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Research Article

Exploring the miRNA-126 and IL-21 Regulatory Pathway in Rheumatoid Arthritis Patients

Ahmed Abdulridha Ameen Shlash [1*]

[1] *Department of Medical Laboratory Techniques, College of Health and Medical Technologies/Kufa, Al Furat Al Awsat Technical University, Kufa, Iraq.*
[*] *Corresponding author: dr.ahmedameen39@gmail.com*

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease driven by a network of pro-inflammatory cytokines and epigenetic regulators that together sustain synovial inflammation and joint damage. Interleukin-21 (IL-21), produced mainly by T follicular helper and Th17 cells, has been implicated in the activation of synovial fibroblasts, osteoclastogenesis and autoantibody production, while microRNA-126 (miRNA-126) has emerged as a regulator of immune cell signalling with reported, though inconsistent, alterations in RA synovial tissue. Whether circulating levels of these two molecules move together in RA patients has not been well characterised. **Objective:** To measure serum IL-21 concentration and relative miRNA-126 expression in RA patients compared with healthy controls, to evaluate their association with rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody status, to test the correlation between the two markers, and to assess their individual diagnostic performance. **Method:** Fifty RA patients recruited from teaching hospitals and outpatient clinics in Najaf, Iraq, and forty age- and sex-comparable healthy controls were enrolled. RF was assessed by latex agglutination and anti-CCP antibody by ELISA. Serum IL-21 was measured by sandwich ELISA. Total RNA was extracted from serum and reverse-transcribed, and miRNA-126 relative expression was determined by one-step RT-qPCR using U6 as the reference gene and the 2∧-ΔΔCt method. **Results:** RA patients had significantly higher serum IL-21 (178.2 ± 42.4 ng/L versus 126.6 ± 14.0 ng/L, $p < 0.001$) and miRNA-126 fold-change (2.62 ± 1.19 versus 1.07 ± 0.37, $p < 0.001$) than controls. RF and anti-CCP were positive in 82.0% and 92.0% of RA patients, respectively, and in none of the controls. miRNA-126 and IL-21 correlated strongly in RA patients (Pearson $r = 0.936$, $p < 0.001$) but not in controls ($r = -0.02$, $p = 0.88$). Receiver operating characteristic analysis showed excellent discrimination for both markers (miRNA-126: AUC 0.961; IL-21: AUC 0.965). **Conclusion:** Circulating miRNA-126 and IL-21 are jointly elevated in RA and tightly correlated in patients but not in healthy individuals, consistent with a disease-specific coupling between this microRNA and its putative downstream cytokine target. Both markers show strong individual diagnostic accuracy and merit further evaluation as combined, minimally invasive biomarkers of RA.

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1. Introduction

Rheumatoid arthritis (RA) is a long-lasting, systemic inflammatory condition characterised by ongoing synovitis and the gradual deterioration of cartilage and bone; several people also have extra-articular symptoms that exacerbate the total disease burden. Approximately 18 million individuals are now believed to be afflicted with RA globally, a number that has consistently increased over the last thirty years, with women impacted at more than double the rate of males. The precise factors that initiate the illness are inadequately understood. A more recent immunological research has supported the prevailing view that rheumatoid arthritis develops from a combination of genetic susceptibility environmental factors and a self perpetuating system of cytokines autoantibodies and epigenetic modifiers which maintains synovial inflammation long after the original triggering event has gone. The complexity of the mechanism is reflected in the contemporary management of the disease: treat-to-target approaches today use an increasing range of synthetic and biological disease-modifying therapies, each targeting a distinct point in this network.

One of these nodes is IL-21, a member of the common y-chain cytokine family with structural homology to IL-2, IL-4, and IL-15. IL-21 is mainly produced by activated CD4+ T cells, especially the T follicular helper (Tfh) and Th17 subsets, which are accumulated in the rheumatoid synovium [1]. In T cells, B cells, monocytes/macrophages and fibroblast-like synoviocytes, receptor signalling activates JAK-STAT, MAPK and PI3K/Akt pathways to promote Th17 differentiation, germinal-center B-cell responses and autoantibody synthesis, and osteoclast development and cartilage degradation. Clinically, IL-21 levels have been found to be elevated in synovial fluid and serum of rheumatoid arthritis patients, and correlate with Tfh-like cell proliferation markers, anti-CCP antibody levels, and composite measures of disease activity such as DAS28 [2, 3]. Both a genetic association study of a Mexican population and an independent study of a Chinese population have shown increased circulating IL-21 levels in RA patients compared with matched controls, and variations in IL-21/IL-21R polymorphisms, which could partially account for the reasons behind the different levels of patients [3, 4]. Taken together, these findings have established IL-21 as a plausible activity marker and a target of ongoing research for combined cytokine inhibition.

A unique aspect of rheumatoid arthritis biology is microRNAs. miRNAs are short non-coding RNAs of 19 to 24 nucleotides that regulate gene expression at the post-transcriptional level by binding to the 3'-untranslated region of target messenger RNAs resulting in translational repression or complete degradation of the transcript. Because a single miRNA can act on dozens of targets at once, this class of molecule is well suited to coordinating broad shifts in immune cell behaviour, and dysregulated miRNA expression has now been linked to a wide range of autoimmune conditions. Among the panel of miRNAs studied in RA to date which includes miR-16, miR-21, miR-146a, miR-155 and miR-223, several of which have shown diagnostic promise in recent cohorts [5, 6]. miRNA-126 stands out for its dual role in vascular and immune biology. Encoded within an intron of the EGFL7 gene, miR-126 has been shown in RA synovial fibroblasts to promote proliferation and resist apoptosis by repressing PIK3R2 and activating PI3K/Akt signalling [7]; conversely, in a collagen-induced arthritis model, restoring miR-126 in fibroblast-like synoviocytes suppressed IL-23R signalling and lowered TNF-α and IFN-γ output [8]. These two mechanistic studies point in opposite directions with respect to the net effect of miR-126 on joint inflammation, and clinical data on circulating miR-126 in RA patients remain comparatively sparse a gap that broader miRNA biomarker panels have only partly begun to close [9, 10]. In systemic lupus erythematosus, a related autoimmune disease, miR-126 has been shown to bind DNMT1 transcripts directly in CD4+ T cells, lowering DNMT1 protein levels and producing a hypomethylated, hyperactive T-cell phenotype [11]; serum miR-126 has itself been put forward as a diagnostic biomarker in that disease [12].

IL-21 production by Tfh and Th17 cells and miRNA-driven epigenetic remodelling of CD4+ T cells both converge, in principle, on the same population of autoreactive lymphocytes. That overlap led us to ask a fairly simple question: do circulating miRNA-126 and IL-21 rise together in RA, and do they move in step within individual patients, even if neither marker on its own explains disease pathogenesis? To answer this, we measured serum IL-21 and relative miRNA-126 expression side by side in a cohort of RA patients and matched healthy controls, related both markers to the conventional serological tests already used in RA classification (RF and anti-CCP antibody), tested directly whether the two markers correlate with one another, and assessed how well each discriminates patients from controls.

2. Methods

2.1. Study design and setting

This case-control study was conducted on patients attending rheumatology and internal medicine consultation clinics at Al-Sadr Medical City, Najaf Teaching Hospital, Al-Zahraa Teaching Hospital, Al-Hakeem General Hospital, and an affiliated private clinic, all in Najaf Governorate, Iraq.

2.2. Study population

Fifty patients with a clinical diagnosis of rheumatoid arthritis were enrolled. Forty apparently healthy individuals with no personal or family history of autoimmune or chronic inflammatory disease, comparable in age and sex distribution to the patient group, were recruited as controls. Patients with overlapping autoimmune conditions, active infection, malignancy, or pregnancy were excluded .

2.3. Blood sample collection and processing

Venous blood was drawn from each participant under aseptic conditions and allowed to clot at room temperature before centrifugation to separate serum. Serum aliquots were divided for immediate serological testing and for storage at -80°C prior to RNA extraction, avoiding repeated freeze-thaw cycles.

2.4. Rheumatoid factor testing

Serum rheumatoid factor (RF) was determined qualitatively by latex slide agglutination, in which latex particles coated with human gammaglobulin are agglutinated by RF present in the test serum. Fifty microlitres of serum and one drop of the latex reagent were mixed on

the test slide and rotated at 80–100 rpm for two minutes; visible agglutination was read as positive, corresponding to an RF concentration of at least 8 IU/mL.

2.5. Anti-cyclic citrullinated peptide (anti-CCP) antibody testing

Anti-CCP IgG antibody was measured qualitatively by a reverse-phase enzyme immunoassay (Human Anti-CCP ELISA Kit, Cat. No. ED0108Hu, BT Lab, China) according to the manufacturer's instructions. Diluted serum samples and controls were incubated on antigen-precoated microplates, followed by an HRP-conjugated detection antibody, TMB substrate, and stop solution, with absorbance read at 450 nm. Samples with optical density at or above the kit cut-off (mean negative control OD + 0.15) were classified as positive.

2.6. Serum IL-21 quantification

Serum IL-21 concentration was measured by sandwich ELISA. Standards and samples were added to antibody-precoated wells together with biotinylated anti-IL-21 antibody and streptavidin-HRP, incubated at 37°C, washed, and developed with TMB substrate before absorbance was read at 450 nm. Sample concentrations were interpolated from the standard curve generated on each plate.

2.7. RNA extraction

Total RNA, including the small-RNA fraction containing circulating miRNA, was extracted from 500 µL serum aliquots using the TransZol Up Plus RNA Kit, a guanidinium-phenol-based lysis method combined with silica spin-column purification. Serum was lysed in TransZol Up reagent, and chloroform was added to separate the mixture into an upper aqueous phase containing RNA, an interphase, and a lower organic phase. The liquid phase was combined with pure ethanol and subjected to a spin column, which was then rinsed with Clean Buffer and Wash Buffer prior to the elution of RNA in RNase-free water. The concentration and purity of RNA were evaluated using the A260/280 absorbance ratio.

2.8. Reverse transcription and quantitative real-time PCR for miRNA-126

The RNA that was extracted was reverse-transcribed and then amplified in a single closed-tube reaction using the GoTaq® 1-Step RT-qPCR System. Each 20 µL reaction contained GoTaq qPCR Master Mix (2X), forward and reverse primers (50–300 nM final concentration each), GoScript RT Mix, and RNA template, made up to volume with nuclease-free water. The primer sequences used for miRNA-126 and for the U6 small nuclear RNA reference gene are shown in Table 1. Thermocycling comprised reverse transcription at $\geq$37°C for 15 minutes, RT inactivation/polymerase hot-start activation at 95°C for 10 minutes, followed by 40 cycles of denaturation (95°C, 10–15 s) and combined annealing/extension (60°C, 30–60 s), with a final dissociation step to confirm amplicon specificity. Relative miRNA-126 expression was calculated by the 2∧-ΔΔCt method, using the difference between the miRNA-126 and U6 cycle threshold (Ct) values in each sample relative to the mean of the control group.

Table 1: Primer sequences used for RT-qPCR

Target	Forward primer (5'→3')	Reverse primer (5'→3')	Ref.
miRNA-126	GGGTCGTACCGTGAGTAAT	CAGTGCGTGTCGTGGAGT	[12]
U6 (reference)	GTTTTGTAGTTTTTGGAGTTAGTGTTGTGT	CTCAACCTACAATCAAAAACAACACAAACA	

2.9. Statistical analysis

Data were analysed using IBM SPSS Statistics, version 29.0. Continuous variables were tested for normality and presented as mean ± standard deviation together with the range; normally distributed variables were compared between groups using the independent-samples t-test, and non-normally distributed variables were compared using the U test. Categorical variables (sex, RF status, anti-CCP status) were compared using the chi-square test and are presented as frequencies and percentages. Associations between miRNA-126 expression and IL-21 concentration were assessed using Pearson's and Spearman's correlation coefficients, calculated separately within the RA and control groups. Receiver operating characteristic (ROC) curve analysis was performed using the ROC Curve procedure in SPSS to evaluate the diagnostic performance of miRNA-126 and IL-21 in distinguishing RA patients from controls, with the area under the curve (AUC), optimal cut-off , sensitivity and specificity reported; 95% confidence intervals for AUC were computed using the standard asymptotic method. A two-tailed p-value below 0.05 was considered statistically significant throughout.

3. Results

3.1. Demographic characteristics of the study population

Fifty RA patients (36 female, 14 male) and 40 healthy controls (26 female, 14 male) were recruited across five clinical sites in Najaf Governorate. Patients averaged 46.6 ± 12.1 years of age (range 28–70 years), essentially the same as the control group at 45.8 ± 10.6 years (range 24–63 years; $p = 0.737$), and the sex distribution did not differ significantly between groups either ($p = 0.629$). In other words, the control group was well matched to the patients for age and sex, which is what the recruitment strategy was designed to achieve Table 2.

Table 2: Demographic characteristics of RA patients and healthy controls

Characteristic	RA patients (n = 50)	Controls (n = 40)	p-value
Age, years (mean ± SD)	47.6 ± 12.2	45.8 ± 10.6	0.737
Age range, years	28–70	24–63	—
Female, n (%)	36 (72.0%)	26 (65.0%)	0.629
Male, n (%)	14 (28.0%)	14 (35.0%)	0.629

3.2. Serological markers: rheumatoid factor and anti-CCP antibody

Rheumatoid factor came back positive in 41 of 50 RA patients (82.0%) and in none of the 40 controls. Anti-CCP antibody showed an even higher positivity rate — 46 of 50 patients (92.0%), again versus zero in controls — and both differences were highly significant ($p<0.001$ for each comparison, Table 3). Taken together, the high positivity rates for both markers point to a predominantly seropositive RA cohort, which is consistent with what the ACR/EULAR serological domain would predict for a group of this kind [13, 14] .

Table 3: RF and anti-CCP status in RA patients and controls

Test	Result	RA patients (n = 50)	Controls (n = 40)	p-value
RF (latex agglutination)	Positive	41 (82.0%)	0 (0.0%)	<0.001
	Negative	9 (18.0%)	40 (100.0%)	
Anti-CCP (ELISA)	Positive	46 (92.0%)	0 (0.0%)	<0.001
	Negative	4 (8.0%)	40 (100.0%)	

3.3. Serum IL-21 is elevated in RA patients

Serum IL-21 concentration was significantly higher in RA patients (178.2 ± 42.4 ng/L; range 135.8–317.2 ng/L) than in controls (126.6 ± 14.0 ng/L; range 98.7–148.1 ng/L; Mann-Whitney U test, $p<0.001$; Table 4, Figure 1A). The IL-21 value distribution among patients had a significant right skew, with a portion of patients presenting very high levels above 250 ng/L, whereas control values were tightly grouped around the mean of the population.

3.4. Serum miRNA-126 expression is up-regulated in RA patients

Relative miRNA-126 expression, normalised to U6 and expressed as fold-change by the 2∧-ΔΔCt method, was significantly higher in RA patients (2.62 ± 1.19; range 1.10–7.01) than in controls (1.07 ± 0.37; range 0.49–1.64; Mann-Whitney U test, $p<0.001$; Table 4, Figure 1). As with IL-21, the RA group showed a wider spread of values than controls, including several patients with fold-changes above 5.

Table 4: Serum IL-21 and miRNA-126 expression in RA patients and controls

Parameter	RA patients (n = 50) Mean ± SD	Controls (n = 40) Mean ± SD	p-value
Serum IL-21 (ng/L)	178.2 ± 42.4	126.6 ± 14.0	<0.001
miRNA-126 (fold-change,2∧-ΔΔCt)	2.62 ± 1.19	1.07 ± 0.37	<0.001

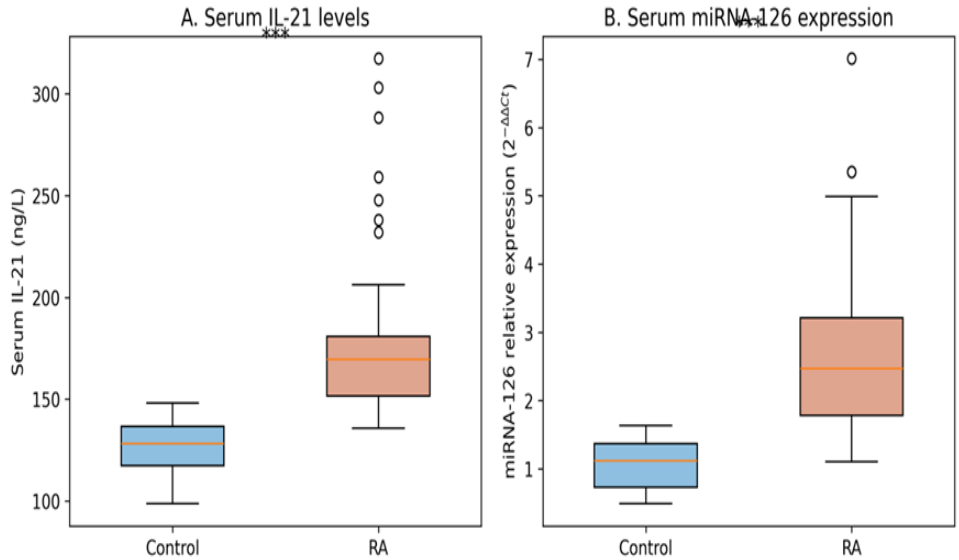

Figure 1: Serum IL-21 concentration (A) and relative miRNA-126 expression (B) in RA patients against healthy controls. Boxes show median and interquartile range; whiskers show the full range. *** $p<0.001$, Mann-Whitney U test.

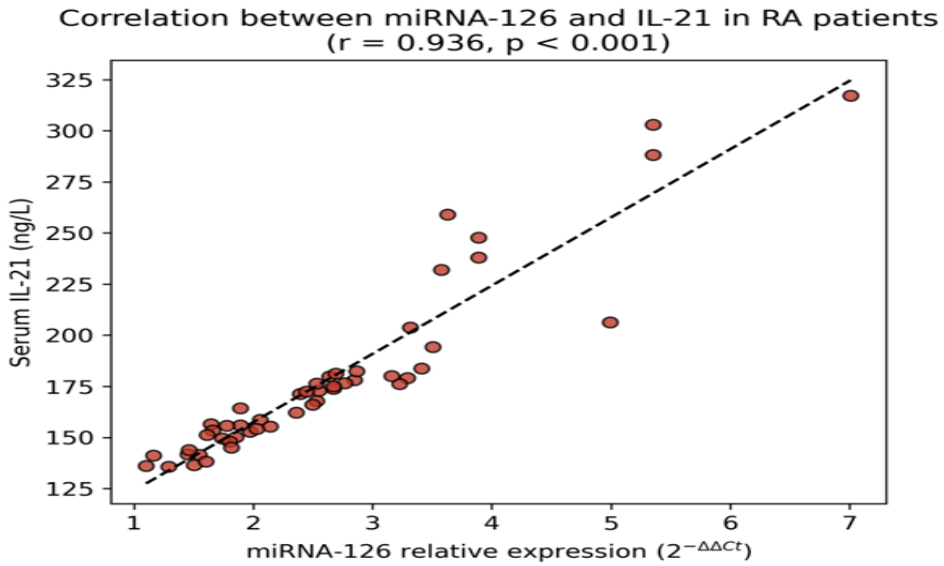

Figure 2: Correlation between relative miRNA-126 expression and serum IL-21 concentration in RA patients (Pearson r = 0.936, p ¡ 0.001; n = 50). Dashed line shows the linear fit.

Table 5: Diagnostic performance of miRNA-126 and IL-21 for discriminating RA patients from controls

Marker	Cut-off	AUC (95% CI)	Sensitivity	Specificity	95% CI
miRNA-126 (fold-change)	1.65	0.961	82.0%	100%	0.922–0.991
IL-21 (ng/L)	149.6	0.965	80.0%	100%	0.929–0.989

3.5. miRNA-126 correlates with IL-21 in RA patients

miRNA-126 correlates with IL-21 in rheumatoid arthritis patients. A significant positive correlation was observed between miRNA-126 expression and serum IL-21 levels in the RA study group (Pearson r = 0.936, p<0.001; Figure 2) indicating that subjects with high miRNA-126 expression had high circulating IL-21 levels. Such an association was nearly absent in the control group (Pearson r = -0.02, p = 0.880). When combining the two groups, the overall association was still strong (r = 0.918, p<0.001), but mainly based on the between-group differentiation. The fact that this link is disease specific, i.e. observed in patients but not in healthy individuals, suggests that such an association between miRNA-126 and IL-21 represents an active pathogenic mechanism in RA rather than a basic physiological relationship between the two entities.

3.6. Diagnostic performance of miRNA-126 and IL-21

ROC curve analysis showed that both markers discriminated RA patients from healthy controls with high accuracy. miRNA-126 achieved an AUC of 0.961 (95% CI 0.922–0.991); at the Youden-optimal cut-off of 1.65-fold change, sensitivity was 82.0% and specificity was 100%, with a positive predictive value of 100% and a negative predictive value of 80.0% in this cohort. Serum IL-21 performed comparably, with an AUC of 0.965 (95% CI 0.929–0.989); at a cut-off of approximately 149.6 ng/L, sensitivity was 80.0% and specificity was 100%, with identical positive and negative predictive values to miRNA-126 at their respective optimal cut-offs Table 5, Figure 3. The perfect specificity observed for both markers reflects the complete absence of values above the optimal cut-off in the control group in this dataset, and should be interpreted with the sample size of the study in mind.

4. Discussion

In the current study, we aimed to simultaneously investigate two molecules from different layers of rheumatoid arthritis immunopathology, a cytokine effector (IL-21) and a post-transcriptional regulator (miRNA-126) and to explore whether their circulating levels correlate in patients. Three conclusions are especially striking. These markers were significantly increased at the beginning in RA patients compared to controls, in line with much prior work on the link between IL-21 and Th17/Tfh-driven synovial inflammation and osteoclastogenesis [1–4, 15], and has also contributed to the expanding body of data on circulating miRNA-126 and other miRNAs in autoimmune diseases [5–7, 9–12]. Secondly, a significant correlation between the two markers was found in RA patients, but not in the control group, which is difficult to explain by common measurement error or constant physiological connection and may suggest a possible association between miRNA-126 expression and IL-21 production activated specifically during the disease. Third, all the markers showed good diagnostic performance in ROC analysis, as for serological markers (RF, anti-CCP) currently included in the standard RA classification.

The change observed in miRNA-126, its up-regulation in RA patients, is consistent with mechanistic studies demonstrating that overexpression of miR-126 in RA synovial fibroblasts inhibits PIK3R2 and activates PI3K/Akt signalling, promoting fibroblast proliferation and resistance to apoptosis, which would be expected to maintain synovial hyperplasia rather than resolve it. This is in line with the trend seen in systemic lupus erythematosus, where increased miR-126 expression in CD4+ T cells suppresses DNMT1 and leads to a hypomethylated, hyperactive T-cell phenotype associated with excessive immunoglobulin production [11, 12]. However, research is not

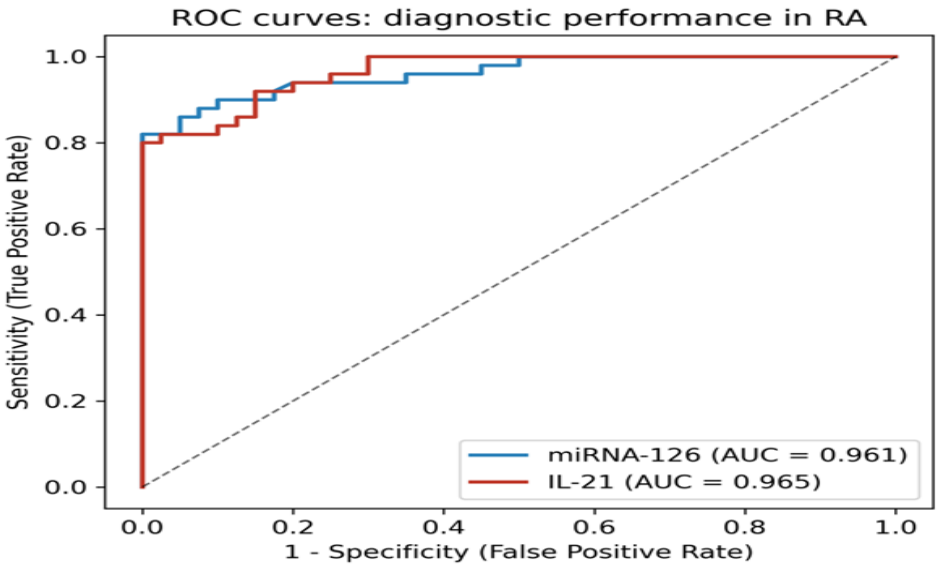

Figure 3: Receiver operating characteristic (ROC) curves for miRNA-126 and serum IL-21 in discriminating RA patients from healthy controls.

unanimous with one team using a model of collagen induced arthritis found that miR-126 was decreased in RA patients compared to controls and that reintroduction of miR-126 in this context inhibited IL-23R signalling and pro-inflammatory cytokine production in fibroblast-like synoviocytes. Adding to this complex scenario is a wealth of data on miRNA biomarkers in RA, with some circulating miRNAs being increased during disease progression and correlating with activity parameters, while others are decreased or do not change significantly [5, 6, 9]. The discrepancy in miR-126 could be attributed to the biological compartment studied (serum in this case, as opposed to synovial tissue or synovial fluid in others), differences in duration of illness and disease activity between cohorts, or the cell populations contributing to the circulating signal. It is clear that the dysregulation of miR-126 in rheumatoid arthritis is not a consistent unidirectional event, and studies that assess serum, synovial fluid and synovial tissue expression from the same individuals will greatly help clarify this problem.

The strong positive correlation between miRNA-126 and IL-21 in patients with rheumatoid arthritis is, as far as we know, a relatively recent observation and many non-exclusive interpretations appear plausible. The circulating miRNA-126 signal could possibly be contributed to by IL-21-secreting Tfh and Th17 cells. This suggests that these two would increase in parallel, as they come from the same proliferated, activated cohort of lymphocytes. Epigenetic changes induced by miRNA-126 in CD4+ T cells, like those reported in lupus [11], might lower the threshold for IL-21 gene transcription, making the microRNA an active participant in cytokine production rather than a passive observer. A third, more cautious hypothesis, is that both indicators are responding independently but simultaneously to the factors influencing disease activity at any given time, with no one causing the other. The cross-sectional approach of this study cannot distinguish between these scenarios, and only mechanistic studies of miR-126 gain- and loss-of-function assays in Tfh/Th17 cells with direct quantification of IL-21 production could reveal which, if any, is true. IL-21 has been consistently reported to associate with DAS28 and anti-CCP levels in independent cohorts [2–4] and it may be worthwhile to explore whether the association is stronger or weaker in the presence of disease activity.

The similar AUCs observed for miRNA-126 and IL-21 in this group suggest that either marker can be used independently for RA case detection with specificity levels equal to or greater than RF and anti-CCP antibody assays and with a sensitivity of approximately 80%, from a clinical-biomarker perspective. Given their biologic interdependence, the combination of the two markers is unlikely to add much diagnostic precision above their individual contributions, as has been the experience with other multi-biomarker panels in rheumatoid arthritis, where composite scores have not always exceeded the power of their most effective single element. A more useful application may be in tracking disease progression or therapeutic response over time and would require longitudinal rather than cross-sectional sampling.

5. Conclusion

RA patients have significantly higher serum IL-21 and relative miRNA-126 expression compared to healthy controls, and there is a strong correlation between them in the patient group, but this correlation is absent in healthy individuals. Each marker alone showed high accuracy in distinguishing RA patients from controls, supporting their use as minimally invasive biomarkers complementary to RF and anti-CCP antibody tests. The close association of the two markers in the patients raises the possibility of a common regulatory pathway linking miRNA-126 to IL-21 production in RA, which should now be directly tested in longitudinal and mechanistic studies.

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Disclaimer (Artificial Intelligence): The author(s) hereby declare that NO generative AI technologies such as Large Language Models

(ChatGPT, COPILOT, etc.), and text-to-image generators have been used during writing or editing of manuscripts.

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