https://doi.org/10.31925/farmacia.2025.6.23 **ORIGINAL ARTICLE**

PHARMACOGENOMIC INSIGHTS INTO PSORIASIS TREATMENT: IMPACT OF *TNF-α* GENE POLYMORPHISMS ON ETANERCEPT RESPONSE AND SERUM *TNF-α* IN IRAQI PATIENTS WITH MODERATE TO SEVERE PSORIASIS

ABEER KADHIM JAMAAH [1]*, FADYA Y. AL-HAMADANI [1], ALI FADHIL AL-SAADI [2]

[1]*Clinical Pharmacy Department, College of Pharmacy, University of Baghdad, Iraq*
[2]*Dermatology and Venereology Centre, Medical City, Baghdad, Iraq*

**corresponding author: abeer.jumaa@copharm.uobaghdad.edu.iq*

Manuscript received: August 2025

Abstract

Psoriasis is a chronic inflammatory condition that requires effective treatment. Genetic variability, particularly in the *Tumour Necrosis Factor-alpha* (TNF-α) gene, may influence patients' response to biological therapies such as etanercept. This study evaluated the association of four *TNF-α* gene polymorphisms (*rs361525* G/A, *rs673* G/A, *rs1800629* G/A, and *rs1800750* G/A) with serum TNF-α levels and response to etanercept in Iraqi patients with psoriasis. A retrospective study was conducted on 80 patients with moderate-to-severe psoriasis who received etanercept for at least six months. Patients were categorised as responders (≥ 75% PASI reduction) or non-responders (≤ 50% PASI reduction). Genotyping was performed using PCR and Sanger sequencing. A significant association was observed between the *rs673* G/A polymorphism and etanercept response: the GA genotype was predominantly present in responders and showed a negative association with non-response (phi = -0.318, p = 0.007), whereas the GG genotype demonstrated a positive association (phi = 0.411, p = 0.0007). Non-responders had significantly higher post-treatment serum TNF-α levels compared with responders. These findings suggest that the rs673 G/A polymorphism and TNF-α levels may be associated with etanercept response. However, larger studies are needed to validate these associations before clinical implementation.

Rezumat

Psoriazisul este o afecțiune inflamatorie cronică care necesită un tratament eficient. Variabilitatea genetică, în special în gena factorului de necroză tumorală alfa (TNF-α), poate influența răspunsul pacienților la terapiile biologice, spre exemplu la etanercept. Acest studiu a evaluat asocierea a patru polimorfe ale genei *TNF-α* (*rs361525* G/A, *rs673* G/A, *rs1800629* G/A și *rs1800750* G/A) cu nivelurile serice de TNF-α și răspunsul la etanercept la pacienți irakieni cu psoriazis. A fost realizat un studiu retrospectiv pe 80 de pacienți cu psoriazis moderat până la sever care au primit etanercept timp de cel puțin șase luni. Pacienții au fost clasificați ca fiind respondenți (reducere PASI ≥ 75%) sau non-respondenți (reducere PASI ≤ 50%). Genotiparea a fost realizată utilizând PCR și secvențierea Sanger. S-a observat o asociere semnificativă între gena rs673 G/A și răspunsul la etanercept: genotipul GA a fost prezent în mod predominant la pacienții care au răspuns la tratament și a prezentat o asociere negativă cu lipsa răspunsului (phi = -0.318, p = 0.007), în timp ce genotipul GG a demonstrat o asociere pozitivă (phi = 0.411, p = 0.0007). Pacienții care nu au răspuns la tratament au prezentat niveluri serice de TNF-α post-tratament semnificativ mai ridicate în comparație cu pacienții care au răspuns la tratament. Aceste rezultate sugerează că gena *rs673* G/A și nivelurile de TNF-α pot fi asociate cu răspunsul la etanercept. Cu toate acestea, sunt necesare studii mai ample pentru a valida aceste asocieri înainte de implementarea clinică.

Keywords: psoriasis, pharmacogenetics, etanercept, polymorphisms

Introduction

Psoriasis is a common, chronic inflammatory disease that affects approximately 125 million individuals worldwide, with a prevalence ranging from 0.33% to 0.6% in different populations and ethnic groups [1, 2]. It is common in young adults, who are often uncomfortable with the visible, sore, and scaly plaques and are affected by them in terms of their quality of life [3, 4]. The disease is frequently associated with comorbidities such as psoriatic arthritis [5], depression, cardiovascular disease, and metabolic syndrome, adding to the patient burden and cost of care [6].

Psoriasis is characterised by a dysregulated immune system, specifically a T cell-mediated immune disorder with an upregulation of T helper type 1/17 (Th1/Th17) cytokines [7], including TNF-α, various interleukins (ILs), and interferon-gamma. The complex interplay among multiple cytokines and growth factors has led to advances in treatment, particularly biologic therapies targeting these agents [8]. Biologics, particularly anti-TNF agents, represent a significant breakthrough for individuals with

moderate-to-severe plaque psoriasis. Infliximab shows the highest efficacy among these, followed by certolizumab, adalimumab, and etanercept [9].

Etanercept (ETN), a TNF-α inhibitor, is effective in treating psoriasis by modulating inflammation and immune response. However, some patients do not respond adequately [10], necessitating a change in treatment. This trial-and-error approach leads to suboptimal patient care and increased healthcare costs, highlighting the need for precise, individualised treatment selection. Pharmacogenetics offers a promising solution, though research on the interplay between genetics and biologics in psoriasis is limited compared to inflammatory bowel disease and rheumatoid arthritis [11].

The TNF gene, located on chromosome 6 (6p21.33), encodes a pro-inflammatory cytokine crucial to psoriasis pathogenesis by inducing T-cell production and subsequent epidermal keratinocyte proliferation [8, 12]. Since TNF is the direct target of TNF inhibitors used in psoriasis treatment, genetic variations within the TNF gene directly influence the efficacy of these drugs [13]. The promoter region of the TNF-α gene is highly polymorphic, making genetic variation a critical determinant of treatment response [14]. Polymorphism testing may help identify patients who are likely to respond well or poorly to treatment. Early identification of non-responders facilitates quicker transitions to alternative medications, thereby improving therapeutic outcomes [15, 16].

Pharmacogenomic and pharmacogenetic research seeks to utilise insights regarding gene variants that influence medication response to develop individualised treatment approaches, enhancing effectiveness and safety [17].

The association between genetic polymorphisms and response to biological drugs has been examined in recent reviews and research in Iraq, with particular attention to single-nucleotide polymorphisms (SNPs) in genes such as TNF and ILs [18-24]. However, no previous research has specifically examined the impact of the rs673 (-244) G/A polymorphism on etanercept response in psoriasis patients, nor have any empirical studies in Iraq investigated how SNPs in the TNF-α promoter region affect etanercept outcomes in this specific patient population. Therefore, this study was designed to investigate whether SNPs in the TNF-α gene promoter at positions rs361525 (-238) G/A, rs673 (-244) G/A, rs1800629 (-308) G/A, and rs1800750 (-376) G/A influence the effectiveness of etanercept in a sample of Iraqi psoriasis patients.

Materials and Methods

Study design

This research is part of a comprehensive retrospective cohort study carried out from April 2024 to February 2025. The study enrolled a cohort of 80 Iraqi individuals diagnosed with moderate-to-severe psoriasis. The participants were selected from the Centre of Dermatology and Venereology at Baghdad Teaching Hospital in Baghdad, Iraq. This institution provides medical services to a diverse variety of communities in Iraq, including rural, urban, and inner-city areas across many governorates. The Scientific and Ethical Committee of the College of Pharmacy at the University of Baghdad and the Dermatology and Venereology Centre at Baghdad Teaching Hospital granted ethical approval with the number (RECO-62024R) on the 3rd of April 2024.

Patients' selection

Ninety-three individuals with moderate to severe psoriasis were enrolled in the study and received ETN as monotherapy, fulfilling the inclusion criteria specified below. Nevertheless, only 85 patients consented to participate in this study, and only 80 fulfilled the criteria; the 5 patients were excluded due to missing data.

Inclusion Criteria

Participants were included in the study if they met all of the following criteria: diagnosis of moderate to severe chronic plaque psoriasis, defined by a Psoriasis Area and Severity Index (PASI) score > 10 at the time of recruitment [25, 26], age ≥ 18 years old, received the standard etanercept protocol: 50 mg twice weekly for 3 months, followed by 50 mg once weekly and completed a minimum total treatment duration of six continuous months before assessment.

The PASI score is calculated by evaluating the degree of Erythema (E), Induration (I), and Desquamation (D) on a 0 - 4 scale, and multiplying the sum of these severity scores by the Area Score (A) for each of the four body regions (Head (H), Upper Limbs (UL), Trunk (T), and Lower Limbs (LL)). The final score is determined by the weighted sum of the four body regions according to the following standard formula: PASI = 0.1 (EH + IH + DH) AH + 0.2 (EUL + IUL + DUL) AUL + 0.3 (ET + IT + DT) AT + 0.4 (ELL + ILL+ DLL) ALL. The area score ranges from 0 to 6, representing the percentage of area involvement (*e.g.*, 1 for < 10% and 6 for 90-100%) [27].

The exclusion criteria

Patients must be excluded if they have used etanercept for less than 6 months or if they are receiving any other biologic medication. Individuals with a skin condition other than psoriasis or a psoriasis subtype other than plaque psoriasis were also excluded. Furthermore, exclusion applies to patients taking other medications known to exacerbate psoriasis (*e.g.*, beta-blockers, antimalarials, NSAIDs, lithium, or tetracycline). Patients with an intermediate treatment response (PASI 50–75%) were excluded *a priori* by design, as the study aimed to compare two clearly defined response categories (responders ≥ 75% and non-responders ≤ 50%) to reduce heterogeneity in treatment response.

Patient classification:

The patients were categorised into two distinct groups based on their response to ETN. Treatment response was assessed by the change in the ΔPASI, defined as the difference in PASI score from baseline to the end of treatment.

Patients who achieved a reduction of ≤ 50% were categorised as non-responders, and those with a decrease of ≥ 75% were classified as good responders [25, 28]. Group A comprised 40 psoriasis patients who responded to ETN. The second cohort (Group B) comprised 40 psoriasis patients who showed no response to ETN.

Data collection

Data on demographic characteristics (such as age, sex, body mass index, disease duration, family history, comorbidities, laboratory data such as TNF-α level, in addition to clinical severity of the psoriasis assessed using PASI and percentage of Body Surface Area affected by psoriasis (BSA%), were collected through direct patient interviews utilising a patient information chart expressly developed for this study.

Collection and processing of samples

Five millilitres of venous blood were collected from the forearm vein of each participant. Subsequently, 2 millilitres of the collected blood sample were put into an ethylenediaminetetraacetic acid (EDTA) tube for Deoxyribonucleic Acid (DNA) extraction and analysis. Concurrently, the remaining 3 mL of blood was placed in a gel tube and centrifuged for 10 minutes at 3000 rpm. The isolated serum was stored in aliquots in Eppendorf tubes and frozen at -20°C until the sample collection was finalised. Subsequently, TNF-α quantification was performed using the Enzyme-Linked Immunosorbent Assay method. The serum TNF-α level was ascertained using the Eliza kit provided by Wuhan Fei Yue Biotechnology (Wuhan, China, catalogue no. FY-EH1405). This assay utilises the quantitative sandwich enzyme immunoassay methodology [29].

Genotyping

Genomic DNA was isolated from peripheral blood leukocytes (cryopreserved EDTA blood specimens) using the Easy Pure Blood Genomic DNA Kit (TransGen Bio-tech, China, Catalogue No: EE121). The concentration of DNA samples that demonstrated acceptable integrity was assessed using a Nanodrop spectrophotometer (Thermo Fisher Scientific, USA) equipped with essential computerised software for control and data recording, following the use of an elution buffer as a blank solution. Two microliters of the purified DNA were introduced into the Nanodrop to determine the concentration in ng/μL. The concentration ranged from 31 to 54 ng/μL. The Nanodrop spectrophotometer was used to determine DNA purity by measuring the sample's absorbance at 260 and 280 nm. The A260/A280 ratio ranged from 1.7 to 1.9, indicating the purity of the DNA sample.

Quality control measures were implemented to ensure genotyping accuracy. Approximately 10% of the samples were randomly selected and re-genotyped for confirmation, yielding 100% concordance. All SNPs demonstrated high genotyping quality, with a call rate exceeding 98%. The sequencing reactions showed a success rate of > 95% across all samples. No discrepancies were observed between duplicate samples.

Primers and primer optimisation

The Geneious Prime program was used to design Polymerase chain reaction (PCR) primers. To use the software, the sequence should be in FASTA format available in the National Centre for Biotechnology Information (NCBI) database. They were synthesised and lyophilised by Alpha DNA Ltd. (Canada).

Table I

Primers for genotyping detection of the *TNF-α* gene

Gen	DNA primers	Sequence (5′→3′ direction)	Primer length (nt)	Product size (bp)	Annealing Temperature (°C)
TNF-α	Forward	CAGGACCTCCAGGTATGGAA	20	752	58
	Reverse	CTCATCTGGAGGAAGCGGTA	20		

A stock solution of the primer at a concentration of 100 pmol/μL was prepared by dissolving the lyophilised primer in nuclease-free water according to the manufacturer's instructions and stored at -23°C. After that, 10 μL of the stock solution (stored at -20°C) was diluted with 90 μL of nuclease-free water to prepare a working solution at 10 pmol/μL.

The ideal annealing temperature for primers was determined by amplifying the DNA template with a pair of primers (Forward/Reverse) at 54, 56, and 58°C. The optimal annealing temperature for the primer was 58°C, yielding distinct, well-defined bands on an agarose gel; hence, it was employed in the present study.

PCR amplification and sequencing of PCR products

PCR amplifications were performed in a total volume of 25 μL *per* reaction, using the following components: 12.5 μL of EasyTaq® PCR Super Mix, 1 μL each of the 10 pmol forward and reverse primers, 4 μL of template DNA, and 6.5 μL of nuclease-free water. The tube containing all components was briefly centrifuged to sediment the contents and remove any air bubbles. The tube was placed within the PCR well, and the PCR protocol was executed. The PCR application (QIAamplifier96, QIAGEN, Germany) was employed to execute PCR cycling according to the specified temperature protocol. The cycling protocol began with an initial

denaturation at 94°C for 5 min, followed by 35 cycles of denaturation (94°C for 30 sec), annealing (58°C for 30 sec), and extension (72°C for 30 sec), concluding with a final extension at 72°C for 5 min. Sanger's method was used for DNA sequencing to determine the presence or absence of SNPs within the TNF promoter amplicon. The PCR product was sent to Macrogen Corporation, Korea, for Sanger sequencing on an ABI 3730XL automated DNA sequencer. Geneious Prime was used to compare the sequencing results with the standard TNF-α gene sequence.

Statistical analysis

The data were analysed using SPSS for Windows version 29.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± SD of the values. Alleles and genotypes are represented as percentages and frequencies. A Shapiro-Wilk test was employed to assess the normality of the results. The unpaired t-test was used for normally distributed data to determine whether there is a significant difference in demographic features and parameters between the responding and non-responding groups. The difference between the means of more than two groups was analysed using a one-way analysis of variance (ANOVA). A *post-hoc* analysis was conducted whenever ANOVA indicated a significant difference among the three sample means. The Chi-square test or Fisher's exact test was employed to assess differences in proportions between groups. Fisher's exact test was employed when any predicted value in a 2 x 2 comparison is less than 5. The Phi correlation coefficient (phi) was employed to assess the relationship between each genotype and the probability of non-responsiveness. The binary logistic regression analysis was employed to determine the correlation between TNF-α levels and the likelihood of becoming a non-responder. A probability of less than 0.05 indicates a significant difference. The receiver operating characteristic (ROC) curve was used to assess the validity of TNF-α levels as an indicator of response to etanercept. The area under the curve (AUC), as well as sensitivity and specificity, were used to assess the diagnostic accuracy.

Results and Discussion

Demographic data and clinical characteristics of the study groups.

Demographic and clinical characteristics were compared between the responders' and non-responders' groups. Statistically significant differences in TNF-α levels were observed after 6 months of treatment, with non-responders exhibiting considerably higher levels than responders (p = 0.001). As expected, significant differences were also found in disease severity after 6 months of treatment, where responders showed markedly lower PASI scores (2.04 ± 0.989 *vs*. 13.68 ± 3.803, p = 0.01) and BSA% scores (2.89 ± 0.908 *vs*. 22.06 ± 6.916, p = 0.01) compared to non-responders, as seen in Table II.

Table II

Demographic data and clinical characteristics of the study groups

Category		Responders group n = 40	Non-responders group n = 40	p-Value
Age (years)		38.80 ± 9.40	41.05 ± 13.12	0.381 [a]
Gender	**Male n (%)**	21 (52.5)	26 (65)	0.2 [b]
	Female n (%)	19 (47.5)	14 (35)	
Family history	**Yes n (%)**	18 (45)	25 (62.5)	0.1[b]
	No n (%)	22 (55)	15 (37.5)	
BMI		29.21 ± 5.074	31.73 ± 7.157	0.07[a]
Disease duration (years)		13.20 ± 4.081	15.10 ± 5.038	0.3[a]
TNF-α (pg/mL)		91.45 ± 29.539	145.65 ± 48.148	**0.001* [a]**
Baseline PASI		19.87 ± 5.469	19.35 ± 4.573	0.8 [a]
PASI after 6 months		2.04 ± 0.989	13.68 ± 3.803	**0.01* [a]**
Baseline BSA%		29.37 ± 8.678	30.88 ± 7.26	0.6 [a]
BSA% after 6 months		2.89 ± 0.908	22.06 ± 6.916	**0.01* [a]**
Comorbidities	**Diabetes n (%)**	2 (5)	7 (17.5)	0.15 [c]
	Hypertension n (%)	3 (7.5)	9 (22.5)	0.11 [c]
	Nail psoriasis n (%)	5 (12)	11 (27)	0.09 [b]

Results are presented as means ± standard deviation or frequency (%). a. Independent two-sample t-test. b. Chi-square test. c. Fisher's exact test. *: significant

Prevalence of genotype polymorphism

Table III shows that all variants were polymorphic within the studied cohort. Notably, the GG genotype was the most prevalent for all variants except rs1800629 (-308) G/A; this variant showed a more balanced distribution of genotypes compared to the other studied polymorphisms. While the GG genotype remained the most frequent at 67.5% (n = 54), the heterozygous GA genotype was considerably more common than for the other variants, observed in 21 individuals (26.25%). The G allele was the major allele for all four variants, with frequencies ranging from 80.63% rs1800629 (-308) G/A to 95.63% rs1800750 (-376) G/A. Regarding Hardy-

Weinberg Equilibrium (HWE), for all tested SNPs, the observed genotype frequencies did not significantly deviate from those expected under HWE ($p > 0.5$), indicating that the population is in genetic equilibrium at these loci (Table IV).

Table III

Genotypes and allele frequencies of TNF-α rs361525 (-238) G/A, rs673 (-244) G/A, rs1800629 (-308) G/A, and rs1800750 (-376) G/A gene polymorphisms in psoriasis patients. N=80 patients

Genotypes				
rs361525 (-238) G/A	**Genetic variant**	**GG**	**GA**	**AA**
	No. (%)	71 (88.75)	8 (10)	1 (1.25)
	Allele	**G**	**A**	
	No. (%)	150 (93.75)	10 (6.25)	
rs673 (-244) G/A	**Genetic variant**	**GG**	**GA**	**AA**
	No. (%)	70 (87.5)	9 (11.25)	1 (1.25)
	Allele	**G**	**A**	
	No. (%)	149 (93.13)	11 (6.87)	
rs1800629 (-308) G/A	**Genetic variant**	**GG**	**GA**	**AA**
	No. (%)	54 (67.5)	21 (26.25)	5 (6.25)
	Allele	**G**	**A**	
	No. (%)	129 (80.63)	31 (19.37)	
rs1800750 (-376) G/A	**Genetic variant**	**GG**	**GA**	**AA**
	No. (%)	74 (92.5)	5 (6.25)	1 (1.25)
	Allele	**G**	**A**	
	No. (%)	153 (95.63)	7 (4.37)	

Table IV

Hardy-Weinberg Equilibrium Analysis of TNF-α rs361525 (-238) G/A, rs673 (-244) G/A, rs1800629 (-308) G/A, and rs1800750 (-376) G/A gene polymorphisms in psoriasis patients. N = 80 patients

SNP ID	**Observed Genotypes**	**Expected Genotypes**	**p-value**
rs361525 (-238) G/A	GG = 71 GA = 8 AA = 1	GG = 70.31 GA = 9.38 AA = 0.31	0.186
rs673 (-244) G/A	GG = 70 GA = 9 AA = 1	GG = 69.38 GA = 10.26 AA = 0.38	0.280
rs1800629 (-308) G/A	GG = 54 GA = 21 AA = 5	GG = 52.00 GA = 24.99 AA = 3.04	0.160
rs1800750 (-376) G/A	GG = 74 GA = 5 AA = 1	GG = 73.15 GA = 6.70 AA = 0.35	0.200

Regarding the difference in genotype and alleles frequencies, while rs361525 (-238) G/A and rs1800750 (-376) G/A showed no significant differences in genotype or allele frequencies between the groups, the rs673 (-244) G/A variant exhibited a significant association at the genotype level, with the GG genotype being less frequent in responders and the GA genotype exclusively observed in this group ($p = 0.02$), with the G allele being more prevalent in non-responders (100%) while the A allele was solely present in responder (13.75%) ($p = 0.02$). Similarly, for rs1800629 (-308) G/A polymorphism, the G allele was significantly more frequent in non-responders (87.5%) than in responders (73.75%) ($p = 0.03$), suggesting a potential role for the A allele in contributing to treatment response (Table V).

Association between genotypes and the probability of being a non-responder

Phi coefficient was calculated to assess the strength and direction of association between each genotype and non-responder status. The analysis revealed a statistically significant association between the *rs673* (-244) G/A polymorphism and non-responder status. Specifically, the GG genotype showed a highly significant positive association (phi = 0.411, $p = 0.0007$), while the GA genotype exhibited a significant negative association (phi = -0.318, $p = 0.007$). Although other genotypes showed positive or negative associations, none were statistically significant, as shown in Table VI.

Table V

Difference in genotype frequencies of TNF-α rs361525 (-238) G/A, rs673 (-244) G/A, rs1800629 (-308) G/A, and rs1800750 (-376) G/A gene polymorphisms between responders and non-responders

Genotypes		Responders group (n = 40) No. (%)	Non-responders' group (n=40) No. (%)	p-Value
rs361525 (-238) G/A	**GG**	35 (87.5)	36 (90)	0.7
	GA	5 (12.5)	3 (7.5)	0.4
	AA	0 (0)	1 (2.5)	0.4
	G	75 (93.75)	75 (93.75)	1
	A	5 (6.25)	5 (6.25)	
rs673 (-244) G/A	**GG**	30 (75)	40 (100)	**0.02***
	GA	9 (22.5)	0 (0)	**0.02***
	AA	1 (2.5)	0 (0)	0.4
	G	69 (86.25)	80 (100)	**0.02***
	A	11 (13.75)	0 (0)	
rs1800629 (-308) G/A	**GG**	24 (60)	30 (75)	0.1
	GA	11 (27.5)	10 (25)	0.7
	AA	5 (12.5)	0 (0)	0.09
	G	59 (73.75)	70 (87.5)	**0.03***
	A	21 (26.25)	10 (12.5)	
rs1800750 (-376) G/A	**GG**	37 (92.5)	37 (92.5)	1.0
	GA	2 (5)	3 (7.5)	0.6
	AA	1 (2.5)	0 (0)	0.4
	G	76 (95)	77 (96.25)	0.7
	A	4 (5)	3 (3.75)	

Table VI

Phi coefficient and statistical association between each genotype and non-responder status among study participants

SNP	Genotype	phi-coefficient	p-Value
rs361525 (-238) G/A	**GG**	0.068	0.561
	GA	0	1
	AA	0.005	0.967
rs673 (-244) G/A	**GG**	0.411	**0.0007 ***
	GA	-0.318	**0.007 ***
	AA	0	1
rs1800629 (-308) G/A	**GG**	0.196	0.095
	GA	0	1
	AA	- 0.206	0.078
rs1800750 (-376) G/A	**GG**	0.08	0.496
	GA	0.009	0.942
	AA	0	1

Table VII

Association of the change in PASI over six months between different genotypes in TNF-α rs361525 (-238) G/A, rs673 (-244) G/A, rs1800629 (-308) G/A, and rs1800750 (-376) G/A genotypes

Genotypes					
rs361525 (-238) G/A	**Genetic variant**	**GG+**	**GA**	**AA**	**p - Value**
	ΔPASI	-11.51 ± 5.63	-12.36 ± 4.76	-0.8 ± 0.0	0.8
rs673 (-244) G/A	**Genetic variant**	**GG+**	**GA**	**AA**	0.02*
	ΔPASI	-10.45 ± 5.30 ǂ	-19.42 ± 7.75 ǂ	-12.30 ± 0.0	
rs1800629 (-308) G/A	**Genetic variant**	**GG+**	**GA**	**AA**	0.1
	ΔPASI	-10.58 ± 4.87	-12.09 ± 4.99	-18.88 ± 7.44	
rs1800750 (-376) G/A	**Genetic variant**	**GG+**	**GA**	**AA**	0.9
	ΔPASI	-11.65 ± 5.45	-11.20 ± 5.58	-12.30 ± 0.0	

Data were expressed as mean ± SD. Statistical analyses were performed by ANOVA followed by Duncan's Post Hoc test . *: Significant difference between the groups. +: The wild genotype. ǂ: Significant difference between the genotypes according to Duncan's multiple range comparisons.

The Correlations between the genotypes and the difference in the PASI score

As shown in Table VII, an analysis of ΔPASI, where more negative values indicate greater improvement, revealed a significant association with the rs673 (-244) G/A variant (p = 0.02). Specifically, individuals carrying the GA genotype showed a significantly greater mean improvement in PASI scores (-19.42)

than those with the GG genotype (-10.45), as confirmed by Duncan's post hoc test. While the rs1800629 (-308) G/A variant showed a trend towards greater improvement with the AA genotype (mean ΔPASI = -18.88), this difference did not reach statistical significance (p = 0.1).

Comparison of Serum TNF Concentrations Across Genotypes in Psoriatic Patients

Although no statistically significant overall associations were found between the examined TNF-α gene polymorphisms and serum TNF-α levels across various genotypes, a notable pattern emerged when patients were stratified by treatment response. Serum TNF-α levels were significantly elevated in non-responders with psoriasis compared with responders across multiple genotypes. The GG genotype consistently showed markedly elevated TNF-α levels in non-responders across all four genetic variants (p = 0.001). Comparable substantial discrepancies were seen for the GA genotype in rs361525, rs1800629, and rs1800750. This indicates that although genotype alone may not determine total TNF-α levels, the interaction between specific genetic variations and clinical response suggests that TNF-α may serve as an associated marker reflecting disease activity and treatment response in psoriatic patients (Table VIII, Table IX).

Table VIII

TNF-α level in different genotypes

Genotypes					
rs361525 (-238) G/A	**Genetic variant**	**GG**	**GA**	**AA**	**p - Value**
	TNF-α	121.5 ± 49.29	93.1 ± 32.04	111 ± 0	0.28
rs673 (-244) G/A	**Genetic variant**	**GG**	**GA**	**AA**	
	TNF-α	120.57 ± 50.24	103.89 ± 28.93	109 ± 0	0.61
rs1800629 (-308) G/A	**Genetic variant**	**GG**	**GA**	**AA**	
	TNF-α	122.70 ± 54.30	111.71 ± 31.52	102.40 ± 25.77	0.50
rs1800750 (-376) G/A	**Genetic variant**	**GG**	**GA**	**AA**	
	TNF-α	120.46 ± 48.67	92.20 ± 39.91	109 ± 0	0.44

Data were expressed as mean ± SD. Statistical analyses were performed by ANOVA

Table IX

Comparison of serum TNF-α concentrations across genotypes in psoriatic patients classified by treatment response

		Groups				
		response		**non-response**		**p - value**
		Mean TNF-α	**SD**	**Mean**	**SD**	
rs361525 (-238) G/A	**GG**	93.77	22.54	143.50	41.93	**0.001****
	GA	75.20	19.69	123.00	5.20	**0.02***
	AA	0.0	0.0	111.00	0.0	-
rs673 (-244) G/A	**GG**	87.13	21.40	145.65	38.13	**0.001****
	GA	103.89	28.93	0.0	0.0	-
	AA	109.00	0.0	0.0	0.0	-
rs1800629 (-308) G/A	**GG**	88.75	20.23	134.87	54.28	**0.001****
	GA	92.36	22.04	133.00	17.61	**0.01****
	AA	102.40	25.77	0.0	0.0	-
rs1800750 (-376) G/A	**GG**	93.27	28.87	147.65	49.51	**0.001****
	GA	49.00	0.00	121.00	8.66	**0.002****
	AA	109.00	0.0	0.0	0.0	

Data were expressed as mean ± SD. Statistical analyses were performed by an unpaired t-test

ROC Curve for Post-Treatment TNF-α Concentration

The ROC curve for TNF-α is presented in Table X and Figure 1. The AUC for TNF-α was 0.88, which was statistically significant (p = 0.0001), indicating excellent discriminative power. The optimal cut-off value for TNF-α concentration, determined by the ROC analysis, was 123.0 pg/mL. At this cut-off, the test demonstrated a sensitivity of 77% and a specificity of 90%.

Association between TNF-α and the likelihood of being a non-responder

A binary logistic regression analysis revealed that TNF-α concentration was a significant predictor of non-response (p = 0.0004). The model explained a substantial proportion of the variance in non-response, as indicated by a pseudo-R-squared (*e.g.*, Nagelkerke R-squared) of 0.498. The positive coefficient (β = +0.0792) suggests that higher post-treatment TNF-α concentrations are associated with an increased likelihood of being a non-responder. Specifically, the odds ratio (OR) for TNF-α concentration means that for every one-unit increase in post-treatment TNF-α concentration, the odds of being a non-responder increase by approximately 8.2% (Table XI).

Table X

ROC Curve for Post-Treatment TNF-α Concentration

Area Under the ROC Curve							
Test Result Variable(s): TNF							
Area	**Std. Error**	**Asymptotic Lower Sig.**	**Asymptotic 95% Confidence Interval**		**The best cut-off**	**Sensitivity %**	**Specificity %**
			Lower Bound	**Upper Bound**			
0.88	0.034	0.0001	0.830	0.965	123.0	77	90

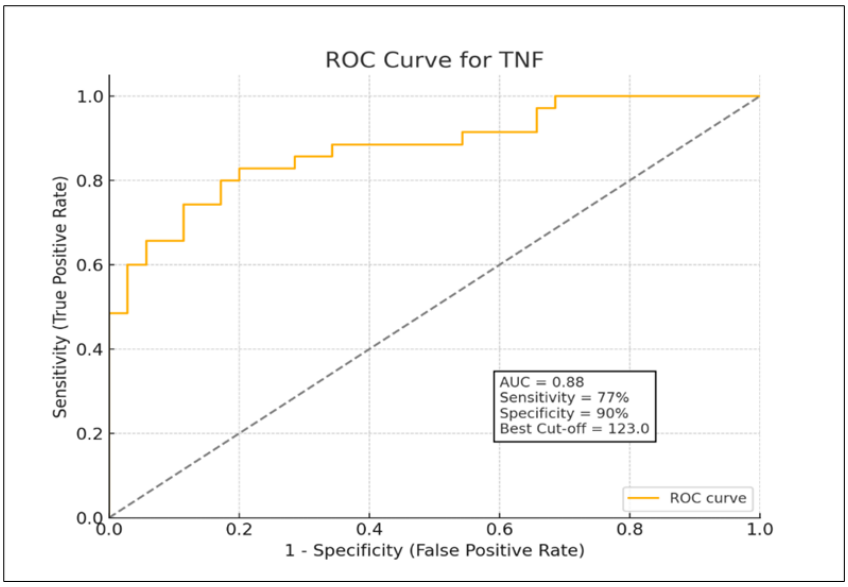

Figure 1.
ROC curve for post-treatment TNF-α concentration

Table XI

Logistic regression: TNF as predictors of non-response

Variable	**Coefficient (β)**	**p - value**	**95% CI for β**	**OR**	**95% CI for OR**
Intercept	-13.57	0.0002*	[-20.67 - -6.47]		
TNF concentration	+0.0792	0.0004*	[0.0357 - 0.1228]	1.082	[1.036 - 1.131]

An efficient inhibitor of TNF-α, ETN, is used to treat psoriasis, a common skin condition marked by inflammation and an immunological reaction. Even with its effectiveness, some patients weren't responsive to ETN [10]. Research indicates that approximately 49.4% of patients demonstrate an inadequate response to anti-TNF therapies, which can include ETN. Similarly, another study reported that roughly 49% of patients may not respond effectively to ETN treatment within the initial months of therapy [30, 31]. The advancement of stratified medicine requires the identification of reliable, validated biomarker panels. Genetic variants are appealing as potential biomarkers because they require only a single test; in various medical fields, they have been shown to correlate with treatment outcomes [32, 33]. Some SNPs in the promoter regions of the TNF-α gene were examined for their potential impact on TNF-α or cytokine production, thereby affecting psoriasis susceptibility or severity [13, 34].

The demographic characteristics of the study revealed that the mean age and duration of psoriasis were comparable to those found in a previous Iraqi studies on psoriasis patients, particularly those examining quality of life or metabolic syndrome [3, 35]. The variance in the male-to-female ratio was also consistent with other Iraqi studies, with males constituting a larger proportion of the sample than females [3, 36, 37].

While two previous studies in Iraq [38, 39] examined the association between a polymorphism in the TNF-α gene promoter and psoriasis, they did not evaluate the association between these SNPs and ETN responsiveness. Numerous studies have studied the impact of SNP combinations in the TNF-α gene on the efficacy of TNF-α antagonists in psoriasis. For instance, the SNPs -238 G/A, -308 G/A, and -857 C/T in the TNF-α gene and their association with therapeutic efficacy were evaluated in 97 Italian psoriatic patients who received ETN [40]. Likewise, a correlation investigation evaluated four TNF-α-associated SNPs -1031 C/T, -238 G/A, -308 G/A, and -857 C/T was conducted in Spain, involving 109 psoriatic patients who were at least six months of treatment with TNF-α inhibitors [41]. Moreover,

meta-analyses have been conducted to examine the association between multiple SNPs and TNF-inhibitor efficacy, including the -308 G/A, -857 C/T, and -238 G/A polymorphism [42]. However, the present study was the only study examining the associations between rs361525 (-238) G/A, rs673 (-244) G/A, rs1800629 (-308) G/A, and rs1800750 (-376) G/A and ETN responsiveness in psoriasis.

Regarding the TNF-α -244 G/A polymorphism, the present study found that 87.5% of patients had the GG genotype, 11.25% had the GA genotype, and the AA genotype had the lowest prevalence. Moreover, the G allele frequency is 93.13%, while the A allele frequency is 6.87%. Few studies provide contradictory evidence on the prevalence of this SNP; however, all studies indicate that the GG genotype is the most prevalent. X Li *et al*. [43] found that the GG genotype frequency is 97% of 452 Chinese women with cervical cancer, while Oyedeji SI *et al*. [44] revealed that the GG genotype was found in 75% and GA in 25% of 96 Nigerian patients with severe malaria. Another study compared a control group with individuals with juvenile idiopathic arthritis and found that the TNF-α -244 G/A polymorphism was observed solely in healthy Caucasian children in the control group [45].

This study may be among the first to evaluate the correlation between the TNF-α -244 G/A polymorphism and the response to ETN in patients with psoriasis. The TNF-α -244 G/A variant was significantly associated with ETN response at both the genotype and allele levels ($p = 0.02$). It is worth noting that the GG genotype was significantly less frequent in responders (75%) than in non-responders (100%), while the GA genotype was observed exclusively in the responder group (22.5%). At the allele level, the G allele was highly prevalent in non-responders (100%), whereas the A allele was detected only in the responders (13.75%). It suggests that the presence of at least one A allele at the -244 locus is not merely associated with response, but may be a potential contributor to a good reaction to ETN in this population. As a promoter-region polymorphism, the TNF-α -244 G/A variant may influence transcriptional activity and could be associated with altered TNF-α expression or downstream signalling, potentially contributing to differences in treatment response [46]. The Phi correlation analysis was consistent with these findings: the -244 GG genotype demonstrated a highly significant positive association with non-responder status (phi = +0.411, $p = 0.0007$), whereas the GA genotype demonstrated a negative association (phi = -0.318, $p = 0.007$), suggesting that the presence of the A allele may be linked to a more favourable response. Similarly, the -244 G/A polymorphism showed a statistically significant correlation with ΔPASI ($p = 0.02$), with patients carrying the GA genotype exhibiting greater mean PASI improvement than those with the GG genotype. These patterns together suggest that the -244 G/A variant may be relevant to explaining variability in clinical response, although further studies are required to confirm its role.

Regarding the TNF-α -308G/A polymorphism, the present study found a high prevalence of the GG genotype (67.5%) among patients, followed by the heterozygous GA genotype, with the homozygous AA genotype being the least prevalent. Moreover, the G allele was identified in over 80% of patients, whereas the A allele was found in only 19%. These results align with those of studies by Kawen *et al*. [38] and Aterehi [39]. Kawen *et al*. examined Iraqi psoriasis patients in Thi-Qar province. They revealed that GG and GA genotypes were present in 78.9% and 21.1% of psoriasis patients, respectively, and that the Frequencies of G and A alleles were 89.5% and 10.5%, respectively. At the same time, Aterehi found that the GG genotype was distributed in 54.6% of psoriasis patients in Babylon Province, and the GA genotype in 37.5%. In contrast to the present study and Aterehi's results, which identified five patients with the AA genotype, Kawen *et al*. [38] findings revealed that none of the patients had the AA genotype.

Several studies have investigated the impact of the TNF-α -308G/A polymorphism on responsiveness to TNF-α blockers in patients with psoriasis and psoriatic arthritis [40-42, 47]. The current study results revealed no significant difference in the genotypes of the -308G/A polymorphism between the respondent and non-respondent groups; although less prominent than TNF-α -244 G/A, the -308 G/A polymorphism also showed a significant association, with the G allele being more frequent in non-responders (87.5%) than in responders (73.75%) ($p = 0.03$). This suggests a potential, albeit weaker, role for the A allele in contributing to treatment response. Despite lacking statistical significance ($p = 0.1$), a noticeable trend indicated enhanced PASI improvement associated with the AA genotype (mean ΔPASI = -18.88), hence reinforcing the possible beneficial effect of the A allele.

The result is consistent with Gallo *et al*. [41] and Vasilopoulos *et al*. [47], who reported no association between the TNF-α -308 G/A polymorphism and anti-TNF-α response. In contrast to our results, some studies report a better response in patients with the -308 GG genotype compared to the GA genotype and show that the A allele is associated with a poor response in patients with psoriasis, rheumatic arthritis, and spondyloarthritis [22, 40, 48]. The divergence between this study and others can be ascribed to the fact that the -308 A allele is linked to other genes that may influence resistance to ETN [49]. Nonetheless, this linkage disequilibrium with other genes may be absent in our sample, as is the current study's limited

representation of the A allele or ethnic variation. Moreover, discrepancies in the concept of "response" across studies, coupled with other research's focus on various disorders, may have contributed to this discrepancy.

The GG genotype is highly prevalent for the TNF-α -238 G/A variant, with a frequency of 88.75%, which is consistent with a survey from Thi-Qar that reported a frequency of 86.5% for the GG genotype in psoriasis patients [38].

In contrast to the TNF-α -244 G/A and -308 G/A polymorphisms, the TNF-α -238 G/A and -376 G/A polymorphisms showed no significant differences in genotype or allele frequencies between responders and non-responders. A similar result was obtained in Vasilopoulos *et al*. [47] and Scardapane *et al*. [45]; they did not find a significant association between the TNF-α -238 G/A polymorphism and anti-TNF response. On the other hand, De Simone *et al*. [40] found that heterozygous GA individuals showed a significantly higher non-response rate in psoriasis patients treated with ETN. At the same time, Membrive-Jimenez *et al*. [50] observed that 238 G allele carriers showed an association with a response to ETN. Additionally, Gallo *et al*. [41] reported an association between the -238 GG genotype and a favourable reaction to anti-TNF-α therapy. Nonetheless, this association was not substantiated when clinical efficacy was assessed after three months of treatment, and considerable disparities were identified in the sub-analysis of different anti-TNF medications. This discrepancy may be due to variations in study design, patient populations (*e.g*., disease severity, ethnicity, sample size), which reduce the generalizability of the findings [51]. Furthermore, Falvo *et al*. assert that single-nucleotide polymorphisms exert a neutral influence on TNF gene transcription. This suggests that although the allele may exist, it does not significantly alter TNF expression or function in the human body. The regulation of TNF gene expression is primarily determined by transcription factor recruitment and chromatin organisation, rather than by individual polymorphisms [52]. The comparison is inapplicable to other studies, as no prior research has investigated the relationship between the TNF-α -376 G/A polymorphism and the response to ETN or other TNF-α antagonists.

The TNF-α -238 G/A and TNF-α -376 G/A polymorphisms exhibited no significant variations in genotype or allele frequencies between responders and non-responders, nor did they show substantial relationships with ΔPASI. By clearly identifying the SNPs that did not exhibit significant relationships, the study offers valid negative data. This refines the scope for forthcoming pharmacogenomic research, averting superfluous inquiries into genetic variants that may lack clinical significance for ETN responsiveness in this context. This facilitates a more effective distribution of research resources and helps build a more precise understanding of the specific genetic framework that affects therapeutic efficacy.

Regarding the correlation between SNP genotypes and circulating TNF-α levels, none of the analysed SNPs showed a significant association. Results were concurred with those of Mohammed *et al*. [21, 22], which detected a non-significant difference in the TNF-α circulating level concerning the TNF-α -308 G/A and -376 G/A polymorphism. This finding is corroborated by a later investigation that documents an absence of correlation between the TNF-α -308 G/A and -238 G/A, and -376 G/A polymorphisms and circulating levels of TNF-α, in Jabbar's study [53], and is contradictory to reports that show an association, such as Hagag *et al*. [34], and Li C *et al*. [54], revealed that AA and GA genotypes showed higher TNF-α serum levels. Additionally, Hagag *et al*. [34] and Elfarargy *et al*. [55] reported that the -308 GG genotype is associated with a considerably higher TNF-α serum level than the GA and AA genotypes. In this study, the -308 GG genotype has a higher TNF-α serum level than the GA and AA genotypes, but this difference does not reach significance. The observed disparity between the current study and previous research findings may be attributed to a significant within-group variability, particularly in the GG genotype group, and a small sample size in the AA genotype, which may have limited the statistical power to detect a significant difference. Additionally, the ethnic backgrounds of the patients may contribute to this discrepancy, as stratification analysis has shown that other ethnic groups can harbour distinct risk alleles [56].

The observation that non-responders continuously display elevated TNF-α levels aligns with extensive evidence suggesting that elevated inflammatory markers can predict adverse outcomes in chronic inflammatory illnesses [57, 58]. This study extends this by demonstrating the excellent discriminative power of post-treatment TNF-α levels (AUC 0.88, ideal cut-off 123.0 pg/mL) for identifying ETN non-response. These results indicate that TNF-α measured after treatment may reflect the inflammatory status associated with treatment outcome and could be helpful in characterising response patterns in this context.

Beyond genetic susceptibility, the study highlights that post-treatment TNF-α levels are closely associated with non-response. The consistently higher TNF-α concentration observed in non-responder across different genotypes suggests that monitoring TNF-α levels during therapy may provide helpful information about the patient's inflammatory status and their overall treatment outcome.

Although our study did not measure serum drug concentrations or anti-drug antibodies, these factors

are acknowledged contributors to treatment variability. Literature demonstrates that differential drug levels, often influenced by genetic variability, distinguish responders from non-responders [59]. Likewise, genotype may affect susceptibility to the development of autoantibodies against anti-TNF-α medications, which correlate with reduced serum drug concentrations and treatment failure [60]. In the current study, all patients strictly adhered to a uniform ETN dosing schedule. Crucially, pharmacokinetic variability is unlikely to have significantly influenced the treatment response observed here, as ETN is characterised by its low immunogenicity and a remarkably stable pharmacokinetic profile compared to monoclonal antibody TNF-α inhibitors [61]. Therefore, while genetic variability influencing pharmacokinetics or autoantibody formation remains a compelling area for future research, it is unlikely that these factors were the primary drivers of the differential treatment response by genotype in this cohort.

This work contributes to addressing the gap in the literature as no previous studies have evaluated the association between the *rs673*(-224) G/A polymorphism and response to ETN in patients with psoriasis. The observed association between *rs673* (-244) G/A and treatment response, particularly the higher frequency of the GA genotype and the A allele among responders, provides initial evidence that this variant may be relevant as a pharmacogenetic predictor for anti-TNF therapy in psoriasis. These findings are exploratory and highlight the need for further investigation and validation in larger cohorts.

Conclusions

This study provides initial findings into the pharmacogenomics of psoriasis by suggesting a potential association between the rs673 (-244) G/A polymorphism and response to ETN in Iraqi patients. In addition, the findings support the possible role of post-treatment TNF-α concentration as a complementary biomarker of treatment response. While these results are exploratory, they contribute to the growing body of evidence on personalised approaches in psoriasis management. Further validation in larger and multi-centre cohorts is needed before these markers can be considered for clinical application.

Conflict of interest

The authors declare no conflict of interest.

References

1. Arnold KA, Treister AD, Lio PA, Alenghat FJ, Association of atherosclerosis prevalence with age, race, and traditional risk factors in patients with psoriasis. *JAMA Dermatol.*, 2019; 155(5): 622-623.
2. Jung KJ, Kim T, Lee JW, Lee M, Oh J, Lee S, Chang H, Jee SH, Lee M, Increased risk of atherosclerotic cardiovascular disease among patients with psoriasis in Korea: A 15-year nationwide population-based cohort study. *J Dermatol.*, 2019; 46(10): 859-866.
3. Abdulridha SH, Kadhim DJ, Razzak SAA, Assessment of Quality of Life in a Sample of Iraqi Patients with Psoriasis. *Iraqi J Pharm Sci.*, 2020; 29(2): 161-168.
4. Armstrong AW, Bohannan B, Mburu S, Coates LC, Ogdie A, Alarcon I, Kasparek T, Frade S, Barrio SF, Augustin M, Patient perspectives on psoriatic disease burden: results from the global psoriasis and beyond survey. *Dermatology*, 2023; 239(4): 621-634.
5. Mahmutović E, Dolićanin Z, Todorović ST, Milićević S, Doder R, Bošković K, Psoriasis and Psoriatic Arthritis. *Arch Phys Med Rehabil.*, 2018; 99(12): e211.
6. Nowowiejska J, Baran A, Grabowska P, Lewoc M, Kaminski TW, Flisiak I, Assessment of life quality, stress and physical activity among patients with psoriasis. *Dermatol Ther (Heidelb).*, 2022; 12(2): 395-406.
7. Baliwag J, Barnes DH, Johnston A, Cytokines in psoriasis. *Cytokine*, 2015; 73(2): 342-350.
8. Griffiths CEM, Barker JNWN, Pathogenesis and clinical features of psoriasis. *Lancet*, 2007; 370(9583): 263-271.
9. Armstrong AW, Puig L, Joshi A, Skup M, Williams D, Li J, Betts KA, Augustin M, Comparison of biologics and oral treatments for plaque psoriasis: a meta-analysis. *JAMA Dermatol.*, 2020; 156(3): 258-269.
10. Li S, Li G, Li X, Wu F, Li L, Etanercept ameliorates psoriasis progression through regulating high mobility group box 1 pathway. *Skin Res Technol.*, 2023; 29(4): e13329.
11. Prieto-Pérez R, Cabaleiro T, Daudén E, Ochoa D, Roman M, Abad-Santos F, Genetics of psoriasis and pharmacogenetics of biological drugs. *Autoimmune Dis.*, 2013; 2013(1): 613086.
12. Boyman O, Hefti HP, Conrad C, Nickoloff BJ, Suter M, Nestle FO, Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and tumor necrosis factor-α. *J Exp Med.*, 2004; 199(5): 731-736.
13. Wang L, Zhou H, A meta-analysis of the relationship between tumor necrosis factor-α polymorphisms and psoriasis. *Dermatology*, 2021; 237(1): 39-45.
14. Baseggio L, Bartholin L, Chantome A, Charlot C, Rimokh R, Salles G, Allele-specific binding to the-308 single nucleotide polymorphism site in the tumour necrosis factor-alpha promoter. *Eur J Immunogenet.*, 2004; 31(1): 15-19.
15. Bergman MJ, Kivitz AJ, Pappas DA, Kremer JM, Zhang L, Jeter A, Withers JB, Clinical utility and cost savings in predicting inadequate response to anti-TNF therapies in rheumatoid arthritis. *Rheumatol Ther.*, 2020; 7: 775-792.
16. Ma MHY, Defranoux N, Li W, Sasso EH, Ibrahim F, Scott DL, Cope AP, A multi-biomarker disease activity score can predict sustained remission in rheumatoid arthritis. *Arthritis Res Ther.*, 2020; 22: 1-12.
17. Ventola CL, Role of pharmacogenomic biomarkers in predicting and improving drug response: part 1: the clinical significance of pharmacogenetic variants. *Pharm Ther.*, 2013; 38(9): 545.
18. Alhilali D, Mohammed S, Genetic polymorphisms at TNF-alpha receptors associated some autoimmune

diseases and response of Anti-TNF biologics. *Iraqi J Pharm Sci.*, 2024; 33(4): 49-58.
19. Mohammed SI, Jasim AL, Jamal MY, Hussain SA, Factors influencing adalimumab treatment response in patients with rheumatoid arthritis: the future of clinical expertise. *Al-Rafidain J Med Sci.*, 2023; 5: 192-204.
20. Mohammed SI, Jamal MY, Alshamari IO, The association of genetic polymorphisms in tumor necrosis factor-alpha and interleukins with disease severity or response to biological therapy in Iraqi rheumatoid arthritis patients: A narrative review. *Al-Rafidain J Med Sci.*, 2023; 4: 24-33.
21. Mohammed SI, Zalzala MH, Gorial FI, The effect of TNF-alpha gene polymorphisms at-376 G/A,-806 C/T, and-1031 T/C on the likelihood of becoming a non-responder to etanercept in a sample of Iraqi rheumatoid arthritis patients. *Iraqi J Pharm Sci.*, 2022; 31(2): 113-128.
22. Mohammed S, Zalzala M, Gorial F, Association of tumor necrosis factor-alpha promoter region gene polymorphism at positions-308G/A,-857C/T, and-863C/A with etanercept response in Iraqi rheumatoid arthritis patients. *Arch Rheumatol.*, 2022; 37(4): 613.
23. Saleh Khudhur S, Saadi Saleh E, Hadi Alosami M, G. Shareef L, Association between polymorphisms within the gene coding for tumor necrosis factor (TNF)-alpha with outcomes of treatment in a sample of Iraqi patients with ankylosing spondylitis taking etanercept: an observational study. *F1000Research.*, 2022; 11: 1576.
24. Khudhur SS, Saleh ES, Alosami MH, The Impact of rs767455 and rs1061622 Polymorphisms on Treatment Outcomes in Iraqi Ankylosing Spondylitis Patients Taking Etanercept. *Egypt J Hosp Med.*, 2022; 89(2): 7831-7839.
25. Daudén E, Puig L, Ferrándiz C, Sánchez-Carazo JL, Hernanz-Hermosa JM, Venereology SPG of the SA of D and, Consensus document on the evaluation and treatment of moderate-to-severe psoriasis: Psoriasis Group of the Spanish Academy of Dermatology and Venereology. *J Eur Acad Dermatology Venereol.*, 2016; 30: 1-18.
26. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CEM, Nast A, Franke J, Antoniou C, Arenberger P, Balieva F, Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res.*, 2011; 303(1): 1-10.
27. Berth-Jones J, Grotzinger K, Rainville C, Pham B, Huang J, Daly S, Herdman M, Firth P, Hotchkiss K, A study examining inter-and intrarater reliability of three scales for measuring severity of psoriasis: Psoriasis Area and Severity Index, Physician's Global Assessment and Lattice System Physician's Global Assessment. *Br J Dermatol.*, 2006; 155(4): 707-713.
28. Loft ND, Skov L, Iversen L, Gniadecki R, Dam TN, Brandslund I, Hoffmann HJ, Andersen MR, Dessau RB, Bergmann AC, Associations between functional polymorphisms and response to biological treatment in Danish patients with psoriasis. *Pharmacogenomics J.*, 2018; 18(3): 494-500.
29. Shah K, Maghsoudlou P, Enzyme-linked immunosorbent assay (ELISA): the basics. *Br J Hosp Med.*, 2016; 77(7): C98-C101.
30. Van Voorhees AS, Mason MA, Harrold LR, Guo N, Guana A, Tian H, Herrera V, Strober BE, Characterization of insufficient responders to anti-tumor necrosis factor therapies in patients with moderate to severe psoriasis: real-world data from the US Corrona Psoriasis Registry. *J Dermatolog Treat.*, 2021; 32(3): 302-309.
31. Kimball AB, Rothman KJ, Kricorian G, Pariser D, Yamauchi PS, Menter A, Teller CF, Aras G, Accortt NA, Hooper M, OBSERVE-5: observational postmarketing safety surveillance registry of etanercept for the treatment of psoriasis final 5-year results. *J Am Acad Dermatol.*, 2015; 72(1): 115-122.
32. Cascella R, Strafella C, Longo G, Maccarone M, Borgiani P, Sangiuolo F, Novelli G, Giardina E, Pharmacogenomics of multifactorial diseases: A focus on psoriatic arthritis. *Pharmacogenomics*, 2016; 17(8): 943-951.
33. Massey J, Plant D, Hyrich K, Morgan AW, Wilson AG, Spiliopoulou A, Colombo M, McKeigue P, Isaacs J, Cordell H, Genome-wide association study of response to tumour necrosis factor inhibitor therapy in rheumatoid arthritis. *Pharmacogenomics J.*, 2018; 18(5): 657-664.
34. Hagag MM, Ghazy MM, Elhelbawy NG, Tumor necrosis factor-α gene promoter-308 and-238 polymorphisms and its serum level in psoriasis. *Biochem Biophys Reports.*, 2021; 27: 101050.
35. Naif AAH, Metabolic syndrome in Iraqi patients with psoriasis: A comparative study. *J Thi-Qar Sci.*, 2015; 5(2): 37-39.
36. Al-Saadi BQH, The role of FASL gene polymorphism (rs: 763110), its serum level and IL21 level with incidence of psoriasis in Iraqi patients. In: *IOP Conference Series: Earth and Environmental Science*, IOP Publishing; 2024: 12029.
37. Abdulkhaliq Roua Jamal, Almawla Saleem Obaid Gatia, Hussain Abdalwahab Bedwi IAK, MRA, A study of the prevalence of psoriasis in the city of Fallujah and its correlation with some immunological and haematological parameters. *Res J Biotechnol.*, 2024; 19(11): 7-13.
38. Kawen AA, Nasyria AAA, Al-Sultany HA, Study of the Genetic Polymorphisms of the Promoter Region of TNF-in Thi-Qar Patients Affected by Psoriasis. *Int J Health Sci (Qassim).*, 2022; 6(S5): 4750-4761.
39. Aterehi MN, Association of Tumor Necrosis Factor-α-308 gene Polymorphism with Psoriasis in Babylon Province. *J Glob Pharma Technol.*, 2017; 9(7).
40. De Simone C, Farina M, Maiorino A, Fanali C, Perino F, Flamini A, Caldarola G, Sgambato A, TNF-alpha gene polymorphisms can help to predict response to etanercept in psoriatic patients. *J Eur Acad Dermatology Venereol.*, 2015; 29(9): 1786-1790.
41. Gallo E, Cabaleiro T, Román M, Solano-López G, Abad-Santos F, García-Díez A, Daudén E, The relationship between tumour necrosis factor (TNF)-α promoter and IL12B/IL-23R genes polymorphisms and the efficacy of anti-TNF-α therapy in psoriasis: a case–control study. *Br J Dermatol.*, 2013; 169(4): 819-829.
42. Caputo V, Strafella C, Cosio T, Lanna C, Campione E, Novelli G, Giardina E, Cascella R, Pharmacogenomics: an update on biologics and small-molecule drugs in the treatment of psoriasis. *Genes*, 2021; 12(9): 1398.
43. Li X, Yin G, Li J, Wu A, Yuan Z, Liang J, Sun Q, The correlation between TNF-α promoter gene

polymorphism and genetic susceptibility to cervical cancer. *Technol Cancer Res Treat.*, 2018; 17: 1533033818782793.
44. Oyedeji SI, Awobode HO, Bassi PUJFK, -308G>A (rs1800629) and -244G>A (rs673) polymorphisms at the promoter region of the TNF-α gene in severe malaria patients in north-central Nigeria. *Niger J Parasitol.*, 2017; 38(2): 205-209.
45. Scardapane A, Ferrante R, Nozzi M, Savino A, Antonucci I, Dadorante V, Balsamo M, Stuppia L, Chiarelli F, Breda L, TNF-α gene polymorphisms and juvenile idiopathic arthritis: Influence on disease outcome and therapeutic response. In: *Seminars in Arthritis and Rheumatism*, Elsevier; 2015. p. 35-41.
46. Abraham LJ, Kroeger KM, Impact of the-308 TNF promoter polymorphism on the transcriptional regulation of the TNF gene: relevance to disease. *J Leukoc Biol.*, 1999; 66(4): 562-566.
47. Vasilopoulos Y, Manolika M, Zafiriou E, Sarafidou T, Bagiatis V, Krüger-Krasagaki S, Tosca A, Patsatsi A, Sotiriadis D, Mamuris Z, Roussaki-Schulze A, Pharmacogenetic analysis of TNF, TNFRSF1A, and TNFRSF1B gene polymorphisms and prediction of response to anti-TNF therapy in psoriasis patients in the Greek population. *Mol Diagn Ther.*, 2012; 16: 29-34.
48. Liu J, Dong Z, Zhu Q, He D, Ma Y, Du A, He F, Zhao D, Xu X, Zhang H, Jin L, Wang J, TNF-α Promoter Polymorphisms Predict the Response to Etanercept More Powerfully than that to Infliximab/Adalimumab in Spondyloarthritis. *Sci Rep.*, 2016; 6(March): 1-9.
49. Guis S, Balandraud N, Bouvenot J, Auger I, Toussirot E, Wendling D, Mattel JP, Nogueira L, Mugnier B, Legeron P, Landt O, Serre G, Roudier J, Roudier C, Influence of -308 A/G polymorphism in the tumor necrosis factor α gene on etanercept treatment in rheumatoid arthritis. *Arthritis Care Res.*, 2007; 57(8): 1426-1430.
50. Membrive-Jimenez C, Zuñiga C, Pérez-Ramirez C, Arias-Santiago S, Jimenez-Morales CMV, 4CPS-218 TNF gene polymorphisms predictors of response to anti-TNF drugs in patients diagnosed with moderate-severe psoriasis. *Eur J Hosp Pharm.*, 2023; 30(suppl 1): A1-A239.
51. Rajesh D, Chowdappa C, Gurumurthy R, Kutty AVM, Balakrishna S, Profile of tumour necrosis factor alpha-308 G/A gene polymorphism in psoriatic patients in Karnataka, India. *J Clin Diagnostic Res JCDR.*, 2017; 11(2): GC01.
52. Falvo JV, Tsytsykova AV, Goldfeld AE, Transcriptional control of the TNF Gene. *Curr Dir Autoimmun.*, 2010; 11(table 1): 27-60.
53. Jabbar SH, Association of genetic variation in tumor necrosis factor-α gene with susceptibility to rheumatoid arthritis in southern Iraq. *Univ Thi-Qar J Sci.*, 2023; 10(1(SI)): 194-200.
54. Li C, Wang G, Gao Y, Liu L, Gao T, TNF-α gene promoter-238G> A and-308G> A polymorphisms alter risk of psoriasis vulgaris: a meta-analysis. *J Invest Dermatol.*, 2007; 127(8): 1886-1892.
55. Elfarargy S, Farag AGA, Azmy RM, Abdullah MS, Study of tumor necrosis factor-α-308 promoter polymorphism in psoriasis vulgaris. *J Egypt Women's Dermatologic Soc.*, 2014; 11(2): 117-122.
56. Lee D, Koo T, Park J, Shin HT, Comparison of risk allele frequencies of Psoriasis-Associated single-nucleotide polymorphisms in different Population groups. *Ann Dermatol.*, 2023; 35(1): 32-38.
57. Jang Din D, Lee AH, Shin HY, Song HR, Park JH, Kang TB, Lee SR, Yang SH, The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current TNF-α inhibitors in therapeutics. *Int J Mol Sci.*, 2021; 22(5): 2719.
58. Albar Z, Albakri M, Hajjari J, Karnib M, Janus SE, Al-Kindi SG, Inflammatory markers and risk of heart failure with reduced to preserved ejection fraction. *Am J Cardiol.*, 2022; 167: 68-75.
59. Jamnitski A, Krieckaert CL, Nurmohamed MT, Hart MH, Dijkmans BA, Aarden L, Voskuyl AE, Wolbink GJ, Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients. *Ann Rheum Dis.*, 2012; 71(1): 88-91.
60. Lecluse LLA, Driessen RJB, Spuls PI, de Jong EMGJ, Stapel SO, van Doorn MBA, Bos JD, Wolbink GJ, Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis. *Arch Dermatol.*, 2010; 146(2): 127-132.
61. Herszényi K, Jókai H, Rencz F, Brodszky V, Nagy E, Holló P, Antidrug antibody formation during tumor necrosis factor α inhibitor treatment of severe psoriatic patients in the real-life practice. *Postepy Dermatol Alergol.*, 2019; 36(5): 589-594.