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TNF-α –308G>A (rs1800629) Polymorphism and Thromboembolic Risk in Iraqi Patients with Warfarin-Treated Hematological Disorders: A Case-Control Study

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Abstract

Tumor necrosis factor-alpha (TNF-α) is a complex pro-inflammatory cytokine with notable pro-coagulant characteristics. The TNF-α promoter polymorphism (rs1800629) is a functional gain-of-function mutation associated with increased cytokine production and altered immunological responses. The impact of thromboembolic risk in warfarin-treated hematological patients in Iraq is still unclear. This prospective case-control study included 320 Iraqi patients undergoing chronic warfarin therapy for hematological diseases and 280 healthy controls. Genotyping of TNF-α –308G>A was conducted by ARMS-PCR. Clinical outcomes, including thromboembolic events, bleeding incidents, and time in therapeutic range (TTR), were prospectively documented. Logistic and multiple linear regression were utilized for adjusted analysis. The frequency of the A allele was markedly higher in patients (21.7%) compared to controls (14.1%; OR = 1.68; 95% CI: 1.23–2.29; p = 0.001). Individuals with the A allele (GA + AA genotypes) demonstrated a 2.18-fold increased risk of thromboembolic problems relative to GG homozygotes (adjusted OR = 2.18; 95% CI: 1.43–3.32; p = 0.001). TNF-α –308A carriers had a lower mean TTR (56.8 ± 14.9% vs. 64.3 ± 16.1% in GG carriers; p = 0.008). The TNF-α genotype

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independently contributed partial $R^2 = 0.031$ to a six-locus pharmacogenetic-cytokine model for warfarin dosage (overall $R^2 = 0.613$). The TNF-α–308A allele serves as an independent risk factor for thromboembolic events in Iraqi patients with warfarin-treated hematological disorders. Genotyping of TNF-α may pinpoint high-risk patients requiring enhanced vigilance and regular INR monitoring. These findings support integrating cytokine gene profiling with pharmacogenetic testing in tailored anticoagulation approaches in the Middle East.

Keywords: TNF-α; rs1800629; Cytokine polymorphism; Thromboembolic risk; Warfarin; Hematological disorders.

Introduction

The inflammatory state intrinsic to many hematological disorders, including myeloproliferative neoplasms (MPNs), hematological malignancies, and conditions associated with chronic immune activation, substantially modulates both the risk of thromboembolic complications and the stability of anticoagulation therapy [1;2]. Among the cytokines mediating this inflammatory-hemostatic crosstalk, tumor necrosis factor-alpha (TNF-α) occupies a central position [3]. TNF-α is a multifunctional pro-inflammatory cytokine with pleiotropic effects on the coagulation cascade: it upregulates tissue factor expression on endothelial cells and monocytes, suppresses thrombomodulin and protein C pathway activity, promotes endothelial dysfunction and platelet hyperactivation, and induces hepatic acute-phase protein synthesis, collectively establishing a prothrombotic hemostatic environment [4;5].

The TNF-α –308G>A promoter polymorphism (rs1800629) is one of the most extensively characterized cytokine gene variants in human genetics. Located within the promoter region of the TNF-α gene on chromosome 6p21.3, this single-nucleotide polymorphism disrupts a transcription factor binding motif, resulting in significantly elevated constitutive and inducible TNF-α production in carriers of the A allele compared to GG homozygotes [4]. Functional studies in stimulated peripheral blood mononuclear cells and whole blood cultures have consistently confirmed that the –308A allele confers a gain-of-function phenotype, with carriers producing 2–3-fold higher TNF-α levels following immune stimulation [5;6].

The clinical relevance of this functional variant spans a wide range of inflammatory, autoimmune, and oncological conditions. In the hematological context, emerging evidence implicates TNF-α –308G>A in modulating disease severity in acute myeloid leukemia (AML) and other hematological malignancies [3], and in influencing transplant-related complications, including graft-versus-host disease and thrombotic microangiopathy [7;8]. The pro-coagulant properties of elevated TNF-α provide a biologically compelling mechanism by

which this polymorphism could elevate thromboembolic risk independently of classical coagulation pathway genetics.

Of particular clinical relevance is the potential interaction between TNF-α-mediated inflammation and warfarin pharmacodynamics. Patients with hematological disorders requiring anticoagulation often experience episodic inflammatory flares that may destabilize INR control through multiple mechanisms: induction of acute-phase proteins that compete for vitamin K-dependent clotting factor synthesis, modulation of hepatic cytochrome P450 enzyme expression (including CYP2C9), and direct effects on platelet activation and vascular biology [8;9]. If carriers of the TNF-α –308A allele chronically produce elevated TNF-α, these destabilizing mechanisms may operate at a persistently higher baseline, translating into measurable reductions in TTR and elevated clinical event rates that cannot be explained by pharmacogenetic factors alone.

Despite the large body of evidence linking TNF-α, 308G>A to inflammatory and oncological outcomes, its specific role in modulating thromboembolic risk and warfarin stability in patients with hematological disorders has not been characterized. Furthermore, TNF-α genotype data from the Iraqi population, and its integration with pharmacogenetic (VKORC1, CYP2C9) determinants in a combined dosing model, are entirely absent from the existing literature. This represents a critical research gap given the distinct genetic architecture and inflammatory disease burden of Middle Eastern populations [10;11].

The present study was designed to: (1) determine TNF-α –308G>A allele and genotype frequencies in Iraqi patients with warfarin-requiring hematological disorders and in healthy controls; (2) assess the independent association of TNF-α –308A allele carrier status with thromboembolic events and INR instability (TTR) after adjustment for pharmacogenetic and clinical covariates; (3) evaluate the contribution of TNF-α genotype to a multi-locus pharmacogenetic-cytokine warfarin dosing model; and (4) provide the first population-level TNF-α –308G>A allele frequency data in an Iraqi hematological cohort as a foundation for future precision anticoagulation algorithms.

Materials and Methods

Study Design and Participants

This prospective case-control study was conducted between January 2023 and December 2024 at Al-Sadder Teaching Hospital and the University of Kufa Medical Center, Najaf, Iraq. Ethical approval was granted by the Institutional Review Board of the University of Kufa, College of Medicine (Protocol No. KUF-IRB-2022-047), and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Cases (n = 320) were adult patients (≥18 years) with established hematological conditions requiring chronic warfarin anticoagulation,

including: deep vein thrombosis/pulmonary embolism (n = 128), myeloproliferative neoplasms with thrombotic complications (n = 74), atrial fibrillation associated with hematological disorders (n = 68), and mechanical heart valve replacement in patients with underlying hematological disease (n = 50). Eligibility required stable warfarin therapy, defined as a consistent dose maintaining INR within the therapeutic target range of 2.0–3.0 for ≥3 consecutive clinic visits over a minimum of 3 months. Exclusion criteria included hepatic or renal dysfunction (ALT >3× ULN; creatinine >1.5× ULN), concurrent use of medications with known warfarin pharmacokinetic interactions, and refusal to provide genetic consent. Controls (n = 280) were age- and sex-matched healthy Iraqi volunteers without personal or family history of hematological disorders, thromboembolism, or cardiovascular disease, and not receiving any anticoagulant, antiplatelet, or immunosuppressive therapy.

Clinical and Laboratory Data Collection

All patients underwent standardized clinical assessment, including demographic data, comorbidities, concomitant medications, indication for anticoagulation, and warfarin therapy duration. Laboratory parameters, including complete blood count (CBC), INR, liver function tests (LFTs), and renal function tests, were collected at baseline and at each follow-up visit. C-reactive protein (CRP) was measured as a surrogate inflammatory marker at baseline. Warfarin daily maintenance dose was defined as the stable dose maintaining INR in the therapeutic range (2.0–3.0). TTR was calculated using the Rosendaal linear interpolation method over a minimum 6-month follow-up [12]. Bleeding events were classified using ISTH criteria. Thromboembolic events were objectively confirmed as new or recurrent venous or arterial thromboembolism during follow-up.

DNA Extraction and TNF-α Genotyping

Genomic DNA was extracted from 5 mL of EDTA-anticoagulated peripheral venous blood using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) per manufacturer's protocol. DNA quality was assessed by NanoDrop spectrophotometry (A260/A280 ratio 1.8–2.0 [13].

TNF-α –308G>A (rs1800629)was genotyped using amplification refractory mutation system PCR (ARMS-PCR) with allele-specific inner primers generating a 181-bp fragment for the G allele and a 117-bp fragment for the A allele, validated against a 268-bp outer control band [14]. PCR amplifications were performed using a thermal cycler under standardized conditions: initial denaturation at 94°C for 5 min; 35 cycles of 94°C for 30 s, 58°C for 45 s, 72°C for 45 s; final extension at 72°C for 7 min. Products were resolved on 2% agarose gels stained with ethidium bromide and visualized under UV. A random 15% of samples was re-genotyped by a blinded second operator; concordance was

99.6%. All genotyping was performed blinded to clinical outcome data.

Statistical Analysis

Hardy-Weinberg equilibrium (HWE) was assessed for TNF-α –308G>A in controls by chi-square goodness-of-fit test. Allele and genotype frequencies between cases and controls were compared by chi-square or Fisher's exact tests. Logistic regression (unadjusted and adjusted for age, sex, BMI, warfarin indication, VKORC1 genotype, and CYP2C9 genotype) was used to estimate ORs with 95% CIs for thromboembolic and bleeding outcomes. Differences in TTR and CRP levels by TNF-α genotype were assessed by one-way ANOVA with Bonferroni post-hoc correction. Multiple linear regression was performed to evaluate TNF-α genotype contribution to a six-locus pharmacogenetic-cytokine warfarin dosing model. Linkage disequilibrium between TNF-α –308G>A and co-studied polymorphisms was assessed using D' and r^2 statistics. All analyses used SPSS version 26.0 (IBM Corp.) and R version 4.3.1; significance was set at $p < 0.05$ (two-tailed) with Bonferroni correction for multiple comparisons where applicable.

Results

Baseline Characteristics

The clinical characteristics of the 320 cases and 280 healthy controls are summarized in Table 1. Cases and controls were well-matched for age (mean 47.2 ± 14.8 vs. 46.9 ± 13.5 years; p = 0.83), sex distribution (55.3% male in cases, 53.9% in controls; p = 0.73), and BMI (27.1 ± 4.2 vs. 26.8 ± 3.9 kg/m²; p = 0.41). Mean warfarin daily maintenance dose was 4.6 ± 1.9 mg/day. Mean TTR was 61.4 ± 16.2%. During follow-up, 48 patients (15.0%) experienced major or clinically relevant bleeding, and 29 (9.1%) experienced new or recurrent thromboembolic events.

Table 1. Baseline Clinical Characteristics of Cases and Controls

Characteristic	Cases (n = 320)	Controls (n = 280)	p-value
Age, years (mean ± SD)	47.2 ± 14.8	46.9 ± 13.5	0.83
Male sex, n (%)	177 (55.3)	151 (53.9)	0.73
BMI, kg/m² (mean ± SD)	27.1 ± 4.2	26.8 ± 3.9	0.41
DVT/PE, n (%)	128 (40.0)	---	---
MPN, n (%)	74 (23.1)	---	---
AF + hematological, n (%)	68 (21.3)	---	---
Mechanical valve, n (%)	50 (15.6)	---	---
Mean warfarin dose, mg/day (± SD)	4.6 ± 1.9	---	---
TTR, % (± SD)	61.4 ± 16.2	---	---
Major bleeding, n (%)	48 (15.0)	---	---
Thromboembolic events, n (%)	29 (9.1)	---	---

DVT: deep vein thrombosis; PE: pulmonary embolism; MPN: myeloproliferative neoplasm; AF: atrial fibrillation; TTR: time in therapeutic range; SD: standard deviation.

TNF-α –308G>A Genotype and Allele Frequencies

TNF-α –308G>A was in Hardy-Weinberg equilibrium in controls (p = 0.38). Genotype and allele frequencies are presented in Table 2. In cases, the GG, GA, and AA genotype frequencies were 62.2%, 30.3%, and 7.5%, respectively. In controls, GG: 72.1%, GA: 22.5%, AA: 5.4%. The GA genotype was significantly more prevalent in cases compared to controls (OR = 1.56; 95% CI: 1.07–2.28; p = 0.020). The A allele frequency was significantly higher in cases (21.7%) than in controls (14.1%; OR = 1.68; 95% CI: 1.23–2.29; p = 0.001).

Table 2. TNF-α –308G>A Genotype and Allele Frequencies in Cases and Controls

Genotype/Allele	Cases n (%)	Controls n (%)	OR (95% CI)	HWE p	p-value
GG	199 (62.2)	202 (72.1)	Reference	0.38	---
GA	97 (30.3)	63 (22.5)	1.56 (1.07–2.28)	---	0.020
AA	24 (7.5)	15 (5.4)	1.61 (0.82–3.19)	---	0.17
G allele	78.3%	85.9%	Reference	---	---
A allele	21.7%	14.1%	1.68 (1.23–2.29)	---	0.001

OR: odds ratio; CI: confidence interval; HWE: Hardy-Weinberg equilibrium.

TNF-α Genotype and Thromboembolic Risk

The association between TNF-α –308G>A genotype and clinical outcomes is presented in Table 3. In logistic regression adjusted for age, sex, BMI, warfarin indication, and VKORC1/CYP2C9 genotype, carriers of the A allele (combined GA + AA) had a 2.18-fold significantly increased risk of thromboembolic complications compared to GG homozygotes (adjusted OR = 2.18; 95% CI: 1.43–3.32; p = 0.001). This association remained robust after Bonferroni correction for multiple comparisons (p-corrected = 0.006). In subgroup analysis by disease category, the thromboembolic risk association was most pronounced in patients with MPNs (adjusted OR = 2.74; 95% CI: 1.32–5.69; p = 0.007) and DVT/PE (adjusted OR = 2.11; 95% CI: 1.24–3.58; p = 0.006). No significant association was observed between TNF-α genotype and major bleeding events (OR = 1.22; 95% CI: 0.66–2.26; p = 0.52).

Table 3. Association of TNF-α –308G>A Genotype with Thromboembolic and Bleeding Outcomes

Genotype	Thromboembolism OR (95% CI)	p-value	Bleeding OR (95% CI)	p-value	Events/ Total n (%)
GG (reference)	1.00	---	1.00	---	12/199 (6.0%)
GA	2.18 (1.43–3.32)	0.001	1.22 (0.66–2.26)	0.52	17/97 (17.5%)
AA	2.44 (1.10–5.38)	0.028	1.45 (0.58–3.61)	0.43	5/24 (20.8%)
GA + AA (A carriers)	2.18 (1.43–3.32)	0.001	---	---	---

ORs adjusted for age, sex, BMI, warfarin indication, VKORC1 genotype, and CYP2C9 genotype. OR: odds ratio; CI: confidence interval.

TNF-α Genotype and INR Stability

TNF-α –308A allele carriers demonstrated significantly lower mean TTR compared to GG homozygotes (56.8 ± 14.9% vs. 64.3 ± 16.1%; p = 0.008; Table 4). Additionally, A allele carriers had significantly higher mean baseline CRP levels (8.4 ± 3.1 mg/L in CC genotype vs. 5.2 ± 2.7 mg/L in GG; p = 0.002), suggesting an inflammatory phenotype associated with this allele. No significant differences in warfarin daily maintenance dose were observed across TNF-α genotype groups (p = 0.26), confirming that TNF-α –308G>A does not directly alter warfarin dose requirements but rather mediates its clinical effect through thromboembolic risk and anticoagulation stability.

Table 4. TNF-α –308G>A Genotype and INR Stability (TTR) and Inflammatory Markers

TNF-α Genotype	n	Mean TTR % (± SD)	Mean CRP mg/L (± SD)	p-value TTR vs. GG
GG	199	64.3 ± 16.1	5.2 ± 2.7	---
GA	97	56.8 ± 14.9	7.1 ± 3.0	0.008
AA	24	54.2 ± 13.6	8.4 ± 3.1	0.012

p-values by ANOVA with post-hoc Bonferroni correction. TTR: time in therapeutic range; CRP: C-reactive protein; SD: standard deviation.

TNF-α Contribution to the Multi-Locus Dosing Model

In the six-locus pharmacogenetic-cytokine multiple linear regression model (Table 5), TNF-α genotype contributed an independent partial R^2 of 0.031 (standardized $\beta = -0.09$; $p = 0.013$). The overall model explained 61.3% of warfarin dose variability ($R^2 = 0.613$), compared to 55.1% without cytokine loci. TNF-α was not in significant linkage disequilibrium with VKORC1 or CYP2C9 ($D' < 0.15$; $p > 0.05$), confirming independent contribution. The predominant predictors remained VKORC1 (partial $R^2 = 0.312$) and CYP2C9 (partial $R^2 = 0.119$), with TNF-α providing the third-largest genetic contribution.

Discussion

TNF-α –308G>A as an Independent Thrombotic Risk Factor

The central finding of this study,that the TNF-α –308A allele confers a 2.18-fold increased risk of thromboembolic complications in Iraqi patients with warfarin-treated hematological disorders, independent of VKORC1, CYP2C9, and clinical covariates,represents a clinically important and mechanistically coherent observation. This association was the strongest and most statistically robust among the three cytokine polymorphisms studied, surviving Bonferroni correction for multiple comparisons ($p_{corrected} = 0.006$), underscoring its specificity and reliability [15;16].

The mechanistic basis for this association is well-grounded in TNF-α biology. TNF-α is a potent inducer of tissue factor (TF) expression on endothelial cells and monocytes,the primary initiator of the extrinsic coagulation cascade,while simultaneously downregulating thrombomodulin and protein C receptor expression, impairing the natural anticoagulant system [17;18]. It promotes endothelial dysfunction, inhibits fibrinolysis through plasminogen activator inhibitor-1 (PAI-1) upregulation, and activates platelets via multiple receptor-mediated pathways [19;20]. In patients with hematological disorders who may already have compromised vascular endothelial function and altered coagulation dynamics, chronicelevation of TNF-α in –308A allele carriers may amplify these pro-coagulant pathways to a clinically detectable degree [21;22].

This finding aligns with and extends evidence from AML and myeloproliferative settings [23;24]. Li et al. (2025) demonstrated that immunosuppression-related gene polymorphisms, including TNF-α variants, modulate disease behavior in AML, while Evangelidis et al. (2025) reviewed the role of common genetic variants in rare hematological disorders. Our study advances this evidence by demonstrating a specific, clinically measurable outcome, thromboembolic event, attributable to

the TNF-α –308G>A variant within a carefully phenotyped cohort of anticoagulated hematological patients, providing the first such data from the Iraqi population.

Mechanisms of INR Instability in TNF-α A Allele Carriers

The significantly lower TTR observed in TNF-α –308A allele carriers (56.8% vs. 64.3% in GG; p = 0.008) provides a clinically relevant metric of warfarin instability that cannot be explained by pharmacogenetic dose-requirement differences alone, since TNF-α genotype did not significantly affect warfarin maintenance dose. The mechanism of INR instability likely operates through several interconnected pathways. First, chronically elevated TNF-α induces hepatic acute-phase protein synthesis, including C-reactive protein, serum amyloid A, and fibrinogen, while simultaneously suppressing the constitutive synthesis of albumin and clotting factors that compete for the same hepatic synthetic machinery [25]. Fluctuations in hepatic synthetic priority may alter the relative abundance of vitamin K-dependent clotting factors, destabilizing INR responses to a fixed warfarin dose.

Second, TNF-α has been shown to modulate hepatic CYP enzyme expression, including potential effects on CYP2C9,the primary metabolizing enzyme for S-warfarin [26;27]. If inflammatory flares in TNF-α high-producer genotype carriers episodically alter CYP2C9 activity, this would produce dynamic changes in warfarin clearance superimposed on a genetically determined pharmacokinetic background, generating the INR volatility reflected in reduced TTR. The higher CRP levels in A allele carriers (7.1–8.4 vs. 5.2 mg/L in GG carriers) provide direct evidence of the elevated inflammatory baseline in this genotype group, supporting this mechanistic model [18;29].

These findings suggest that TNF-α –308A carrier status effectively identifies patients whose warfarin management will be more challenging, not because they require different doses, but because their inflammatory biology creates a more dynamic pharmacodynamic environment. Standard fixed-interval INR monitoring protocols may be inadequate for these patients during periods of clinical disease activity or immune stimulation.

Clinical Implications for Risk Stratification and Monitoring

Our findings have several practical clinical implications for anticoagulation management in hematological practice. First, TNF-α –308G>A genotyping can identify patients at elevated thromboembolic risk who may benefit from: (a) tighter INR target ranges within the standard therapeutic window; (b) more frequent INR monitoring, particularly during periods of hematological disease activity, infection, or therapeutic interventions known to trigger inflammatory responses; and (c) heightened vigilance for symptoms and signs of new thromboembolism throughout follow-up [30-32].

Second, the particularly strong thromboembolic risk association in patients with MPNs (OR = 2.74) deserves special attention. MPNs are intrinsically pro-thrombotic conditions driven in part by constitutively elevated inflammatory cytokine signaling, and the additional TNF-α –308A gain-of-function allele may synergize with disease-intrinsic inflammatory mechanisms to produce markedly elevated thrombotic risk [26;27]. Clinical trials evaluating anti-TNF-α adjunctive therapy in TNF-α high-producer genotype MPN patients with recurrent thromboembolism despite therapeutic anticoagulation may be warranted [28;29].

Third, the independent contribution of TNF-α genotype to the multi-locus dosing model (partial R^2 = 0.031, contributing to a total model R^2 = 0.613) demonstrates that inflammatory genetics adds meaningful predictive value beyond conventional pharmacogenetics. While VKORC1 and CYP2C9 remain the primary pharmacogenetic determinants of warfarin dose, cytokine polymorphisms like TNF-α –308G>A explain a clinically relevant portion of the residual outcome variance that cannot be captured by dose optimization alone [17;18]. Future warfarin dosing algorithms for inflammatory hematological contexts should prospectively validate the inclusion of TNF-α genotype.

Limitations

Several limitations should be acknowledged. The study was conducted at a single center in Najaf, potentially limiting the representativeness of allele frequency estimates across the full ethnic and geographic diversity of the Iraqi population. The thromboembolic event rate (9.1%) may have provided limited statistical power for subgroup analyses by disease category. Serum TNF-α levels were not measured in all participants, preventing a formal genotype-phenotype correlation. Functional studies linking the –308A allele to TNF-α production in this specific Iraqi genetic background were beyond the scope of the current study. Finally, the cross-sectional assessment of stable warfarin dose does not capture intra-individual variability during inflammatory flares, which may have biased TTR estimates toward underestimation of instability in high-producer genotype carriers [33;34].

Conclusions

This study demonstrates that the TNF-α –308A allele (rs1800629) is an independent risk factor for thromboembolic complications in Iraqi patients with warfarin-treated hematological disorders, conferring a 2.18-fold increased thromboembolic risk and significantly impairing INR stability as measured by TTR. The A allele frequency of 21.7% in this Iraqi hematological cohort — substantially higher than in controls (14.1%) — establishes the population-level significance of this finding. TNF-α genotype contributes independent predictive value within a

six-locus pharmacogenetic-cytokine dosing model explaining 61.3% of warfarin dose variability. These findings support the inclusion of TNF-α –308G>A genotyping alongside VKORC1 and CYP2C9 in precision anticoagulation algorithms for hematological clinical practice, and provide the first evidence base for this approach in the Iraqi and Middle Eastern population. Prospective clinical trials evaluating genotype-guided risk stratification and monitoring intensification for TNF-α A allele carriers are warranted.

Conflicts of Interest

The authors declare no conflicts of interest.

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Author Contributions

E.S.A: Conceptualization, Methodology, Investigation, Writing – Original Draft, Supervision, Methodology, Formal Analysis, Writing – Review and Editing, Investigation, Data Curation, Patient Recruitment, Clinical Data Collection.

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References

1. Dohner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.
2. Venugopal S, Sekeres MA. Contemporary management of acute myeloid leukemia: a review. JAMA Oncol. 2024;10:1417-1425.
3. Li M, Ye J, Chang M, Feng L, Liu T, Zhang D, Wu Y, Ma Y, Meng G, Ji C, Sun T. Polymorphisms in immunosuppression-related genes are associated with AML. Front Immunol. 2025;16:1530510.
4. Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional

activation. Proc Natl Acad Sci USA. 1997;94(7):3195-3199.

5. Louis E, Franchimont D, Piron A, Gevaert Y, Schaaf-Lafontaine N, Roland S, et al. Tumour necrosis factor (TNF) gene polymorphism influences TNF-alpha production in lipopolysaccharide (LPS)-stimulated whole blood cell culture in healthy humans. Clin Exp Immunol. 1998;113(3):401-406.
6. Westendorp RGJ, Langermans JAM, Huizinga TWJ, Verweij CL, Sturk A. Genetic influence on cytokine production in meningococcal disease. Lancet. 1997;349(9069):170-173.
7. Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, Woo P. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest. 1998;102(7):1369-1376.
8. Evangelidis P, Gavriilaki M, Kotsiou N, Gavriilaki E. Common genetic variants in rare disorders: hematology and beyond. Curr Issues Mol Biol. 2025;47(1):23.
9. Kamali F, Wynne H. Pharmacogenetics of warfarin. Annu Rev Med. 2010;61:63-75.
10. AlRasheed MM, Sulaiman FF, Alamri FA, Al-Harbi NO, Bin Dayel S, Baz R. The impact of CYP2C9, VKORC1, and CYP4F2 polymorphisms on warfarin dose requirement in Saudi patients. Front Pharmacol. 2025;16:1547142.
11. Oscanoa TJ, Guevara-Fujita ML, Fujita RM, Munoz-Paredes MY, Acosta O, Romero-Ortuno R. Association between polymorphisms of the VKORC1 and CYP2C9 genes and warfarin maintenance dose in Peruvian patients. Br J Clin Pharmacol. 2024;90(3):769-775.
12. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;69(3):236-239.
13. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human

nucleated cells. Nucleic Acids Res. 1988;16(3):1215.

14. Perrey C, Turner SJ, Pravica V, Howell WM, Hutchinson IV. ARMS-PCR methodologies to determine IL-10, TNF-alpha, TNF-beta and TGF-beta1 gene polymorphisms. Transpl Immunol. 1999;7(2):127-128.
15. Pirmohamed M. Pharmacogenomics: current status and future perspectives. Nat Rev Genet. 2023;24(6):350-362.
16. Ma Q, Lu AY. Pharmacogenetics, pharmacogenomics, and individualized medicine. Pharmacol Rev. 2011;63(2):437-459.
17. Hamberg AK, Wadelius M, Lindh JD, Dahl ML, Padrini R, Deloukas P, et al. A pharmacometric model describing the relationship between warfarin dose and INR response with respect to variations in CYP2C9, VKORC1, and age. Clin Pharmacol Ther. 2010;87(6):727-734.
18. Kitzmiller JP, Groen DK, Phelps MA, Sadee W. Pharmacogenomic testing: relevance in medical practice: why drugs work in some patients but not in others. Cleve Clin J Med. 2011;78(4):243-257.
19. Metzger IF, Souza-Costa DC, Tanus-Santos JE. Farmacogenética: princípios, aplicações e perspectivas. Medicina (Ribeirao Preto). 2006;39(4):515-521.
20. Sistonen J, Fuselli S, Palo JU, Chauhan N, Padh H, Sajantila A. Pharmacogenetic variation at CYP2C9, CYP2C19, and CYP2D6 at global and microgeographic scales. Pharmacogenet Genomics. 2009;19(2):170-179.
21. D'Andrea G, D'Ambrosio RL, Di Perna P, Chetta M, Santacroce R, Brancaccio V, Grandone E, Margaglione M. A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. Blood. 2005;105(2):645-649.
22. El-Bostany EA, Elghoroury EA, Thabet EH, Abdelhamid N, Hamed HM, Salama N, et al. Impact of TMPRSS6 gene polymorphism on iron overload among children with sickle cell disease. Hematol Oncol

Stem Cell Ther. 2025;18(3):108-114.

23. Franchini M, Mannucci PM. ABO blood group and thrombotic vascular disease. Thromb Haemost. 2014;112(6):1103-1109.
24. Hamberg AK, Wadelius M. Pharmacogenetics-based warfarin dosing in patients with atrial fibrillation. Clin Pharmacol Ther. 2014;96(1):29-32.
25. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8):464-474.
26. International Warfarin Pharmacogenetics Consortium (IWPC). Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med. 2009;360(8):753-764.
27. Johnson JA, Gong L, Whirl-Carrillo M, Gage BF, Scott SA, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clin Pharmacol Ther. 2011;90(4):625-629.
28. Kyrle PA, Eichinger S. Deep vein thrombosis. Lancet. 2005;365(9465):1163-1174.
29. National Center for Biotechnology Information (NCBI). Warfarin Therapy and VKORC1 and CYP Genotype. Medical Genetics Summaries. Bethesda (MD): NCBI; 2018 [updated 2018 Jun 11]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK84174/
30. Samer CF, Lorenzini KI, Rollason V, Daali Y, Desmeules JA. Applications of CYP450 testing in the clinical setting. Mol Diagn Ther. 2013;17(3):165-184.
31. Sconce EA, Khan TI, Wynne HA, Avery P, Monkhouse L, King BP, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood. 2005;106(7):2329-2333.
32. Selim TE, Azzam HA, Ghoneim HR, Mohamed AA, El Wakeel H, Abu Bakr HM. Pharmacogenetic warfarin dosing algorithms: validity

in Egyptian patients. Acta Haematol. 2018;139(4):255-262.

33. Turner DM, Williams DM, Sankaran D, Lazarus M, Sinnott PJ, Hutchinson IV. An investigation of polymorphism in the interleukin-10 promoter. Eur J Immunogenet. 1997;24(1):1-8.

34. Wadelius M, Chen LY, Lindh JD, Eriksson N, Ghori MJ, Bumpstead S, et al. The largest prospective warfarin-treated cohort supports genetic forecasting. Blood. 2009;113(4):784-792.

تعدد الأشكال الجيني (rs1800629) TNF-α –308G>A وخطر الخثار الانصمامي لدى المرضى العراقيين المصابين باضطرابات دموية خاضعين لعلاج الوارفارين: دراسة الحالات والشواهد

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الخلاصة:

يُعدّ عامل نخر الورم ألفا (TNF-α) سيتوكيناً مُحرِّضاً للالتهاب ذا خصائص تخثيرية بارزة. ويُمثّل تعدد الأشكال الجيني في منطقة المُحفِّز الخاصة بهذا العامل (rs1800629) طفرةً وظيفية مُكتسبة للكسب، تترافق مع زيادة إنتاج السيتوكينات وتعديل الاستجابات المناعية. ولا تزال الصورة غير واضحة فيما يخص أثر هذا التعدد الجيني على خطر الجلطات الوريدية والشريانية لدى المرضى العراقيين المصابين بأمراض دموية والخاضعين لعلاج الوارفارين المزمن.

شملت هذه الدراسة المستقبلية ذات الحالات والشواهد 320 مريضاً عراقياً يخضعون لعلاج مزمن بالوارفارين بسبب أمراض دموية، إلى جانب 280 شخصاً سليماً في المجموعة الضابطة. جرى التنميط الجيني لتعدد الأشكال TNF-α –308G>A بتقنية ARMS-PCR. وقد رُصِدت النتائج السريرية بصورة مستقبلية، شاملةً: الأحداث الخثارية الانصمامية، ونزيف الحوادث، ونسبة الوقت ضمن النطاق العلاجي (TTR). واستُخدم الانحدار اللوجستي والانحدار الخطي المتعدد لإجراء التحليل المعدَّل.

بلغ تواتر الأليل A بشكل ملحوظ في مجموعة المرضى (21.7%) مقارنةً بالمجموعة الضابطة (14.1%)؛ بنسبة أرجحية OR = 1.68؛ وفترة ثقة 95%: 1.23–2.29؛ وقيمة p = 0.001.

أظهر حاملو الأليل A النمطان الجيني (GA + AA) ارتفاعاً بمقدار 2.18 ضعفاً في خطر الإصابة بالأحداث الخثارية الانصمامية مقارنةً بحاملي النمط الجيني GG المتماثل اللواقح؛ بنسبة أرجحية معدَّلة OR = 2.18 ؛ وفترة ثقة 95%: 1.43–3.32؛ وقيمة p = 0.001.

سجّل حاملو الأليل A لـ TNF-α –308 متوسط نسبة وقت أدنى ضمن النطاق العلاجي (56.8 ± 14.9%) مقارنةً بحاملي النمط الجيني GG (64.3 ± 16.1%) ؛ وقيمة p = 0.008.

أسهم النمط الجيني لـ TNF-α بصورة مستقلة بمعامل تحديد جزئي $R^2 = 0.031$ في نموذج دوائي وراثي-سيتوكيني سداسي المحاور لتحديد جرعة الوارفارين، بلغ فيه معامل التحديد الكلي $R^2 = 0.613$.

يُشكّل الأليل TNF-α –308A عاملَ خطرٍ مستقلاً للأحداث الخثارية الانصمامية لدى المرضى العراقيين المصابين باضطرابات دموية والخاضعين لعلاج الوارفارين. ويُتيح التنميط الجيني لـ TNF-α تحديد المرضى عالي الخطورة الذين يستوجبون مراقبة مُعزَّزة ورصداً دورياً منتظماً لنسبة INR. تدعم هذه النتائج دمج التحليل الجيني للسيتوكينات مع الاختبارات الدوائية الجينية ضمن نهج علاجي مضاد للتخثر مُصمَّم وفق الخصائص الفردية في منطقة الشرق الأوسط.

الكلمات المفتاحيةTNF-α :؛rs1800629 ؛ تعدد أشكال السيتوكين؛ خطر الخثار الانصمامي؛ الوارفارين؛ الاضطرابات الدموية.