Original Article

Investigating the Association of Gene Expression of IL-37 Isoforms a and b and Serum IL-37 with Rheumatoid Arthritis Activity and Severity

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Abstract

Background: New rheumatoid arthritis (RA) biomarkers, such as serum interleukin-37, may aid in the identification and management as well as improved monitoring of disease severity, activity, and effectiveness of the therapy. **Objectives:** This study aims to assess the association between gene expressions of interleukin (IL)-37 isoform-a and isoform-b and serum IL-37 levels with the severity and activity of RA. **Materials and Methods:** This is a case–control study of 140 participants. The samples were collected using fresh blood and serum samples. The sample consisted of 64 females and six males in both the patient and control groups. The serum IL-37 level was measured using enzyme-linked immunosorbent assay. Immune markers such as anti-cyclic citrullinated peptide (anti-CCP), erythrocyte sedimentation rate (ESR), rheumatoid factor, and C-reactive protein (CRP) were also measured. Gene expression for IL-37 isoforms was measured by real-time quantitative polymerase chain reaction (PCR). DAS-28-ESR, DAS-28-CRP, and CDAI were used to calculate the activity of RA as well as the severity of disease. **Results:** The serum levels of IL-37 were significantly higher in patients than in controls. Activity parameters, as stated by DAS-28 ESR, DAS-28 CRP, CDAI, and SDAI, showed a positive correlation with serum levels of IL-37. The levels of IL-37 correlated significantly with the treatment response. There was a significant correlation between IL-37 levels and ESR, CRP, and anti-CCP levels. IL-37 isoform-a mRNA expression, measured by RT-qPCR, was upregulated in patients with severity. In addition, the isoform-b gene expression was downregulated, in contrast to control groups for both genes, who showed normal expression for these genes. **Conclusion:** Serum IL-37 and IL-37 isoform-a are promising biomarkers for the diagnosis of RA, assessing disease activity and severity in patients with RA, and offering possible future therapeutic applications for RA patients, while IL-37 isoform-b is considered a weak biomarker for diagnosing RA.

Keywords: Activity, anti-inflammatory cytokines, IL-37 isoform-a, IL-37 isoform-b, mRNA, pro-inflammatory cytokines, Rheumatoid arthritis, RT-qPCR

Introduction

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disorder that mostly affects the joints in the hands and feet, leading to deterioration of cartilage and bones, causing disability.[1] RA is the most common inflammatory arthritis in Iraq; it is observed in (0.1–0.24) of the Iraqi population.[2]

The most prevalent clinical manifestation is chronic polyarticular swelling, particularly in small joints, which causes bone erosion,progressive joint deterioration, and deformities. Additionally, RA does not cause an immediate danger to life; it results in a decrease in patients' quality of life and significant economic burdens on the society.[3]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_528_24

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Submission: 28-May-2024 **Accepted:** 23-Dec-2024 **Published:** 28-Jun-2025

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How to cite this article: Razzaq FH, Obaid RF. Investigating the association of gene expression of IL-37 isoforms a and b and serum IL-37 with rheumatoid arthritis activity and severity. Med J Babylon 2025;22:588-94.

However, autoimmunity and systemic inflammation are primarily involved in the pathogenesis process, as determined by the detection of autoantibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (ACCP).[4]

In addition, clinical symptoms, physical examination, family history, imaging results, and other laboratory biomarkers such as C-reactive protein (CRP) and ACCPs are the primary determinants that aid in the diagnosis of RA.[5]

Over the past 5 years, significant advancements have been made in the identification of new biomarkers. These biomarkers aid clinicians in selecting the most effective therapy approach and enable identifying accurate RA biomarkers at a pre-clinical stage of disease.[6]

Interleukin (IL)-37 stands among the recently delineated progenies of the IL-1 cytokine family. This implies that instead of playing a role in enhancing inflammatory responses by promoting the body's innate and adaptive immunity, IL-37 shows anti-inflammatory properties through inhibiting the expression of tumor necrosis factor (TNF)-α, IL-6, and IL-1β, which are pro-inflammatory cytokines. In contrast to conventional therapies for autoimmune diseases, the impact of IL-37 involves modulating inflammation: it can have far-reaching effects in various inflammatory diseases such as RA, osteoarthritis or obesity, even including IBD and asthma.[7] The activity and severity of RA tell us about our anti-inflammatory agents fighting against pro-inflammatory agents that cause this disease.[8]

The IL-37 gene is part of the IL-1 family cytokines' family on chromosome 2q12–13. This place in the chromosome 2q12–13 harbors most genes for IL-1 family cytokines.[9]

It has played a role in various body parts including bone marrow, thymus, lymph nodes, immune cells, and monocytes. IL-37 has five different splice variants identified as IL-37 (a–e). Among these forms, IL-37b stands out as the most dominant version. It is also the most effective version with the highest length; it contains five exons from 6, for instance.[10]

The IL-37 type-a is found in many body parts such as the placenta, colon, lung, testis, and brain. It is first synthesized as a precursor and then changes to become active.[11]

The study was designed to investigate the serum levels of IL-37 and the expression of IL-37 in peripheral polymorphonuclear cells in comparison to control individuals, considering them as optimal biomarkers to predict RA activity and severity in newly diagnosed patients and planning new therapeutic protocols. Currently, as the reader is aware, this is the first research to investigate the expression of IL-37 isoforms in RA patients.

Materials and Methods

A case–control study was conducted on 140 participants (70 cases and 70 controls). The samples included 64 females and six males in both groups.

Inclusion criteria

Patients who were diagnosed by a rheumatologist categories based on ACR/EULAR criteria and with a score equal to or greater than 6. They were classified into remission, mild, moderate, and severe depending on their disease activity scores, as measured by CDAI, SDAI, DAS-28-CRP, and DAS-28-erythrocyte sedimentation rate (ESR).

Exclusion criteria

Patients with other autoimmune illnesses, central nervous system, and cardiovascular disorders; who have recently had surgery; those with wounds, acute inflammation, infectious diseases, and cancer; patients over the age of 70 and under the age of 20; pregnant women; patients diagnosed with diabetes mellitus; COVID-19 patients; or those with any congenital disorders.

Laboratory tests

Every patient and control underwent a number of laboratory tests, including the hematological testing CBC by automated analyzer and ESR by Westergren tube method, serum IL-37 and ACPA by enzyme-linked immunosorbent assay (ELISA), CRP by the Cobas C311 automated method, and RF measured by two methods: agglutination and ichroma RF IgM analyzer.

Real-time quantitative polymerase chain reaction (RT-qpcr)

During the blood collection process, for gene expression for only 70 samples (40 patients and 30 controls), 1 mL of TRIzol reagent was added to each ml of blood within EDTA tubes. The samples were kept in a deep freezer at −80°C until the work began. After completely melting of test tubes at room temperature, PBMCs were obtained from blood samples, and the RNA was extracted using a specialized lysing buffer that lysed cells, in addition to other reagents such as chloroform, which when added to the solution and centrifuged will separate into an upper part that is white and contains RNA, and a lower part that is pink and contains other blood components. Isopropanol and ethanol also are added to the solution for dissolved proteins and other impurities. RNA is reverse-transcribed and amplified later by RT-qPCR using one-step kit (Promega-USA) and the following primers:[12]

IL-37-a forward: *GGGAAACAGAAACCAAAGGA*

IL-37-a reverse: *CCCAGAGTCCAGGACCAGTA*

IL-37-b forward: *AGCCTCCCCACCATGAATTT*

IL-37-b reverse: *ATTCCCAGAGTCCAGGACCA*

HPRT1 (housekeeping gene)

forward: *TGGAAAGGGTGTTTATTCCTCAT*

reverse*: ATGTAATCCAGCAGGTCAGCAA*

PCRs were amplified with the following steps: denaturation at 95°C, annealing at 60°C and extension at 72°C for 45 cycles.

Ethical approval

The ethics committee of the Faculty of Medicine gave its approval to this study before it began. Every patient was asked to provide their informed consent, approved by the Rheumatology Unit.

Statistical analysis

The data from both research groups were gathered and analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS, IBM Company, Chicago, IL 60606, USA). Statistical analysis included representing continuous variables using the mean, standard deviation, and standard error. Categorical variables were reported as frequencies and percentages. Based on the normality test, it is indicated that the variables follow a normal distribution. The results were reported as the mean ± standard deviation. A *t* test was used to compare the means between two groups, while ANOVA was used for multi-group comparison of means. Statistical significance was defined as a *P* value of less than 0.05, and high significance was considered if the *P* value was <0.001. The chi-square (χ^2) test was used to compare two categorical variables.

Results

IL-37 levels between RA patients and healthy control participants were compared, and the findings are shown in [Table 1]. The mean levels of IL-37 were (49.82) in patients with RA and (18.20) control participants. The difference was statistically highly significant ($P < 0.001$).

In order to determine the IL-37 cutoff value and assess its ability to predict RA illness, a receiver operator characteristic (ROC) curve study was conducted. The findings are displayed in [Figure 1]. The cutoff value for IL-37 was more than 24.52 ng/ml, with 84.3 sensitivity and 84.3 specificity, and the area under the curve was 0.823.

This study shows elevated levels of IL-37 in the older patient group (over 50 years) as shown in [Table 2] and had the highest value (mean=56.48).

Table 1: IL-37 level in patients with rheumatoid arthritis and control group

IL-37 levels	Cases –control comparison		*P*
	Patients *n* = 70	Control group *n* = 70	
Mean±SD	49.82 ± 10.48	18.20 ± 6.10	<0.001 HS
Range	1.96–134.93	0.66–48.00	

This study demonstrates a significant correlation between IL-37 levels and CRP ($P = 0.001$). IL-37 was positively correlated with anti-CCP ($P = 0.041$), and IL-37 was correlated with ESR ($P = 0.021$), as shown in [Table 3].

The current findings indicate that the average levels of IL-37 were notably elevated in patients with severe DAS-ESR and severe DAS-CRP ($P = 0.001$), as shown in [Table 4]. A significant association was observed between IL-37 and CDAI and SDAI as activity parameters, ($P = 0.001$). The current findings indicate that the mean levels of IL-37 were notably elevated in severe cases compared to those with other CDAI scores.

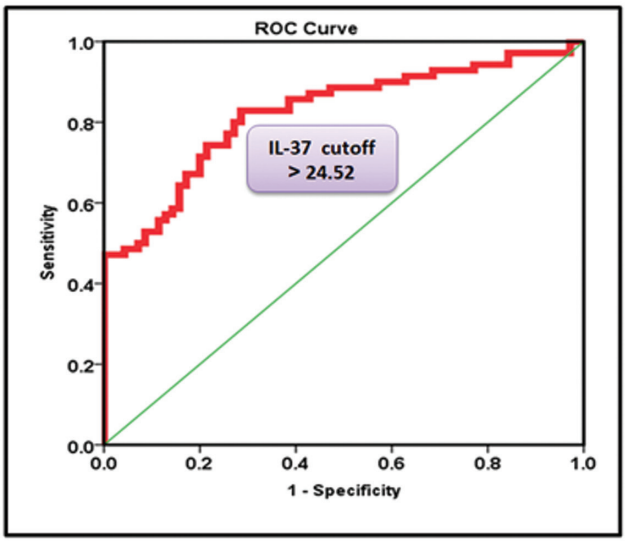

Figure 1: Receiver operator characteristic curve analysis of IL-37 for the calculation of a possible diagnostic cutoff value

Table 2: Frequency distribution of the IL-37 level according to some characteristics

Characteristics		*N*	IL-37 level Mean±SD	*P*
Age groups	<40 years	17	46.66 ± 8.48	0.252 A NS
	40–49 years	22	42.36 ± 5.72	
	≥ 50 years	31	56.48 ± 1.32	
Gender	Male	64	34.57 ± 11.26	0.231 NS
	Female	6	51.21 ± 10.6	
Treatment response	Poor	36	60.67 ± 11.99	0.011 A S
	Good	25	36.09 ± 9.17	
	No-treatment	9	44.55 ± 9.62	
BMI	Normal	9	53.43 ± 7.87	0.454 A NS
	Overweight	29	42.56 ± 8.87	
	Obese I	15	52.26 ± 9.42	
	Obese II	13	62.38 ± 8.89	
	Obese III	4	44.32 ± 9.75	

n: Number of cases, SD: Standard deviation, †: Independent-samples *t* test, A: One-way ANOVA test, S: Highly significant at $P \leq 0.05$, NS: Not significant at $P < 0.05$

Table 3: Correlation between different parameters

Parameter	IL-37		CRP		RF		Anti-CCP	
	R	*P*	*R*	*P*	*R*	*P*	*r*	*P*
IL-37	1							
CRP	0.440	0.001*	1					
RF	0.132	0.310	0.242	0.043*	1			
Anti-CCP	0.238	0.041*	0.051	0.672	0.075	0.559	1	

Table 4: Frequency distribution of serum IL-37 levels according to rheumatoid arthritis activity and severity scores

Characteristic	Remission *n* = 2	CDAI	Moderate *n* = 35	Severe *n* = 29	*P* value
		Mild *n* = 4			
IL-37 ng/ml (mean)	27.63	39.04	29.74	79.77	0.001
		SDAI			
	Remission *n* = 2	Mild *n* = 7	Moderate *n* = 33	Severe *n* = 28	
	21.65	33.98	30.55	81.30	
		DAS-28ESR			
	Remission *n* = 2	Mild *n* = 0	Moderate *n* = 43	Severe *n* = 25	
	21.65		31.39	63.66	
		DAS-28CRP			
	Remission *n* = 3	Mild *n* = 5	Moderate *n* = 41	Severe *n* = 21	
	18.96	22.68	41.27	77.3	
		Severity			
	Remission *n* = 3	Low *n* = 13	Moderate 27	High 27	
	30.32	32.60	51.97	63.35	

Table 5: Isoform-a gene expression in patients with rheumatoid arthritis and the control group

	Isoform-a gene expression		*P*
	Patients *n* = 40	Controls *n* = 30	
Mean±SD	5.30 ± 1.31	1.10 ± 0.47	< 0.001 † HS

Gene expression results

The mean expression levels of the isoform-a gene were 5.30 ± 1.31 and 1.10 ± 0.47 in patients with RA and controls, respectively, as shown in [Table 5].

The comparison was conducted to assess the expression of isoform-a in relation to RA activity and severity scores. The findings are shown in [Table 6]. The current findings indicate that there is no significant difference in the expression of isoform-a based on RA activity and severity levels ($P > 0.05$), but the expression is elevated within groups with severe activity and parameters.

The isoform-b expression was downregulated in patients compared to controls who had normal expression of IL-37-b (mean levels for patients were 0.13 ± 0.030 versus 1 ± 0.33 for controls), as shown in [Table 7].

The study assessed the expression of isoform-b in relation to activity and severity parameters in RA patients. The findings are presented in [Table 8]. The current findings indicate that there is no significant difference in the expression of isoform-b based on all RA activity and severity parameters ($P > 0.05$).

Discussion

This research assesses the mean serum level of IL-37, which was highly significant in RA patients (49.82), compared to the control group (18.20) ($P < 00.1$). The findings are consistent with the findings by [13,14] as shown in [Table 1].

Pro-inflammatory triggers increase IL-37 expression, which suppresses inflammation via a variety of routes. Intracellularly, the IL-37/SMAD-3 combination inhibits inflammatory pathways, while increasing the production of anti-inflammatory cytokines. Extracellularly, IL-37 binds to IL-18Ra and IL1R8. As a result, anti-inflammatory pathways are activated, and pro-inflammatory pathways are suppressed.[15]

This research has demonstrated that IL-37 expression is elevated in patients with RA, suggesting that serum levels of IL-37 might serve as a diagnostic biomarker for RA, which may distinguish between patients with RA and healthy individuals. but this strategy is ineffective in controlling inflammation in active RA due to insufficient IL-37 expression or the limited impact of IL-37.

This study shows elevated levels of IL-37 in the older patient age group (over 50 years) and had the highest

Table 6: Distribution of isoform-a according to rheumatoid arthritis activity and severity scores

Characteristic	Remission $n = 2$	CDAI	Moderate $n = 20$	Severe $n = 16$	*P* value
		Mild $n = 2$			
Isoform-a gene expression (mean)	5.23	5.03	5.17	5.40	0.915
		SDAI			
	Remission $n = 2$	Mild $n = 3$	Moderate $n = 15$	Severe $n = 20$	
	5.81	6.01	5.07	5.42	0.502
		DAS-28ESR			
	Remission $n = 2$	Mild $n = 0$	Moderate $n = 27$	Severe $n = 2$	
	4.91		4.73	5.56	0.130
		DAS-28CRP			
	Remission $n = 2$	Mild $n = 2$	Moderate $n = 19$	Severe $n = 17$	
	5.01	4.86	5.24	5.35	0.869
		Severity			
	Remission $n = 2$	Low $n = 3$	Moderate 18	High 17	
	4.59	5.40	5.19	5.80	0.758

Table 7: Isoform-b gene expression in patients with rheumatoid arthritis and controls

	Isoform-b gene expression		*P* value
	Patients $n = 40$	Controls $n = 30$	
Mean± SD	0.13 ± 0.030	1 ± 0.33	<0.001 S

mean value (56.48), which is in agreement with.[14] IL-37 increases cytokine production in aged T-cells and decreases the surface expression of apoptosis. Recombinant IL-37 therapy enhances T-cell activity and effectiveness. IL-37 is associated with youthful restoration of gene expression levels of PDCD1, LAT and STAT4 in old CD4 + T-cells, and LAT in aged CD8 + T-cells, while also reducing surface expression of immuno-inhibitory proteins (PDCD1, PD1).[8] Therefore, IL-37 may reverse aging-associated "immunosenescence" and improve the activity of aged T-cells, suggesting that pharmacological compounds of recombinant IL-37 specific drugs may be an option for RA patient therapy. Further studies are needed to determine the exact effects and effective doses of these medications.[16]

The levels of IL-37 significantly increased within the RA patient group, which was poorly responsive to treatment ($P = 0.011$).[13] align with this finding. IL-37 shows a notable correlation with TNF-α and IL-17 in RA patients. TNF-α may significantly enhance the production of IL-37 in PBMCs. After DMARDS therapy, the plasma levels of TNF-α, IL-17, and IL-37 were dramatically reduced in medication responders, in contrast to non-responders who continuously had high levels of TNF-α and IL-37.

There was a positive correlation between IL-37 and CRP levels in RA patients ($P = 0.001$). The results of the study by Yuan *et al*.[13] were compatible with the same result. CRP is recognized as an acute marker of inflammation. Elevated CRP levels in RA cause macrophages to generate IL-6.[17] Elevated pro-inflammatory cytokine levels, including IL-6, mostly increase IL-37 expression. Pro-inflammatory cytokines trigger IL-37 during the first stage of RA.

IL-37 in this study is positively correlated with ACCP ($P = 0.041$). This finding is in agreement with that by Cao *et al*. and Zayed *et al*.[18,19]

About the diagnostic role of IL-37 in the identification of RA, the receiver operating characteristic (ROC) curve as shown in [Figure 1] shows that serum IL-37's optimal diagnostic cutoff levels were equal to or less than 24.52 pg/ml with 84.3 sensitivity and 84.3 specificity, and the area under the curve was 0.823. This finding was in line with those by Yuan *et al*.[13] and Al-Tae *et al*.[14] These data suggest that IL-37 is a good biomarker for RA diagnosis.

According to the findings of this study, a significant association exists between IL-37 and CDAI and SDAI as activity parameters ($P = 0.001$). The current findings indicate that the average levels of IL-37 were notably elevated in severe cases compared to those with other CDAI scores. This finding aligns with those by[18] and Yuan *et al*.[20] In contrast to Jasim *et al*.[21] who found that there was no an association between CDAI and IL-37.

This study found a clear association between IL-37 and RA patients' severity ($P = 0.022$). Elevated levels of IL-37 are associated with severe cases compared to lower categories. These findings were consistent with those of Zhu *et al*.,[10] who found that the serum concentration of IL-37 correlated tightly with RA severity. In contrast, another study done in Mosul, Iraq, by Al-Tae *et al*.[14] found that there was no significant association between IL-37 and RA severity.

Missense mutations in IL-1β, TNF-α, and IL-6 are few in comparison to coding mutations in their receptors,

Table 8: Distribution of isoform-b according to rheumatoid arthritis activity and severity scores

Characteristic	Remission $n = 2$	CDAI	Moderate $n = 20$	Severe $n = 16$	*P* value
		Mild $n = 2$			
Isoform-b gene expression (mean)	0.124	0.134	0.128	0.141	0.463
		SDAI			
	Remission $n = 2$	Mild $n = 3$	Moderate $n = 15$	Severe $n = 20$	
	0.143	0.132	0.13	0.141	0.759
		DAS-28ESR			
	Remission $n = 2$	Mild $n = 0$	Moderate $n = 11$	Severe $n = 27$	
	0.127		0.128	0.141	0.431
		DAS-28CRP			
	Remission $n = 2$	Mild $n = 2$	Moderate $n = 19$	Severe $n = 17$	
	0.161	0.141	0.132	0.143	0.556
		Severity			
	Remission $n = 2$	Low $n = 3$	Moderate $n = 18$	High $n = 17$	
	0.149	0.140	0.134	0.135	0.930

intracellular proteins, and kinases that are important for signal transduction. Missense mutations in the coding sequence of IL-37 are linked to human illnesses. The single-nucleotide polymorphism (SNP) in IL-37b (*rs3811047*), which results in a threonine–alanine substitution in amino acid 42 on exon 6, has been linked to decreased disease severity in some individuals with RA.[22]

Isoform-a gene expression

The mean expression levels of the isoform-a gene were 5.30 ± 1.31 and 1.10 ± 0.47 in patients with RA and controls, as shown in [Table 5], respectively. The mean expression level was significantly higher in patients with RA compared to controls ($P < 0.001$). During gene expression, a phenomenon known as alternative splicing occurs, allowing for the inclusion or deletion of various combinations of exons (coding sections) within a gene from the final messenger RNA (mRNA) transcript. This method enables a solitary gene to generate several mRNA isoforms, which may then lead to the formation of distinct protein isoforms.[23] The investigations corresponded to five distinct isoforms, including IL-37a, IL-37b, IL-37c, IL-37d, and IL-37e, which have an anti-inflammatory effect by suppressing the synthesis of pro-inflammatory cytokines and chemokines. The isoform-a is initially synthesized as a precursor and then undergoes post-translational changes to generate its active version.[11] IL-37 is normally released by immune cells, namely, macrophages and dendritic cells. After pro-inflammatory stimuli or agonists for TLRs, the expression of IL-37 occurs extracellularly in both precursor and mature forms. To form a triple complex, IL-37 interacts with IL18Rα and attracts IL-1R8. The control of IL-37 gene expression is complicated and may be affected by several variables, such as inflammatory stimuli and cellular stress. IL-37 isoform-a increases in response to pro-inflammatory cytokines, including IL1β and TNF-α, as well as toll-like receptor (TLR) ligands. Transcription factors, including NF-κB, STAT1, and STAT3, have an important role in controlling the production of IL-37.[24]

The comparison helps assess the expression of isoform-a in relation to RA activity and severity scores. The findings are shown in [Table 6]. The current findings indicate that there is no significant variation in the expression of isoform-a based on RA activity and severity levels ($P > 0.05$). However, regarding severity and activity parameter classification, it is markedly increased within the patient groups with severity. Genetic differences might influence the control of IL-37 levels. Specific genetic variations or alterations may impact the synthesis and function of IL-37, possibly resulting in elevated levels in individuals with RA. Nevertheless, more investigations are required to demonstrate a conclusive genetic connection. For example, a community of Egyptian individuals with RA showed a correlation between the IL-37 gene, specifically the IL-37 gene *rs3811047* SNP, and increased disease activity.[24,25]

Isoform-b gene expression

The isoform-b expression was downregulated in patients compared to controls who were within normal expression of IL-37-b (mean levels for patients was 0.13 versus 1 for controls), as shown in [Table 7]. At elevated levels, the process of IL-37 dimerization may function as a negative feedback mechanism to prevent severe immunosuppression.[11] Some studies have indicated that the mRNA of IL-37 b is unstable and remains at low levels in resting human peripheral mononuclear cells (PBMCS), especially after taking DMARDS, which causes a decrease in PBMC proliferation. It has been shown that SMAD-3, a molecule that regulates gene expression in the TGF-β pathway, plays a crucial role in the biological impacts of IL-37b by facilitating the movement of IL-37b to the nucleus.[26]

IL-37b has the ability to inhibit the function of dendritic cells. DCs, which play a crucial role in the immune system by

receiving, integrating, and transmitting information across different types of cells. They serve as a link between innate and adaptive immune responses. IL-37b reduces the surface expression of the co-stimulatory molecules CD86 (B7-2) and MHC II on the surface of DCs, which are important activators for CD4 + T-cells. This, together with creating an anti-inflammatory cytokine environment, can lead to attenuation of T-cell responses.[27] IL-37b is the longest transcript variant, the most biologically active, and the most studied isoform. These data suggest a possible therapeutic effect of this isoform, particularly if the researchers act to improve the stability of its mRNA.[28,29] The same process of mRNA regulation is observed in IL-37d. The downregulation of IL-37b has been proposed to occur in conjunction with the upregulation of isoform-e and isoform-c, while the underlying mechanisms remain unidentified[12] and the findings of this study support this theory.

The study assessed the expression of isoform-b in relation to activity and severity parameters in RA patients. The findings are presented above in [Table 8]. The current findings indicate that there is no significant difference in the expression of isoform-b based on all RA activity and severity parameters ($P > 0.05$). This study was constrained by the lack of genetic data and was restricted to a single time point. Racial or ethnic disparities in RA during the early stages of the illness should be taken into consideration.

Conclusion

Serum IL-37 and IL-37 isoform-a are promising biomarkers for the diagnosis of RA, assessing disease activity and severity in patients with RA, and offering possible future therapeutic applications for RA patients, while IL-37 isoform-b considered as weak biomarker for diagnosing RA.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Xiang S, Wang R, Hua L, Song J, Qian S, Jin Y, *et al*. Assessment of bidirectional relationships between mental illness and rheumatoid arthritis: A two-sample mendelian randomization study. J Clin Med 2023;12:944.
2. Almurshedi S, Alasady R. The role of interleukin-22 in the diagnosis and evaluation of disease activity in rheumatoid arthritis. Kufa Med J 2023;19:112-22.
3. McGonagle D, Watad A, Savic S. Mechanistic immunological based classification of rheumatoid arthritis. Autoimmun Rev 2018;17:1115-23.
4. Baraka EA, Balata MG, Ahmed SH, Khamis AF, Elattar EA. Interleukin-37 as an anti-inflammatory cytokine: Does its relation to disease activity suggest its potential role in rheumatoid arthritis therapy. Egypt Rheumatol Rehabil 2021;48:1-9.
5. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: A review. JAMA 2018;320:1360-72.
6. Jiang Y, Zhong S, He S, Weng J, Liu L, Ye Y, *et al*. Biomarkers (mRNAs and non-coding RNAs) for the diagnosis and prognosis of rheumatoid arthritis. Front Immunol 2023;14:1-23.
7. Ragab D, Mobasher S, Shabaan E. Elevated levels of IL-37 correlate with T cell activation status in rheumatoid arthritis patients. Cytokine 2019;113:305-10.
8. Cavalli G, Tengesdal IW, Gresnigt M, Nemkov T, Arts RJW, Domínguez-Andrés J, *et al*. The anti-inflammatory cytokine interleukin-37 is an inhibitor of trained immunity. Cell Reports 2021;35:108955.
9. Shilovskiy IP, Dyneva ME, Kurbacheva OM, Kudlay DA, Khaitov MR. The role of interleukin-37 in the pathogenesis of allergic diseases. Acta Naturae 2019;11:54-64.
10. Zhu J, Xie C, Qiu H, Shi L. Correlation between level of interleukin-37 and rheumatoid arthritis progression. Int J General Med 2021;14:1905-10.
11. Pan Y, Wen X, Hao D, Wang Y, Wang L, He G, *et al*. The role of IL-37 in skin and connective tissue diseases. Biomed Pharmacotherapy 2020;122:109705.
12. Jia H, Liu J, Han B. Reviews of interleukin-37: Functions, receptors, and roles in diseases. Biomed Res Int 2018;2018:1-14.
13. Yuan ZC, Wang JM, Huang AF, Su LC, Li SJ, Xu WD. Elevated expression of interleukin-37 in patients with rheumatoid arthritis. Int J Rheumatic Dis 2019;22:1123-9.
14. Al-Tae F, Al-Harbi A, Turki K, Sood M. Interleukin -37 in rheumatoid arthritis: Correlation with clinical severity and genetic polymorphisms in Mosul city, Iraq. Egyptian J Immunol 2023;30:162-73.
15. Su Z, Tao X. Current understanding of IL-37 in human health and disease. Front Immunol 2021;12:1-18.
16. Cavalli G, Koenders M, Kalabokis V, Kim J, Tan AC, Garlanda C, *et al*. Treating experimental arthritis with the innate immune inhibitor interleukin-37 reduces joint and systemic inflammation. Rheumatology 2016;55:2220-9.
17. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol 2018;9:1-11.
18. Cao S, Shi H, Sun G, Chen Y, Hou G, Wang D, *et al*. Serum IL-37 level is associated with rheumatoid arthritis and disease activity: A meta-analysis. Biomed Res Int 2021;2021:1-7.
19. Zayed NS, Obaid RF, Hamza AA. Association of cellular communication network factor 3 (CCN3) with rheumatoid arthritis disease and it's severity (case-control study). Med Sci J Adv Res 2022;3:201-8.
20. Yuan ZC, Wang JM, Huang AF, Su LC, Li SJ, Xu WD. Elevated expression of interleukin-37 in patients with rheumatoid arthritis. Int J Rheum Dis 2019;22:1123-9.
21. Jasim ME, Jameel KS, Awadh IN. Estimation of interleukin 32 and interleukin 37 serum levels in iraqi patients with rheumatoid arthritis. Arch Razi Inst 2023;78:743-50.
22. El-Sayed EH, Saleh MH, Al-Shahaly MH, Toraih EA, Fathy A. IL-37 gene variant (rs3811047): A marker of disease activity in rheumatoid arthritis: A pilot study. Autoimmunity 2018;51:378-85.
23. Kelemen O, Convertini P, Zhang Z, Wen Y, Shen M, Falaleeva M, *et al*. Function of alternative splicing. Gene 2013;514:1-30.
24. Zeng H, Zhou K, Ye Z. Biology of interleukin-37 and its role in autoimmune diseases (Review). Exp Ther Med 2022;24:1-10.
25. Cavalli G, Dinarello CA. Suppression of inflammation and acquired immunity by IL-37. Immunol Rev 2018;281:179-90.
26. Sharma S, Kulk N, Nold MF, Gräf R, Kim SH, Reinhardt DS, *et al*. The IL-1 family member 7b translocates to the nucleus and down-regulates proinflammatory cytokines. Immunol 2008;180:5477-82.
27. Nold MF, Nold-Petry CA, Zepp JA, Palmer BE, Bufler P, Dinarello CA. IL-37 is a fundamental inhibitor of innate immunity. Nat Immunol 2010;11:1014-22.
28. Boraschi D, Lucchesi D, Hainzl S, Leitner M, Maier E, Mangelberger D, *et al*. IL-37: A new anti-inflammatory cytokine of the IL-1 family. Eur Cytokine Netw 2011;22:127-47.
29. Diab BA, Obaid RF. Impacts of Hashimoto's thyroiditis on rheumatoid arthritis activity and its complication among Iraqi patients with rheumatoid arthritis. Med J Babylon 2024;21:646-52.