COMBINED *TNF-α -308* (rs1800629) GENOTYPE AND TYG INDEX FOR IDENTIFYING METABOLIC SYNDROME IN A VIETNAMESE ADULT COHORT

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The triglyceride-glucose (TyG) index is a robust surrogate for insulin resistance. This study evaluated the diagnostic and discriminative utility of combining the TyG index with the TNF-α -308G>A (rs1800629) genotype for early identification of Metabolic Syndrome (MetS) in a Vietnamese cohort, accounting for Metabolic Dysfunction-Associated Steatotic Liver Disease (MAFLD). This cross-sectional analysis included 311 medical and administrative staff. MetS was defined by harmonized criteria. The TyG index and TNF-α -308 genotypes were analyzed using multivariable logistic regression and Area Under the Receiver Operating Characteristic (AUC-ROC) curves, with stratification by MAFLD status. MetS prevalence was 17.4%. The TyG index was a highly significant independent discriminator of MetS (Adjusted OR = 59.73, p < 0.001). The TNF-α -308 A-allele carrier status did not significantly associate with MetS (Adjusted OR = 0.26, p = 0.120). The combined model yielded an AUC of 0.955 versus 0.952 for the reference model (ΔAUC = +0.003). While incremental AUC was slightly higher in the MAFLD subgroup (ΔAUC = +0.014), the synergistic effect was not statistically significant. The TyG index demonstrates excellent diagnostic utility for MetS. However, incorporating the TNF-α -308 genotype does not provide clinically meaningful incremental discriminative value in this population.

Keywords: Metabolic Syndrome, TyG index, *TNF-α -308*, MAFLD, discriminative utility.

I. INTRODUCTION

Metabolic syndrome (MetS) represents a global public health crisis, characterized by a cluster of interrelated cardiometabolic risk factors including central obesity, dyslipidemia, hypertension, and impaired glucose tolerance.[1] The pathogenesis of MetS is heavily driven by chronic low-grade inflammation and systemic insulin resistance (IR). The liver is centrally implicated in this metabolic cascade; consequently, Metabolic Dysfunction-Associated Steatotic Liver Disease (MAFLD) - which shares an extensive pathophysiological overlap with MetS - frequently acts as both a consequence and a catalyst of severe metabolic derangement.[2]

Early identification of IR is crucial for implementing preventative strategies. Recently, the triglyceride-glucose (TyG) index has emerged as a robust, cost-effective, and highly accessible surrogate marker for IR.[3] Extensive prospective cohorts have demonstrated that the TyG index is at least as effective as traditional metrics, such as HOMA-IR, in identifying incident MetS across diverse populations.[4] However, while biochemical indices capture dynamic metabolic stress, the pathogenesis of MetS is also governed by innate genetic susceptibility.[5] Tumor necrosis factor-alpha (TNF-α) is a primary pro-inflammatory cytokine that bridges obesity, hepatic lipid accumulation, and IR. The functional single-nucleotide

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Received: 15/03/2026
Accepted: 31/03/2026

polymorphism rs1800629 (a G>A substitution at position *-308* in the promoter region) enhances *TNF-α* transcription in A-allele carriers.[6] While the A-allele has been linked to increased MetS and MAFLD risk in certain Middle Eastern and Caucasian cohorts, findings remain globally heterogeneous, leaving gene-environment interactions in Southeast Asian populations largely unexplored.[5,7]

Mechanistically, TNF-α activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which promotes hepatic insulin resistance through serine phosphorylation of insulin receptor substrate-1 (IRS-1) and enhances hepatic lipogenesis. This inflammatory cascade directly links the TNF-α genotype to the metabolic pathways captured by the TyG index, providing a biological rationale for evaluating their combined utility.

Combining a fixed genetic marker of inflammation with a dynamic biochemical index of IR aligns with precision-medicine principles and theoretically offers refined early risk stratification. Therefore, this study aimed to evaluate the independent and incremental discriminative utility of combining the TyG index with *TNF-α -308* genotyping for identifying MetS in a Vietnamese adult health-check-up cohort. Furthermore, we specifically sought to determine whether this discriminative utility is amplified when stratified by concurrent MAFLD status.

II. SUBJECTS AND METHODS

1. Study Design and Setting

This study is a secondary, cross-sectional analysis utilizing existing data derived from a broader prospective health-check cohort. The primary objective of this specific analysis was to evaluate the diagnostic and discriminative utility of combining the functional *TNF-α -308* (rs1800629) genotype with the Triglyceride-Glucose (TyG) index for the early identification of Metabolic Syndrome (MetS). The source population comprised medical and administrative staff from Nguyen Tri Phuong (NTP) Hospital and Pham Ngoc Thach (PNT) University of Medicine, who underwent their annual occupational health examinations.

2. Study Population and Sampling

The parent cohort data were collected between October 31, 2022 (7 days after the earliest ethical committee approval) and December 21, 2023 (30 days after the latest ethical committee approval). During this period, a total of 700 participants were recruited for the primary studies.

For this secondary manuscript, a refined analytical subset of 311 participants was extracted from the existing dataset. Inclusion in this specific sub-analysis required participants to have non-missing data for the *TNF-α -308* (rs1800629) genotype. Exclusion criteria were applied sequentially to remove individuals with conditions that could severely confound metabolic or hepatic assessments, including pregnancy, significant alcohol consumption, autoimmune or drug-induced liver disease, active infection or malignancy, and advanced renal impairment defined as an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m². Records missing critical core covariates required for multivariable modeling were also excluded.

Data Collection and Variables

All clinical, anthropometric, and laboratory data utilized in this analysis were retrieved from the same clinical visit to prevent temporal bias. The primary outcome was the presence of MetS, treated as a binary variable and defined by harmonized criteria requiring the presence of at

least 3 of the following 5 metabolic abnormalities (central obesity, elevated triglycerides, reduced high-density lipoprotein cholesterol, elevated blood pressure, and elevated fasting glucose).

The TyG index was calculated using the validated formula: ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2]. Genotyping for the *TNF-α -308* single-nucleotide polymorphism categorized individuals into *GG*, *GA*, and *AA* genotypes. Given the characteristic low minor A-allele frequency in Asian populations, a dominant genetic model (GG versus GA+AA) was used to preserve statistical power during association testing. Core covariates included age, sex, Asian-specific Body Mass Index (BMI), eGFR, and Metabolic Dysfunction-Associated Steatotic Liver Disease (MAFLD) status. MAFLD was defined by established 2023 criteria and utilized as a stratification variable to evaluate pathophysiological effect modification.

Statistical Analysis

Statistical analyses were designed in accordance with the STROBE and TRIPOD guidelines for observational biomarker studies. Baseline characteristics were summarized for the overall cohort and stratified by MetS status using means for continuous variables and counts (percentages) for categorical variables. The distribution of the *TNF-α* genotype was assessed for deviations from the Hardy-Weinberg equilibrium in the non-MetS control group using a Chi-squared test.

To evaluate independent discriminators of MetS, a sequence of multivariable logistic regression models was constructed. A base reference model evaluated the TyG index adjusted for age, sex, BMI, and eGFR. The combined full model additionally integrated the dominant *TNF-α* genetic variant to quantify its independent effect within the metabolic cascade. Results were reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

The primary discriminative performance and incremental utility of adding the genotype to the TyG index were evaluated using the Area Under the Receiver Operating Characteristic curve (AUC-ROC). To address the hypothesis that hepatic inflammation amplifies the functional effect of the *TNF-α* variant, discriminative ROC models were further stratified by MAFLD status. Formal statistical interaction testing (TyG × Genotype × MAFLD) was conducted to assess synergistic multiplicative effects. Two-sided p-values < 0.05 were considered statistically significant. All analytical steps were executed using Python (version 3.x, featuring pandas, statsmodels, and scikit-learn libraries).

3. Ethical Considerations

The parent studies from which this data was derived, as well as the data collection protocols, were conducted in rigorous accordance with the Declaration of Helsinki. Informed consent was obtained from all participating staff members prior to their enrollment in the primary cohort. Institutional review board and ethical committee approvals covering the participant recruitment and data collection were independently granted by three separate regulatory bodies: The Biomedical Research Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City (Approval No. 788/HĐĐĐ-ĐHYD, dated October 24, 2022); The Biomedical Research Ethics Committee of Pham Ngoc Thach University of Medicine (Approval No. 859/TĐHYKPNT-HĐĐĐ, dated April 20, 2023); and The Biomedical Research Ethics Committee of Nguyen Tri Phuong Hospital (Approval No. 2572/NTP-HĐĐĐ, dated November 21, 2023). Official administrative clearance for data collection at the clinical site was granted by

the Pham Ngoc Thach University of Medicine Polyclinic (Decision No. 319/QĐ-PKĐK, dated November 30, 2022).

III. RESULTS

1. Baseline Characteristics and Genotype Distribution

Following the sequential application of inclusion and exclusion criteria, 311 individuals with complete genetic, laboratory, and clinical covariate data were retained for the analytic cohort. The prevalence of Metabolic Syndrome (MetS), defined by the presence of ≥ 3 metabolic criteria, was 17.4% (n=54). The demographic and clinical profiles, stratified by MetS status, are summarized in Table 1. Individuals with MetS were generally older and exhibited higher mean Body Mass Index (BMI) and Triglyceride-Glucose (TyG) index values than non-MetS controls.

Genotyping for the *TNF-α -308* (rs1800629) variant revealed frequencies of 86.8% (n=270) for the GG genotype, 12.2% (n=38) for the GA genotype, and 1.0% (n=3) for the AA genotype, aligning with expected distributions for this population. The distribution of genotypes within the non-MetS control group did not deviate significantly from Hardy-Weinberg equilibrium (χ^2 = 1.345, p = 0.510). The minor A-allele frequency in the control population was 8.0%. Given the low frequency of the homozygous AA genotype, a dominant genetic framework (GG vs. GA+AA) was utilized for all subsequent multivariable analyses.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Cohort Stratified by Metabolic Syndrome Status

Clinical Parameter	Total Cohort (n=311)	Non-MetS Controls (n=257)	MetS Cases (n=54)
Age (years)	37.60	36.86	41.17
Body Mass Index (kg/m²)	22.71	22.06	25.80
TyG Index	8.30	8.12	9.21
eGFR (mL/min/1.73m²)	102.29	102.86	99.59

Continuous variables are presented as the mean.

2. Multivariable Discriminators of Metabolic Syndrome

A multivariable logistic regression model was constructed to evaluate the independent association of the *TNF-α -308* genotype with MetS, adjusting for TyG, age, sex, BMI, and eGFR (Table 2). The TyG index demonstrated a highly significant, independent association with MetS (Adjusted OR = 59.73, 95% CI [15.99, 223.16], p < 0.001). Conversely, the addition of the A-allele carrier status (GA+AA) did not yield a statistically significant association with the presence of MetS (Adjusted OR = 0.26, 95% CI [0.05, 1.42], p = 0.120). This stark disparity in effect sizes is visually represented in Figure 1.

Table 2. Multivariable Logistic Regression Analysis of Independent Discriminators for Metabolic Syndrome

Discriminator Variable	Adjusted Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
TyG Index	59.73	15.99 - 223.16	<0.001
TNF-α Genotype (GA+AA vs GG)	0.26	0.05 - 1.42	0.120
Age (per 1-year increase)	1.01	0.95 - 1.08	0.637
Gender (Male vs Female)	1.02	0.36 - 2.88	0.972
Body Mass Index (per 1 kg/m²)	1.37	1.18 - 1.60	<0.001
eGFR	1.00	0.95 - 1.04	0.848

The model evaluates the additive effect of the TNF-α -308 genotype under a dominant genetic model, adjusting for core clinical covariates. OR: Odds Ratio; CI: Confidence Interval; TyG: Triglyceride-Glucose Index; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate.

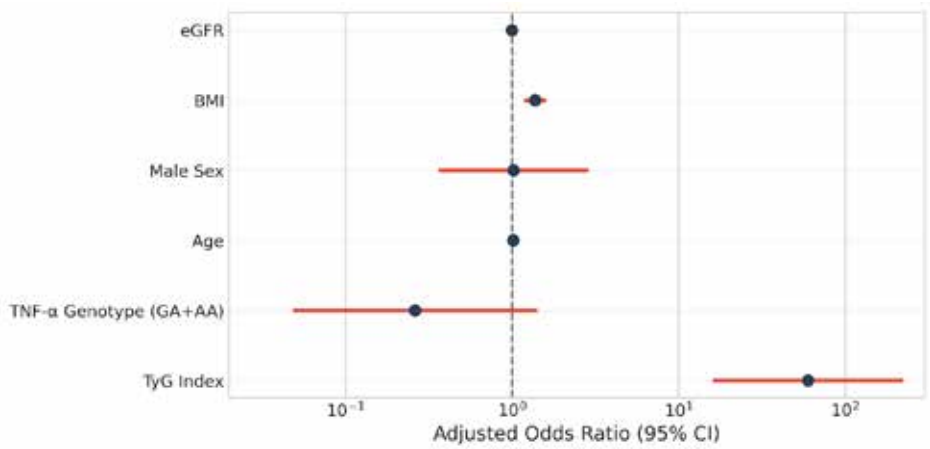

Figure 1. Forest Plot of Multivariable Discriminators for Metabolic Syndrome

Adjusted OR and 95%CI for the primary clinical and genetic discriminators. The logarithmic scale emphasizes the dominant independent association of the TyG index, compared with the non-significant contribution of the TNF-α genotype. OR: Odds Ratio; CI: Confidence Interval; TyG: Triglyceride-Glucose Index.

3. Discriminative Performance and Incremental Utility

The discriminative capacity of the models was evaluated using the Area Under the Receiver Operating Characteristic Curve (AUC-ROC). The reference model (TyG index and clinical covariates) achieved an excellent baseline discrimination with an AUC of 0.952 (Figure 2). The combined model, which incorporated the *TNF-α -308* genotype, yielded an AUC of 0.955. The incremental discriminative utility provided by the genetic variant was marginal (ΔAUC = +0.003) and did not meet the pre-specified threshold for a clinically meaningful improvement (ΔAUC ≥ 0.05).

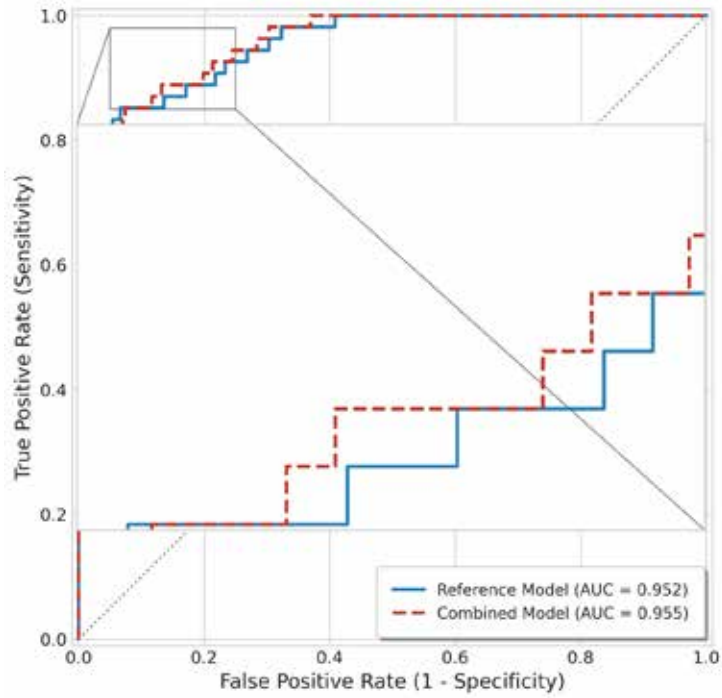

Figure 2. Receiver Operating Characteristic (ROC) Curves for the Identification of Metabolic Syndrome

The solid blue line represents the reference model (TyG index, age, sex, BMI, and eGFR). The dashed red line represents the combined model incorporating the TNF-α -308 (rs1800629) genotype. The magnified inset (center-right) highlights the high-sensitivity threshold, demonstrating the marginal separation between the two discriminative models. AUC: Area Under the Curve.

4. Subgroup Analysis by MAFLD Status

To test the hypothesis that concurrent hepatic inflammation might amplify the functional impact of the *TNF-α* variant, discrimination was further stratified by Metabolic Dysfunction-Associated Steatotic Liver Disease (MAFLD) status (Figure 3). In the non-MAFLD control subgroup (n=240), the combined model offered a negligible improvement over the reference model (ΔAUC = +0.002). Within the MAFLD subgroup (n=71), the incremental value of the genotype was comparatively larger (ΔAUC = +0.014). However, formal interaction testing (TyG × Genotype × MAFLD) did not reveal a statistically significant multiplicative effect ($p > 0.05$), indicating that the discriminative utility of the *TNF-α -308* variant remains constrained across subgroups by the high baseline discrimination established by the TyG index.

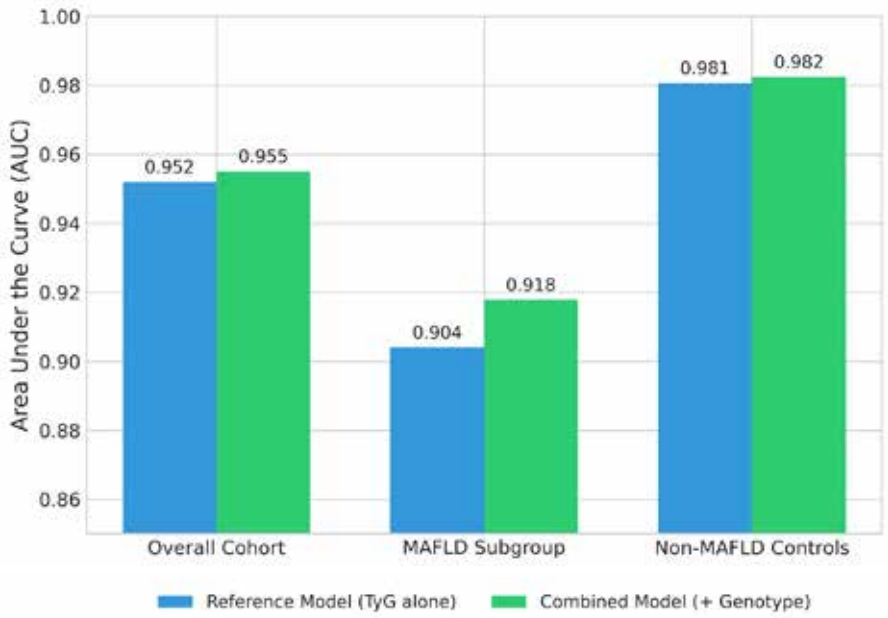

Figure 3. Incremental Discriminative Utility of the Combined Model Stratified by MAFLD Status

Comparison of the Area Under the Curve (AUC) between the reference model (TyG index alone) and the combined model (+ TNF-α genotype) across the overall cohort, individuals with Metabolic Dysfunction-Associated Steatotic Liver Disease (MAFLD), and non-MAFLD controls. MAFLD: Metabolic Dysfunction-Associated Steatotic Liver Disease.

IV. DISCUSSION

This cross-sectional study investigated the utility of combining the *TNF-α -308* (rs1800629) genotype with the TyG index for the early identification of MetS in a Vietnamese adult cohort. Our primary finding demonstrates that the TyG index is a strong, independent discriminator of MetS (AUC > 0.95). However, contrary to our initial hypothesis, the addition of the *TNF-α -308* genotype did not yield a clinically meaningful incremental improvement in discriminative performance, nor did it exhibit an independent multivariable association with MetS. While the incremental value of the genotype was marginally higher in patients with concurrent MAFLD compared to non-MAFLD controls, formal interaction testing revealed no significant multiplicative effect.

An important methodological consideration is that the TyG index incorporates fasting triglycerides and fasting glucose, both of which are also components of the harmonized MetS definition. This inherent overlap may inflate the observed AUC, as the discriminator and the outcome share common variables. While this circularity does not invalidate the TyG index as a clinical screening tool, it limits the interpretability of the extremely high AUC (0.952) as a measure of true discriminative ability for MetS as a syndrome beyond its constituent components.

Our findings strongly corroborate the rapidly expanding body of literature that positions the TyG index as a premier point-of-care biomarker for metabolic dysfunction.[8] The notable discriminative power of the TyG index-

alongside standard anthropometrics like BMI-suggests a diagnostic "ceiling effect." In routine screening contexts, these readily accessible clinical parameters are sufficiently informative for identifying MetS, leaving negligible statistical variance for a single-gene marker to capture.[4,9,10]

The lack of an independent association between the rs1800629 A-allele and MetS in our cohort contrasts with studies in Egyptian and specific European populations, in which the A-allele has been a strong risk factor.[7,11] This discrepancy highlights the critical role of ethnic heterogeneity in genetic architecture. In our Vietnamese cohort, the minor A-allele frequency was approximately 8.0%, which is consistent with Southeast Asian norms but substantially lower than Caucasian frequencies.[12] In populations where a pro-inflammatory variant is relatively rare, its population-level penetrance and impact on complex, polygenic traits like MetS are inherently diluted.

Furthermore, we hypothesized that the underlying hepatic inflammation characteristic of MAFLD might amplify the functional impact of the *TNF-α* variant, unmasking its discriminative utility. While the genotype showed a slightly larger AUC improvement in the MAFLD subgroup (ΔAUC = +0.014) than in healthy controls (ΔAUC = +0.002), the absolute improvement remained sub-clinical. This suggests that while MAFLD is a state of pronounced metabolic vulnerability, a single inflammatory single-nucleotide polymorphism does not reliably differentiate downstream MetS risk beyond the severity already captured by fasting lipids and glucose.

This study possesses several strengths, notably the novel integration of an inflammatory genetic marker with a validated IR index, the stratification by modern MAFLD criteria, and the provision of much-needed ethnic-specific data for a Vietnamese population. Several limitations warrant consideration. First, the cross-sectional design precludes causal inference or temporal prediction. Second, participants were hospital staff, introducing potential healthy-worker selection bias that limits generalizability to the broader Vietnamese population. Third, important confounders including smoking status, dietary patterns, physical activity level, and medication use were not available for adjustment, representing potential sources of residual confounding. Fourth, the inclusion of BMI and MAFLD as covariates warrants caution, as these may function as mediators rather than confounders on the causal pathway between TyG/genotype and MetS, potentially introducing over-adjustment bias. Fifth, the sample size of 311 participants with a minor allele frequency of 8.0% yielded only 41 A-allele carriers (38 GA + 3 AA), providing limited statistical power for detecting modest genetic effects and precluding analysis under a recessive genetic model. Sixth, model evaluation relied exclusively on AUC-ROC without complementary metrics such as Net Reclassification Improvement (NRI), Integrated Discrimination Improvement (IDI), or decision curve analysis, which would provide a more comprehensive assessment of incremental clinical value. Finally, the absence of an external validation cohort limits the generalizability of the reported model performance.

V. CONCLUSION

In conclusion, the TyG index demonstrates excellent independent diagnostic utility for identifying Metabolic Syndrome in the Vietnamese adult health-check-up population. However, the integration of the *TNF-α -308* (rs1800629) genotype into the discriminative model does not provide a clinically meaningful

incremental improvement in discrimination. Although individuals with concurrent MAFLD exhibited a marginally higher discriminative benefit from the genetic marker, the overall synergistic effect remains negligible and falls short of clinical utility thresholds. Given the low minor A-allele frequency characteristic of this ethnic demographic, routine screening utilizing accessible biochemical surrogates like the TyG index appears effective for MetS screening in this population. Consequently, incorporating this specific inflammatory polymorphism into early MetS risk stratification protocols does not appear warranted based on the current evidence. These findings should be interpreted within the constraints of the cross-sectional design, potential healthy-worker selection bias, and residual confounding, and require validation in independent cohorts.

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