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Propensity Score Matching Analysis of the Association between TNF-α Gene Polymorphisms and Postoperative Pulmonary Infection after Heart Valve Replacement

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ABSTRACT

This study aimed to investigate the association between tumor necrosis factor-α (*TNF-a*) gene polymorphisms and the risk of pulmonary infection following heart valve replacement surgery, while controlling for potential clinical confounders.

A total of 200 patients who underwent heart valve replacement surgery between January 2022 and December 2024 were included. *TNF-a* genotyping was performed using TaqMan probe-based real-time quantitative PCR. Propensity score matching (PSM, 1:1) was applied to balance baseline characteristics such as age, sex, body mass index, comorbidities, and operative factors. Logistic regression and stratified analyses were used to assess the impact of genetic and clinical risk factors on postoperative pulmonary infection.

After PSM, 51 matched pairs were analyzed. The *TNF-a* −308A allele (rs1800629) was significantly associated with an increased risk of pulmonary infection. Stratified analysis revealed that this genetic effect was more pronounced in male patients. The infection rate among carriers of the *TNF-a* −238A allele (rs361525) was 85.7%, significantly higher than that of the GG genotype (44.3%). Prolonged aortic cross-clamp time, extended cardiopulmonary bypass duration, and reduced left ventricular ejection fraction were identified as independent clinical risk factors.

The *TNF-a* −308G/A polymorphism significantly increases the risk of pulmonary infection following heart valve replacement, particularly in patients with prolonged myocardial ischemia or impaired cardiac function. Preoperative genetic screening and optimization of surgical strategies may help reduce infection risk in high-risk individuals.

Keywords: Heart valve replacement surgery; Propensity score matching analysis; Pulmonary infection; *TNF-a* gene polymorphism

INTRODUCTION

Heart valve disease, caused by rheumatic fever, congenital malformations, and degeneration, impairs blood flow, leading to cardiac dysfunction.[1] Heart valve replacement (HVR) restores cardiac function and improves survival,[2] yet postoperative pulmonary infection, with an incidence of 2.4% to 41.7%, is a major complication linked to adverse outcomes and mortality.[3] While surgical trauma and bypass duration are established risks, host genetics are increasingly recognized as critical.[4]

Tumor necrosis factor-α (*TNF-α*), a key inflammatory cytokine, has 2 well-characterized

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promoter polymorphisms (−308G/A rs1800629; −238G/A rs361525) that regulate its expression and correlate with inflammatory diseases.[5,6] However, evidence linking these polymorphisms to post-HVR pulmonary infection—especially with confounder control—is scarce. Propensity score matching (PSM) balances baseline characteristics to mitigate bias,[7] enabling robust genetic association analysis.

We used PSM to explore the association between *TNF-α* −308G/A/−238G/A polymorphisms and post-HVR pulmonary infection. Integrating genetic and clinical data, we aimed to develop a precise risk model for early high-risk patient identification and individualized interventions, advancing understanding of postoperative infection mechanisms and perioperative precision medicine.

MATERIALS AND METHODS

General Information

One hundred eighty-three patients who underwent HVR in our hospital (January 2022 to December 2024) were enrolled, divided into a pulmonary infection group (n = 54: 28 males, 26 females; age 40–76 years, mean 59.11±7.90 years) and a noninfection group (n = 129: 72 males, 57 females; age 40–73 years, mean 57.50±6.80 years) by postoperative infection status.

Inclusion and Exclusion Criteria

Inclusion criteria included the following: (1) met valvular heart disease diagnostic criteria and (2) had HVR indications. Exclusion criteria included the following: (1) malignant tumors and (2) severe infections within 3 months.

The study was approved by the Medical Ethics Committee of Zibo Central Hospital.

Detection of *TNF-α* Gene Polymorphisms

Sample Collection and Genomic DNA Extraction

Five milliliters of fasting venous blood were collected from each patient, anticoagulated with 3.2% sodium citrate in vacuum tubes (Jiangsu Kangjian Medical, China), and centrifuged at 3000 rpm. The buffy coat (leukocyte fraction) was stored at −80 °C for genomic DNA extraction using a DNA isolation kit (Tiangen Biotech, Beijing, China).

Primer Design

Primers were designed with GC 40% to 60%, Tm 58°C to 60°C (forward/reverse difference≤2°C), no consecutive 3′ G/C or primer dimers, and validated by NCBI Primer-BLAST:

For *TNF-α* −308 (rs1800629, NC_000006.12): Forward 5′-GAGGGCCCTCTGCAA-3′ (15 bp) and reverse 5′-CGTCAGCAGGAGTCAGGAT-3′ (20 bp); amplicon 83 bp.

For *TNF-α* −238 (rs361525, NC_000006.12): Forward 5′-CAGGGGCCTGGAGGAC-3′ (17 bp) and reverse 5′-GCTGGGTCAGGGTATCTGA-3′ (20 bp); amplicon 53 bp.

Probe Design

Probes (Tm 8°C to 10°C higher than primers, no 5′ G, variant base at position 5) were validated by NCBI Primer-BLAST:

For *TNF-α* −308: G allele (FAM-CTGGCTCCTGGAGTT-BHQ1, 18 bp); A allele (VIC-CTGACTCCTGGAGTT-BHQ1, 18 bp).

For *TNF-α* −238: G allele (FAM-CCCTCTGCGGAGTC-BHQ1, 15 bp); A allele (VIC-CCCTCTGCAGAGTC-BHQ1, 15 bp).

Quantitative Real-Time PCR (qPCR) System and Conditions

The 20-μL system included 10 μL of 2× FastStart Universal Probe Master Mix (Roche, Basel, Switzerland), 0.5 μL of each primer (250 nM), 0.3 μL of each probe (150 nM) (Thermo Fisher Scientific, Waltham, MA, USA), 2 μL of DNA template (50 ng), and RNase-Free water to 20 μL. The samples were run on an ABI 7500 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA): 95 °C pre-denaturation for 10 minutes; 40 cycles of 95 °C for 15 seconds, and 62 °C annealing/extension for 30 seconds. Triplicate technical repeats were performed per sample.

Genotype Interpretation

Genotype GG: FAM cycle threshold (Ct) <30, no VIC signal; AA: VIC Ct <30, no FAM signal; GA: valid signals in both channels (Ct difference ≤2). The no-template control (NTC) showed no amplification.

Methodological Validation

Positive controls included 5 Sanger-confirmed GG/GA/AA samples, with NTC as a negative control. Sensitivity was tested by a 10-fold dilution (50 ng/μL to 0.05 ng/μL). Ten percent of the samples were validated by Sanger sequencing (primers: forward 5′-

TCCCCAAAGAAATGGAGGAC-3′, reverse 5′-AGGGATACCACCCCTCCTC-3′; Tsingke Biotechnology, Beijing, China). Kappa consistency was analyzed with SPSS 26.0 (IBM Corp, Armonk, NY, USA).

Observational Indicators

Demographics included age, sex, body mass index (BMI), and smoking and alcohol history. Chronic diseases included hypertension, diabetes, hyperlipidemia, coronary heart disease, cerebral infarction or hypoperfusion, and chronic obstructive pulmonary disease (COPD). Preoperative laboratory values included white blood cell (WBC) count, C-reactive protein (CRP), albumin (Alb), hemoglobin (Hb), creatinine (Cr), left ventricular ejection fraction (LVEF), and interleukin 6 (IL-6). Surgical indicators included cardiopulmonary bypass (CPB) time, aortic cross-clamp time, operative duration, and intraoperative blood loss. Postoperative outcomes included intensive care unit (ICU) stay, mechanical ventilation time, pulmonary infection (chest x-ray infiltrates/effusion, rales, positive cultures, and sputum changes; excluding tuberculosis or tumors), and pathogen type.

Statistical Methods

Data were analyzed using SPSS 26.0. Normally distributed data were expressed as the mean±SD and compared using an independent samples *t* test. Nonnormally distributed data were expressed as the median (P25, P75) and compared using the Mann-Whitney U test. Categorical data were expressed as frequencies and percentages and compared using the χ^2 test or Fisher exact test. Propensity score matching (1:1 nearest neighbor, caliper 0.02) balanced data with *TNF-α* rs1800629 (GA/AA vs GG) as the exposure, matching age, sex, BMI, comorbidities, LVEF, surgery type, CPB time, preoperative WBC count, and IL-6. Logistic regression identified independent risk factors, and stratified analyses were performed by sex and age. A 2-sided $p<0.05$ was considered significant.

RESULTS

Comparison of Basic Characteristics between Infection and Noninfection Groups

Before PSM, the prevalence of hyperlipidemia was higher in the infection group ($p<0.05$). After PSM, 51 patient pairs were matched, and all baseline covariates were balanced ($p>0.05$). Before matching, the infection group had a higher WBC count and albumin levels, longer aortic cross-clamp and CPB durations, and a lower LVEF compared with the noninfection group ($p<0.05$). After matching, the infection group still had higher hemoglobin levels, longer aortic cross-clamp and CPB durations, and a lower LVEF ($p<0.05$).

Model Validation

The PSM model was evaluated via receiver operating characteristic (ROC) curve and cross-validation: the area under the curve was 0.965 (95% confidence interval [CI], 0.93 to 0.999), showing no significant overfitting, good stability, and reliable clinical value.

Frequency Distribution of *TNF-α* −308G/A and −238 Genotypes after PSM Matching

For *TNF-α* −308 (rs1800629, GG/GA/AA), the infection group (n=51) showed GG 36.1% (26/72), GA 84.2% (16/19), and AA 81.8% (9/11); the noninfection group (n=51) showed GG 63.9% (46/72), GA 15.8% (3/19), and AA 18.2% (2/11). The genotype distribution differed significantly ($\chi^2=18.905$; $p<0.05$). The A allele frequency was 82.9% (34/41) vs 17.1% (7/41) ($\chi^2=22.253$; $p<0.05$). For *TNF-α* −238 (rs361525, GG/GA), the infection group (n=51) showed GG 44.3% (39/88) and GA 85.7% (12/14); the noninfection group (n=51) showed GG 55.7% (49/88) and GA 14.3% (2/14). The genotype distribution differed significantly ($\chi^2=6.706$; $p<0.05$). The A allele frequency was 85.7% (12/14) vs 14.3% (2/14) ($\chi^2=6.212$; $p<0.05$).

Stratified Analysis of *TNF-α* −308G/A and Infection Risk

Gender stratification revealed significant heterogeneity. In males, the GA genotype increased risk compared with GG, with AA having the highest risk. In females, GA/AA had a nonsignificantly elevated risk trend ($p>0.05$). Age stratification showed differing associations. In patients younger than 60 years (<60 years), GA/AA significantly increased risk; in patients 60 years and older (≥60 years), only AA was significant (odds ratio [OR], 10.44; 95% CI, 2.23 to 64.77; $p<0.05$), while GA was nonsignificant, possibly due to age-related factors masking the genetic effect. Smoking and gender were significant risks in patients 60 years and older, suggesting age-specific risks and the need for individualized prevention.

Multivariable Analysis of Pulmonary Infection and *TNF-α* Genotypes After HVR

In multivariate logistic regression, the *TNF-α* −308 AA genotype was a significant risk factor (upper 95% CI > 1000, unstable due to small sample). LVEF was protective (a 1% increase reduced risk by 25%). Intraoperative aortic cross-clamp time and CPB time were independent risks (each additional hour increased risk by 21.7% and 12.3%, respectively). Platelet count and hemoglobin showed no significant association (p>0.05; Table 1).

Table 1. Multivariate logistic regression analysis of pulmonary infection risk after heart valve replacement.

Variable	B	SE	Wald	*p*	Exp(B)	Lower 95% CI	Upper 95% CI
TNF-α −308 gene locus			6.221	0.045			
TNF-α −308 locus GA	1.219	1.285	0.901	0.343	3.384	0.273	41.965
TNF-α −308 locus AA	3.898	1.607	5.884	0.015	49.299	2.114	1149.784
Left ventricular ejection fraction	−0.288	0.091	9.920	0.002	0.750	0.627	0.897
Duration of aortic occlusion, h	0.197	0.058	11.519	0.001	1.217	1.087	1.364
Duration of cardiopulmonary bypass, h	0.116	0.033	12.281	<0.001	1.123	1.053	1.199
Platelets	−0.018	0.019	0.922	0.337	0.982	0.946	1.019
Hemoglobin	−0.040	0.037	1.159	0.282	0.961	0.893	1.033

CI: confidence interval; HVR: heart valve replacement; SE: standard error; *TNF-α*: tumor necrosis factor-α. B: regression coefficient; Exp(B): odds ratio.

DISCUSSION

Heart valve replacement replaces stenotic or calcified valves with artificial ones to preserve cardiac function, but its trauma induces immunosuppression, impairing pathogen resistance and increasing postoperative mortality.[8] The mechanism of post-HVR pulmonary infection is unclear: valvular heart disease causes pulmonary congestion and impaired gas exchange; endotracheal intubation reduces oral hygiene, raising oropharyngeal bacterial load and pathogen entry; and ventilator contamination and prolonged intubation-induced airway damage further promote infection.[9,10] With broad-spectrum antibiotics altering pathogen spectra and resistance,[11] individual susceptibility—especially inflammatory cytokine gene polymorphisms—has become a focus.

In this study, 54 of 183 HVR patients (29.5%) developed a postoperative pulmonary infection. The *TNF-α* −308 AA genotype, reduced LVEF, prolonged aortic cross-clamp time, and extended CPB duration were identified as susceptibility factors.

Pulmonary infection is driven by excessive or persistent inflammation.[12] Tumor necrosis factor-α, a key NF-κB-activated mediator from monocytes and macrophages,[13] exerts immunoregulatory and pro-inflammatory effects; its overexpression enhances inflammatory cell adhesion and IL-6 and IL-8 release, aggravating infection.[14] Post-HVR stress activates the *TLR4*/*MyD88* pathway, triggering NF-κB and *TNF-α* transcription. Mature TNF-α acts via autocrine and paracrine signaling on TNFR, amplifying inflammation through positive feedback.[15] It also induces PLA2 activation, upregulates neutrophil adhesion molecules, and increases reactive oxygen species, impairing microvascular barriers and enhancing lung susceptibility to pathogens.[16] The *TNF-α* −308 promoter polymorphism is well-studied: the AA genotype forms a compact promoter-enhancer loop sustaining transcription, and A allele carriers have higher TNF-α levels.[17]

Stratified analysis showed that *TNF-α* −308 GA/AA increased infection risk in males (vs GG), with no significance in females. This gender difference may relate to female estrogen inhibiting *TNF-α*–mediated endothelial inflammation via the following mechanisms:

(1) ERα binding NF-κB p65 to block nuclear translocation; (2) promoting *microRNA*-146a to target and degrade *TNF-α* pathway molecules (eg, TRAF6); and (3) enhancing alveolar macrophage M2 polarization.[18,19] 17β-Estradiol alleviates *TNF-α*–induced ICAM-1 and VCAM-1 expression, suppresses oxidative stress and monocyte adhesion, and mitigates endothelial injury. Elderly patients' comorbidities (diabetes, hypertension, hyperlipidemia) activate *TNF-α* via metabolic dysregulation, contributing to differential polymorphism effects—mechanisms requiring further study.

A preoperative low LVEF reduces cardiac output and compliance, increasing pulmonary venous pressure, edema, and epithelial barrier damage. Prolonged aortic cross-clamp time causes myocardial exhaustion, activates the pulmonary vascular *TLR9*/NF-κB pathway, induces IL-8 and MCP-1, and promotes neutrophil accumulation; reperfusion oxidative stress damages alveolar tight junctions, increasing vascular permeability.[20] Extended CPB disrupts immune function, induces immunosuppression, and, via blood dilution and coagulation dysfunction, raises bleeding, exudation, and infection risk.

Clinical recommendations include preoperatively enhancing airway humidification and timed noninvasive suction; considering *TNF-α* inhibitors 72 hours preoperatively for *TNF-α* −308 A allele carriers (blocking NF-κB to reduce inflammatory peaks). Optimizing CPB management (eg, leukocyte filtration, short-term NF-κB inhibitors) for high-risk patients is advised. Postoperatively, administer anti-*TNF-α* nanobodies and broad-spectrum antibiotics within 24 to 72 hours to balance anti-inflammatory and anti-infective needs.

Limitations of this study include its single-center design, geographic and population restrictions, and analysis of only two *TNF-α* polymorphisms (−308, −238), excluding other inflammatory cytokine loci and gene-gene/gene-environment interactions. Future research should expand the sample size, conduct multicenter validation, integrate multi-omics to clarify mechanisms, and combine AI to develop risk prediction tools, advancing personalized perioperative infection management.

The *TNF-α* promoter polymorphisms may serve as genetic markers for predicting post-valve replacement pulmonary infection risk. Combined with perioperative clinical indicators, they aid in early identification and individualized prevention of high-risk patients. Large-scale, multicenter studies are needed to validate these findings and inform precise postoperative infection management.

STATEMENT OF ETHICS

This study was approved by the Medical Ethics Committee of Zibo Central Hospital.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The data supporting the findings of this study can be obtained from the corresponding author upon request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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