Circulating miR-21, Oxidative Stress Biomarkers, and Inflammatory Indices in Ulcerative Colitis

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Abstract
Ulcerative colitis is a colonic inflammatory disease that is long-term. Inflammatory, oxidative stress, and molecular activation biomarkers could enhance the evaluation of the disease. The circulation of the miR-21 is also relevant in mucosal inflammation and its clinical significance in ulcerative colitis is yet to be determined. This study tries to measure circulating miR-21, oxidative stress biomarkers and inflammatory indices in patients with ulcerative colitis and to test associations between them and disease activity, fecal calprotectin and composite inflammatory oxidative stress indices. This case–control study included 121 adults recruited at the Teaching Hospital for Digestive and Liver Diseases, Medical City, Baghdad, from 9 February 2025 to 23 October 2025. A total of 88 patients who had confirmed ulcerative colitis and 33 healthy controls were included in the sample. There were active disease and remission. Standard immunochemical and colorimetric measures were taken of serum CRP, IL-6, MDA, TAC and SOD. qRT-PCR was used to determine the levels of circulating miR-21. Fecal calprotectin and Mayo endoscopic subscore also were noted. Correlations, group comparisons, effect sizes, ROC analysis and exploratory regression models were carried out. Compared with controls, patients with ulcerative colitis had higher CRP, IL-6, MDA, miR-21, fecal calprotectin, IOSI, and Advanced IOSI, and lower TAC and SOD (all $p < 0.001$). CRP, IL-6, MDA, fecal calprotectin, IOSI, Advanced IOSI, TAC and SOD were significantly higher in active disease than remission (all $p < 0.001$). The level of circulating miR-21 was higher in comparison to controls but lower in active disease than in remission ($p = 0.026$). There was a strong correlation between IOSI and Advanced IOSI and fecal calprotectin. There was very high discrimination of a number of markers in this resultsset using ROC including CRP, IL-6, fecal calprotectin, IOSI and Advanced IOSI. The results indicate that there is a strong association between ulcerative colitis, systemic inflammation and oxidative imbalance. It seems that circulating miR-21 can be relevant, yet its activity can vary in response to activity states, and be altered by treatment. Composite inflammatory-oxidative stress indexes were well-performing and potentially provide a convenient summary of multi-marker perturbation. Clinical adoption still needs to be externally validated.

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Keywords: ulcerative colitis, miR-21, oxidative stress, IL-6, fecal calprotectin biomarker

Introduction

Ulcerative colitis (UC) is a persistent inflammatory condition which begins at the rectum and then runs in a continuous manner through the colonic mucosa. The disease tends to have a relapsing and remitting pattern. The most frequent ones are rectal bleeding, diarrhea, urgency, abdominal pain, and weight loss. Pathways to cancer surveillance and nutrition, as well as quality of life and work capacity, can also be impaired by long-term disease.

These characteristics put UC as a clinical and a public health concern [1, 4].

Inflammatory bowel disease has had varying epidemiology. Previously high-burden areas were predominantly North America and Western Europe. Recent reviews indicate that the incidence and prevalence have increased in recently industrialized areas. The trend is highly apparent in Asia and other low-incidence environments. This transformation implies that interactions between environmental exposures, diet, urbanization, and host susceptibility are very strong in the expression of the disease [13, 5, 19]

This is an epidemiologic transition in the Middle East. The Arab world and Iran have systematic reviews that indicate that ulcerative colitis is becoming a known issue in the region though strong registry results is still lacking in most countries. This is important as local disease behavior, delay of diagnosis, and access to treatment, and biomarker performance may not conform to trends documented in Europe or North America. The regional results are still required, particularly in Iraq and similar environments [18, 22, 15].

The UC pathogenesis is complicated. It is characterized by the dysregulation of immune activation, epithelial barrier dysfunction, the microbial imbalance, and prolonged cytokine signalling. Some of the reviews tell about hyper-inflammatory mucosal immune responses involving the involvement of innate cells, T cells, chemokines and pro-inflammatory mediators. Interleukin-6 (IL-6) is significant as it connects mucosal stimulation to systemic inflammation and acute-phase cues. This inflammatory axis is reflected by C-reactive protein (CRP) which is commonly used in practice, but not specific to inflammation of the colon [6, 8, 9]. Oxidative stress is another major component of UC biology. Activated leukocytes and inflamed mucosa generate reactive oxygen species. When antioxidant defenses become insufficient, lipid peroxidation, protein oxidation, and DNA injury increase. Malondialdehyde (MDA) is commonly used as a marker of lipid peroxidation. Total antioxidant capacity (TAC) and superoxide dismutase (SOD) reflect the counter-regulatory antioxidant system. Reviews and clinical studies generally report increased oxidative damage and reduced antioxidant reserve in active inflammatory bowel disease [23, 20, 12].

Among fecal biomarkers, calprotectin is one of the most useful noninvasive markers of intestinal inflammation. It correlates with neutrophil migration into the intestinal lumen. It is often used to distinguish inflammatory disease from functional disorders and to monitor activity or mucosal healing in UC. Meta-analytic and regional studies have shown that fecal calprotectin is strongly associated with disease activity, although cut-off values vary across populations and assays [24, 3, 10]. There is an added intrigue, microRNAs. They are tiny non-coding RNAs that regulate the translation and stability of the messenger RNAs. The dysregulation of microRNA networks has been reported to be in inflammatory bowel disease. miR-21 is one of the most actively researched molecules as it is associated with epithelial injury, immune signaling, apoptosis, and barrier dysfunction. The reviews observe that miR-21 has a high potential to be used clinically, but its particular use may depend on the tissue, feces, serum, and disease stage [2, 14, 17]. The more recent Asian studies are also inclined to the biological role of miR-21 in UC. As one example, Ke *et al*. associated increased miR-21 levels with inflammatory activation and disease progression, with other studies indicating that the behaviour of serum or fecal microRNA might be context-dependent based on the compartment of sample and treatment. This means that miR-21 cannot be interpreted alone. It can prove more beneficial to be studied along with the classic inflammatory and oxidative stress indicators [11, 14].

Against this background, the current study analyzed the circulating levels of miR-21, biomarkers of oxidative stress and levels of inflammatory indices in patients with UC who were treated in a tertiary center in Baghdad. The comparison of patients with healthy controls was performed, the difference between active disease and remission, the correlation of the biomarkers with fecal calprotectin and endoscopic activity was evaluated, and whether composite inflammatory-oxidative stress indices could improve the interpretation of biomarkers in this cohort region [19, 18].

Materials and Methods

This case control study was done in the Teaching Hospital of Digestive and Liver Diseases, Medical City, Baghdad, Iraq. The collection of results and samples was done between 9 February 2025 and 23 October 2025. The Ethics Committee of Baghdad University -Baghdad Teaching Hospital, Iraq gave ethical approval to this study (Approval Reference No: REC/ARU/2025/0157 Date:10/1/2025). The informed consent was in writing by all the participants. The last sample had 121 adults. Eighty-eight patients with confirmed ulcerative colitis and thirty-three age- and sex-matched healthy controls were taken. Ulcerative colitis was diagnosed through clinical, endoscopic and histopathological criteria. Clinical and endoscopic findings were further used to classify patients into active disease or remission. Adults of 18 years and above. Other inflammatory or autoimmune illnesses, malignancy, active infection, recent non-standard immunomodulatory or antioxidant therapy were inclusion criteria. Demographic and clinical variables were measured. These were age, sex, duration of the disease, type of treatment used as well as response to treatment. Blood samples were taken through the venous blood and centrifuged.

Serum was stored at −80°C until analysis. Stool samples were collected for fecal biomarker assessment. CRP was measured by immunoturbidimetric assay using Roche Diagnostics reagent (Cat. No. 04628918190) on a Cobas analyzer. IL-6 was measured by sandwich ELISA using R&D Systems kit D6050. Oxidative stress and antioxidant markers were measured by standardized colorimetric assays. MDA was measured by the TBARS method with Cayman Chemical kit 10009055. TAC was measured with Sigma-Aldrich kit MAK187. SOD activity was measured with Cayman Chemical kit 706002.

Circulating miR-21 expression was quantified by qRT-PCR. Total RNA was extracted with the miRNeasy Mini Kit (Qiagen, Cat. No. 217004). Reverse transcription was performed with the TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems, Cat. No. 4366596). Amplification was carried out using TaqMan MicroRNA Assays for miR-21 (Assay ID 000397) on an Applied Biosystems 7500 Real-Time PCR System. Relative expression was calculated by the $2^{-\Delta\Delta Ct}$ method.

Fecal calprotectin was measured using a quantitative ELISA kit (Bühlmann fCAL, Cat. No. EK-CAL). Endoscopic disease activity was evaluated with the Mayo Endoscopic Subscore (0–3) by experienced gastroenterologists who were

blinded to laboratory findings. Composite inflammatory–oxidative stress indices, namely IOSI and Advanced IOSI, were calculated from CRP, IL-6, MDA, TAC, and SOD according to predefined study criteria. Standard laboratory equipment included a BioTek ELx800 or Thermo Scientific Multiskan FC microplate reader and an Eppendorf 5804R centrifuge.

Continuous variables were summarized as mean ± standard deviation. Categorical variables were presented as frequencies and percentages. Group comparisons were performed with independent-samples t tests or Mann–Whitney U tests when distributional assumptions were not satisfied, and categorical variables were compared with chi-square testing. Correlation analysis used Pearson or Spearman coefficients as appropriate. applying receiver operating characteristic (ROC) analyses for sensitivity and specificity, A two-sided p value below 0.05 was considered statistically significant.

Results

The study included 88 patients with UC and 33 healthy controls. Age was comparable between groups (47.42 ± 16.61 years in UC vs 48.85 ± 14.69 years in controls, p = 0.648). Sex distribution was also similar (p = 0.539). Within the UC group, 43 patients had active disease and 45 were in remission. Mean disease duration was 8.24 ± 3.78 years. Treatment distribution was balanced across biologic therapy (n = 32), 5-ASA (n = 29), and corticosteroid therapy (n = 27). Forty-six patients were classified as responders and 42 as non-responders.

Table 1: Baseline demographic and clinical characteristics of the study population.

Variable	UC	Control	p value
Age (years)	47.42 ± 16.61	48.85 ± 14.69	0.648
Female sex, n (%)	50 (56.8%)	16 (48.5%)	0.539
Disease duration (years)	8.24 ± 3.78	—	—
Disease activity, n	Active 43; Remission 45	—	—
Treatment type, n	Biologic 32; 5-ASA 29; Steroid 27	—	—
Treatment response, n	Yes 46; No 42	—	—

Patients with UC showed a broad inflammatory and oxidative disturbance. CRP, IL-6, MDA, circulating miR-21, fecal calprotectin, IOSI, and Advanced IOSI were all markedly higher in UC than in controls. In contrast, TAC and SOD activity were markedly lower. Effect sizes were large for all major biomarkers. The strongest standardized differences were observed for circulating miR-21, IOSI, and Advanced IOSI. These results support the first study objective and indicate that the disease signal in this cohort was not limited to one biomarker family.

Table 2: Comparison of inflammatory, oxidative stress, and molecular markers between UC and control groups.

Variable	UC (n=88)	Control (n=33)	p value	Cohen's d
CRP (mg/L)	38.57 ± 27.21	1.89 ± 0.73	<0.001	1.58
MDA (nmol/mL)	6.73 ± 3.38	1.23 ± 0.41	<0.001	1.90
TAC (mmol/L)	1.19 ± 0.56	2.68 ± 0.53	<0.001	-2.71
IL-6 (pg/mL)	73.13 ± 52.93	5.48 ± 2.81	<0.001	1.49
SOD activity (U/mL)	132.20 ± 65.43	287.27 ± 35.98	<0.001	-2.63
Circulating miR-21 (relative expression)	3.90 ± 1.12	1.05 ± 0.32	<0.001	2.94
Fecal calprotectin (ug/g)	776.91 ± 445.28	55.39 ± 21.40	<0.001	1.89
Endoscopic score	2.07 ± 0.83	0.00 ± 0.00	<0.001	2.92
IOSI	8.23 ± 3.02	1.06 ± 0.59	<0.001	2.76
Advanced IOSI	10.25 ± 3.13	1.51 ± 0.73	<0.001	3.23

When UC patients were stratified by activity status, the active group showed substantially higher CRP, MDA, IL-6, fecal calprotectin, IOSI, and Advanced IOSI than the remission group. TAC and SOD activity were substantially lower in active disease. All of these contrasts were highly significant. Circulating miR-21 showed a different pattern. It remained elevated in the patient cohort overall, but it was modestly lower in active disease than in remission (3.63 ± 1.03 vs 4.16 ± 1.15, p = 0.026). Endoscopic score did not differ significantly between active disease and remission in this resultsset (p = 0.315).

Table 3: Comparison of biomarkers between active ulcerative colitis and remission.

Variable	Active (n=43)	Remission (n=45)	p value	Cohen's d
CRP (mg/L)	63.25 ± 16.83	14.99 ± 5.38	<0.001	3.90
MDA (nmol/mL)	9.53 ± 2.54	4.05 ± 1.19	<0.001	2.78
TAC (mmol/L)	0.69 ± 0.17	1.67 ± 0.32	<0.001	-3.78
IL-6 (pg/mL)	119.78 ± 35.95	28.54 ± 12.10	<0.001	3.43
SOD activity (U/mL)	74.59 ± 20.47	187.26 ± 41.50	<0.001	-3.42
Circulating miR-21 (relative expression)	3.63 ± 1.03	4.16 ± 1.15	0.026	-0.48
Fecal calprotectin (ug/g)	1155.42 ± 329.39	415.22 ± 121.12	<0.001	3.01
Endoscopic score	1.98 ± 0.86	2.16 ± 0.80	0.315	-0.22
IOSI	10.91 ± 1.66	5.68 ± 1.32	<0.001	3.49
Advanced IOSI	12.94 ± 1.81	7.67 ± 1.55	<0.001	3.13

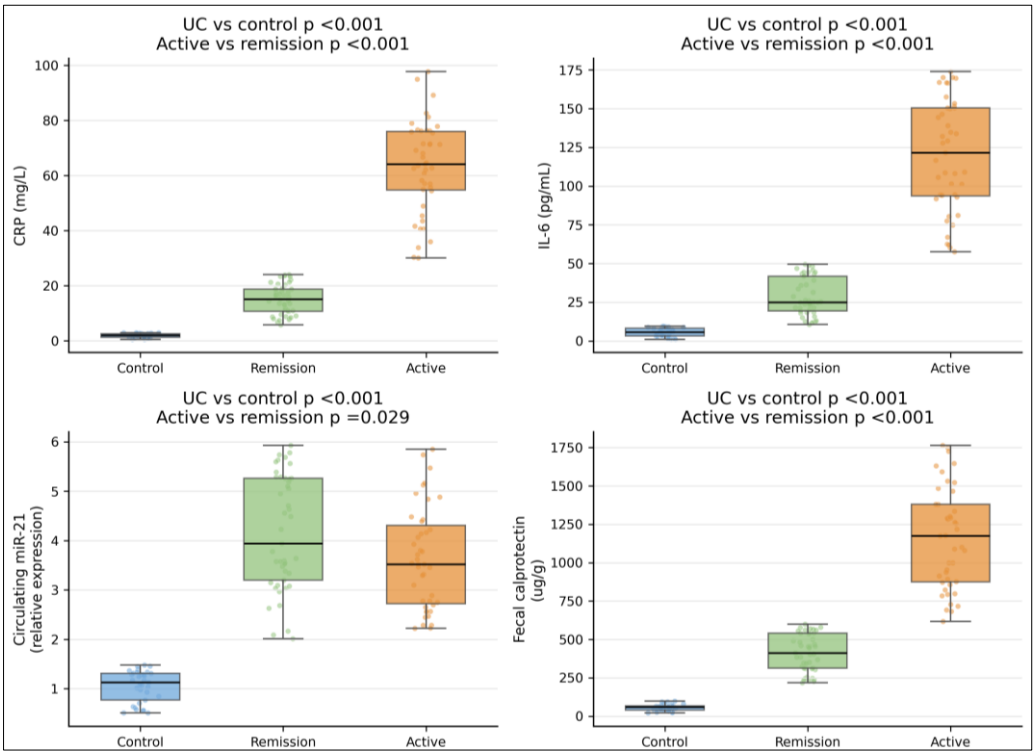


Fig 1: Distribution of selected biomarkers across controls, remission, and active disease.

ROC analysis showed excellent discrimination in this resultsset. For distinguishing UC from controls, CRP, IL-6, circulating miR-21, fecal calprotectin, IOSI, and Advanced IOSI each showed an AUC of 1.000. TAC and SOD also performed strongly, with AUC values above 0.97. For distinguishing active disease from remission, CRP, MDA, IL-6, SOD, fecal calprotectin, and IOSI all showed near-perfect or perfect discrimination. By contrast, miR-21 alone had only modest activity-state discrimination, with an AUC of 0.635. A multi-marker cross-validated logistic model yielded an AUC of 1.000 for both classification tasks in this resultsset. Because these values are unusually high, they should be interpreted as internal performance only and not as proof of immediate clinical generalizability.

Table 4: ROC performance for discrimination between UC and controls.

Marker	AUC	Optimal cutoff	Sensitivity (%)	Specificity (%)
CRP (mg/L)	1.000	>= 5.84	100.0	100.0
IL-6 (pg/mL)	1.000	>= 10.60	100.0	100.0
Circulating miR-21 (relative expression)	1.000	>= 2.01	100.0	100.0
Fecal calprotectin (ug/g)	1.000	>= 218.00	100.0	100.0
IOSI	1.000	>= 3.17	100.0	100.0
Advanced IOSI	1.000	>= 4.31	100.0	100.0
TAC (mmol/L)	0.975	<= 1.85	83.0	100.0
SOD activity (U/mL)	0.983	<= 219.14	88.6	100.0

Table 5: ROC performance for discrimination between active disease and remission.

Marker	AUC	Optimal cutoff	Sensitivity (%)	Specificity (%)
CRP (mg/L)	1.000	>= 30.06	100.0	100.0
MDA (nmol/mL)	1.000	>= 6.01	100.0	100.0
TAC (mmol/L)	1.000	<= 1.00	100.0	97.8
IL-6 (pg/mL)	1.000	>= 57.56	100.0	100.0
SOD activity (U/mL)	1.000	<= 109.64	100.0	100.0
Circulating miR-21 (relative expression)	0.635	<= 4.48	81.4	46.7
Fecal calprotectin (ug/g)	1.000	>= 617.00	100.0	100.0
IOSI	1.000	>= 8.04	100.0	100.0
Advanced IOSI	0.991	>= 9.48	100.0	91.1

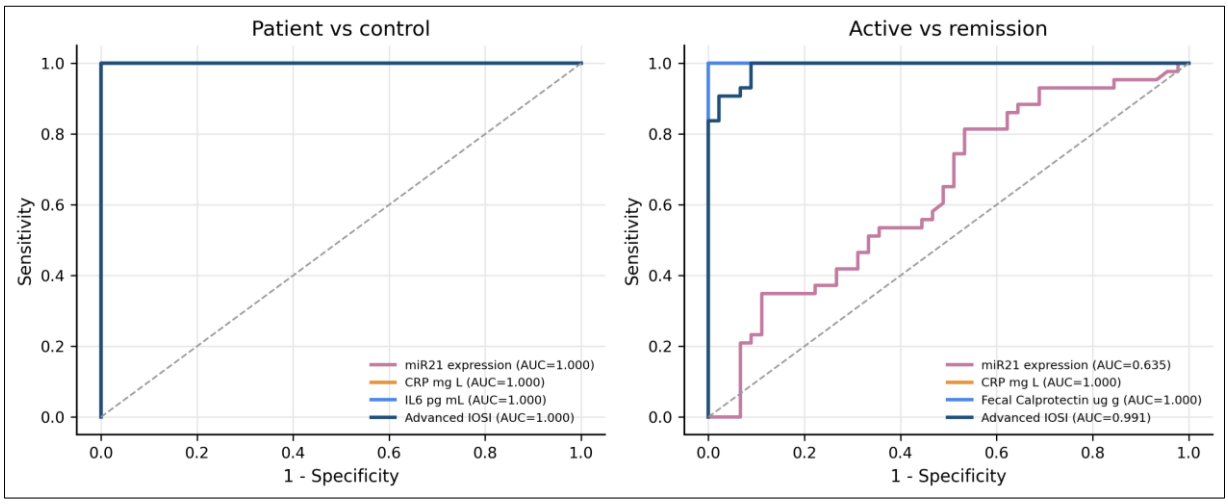


Fig 2: ROC curves for selected biomarkers in the two main classification tasks.

Among patients with UC, fecal calprotectin correlated strongly with CRP (rho = 0.718), MDA (rho = 0.741), IL-6 (rho = 0.698), IOSI (rho = 0.731), and Advanced IOSI (rho = 0.710). It correlated inversely with TAC (rho = −0.746) and SOD (rho = −0.765). The correlation with circulating miR-21 was weak and not statistically significant (rho = −0.193, p = 0.071). The same pattern was observed in the correlation matrix, whereby miR-21 was loosely correlated with the tight inflammatory-oxidative cluster. In an exploratory logistic model, standardized Advanced IOSI continued to be significantly related to active disease, but miR-21 did not continue to be significantly important after individual control. The log-IOSI and log fecal calprotectin were strongly predicted by a log-IOSI, and the log-miR-21 did not in an exploratory linear model. These results indicate that miR-21 might be able to contain biological results, whereas composite inflammatory-oxidative indices were more direct in this cohort to capture the disease burden.

Table 6: Correlation of selected markers with fecal calprotectin in patients with UC.

Marker	Spearman rho	p value
CRP (mg/L)	0.718	<0.001
MDA (nmol/mL)	0.741	<0.001
TAC (mmol/L)	-0.746	<0.001
IL-6 (pg/mL)	0.698	<0.001
SOD activity (U/mL)	-0.765	<0.001
Circulating miR-21 (relative expression)	-0.193	0.071
IOSI	0.731	<0.001
Advanced IOSI	0.710	<0.001

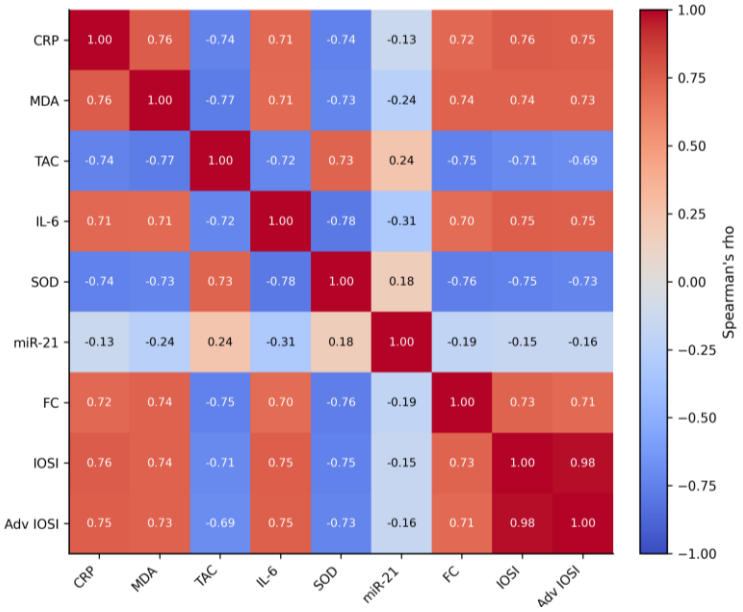
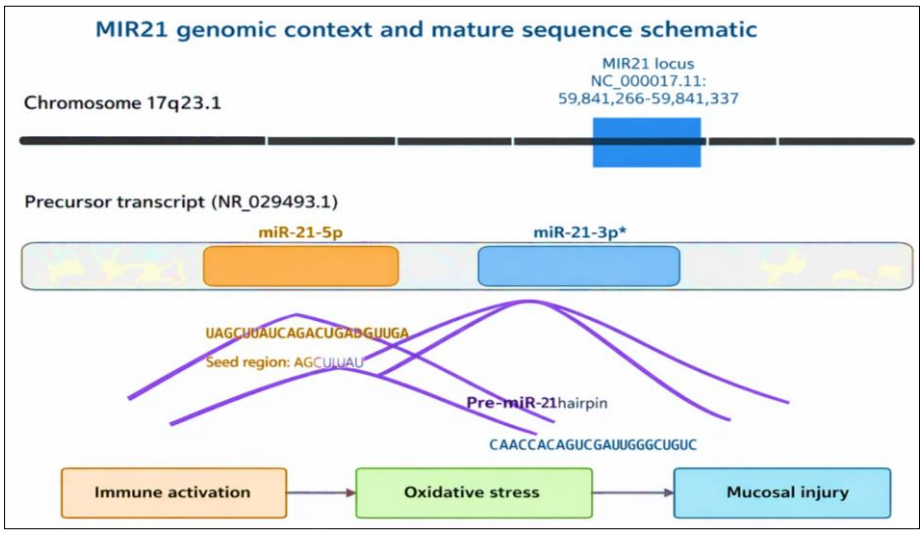


Fig 3: Spearman correlation matrix for inflammatory, oxidative, and molecular biomarkers among patients with UC.



Source note: sequence and locus modified by NCBI Gene MIR21 (Gene ID 406991; RefSeq NR_029493.1) and miRBase MIMAT0000076.

Fig 4: MIR21 genomic setting and mature sequence schematic as a means of facilitating interpretation of circulating miR-21 results.

The type of treatment did not significantly differ in terms of activity state (chi-square p = 0.393) or response classification (chi-square p = 0.823). The levels of most biomarkers were also not significantly different among categories of treatment-response. The only constant exception was circulating miR-21 that was reduced in responders compared to non-responders. This result is considered as exploratory since the sample size was small and the treatment groups were non-homogenous.

Table 7: Selected biomarkers according to response to treatment in the UC group.

Marker	Responder (n=46)	Non-responder (n=42)	p value
CRP (mg/L)	39.52 ± 26.43	37.53 ± 28.31	0.735
IL-6 (pg/mL)	81.38 ± 56.26	64.08 ± 48.07	0.124
Circulating miR-21 (relative expression)	3.66 ± 1.05	4.17 ± 1.14	0.030
Fecal calprotectin (ug/g)	811.09 ± 470.59	739.48 ± 418.24	0.452
IOSI	8.58 ± 3.20	7.86 ± 2.80	0.264
Advanced IOSI	10.63 ± 3.26	9.83 ± 2.97	0.233

Discussion

There was a consistent pattern in this study. UC patients were characterized by increased inflammatory load, oxidative stress, and increased miR-21 in the circulation compared to healthy controls. Active disease patients also had poorer inflammatory and oxidative profiles compared to the remission. These key findings are aligned with the overall idea that UC is a disease that involves chronic immune activation and tissue damage, and that laboratory correlates are elevated in concert with disease burden [4, 8].

The inflammatory results were significant. CRP and IL-6 were significantly increased in UC and both increased more in active disease. This is consistent with previous research that IL-6 correlates with disease severity and that circulating IL-6 is equivalent to inflammatory burden in inflammatory bowel disease. These findings are also consistent with more recent studies that indicate that CRP based indices can still be used in the assessment of activity despite the fact that they are not disease-specific markers [21, 16, 7].

Fecal calprotectin was also very effective in this study. It distinctly divided patients and controls as well as active disease and remission. This finding is consistent with previous Middle Eastern studies and even larger systematic reviews. The good correlation between fecal calprotectin and IOSI-related markers in our cohort also confirms the hypothesis that luminal neutrophil activity and systemic inflammation tends to shift concurrently in UC, particularly when there is an active disease [24, 3, 10].

The profile of the oxidative stress was also quite easy to read. The highest MDA was in UC and the highest in active disease. TAC and SOD migrated opposite to one another. This trend is very biologically plausible. Oxidative stress is augmented as the inflamed mucosa produces reactive oxygen species, and the antioxidant defenses are either depleted or overwhelmed. This was also reported among Turkish patients and subsequent reviews that synthesized oxidative imbalance among inflammatory bowel disease cohorts [23, 20, 12].

One of the interesting findings was the circulation of miR-21. In the current study, miR-21 was evidently significantly elevated in the UC as compared to controls. This concurs with previous studies that have reported miR-21 as one of the most disregulated microRNAs in intestinal inflammation. MiR-21 is associated with epithelial damage, inflammatory signaling, and barrier dysfunction, which have been reviewed and mechanistically performed to support its biological relevance in UC [2, 14, 17].

The result of the circulating miR-21 activity-state was not clean, though. Active disease presented with a slight decrease in miR-21 circulation as compared to remission in our cohort. This is unlike in part of the Asian reports such as that of Ke *et al*. where there was an increased miR-21 that followed a more severe disease. There are a number of reasons. To begin with, circulating and tissue compartments might not behave in a similar manner. Second, exposure to treatment can change the kinetics of release. Third, alterations in immune-cell composition can alter serum microRNA pools. Due to

these reasons, miR-21 cannot be considered as an independent severity marker and should be interpreted [11, 14]. The best result of this study was given by the composite indices IOSI and Advanced IOSI. These indices are a combination of inflammatory and oxidative indicators into an integrated signal. They demonstrated large effect sizes, good correlations with fecal calprotectin and near-perfect ROC in our cohort. That does not imply that they are universal best biomarkers. It implies that the inflammatory-oxidative axis was better represented by integrated markers in this resultsset than by any single marker. The idea aligns with the precision-medicine reasoning, as multi-marker panels tend to perform better than single tests [1]; [12].

The regional context is important. Inflammatory bowel disease is on the rise in the burden of the disease in Asia, and the Arab world is not left behind with increasing awareness of UC. Nevertheless, numerous biomarker studies continue to be based in Europe, China, or North America. Information in Iraq is scarce. That is why the current study can be considered valuable in addition to the biomarker results. It gives a local profile that classic inflammatory markers, oxidative stress markers, fecal calprotectin, and miR-21 are all possible to be analyzed simultaneously in a Baghdad cohort. It can be utilized in comparisons on a regional level and multicenter validation in the future [19, 15, 18].

Conclusion

In this cohort, ulcerative colitis in Baghdad was found to have powerful inflammatory and oxidative signature. CRP, IL-6, MDA, fecal calprotectin, IOSI, and Advanced IOSI levels rose evidently in the patients, particularly in active disease. TAC and SOD went in the negative direction. There was also an increased level of circulating miR-21 in UC compared to healthy controls. Nevertheless, its trend between states of activity was more complicated, as the values were a bit lower in active disease than in remission. This implies that the expression of miR-21 in the circulation could be indicative of more than mere disease severity. Inflammatory-oxidative indices based on composite indices provided the most consistent overall signal in this resultsset. They were well correlated with fecal calprotectin and had very high classification performance. The results favour the concept of multi-marker evaluation instead of using a single biomarker. Nonetheless, the findings are to be viewed with some caution since this was a one-center study and a number of ROC values were quite high. Greater regional researches are required. The future research should involve a comparison of serum and tissue miR-21, validate the thresholds of IOSI, and test the ability of these markers to predict relapse, treatment response, and mucosal healing in the long term.

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