

Review

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Review

Potential miRNAs as Diagnostic Biomarkers for Differentiating Disease States in Ulcerative Colitis: A Systematic Review

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Abstract

Background: Ulcerative colitis (UC) is a chronic inflammatory disease that affects the colon, triggering persistent inflammation and ulceration, resulting in a severe impact on patients' quality of life. Currently, the standard diagnostic methods for UC include invasive procedures such as colonoscopy and the use of non-specific inflammatory markers like C-reactive protein, which can be inconvenient or painful and lack specificity. This underscores the need for non-invasive and highly specific biomarkers for UC. MicroRNAs (miRNAs) are small non-coding RNAs, typically 22 nucleotides in length, which are well described as gene expression regulators. Several studies have reported their differential expression in various pathological conditions, including UC. Due to their role in gene regulation and stability in biological fluids, miRNAs present a promising opportunity as biomarkers. This systematic review explores the potential use of miRNAs as diagnostic biomarkers to distinguish between active and inactive ulcerative colitis. **Methods:** Following PRISMA guidelines and based on inclusion and exclusion criteria, seven studies, encompassing a total of 514 participants (181 with active UC and 116 with inactive UC), were included. **Results:** Multiple miRNAs exhibiting differential expression between active and inactive UC were identified. Most notably, miR-21, miR-126, miR-146b-5p, and miR-223 exhibited consistent upregulation in active UC, suggesting their potential as diagnostic biomarkers. Supporting these findings is the fact that these miRNAs are involved in inflammatory pathways, further highlighting their relevance to the pathogenesis of UC. **Conclusions:** This review emphasizes the need for further validation studies with larger cohorts to confirm the utility of miRNAs as diagnostic tools in UC, which could enhance non-invasive disease monitoring and inform therapeutic decision-making.

Keywords: ulcerative colitis (UC); MicroRNAs; active ulcerative colitis (aUC); inactive ulcerative colitis (iUC); biomarkers

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder that affects the colon and rectum. It is distinguished by continuous inflammation without healthy areas between affected regions. This inflammation is confined to the rectum and large intestine, specifically targeting the mucosal layers of the epithelium [1]. A hallmark of UC is the formation of inflammation-induced ulcers in the colon barrier. Symptoms include rectal bleeding, abdominal pain (usually in the lower left quadrant), need to defecate, and bloody diarrhea. Complications that typically arise include colonic issues such as toxic megacolons, perforations, and colitis-associated cancer. Extra-intestinal complications involve arthritis, primary sclerosing cholangitis (PSC), weight loss, anemia, and blood clots (thromboembolism), all of which significantly affect an individual's quality of life. The diagnosis is based on medical history, along with radiographic, histological, and endoscopic examinations [1,2]. Treatment options typically include immunosuppressants, anti-inflammatories, biologics, and surgery for severe cases [3–5]. Although its precise etiology is uncertain, UC is thought to have a

complex etiology that includes both environmental and genetic variables [6]. Specific data on the global prevalence and incidence of UC are limited. However, inflammatory bowel disease (IBD) in general has a high prevalence in developed or industrialized countries, possibly due to longer life spans with disability, while its incidence appears to be decreasing. Conversely, newly or rapidly industrializing countries are experiencing an increase in incidence. For instance, the annual prevalence of UC per 100,000 persons increased significantly from 5 in 2010 to 98 in 2019 in Japan, and from 158 to 233 in the US during the same period. In the UK, as of December 2018, the prevalence and incidence of UC were reported to be 397 and 15.7 per 100,000 people, respectively, with age being a major factor influencing these trends [7–10]. Currently, UC diagnosis and monitoring rely on invasive methods like colonoscopy, alongside non-specific biomarkers such as C-reactive protein and erythrocyte sedimentation rate. While fecal calprotectin is more specific, there remains a need for improved biomarkers. MicroRNAs (miRNAs) have emerged as promising biomarkers for a variety of diseases due to their easy accessibility, and high stability, specificity, and sensitivity [11–14]. They are stable in numerous biological samples, including blood and other body fluids, and can be detected with great sensitivity. MiRNAs are small non-coding RNAs, typically 18-22 nucleotides in length, primarily involved in regulating gene expression, and have been associated with various physiological and pathological conditions, including UC. Their biogenesis involves transcription from DNA into pri-miRNA, processing into pre-miRNA, and finally maturation into miRNA. Their mechanism of action includes interaction with the 3' UTR of target mRNA, leading to either target degradation or repression. Their presence has been detected in blood, feces, and tissue, and they have been found to be quite stable, making them excellent candidates as non-invasive biomarkers [12,15,16]. Therefore, the purpose of this systematic review is to address the question: "Do miRNAs possess the potential to serve as biomarkers for differentiating ulcerative colitis based on disease state?" This is conducted in line with the PICO ("population", "intervention", "comparison", "outcome") approach.

1. Methods

2.1. Search Strategy and Eligibility Criteria

The search for this systematic review was conducted from inception till 4th September 2024, in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines and registered on PROSPERO with registration No CRD42024597537 [17]. Databases utilized included PubMed, Embase and Web of Science. Search terms used included ("mir") OR ("microrna") OR ("mirna") AND ("biomarkers") AND ("ulcerative colitis") OR ("active ulcerative colitis") OR ("inactive ulcerative colitis"). Detailed search strategy is given in Table 1.

Table 1. Detailed search strategy.

Database	Keywords	Results
PubMed	("microRNA" OR "miRNA" OR "mir" OR "microRNAs" OR "miRNAs")	222,472
	("biomarker" OR "biomarkers" OR "diagnostic marker" OR "molecular marker")	927,326
	("ulcerative colitis" OR "active ulcerative colitis" OR "inactive ulcerative colitis" OR "remission ulcerative colitis" OR "flare ulcerative colitis" OR "quiescent ulcerative colitis")	66,276
	#1 AND #2 AND #3	117
Web of Science	microRNA OR miRNA OR mir OR microRNAs OR miRNAs AND biomarker OR biomarkers OR diagnostic marker OR molecular marker AND ulcerative colitis OR active ulcerative colitis OR inactive ulcerative colitis OR remission ulcerative colitis OR flare ulcerative colitis OR quiescent ulcerative colitis	712

	microRNA OR miRNA OR mir OR microRNAs OR miRNAs AND biomarker OR biomarkers OR diagnostic marker OR molecular marker AND ulcerative colitis OR active ulcerative colitis OR inactive ulcerative colitis OR remission ulcerative colitis OR flare ulcerative colitis OR quiescent ulcerative colitis	276
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Screening of identified records was performed by two independent investigators (P.C.M and A.U.K) by title and abstract first, and later full text screening was carried out. Studies fulfilling the pre-defined inclusion criteria utilizing PICO approach were included as outlined in Table 2.

Table 2. PICO based inclusion and exclusion criteria.

Parameters	Inclusion Criteria	Exclusion Criteria
Population	Adult Individuals with a Confirmed Diagnosis of Ulcerative Colitis and Differentiation based on Disease State	Studies about adult Individuals with non-UC conditions (e.g., Crohn's disease, general IBD, etc.).
Intervention	miRNAs as Diagnostic Tool to Assess UC Disease State	Studies that use any other biomolecules as biomarkers.
Comparison	N/A	N/A
Outcome	miRNAs as Diagnostic Biomarker for Differentiating Active and Inactive UC	No Significant change in miRNA expression level capable of differentiating Active UC from Inactive UC

2.2. Quality Assessment and Critical Appraisal

Quality assessment of each individual study was carried out using the Newcastle–Ottawa Scale (NOS), which is based on three broad criteria the first being the Selection of population being studied, second Comparability checks for variables other than what is being studied and how well these are taken care of, and lastly how accurate are the procures carried out during these studies and are the same for both sets of populations under study. The assessment of all studies is presented in Table 3. The most frequently encountered risk of bias was that associated with control of confounding factors (all studies) and attrition bias (all studies). By adding up all the individual criteria to get the total score for each individual study according to which, five studies (71%) scored (≥56%) classified as “fair” quality with “moderate risk of bias” while two studies (29%) scored (77.77%) were classified as “good” quality having “low risk of bias”.

Table 3. Quality assessment of studies based on Newcastle Ottawa Scale (NOS).

Author, Year	Study Design	NOS Score		
		Selection	Comparability	Outcome/Exposure
Feng et al., 2012	Case-Control	☆☆☆☆		☆☆
Coskun et al., 2013	Cohort	☆☆☆☆		☆
Van der Goten et al., 2014	Case-Control	☆☆☆☆	☆	☆☆
Schönauen et al., 2017	Cohort	☆☆☆☆		☆
Yahong et al., 2018	Case-Control	☆☆☆☆		☆☆
Peng et al., 2019	Cohort	☆☆☆☆	☆	☆☆
El Sabbagh et.al., 2023	Case-Control	☆☆☆☆		☆☆

Study quality was assessed using the Newcastle-Ottawa Scale (NOS), covering Selection (4 stars), Comparability (2 stars), and Outcome/Exposure (3 stars). Scores range from 0 to 9, with ≥7 indicating high quality, 4–6 moderate, and <4 low. Assessments were performed independently, with disagreements resolved by consensus.

2.3. Data Extraction

Two reviewers independently extracted data using a standardized form. Information collected included study characteristics (first author, year, country, design), participant details (sample size, age, sex, disease status), and miRNA measurement methods (specimen type, extraction and quantification platforms, normalization techniques). Key findings on differential miRNA expression between active and inactive ulcerative colitis were recorded, along with reported diagnostic implications. Discrepancies were resolved through discussion or third-party consultation.

2.4. Data Synthesis

A narrative synthesis was conducted to evaluate the diagnostic potential of miRNAs in distinguishing active from inactive ulcerative colitis. Studies were analyzed thematically, focusing on consistent miRNA expression patterns, direction of regulation, and association with disease activity markers. Findings were grouped by miRNA identity and clinical context to identify recurring biomarkers and methodological trends.

2. Results

Seven studies have been included by following the search criteria in this systematic review. Studies included a total of 514 participants (Active UC 181, Inactive UC 116). Detailed selection strategy is given in Figure 1. Data extracted from each included study comprised of study characteristics (authors, year, design), participant details (sample size, demographics), miRNA measurement methods and key findings about miRNAs expression pattern in each individual study in different disease states, this information is collected and presented in Table 4 and Table 5.

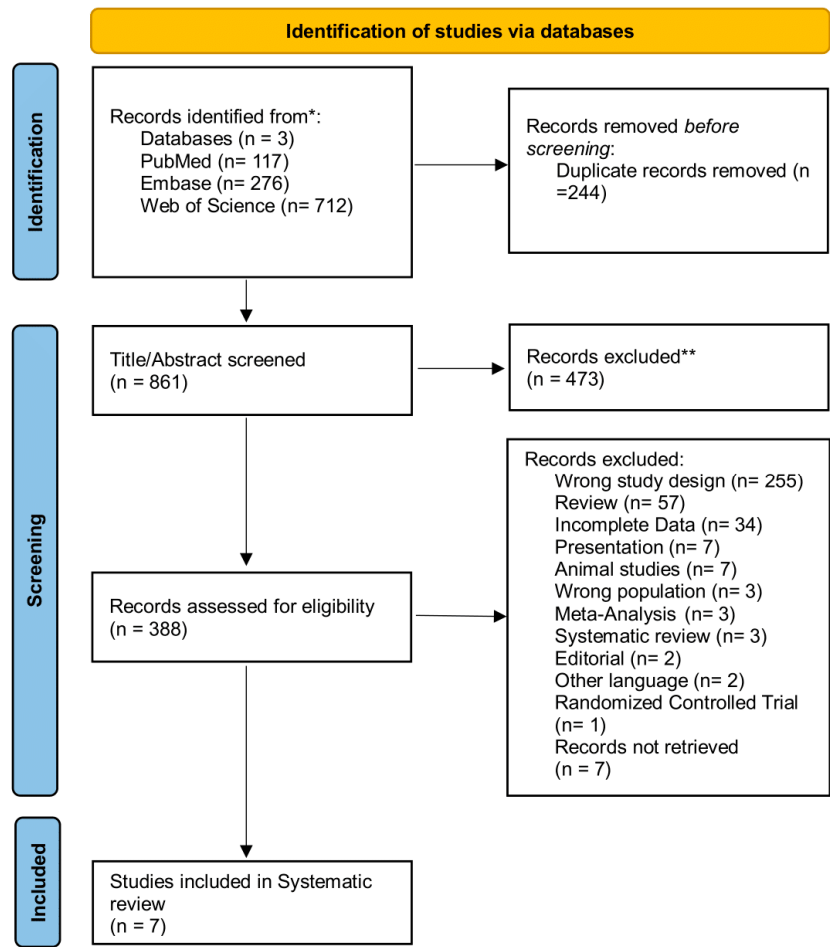


Figure 1. PRISMA Flow Chart for Search Strategy.

Table 4. General characteristics of included studies.

Author and Year	Study Design	Sample Type	Sample Size (aUC/iUC/HC)	Gender (M/F)	miRNA Measurement
Feng et al., 2012	Case-control	Pinch biopsies	12/10/15	5/7, 4/6, 7/8	qRT-PCR
Coskun et al., 2013	Cohort	Pinch biopsies	20/19/20	9/11, 6/13, 10/10	miRNA microarray, qPCR
Van der Goten et al., 2014	Case-control	Colonic mucosal biopsies	10/7/10	6/4, 4/3, 5/5	miRNA microarray, qRT-PCR
Schönauen et al., 2017	Cohort	Serum and Fecal Samples	10/8/35	4/6, 4/4, 14/21	qPCR
Yahong et al., 2018	Case Control	Fecal Samples	41/25/66	NR	miRNA microarray, qPCR
Peng et al., 2019	Cohort	Serum Samples	55/45/41	NR	qRT-PCR
El Sabbagh et al., 2023	Case Control	Blood Samples	33/2/30	NR	qPCR

Table 5. Summary of Differentially Expressed Circulating miRNAs in Ulcerative Colitis Stratified by Disease Activity.

Author (Year)	miRNAs Studied	Disease Duration (yrs) mean (range)	Disease Activity Method	Key Findings
Feng et al. (2012)	miR-21, miR-126, miR-375	1.8 (0.5–4) aUC, 4 (2–6) iUC	UCDAI: 0.9 (0–2) iUC, 8.91 (8–10) aUC	miR-126 (↑18-fold, P < 0.05) in aUC vs HC. miR-21 (↑14.7-fold, P < 0.05) in aUC vs HC. No significant changes in iUC vs HC. miR-20b (↑ P < 0.05) in aUC vs HC. let-7e (↑ P < 0.05) in iUC vs HC. miR-98 (↑ P < 0.05) in iUC vs aUC and HC. miR-125b-1 (↑ P < 0.01) in aUC vs HC.
Coskun et al. (2013)	miR-20b, -99a, -203, -26b, -98, -125b-1, let-7e	15/5 aUC, 8/11 iUC	Mayo: 0 (0-1) iUC, 6 (2-12) aUC	
Van der Goten et al. (2014)	miR-21-5p, miR-31-5p, miR-146a-5p, miR-155-5p, miR-650, miR-196b-5p, miR-200c-3p, miR-375, miR-200b-3p, miR-422a	7.1 (0.6–20.1) aUC, 6.6 (4.0–14.4) iUC	Mayo: 0 (±0.5) iUC, 8 (±1.5) aUC	miR-21-5p, miR-31-5p, miR-146a-5p, miR-155-5p, miR-650, miR-375 (↑) in aUC vs HC. miR-196b-5p, miR-196b-3p, miR-200c-3p (↓) in aUC vs HC.
Schönauen et al. (2017)	miR-16, miR-21, miR-155, miR-223	NR	Mayo: ≤5.27 iUC, >5.27 aUC	miR-21, miR-223 (↑) in iUC vs HC serum. miR-21, miR-155 (↓) in aUC vs iUC serum. miR-16, miR-155, miR-223 (↓) in aUC vs HC feces. miR-155 (↓) in aUC & iUC vs HC feces.
Yahong et al. (2018)	miR-199a, miR-223-3p, miR-1226, miR-548ab, miR-515-5p	6.5 aUC, 11.5 iUC	Modified Mayo: ≤2 iUC, >2 aUC	miR-515, miR-548ab, miR-1226 (↓) in aUC vs HC and iUC vs HC. miR-199a-5p, miR-223-3p (↑) in aUC vs HC and iUC.
Peng et al. (2019)	miR-197-5p, miR-603, miR-145-3p, miR-574-3p, miR-34a-5p, miR-323a-3p, miR-141-3p, miR-146b-5p, miR-193b-3p, miR-31-5p, miR-27a, miR-27b, miR-944, miR-204-3p, miR-206, miR-24-1-5p, miR-135b-5p	NR	Mayo: ≤2 iUC, >2 aUC	miR-146b-5p (↑) in aUC vs iUC and HC.
El Sabbagh et al. (2023)	miR-106a, miR-146b	NR	Mayo: No specific cut values	No significant change between aUC and iUC.

aUC = active ulcerative colitis; iUC = inactive ulcerative colitis; HC = healthy controls; UCDAI = Ulcerative Colitis Disease Activity Index; Modified Mayo and Mayo = clinical scoring systems for UC activity; NR = not reported; ↑ = increased expression relative to comparison group; ↓ = decreased expression relative to comparison group; P < 0.05 and P < 0.01 indicate levels of statistical significance reported in the respective studies.

3. Discussion

The data from the included studies reveal a significant variation in miRNA expression levels that correlate with disease activity in ulcerative colitis. Such findings offer valuable insights into miRNAs as potential diagnostic biomarkers for disease activity and progression in UC. This aligns with several reports that provide evidence of the promising role of miRNAs as diagnostic biomarkers of the development of colitis-associated cancer [18–20].

In this systemic review we have highlighted trends and patterns that result from differential expressions of miRNAs in active ulcerative colitis (aUC) and inactive ulcerative colitis (iUC).

In particular, Feng et al. (2012) showed a significant upregulation of miR-21 (14.7-fold) and miR-126 (18-fold) in colonic tissues of aUC vs healthy controls (HC) [15]. In contrast, there were no noticeable alterations in miRNA expression levels when comparing iUC to HC. These findings highlight the potential role of miR-21 and miR-126 as diagnostic biomarkers specifically for active UC. Indeed, miR-21's role in the negative regulation of PDCD4 [21,22], RhoB [21], and NOS-2 induced cellular damaging, while its suppression of PTEN led to PTEN repression an increase of PI3K/Akt activity, cellular pathways that may be involved in the development of UC. Thus, the overexpression of miR-21 in macrophages could potentially trigger oxidative stress-induced cellular damage, which could be a contributing factor involved in UC pathogenesis [23–26].

Another study conducted by Coskun et al. (2013) identified a distinct set of differentially expressed miRNAs in aUC and iUC compared to HCs, such miRNAs include miR-20b ($\uparrow P < 0.05$) in aUC vs HC, miR-125b-1 ($\uparrow P < 0.01$) in aUC vs HC, let-7e ($\uparrow P < 0.05$) in iUC vs HC, miR-98 ($\uparrow P < 0.05$) in iUC vs aUC and HC [23,24,27,28]. Following up on these results, Van der Goten et al. (2014) expanded the panel of miRNAs with similar expression patterns and observed an increase of miR-21-5p, miR-31-5p, and miR-155-5p in aUC compared to HC [25,29–32]. To elucidate the functional relevance of these miRNAs, several have been investigated in the context of specific inflammatory signaling pathways. For instance, let-7e seems to be involved in Toll-like receptor (TLR)-associated signaling pathways, while miR-98 targeted pro-inflammatory genes such as MYC and IL-6 [33–36]. Notably, miR-155 inhibition reduced DSS-induced colonic damage, prevented the development of Th17 cells, and alleviated colitis associated inflammation by inactivating NF- κ B signaling [37,38]. Studies carried out by Yahong et al. (2018) revealed that miR-199a-5p and miR-223-3p were upregulated in aUC compared to iUC and HCs [38]. Specifically, miR-199a-5p was involved in intestinal barrier dysfunction, whereas the elevated levels of miR-223-3p might contribute to UC pathogenesis by negatively regulating autophagy and IKK α inhibition, which is a potential regulator of inflammation [24,39–41].

Interestingly, Peng et al. (2019) [42], reported that miR-146b-5p was overexpressed in serum samples of aUC in comparison to both iUC and HCs. These findings were further supported by El Sabbagh et al. (2023) [43], who confirmed the potential of miR-146b-5p as a biomarker indicative of active disease. Remarkably, multiple studies have identified an overlap in the overexpression of several miRNAs including miR-21, miR-223, and miR-146b-5p suggesting their promise as diagnostic biomarkers for monitoring disease activity in UC.

The consistent overexpression of miR-21, miR-223, and miR-146b-5p across multiple studies highlights their strong potential as diagnostic biomarkers. Moreover, their established roles in inflammatory pathways further support their suitability as targets for clinical research in ulcerative colitis.

4. Conclusion

Collectively these findings emphasize the involvement of specific miRNAs in ulcerative colitis pathogenesis indicating their potential as biomarkers for assessing disease activity. Future investigations involving larger cohorts are essential to further validate the diagnostic potential of miRNAs, and to explore their therapeutic applications which could ultimately enhance the clinical management of ulcerative colitis.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

UC	Ulcerative Colitis
aUC	Active Ulcerative Colitis
iUC	Inactive Ulcerative Colitis
HC	Healthy Controls
miRNA	MicroRNA
qPCR / qRT-PCR	Quantitative Real-Time Polymerase Chain Reaction
NOS	Newcastle-Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
UCDAI	Ulcerative Colitis Disease Activity Index
PICO	Population, Intervention, Comparison, Outcome
PSC	Primary Sclerosing Cholangitis
NF-κB	Nuclear Factor Kappa-light-chain-enhancer of Activated B cells
DSS	Dextran Sulfate Sodium
PI3K/Akt	Phosphoinositide 3-Kinase/Protein Kinase B
PTEN	Phosphatase and Tensin Homolog
IKKα	IκB Kinase α
TLR	Toll-Like Receptor
mRNA	Messenger RNA
UTR	Untranslated Region

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