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Original article

Serum IL-41 Levels in Rheumatoid Arthritis Patients: Relationship with Disease Activity and Radiological Scores

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Abstract:

Background: IL-41 is regarded as an anti-inflammatory cytokine linked to several inflammatory conditions including arthritis, sepsis, colitis and chronic obstructive pulmonary disease. This research aimed to evaluate serum IL-41 levels in cases with rheumatoid arthritis (RA) and to explore the relationship between IL-41 levels and disease activity (DA), along with radiological assessments including musculoskeletal ultrasound. **Methods:** This case-control research included 80 participants divided into two groups: Group A (RA cases) and Group B (age- and sex-matched healthy controls). **Results:** Serum IL-41 levels are elevated in the RA group than control one with a significant $p< 0.001$. IL-41 demonstrated a significant positive correlation with multiple clinical and inflammatory markers, including HAQ, VAS, swollen and tender joint counts, DA and functional impairment (components of RASS), DAS28, and ESR ($p< 0.001$). **Conclusion:** IL-41 demonstrated strong capability to differentiate RA cases from healthy individuals and to distinguish between high and low DA states. These observations suggest IL-41 may act as a valuable biomarker for diagnosing RA and monitoring DA. The absence of correlation with radiological measures indicates that IL-41 primarily reflects inflammatory activity rather than structural joint damage.

Keywords: IL-41; Rheumatoid Arthritis; Radiological Scores; Disease Activity.

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Introduction

Rheumatoid arthritis (RA) is a persistent inflammatory condition impacting roughly 0.3% to 1.0% of individuals worldwide, predominantly manifesting as joint pain and stiffness. [(1)].

RA significantly compromises quality of life through symptoms such as fatigue, synovial inflammation, and joint deformities, ultimately impairing physical capabilities, daily functioning, and occupational productivity. [(2)].

RA predominantly impacts women in midlife, with a reported female-to-male ratio of approximately 2–3:1. The disease's pathogenesis is orchestrated through a dynamic and multifaceted interplay among immune and stromal cells. B cells function as antigen-presenting cells, initiating T cell activation. These activated T lymphocytes, in turn, prompt macrophages to secrete pro-inflammatory cytokines, which fuel synovial fibroblast hyperplasia and influence osteoblast lineage commitment, thereby contributing to the chronic inflammatory milieu and joint remodeling characteristic of RA[(1)].

Interleukin-41 (IL-41), also referred to Metrnl, meteorin-like, Cometin, or Subfatin, is a recently discovered immunoregulatory cytokine with approximately 40% amino acid sequence similarity to meteorin (Metrn). Initially characterized in 2004 as a neurotrophic factor, IL-41 distinguishes itself from Metrn by exhibiting broader tissue distribution, particularly in macrophages and barrier sites, rather than being restricted to neural tissues. Its expression is inducible by cytokines such as TNF and IL-17A, -12, and -4 while it is negatively regulated by interferons and transforming growth factor (TGF) [(3)].

Recent observations also suggest a role for IL-41 in metabolic disorders such as obesity and insulin resistance, functioning as an adipokine that enhances adipocyte differentiation and improves insulin sensitivity, particularly within white adipose tissue [(4)].

Elucidating cytokine involvement in RA pathogenesis is essential for understanding its underlying mechanisms. IL-41, secreted by hypertrophic chondrocytes and osteoblasts within trabecular bone, has been reported to inhibit osteoblast differentiation in affected joints. IL-41 is also produced by fibroblasts, and its concentration in synovial fluid is significantly increased in cases with RA and psoriasis in contrast with those with osteoarthritis (OA) or gout [(5)].

This research aimed to quantify serum IL-41 levels in cases with RA and to examine the relationship between these concentrations and disease activity (DA), alongside radiological assessments, including musculoskeletal ultrasound observations. [(6)]

Patients and methods:

Patients:

This case-control research included 80 participants recruited from both the inpatient and outpatient clinics of the Rheumatology, Rehabilitation, and Physical Medicine departments at Benha University Hospitals. The recruitment phase spanned from July 2024 to December 2024. Ethical approval for the research was granted by the Ethical Scientific Committee at Benha University under approval code Ms 41-3-2024. Prior to inclusion, all participants received comprehensive information regarding the research's aims, procedures, and potential risks, after which they provided both verbal and written informed consent, in compliance with ethical guidelines for human subject's research.

Eligibility criteria required participants to have a confirmed diagnosis of rheumatoid arthritis based on the 2010 ACR/EULAR classification criteria and to be 18 years of age or older. Individuals were excluded if they had other autoimmune conditions, malignancies, or neurological disorders such as Parkinson's or Alzheimer's

disease, given the potential influence of these conditions on IL-41 levels. Cases under 18 years of age were also excluded.

Grouping: Enrolled participants were divided into two equal groups: **Group A** (RA) and **Group B** (age- and sex-matched healthy controls from hospital staff and relatives).

Approval code: MS 41-3-2024

Methods:

All enrolled participants underwent a comprehensive evaluation including detailed medical history taking and thorough clinical examination performed by trained rheumatologists. Laboratory investigations were systematically conducted and included complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) antibodies.

Indices of disease activity and severity: Assessment of DA was conducted using the DA Score involving 28 joints combined with ESR measurement (DAS28-ESR) [(7)], a validated composite index frequently used in clinical practice and research to quantify RA activity. The DAS28-ESR scores were interpreted based on standard cut-offs as follows: remission was defined as a score less than 2.6, low DA (LDA) ranged between 2.6 and 3.2, moderate activity was assigned to scores greater than 3.2 and up to 5.1, while high DA was defined as any score exceeding 5.1.

Rheumatoid Arthritis Severity Scale RASS: The RASS comprises three separate visual analog scales (VAS), each consisting of 10-centimeter lines designed to individually assess DA, functional impairment, and physical damage. The endpoints of these scales are anchored at 0, representing the absence of DA, functional impairment, or physical damage, and 100, indicating the most severe RA manifestations in these domains that the evaluator has ever encountered. The scores obtained from each subscale are then summed to produce an overall health status index, referred to as the RASS Total score[(8)].

Modified Health Assessment Questionnaire (mHAQ): The mHAQ is a validated instrument developed to evaluate cases' functional capacity. It consists of eight items that assess various daily activities including dressing and grooming, arising from a seated position, walking, eating, reaching, personal hygiene, gripping, and common routine tasks. The scoring system yields a total score between 0.0 and 3.0, where elevated scores correspond to greater functional impairment and increased disability. Scores below 0.3 are interpreted as normal functional ability. The mHAQ scores are further categorized into mild functional loss (<1.3), moderate impairment (1.3 to 1.8), and severe disability (>1.8), facilitating stratification of case disability levels[(9)].

Radiological assessment: Plain radiographs of both hands and feet were obtained for all participants to evaluate structural joint changes. The radiographic images were systematically reviewed and scored using the modified Larsen's scoring system, a validated and widely adopted method for quantifying joint damage and erosive changes in RA[(10)].

Musculoskeletal ultrasound assessment (MSUS): Ultrasound evaluations were carried out using the Logiq P9 ultrasound system, equipped with a high-frequency linear array transducer. Both grey-scale ultrasound (GSUS) and power Doppler ultrasound (PDUS) techniques were employed to assess synovial and periarticular pathology. The German US7 scoring system was utilized as a standardized tool to examine seven clinically significant joints in the hand and forefoot. This scoring system enables the semi-quantitative evaluation of synovitis, tenosynovitis, and erosions, thereby offering a sensitive measure of disease activity and joint involvement[(11)].

Ultrasound Assessment:

Musculoskeletal ultrasonography was performed utilizing the US7 scoring system to assess joint involvement in the clinically affected hand and forefoot. This validated protocol targets specific joints, namely the wrist, MCP joints II and III, PIP joints II and III, and MTP joints II and V. The evaluation encompassed the detection of synovitis, tenosynovitis/paratenonitis, and bone erosions.

Synovitis and synovial vascularity were assessed using both grey-scale ultrasound (GSUS) and power Doppler ultrasound (PDUS) and graded semi-quantitatively on a scale from 0 to 3. Synovitis was classified as grade 0 (absent), grade 1 (mild), grade 2 (moderate), and grade 3 (severe). PDUS was employed to evaluate synovial perfusion, with grading based on the extent of color Doppler signal: grade 0 indicating no detectable signal, grade 1 indicating ≤25%, grade 2 indicating 26–50%, and grade 3 representing >50% of the synovial area. A positive Doppler signal was interpreted as a marker of active inflammatory synovitis.

In contrast, tenosynovitis and erosions were evaluated dichotomously, recorded as either present (1) or absent (0).

Joint-specific assessments included the dorsomedial, palmar, and ulnar aspects of the wrist for evaluation of synovitis, tenosynovitis, and erosions using both GSUS and PDUS. MCP joints II and III were assessed in multiple planes, including the medial (radial) aspect of MCP II specifically for erosion detection. Palmar views of MCP II and III were additionally scanned to identify synovitis and tenosynovitis. PIP joints II and III were examined dorsally with PDUS for signs of synovitis and erosions, and palmarly using GSUS and PDUS for comprehensive assessment of synovial pathology and erosive changes[12].

Measurement of serum IL41 by ELISA using the commercially available kit

Quantification of serum IL-41 concentrations was conducted using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, in accordance with the manufacturer's protocol. Initially, all reagents, standards, and serum samples were prepared as instructed. Each sample was then incubated with enzyme-conjugated antibodies at 37°C for 60 minutes to facilitate antigen–antibody interaction.

Following incubation, non-bound components were eliminated by washing the microplate wells with buffer prepared via a 1:30 dilution of concentrate with distilled water. Subsequently, 50 µL of chromogen solutions A and B were added to each well, gently mixed, and incubated at 37°C for 10 minutes in a dark environment. The enzymatic reaction was terminated by the addition of 50 µL stop solution, resulting in a rapid color change from blue to yellow.

Optical density (OD) readings were obtained at a wavelength of 450 nm within 15 minutes of stopping the reaction. A standard calibration curve was generated based on OD values of known concentrations using linear regression. The corresponding IL-41 levels in each sample were calculated from the standard curve according to their individual OD values.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD), and intergroup comparisons were assessed using the independent samples Student's *t*-test. Categorical variables were summarized as frequencies and percentages, with group comparisons conducted via the Chi-square test or Fisher's exact test, as appropriate. Correlations between variables were examined using Spearman's rank correlation coefficient (*r*), given the non-parametric nature of some data. A two-tailed *p*-value of less than 0.05 was considered statistically significant in all analyses.

Results:

No significant differences were observed between the two groups in terms of age, BMI, or sex distribution, indicating comparability across baseline characteristics. However, IL-41 levels were significantly higher in the RA group in contrast with the control one ($p < 0.001$) **(Table 1).**

Table 2 outlines the descriptive data for clinical features, DA indices, RASS domains, extra-articular involvement, and laboratory observations within the RA group. **Table 3** summarizes IL-41 levels, ultrasound observations, and treatment profiles among cases.

Correlation analysis exhibited no significant associations between IL-41 and age or BMI ($p > 0.05$). Similarly, IL-41 exhibited weak, non-significant correlations with disease duration and the physical damage domain of RASS ($p > 0.05$). In contrast, moderate positive correlations were observed between IL-41 and HAQ, VAS, swollen joint count, and DA as measured by RASS, all statistically significant ($p < 0.05$). Stronger positive correlations were identified between IL-41 and DAS28-ESR, functional impairment (RASS), and tender joint count, with high statistical significance ($p < 0.001$).

IL-41 also demonstrated weak, non-significant correlations with Hb, RBCs, WBCs, ESR, CRP, and anti-CCP ($p > 0.05$). A moderate inverse correlation was noted with platelet count, which reached statistical significance ($p < 0.05$). No significant relationship was found between IL-41 and US7 score ($p > 0.05$) **(Table 4).**

The multiple linear regression analysis revealed no significant association between IL-41 levels and the demographic variables (age, sex, and BMI), as indicated by the overall non-significant model ($p = 0.62$) . And the multiple linear regression analysis indicates a statistically significant model linking IL-41 levels to disease duration, activity, and severity ($p = 0.019$). Among the predictors, only DAS28-ESR showed a significant positive association with IL-41 ($B = 59.633$, $p = 0.034$). Other variables, including disease duration, HAQ, and RASS components (disease activity, physical damage, and functional impairment), did not show statistically significant associations ($p > 0.05$). **(Table 5).**

The multiple linear regression analysis revealed no statistically significant associations between IL-41 levels and the various radiologic findings. And the multiple linear regression analysis demonstrates a significant overall relationship between IL-41 levels and clinical variables ($p = 0.005$). Notably, the number of tender joints was a significant positive predictor of IL-41 levels ($B = 6.336$, $p = 0.036$). In contrast, the number of swollen joints and VAS score showed no significant associations ($p = 0.622$ and $p = 0.499$, respectively). **(Table 6).**

In terms of diagnostic performance, IL-41 exhibited excellent capacity to discriminate between RA cases and healthy controls, yielding an AUC of 0.928 ($p < 0.001$; 95% CI: 0.871–0.985). The best cutoff point was 171.537 pg/mL, with a sensitivity of 87.5%, specificity of 92.5%, PPV of 92.11%, and NPV of 88.10%. Additionally, IL-41 demonstrated moderate accuracy in distinguishing patients with high DA from those with lower activity or remission. The AUC for this analysis was 0.783 ($p=0.002$; 95% CI: 0.602–0.964), with an optimal threshold of 204.93 pg/mL, sensitivity of 93.3%, specificity of 60%, PPV of 86.67%, and NPV of 60% **(Figure 1).**

Figure 2 represents ultrasound image of some of our cases.

Table 1: Comparison between Rheumatoid group and control group according to demographic data, IL-41 serum levels.

		RA group n=40	Control group n=40	P-value
Age		48(11.46)	47.55(6.42)	0.878
Sex	Male	4(25%)	4(25%)	1
	Female	36(75%)	36(75%)	
BMI		31.11(4.61)	30.25(2.61)	0.154
IL-41		271.26(116.6)	112.05(47.95)	< 0.001*

Data are presented as Mean (± SD) or frequency (%), *: statistically significant as P value <0.05.

Table 2: Descriptive statists of clinical data, Disease activity, RASS, Extra articular, and laboratory data manifestations of cases groups.

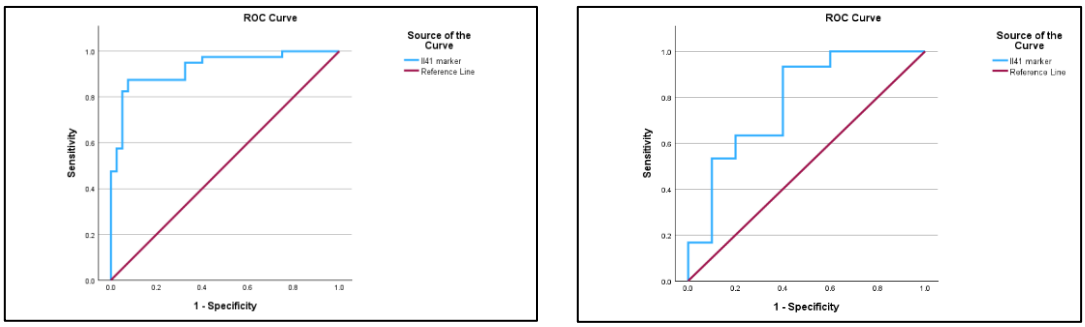
Rheumatoid cases (n=40)	
Disease duration (years)	12.82(9.35)
DAS28ESR	6.24(1.34)
HAQ	1.46(0.71)
No of tender joint	13.35(7)
No of swollen joint	5.9(4.07)
VAS	6.77(2.05)
Disease activity	
DAS28ESR	
Remission DAS28	1(3%)
Low DAS28	1(3%)
Moderate DAS28	8(20%)
High DAS28	30(75%)
RASS	
Disease activity	52.32(19.26)
Physical damage	30.92(17.79)
Functional impairment	43.57(19.81)
Extra articular manifestations	
Rheumatoid nodule	4(10%)
Eye affection(e.g.) Scleritis	11(27%)
cardiac	4(10%)
Interstitial lung disease	2(5%)
CATRACT	1(2.5%)
Laboratory data	
HB (g/dL)	11.59(1.52)
RBCs (million/µL)	4.29(0.55)
WBCs (10^3/µL)	7.07(2.47)
PLT (10^3/µL)	256.3(69.22)
ESR (mm/hr.)	59.52(33.17)
CRP (mg/L)	32.7(37.14)
RF (IU/mL)	50.98(89.66)
Anti CRP (U/mL)	205.8(204.5)

Data are presented as Mean (± SD) or frequency (%),

Table 3: Descriptive statists of serum IL-41 levels, Radiological features and medications in cases group

Rheumatoid cases (n=40)	
IL41 (pg/ml)	271.26(116)
Radiological features	
Plain X-ray (modified Larsen's score)	38.07(22.56)
Ultrasound 7 score	
Synovites Gs	7.3(3.31)
Synovites pd	3.3(3.03)
Tenosynovites Gs	5.1(2.95)
Tenosynovites pd	3.35(2.44)
Erosion	3.3(1.87)
Total	22.35(10.73)
Treatment	
Steroid	26(65%)
MTX	19(47.5%)
Leflunomide	23(57.5%)
Hydroxychloroquine	27(67.5%)
Salazopyrine	1(2.5%)
Mycophenolate mofetil	1(2.5%)
Etanercept	3(7.5%)
Adalimumab	2(5%)
Baricitinib	1(2.5%)
Rituximab	1(2.5%)

Data are presented as Mean (± SD) or frequency (%),
*: statistically significant as P value <0.05



(A) (B)

Figure 1: ROC curve for IL-41 to (A) Rheumatoid group (vs control) and (B) High active cases (vs Moderate & Low and Remission).

Table 4: Relation between serum IL-41 levels and demographic data, between serum IL-41 levels and clinical data, between serum IL-41 levels and Laboratory results of cases and between serum IL-41 levels and radiology records of cases including modified Larsen's score and ultrasound 7 scores.

IL-41		r	P-value
Age		0.21	0.194
BMI		-0.016	0.924
clinical data			
Disease duration(years)		0.008	0.959
DAS28ESR		0.516	<0.001
HAQ		٠.320*	0.044
	Disease activity	٠.480**	0.002
RASS	Physical damage	0.279	0.081
	Functional impairment	0.504	<0.001
No of tender joint		٠.519**	0.001
No of swollen joint		٠.402*	0.010
VAS		0.331	0.037
Laboratory results			
HB		-0.069	0.671
RBCs		-0.246	0.127
WBCs		-0.221	0.171
PLT		-0.377*	0.016
ESR		0.199	0.219
CRP		0.169	0.296
RF		0.289	0.072
Anti CRP		-0.001	0.994
Larsen's score and ultrasound 7 scores			
modified Larsen score		0.193	0.232
Synovites Gs		0.201	0.213
Synovites pd		0.16	0.326
Tenosynovites Gs		0.211	0.192
Tenosynovites pd		0.06	0.711
Erosion		0.309	0.053
Total		0.173	0.284

r=Pearson`s correlation

Table 5: Multiple linear regression between IL-41 and demographic data. Multiple linear regression between IL-41and disease duration, activity, and severity.

IL-41		**B**	**SE**	**Beta**	**t**	**p-value**
Age		2.095	1.674	0.206	1.252	0.219
Sex		-19.254	62.965	-0.050	-0.306	0.762
BMI		-0.764	4.128	-0.030	-0.185	0.854
R^2 =0.218, adjusted R^2= -0.048, SE =118.4, p-value = 0.62						
IL-41		**B**	**SE**	**Beta**	**t**	**p-value**
Disease duration (years)		-1.861	1.941	-0.149	-0.958	0.345
DAS28ESR		59.633	26.997	0.685	2.209	**0.034**
HAQ		-52.144	41.384	-0.319	-1.260	0.216
	Disease activity	0.653	1.799	0.108	0.363	0.719
RASS	**Physical damage**	0.026	1.418	0.004	0.018	0.986
	Functional impairment	0.925	0.986	0.157	0.938	0.355
R^2 =0.353, adjusted R^2= 0.235, SE =101.97, p-value = 0.019						

R2: Coefficient of determination , R: coefficient of regression, B: Unstandardized Coefficients, Beta: Standardized Coefficients, SE: Estimates Standard error, t: t-test of significance

Table 6: Multiple linear regression between IL-41 and Radiology records. And Multiple linear regression between IL-41 and Clinical data.

IL-41	**B**	**SE**	**Beta**	**t**	**p-value**
Xray (Modified Larsen's score)	-0.092	0.994	-0.018	-0.093	0.927
Synovites Gs	6.503	10.146	0.185	0.641	0.526
Synovites pd	0.000	9.778	0.000	0.000	1.000
Tenosynovites Gs	17.078	9.975	0.432	1.712	0.096
Tenosynovites pd	-24.952	12.789	-0.523	-1.951	0.060
Erosion	13.735	12.344	0.220	1.113	0.274
R^2 =0.231, adjusted R^2= 0.091, SE =111.15, p-value = 0.164					
IL-41	B	SE	Beta	t	p-value
No of tender joint	6.336	2.912	0.384	2.176	0.036
No of swollen joint	2.819	5.674	0.099	0.497	0.622
VAS	7.978	11.683	0.141	0.683	0.499
R^2 =0.3, adjusted R^2= 0.242, SE =101.55, p-value = 0.005					

R2: Coefficient of determination , R: coefficient of regression, B: Unstandardized Coefficients, Beta: Standardized Coefficients, SE: Estimates Standard error, t: t-test of significance

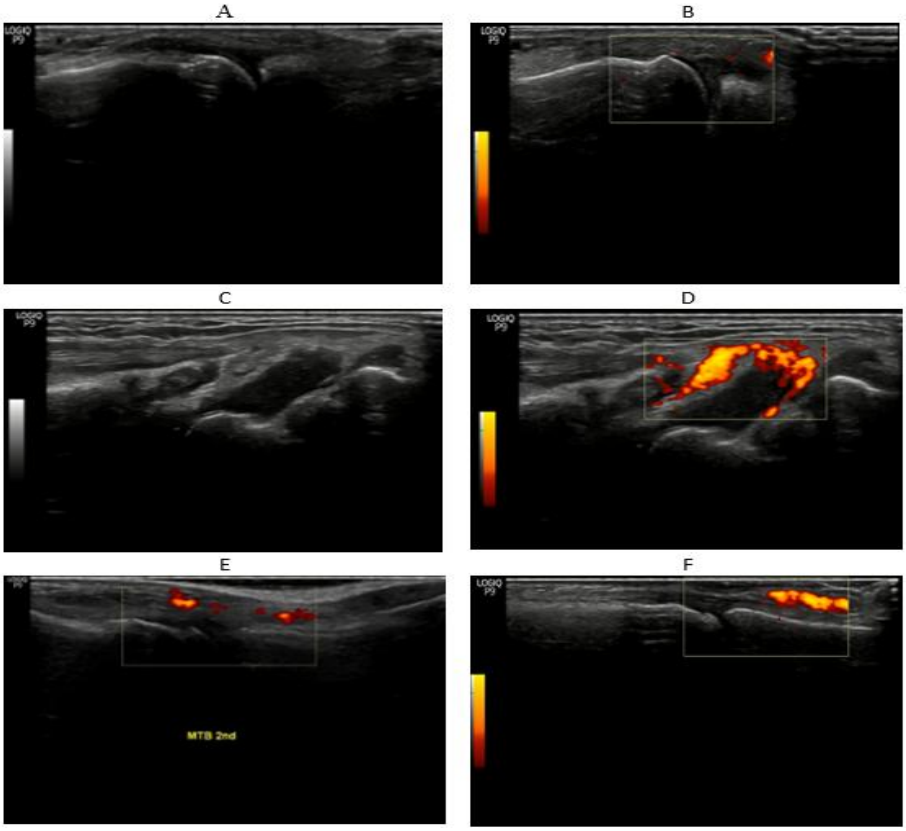


Figure 2: A) Dorsal longitudinal scan showing Tenosynovitis of the 3rd flexor tendon and synovitis of the 3rd MCP joint. (B) Dorsal longitudinal power doppler scan showing Tenosynovitis of the 2nd flexor tendon and synovitis of the 2nd MCP joint. (C) Dorsal longitudinal grey scale ultrasonography of the wrist showing marked joint cavity enlargement due to hypoechoec synovial fluid and hyperechoec synovial proliferation. (D) Power doppler ultrasonography of the wrist showing marked increased vascularity within hypertrophied synovium. (E) Power doppler ultrasonography of the 2nd MTP denoting increased vascularity within the hypertrophied synovium. (F) Power doppler ultrasonography of the 2nd PIP joint denoting increased vascularity within the hypertrophied synovium together with tenosynovitis.

Discussion:

The research cohort consisted of 40 cases with RA, having a mean age of 48 years and a predominant female representation of 90.2%, which is consistent with the established demographic characteristics of rheumatoid arthritis.

Correspondingly, a research conducted by Risha and colleagues reported a mean age of 45.4 ± 8.3 years, with females comprising 90% and males approximately 10% of their case population [(13)].

In this research, the mean duration of disease was 12.82 years, indicating a group with well-established RA. Most cases (75%) exhibited high DA (HDA) according to DAS28-ESR scores, with an average score of 6.24, reflecting significant ongoing inflammatory activity. This finding is comparable to another investigation of RA cases where the mean DAS28 score was 3.6 ± 1.3. In that cohort, 23.1% of cases had LDA, 13.3% were in remission, 33.3% presented with moderate DA, and 30.3% had HDA, demonstrating a spectrum of disease severity (DS) within the population[(14)].

Extra-articular manifestations identified in the current research included rheumatoid nodules in 10% cases, ocular involvement such as scleritis in 27%, cardiovascular disease in 10%, interstitial lung disease in 5%, and cataracts in 2.5% of cases.

El-Baz and collaborators found that all RA cases exhibited extra-articular features, particularly respiratory system involvement which was observed in 74% of cases. Hematological abnormalities were present in 68%, while ocular and cardiovascular complications were each reported in 46% of cases. Additionally, skin involvement affected 24%, gastrointestinal manifestations were present in 22%, and renal impairment occurred in 10%. Neurological manifestations, including peripheral neuritis or mononeuritis multiplex, were the least frequent, affecting only 8% of the RA cases studied [(15)].

A significant outcome of our research is the markedly elevated serum IL-41 levels observed in RA cases (mean 271.26 pg/mL) relative to healthy controls (mean 112.05 pg/mL, $p < 0.001$). This substantial increase indicates a role for IL-41 in the inflammatory pathways underlying RA. Furthermore, IL-41 demonstrated strong diagnostic performance, with an AUC of 0.928, sensitivity of 87.5%, and specificity of 92.5% at a cutoff value of 171.537 pg/mL, showing its ability as a reliable biomarker for RA diagnosis.

Comparable results were obtained by Zhang and colleagues, who analyzed serum IL-41 levels in a cohort consisting of 159 RA cases, 28 OA cases, and 50 healthy individuals. Their observations revealed significantly elevated IL-41 levels in RA cases as opposed to both OA cases and healthy controls, with no notable difference between the latter two groups [(16)].

Our observations revealed significant positive correlations between serum IL-41 levels and several DA markers in RA. Strong correlations were identified with DAS28-ESR ($r=0.516$, $p < 0.001$), tender joint count ($r=0.519$, $P=0.001$), and functional impairment as measured by RASS ($r=0.504$, $p < 0.001$). Moderate positive correlations were also observed between IL-41 and HAQ scores ($r=0.320$, $P=0.044$), swollen joint count ($r=0.402$, $P=0.010$), and VAS for pain ($r=0.331$, $P=0.037$). These data suggest that IL-41 levels increase in parallel with worsening DA and functional limitation. Stronger correlations may reflect the high proportion of cases with active diseases in our cohort.

Furthermore, IL-41 demonstrated the ability to distinguish cases with HDA from those in moderate, low activity, or remission states, with an AUC of 0.783 ($P=0.002$). At a cutoff of 204.93 pg/mL, it exhibited high sensitivity (93.3%) and moderate specificity (60%). Multiple linear regression confirmed DAS28-ESR as an independent predictor of IL-41 levels

(P=0.034). When clinical variables were analyzed separately, tender joint count emerged as the strongest independent predictor (P=0.036), indicating that IL-41 may be particularly linked to pain and tenderness in RA.

These results are consistent with those reported by Zhang and associates, who found positive correlations between IL-41 and DAS28 as well as CRP, but no significant association with ACCP antibodies [(16)].

Similarly, Gong and associates reported a positive association between IL-41 and DAS28, verifying its role in inflammation and DA[(17)].

Kandeel and collaborators revealed a positive correlation between IL-41 and DAS28. These observations suggest that IL-41 may serve as a potential biomarker for evaluating DA in RA. Combining our results with previous research, we propose that IL-41 might play a protective role in RA cases, with its levels potentially increasing in parallel with the upregulation of inflammatory cytokines[(18)].

Furthermore, Jocić and colleagues assessed serum IL-41 as a biomarker for RA, evaluating its relationship with DA, treatment efficacy, and case response in a cohort of 189 cases. They found a significant association between IL-41 levels and DA indices including DAS28-ESR, CDAI, and SDAI, indicating a possible role for IL-41 in modulating inflammation and DA in RA[(19)].

Our research identified strong positive correlations between IL-41 levels and several RA DA measures, including DAS28-ESR, tender joint count, and functional impairment. Moderate positive associations were also observed with pain assessments and swollen joint counts, indicating that IL-41 levels escalate in parallel with increasing DS. Furthermore, elevated IL-41 effectively discriminated against cases with HDA from those exhibiting diminished activity or remission, underscoring its potential utility as a biomarker for DS assessment. Multiple regression analysis revealed DAS28-ESR as an independent predictor of IL-41 levels, highlighting the direct relationship between inflammatory burden and IL-41 expression. Additionally, tender joint count independently predicted IL-41 levels, suggesting a specific involvement of IL-41 in pain-related mechanisms in RA. Taken together, these observations, in conjunction with prior research, verify the hypothesis that IL-41 may play an active role in RA-associated inflammation and could serve as a valuable marker for monitoring disease progression and therapeutic response.

Among laboratory parameters examined, only platelet count exhibited a significant inverse correlation with IL-41 (r=-0.377, P=0.016). This result is somewhat counterintuitive, as platelet levels are generally elevated during inflammatory conditions. The observed negative association may reflect complex regulatory interactions between IL-41 and platelet production or consumption in the context of active RA. This observation aligns with the observations of Gong and colleagues, who also reported negative correlations between IL-41 and platelet counts[(17)].

Interestingly, traditional inflammatory markers such as ESR and CRP did not exhibit significant correlations with IL-41 levels in our research, despite their well-established roles as indicators of DA. This lack of association suggests that IL-41 may reflect distinct facets of RA pathophysiology not captured by conventional acute phase reactants.

Bartlett and colleagues similarly observed that certain cytokines in RA may be dissociated from traditional inflammatory markers, proposing that biomarkers like GlycA may represent inflammatory pathways not reflected by ESR, hsCRP, IL-1β, IL-6, IL-18, or TNF-α[(20)].

Contrary to these observations, Kandeel and collaborators reported positive correlations between IL-41 and both ESR and CRP[(18)].

Our research revealed comparable levels between IL-41 and both RF and anti-CCP, with p-values exceeding 0.05.

This finding is consistent with the observations of Kandeel and collaborators, who reported that serum IL-41 levelss did not correlate with RF or anti-CCP levels [(18)].

Similarly, Jocić and colleagues found no association between IL-41 levels and ACPA, further verifying these results[(19)].

Our research revealed insignificant relations between IL-41 levels and radiological parameters, including modified Larsen's score or any ultrasound 7 score components. This contrasts with the strong associations observed with clinical DA measures.

Multiple regression analysis confirmed the lack of independent association between IL-41 and radiological parameters. This dissociation between IL-41 and structural damage suggests that IL-41 might be more closely linked to inflammatory DA than to joint destruction mechanisms. Alternatively, the cross-sectional nature of our research might not capture the relationship between IL-41 and radiographic progression, which would require longitudinal assessment.

Jocić and colleagues evaluated serum IL-41 levels in RA cases and found that IL-41 levelss were associated with DA and treatment efficacy. The research concluded that IL-41 could act as a potential biomarker to assess treatment responses in RA cases [(19)].

Park and colleagues reported that a considerable rate of radiographic progression occurred in RA cases who were in low DA (LDA) or clinical remission. This finding highlights that structural joint damage can progress independently of clinical DA measures, suggesting that factors other than those captured by standard clinical assessments, possibly including specific cytokines like IL-41, may influence joint destruction [(21)].

Our observations verify the notion that IL-41 might serve as a biomarker for DA in RA. With an expanded sample size is essential to clarify the function of IL-41 in progress of cartilage and bone erosions, as well as structural joints structural destruction in RA patients. Additional extensive long-term investigations are advised.

Conclusion:

Our research demonstrates significantly elevated serum IL-41 levels in RA cases as opposed to healthy controls, with strong correlations between IL-41 and clinical measures of DA. IL-41 exhibited excellent discriminatory ability between RA cases and controls, and good ability to distinguish HDA from diminished activity states. These observations suggest that IL-41 may serve as a valuable biomarker for RA diagnosis and DA assessment. The lack of association with radiological parameters indicates that IL-41 might specifically reflect inflammatory disease activity rather than structural damage.

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Author contribution

The authors contributed equally to the research.

Conflicts of interest

No conflicts of interest

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