



Expression of IRAK3 and TNIP1 Genes in Iraqi Patients with Rheumatoid Arthritis and Their Association with Disease Activity

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease that features continuous joint inflammation and destruction. IRAK3 and TNIP1 have been shown to act as negative regulator of the TLR-NF-kappaB inflammatory response signaling pathway. However, the expression patterns of the two genes among Iraqi individuals with RA are yet to be clarified. **Methods:** A case-control study included 50 RA patients and 50 age- and sex-matched healthy controls. The relative gene expression of IRAK3 and TNIP1 in the peripheral blood was assessed using RT-qPCR. Disease activity was assessed using the Disease Activity Score 28 based on erythrocyte sedimentation rate (DAS28-ESR), and correlation analysis was done with various clinical parameters. **Results:** Both IRAK3 and TNIP1 were significantly downregulated in RA patients compared with healthy controls (0.56-fold and 0.61-fold reductions, respectively; both $P < 0.001$). Expression of both genes progressively decreased with increasing disease activity and demonstrated significant inverse correlations with DAS28-ESR (IRAK3: $\rho = -0.61$ and TNIP1: $\rho = -0.58$; both $P < 0.001$). Both genes also showed significant inverse correlations with ESR, CRP, and anti-CCP. **Conclusion:** IRAK3 and TNIP1 are markedly reduced in RA patients from Iraq and have an inversely correlation with disease activity and inflammation markers. These findings suggest that impaired negative regulation of the TLR-MyD88-NF- κ B pathway may be associated with the inflammatory activity in RA. IRAK3 and TNIP1 may have potential as biomarkers of disease activity.

Keywords: IRAK3, TNIP1, rheumatoid arthritis, gene expression, disease activity.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune condition that mostly affects the small joints of the hands and feet. It causes inflammation, disability, and joint degeneration. Additionally, it is associated with substantial socioeconomic burden and morbidity due to its systemic manifestations [1, 2]. To improve long-term results, early diagnosis is essential [3]. The development of RA is influenced by immunological, environmental, and genetic factors; autoantibodies are present before symptoms [4]. Smoking and other environmental factors can trigger or contribute to autoimmune reactions. Inflammation is mostly caused by dysregulated innate immunity, since immune cells in the synovial membrane produce pro-inflammatory cytokines (such as IL-6, IL-1 β , and TNF- α), which destroy joints and point to possible treatment targets [5].

By activating MyD88 and creating Myddosome complexes, toll-like receptors (TLRs), which identify molecular patterns in damaged tissues, stimulate innate immune cells in rheumatoid arthritis. This activation triggers pathways like nuclear factor of kappa light chain enhancer (NF- κ B) by releasing pro-inflammatory cytokines that sustain synovial inflammation. NF- κ B is disrupted in rheumatoid arthritis despite its normal regulatory systems, which highlights its potential as a therapeutic target and contributes to prolonged inflammation and joint damage. NF- κ B is crucial in controlling the expression of genes associated with immunological responses [6-8].

By blocking the Toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) pathways, interleukin-1 receptor-associated kinase 3 (IRAK3) functions as a negative regulator of the innate immune response, avoiding excessive inflammation [9,10]. Chronic inflammation is associated with its disruption, especially in rheumatoid arthritis, where IRAK3 levels have been reported to be altered. Faster disease progression and increased inflammatory responses are associated with IRAK3 loss, indicating its function in immune homeostasis control and its potential as a biomarker for immunological dysregulation in rheumatoid arthritis [11].

By preventing NF- κ B activation downstream of Toll-like receptors, TNF, and IL-1 receptors signaling, TNFAIP3-interacting protein 1 (TNIP1), also known as ABIN-1, is essential for regulating inflammatory signaling [12,13]. Rheumatoid arthritis and other autoimmune illnesses are linked to its malfunction, although little is known about TNIP1 in this regard, particularly about Iraqi patients. Current research overlooks the gene expression of IRAK3 and TNIP1, two essential negative regulators of inflammation, in favor of concentrating mostly on populations in Europe and East Asia. Examining these expressions in Iraqi patients may help uncover novel indicators for rheumatoid arthritis activity and shed light on disease processes [13, 14].

In this study, we hypothesized that altered expression of IRAK3 and TNIP1 is linked to immunological dysregulation and increased disease activity in individuals with rheumatoid arthritis. Our objectives were to assess the expression levels of these genes in Iraqi patients using RT-qPCR, investigate their relationships with immunological and inflammatory markers, such as ESR, CRP, RF, and anti-CCP, and assess their relationship with disease activity as assessed by DAS28-ESR.

Materials and Methods

Study Design and Participants

This case-control study was conducted from February to May 2026 at Al-Hussien Teaching Hospital in Iraq and involved 100 participants, who were divided into 50 patients with rheumatoid arthritis (RA) and 50 healthy individuals who did not have any other autoimmune or chronic inflammatory conditions. RA was diagnosed according to the classification criteria published by ACR/EULAR in 2010. Patients with a confirmed diagnosis of RA were eligible for inclusion if they met the predefined criteria. Those with other autoimmune disorders, acute or chronic inflammatory illnesses, or conditions that might affect inflammation or gene expression patterns were excluded. Participants were recruited using consecutive sampling until the required sample size was reached. Information on current medications and treatment status was also recorded for RA patients. A rheumatologist performed a thorough clinical assessment of the participants, recording clinical and demographic information and using the DAS28-ESR to measure disease activity among RA patients. All participants provided written informed consent, and the study was approved by the Research Ethics Committee of the Al-Muthanna Health Directorate, Iraq (Approval No. 2674), in accordance with the Declaration of Helsinki.

RNA Extraction and Gene Expression Analysis

For molecular analysis, 2 to 3 milliliters of peripheral blood samples were obtained in EDTA tubes. Following collection, samples were quickly processed and delivered to the lab under suitable circumstances. The QIAamp RNA Blood Mini Kit (Qiagen, Hilden, Germany) was used to extract total RNA from whole blood in accordance with the manufacturer's instructions. RNA samples were stored at -80 °C until further molecular analysis. Using a NanoDrop™ 2000 Spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA), the absorbance ratio at 260/280 nm was measured to determine the concentration and purity of RNA. The analysis only included RNA samples having an A260/A280 ratio between 1.8 and 2.1.

Using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA) and according to the manufacturer's instructions, complementary DNA (cDNA) was synthesized from 1 µg of total RNA. The resulting cDNA was stored at -20°C until quantitative real-time PCR analysis.

Quantitative real-time PCR (RT-qPCR) was performed using PowerUp™ SYBR™ Green Master Mix (Applied Biosystems, USA) on a QuantStudio™ 5 Real-Time PCR System (Applied Biosystems, USA). According to the manufacturer's suggested concentrations, each reaction was carried out in a final volume of 20 µL and included forward and reverse primers, cDNA template, nuclease-free water, and SYBR Green Master Mix. Every sample underwent technical duplicate analysis. An initial denaturation at 95°C for two minutes, forty cycles of denaturation at 95°C for fifteen seconds, and annealing/extension at 60°C for sixty seconds comprised the amplification process. At the conclusion of the amplification cycles, a melting-curve analysis was carried out to confirm the amplified products' specificity. Every run contained a no-template control (NTC) to keep an eye out for any contamination or nonspecific amplification. The internal reference gene for normalizing target gene expression was the housekeeping gene GAPDH. IRAK3, TNIP1, and

GAPDH primer sequences are presented in Table 1. Relative gene expression analysis was performed using the healthy control group as the calibrator. The comparative threshold cycle ($2^{-\Delta\Delta Ct}$) method described by Livak and Schmittgen (2001) [15] was used to calculate relative gene expression levels.

Table 1. Primer sequences used for quantitative real-time PCR.

Gene	Primer Sequence (5'→3')
IRAK3	Forward: ACCCAAACCTAACTGATTTTGCCA
	Reverse: AGAGAAATTCCGAGGGCAGG
TNIP1	Forward: CCACCACCTTCTCCCTCCTT
	Reverse: GCATCTTCACCTTCTTCTCG
GAPDH	Forward: GGAGCGAGATCCCTCCAAAAT
	Reverse: GGCTGTTGTCATACTTCTCATGG

Statistical analysis

IBM SPSS Statistics version 26.0 was used for statistical analysis, and data were presented as mean $\pm$ SD or median (IQR). The normality of continuous variables was assessed using the Shapiro–Wilk test. The independent-samples t-test or Mann-Whitney U test was used to compare groups, and Spearman's correlation coefficients were used to examine correlations between gene expression and clinical parameters. The $2^{-\Delta\Delta Ct}$ technique was used to assess relative gene expression, and a P-value of less than 0.05 was considered statistically significant.

Results

Age, sex, and body mass index did not significantly differ between the groups in study, which included 50 RA patients and 50 healthy controls ($P > 0.05$). However, compared to the healthy controls, RA patients had significantly higher erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, and higher proportions of rheumatoid factor (RF) positivity and anti-cyclic citrullinated peptide (anti-CCP) positivity, as shown in Table 2.

Table 2. Demographic and clinical characteristics of the study participants

Variable	RA Patients (n=50)	Controls (n=50)	P-value
Age (years)	48.6 $\pm$ 11.2	46.9 $\pm$ 10.8	0.432
Female, n (%)	42 (84.0)	40 (80.0)	0.602
Male, n (%)	8 (16.0)	10 (20.0)	0.602
BMI (kg/m ²)	27.5 $\pm$ 3.9	26.8 $\pm$ 3.4	0.381
Disease duration (years)	6.4 $\pm$ 3.8	—	—
DAS28-ESR	4.87 $\pm$ 1.09	—	—
ESR (mm/h)	42.5 $\pm$ 18.4	11.6 $\pm$ 5.2	<0.001

Variable	RA Patients (n=50)	Controls (n=50)	P-value
CRP (mg/L)	19.4 ± 11.7	3.2 ± 1.4	<0.001
RF positive, n (%)	39 (78.0)	0	<0.001
Anti-CCP positive, n (%)	41 (82.0)	0	<0.001

The 2- $\Delta\Delta$ Ct method was used to measure the expression levels of TNIP1 and IRAK3 in rheumatoid arthritis patients in comparison to healthy controls. IRAK3 had a median relative expression of 0.56 (0.41–0.74) vs. 1.00 (0.86–1.18) in controls, corresponding to a 44% reduction in expression ($P < 0.001$). Similarly, TNIP1 demonstrated median of 0.61 (0.47–0.79) in patients compared with 1.00 (0.88–1.15) in controls, corresponding to a 39% reduction in expression ($P < 0.001$), as shown in Figure 1 and Table3.

Table 3. Relative expression of IRAK3 and TNIP1 in rheumatoid arthritis patients and healthy controls

Gene	RA Patients, Median (IQR)	Controls, Median (IQR)	Fold Change	P-value
IRAK3	0.56 (0.41–0.74)	1.00 (0.86–1.18)	0.56 ↓	<0.001
TNIP1	0.61 (0.47–0.79)	1.00 (0.88–1.15)	0.61 ↓	<0.001

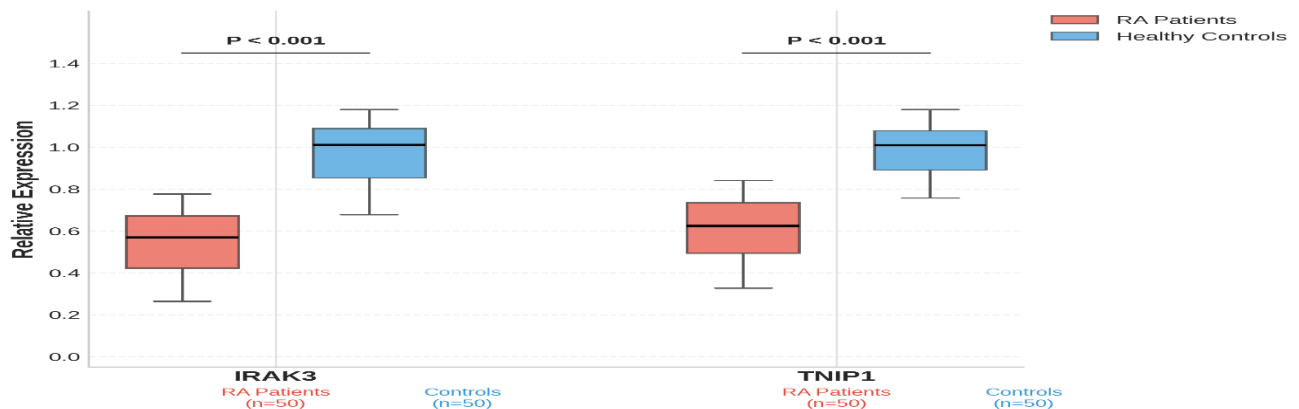


Figure 1. Relative expression of IRAK3 and TNIP1 in patients with rheumatoid arthritis and healthy controls.

IRAK3 and TNIP1 expression levels decrease when rheumatoid arthritis disease activity increases, as seen in Table 4 and Figure 2. Patients in remission had the greatest median expression, followed by those with low and moderate activity; individuals with high activity had the lowest levels. The four DAS28-ESR groups showed statistically significant differences ($P < 0.001$).

Table 4. Relative gene expression according to disease activity

DAS28-ESR Category	N	IRAK3, Median (IQR)	TNIP1, Median (IQR)
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Remission	8	0.94 (0.82–1.07)	0.91 (0.79–1.02)
Low	12	0.81 (0.69–0.92)	0.79 (0.68–0.88)
Moderate	18	0.60 (0.51–0.70)	0.58 (0.49–0.67)
High	12	0.39 (0.31–0.47)	0.41 (0.33–0.49)
P-value		<0.001	<0.001

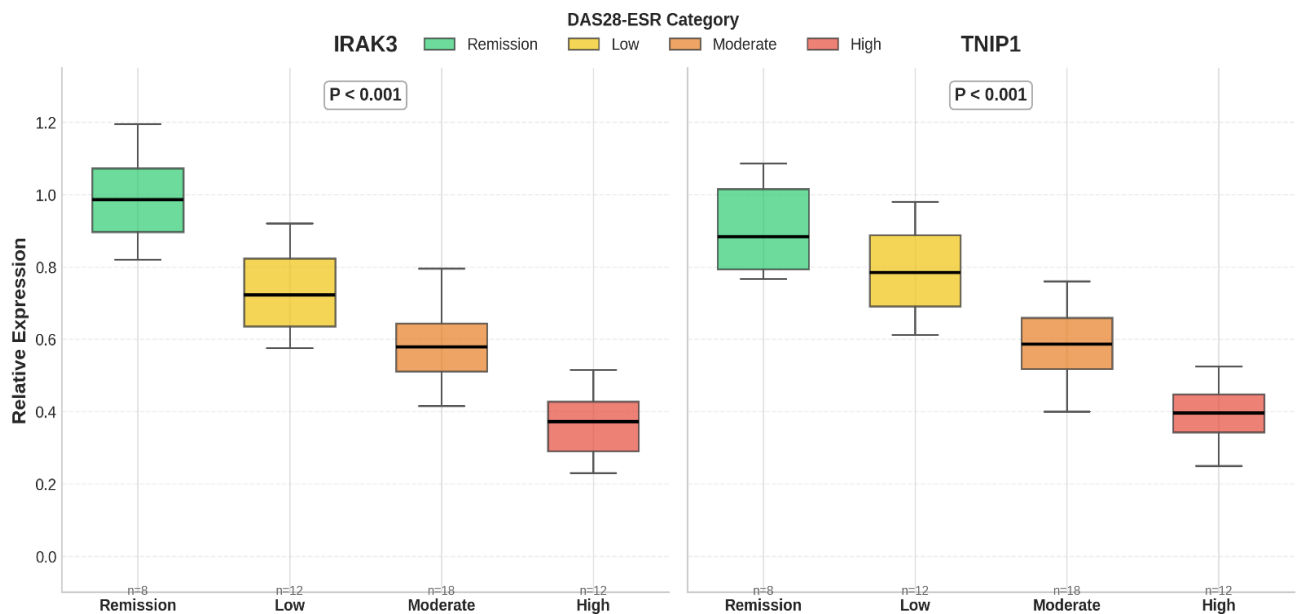


Figure 2. Relative expression of *IRAK3* and *TNIP1* across DAS28-ESR disease activity categories in patients with rheumatoid arthritis.

The associations between the expression levels of *TNIP1* and *IRAK3* and other clinical indicators in patients with rheumatoid arthritis are shown in Table 5. Both genes showed strong negative associations with DAS28-ESR, ESR, CRP, and anti-CCP, indicating that elevated inflammation and disease activity are associated with lower expression levels. The strongest inverse connection was seen between *IRAK3* and DAS28-ESR ($\rho = -0.61$, $P < 0.001$), closely followed by *TNIP1* ($\rho = -0.58$, $P < 0.001$). *TNIP1*'s connection with RF was not significant ($\rho = -0.25$, $P = 0.071$), although *IRAK3*'s correlation was weak ($\rho = -0.28$, $P = 0.048$).

Table 5. Correlation of *IRAK3* and *TNIP1* Expression with Clinical and Laboratory Parameters

Variable	<i>IRAK3</i> (ρ)	P-value	<i>TNIP1</i> (ρ)	P-value
DAS28-ESR	-0.61	<0.001	-0.58	<0.001
ESR	-0.53	<0.001	-0.49	0.001

Variable	IRAK3 (ρ)	P-value	TNIP1 (ρ)	P-value
CRP	-0.47	0.002	-0.44	0.004
RF	-0.28	0.048	-0.25	0.071
Anti-CCP	-0.35	0.013	-0.31	0.026

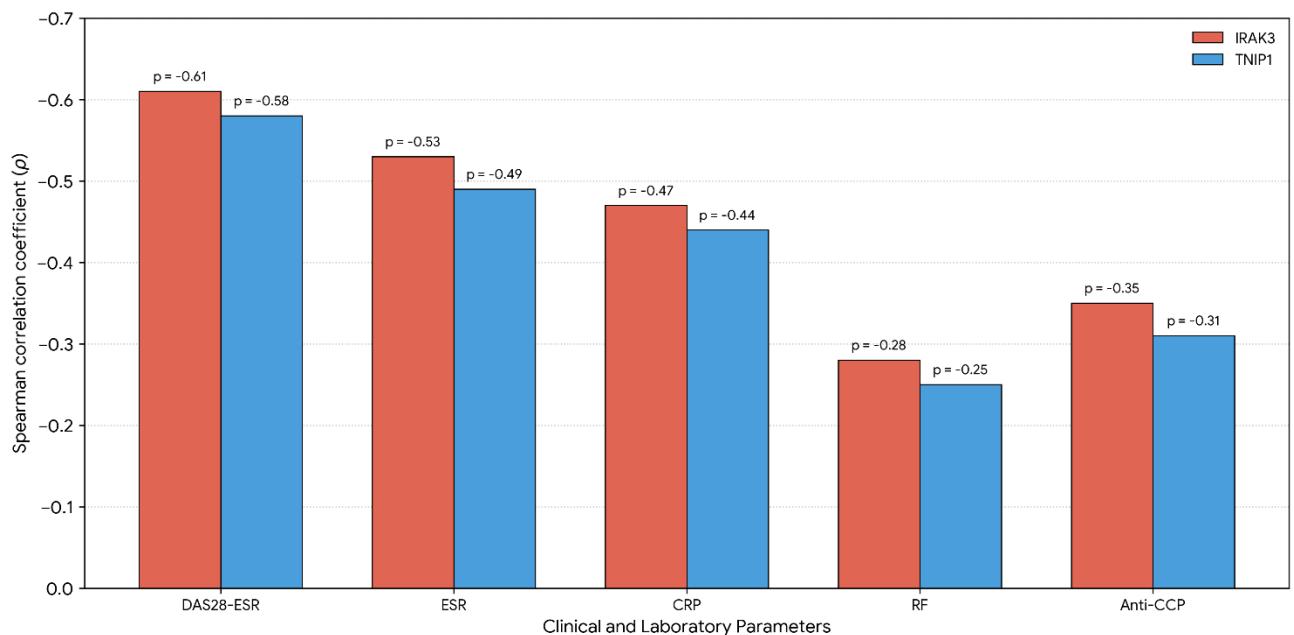


Figure 3. Spearman Correlation of IRAK3 and TNIP1 Expression with Clinical and Laboratory Parameters in Patients with Rheumatoid Arthritis

Discussion

When compared to healthy controls, the expression levels of the negative immunological regulators IRAK3 and TNIP1 were significantly downregulated in Iraqi patients with rheumatoid arthritis. DAS28-ESR, ESR, CRP, and anti-CCP were inversely correlated with both genes' expression levels, which declined as disease activity increased. These findings suggest that decreased expression of TNIP1 and IRAK3 may be associated with rheumatoid arthritis and the dysregulation of inflammatory signaling. Overall, the results corroborate the theory that increased inflammatory activity in the condition is correlated with disruption of endogenous negative regulators within the TLR–MyD88–NF- κ B signaling pathway.

The study indicates that the peripheral blood IRAK3 expression in patients with rheumatoid arthritis is significantly lower than that of healthy individuals. The TLR–MyD88–NF- κ B signaling pathway is negatively regulated by IRAK3. This control may be compromised by its reduced expression, which might result in increased production of pro-inflammatory cytokines and prolonged NF- κ B activation, which would contribute to chronic inflammation. These findings are somewhat

consistent with those of [16], who observed a comparable decrease in IRAK3 in CD14⁺ monocytes from rheumatoid arthritis patients, especially those with high disease activity.

On the other hand, elevated IRAK3 levels in rheumatoid synovial tissue were found by [11], suggesting possible tissue-specific regulation. While lower levels in circulating cells indicate compromised systemic inflammatory signaling control, this discrepancy may reflect a possible compensatory response within inflammatory tissues. Overall, the results lend credence to the idea that persistent inflammation in rheumatoid arthritis and impaired innate immune regulation is associated with reduced peripheral IRAK3 levels.

The current study showed that rheumatoid arthritis (RA) patients had significantly lower TNIP1 expression than healthy individuals. A20-binding inhibitor of NF- κ B activation 1 (ABIN-1), which is essential for modulating the TNFAIP3–NF- κ B signaling pathway and preserving immunological homeostasis, is encoded by TNIP1. The A20/ABIN-1 complex's inhibitory action may be reduced by decreased TNIP1 expression, resulting in prolonged pro-inflammatory cytokine production and NF- κ B activation. These findings are consistent with [17] who identified the TNFAIP3–ABIN-1 complexes as a crucial modulator of inflammatory signaling in rheumatoid arthritis, corroborate this biological process. Furthermore, according to [18], prolonged activation of the NF- κ B pathway is a major contributor to osteoclast activation, oxidative stress, synovial inflammation, and joint deterioration in RA.

According to [19], polymorphisms in the TNIP1 locus have been connected to an increased risk of RA, highlighting the gene's importance in the disease's pathogenesis. Previous research, however, mostly concentrated on genetic vulnerability rather than TNIP1 expression. All of these results point to the possibility that dysregulated NF- κ B signaling, which promotes persistent inflammation and increased disease activity in RA patients, may be associated with decreased TNIP1 expression.

The present study establishes significant inverse correlations between IRAK3 and TNIP1 expression levels and various disease activity and inflammatory parameters indices in rheumatoid arthritis (RA), including DAS28-ESR, ESR, CRP, and anti-CCP. The TLR–MyD88–NF- κ B pathway is inhibited by IRAK3 and TNIP1, which are endogenous negative regulators of inflammatory signaling. Their decreased expression may result in compromised feedback mechanisms that worsen inflammation, increasing NF- κ B activation and pro-inflammatory cytokine production. These finding may help explain the associated between reduced expression of these genes and increased disease activity.

Although there are few direct studies on TNIP1 in relation to clinical activity in RA, supporting evidence from [16] demonstrated lower IRAK3 expression in RA patients, especially those with high disease activity (fold change = -1.78, $P = 0.030$). These connections are supported by indirect data from [20], which show links between gene expression patterns and disease severity in early RA.

Specifically, [21] found a correlation between disease activity indicators and K2P5.1 expression in peripheral CD4 T cells. According to the current findings, TNIP1 and IRAK3 may have potential as molecular biomarkers for assessing inflammatory status and monitoring RA disease

activity. The observed association with anti-CCP may indicate potential relationship between these gene expression patterns and autoimmune activity in RA, although further studies are need to confirm this association. To validate the potential of IRAK3 and TNIP1 in clinical monitoring and treatment decision-making for RA patients, further multicenter studies with bigger cohorts are necessary.

Strengths of the Study

The present study has several strengths, including its unique evaluation of IRAK3 and TNIP1 expression in peripheral blood from Iraqi rheumatoid arthritis patients. The relationship between these expressions and inflammatory markers and disease activity is also examined. Healthy controls are included in the study, and quantitative real-time PCR is used to accurately quantify gene expression.

Limitations of the Study

Despite the study's strengths, there are a number of limitations. The results may not be as broadly applicable as they may be due to the limited sample size and single-center methodology. Furthermore, synovial tissue was not included in the gene expression study, which was limited to peripheral blood. Additionally, the cross-sectional design makes it impossible to assess causal linkages or changes in gene expression after therapy.

Conclusion

This study found significantly reduced levels of IRAK3 and TNIP1 in rheumatoid arthritis patients compared to healthy controls, with expression decreasing alongside disease activity and correlating inversely with inflammatory markers. This suggests that these genes may contribute to persistent inflammation in rheumatoid arthritis by adversely regulating the TLR–MyD88–NF- κ B pathway. The results suggest TNIP1 and IRAK3 as possible biomarkers for tracking inflammation and disease activity. To validate these findings and evaluate their clinical relevance in rheumatology, more multicenter research is required.

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Conflict of Interest: The authors declare no conflict of interest

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