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ORIGINAL RESEARCH

# *TNF-α* rs1800629 Polymorphism in Vietnamese COPD Patients: Exploratory Evidence for Recessive Protective Association and Clinical Correlates

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**Background:** Chronic obstructive pulmonary disease (COPD) poses a significant health burden in Vietnam. The *TNF-α* rs1800629 (−308G/A) polymorphism is an influential factor in disease pathogenesis. However, its association is inconsistent across the studied populations. This study addresses this gap in Vietnam by examining allele frequencies and clinical associations in stable COPD patients.

**Methods:** A cross-sectional study recruited 320 healthy controls and 266 stable COPD patients (per GOLD 2023 criteria) from October 2024 to August 2025. Clinical data were collected from medical records and direct interrogation. Genotyping was performed using PCR-RFLP. The dataset used for sensitivity analyses (2,660 observations) was created through multiple imputations to address missing clinical data. Associations of the rs1800629 with disease susceptibility and selected clinical management parameters were analyzed using Chi-square/Fisher's exact tests, multivariable logistic regression, and sensitivity analysis.

**Results:** The A allele frequencies were 8.83% (COPD), 6.88% (controls), and 7.77% overall ($p > 0.05$). Patients were predominantly male smokers over 40 years, with moderate-severe symptoms (CAT ≥10, mMRC 3) and A/B severity groups. Under a recessive model, the AA genotype was associated with ~96% reduced susceptibility (adjusted OR 0.039, 95% CI 0.002–0.62, p=0.022). Regression identified smoking (OR 1.83–2.35), family history (OR 2.04), and onset ≥40 years (OR 2.88–3.36) as independent symptom influences. Sensitivity analysis further supported the protective effect of the AA genotype and revealed GA protective effects on symptomatic outcomes (OR<1, $p<0.05$).

**Conclusion:** Our findings suggest a possible protective recessive association of the *TNF-α* rs1800629 (−308G/A) polymorphism with COPD susceptibility, symptom burden, and exacerbation risk. However, the wide confidence intervals arising from the rarity of the AA genotype and the use of multiply imputed data mean these signals are exploratory. Larger multi-center studies with comprehensive exposure assessment are needed to confirm these observations.

**Keywords:** COPD, TNF-α, rs1800629, polymorphism, Vietnam

## Introduction

With nearly 600 million cases projected by 2050 and being a leading cause of mortality in Vietnam, chronic obstructive pulmonary disease (COPD) is becoming an increasingly serious global health burden, particularly in low- and middle-income countries.[1–3] This chronic respiratory disease is characterized by persistent airway obstruction, causing shortness of breath, cough, and sputum production, associated with bronchitis and emphysema.[4]

While historically framed through a monolithic lens of tobacco-induced lung injury, the last decade of research has radically redefined COPD as a complex, heterogeneous syndrome resulting from a lifetime of intricate gene-environment (GxE) interactions. In Vietnam, COPD risk is also shaped by non-smoking exposures such as biomass fuel combustion,

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urban air pollution and occupational dusts, which may interact with genetic susceptibility.[5] The 2025 Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD Report) underscores the critical need to move beyond a "one-size-fits-all" therapeutic approach toward precision medicine, yet translating burgeoning genetic insights into routine clinical practice remains a significant implementation gap. The last decade has witnessed a paradigm shift in our understanding of COPD genetics. We have transitioned from identifying single candidate genes with limited reproducibility to uncovering complex networks of susceptibility through large-scale Genome-Wide Association Studies (GWAS). Candidate-gene studies like ours focus on a predefined variant and therefore have higher power to detect modest effects in small samples but cannot discover novel loci, whereas GWAS scans the entire genome and requires large cohorts to account for multiple testing.[6] While Alpha-1 Antitrypsin Deficiency (AATD) remains the only proven monogenic cause with clear guidelines for testing and replacement therapy, it accounts for a minor fraction (1–2%) of cases. The bulk of genetic risk has been shown to be polygenic, governed by hundreds of common variants with modest individual effect sizes but substantial aggregate impact. The identification of monogenic determinants remains strategically vital for understanding disease mechanisms and improving management outcomes.

TNF-α was well established as a central inflammatory cytokine in COPD, secreted by activated macrophages, amplifying the immune response, releasing neutrophils, and contributing to lung tissue destruction, with elevated levels in smokers.[7–11] Inhibitors targeting TNF-α are currently being investigated as a promising new treatment approach for COPD patients.[12]

The *TNF-α* gene promoter contains SNPs (single nucleotide polymorphisms) influencing expression, with rs1800629 (−308G/A) most studied for altering TNF-α levels, increasing COPD risk and severity in some populations.[13–16] The allele frequencies of this variant exhibit apparent differences by geographic region and ethnicity, with the "A" allele is lower in Asia compared to Europe and the Americas.[17,18] The A allele is often associated with reduced lung function (lower FEV1), disease severity according to GOLD classification (groups B, E), and demographic factors such as age of onset, gender, smoking, or biomass smoke exposure, increasing disease progression risk in some populations.[14,18–20] In Southeast Asia, studies from Thailand, Malaysia, the Philippines, and Indonesia have yielded conflicting results (A allele increases risk in Thailand, no association in the Philippines, and protective in Indonesia), creating a regional data gap.[18,21,22] Vietnam, with its geographic position and genetic history within this diverse context, may follow the pattern of Thailand and Indonesia, or exhibit a unique association, combined with the burden of comorbidities such as cardiovascular disease and diabetes, making the investigation of the relationship between rs1800629 and COPD in Vietnam a pressing scientific need.

In light of these needs, we hypothesize that the A allele of this SNP increases COPD risk and severity in Vietnamese patients, particularly in smokers. Therefore, we conducted this study to (1) determine the rs1800629 allele frequency and (2) assess its association with COPD susceptibility and exacerbation risk. Because the A allele is rare, we planned to examine multiple inheritance models (additive, dominant, recessive and overdominant) to capture potential effects. This research contributes to filling the COPD genetic gap in Vietnam, opening avenues for biomarkers to support personalized treatments. As a preliminary investigation, the present study explores whether the rs1800629 A allele may influence COPD susceptibility or progression and generates hypotheses for future research.

# Patients, Materials and Methods

## Patients and Study Design

This cross-sectional study was conducted on adults (aged 18 years and older) with stable COPD according to GOLD 2023 criteria,[4] conveniently recruited from Nguyen Tri Phuong Hospital from October 2024 to August 2025. Patients with mental health issues, non-cooperation, pregnant women, those diagnosed with malignancies, or those with insufficient blood samples or DNA that could not be re-collected for genetic analysis were excluded. The control group consisted of volunteers from Pham Ngoc Thach University of Medicine, screened through interviews and clinical examinations by trained physicians to exclude a personal history of the disease. The study population primarily comprised residents of Ho Chi Minh City.

COPD diagnosis required a post-bronchodilator FEV1/FVC ratio < 0.70. Spirometry at the enrollment hospital followed the 2019 ATS/ERS Standardization guidelines. Pre- and post-bronchodilator tests were performed when indicated using a KoKo spirometer (nSpire Health/KoKo PFT), a validated flow-based device meeting ATS/ERS and ISO 26782 standards (±2.5% error). The device was calibrated daily using a 3-L syringe at multiple flow rates to ensure volume accuracy within ±3%. Trained technicians performed at least three acceptable manoeuvres, with FVC/FEV1 repeatability ≤150 mL or ≤5%; only tests graded A–C with real-time feedback were analysed. For reversibility testing, 400 µg salbutamol was administered via metered-dose inhaler with spacer, and spirometry was repeated 10–15 minutes later. Reversibility was defined as an increase in FEV1 of ≥12% and ≥200 mL in accordance with GOLD/ATS/ERS guidelines. COPD exacerbations were defined as a worsening of respiratory symptoms that necessitated increased medication, an emergency visit, or hospitalisation.

With an A allele frequency from a meta-analysis of 0.11,[23] the sample size was calculated to detect a 5% allele frequency difference with 80% power and $\alpha = 0.05$, requiring at least 151 cases and 302 controls. Informed consent was obtained from all participants. By the end of the study, 266 stable COPD patients and 320 controls were recruited. Only 151 COPD patients had complete clinical data for analysis (Figure 1), which may introduce selection bias; missing covariate values were addressed using multiple imputation.

## Patients' Data Collection

Data was collected from each participant using a standardized, pre-tested questionnaire administered by trained researchers to ensure consistency and minimize interviewer bias. The questionnaire recorded characteristics such as age, gender, smoking history, family history of COPD, and COPD-related features (age at diagnosis, dyspnea level using the modified Medical Research Council dyspnea scale (mMRC), exacerbation history in the past 12 months, disease impact on life using the COPD Assessment Test (CAT), to assess exacerbation risk according to GOLD 2023 groups A, B, and E).[4] Clinical information was cross-verified with medical records. All data were recorded in secure forms and double-entered for accuracy. The questionnaire did not capture biomass fuel use, urban air pollution or occupational exposures, limiting the ability to assess gene–environment interactions.

## *TNF-α* rs1800629 Genotyping

Genotyping was performed blinded to clinical information. The testing procedure was performed according to the published protocol of Correa et al, which was later validated locally.[24] After extraction, genomic DNA was amplified by PCR using primers 5′–AGG CAA TAG GTT TTG AGG GCC AT–3′ (forward) and 5′–TCC TCC CTG CTC CGA TTC CG–3′ (reverse). The PCR protocol comprised an initial denaturation at 94°C for 2 min, followed by 35 cycles of 94°C for 15s, 58°C for 15s, and 72°C for 10s, with a final extension at 72°C for 1 min. The 107 bp product was digested with the NcoI restriction enzyme, yielding fragments of 87 bp + 20 bp for the G allele and 107 bp for the A allele. Samples were analyzed in duplicate, with discrepancies resolved by a third run. The remaining DNA was stored at −20°C in accordance with ethical guidelines.

## Statistical Analysis

Data were analyzed using Stata version 14.2 (StataCorp LLC). Categorical variables (age groups, age of onset, gender, smoking history, genotypes, dyspnea levels, disease impact levels, exacerbation frequency, disease severity) were presented as n (%). Continuous variables (age, CAT score, mMRC score) were assessed for normality (Shapiro–Wilk test) and reported as median (interquartile range, IQR). Hardy-Weinberg equilibrium (HWE; checks allele frequency stability) was evaluated using $\chi 2$-test. Associations between this SNP and COPD, clinical features, and exacerbation risk were evaluated using $\chi 2$ or Fisher's exact tests across genetic models: additive (0–1–2 risk alleles for GG/GA/AA), dominant (GG vs GA+AA), recessive (AA vs GG+GA), and overdominant (AA+GG vs GA). Multivariable logistic regression identified independent factors influencing exacerbation risk, including genotype, smoking history, age of onset, and family history, representing progression, and genetic influences. Significance was assessed (Wald test); results presented as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). $p < 0.05$ was considered significant. Multiple inheritance models were examined because the A allele is rare and different modes of inheritance may reveal subtle effects.

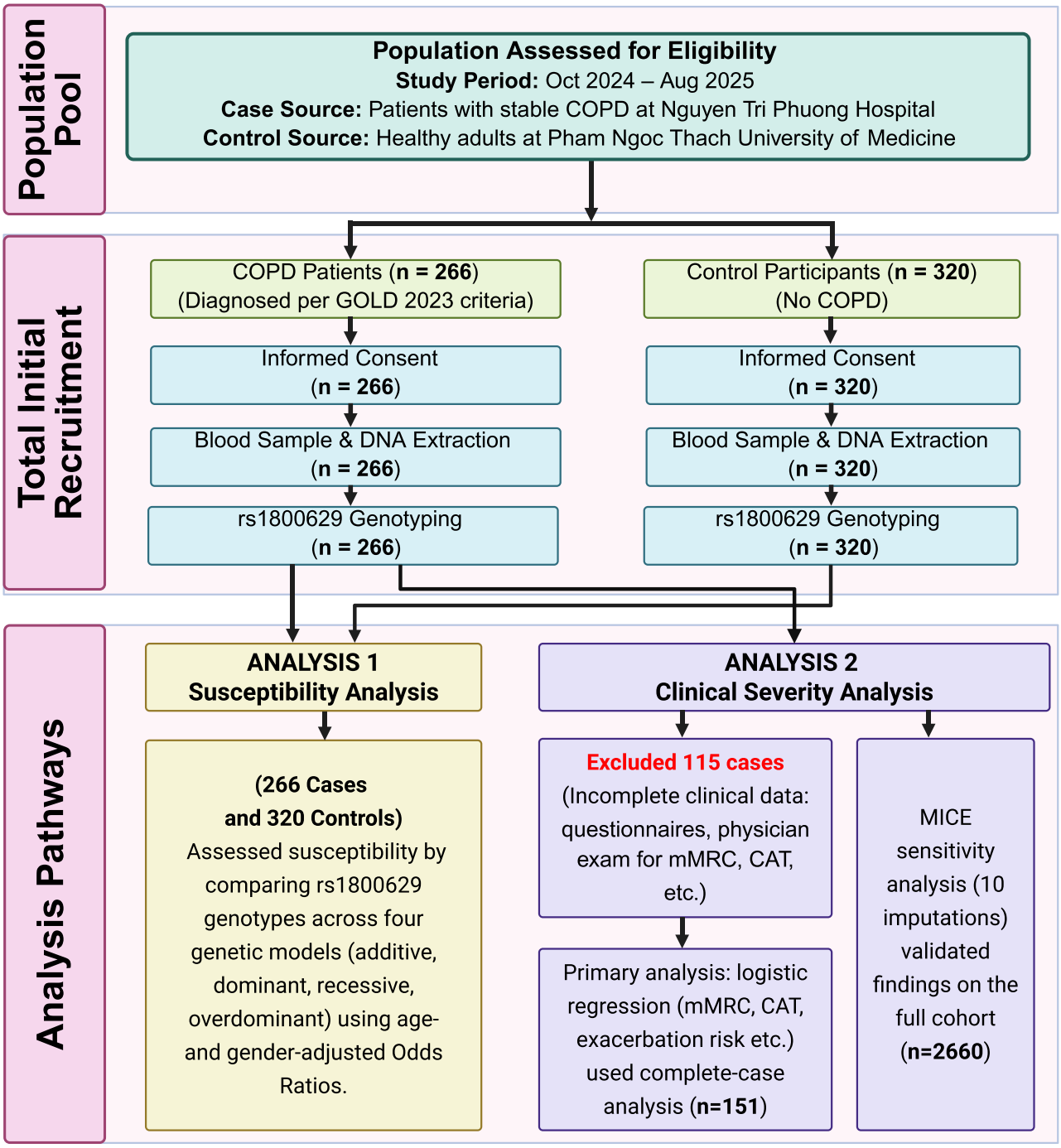


**Figure 1** Flow diagram for participant recruitment and study procedures.
**Abbreviations**: COPD, chronic obstructive pulmonary disease; DNA, Deoxyribonucleic acid; mMRC, modified Medical Research Council dyspnea scale; CAT, COPD Assessment Test; MICE, Multiple Imputation by Chained Equations.

## Sensitivity Analysis

To evaluate result robustness and handle missing data, multiple imputations by chained equations (MICE) (White, Royston, and Wood 2011) were applied using age, gender, and genotype to generate 10 imputed datasets, yielding a pooled set of 2,660 observations for enhanced power. Logistic regression reassessed associations between predictors (smoking, exacerbation history, age of onset) and severity outcomes (mMRC, CAT, exacerbations, A/B/E groups). Genotype was tested across additive, dominant, recessive, and overdominant models. Data visualization was created

using Flourish Studio (https://flourish.studio/) and Biorender (https://www.biorender.com/). Findings from the imputed analyses should be considered exploratory and may reflect modelling assumptions or residual confounding.

## Ethical Approval

This study was approved by the Ethics Committee of Pham Ngoc Thach University of Medicine (No. 1165/TĐHYKPNT-HĐĐĐ dated October 16, 2024) and the Ethics Committee of Nguyen Tri Phuong Hospital (No. 2514/NTP-HĐĐĐ dated December 5, 2024). The study was conducted in compliance with the principles of the Helsinki Declaration and Good Clinical Practice guidelines (ICH-GCP). All participants were provided with complete information about the study and gave written informed consent. All personal data were anonymized using unique identifiers, with electronic study records stored in password-protected databases accessible only to the research team. Biological samples were labeled with corresponding codes and stored at −20°C in accordance with biosafety standards, with a maximum retention period of 5 years after study completion, after which they would be disposed of in accordance with institutional regulations. Participants were clearly informed of their right to withdraw from the study at any time without any consequences. The study provided no financial incentives to ensure that participation was completely voluntary.

# Results

## Characteristics of the Study Population

During the study period, 266 COPD patients and 320 control (non-COPD) individuals were recruited, of which 151 patients had complete clinical characteristics, met inclusion criteria, and consented to participate. Excluded patients (n=115) showed similar age (median 67 vs 68 years, $p$=0.54) and gender distribution (89% vs 91% male, $p$=0.68) (data not shown), suggesting data missing completely at random. The general characteristics of the study population are presented in Table 1.

The COPD group had a higher median age and a lower proportion of females than the control group, with statistically significant differences ($p < 0.0001$). Genotype frequencies of this variant were similar between the two groups and the overall population, with the G allele predominant. Figure 2 illustrates the allele and genotype frequencies and distributions of the *TNF-α* rs1800629 variant across three population groups: (A) COPD group; (B) control group; and (C) overall population, with the observed (red line) and expected (orange-yellow line) distributions shown. Pairwise comparisons (Fisher's Exact test) show that the areas covered by the colored lines nearly overlap on all axes, suggesting that the surveyed population pairs are in HWE, meaning observed frequencies closely match expected frequencies (all $p_{HWE} > 0.05$).

**Table 1** Demographic Characteristics and rs1800629 Variant in the Study Population: Comparison Between COPD Patients and Controls

| Characteristics | | Overall Population (N=586) | Patients (N=266) | Controls (N=320) | *p*-value |
|---|---|---|---|---|---|
| **Age** (years old) median (IQR) | | 44.00 (35–63) | 68.00 (62–74) | 38.50 (31–44) | <0.0001[a] |
| **Gender** (female) (n, %) | | 237 (40.44%) | 27 (10.15%) | 210 (65.63%) | <0.0001[b] |
| **rs1800629 Genotype** | **Allele A** (%) | 7.77% | 8.83% | 6.88% | 0.212[c] |
| | **AA** (n, %) | 5 (0.85%) | 2 (0.75%) | 3 (0.94%) | 0.320[b] |
| | **GA** (n, %) | 81 (13.82%) | 43 (16.17%) | 38 (11.88%) | |
| | **GG** (n, %) | 500 (85.32%) | 221 (83.08%) | 279 (87.19%) | |
| | $p_{HWE}$[b] | 0.381 | 0.628 | 0.176 | |

**Notes**: [a]Mann–Whitney test; [b]Fisher's Exact test; [c]Chi-square test; $p_{HWE}$: $p$-value for Hardy-Weinberg equilibrium.
**Abbreviation**: IQR, interquartile range.

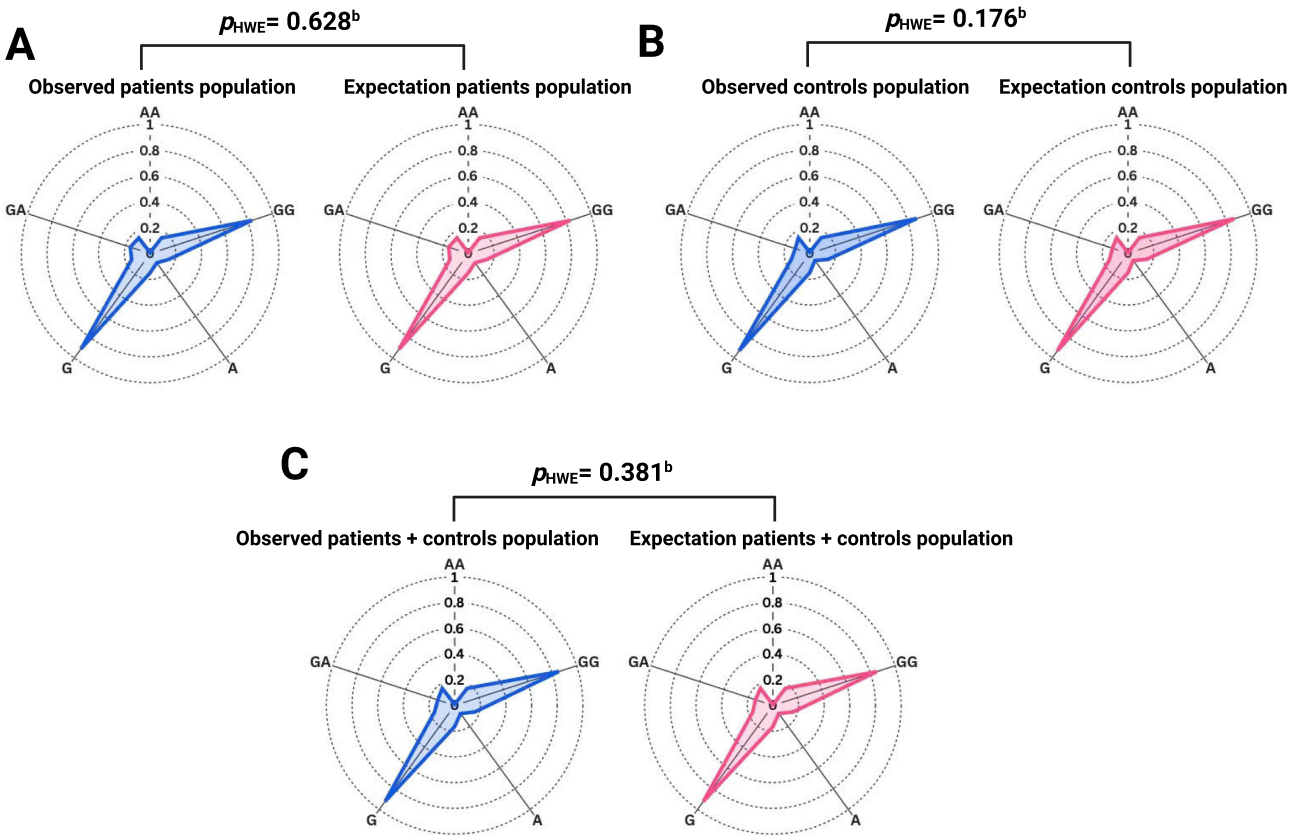


**Figure 2** Hardy-Weinberg equilibrium model for rs1800629 variant distribution in *TNF-α* gene: COPD patients, controls, and overall population. (**A**) Patient group; (**B**) Control group; (**C**) Entire study population; bFisher's Exact test; $p_{HWE}$: *p*-value for Hardy-Weinberg equilibrium.

## Association Between *TNF-α* rs1800629 Variant and COPD Susceptibility

To clarify the impact of the variant genotype on disease susceptibility, the study examined differences in genotype distribution between groups across different genetic models (Table 2).

**Table 2** Association of the rs1800629 Variant with COPD Susceptibility Across Genetic Models

| Genetic Models | Patients (N=266) | Controls (N=320) | Crude | | Age- and Gender-Adjusted | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value[e] |
| Additive model | | | | | | |
| GG | 221 (83.08%) | 279 (87.19%) | 1.00 | – | 1.00 | – |
| GA | 43 (16.17%) | 38 (11.88%) | 1.43 (0.89–2.28) | 0.138[c] | 1.41 (0.40–4.99) | 0.593 |
| AA | 2 (0.75%) | 3 (0.94%) | 0.84 (0.14–5.08) | 0.851[b] | **0.04 (0.002–0.65)** | **0.023** |
| Dominant model | | | | | | |
| GG | 221 (83.08%) | 279 (87.19%) | 1.39 (0.88–2.19) | 0.163[c] | 1.004 (0.30–3.30) | 0.995 |
| GA+AA | 45 (16.92%) | 41 (12.81%) | | | | |

(*Continued*)


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**Table 2** (Continued).

| Genetic Models | Patients (N=266) | Controls (N=320) | Crude | | Age- and Gender-Adjusted | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value[e] |
| Recessive model | | | | | | |
| GG+GA | 264 (99.25%) | 317 (99.06%) | 0.80 (0.13–4.83) | 0.808[b] | **0.039 (0.002–0.62)** | **0.022** |
| AA | 2 (0.75%) | 3 (0.94%) | | | | |
| Overdominant model | | | | | | |
| GG+AA | 223 (83.83%) | 282 (88.12%) | 1.43 (0.89–2.29) | 0.135[c] | 1.46 (0.42–5.05) | 0.546 |
| GA | 43 (16.17%) | 38 (11.88%) | | | | |

**Notes**: [b]Fisher's Exact test; [c]Chi-square test; [e]Wald test; "-": no data. Bold values indicate statistical significance ($p < 0.05$).
**Abbreviations**: OR, Odds Ratio; CI, confidence interval.

From the crude data, Table 2 shows no statistically significant differences in genotype and allele distributions between patients and controls across the genetic models (as described in the Methods section), with all *p*-values > 0.05. After adjustment for age and gender, we observed the following: In the additive model, GA vs GG yielded an adjusted OR of 1.41 ($p$=0.593), suggesting COPD risk in GA carriers. Moreover, AA vs GG showed an adjusted OR of 0.04 (95% CI: 0.002–0.65, $p$=0.023), indicating a reduced risk in AA carriers relative to GG carriers. In the recessive model, AA vs GA and GG showed an adjusted OR of 0.039 (95% CI: 0.002–0.62; $p = 0.022$), indicating a 96.1% lower risk in AA carriers. In contrast, the dominant and overdominant models revealed no statistically significant associations (GA+AA vs GG and GA vs GG+AA, respectively).

## Association Between *TNF-α* rs1800629 Variant and Selected COPD Clinical Management Parameters

In the group of 151 COPD patients, the majority were males over 40 years old with a smoking history; CAT impact levels were mainly ≥10 points, mMRC commonly at level 3, and disease severity concentrated in groups A and B. The rs1800629 genotype frequencies were predominantly GG, with no AA, compared to the expected population distribution, which was in HWE ($p_{HWE} = 0.603$). Since no cases with the AA genotype were found, Table 3 examines the distribution

**Table 3** Association of the rs1800629 Variant with COPD Exacerbation Risk Across Genetic Models

| Genetic Models | Exacerbation Risk (N=151) | | | *p*-value[c] |
|---|---|---|---|---|
| | A | B | E | |
| Additive model | | | | 0.78 (GA-GG) |
| GG | 49 | 46 | 30 | |
| GA | 12 | 9 | 5 | |
| AA | 0 | 0 | 0 | |
| Dominant model | | | | 0.78 |
| GG | 49 | 46 | 30 | |
| GA+AA | 12 | 9 | 5 | |

(*Continued*)

**Table 3** (Continued).

| Genetic Models | Exacerbation Risk (N=151) | | | *p*-value[c] |
|---|---|---|---|---|
| | A | B | E | |
| Recessive model | | | | |
| GG+GA | 61 | 55 | 35 | – |
| AA | 0 | 0 | 0 | |
| Overdominant model | | | | |
| GG+AA | 49 | 46 | 30 | 0.78 |
| GA | 12 | 9 | 5 | |

**Notes**: [c]Chi-square test.

of GG vs GA genotypes by age, gender, smoking history, family history, mMRC score, CAT score, exacerbation count, and severity classification, with all *p*-values > 0.05.

To predict the influence of selected patient characteristics on exacerbation risk, multivariable logistic regression models were constructed and analyzed (Figure 3).

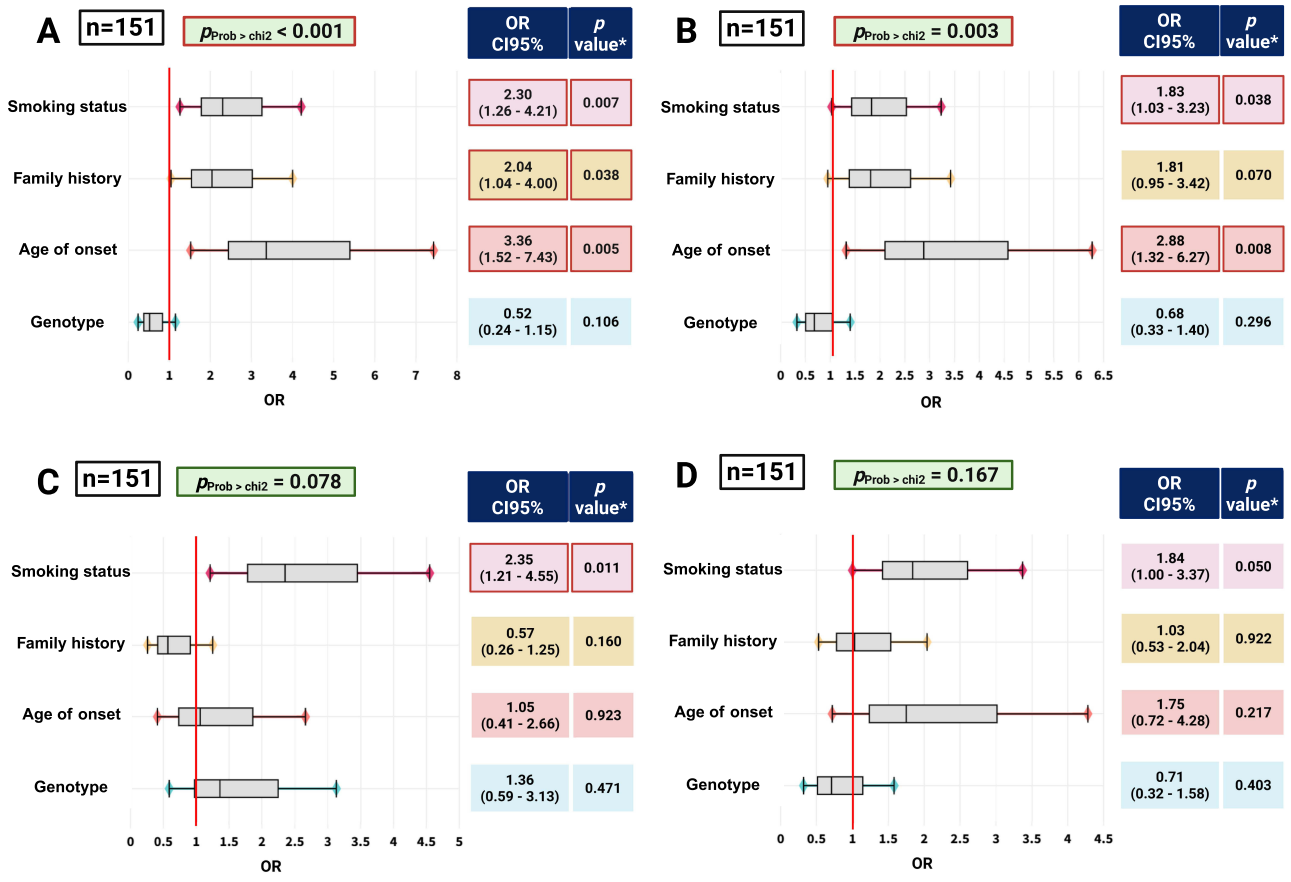


**Figure 3** Coefficient plot (Coefplot) of multivariable logistic regression models predicting the influence of selected patient characteristics on exacerbation risk. (**A**) mMRC scale; (**B**) CAT scale; (**C**) COPD exacerbation history; (**D**) exacerbation risk; *: Wald test; n: sample size; Prob > chi2: *p*-value for the overall model significance. Red frames indicate $p<0.05$. Vertical line: OR=1 (no effect).

**Abbreviations**: OR, Odds Ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council dyspnea scale; CAT, COPD Assessment Test.


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**Table 4** Comparison of Logistic Regression Results: Original Versus Sensitivity Analysis

| Influencing Factors | Outcomes | Original Analysis (151 Observations)* | Sensitivity Analysis (2660 Observations)# | Comparative Conclusions |
|---|---|---|---|---|
| Smoking | mMRC, CAT, exacerbations count, A/B/E | Significant ($p \leq 0.05$) | Highly significant ($p<0.001$) | Reinforcement |
| Family history of COPD | mMRC | Significant ($p=0.038$) | Highly significant ($p<0.001$) | Reinforcement |
| | CAT | Not significant ($p=0.070$) | Highly significant ($p<0.001$) | Elucidation and reinforcement |
| Age of onset | mMRC, A/B/E | Significant ($p<0.01$) | Highly significant ($p<0.001$) | Reinforcement |
| | CAT | Significant ($p=0.008$) | Not significant ($p>0.19$) | Inconsistent |
| Genotype | mMRC, CAT, A/B/E | Not significant ($p>0.1$) | Significant ($p<0.01$) (protective role) | Novel Findings, elucidation |

**Notes**: *: detailed data from Figure 3; #: data not shown.

Analyzed variables include smoking history, family history of COPD, age of onset, and rs1800629 genotype. Considering the four models overall, based on $p_{prob}$>chi2 compared to the $p$-value cutoff of 0.05, only models 3A (Influence on mMRC score) and 3B (Influence on CAT score) are statistically significant; models 3C (exacerbation history) and 3D (exacerbation risk) have $p > 0.05$. After controlling for other factors, examining each variable individually, data from Figure 3 show: smoking elevates odds of higher mMRC (OR 2.3), CAT (OR 1.83), and exacerbation groups (OR 2.35; all $p<0.05$); family history increases mMRC odds (OR 2.04, $p<0.05$); onset ≥40 years raises mMRC (OR 3.36, strongest factor) and CAT odds (OR 2.88; both $p<0.05$); and GA vs GG genotype has no significant influence across models.

The logistic regression results from two datasets - the original analysis on 151 cases (corresponding to 151 observations) and the sensitivity analysis on the imputed dataset expanded to 2660 observations (266 cases × 10 iterations) - are summarized in Table 4, which shows that the missing data imputation process and sensitivity analysis reinforced most key results from the original analysis. The sensitivity analysis revealed an association between exacerbation history and CAT score ($p < 0.001$). It demonstrated a protective effect of the heterozygous GA genotype on symptomatic severity measures (mMRC, CAT) and A/B/E risk classification (OR < 1, $p < 0.05$ in additive or over-dominant models), suggesting reduced odds of worse clinical outcomes in GA carriers compared to GG homozygotes.

## Discussion

The pathogenesis of Chronic Obstructive Pulmonary Disease (COPD) is complex and multifactorial, prominently featuring the inflammatory cytokine Tumor Necrosis Factor-alpha (TNF-α) as a critical mediator.[25] In COPD, TNF-α is involved in inflammatory processes that lead to airway obstruction, alveolar damage, and overall disease progression. Elevated levels of TNF-α are consistently observed in the lung tissues and systemic circulation of COPD patients, reflecting both local and systemic inflammation.[26,27] This cytokine not only promotes the survival and activation of macrophages and neutrophils but also induces the production of other inflammatory mediators, including Interleukin-6 (IL-6) and IL-8, exacerbating the inflammation observed in COPD.[28] Furthermore, TNF-α activates nuclear factor kappa B (NF-κB), a transcription factor that enhances the expression of multiple pro-inflammatory genes, thereby perpetuating the inflammatory cycle characteristic of COPD.[28]

Genetic factors also contribute to TNF-α's role in COPD pathogenesis. Despite numerous studies, the role of *TNF-α* rs1800629 in COPD remains a medical gap that needs to be filled.[18,23] This study aimed to test the hypothesis that the A allele of this SNP may be associated with increased COPD susceptibility and exacerbation risk in Vietnamese patients.

The *TNF-α* rs1800629 A allele was rare in this Vietnamese cohort, accounting for 7.8% of alleles overall (8.83% in patients, 6.88% in controls). As a result, only 5 participants (0.85%) were homozygous AA, while GA heterozygotes accounted for about 13.82% of the cohort, and GG homozygotes accounted for 85.32%. Such a skewed distribution is consistent with reports from other populations, such as the Philippines and Indonesia, where it is lower than in Europe (14.9%).[17,18,21,22] The slightly higher A-allele frequency among COPD patients (8.83%) compared with controls (6.88%) did not translate into significant differences in GA and AA genotype frequencies ($p$=0.32; Table 1). The predominance of

the G allele suggests that any protective effect of the A allele can be detected only in large cohorts; small numbers of AA individuals yield wide confidence intervals and limit the power of association analyses. In addition, we did not collect data on biomass fuel use, urban air pollution or occupational exposures, which are prevalent in Vietnam and may confound genetic associations; future studies should measure these exposures to allow gene–environment analyses.

Low minor-allele counts also create statistical challenges. Traditional $\chi^2$-tests for Hardy–Weinberg equilibrium (HWE) assume sufficient sample size and cell counts. Still, simulation work has shown that the $\chi^2$-test can be liberal when there are few copies of the minor allele. In the present study, the A allele was so rare that Fisher's exact test was used for the comparison of genotype frequencies ($p = 0.320$) and to assess HWE. Despite the low frequency of the A allele, genotype distributions in both the COPD and control groups conformed to HWE (Table 1 and Figure 2). This agreement implies that genotyping was reliable and that the allele frequencies in both groups reflect random mating rather than genotyping errors or population stratification. While the primary analysis with 151 complete cases showed no significant association between rs1800629 genotype and clinical severity measures (Table 3 and Figure 3), the sensitivity analysis using multiple imputation revealed a previously masked protective pattern. Specifically, GA heterozygotes demonstrated significantly reduced odds of moderate-to-severe dyspnea (mMRC ≥3), high symptom burden (CAT ≥10), and elevated exacerbation risk (GOLD groups B/E) compared to GG homozygotes (OR < 1, $p < 0.01$) when analyzed across 2,660 imputed observations. This finding suggests that the null result in the original analysis likely reflected insufficient statistical power due to the combination of small sample size (n=151), low A-allele frequency (8.83%), and missing covariate data, rather than a true absence of association. Because genotypes were not imputed, these imputation-based findings should be viewed as exploratory and hypothesis-generating. The protective signal observed in GA carriers contrasts with the recessive protective pattern seen for AA homozygotes in susceptibility analyses (Table 2), suggesting allele-dose-dependent effects: homozygous AA may confer strong protection against disease onset, while heterozygous GA may attenuate disease progression and symptom severity among those already diagnosed with COPD. This heterozygote advantage pattern has biological plausibility, as intermediate TNF-α expression levels (hypothetically associated with GA genotype) might optimize inflammatory balance, sufficient for pathogen clearance but insufficient to drive chronic tissue damage. The HWE conformity also suggests that the slight excess of GA heterozygotes in the patient group is likely a chance finding rather than a genuine departure from equilibrium.

The rarity of the A allele nonetheless complicates interpretation. First, the low allele frequency means that the difference in A-allele carriage between the COPD and control groups is modest (8.83% vs 6.88%), and statistical significance would require a much larger sample. Second, very few AA homozygotes were present (two COPD patients and three controls), so effect estimates for the recessive model are imprecise. Third, minor allele frequencies often vary across ethnicities. Population-specific differences mean that findings from one ethnic group may not generalize to others. Finally, low counts of the rare genotype can cause the exact HWE test to lose power; although no deviation was detected here, minor deviations could remain undetected. These limitations underscore the need to replicate the association in larger cohorts. They also highlight the importance of collecting comprehensive exposure data, including biomass and occupational exposures, to account for potential confounders.

In this case – control cohort, crude comparisons did not show a significant excess of the A allele among COPD patients. However, when genotypes were modelled recessively, the small subgroup of AA homozygotes showed a substantial reduction in COPD odds compared with the GG, GA, and GG+GA groups, suggesting a potential protective signal. Adjusted analyses indicated a recessive protective pattern (Table 2), supported by additive (OR 0.04) and recessive models (OR 0.039), resulting in a ~96% risk reduction. Because only two COPD patients carried the AA genotype and no AA individuals were observed among controls, these effect estimates are imprecise with wide confidence intervals; the apparent protective effect should therefore be interpreted cautiously. Thus, the ~96% reduction should not be interpreted as a definitive effect but rather as a preliminary observation that requires confirmation.

The demographic profile of our participants underscores the overwhelming influence of age and sex on COPD susceptibility. International analyses consistently show that COPD prevalence and mortality rise steeply after mid-life, reflecting the cumulative nature of lung injury, and remain higher in men in many regions due to historically higher smoking rates and more intense occupational exposures.[29]

An early meta-analysis of 25 studies (3,283 cases, 4,539 controls) found that the A allele modestly increased COPD susceptibility overall, particularly in Asians.[30] A further updated meta-analysis of 38 studies reached similar conclusions and suggested that AA carriers are at the highest risk.[18] The most recent and methodologically stringent synthesis of 27 case–control studies (3,473 COPD cases, 4,935 controls) confirmed that the GA genotype confers approximately 35% higher COPD risk in Asians (GA vs GG OR = 1.35) when smoking status is not accounted for.[23] These pooled results appear to contrast with the neutral or even protective pattern observed in our Vietnamese sample. Closer inspection of individual Asian cohorts, however, reveals substantial heterogeneity that aligns more closely with our data. In Indonesian heavy smokers, Tarigan et al found that GA+AA genotypes at −308 were more common in smoking controls than in COPD patients, with an OR of 0.44 (95% CI 0.22–0.85), and concluded that the −308A allele behaved as a protective factor in that population.[22] In Thailand, Chierakul et al reported no association between −308G/A and smoking-related COPD.[31] More recently, Hipolito et al examined COPD patients with hyperactive airways in the Philippines and again found no significant association between rs1800629 and COPD status, with a trend towards reduced odds of disease among carriers of the G/A genotype, in the context of very low A-allele frequency (5%).[21] As a candidate-gene study, our work cannot discover new risk loci; future genome-wide association studies (GWAS) with larger sample sizes and comprehensive exposure data will be required to fully elucidate the genetic architecture of COPD in Vietnam.

Several factors may explain these inconsistent observations across Asian populations. First, the baseline frequency of the A allele is low and varies by ethnicity; even modest differences in sampling or genotyping error can disproportionately influence effect estimates when only a handful of AA carriers are present, as in our cohort. Second, COPD case definitions and phenotypes differ, some studies focus on smoking-related emphysema, others on chronic bronchitis or COPD with asthma-like features, and still others on spirometry airflow limitation in community samples, each of which may be driven by slightly different inflammatory pathways. Third, and critically, to understand genetic susceptibility, one must first characterize the environmental pressures that select for or activate pathological traits. The risk profile for COPD is multifactorial, involving a complex interplay between inhalational exposures, socioeconomic status, and systemic host factors that modulate the lung's defense mechanisms. As a consequence, discrepancies in A-allele-related phenotypes could arise from gene-environment interactions and from potential haplotypes that modulate the protective effect of the AA genotype. In the most recent meta-analysis, the association between rs1800629 and COPD disappeared when analyses were restricted to smokers, suggesting that heavy tobacco exposure can overshadow modest genetic effects or that the variant may matter more in mixed-exposure or never-smoker COPD.[23] Our Vietnamese cohort, dominated by older male smokers with clinically established COPD, is therefore a setting where substantial environmental risk may dilute any small genetic effect and where residual confounding by unmeasured exposures (eg occupational and biomass smoke) remains possible. Future studies should therefore integrate detailed exposure assessment to permit gene–environment interaction analyses.

In the disease cohort, the substantial proportion of missing clinical data underscores potential selection bias and should be considered when interpreting the results (Table 1). The *TNF-α* rs1800629 variant showed, at most, a modest and inconsistent relationship with exacerbation risk, and classical clinical risk factors clearly overshadowed its effect. From the crude genotypic comparisons in Table 3, carriers of the GA genotype did not differ from GG homozygotes in terms of exacerbation history categories, GOLD A/B/E risk groups, CAT score, or mMRC dyspnoea levels; all *p*-values were >0.05. In Table 3, genotype distributions across GOLD A, B, and E groups were nearly identical under additive, dominant, recessive, and overdominant models, with a common *p*-value of 0.78 and no AA homozygotes observed (reflecting the low A-allele frequency). Thus, at the descriptive level, rs1800629 did not segregate with exacerbation risk as defined by the GOLD A/B/E framework. Multivariable models further support the notion that exacerbation risk in this Vietnamese COPD cohort is primarily driven by clinical exposures rather than this single *TNF-α* polymorphism. The original logistic regression analysis, therefore, indicates that rs1800629 is not a significant determinant of exacerbation burden in this population, in contrast to strong environmental and familial influences (Figure 3). The sensitivity analysis using multiple imputations (Table 4) adds nuance to this negative primary result. When the dataset was expanded to 2,660 imputed observations, most key findings on smoking, family history, and age of onset were preserved. Still, they became highly significant ($p<0.001$), reinforcing their central role in exacerbation risk. Importantly, the sensitivity analysis, by expanding the dataset to 2,660 observations, unmasked a statistically significant protective association

between the heterozygous GA genotype and key clinical outcomes (mMRC, CAT, and GOLD A/B/E risk) (OR < 1, $p$ < 0.01). While the original analysis lacked the statistical power to detect this modest effect, the imputation process suggests that possessing the A allele (in the GA state) may indeed attenuate symptom burden and exacerbation risk, reinforcing the potential protective nature of this variant in the Vietnamese population. However, because genotypes themselves were not imputed, the newly observed protective signal is exploratory and might also reflect modelling assumptions, residual confounding, or chance. The overall interpretation should therefore be cautious: if the A allele has any effect on exacerbation risk in this cohort, it is likely small and context dependent. This finding should stimulate future hypothesis-driven research rather than serve as definitive evidence.

Biologically, TNF-α's role in exacerbation pathophysiology is highly plausible. TNF-α is a central pro-inflammatory cytokine in COPD, amplifying neutrophilic inflammation, driving matrix degradation, and contributing to systemic effects such as cachexia.[32,33] Multiple studies have demonstrated increased TNF-α levels in sputum and serum during acute exacerbations compared with the stable state, often in parallel with other cytokines such as IL-6 and IL-8.[34,35] These observations are consistent with the broader literature in which TNF-α is repeatedly implicated as a biomarker and effector in exacerbation biology, even if anti-TNF biologics have not translated into effective COPD therapies in clinical trials.[36] The rs1800629 variant lies in the *TNF-α* promoter, where functional studies have shown that the rarer A allele (historically termed TNF2) can act as a stronger transcriptional activator and is associated with higher circulating TNF-α levels in several immune-mediated conditions.[37,38] The genetic evidence linking rs1800629 specifically to exacerbation risk is considerably weaker and less consistent than that linking circulating *TNF-α* protein levels to exacerbation events.

The potential epistatic interactions between *TNF-α* −308G/A and other genetic variants, especially those of other cytokine and inflammatory genes, influencing COPD susceptibility and severity have not been comprehensively elucidated. The proportion of individuals with a combination of normal *GG* genotype of the *TNF-α* −308G/A variant and heterozygous *AG* genotype of the *LTA* +252A/G variant was significantly higher in COPD patients (28.5% versus 18.4% in controls; $X^2 = 4.14$, $p < 0.05$; OR = 1.75, CI = 1.01–3.04). This study established, for the first time, that LTA gene alleles and their combinations with *TNF-α* gene polymorphic variants are associated with predisposition to COPD and its severity, even though the *TNF-α* −308G/A variant itself was not shown to be associated with COPD.[39] A systematic review and meta-analysis, comprising 183 studies across 78 articles, evaluating 50 polymorphisms in 12 cytokine genes related to COPD, identified four specific cytokine variants, including *TNF-α* rs1800629, *TGF-β1* rs6957, *IL-13* rs1800925, and *IL-6* rs1800796, that were significantly associated with an increased risk of developing COPD.[40] However, no epistatic interaction has been examined.

This study has several limitations. First, cross-sectional design is well-suited to studying allele frequencies and associations but limits causal inference. Second, convenience sampling from a single center (Ho Chi Minh City) may introduce bias and fail to represent Vietnam nationally.[41] Third, the small sample size (151/266 with complete data) reduces power. Critically, only 2/266 COPD patients carried the AA genotype, yielding a protective OR (0.039) with a wide CI (0.002–0.62) that, while statistically significant, requires validation through regional meta-analysis or multi-center replication to confirm stability (Lin et al 2014). Fourth, unadjusted confounders such as air pollution or occupational exposure (GOLD 2023; Yang et al 2021) may contribute to the lower reliability of negative results regarding rs1800629 associations with COPD characteristics and exacerbation risk prediction models. Fifth, PCR-RFLP is reliable but does not detect haplotypes or other variants, potentially limiting comprehensiveness in analyzing genetic influences. These limitations underscore the need for larger, multi-centre studies that collect comprehensive exposure data and utilise genome-wide approaches to identify additional genetic determinants.

Despite these constraints, this study offers actionable translational insights. Scientifically, this study contributes to addressing Vietnam's COPD genetic gap, providing preliminary evidence on Southeast Asian inconsistencies in AA protection and emphasizing non-genetic roles in "deep phenotyping". While AA's protective association requires validation (see above), current findings support three pragmatic applications: (1) Enhanced smoking cessation counseling for GG carriers, who demonstrated 1.83–2.35-fold increased odds of symptomatic severity (mMRC/CAT scores, $p$<0.05) when smoking; (2) Earlier spirometry screening (age <40) in families with COPD history and GG genotype, given the independent effect of age of onset ≥40 years (OR 2.88–3.36, $p$<0.001); (3) Genotype-enriched clinical trials of TNF-α inhibitors (eg, etanercept, infliximab), prioritizing GG homozygotes who theoretically exhibit higher TNF-α

activity.[12] These recommendations should be interpreted as hypothesis-generating rather than definitive guidance until replicated in larger cohorts.

Although the vast majority of COPD cases are polygenic, the identification of monogenic determinants remains strategically vital for understanding disease mechanisms.[42] Monogenic syndromes serve as "natural experiments" that illuminate critical bottlenecks in lung homeostasis.[43] While these mutations are rare and account for only a small fraction of the total disease burden, they provide unambiguous causal links to pathology that are often obscured by the "noise" of common, low-effect variants.[44] Uncovering these rare, penetrant drivers allows researchers to define precise molecular endotypes and validate pathway-specific therapeutic targets that may prove effective for the broader population, where the same pathways are disrupted to a lesser degree by environmental stress.[45]

Priority research directions include: (1) Multi-center replication in Vietnamese cohorts (target ≥1,000 cases) or Southeast Asian meta-analysis pooling Thailand, Indonesia, and Philippines data to achieve adequate power for rare AA variant detection; (2) Haplotype analysis to identify epistatic interactions modulating *TNF-α* expression; and (3) Gene-environment interaction modeling, adjusting for occupational exposures and burden of urban pollution. Future studies should also consider conducting genome-wide association studies with detailed exposure assessment to discover novel susceptibility loci and clarify gene–environment interactions.

## Conclusion

The *TNF-α* rs1800629 variant showed a low A allele frequency in stable Vietnamese COPD patients (similar to controls), with rare AA genotypes. Although our recessive analysis suggested that AA carriers had lower COPD susceptibility, this observation is based on only two patients and has wide confidence intervals; it should therefore be regarded as preliminary and interpreted cautiously. In imputed analyses, GA carriers exhibited reduced symptom burden and exacerbation risk, but genotype values were not imputed and these exploratory findings may reflect modelling assumptions or residual confounding. These findings help address Vietnam's COPD genetic data gap and call for larger studies to validate and investigate other genetic determinants. Future research should collect detailed environmental exposure data (eg, biomass fuel use, urban pollution, and occupational dusts) and employ genome-wide approaches to elucidate gene–environment interactions. Larger multi-centre cohorts with comprehensive exposure assessment are needed to confirm these preliminary signals and to identify additional genetic determinants of COPD susceptibility and progression.

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## Disclosure

The authors report no conflicts of interest in this work.

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