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Evaluate the Association Between IL-37 Isoform-C and D Gene Expression with the Severity and Activity of Rheumatoid Arthritis

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ABSTRACT

Background: *Rheumatoid arthritis (RA) is a systemic, chronic autoimmune condition characterized by joint inflammation and pain, leading to the degeneration of the joints and bones, which may develop into deformities. The identification of the potential of new RA biomarkers, such as IL-37 isoforms for diagnosis and treatment applications is now under investigation.* ***Purpose****: This research aims to investigate the connection between the expression of IL37 isoform-c and IL37 isoform-d genes with RA activity and severity, their rules in diagnosis of the disease and for future RA therapeutic purposes.* ***Methods****: A case-control study was conducted on a total of 140 individuals. A total of 70 patients, who were recently diagnosed with rheumatoid arthritis by a rheumatologist, were included in the study, along with 70 control volunteers. The samples were obtained by using freshly acquired blood and serum samples via the use of RT-qPCR, ELISA, and other methods. The sample included 64 females and 6 men in both the patient and control groups. The age ranges from 20 to 70 years. Specimens were gathered between August 2023 and December 2023 from the Rheumatology department at AL-Sader Medical City in Najaf Governorate, Iraq. The blood IL-37 level was quantified using an enzyme-linked immunosorbent assay (ELISA). Additionally, immune markers including Anti-CCP, ESR, RF, and CRP were assessed. The quantification of IL-37 isoforms' gene expression was performed using qRT-PCR. The activity of rheumatoid arthritis (RA) was assessed using DAS28-ESR, DAS28-CRP, and CDAI, which also allowed for the determination of disease severity.* ***Results****: The levels of inflammatory parameters including Anti-CCP, CRP, RF, and ESR were significantly elevated in RA patients in compared to controls. IL-37 isoform-c mRNA expression, as determined by RT-qPCR, has significantly greater expression in the patients' group. It was upregulated in moderate groups of patients. Furthermore, the isoform-d gene was downregulated, in contrast to control groups for both genes, who exhibited normal expression for these genes. And there was a non-significant association between IL37 isoforms c and d expression and RA activity and severity. However, IL37-c expression increased within the moderate patient groups based on severity and activity categorization as compared to controls.* ***Conclusion:*** *IL37 isoform-c and isoform-d are considered as a weak biomarker for diagnosing RA, evaluating disease activity and severity for RA patients.*

Keywords: Rheumatoid Arthritis, Proinflammatory Cytokine, IL-37, Gene Expression, Anti-Inflammatory Cytokine, Severity and Activity.

Article Information

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease that characterized persistent inflammation in the joints and other organs, including the kidney, heart, skin, lung, digestive system, eye, skin, and neurological system. [1] The prevalence rate ranged from 0.5% to 1% of the population and exhibited geographical variance. In Iraq, the prevalence is 1%. The risk factors for RA include genetic predisposition, female gender, obesity, and advanced age. Typical symptoms include morning stiffness, joint soreness, and edema [2].Recently, there is a need for new biomarkers that may aid in the rapid identification of patients with greatest risk of a negative serological result has become very important. A biomarker is often a quantifiable attribute that may serve as a signal of a certain biological state or disease [3].

IL-37 is a kind of anti-inflammatory cytokines. Which is a member of IL-1 family. It is first synthesized as a precursor protein, then cleaved by caspase-1 to generate its mature version. The rules of IL-37 had been shown in different organs and cells [4]. IL-37 is an anti-inflammatory cytokine, is thought to be linked to the development of autoimmune, inflammatory, malignancies, and metabolic diseases. Consequently, it is considered a promising target for treatment of RA [5]. The findings suggests that IL-37 may have a role in lowering production of pro-inflammatory cytokines in individuals with RA. Increasing IL-37 levels during RA serves as a negative feedback mechanism. This increase is caused by elevated production of inflammatory cytokines [6]. The alternative splicing process is responsible for generating the five isoforms of IL37. The 6 exons encode for five isoforms of IL37, namely IL-37a, b, c, d, and e. The isoform b is the longest and most widely studied variant [7]. The IL37-c is resembled to isoforms b, with the exception of a loss that occurs when exon 2 is spliced to exon 5. IL37-d is composed of exons 1,4,5 and 6. In contrast to isoform b, only exon 6 is absent[8].

The purpose of this study is to examine the levels of expression of IL37 isoforms c and in peripheral polymorphonuclear cells (PBMCs) in newly diagnosed patients compared to control participants, which will aid in determining if these isoforms can serve as reliable biomarkers for RA and for predicting the activity and severity of RA, as well as the possibilities of developing new treatment protocols based on these findings. This study Conducted for the first time in Iraq, as a researcher is aware.

METHODS

Case-control research was performed on a total of 140 participants, with 70 individuals classified as cases and 70 individuals classified as controls.

Inclusion criteria:

A rheumatologist diagnosed patients who met the ACR/EULAR criteria and achieved a score of 6 or above. The individuals were categorized into several groups based on their disease activity scores, as determined by CDAI, SDAI, DAS28-CRP, and DAS28-ESR, into remission, mild, moderate, and severe classifications [5].

Exclusion criteria:

Individuals who have been diagnosed with other rheumatological & autoimmune disease, central nervous system, individuals who have recently undergone surgery, individuals with acute inflammation, infectious diseases, cancer patients, individuals over the age of 70 and under the age of 20, and pregnant women.

Laboratory tests:

Each participant, whether a patient or control, underwent several laboratory tests. These tests included hematological tests such as CBC (complete blood count) using an automated analyzer device and ESR (erythrocyte sedimentation rate) using the Westergren method. Additionally, serum IL-37 and ACPA (anti-citrullinated protein antibodies) were measured using enzyme-linked immunosorbent assay (ELISA), CRP (C-reactive protein) was measured using the Cobas C311 automated method, and RF (rheumatoid factor) was measured using agglutination and ichroma RF IgM analyzer method.

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

During the collection of blood, 1 ml of Triazole was mixed with each ml of whole blood in separated EDTA tube prepared specifically for gene expression. This was done for a total of 70 samples, consisting of 40 patients and 30 controls. The specimens were stored in a deep- freezer at -80 °C until the commencement of the project. Later, the mRNA is extracted and subsequently amplified via RT-qPCR using the primers provided below [9]:

Table (1): The primers sequences used in RT-qPCR:

Primer	direction	Sequence	Product	Method
IL-37C	**forward**	***AGTGCTGCTTAGAAGACCCG***	**161 bp**	**RT-qPCR**
	Reverse	***CCCTTTAGAGACCCCCAGGA***		
IL-37D	**forward**	***TGCTGCTTAGAAGGTCCAAA***	**104 bp**	
	Reverse	***GCTATGAGATTCCCAGAGTCCA***		
Housekeeping genes (HPRT1)	**forward**	***TGGAAAGGGTGTTTATTCCTCAT***	**151 bp**	
	Reverse	***ATGTAATCCAGCAGGTCAGCAA***		

RESULTS

The study found that the average ESR level in RA patients was significantly higher than controls (41.96) mm/h versus (10.45) mm/h, as presented in **(Table)**. Regarding CRP levels shown in (table 1), the mean in patients with RA was significantly higher than control subjects (11.98 ± 4.99 vs 12.16 ±4.31), (P≤0.001). This study revealed that the mean RF titer for the patient group was significantly higher than that of controls (30.70 ± 5.39 vs 12.16 ±4.31). Regarding ACCP levels, the mean of RA patients was significantly higher than controls (15.59 ± 2.28 vs 7.94 ± 2.24). as presented in Table 1.

The comparison of isoform-c gene expression was conducted between patients with RA and control participants. The findings are shown in **Table (2)**. The mean expression levels of isoform-c were (1.47 ± 0.79) in patients with RA versus (1.04 ± 0.33) in controls. The Receiver Operator Characteristic (ROC) curve analysis was carried out, and the results are presented **(figure 1)** The isoform-c cut-off value was 1.09-fold with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve of 67.5%, 73.3%, 77.1%, 62.9% and 0.668 (0.540-0.795). The present results indicate isoform-c is considered a weak diagnostic marker.

The current findings indicate that there is no significant variation in the expression of isoform-c based on RA activity and severity levels (p>0.05) as shown in **Table (3)**. but it's markedly increased within the moderate patient group regarding severity and activity parameter classifications. Regarding gene expression results for isoform-d as described in **Table (4)**, it was downregulated in patients in contrast to controls, who had normal expression levels (the mean for patients is 0.485 ± 0.15 versus 1.20 ± 0.45 for controls).

The current findings indicate that there is no significant difference in the expression of isoform-d based on all RA activity and severity parameters (p>0.05) as shown in **Table (5)** below. Additionally, its expression is variable within different disease activity and severity group classifications.

Table 1: inflammatory parameters levels in RA patients and control.

Erythrocyte Sedimentation Rate (ESR) level mm/hr			
Mean ± SD	**41.96 ± 16.40**	**10.45 ± 3.70**	**≤ 0.001 † HS**
Range	5.00 -140.0	4.00-22.00	
C-Reactive Protein (CRP) mg/L			
Mean ± SD	**11.98 ± 4.99**	**2.82 ± 0.861**	**≤ 0.001 † HS**
Range	0.14 -102.00	0.17-16.98	
Rheumatoid Factor IU/mL			
Mean ± SD	**30.70 ± 5.39**	**12.16 ±4.31**	**≤ 0.001 † HS**
Range	6.00 -200.0	8.45-28.40	

Anti-ccp levels U/ml			
Mean ± SD	**15.59 ± 2.28**	**7.94 ± 2.24**	**≤ 0.001 † HS**
Range	4.10 -67.30	3.03-15.00	

Table (2): Isoform C gene expression in patients with RA and the control group.

	isoform-c gene expression		
	Patients ***n*** **= 40**	**Controls** ***n*** **= 30**	***P***
Mean± SD	**1.47 ± 0.79**	**1.04 ± 0.33**	**0.007 † S**

HS: Highly significant at P ≤ 0.001

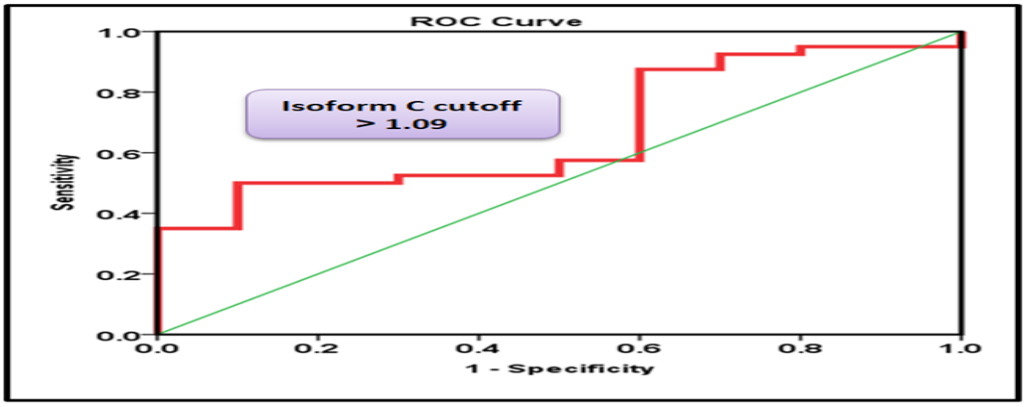

Figure (1): Receiver operator characteristic curve analysis of isoform-c for the calculation of a possible diagnostic cutoff value.

Table (3): Distribution of isoform-c according to RA activity and severity scores.

Characteristic	CDAI				
	Remission n=2	**Mild n=2**	**Moderate n=20**	**severe n=16**	**P value**
Isoform-c gene expression (mean)	**1.43**	**1.51**	**1.56**	**1.51**	**0.213**
		SDAI			
	Remission n=2	**Mild n=3**	**Moderate n=15**	**Severe n=20**	
	1.41	**1.31**	**1.57**	**1.41**	**0.198**
		DAS-28ESR			

	Remission n=2	Mild n=0	Moderate n=11	Severe n=27	
	1.57		1.66	1.35	0.225
		DAS-28CRP			
	Remission n=2	Mild n=2	Moderate n=19	Severe n=17	
	1.45	1.47	1.61	1.54	0.652
		Severity			
	Remission n=2	low n=3	Moderate 18	High 17	
	1.64	1.41	1.71	1.39	0.127

Table (4): Isoform d gene expression in patients with RA and controls.

	Isoform D gene expression		
	Patients *n* = 40	Healthy control *n* = 30	*P*
Mean± SD	0.485 ± 0.15	1.20 ± 0.45	0.001 † S
Range	0.27– 0.77	0.33-1.77	

Table (5): Distribution of isoform-d according to RA activity and severity scores.

Characteristic	CDAI				
	Remission n=2	Mild n=2	Moderate n=20	severe n=16	P value
Isoform-d gene expression (mean)	0.484	0.431	0.536	0.453	0.432 N.S
		SDAI			
	Remission n=2	Mild n=3	Moderate n=15	Severe n=20	
	0.448	0.487	0.531	0.454	0.544 N. S
		DAS-28ESR			
	Remission n=2	Mild n=0	Moderate n=11	Severe n=27	
	0.386		0.497	0.507	0.489
		DAS-28CRP			
	Remission n=2	Mild n=2	Moderate n=19	Severe n=17	
	0.363	0.493	0.613	0.466	0.316 N.S
		Severity			
	Remission n=2	low n=3	Moderate 18	High 17	
	0.471	0.507	0.434	0.536	0.277 N.S.

S: highly significant at P ≤ 0.05; NS: not significant at P > 0.05.

DISCUSSION

The current study found that the average ESR level in RA patients was significantly higher than controls as presented in (table1) and this result is in line with (Yazici S *et al*. 2010) [10] and (Dessein *et al*. 2022) [11]. The erythrocyte sedimentation rate, which is a non-specific inflammatory test, is a physical phenomenon that is linked to the viscosity of plasma and the quantity of RBCS. Specifically, the albumin/globulin ratio is changed. stimulation of IL-6, which activates acute-phase reactants such as fibrinogen leading to elevated ESR [12]. Research on early RA infection indicated that female patients had elevated ESR rather than males [11] and this is in line with the results of this study.

Regarding CRP levels that shown in **(table 1)**, the mean in patients with RA was significantly higher than control subjects, (P≤0.001). This finding is in agreement with (Mohammed *et al*.2023) [13] and (Almurshedi & Alasady, 2023) [14] . CRP is produced in hepatocytes and its transcription is mostly controlled by IL-6, which is activated subsequently by immune complex formation during RA infection. The biologic functions of CRP are activation of the complement system by the classical pathway and assisting the clearance of necrotic cells [15]. CRP is considered an immunological regulator, not only an indicator for inflammation or infection such as nitric oxide release and cytokine production [16].

This research found that there was a statistically significant difference between CRP and DAS-28 CRP (p=0.001). this result is in line with (Serdaroğlu *et al*.2008) [17] ,who also found a significant difference (p<0.05). This study revealed that the mean RF titer for the patient's group was significantly higher than that of controls, as shown in **(table1)**. This result is consistent with (Mohammed *et al*.2023) [13]. RF is one of the main auto-antibodies that is related to RA. RF targets the FC region of IgG, and it's mostly found as IgM, but it is also present as IgG or IgA. Approximately 70% of RA patients are positive for the RF test [18]. The sensitivity is 60-75% and the specificity is 40-85% [19].

Regarding to ACCP levels, the mean of RA patients was significantly higher than controls, as presented in **table 1**. This finding is in agreement with (*Zayed et* al.2022) [20] , (Mohammed *et al*.2023) [13]. ACCP is extremely specific for RA and has a very low incidence in healthy individuals [18]. ACCP helps predict disease severity and the risk of developing bone erosion in patients with RA. ACCP can be detected for as long as ten years before the clinical symptoms of RA start [21].

The comparison of isoform C gene expression was conducted between patients with RA and control participants. The findings are shown in **table (2)**. The mean expression levels of isoform-c were (1.47 ± 0.79) in patients with RA versus (1.04 ± 0.33) in controls. There was a significant increase in gene expression in patients with RA compared to control participants (p<0.05). The biological function of isoform-c hasn't been known yet, but it is working on the downregulation of isoforms B and D by an unknown mechanism [7]. This isoform has a certain role in inflammatory regulation, and it is the shorter version that is shorter than isoform A in about (97) amino acids. Research has shown that it possesses anti-inflammatory properties. It has the ability to decrease the production of pro-inflammatory cytokines and reduce inflammation [22] . IL37-c and IL37-e have the highest levels of inducibility among the other

IL-37 isoform domains, and the results of this study confirm this finding. in comparison to other isoforms.

The precise explanation is not clear, it is suggested to be partly related to the fact that IL37-e and IL37-c have shorter gene and protein sequences compared to others. Additionally, the presence of long or many introns may create a delay in gene expression.

To evaluate the isoform-c cut-off value as well as predict RA as a diagnostic test, receiver operator characteristic (ROC) curve analysis was carried out, and the results are presented **figure (1)** The isoform-c cut-off value was < 1.09-fold with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve of 67.5%, 73.3%, 77.1%, 62.9% and 0.668 (0.540-0.795). The present results indicate isoform-c is considered a weak diagnostic marker.

The current findings indicate that there is no significant variation in the expression of isoform-c based on RA activity and severity levels ($p>0.05$) as shown in **table (3)**. but it's markedly increased within the moderate patient group regarding severity and activity parameter classifications. The precise mechanisms and biological rules of isoform-c are now under investigation and need further study. IL37-c may hinder the development of additional IL-37 by competing with RNA splicing and cleaving enzymes during the maturation process [(22)]. The isoforms c and e don't process the amino acids that are responsible for forming the dimer interface. The lack of β1 to β3 strands suggests that these isoforms don't form dimers. Significantly, the creation of homodimers decreased or completely eliminated IL-37's suppressive activity in both laboratory and living organisms [(23)].

IL37-c and e may also impact the development and function of other isoforms by engaging with competition in the enzyme in the microenvironment in vivo. All cytokines in the IL-1 family, such as IL-1, IL-18, and IL-33, are self-regulated. This means that they are controlled by specific molecules that interact with them. For instance, IL1 is regulated by a molecule called an IL-1 antagonist, and IL-18 is controlled by IL-18 binding protein. Alternatively, IL37-c and e may control gene expression by translocating into the nucleus via SMAD3, even if they are unable to generate receptor dependent effects similar to IL37-b and d [(24); (25)].

Regarding gene Expression results for isoform-d as described in **table (4)**, it was downregulated in patients in contrast to controls, who had normal expression (the mean for patients is 0.485 ± 0.15 versus 1.20 ± 0.45 for controls). One hypothesis suggests that the elevated isoform-c expression works to downregulate isoforms b and d [(7)]. IL-37d exhibited comparable anti-inflammatory functions as IL-37b which suggests they are working synergistically. Nevertheless, IL-37d resembles IL-37b when demonstrated to have an inhibitory effect via the SMAD-3-dependent pathway and facilitates its movement to the nucleus. Other data suggests that IL-37d has a suppressive effect on the expression of IL-6. When IL1-β stimulates a substantial increase in the expression of IL-6, which can be greatly reduced by overexpression of IL-37b and IL-37d in A549 cells [(26)].

The current findings indicate that there is no significant difference in the expression of

isoform-d based on all RA activity and severity parameters (p>0.05) as shown in **table (5)** below. Additionally, its expression is variable within different disease activity and severity group classifications. Epigenetic alterations, namely DNA methylation and histone acetylation, are involved in the regulation of IL-37 production. The IL-37 gene promoter's accessibility and expression may be influenced by certain enzymes, such as DNA methyltransferases and histone deacetylases, which are involved in these alterations. HDAC inhibitors, which are substances that hinder the activity of these enzymes, have been shown to enhance the synthesis of IL-37 [27]. IL-37 isoforms possess a specific characteristic of being able to regulate the expression of inflammatory genes without relying on receptors. Studies have shown that both IL37-b and IL37-d inhibit the production of inflammatory cytokines in cells that lack the IL-37 receptors. This is mostly because they have the ability to get into the nucleus by different routes [28] [26].

CONCLUSION

IL37 isoform-c and isoform-d considered as a weak biomarker for diagnosing RA, evaluating disease activity and severity for RA patients. IL-37 isoform-d is decreased synergistically by the combined influence of the elevation of the other isoforms.

Ethical approval:

Prior to commencement, the ethics committee of the Faculty of Medicine at the University of Kufa granted its approval to this project. Each patient was required to submit their informed permission, and the Rheumatology Unit granted their approval for this research.

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