and Mcl-1 by directly targeting ROCK1 and c-Met. This mechanism significantly decreases angiogenesis and enhances apoptosis in colon cancer cells. Clinically, it is evident that patients with metastatic colorectal cancer (mCRC) who exhibit overexpression of serum miR-148a achieve a more favorable therapeutic response

compared to those undergoing the standard combination therapy of chemotherapy and bevacizumab (5 mg/kg).

Wang et al. [36] reported that microRNA-410 definitively reduces the expression of dickkopf-related protein 1 (DKK-1) in vitro and actively promotes malignant phenotypes in CRC cell lines. This regulatory effect of miR-410 is directly associated with the Wnt/β-catenin signaling pathway. As such, miR-410 is a promising biomarker for predicting the progression of CRC. Another critical mechanism by which miR-410-3p drives CRC progression is the suppression of ZCCHC10 by microRNA-410-3p, which effectively regulates NF-κB activation, significantly promoting the epithelial-mesenchymal transition (EMT), along with enhanced cell migration and invasion in CRC cells [37].

In the context of circRNAs, circRNA-0084764 EYA was significantly upregulated in patients (median: 2.3) compared to controls (median: 0.13). Similarly, circRNA-met oncogene also showed a notable increase in patients (median: 10.18 vs. 0.30). These results indicate that these noncoding RNAs may play a role in disease pathogenesis. Additionally, circRNA-0084764 EYA and circRNA-met oncogene were significantly upregulated in the severe patient group compared to the mild and moderate groups.

CircRNA is essential in driving biological functions through its robust interactions with proteins. It confidently alters protein-protein interactions, effectively blocks proteins from binding to DNA, RNA, and other proteins, recruits chromatin remodelers and transcription factors while modifying enzymes on chromatin, forms circRNA-protein-mRNA ternary complexes that regulate translation and RNA stability with precision, and translocates proteins to the nucleus or cytoplasm as needed. These mechanisms underscore the powerful role circRNA plays in regulating cellular processes [38].

CircRNAs are gaining significant attention for their robust potential in monitoring progressive and recurrent diseases, tracking the effectiveness of chemotherapy, advancing vaccine and drug development, and enhancing personalized medicine approaches. Furthermore, various clinical trials and studies actively evaluate the use of circular RNAs as reliable cancer biomarkers [39].

The overexpression of EYA family members has decisively established itself as a hallmark of cancer. This phenomenon plays a crucial role in driving sustained proliferative signaling, conferring resistance to cell death, promoting angiogenesis, and facilitating both invasion and metastasis [40]. CircEYA1 is undeniably downregulated in cervical adenocarcinoma tissues and has a pivotal role in suppressing cell viability and colony formation while significantly promoting cell apoptosis. This effect is primarily due to its function as a sponge for miR-582-3p, which effectively relieves the repression of the target gene CXCL14 [41]. Additionally, it was downregulated in psoriasis [27].

Genome-wide profiling of circRNAs has unequivocally established critical regulatory relationships among miRNAs, circRNAs, and mRNAs. The CircMET-miR-410-3p-MET motif is essential for the growth of CRC cells. These findings assert that circMET plays a significant role in upregulating the transcription of its host oncogene, MET. Additionally, miR-410-3p effectively binds to the 3′ untranslated region (3’ UTR) of MET mRNA, thereby inhibiting MET expression [19]. Our results conclusively show that in UC, circMET is significantly overexpressed while microRNA-410 is markedly under-expressed. This alteration directly contributes to the upregulation of the MET oncogene, establishing these markers as reliable early predictors for progression to CRC.

The diagnostic performance of various markers in distinguishing patients from controls revealed that the circRNA-met oncogene exhibited the highest sensitivity at 94.83% and a specificity of 100%. This was followed by circRNA-0084764 EYA, which showed a sensitivity of 93.33% and a specificity of 90.70%. Additionally, fecal calprotectin demonstrated a sensitivity of 93.10% and a specificity of 90.00%. These results suggest that these markers could be beneficial for the early diagnosis of UC.

We tested the prognostic efficacy of inflammatory markers in predicting severe cases of UC, and the results are compelling. The marker circRNA-0084764 EYA stands out with the highest sensitivity at 93.33% and a specificity of 90.70%. Following closely is the circRNA-met oncogene, which demonstrates a sensitivity of 86.67% and a specificity of 83.72%. Furthermore, microRNA-410-3p exhibits a sensitivity of 80.00% and a specificity of 72.09%. These findings unequivocally validate the prognostic value of these markers after initiating the treatment.

Measuring circMET levels is essential for identifying and monitoring patients with high MET activity. This approach significantly enhances patient stratification based on MET expression and facilitates the dynamic tracking of therapy responses [42].

MicroRNA-30c stands out as the most effective marker for predicting remission following treatment for UC, boasting an impressive sensitivity of 89.80% and the highest specificity at 88.89%. It is followed by microRNA-148a, which delivers a sensitivity of 75.51% and a specificity of 66.67%. Additionally, microRNA-29a demonstrates a sensitivity of 73.47% and a specificity of 55.56%. These findings establish the critical role of these three microRNAs in predicting treatment responses in UC patients.

Utilizing regression analysis, microRNA-29a, circRNA-0084764 EYA, and circRNA-met oncogene could be independent predictors for assessing the severity of UC.

Additionally, the AOR identifies microRNA-30c as the only independent predictor for evaluating remission in UC.

Conclusion

We firmly believe that circRNAs and microRNAs are essential for UC and play a crucial role in its inflammatory processes. Specifically, microRNA-29a, circRNA-0084764 EYA, and circRNA-met oncogene are definitive biomarkers for determining the severity of UC and its progression to CRC. Additionally, microRNA-30c unequivocally serves as a reliable biomarker for identifying remission in UC and the personalized treatment for each patient.

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Author contributions All authors contributed to the conception and design of the study. The material preparation, data collection, and analysis were conducted by Mai Abouelenin, Safaa Tayel, Naglaa Elabd, Amany Saleh, Eman Elmasry, Huda Abd-Elhafiz, Ghada Elgarawany, Randa Seddik, Mahmoud Rizk, Osama Elbahr, Mohammed Elhelbawy and Heba Khader. The first draft of the manuscript was written by Mai Abouelenin, Safaa Tayel, Naglaa Elabd, Amany Saleh and Randa Seddik. All authors reviewed and approved the final manuscript.

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Data availability The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate Ethics approval and consent to participate: Prior to enrolment, each participant received an explanation of the study and the opportunity to provide written, informed consent after the research objectives and questions were explained. With Institutional Review Board (IRB) approval number 3/2023TROP11, the research methodology and sample size calculation were approved by the Faculty of Medicine's Research Ethics Committee at Menoufia University in Egypt. The study was conducted in compliance with the Helsinki Declaration.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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