

ASSOCIATION OF MICRO-RNA EXPRESSION PROFILES WITH DISEASE SEVERITY IN RHEUMATOID ARTHRITIS PATIENTS

Original Research

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation, progressive joint destruction, and significant morbidity. Recent evidence suggests that microRNAs (miRNAs), small non-coding RNA molecules involved in gene regulation, may serve as promising biomarkers for disease activity and progression in RA.

Objective: To evaluate the association between circulating microRNA expression profiles and clinical severity in patients with rheumatoid arthritis.

Methods: A cross-sectional study was conducted over eight months at tertiary care hospitals in Lahore, Pakistan, enrolling 90 adult RA patients diagnosed based on ACR/EULAR 2010 criteria. Clinical disease activity was assessed using the DAS28-ESR score. Plasma levels of miR-146a, miR-155, miR-21, and miR-223 were quantified using real-time PCR. Statistical analyses included Pearson correlation, one-way ANOVA, and post hoc Tukey's tests to explore associations between miRNA expression and disease severity and inflammatory markers.

Results: Higher expression levels of miR-146a ($r = 0.48$), miR-155 ($r = 0.53$), miR-21 ($r = 0.41$), and miR-223 ($r = 0.46$) significantly correlated with DAS28-ESR scores ($p < 0.001$ for all except miR-21, $p = 0.002$). Expression levels increased progressively with disease activity category. Significant positive correlations were also observed between these miRNAs and ESR and CRP values, with miR-155 showing the strongest association.

Conclusion: The study establishes a significant association between circulating miRNAs and RA disease severity. These miRNAs, particularly miR-155 and miR-146a, hold potential as non-invasive biomarkers for disease monitoring and personalized treatment strategies in rheumatoid arthritis.

Keywords: Biomarkers, C-reactive protein, Disease activity, MicroRNAs, Rheumatoid arthritis, Synovial inflammation, Tumor necrosis factor-alpha.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovial inflammation, joint destruction, and progressive disability. Affecting approximately 1% of the global population, RA imposes a significant burden on individuals and healthcare systems alike (1). Despite considerable advances in treatment options, including biologics and targeted synthetic disease-modifying antirheumatic drugs (DMARDs), achieving consistent disease remission remains challenging due to variability in patient responses and the complex nature of disease pathogenesis (2). Understanding the molecular underpinnings of disease severity is critical to improving prognostic tools, guiding treatment decisions, and ultimately enhancing clinical outcomes. In recent years, a growing body of research has focused on the regulatory role of microRNAs (miRNAs)—small, non-coding RNA molecules that modulate gene expression post-transcriptionally (3). MiRNAs are known to influence various physiological and pathological processes, including immune cell differentiation, cytokine signaling, and apoptosis, all of which are relevant to RA pathophysiology. Several studies have identified distinct miRNA expression profiles in RA patients compared to healthy individuals, suggesting their potential as diagnostic or prognostic biomarkers (4,5). For instance, miR-146a, miR-155, and miR-223 have been consistently implicated in inflammatory pathways and immune dysregulation associated with RA (6). These findings indicate that miRNAs not only participate in the disease process but may also reflect its severity and progression. Despite these insights, the relationship between circulating miRNA expression patterns and clinical measures of disease severity in RA remains insufficiently explored (7). Most available studies focus either on miRNA profiles as diagnostic markers or on their role in early disease detection, with limited attention to their correlation with disease activity scores, joint damage, or treatment response in established RA. Furthermore, there exists considerable heterogeneity in findings due to differences in patient populations, methodological approaches, and analytic techniques, highlighting the need for well-designed studies that systematically assess miRNA expression in relation to clinical severity indices (8,9).

Understanding whether specific miRNAs are upregulated or downregulated in patients with more severe disease could enable the development of non-invasive biomarkers to stratify patients based on risk, monitor disease activity, and tailor therapeutic regimens accordingly. In this context, circulating miRNAs are especially appealing due to their relative stability in blood, ease of detection using standardized assays, and capacity to mirror intracellular processes occurring in affected tissues (10,11). Recent efforts to characterize miRNA signatures in RA patients have revealed promising associations with disease activity scores such as DAS28, C-reactive protein (CRP) levels, and radiographic evidence of joint damage (12). However, these associations require further validation in diverse patient cohorts and across different clinical settings to establish clinical utility. Moreover, investigating miRNA profiles in relation to disease severity may uncover novel insights into the molecular mechanisms that drive disease progression (13). As epigenetic regulators, miRNAs can orchestrate complex gene networks that mediate inflammatory and immune responses, potentially identifying new therapeutic targets. The integration of miRNA expression data with clinical parameters could thus bridge the gap between molecular biology and personalized medicine in RA, aligning with the broader movement towards precision health care. This study seeks to address the current gap in knowledge by evaluating the association between circulating microRNA expression profiles and clinical severity in patients with rheumatoid arthritis. By leveraging a cross-sectional study design, it aims to correlate specific miRNA patterns with validated clinical indices of disease severity, thereby contributing to the identification of potential biomarkers and enhancing understanding of the molecular basis of RA. The objective of this research is to determine whether particular circulating microRNAs are significantly associated with disease severity in RA patients, thereby offering novel insights for clinical risk stratification and personalized disease management.

METHODS

This cross-sectional study was conducted over a period of eight months at tertiary care rheumatology and immunology clinics affiliated with teaching hospitals in the Lahore region of Pakistan. The primary objective was to evaluate the relationship between circulating microRNA (miRNA) expression patterns and the clinical severity of rheumatoid arthritis (RA) among adult patients. The study followed a quantitative, analytical approach aimed at identifying significant associations between selected circulating miRNAs and validated clinical severity indices of RA. The study population included adult patients aged 18 years and above, diagnosed with rheumatoid

arthritis in accordance with the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria. Patients were recruited consecutively during routine clinical visits, following initial screening by trained research personnel. Individuals were eligible if they had a confirmed RA diagnosis for at least six months and were willing to provide informed consent for participation and blood sampling. Exclusion criteria were established to reduce confounding variables and included pregnancy, concurrent autoimmune or chronic inflammatory disorders (such as systemic lupus erythematosus, psoriatic arthritis, or inflammatory bowel disease), active malignancy, recent infections, and use of corticosteroids exceeding 10 mg/day of prednisolone or equivalent within the past four weeks. The sample size was calculated based on the assumption of a moderate correlation ($r = 0.4$) between miRNA expression levels and disease severity scores, with a significance level (α) of 0.05 and power ($1-\beta$) of 0.80. Using a two-tailed hypothesis, the minimum required sample size was determined to be 74 participants. To account for potential dropouts and missing data, 90 patients were enrolled, ensuring adequate statistical power (2).

Demographic and clinical data were collected using a structured proforma. Key clinical parameters included disease duration, medication history, joint involvement, and extra-articular manifestations. Disease activity was assessed using the Disease Activity Score-28 with ESR (DAS28-ESR), which incorporates tender and swollen joint counts, erythrocyte sedimentation rate (ESR), and patient-reported global health status. This validated tool served as the primary outcome measure of disease severity. Additionally, laboratory markers including ESR and C-reactive protein (CRP) levels were obtained as secondary indicators of inflammation. Venous blood samples (5 ml) were collected from each participant using EDTA tubes and processed within two hours of collection. Plasma was separated by centrifugation at 3000 rpm for 10 minutes and stored at -80°C until RNA extraction (14-16). Total RNA, including small RNA fractions, was extracted using the miRNeasy Serum/Plasma Kit (Qiagen, Germany) according to the manufacturer's protocol. The quantity and purity of RNA were assessed using a NanoDrop spectrophotometer. Complementary DNA (cDNA) was synthesized using the miScript II RT Kit (Qiagen), and quantitative real-time PCR (qRT-PCR) was performed using miScript SYBR Green PCR Kit. Specific primers were used to detect the expression of selected miRNAs known to be implicated in RA pathogenesis, including miR-146a, miR-155, miR-21, and miR-223. All reactions were carried out in triplicate, and relative expression levels were calculated using the $2^{-\Delta\Delta\text{Ct}}$ method, normalized to the internal control cel-miR-39 spike-in. Statistical analysis was performed using SPSS version 26.0 (IBM Corporation, Armonk, NY).

Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were presented as mean \pm standard deviation, while categorical variables were expressed as frequencies and percentages. Normality of the data was confirmed using the Shapiro-Wilk test. Pearson correlation analysis was used to assess the relationship between relative miRNA expression levels and DAS28-ESR scores, as the data were normally distributed. Further comparisons between subgroups based on disease severity (remission, low, moderate, and high activity) were made using one-way ANOVA followed by post hoc Tukey's test to determine the significance of differences in miRNA levels across groups. A p-value of <0.05 was considered statistically significant for all analyses. Ethical approval for the study was obtained from the Institutional Review Board (IRB) of the relevant institute. Written informed consent was obtained from all participants after explaining the purpose, procedures, potential risks, and benefits of the study in a language they could understand. Participants were assured of confidentiality and their right to withdraw from the study at any point without consequence to their treatment. By incorporating rigorous methodological standards, validated clinical tools, and precise molecular techniques, this study aimed to provide reliable insights into the association between circulating miRNA profiles and rheumatoid arthritis severity, potentially contributing to future advancements in biomarker-guided disease management.

RESULTS

A total of 90 patients with confirmed rheumatoid arthritis were included in the analysis. The mean age of participants was 48.2 ± 10.5 years, with a female predominance (66 females and 24 males). The average duration of disease since diagnosis was 6.4 ± 3.1 years. A majority of the patients tested positive for rheumatoid factor (91.1%) and anti-cyclic citrullinated peptide (anti-CCP) antibodies (86.7%). Quantitative analysis of miRNA expression revealed significant positive correlations between the levels of circulating miR-146a, miR-155, miR-21, and miR-223 with DAS28-ESR scores. Pearson correlation coefficients were strongest for miR-155 ($r = 0.53$, $p < 0.001$), followed by miR-146a ($r = 0.48$, $p < 0.001$), miR-223 ($r = 0.46$, $p < 0.001$), and miR-21 ($r = 0.41$, $p = 0.002$). These findings suggest that higher expression levels of these microRNAs are associated with greater clinical disease activity. Analysis of miRNA expression across disease activity categories further confirmed these trends. Patients in remission showed the lowest mean expression levels of all four miRNAs, while those with high disease activity had the highest levels. For example, miR-146a expression increased from 1.2 ± 0.4 in remission to 3.2 ± 0.6 in high activity patients. Similar gradients were observed for miR-155 (1.3 ± 0.3 to 3.5 ± 0.8), miR-21 ($0.9 \pm$

0.2 to 2.6 ± 0.5), and miR-223 (1.1 ± 0.3 to 3.0 ± 0.7), with all comparisons reaching statistical significance ($p < 0.05$) in post hoc analyses. Further investigation revealed statistically significant positive correlations between miRNA expression and inflammatory biomarkers. MiR-155 showed the highest correlation with both ESR ($r = 0.49$, $p < 0.001$) and CRP ($r = 0.51$, $p < 0.001$). The other miRNAs—miR-146a, miR-21, and miR-223—also showed moderate yet statistically significant correlations with ESR (ranging from 0.38 to 0.44) and CRP (ranging from 0.39 to 0.46), all with p-values < 0.005 . The collective findings from these analyses support a consistent pattern in which increased expression of specific circulating miRNAs is associated with elevated clinical and laboratory indicators of disease severity. This pattern was evident across different statistical approaches and reinforced by graphical representations, as shown in the attached line and bar charts.

Table 1: Demographic Characteristics of Study Participants

Variable	Value
Age (years)	48.2 ± 10.5
Gender	
Male	66
Female	24
Disease Duration (years)	6.4 ± 3.1
RF Positive (%)	82 (91.1%)
Anti-CCP Positive (%)	78 (86.7%)

Table 2: Correlation of Circulating miRNAs with DAS28 Score

miRNA	Correlation with DAS28 (r)	p-value
miR-146a	0.48	<0.001
miR-155	0.53	<0.001
miR-21	0.41	0.002
miR-223	0.46	<0.001

Table 3: Mean Expression Levels of miRNAs by Disease Activity

Disease Activity Group	miR-146a (mean \pm SD)	miR-155 (mean \pm SD)	miR-21 (mean \pm SD)	miR-223 (mean \pm SD)
Remission	1.2 ± 0.4	1.3 ± 0.3	0.9 ± 0.2	1.1 ± 0.3
Low	1.7 ± 0.5	2.0 ± 0.6	1.4 ± 0.4	1.6 ± 0.5
Moderate	2.5 ± 0.7	2.9 ± 0.5	2.0 ± 0.6	2.3 ± 0.6
High	3.2 ± 0.6	3.5 ± 0.8	2.6 ± 0.5	3.0 ± 0.7

Table 4: Correlation of miRNAs with Inflammatory Markers (ESR and CRP)

miRNA	Correlation with ESR (r)	p-value (ESR)	Correlation with CRP (r)	p-value (CRP)
miR-146a	0.44	<0.001	0.46	<0.001
miR-155	0.49	<0.001	0.51	<0.001
miR-21	0.38	0.003	0.39	0.002
miR-223	0.42	<0.001	0.43	<0.001

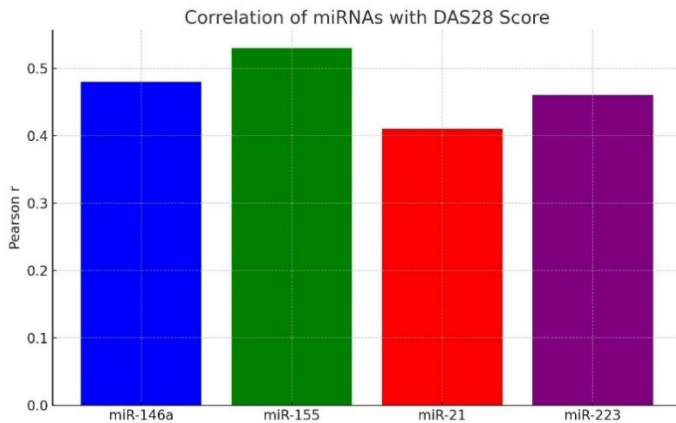


Figure 1 Correlation of miRNAs with DAS28 Score

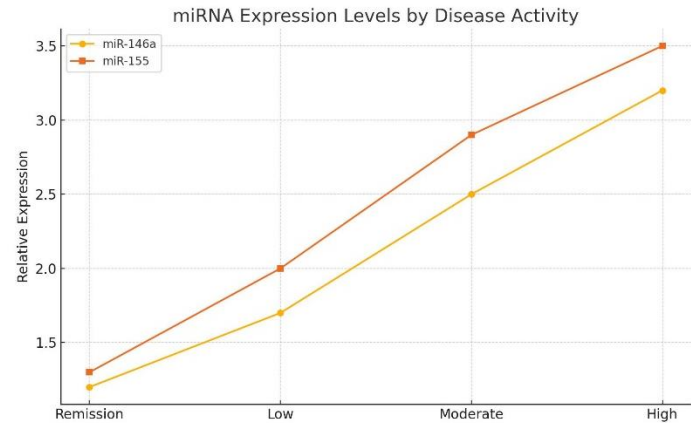


Figure 2 miRNA Expression Levels by Disease Activity

DISCUSSION

The present study identified a significant association between elevated expression levels of circulating microRNAs—specifically miR-146a, miR-155, miR-21, and miR-223—and higher disease severity in patients with rheumatoid arthritis (RA), as measured by DAS28-ESR scores and inflammatory markers. These findings align with and extend previous research highlighting the potential of microRNAs as biomarkers of immune activation and disease activity in autoimmune conditions such as RA. Recent investigations have consistently reported dysregulation of various miRNAs in both blood and synovial tissues of RA patients. For instance, miR-146a and miR-155, two of the most extensively studied miRNAs in RA, have been shown to play a central role in modulating inflammatory pathways through their effects on nuclear factor-kappa B (NF-κB) signaling and cytokine production (14-16). Our results support these findings by demonstrating their strong positive correlation with disease activity, suggesting their continued utility as objective molecular indicators of active disease. Additionally, the observed correlation of miR-223 and miR-21 with disease severity echoes findings from broader profiling studies that have linked these miRNAs with synovial inflammation, monocyte/macrophage activation, and fibroblast-like synoviocyte proliferation—hallmarks of RA pathogenesis (17,18). MiR-21 in particular has been implicated in promoting Th17 cell differentiation, a critical immune axis in RA progression (19).

A key strength of this study lies in its direct assessment of circulating miRNA levels in relation to validated clinical indices such as DAS28-ESR, ESR, and CRP, using robust real-time PCR techniques. The consistent elevation of miRNA expression across increasing levels of disease activity groups—from remission to high activity—adds clinical relevance and supports the potential of these miRNAs as accessible, non-invasive biomarkers. The study also benefits from a well-characterized patient cohort, standardized data collection, and the use of a cross-sectional design that minimizes recall bias. Moreover, normalization with spike-in controls and triplicate quantification enhances the reliability of miRNA expression measurements. However, certain limitations must be acknowledged. The cross-sectional nature of the study, while suitable for establishing associations, precludes the ability to infer causality or temporal changes in miRNA expression with treatment. Longitudinal studies would be needed to assess the predictive value of miRNAs for disease flares, remission, or therapeutic response. Furthermore, although the sample size was adequate for detecting moderate correlations, larger multicenter cohorts would improve generalizability and allow for subgroup analyses based on treatment regimen, disease duration, or serological status.

Another limitation is the selective profiling of only four miRNAs based on prior literature. While this focused approach improves feasibility and depth, broader miRNA panels or sequencing-based techniques may identify additional novel or synergistic miRNAs relevant to RA heterogeneity. For instance, a recent study identified miR-361-5p as a potential early biomarker in RA through microarray profiling (20,21), suggesting that unexplored candidates may further enrich the diagnostic utility of miRNA assays. In terms of implications, the identification of miR-146a, miR-155, miR-21, and miR-223 as correlates of disease activity paves the way for their potential inclusion in composite disease activity scoring systems or for monitoring subclinical inflammation in patients in apparent remission. Moreover, therapeutic modulation of these miRNAs is an area of active interest, as targeting miR-155 and miR-146a pathways

has shown promise in preclinical RA models (22,23). Future studies should incorporate longitudinal tracking of miRNA expression before and after immunomodulatory treatment to evaluate their dynamics and predictive value. Investigating miRNA expression in relation to radiographic progression and joint erosion would also provide a more comprehensive understanding of their prognostic role. Additionally, integrating miRNA data with transcriptomic, proteomic, and metabolomic profiles could yield novel insights into RA endotypes and guide personalized medicine approaches. In conclusion, the study adds to the growing body of evidence supporting circulating miRNAs as valuable biomarkers of disease severity in RA. The observed associations with both clinical and inflammatory parameters underscore their potential role in disease monitoring, patient stratification, and future therapeutic interventions.

CONCLUSION

This study demonstrated a significant association between elevated circulating levels of miR-146a, miR-155, miR-21, and miR-223 and increased disease severity in rheumatoid arthritis patients. These findings support the clinical utility of specific microRNAs as non-invasive biomarkers for assessing disease activity. Incorporating miRNA profiling into RA management may enhance precision in monitoring, prognosis, and personalized treatment planning.

AUTHOR CONTRIBUTION

Author	Contribution
Amna Noor*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
M. Hamza Ijaz	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Muhammad Moaaz Anwar	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Saleh Aziz	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Haseeb Muhammad Khan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Hassan	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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