

Higher triglyceride–glucose–albumin index is inversely associated with monoclonal gammopathy of undetermined significance in U.S. adults using NHANES data

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Abstract

Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder with increasing recognition of its metabolic and inflammatory determinants. The triglyceride–glucose–albumin (TyG-ALB) index, a composite marker integrating insulin resistance and nutritional status, has been linked to cardiometabolic and inflammatory conditions; however, its association with MGUS remains unclear.

Material and methods: This cross-sectional study included 12,796 adults from the National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and continuous NHANES cycles (1999–2004). The TyG-ALB index was calculated as $\ln [TG \text{ (mg/dl)} \times \text{fasting blood glucose (mg/dl)} / 2] \times \text{albumin (g/dl)}$. MGUS was assessed using serum protein electrophoresis, immunofixation, and free light chain assays. Survey-weighted logistic regression models were applied to evaluate the association between TyG-ALB and MGUS.

Results: Among the 12,796 participants, 330 were diagnosed with MGUS. Higher TyG-ALB levels were associated with lower odds of MGUS. In fully adjusted models, participants in the highest tertile of TyG-ALB had lower odds of MGUS compared with those in the lowest tertile [odds ratio (OR) = 0.68, 95% confidence interval (CI): 0.50–0.94]. When analysed as a continuous variable, each one-unit increase in TyG-ALB was associated with 5% lower odds of MGUS (OR = 0.95, 95% CI: 0.92–0.98). Restricted cubic spline analyses revealed a nonlinear inverse association, with an inflection point at a TyG-ALB value of 36.0. Although this inverse association appears counterintuitive because metabolic dysfunction is generally expected to increase MGUS risk, it may be partly explained by the contribution of serum albumin, which reflects better nutritional status and lower systemic inflammation.

Conclusions: In this cross-sectional NHANES analysis, higher TyG-ALB was associated with lower odds of prevalent MGUS; however, temporality and causality cannot be inferred. These findings should be interpreted as hypothesis-generating rather than confirmatory. Independent prospective cohorts are needed to validate the association, establish temporality, and clarify the underlying mechanisms.

Key words: monoclonal gammopathy of undetermined significance, triglyceride–glucose–albumin, inflammatory markers.

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic pre-malignant plasma cell disorder characterised by the presence of a serum monoclonal (M) protein concentration < 30 g/l, bone marrow plasma cells < 10%, and the absence of myeloma-defining CRAB features [1, 2]. Epidemiological studies indicate that MGUS affects approximately 2–3% of individuals aged over 50 years, with prevalence rising to nearly 5% among those older than 70 years. Notably, the prevalence of MGUS is two to three times higher among individuals of African ancestry than among White populations [3]. Although MGUS is generally clinically silent, approximately 1% of affected individuals progress annually to multiple myeloma or other plasma cell or lymphoid malignancies [1, 2, 4–6].

Beyond established prognostic markers such as M-protein isotype, concentration, and serum free light-chain ratio, host-related metabolic and inflammatory factors have received increasing attention in relation to MGUS. Advanced age, male sex, African ancestry, family history, obesity, prior infections, and chronic inflammatory states have been identified as factors associated with MGUS occurrence or progression [7–10]. Several population-based studies have further suggested that obesity, diabetes, metabolic syndrome, and related cardiometabolic abnormalities may be associated with higher MGUS prevalence or progression risk [11–14]. These findings support a potential link between metabolic dysregulation, chronic low-grade inflammation, and plasma cell disorders.

In parallel, nutritional status and systemic inflammation may also be relevant to the biological context of MGUS. Serum albumin, a widely used marker of nutritional status, is also influenced by systemic inflammatory burden. Hypoalbuminaemia is commonly observed in chronic inflammatory states and malnutrition, and low serum albumin levels have been associated with adverse clinical features and disease progression among patients with MGUS [15]. Inflammatory markers, including interleukin-6 and C-reactive protein, have also been implicated in MGUS and multiple myeloma, highlighting the potential importance of the inflammatory microenvironment in plasma cell disorders [16].

The triglyceride–glucose (TyG) index, calculated using fasting triglyceride and glucose concentrations, is a simple and well-validated surrogate marker of insulin resistance [17]. Elevated TyG index values are strongly associated with metabolic syndrome and have been linked to increased risks of atherosclerosis and cardiovascular disease [18–20]. Serum albumin, in contrast, provides complementary information regarding

nutritional and inflammatory status. The triglyceride–glucose–albumin (TyG-ALB) index integrates insulin resistance-related components with serum albumin, thereby combining metabolic and nutritional-inflammatory information into a single composite marker. However, TyG-ALB should not be interpreted as a pure insulin-resistance index, because serum albumin may substantially influence its biological meaning.

Although metabolic syndrome and insulin resistance have generally been associated with higher MGUS prevalence, the association between TyG-ALB and MGUS may not simply mirror that of insulin-resistance indices alone, because TyG-ALB incorporates serum albumin, a marker closely related to nutritional status and systemic inflammation. To date, no study has systematically examined the association between TyG-ALB and MGUS. Therefore, using data from the National Health and Nutrition Examination Survey (NHANES), we investigated the relationship between TyG-ALB and MGUS prevalence among U.S. adults. We therefore hypothesised that a higher TyG-ALB index would be associated with lower MGUS prevalence.

Material and methods

Study design and population

This study was conducted using data from the NHANES, a nationwide program designed to assess the health and nutritional status of the non-institutionalised civilian population in the United States [21]. NHANES employs a complex, stratified, multistage probability sampling design to ensure that the study population is representative at the national level. Data collection is carried out through standardised in-home interviews, physical examinations conducted in mobile examination centres, and laboratory-based assessments using rigorously controlled protocols. The present analysis was based on data obtained from NHANES III (1988–1994) and the continuous NHANES cycles conducted between 1999 and 2004. All survey procedures were reviewed and approved by the Ethics Review Board of the National Centre for Health Statistics, and written informed consent was obtained from all participants prior to participation. Detailed descriptions of survey design, data collection procedures, and laboratory methods are publicly available through the NHANES website. Of the 62,437 participants initially identified, 27,624 were excluded because they were younger than 18 years, 2935 were excluded due to missing measurements of triglycerides, glucose, or albumin, and 19,082 were excluded because MGUS assessment was not available. Ultimately, 12,796 participants were included in the final analysis (Figure 1).

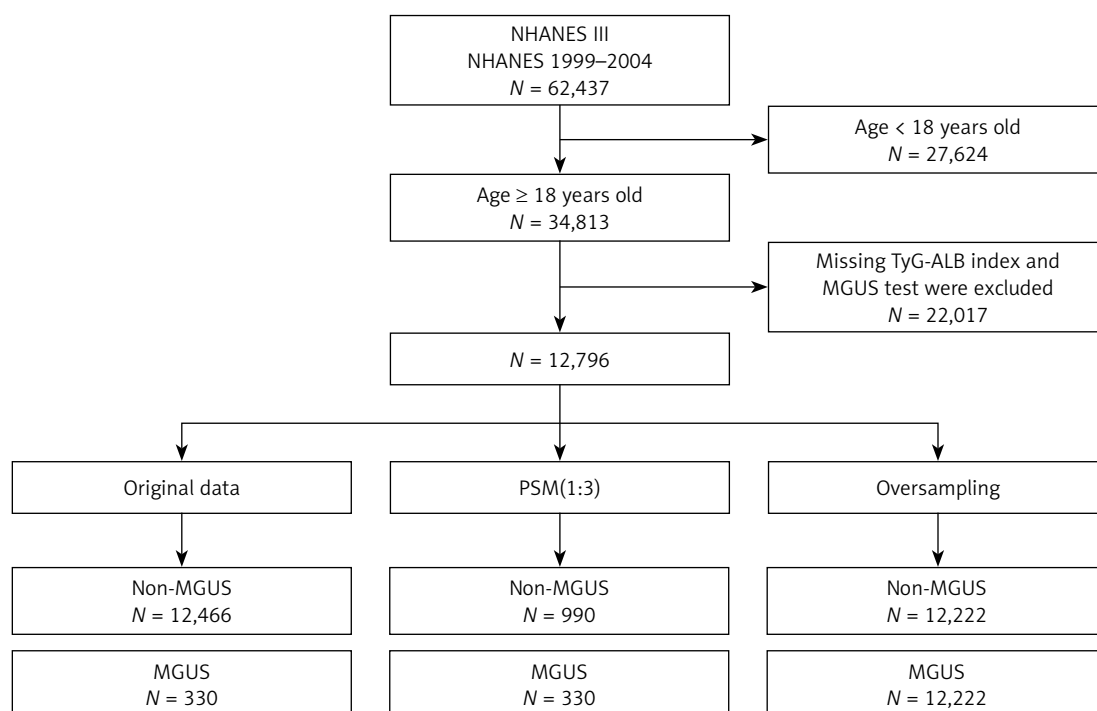


Figure 1. Flowchart of the study

Assessment of MGUS

MGUS testing was performed at the Protein Immunology Laboratory of the Mayo Clinic (Rochester, Minnesota, USA) using previously described methods. Serum protein agarose gel electrophoresis was conducted for age-eligible participants. Samples with suspected or definite M-proteins were further evaluated by serum protein immunofixation electrophoresis and serum free light chain assays. MGUS subtypes were determined based on immunofixation electrophoresis results. All laboratory analyses and interpretations were completed by personnel blinded to participants' demographic and clinical information. Because the present analysis combined NHANES III with NHANES 1999–2004, potential survey-period differences in sample collection, storage duration, and laboratory implementation were considered when interpreting the findings.

Assessment of TyG-ALB

Fasting triglycerides (TG) and fasting blood glucose (FBG) were measured by enzymatic colorimetric assays using blood samples collected after at least 8 h of fasting. The TyG index was calculated as $\ln [TG \text{ (mg/dl)} \times FBG \text{ (mg/dl)} / 2]$. The TyG-ALB index was calculated as $\{\ln [TG \text{ (mg/dl)} \times FBG \text{ (mg/dl)} / 2]\} \times \text{serum albumin (g/dl)}$.

Covariates and clinical definitions

Demographic characteristics collected in this study included sex, age, race/ethnicity, education-

al attainment, family income-to-poverty ratio (IPR), and BMI. Laboratory measurements comprised total cholesterol (TC), TG, HDL-C, FBG, albumin, white blood cell count, neutrophil count, lymphocyte count, and platelet count. BMI was categorised as normal weight, overweight, or obese. Smoking status was classified as never, former, or current smoker; drinking status was categorised as never drinking, moderate drinking, or heavy drinking. Diabetes was defined by any of the following criteria: self-reported physician diagnosis of diabetes; current use of insulin or oral hypoglycaemic agents; $FBG \geq 7.0 \text{ mmol/l}$ (126 mg/dl); random plasma glucose or 2-hour plasma glucose during an oral glucose tolerance test $\geq 11.1 \text{ mmol/l}$ (200 mg/dl); or glycated haemoglobin A1c (HbA1c) $\geq 6.5\%$. Hypertension was defined as a self-reported physician diagnosis of hypertension, current use of antihypertensive medications, or an average systolic blood pressure $\geq 140 \text{ mm Hg}$ or diastolic blood pressure $\geq 90 \text{ mm Hg}$. Estimated glomerular filtration rate (eGFR) was calculated using serum creatinine according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Inflammatory indices were calculated as follows: NLR, defined as the absolute neutrophil count divided by the absolute lymphocyte count; PLR, defined as the absolute platelet count divided by the absolute lymphocyte count; and PPN, calculated as the platelet count multiplied by the neutrophil count. All three inflammatory indices were log-transformed to reduce skewness and mitigate the influence of extreme values.

Statistical analysis

In accordance with NHANES analytic recommendations, survey sampling weights were appropriately applied, and the complex multistage sampling design was taken into consideration in all analyses. Continuous variables were presented as means $\pm$ standard deviations, whereas categorical variables were expressed as percentages. Participants were categorised according to tertiles of the TyG-ALB index. Group differences were compared using weighted Student's *t* tests for continuous variables and weighted χ^2 tests for categorical variables. To minimise the potential impact of sample size imbalance between the MGUS and non-MGUS groups on the stability of the results, multiple data processing and analytical strategies were employed. First, logistic regression models were used to evaluate the association between the TyG-ALB index and MGUS. Three models were constructed: Model 1 was unadjusted; Model 2 was adjusted for age and sex; and Model 3 was adjusted for age, sex, race/ethnicity, educational level, smoking status, drinking status, IPR, BMI, hypertension, diabetes, TC, HDL-C, and eGFR. In addition, we performed sensitivity analyses using progressively adjusted logistic regression models by sequentially adding nutritional factors, liver and kidney function markers, and major chronic comorbidities. To evaluate the potential influence of survey-period heterogeneity in MGUS ascertainment, we repeated the logistic regression analyses separately among participants from NHANES III and NHANES 1999–2004. In these period-specific analyses, TyG-ALB was modelled both as a continuous variable and according to tertiles, using the same covariate adjustment strategy as in the main analysis. Second, propensity score matching (PSM) was performed using a 1 : 3 nearest-neighbour matching algorithm to match participants with MGUS to those without MGUS. A caliper width of 0.05 was applied, defined as 0.05 standard deviations of the propensity score. Covariate balance after matching was assessed using standardised mean differences (SMDs), with an absolute value < 0.1 indicating good balance and values between 0.1 and 0.2 indicating moderate balance. The same statistical analyses were subsequently repeated in the matched cohort. Third, because MGUS was uncommon in the study population, with a prevalence of 2.58%, random oversampling was applied as a sensitivity analysis to address potential class imbalance and to examine the robustness of the association. This approach was used to reduce the potential influence of the small number of MGUS cases on model estimation and to assess whether the observed association was consistent after balancing the outcome distribution. The oversampling procedure was im-

plemented using the ROSE package. The results were expressed as odds ratios (OR) with 95% confidence intervals (CI).

Restricted cubic spline (RCS) analyses with three knots were conducted to explore potential nonlinear associations between the TyG-ALB index and the risk of MGUS. When evidence of nonlinearity was detected, a threshold (inflection point) was estimated, and two-piece logistic regression models were fitted on either side of the inflection point. Subgroup and interaction analyses were further performed according to age, sex, race/ethnicity, educational level, IPR, BMI, smoking status, drinking status, hypertension, and diabetes. Mediation analyses were conducted using the mediation package to evaluate the potential mediating effects of inflammatory markers, including the PLR, NLR, and PPN, on the association between the TyG-ALB index and MGUS. These analyses were adjusted for age, sex, race/ethnicity, educational level, smoking status, drinking status, IPR, BMI, hypertension, diabetes, TC, HDL-C, and eGFR.

All statistical analyses were performed using R software version 4.3.2. A two-sided *p*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 12,796 participants were included in the present analysis, of whom 6036 (47.67%) were male. The mean age of the study population was 46.92 ± 17.95 years, and 5492 (96.96%) participants were non-Hispanic White. Overall, 330 participants were diagnosed with MGUS, among whom 170 (51.52%) were male, with a mean age of 54.72 ± 19.32 years.

Baseline characteristics of participants stratified by tertiles of the TyG-ALB index are summarised in Table I. Participants with higher TyG-ALB levels were more likely to be older, male, and non-Hispanic White, and had a higher prevalence of obesity, former smoking, hypertension, and diabetes. In contrast, higher TyG-ALB levels were associated with lower levels of inflammatory markers and a lower prevalence of MGUS.

Association between the TyG-ALB index and MGUS

Three logistic regression models were constructed to examine the independent association between the TyG-ALB index and MGUS. In the fully adjusted model (Model 3), the multivariable-adjusted ORs and 95% CIs for MGUS across increasing tertiles of TyG-ALB were 1.00 (reference), 0.85 (0.64–1.12), and 0.68 (0.50–0.94), respectively. When TyG-ALB was treated as a continuous vari-

Table I. Characteristics of the study population with various TyG-ALB tertiles

Characteristic	TyG-ALB tertiles				P-value
	Total	T1	T2	T3	
Patient, <i>n</i>	12,796	4,231	4,265	4,300	
Age [years]	46.92 ±17.95	44.17 ±17.92	47.12 ±18.31	49.03 ±17.31	< 0.001
Sex, <i>n</i> (%)					< 0.001
Male	6,036 (47.67%)	1,243 (28.18%)	2,036 (46.27%)	2,757 (65.27%)	
Female	6,760 (52.33%)	2,988 (71.82%)	2,229 (53.73%)	1,543 (34.73%)	
Race, <i>n</i> (%)					< 0.001
Non-Hispanic White	5,492 (76.96%)	1,451 (69.50%)	2,034 (79.24%)	2,007 (80.95%)	
Non-Hispanic Black	3,149 (10.08%)	1,680 (17.99%)	911 (8.65%)	558 (4.89%)	
Mexican American	3,537 (5.29%)	920 (4.55%)	1,110 (4.71%)	1,507 (6.47%)	
Other	618 (7.67%)	180 (7.96%)	210 (7.39%)	228 (7.70%)	
IPR, <i>n</i> (%)					0.054
≤ 1.30	4,150 (19.12)	1,493 (21.86)	1,292 (18.01)	1,365 (17.93)	
1.3–3.5	5,385 (42.51)	1,749 (40.46)	1,814 (43.09)	1,822 (43.65)	
> 3.5	3,261 (38.37)	989 (37.68)	1,159 (38.90)	1,113 (38.42)	
BMI [kg/m ²]					< 0.001
Normal weight	4,815 (41.56%)	1,826 (49.85%)	1,708 (44.30%)	1,281 (31.95%)	
Overweight	4,314 (32.63%)	1,228 (26.91%)	1,401 (32.04%)	1,685 (37.96%)	
Obese	3,667 (25.82%)	1,177 (23.24%)	1,156 (23.65%)	1,334 (30.09%)	
Education level, <i>n</i> (%)					0.4
< High school	8,299 (52.75)	2,746 (53.59)	2,717 (51.58)	2,836 (53.19)	
≥ High school	4,497 (47.25)	1,485 (46.41)	1,548 (48.42)	1,464 (46.81)	
Smoking status, <i>n</i> (%)					0.01
Never	6,429 (50.92)	2,232 (53.31)	2,120 (50.05)	2,077 (49.78)	
Former	4,593 (32.46)	1,395 (29)	1,567 (33.46)	1,631 (34.35)	
Current	1,774 (16.62)	604 (17.69)	578 (16.49)	592 (15.86)	
Drinking status, <i>n</i> (%)					0.083
Never, <i>n</i> (%)	7,502 (52.89)	2,514 (53.74)	2,403 (52.66)	2,344 (52.39)	
Moder, <i>n</i> (%)	2,025 (18.10)	719 (20.09)	661 (17.22)	645 (17.30)	
Heavy, <i>n</i> (%)	3,269 (29.02)	910 (26.17)	1,124 (30.12)	1,235 (30.32)	
Hypertension, <i>n</i> (%)	5,343 (40.35)	1,419 (31.92)	1,782 (38.26)	2,142 (49.41)	< 0.001
Diabetes, <i>n</i> (%)	1,860 (11.78)	382 (6.97)	493 (9.29)	985 (18.22)	< 0.001
HbA1c, %	4.33 ±2.97	4.02 ±2.85	4.40 ±3.33	4.51 ±2.67	0.009
TG [mg/dl]	137.85 ±90.22	88.15 ±42.81	115.76 ±53.75	200.93 ±109.68	< 0.001
TC [mg/dl]	201.14 ±40.86	188.66 ±37.71	200.13 ±38.23	212.52 ±42.67	< 0.001
HDL [mg/dl]	51.92 ±15.57	57.25 ±15.76	53.30 ±15.15	46.12 ±13.82	< 0.001
eGFR [ml/(min·1.73 m ²)]	85.39 ±17.15	85.29 ±17.68	85.16 ±16.80	85.71 ±17.02	0.3
lg(NLR)	0.90 ±0.62	1.00 ±0.63	0.89 ±0.62	0.82 ±0.59	< 0.001
lg(PLR)	2.08 ±0.26	2.09 ±0.26	2.08 ±0.24	2.07 ±0.27	0.002
lg(PPN)	3.67 ±0.67	3.79 ±0.67	3.65 ±0.68	3.59 ±0.65	< 0.001
MGUS, <i>n</i> (%)	330 (2.37)	126 (2.68)	112 (2.46)	92 (2.02)	0.02

Data are presented as means ± standard deviations for continuous variables and unweighted numbers (weighted percentages) for categorical variables, unless otherwise specified. MGUS – monoclonal gammopathy of undetermined significance, BMI – body mass index, IPR – family income-to-poverty ratio, TG – triglycerides, TC – total cholesterol, HDL-C – high-density lipoprotein cholesterol, eGFR – estimated glomerular filtration rate, NLR – neutrophil-to-lymphocyte ratio, PLR – platelet-to-lymphocyte ratio, PPN – platelet–neutrophil product.

Table II. The associations between TyG-ALB and MGUS

TyG-ALB	Model 1		Model 2		Model 3	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
TyG-ALB (Continuous)	0.96 (0.93–0.98)	0.002	0.94 (0.91–0.97)	< 0.001	0.95 (0.92–0.98)	0.002
TyG-ALB						
T1	Ref.		Ref.		Ref.	
T2	0.88 (0.68–1.14)	0.326	0.77 (0.59–0.99)	0.046	0.85 (0.64–1.12)	0.247
T3	0.71 (0.54–0.93)	0.015	0.58 (0.44–0.77)	< 0.001	0.68 (0.50–0.94)	0.021

Model 1: No covariates were adjusted; Model 2: Age and sex were adjusted; Model 3: Age, sex, race, IPR, BMI, education level, smoking status, drinking status, hypertension, diabetes, TC, HDL-C, and eGFR were adjusted; OR – odds ratio, 95% CI – 95% confidence interval, BMI – body mass index, IPR – family income-to-poverty ratio, TC – total cholesterol, HDL-C – high-density lipoprotein cholesterol, eGFR – estimated glomerular filtration rate.

able, each one-unit increase in the TyG-ALB index was associated with 5% lower odds of MGUS (OR = 0.95, 95% CI: 0.92–0.98) (Table II). In additional sensitivity analyses, the inverse association between TyG-ALB and MGUS remained generally consistent after progressively adjusting for nutritional factors, liver and kidney function markers, and major chronic comorbidities (Supplementary Table SI). In period-specific sensitivity analyses, the inverse association between TyG-ALB and MGUS was generally consistent in direction in NHANES III and NHANES 1999–2004 (Supplementary Table SII). These findings suggest that the main association was not driven exclusively by one survey period, although residual heterogeneity in MGUS ascertainment cannot be excluded.

Adjusted association between TyG-ALB and MGUS after propensity score matching

PSM was performed using a 1 : 3 nearest-neighbour matching algorithm to balance baseline characteristics between the MGUS and non-MGUS groups. Figure 2 illustrates covariate bal-

ance before and after matching. After adjustment for potential confounders, an inverse association between the TyG-ALB index and MGUS risk remained evident. The multivariable-adjusted ORs (95% CIs) for MGUS across increasing TyG-ALB tertiles were 1.00 (reference), 1.07 (0.77–1.48), and 0.67 (0.46–0.98), respectively (Table III).

Adjusted association between TyG-ALB and MGUS after oversampling

Table IV presents the multivariable-adjusted associations between TyG-ALB and MGUS in the oversampled dataset. In the unadjusted model (Model 1), compared with the lowest tertile of TyG-ALB, participants in the second and third tertiles exhibited significantly lower odds of MGUS, with OR (95% CI) of 0.92 (0.87–0.98; $p = 0.008$) and 0.74 (0.70–0.79; $p < 0.001$), respectively. After adjustment for age and sex (Model 2), the inverse association became more pronounced, with OR (95% CI) of 0.84 (0.79–0.90; $p < 0.001$) for the second tertile and 0.62 (0.58–0.66; $p < 0.001$) for the highest tertile. In the fully adjusted model (Model 3), which further controlled for race/ethnicity, income, BMI, educational level, smoking and drinking status, hypertension, diabetes, TC, HDL-C, and eGFR, the negative association between TyG-ALB levels and MGUS risk remained statistically significant. Compared with the lowest tertile, the OR (95% CI) was 0.91 (0.86–0.97; $p = 0.006$) for the second tertile and 0.74 (0.68–0.79; $p < 0.001$) for the highest tertile.

Assessment of nonlinear associations

RCS analyses and penalised smoothing spline logistic regression models were applied to further investigate the potential nonlinear relationship between the TyG-ALB index and MGUS. As shown in Figure 3, TyG-ALB exhibited a significant nonlinear inverse association with MGUS odds. After evidence of nonlinearity was observed, a two-piece logistic regression model was used to identify the threshold value. An inflection point was identified

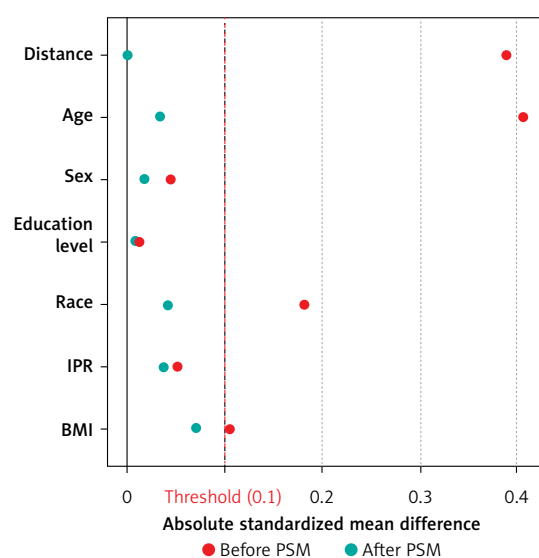


Figure 2. Standardised mean differences of covariates before and after propensity score matching

Table III. The associations between TyG-ALB and MGUS after PSM

TyG-ALB	Model 1		Model 2		Model 3	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
TyG-ALB (Continuous)	0.94 (0.91–0.97)	< 0.001	0.94 (0.91–0.97)	< 0.001	0.95 (0.91–0.98)	0.005
TyG-ALB						
T1	Ref.		Ref.		Ref.	
T2	0.93 (0.68–1.25)	0.611	0.91 (0.67–1.24)	0.549	1.07 (0.77–1.48)	0.704
T3	0.58 (0.42–0.78)	0.001	0.56 (0.41–0.78)	0.001	0.67 (0.46–0.98)	0.039

Model 1: No covariates were adjusted; Model 2: Age and sex were adjusted; Model 3: Age, sex, race, IPR, BMI, education level, smoking status, drinking status, hypertension, diabetes, TC, HDL-C, and eGFR were adjusted; OR – odds ratio, 95% CI – 95% confidence interval, BMI – body mass index, IPR – family income-to-poverty ratio, TC – total cholesterol, HDL-C – high-density lipoprotein cholesterol, eGFR – estimated glomerular filtration rate.

Table IV. Association between TyG-ALB and MGUS after resampling

TyG-ALB	Model 1		Model 2		Model 3	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
T1	Ref.		Ref.		Ref.	
T2	0.92 (0.87–0.98)	0.008	0.84 (0.79–0.90)	< 0.001	0.91 (0.86–0.97)	0.006
T3	0.74 (0.70–0.79)	< 0.001	0.62 (0.58–0.66)	< 0.001	0.74 (0.68–0.79)	< 0.001

Model 1: No covariates were adjusted; Model 2: Age and sex were adjusted; Model 3: Age, sex, race, IPR, BMI, education level, smoking status, drinking status, hypertension, diabetes, TC, HDL-C, and eGFR were adjusted; OR – odds ratio, 95% CI – 95% confidence interval, BMI – body mass index, IPR – family income-to-poverty ratio, TC – total cholesterol, HDL-C – high-density lipoprotein cholesterol, eGFR – estimated glomerular filtration rate.

at a TyG-ALB value of 36.0 (log-likelihood ratio test, $p < 0.05$).

Multivariable logistic regression analyses demonstrated that participants with TyG-ALB values ≥ 36.0 had lower odds of MGUS compared with those below the inflection point (OR = 0.79, 95% CI: 0.75–0.83). Stratified analyses conducted on either side of the inflection point consistently

showed an inverse association between increasing TyG-ALB levels and MGUS odds, in line with the primary findings (Table V).

Subgroup analyses

Subgroup analyses demonstrated generally consistent associations across strata defined by

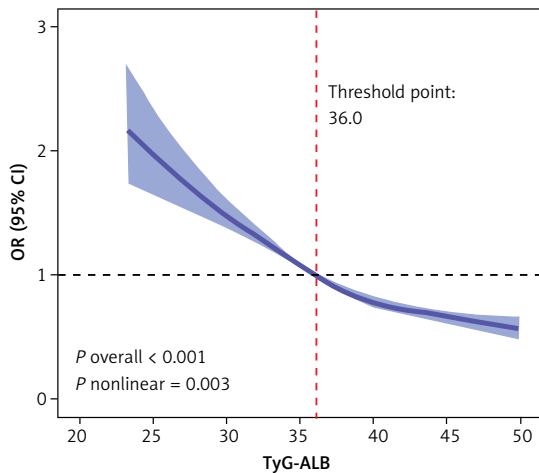


Figure 3. Association between TyG-ALB and MGUS. Models for MGUS were adjusted for age, sex, race/ethnicity, educational level, smoking status, drinking status, family income-to-poverty ratio, body mass index, hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol, and estimated glomerular filtration rate. Wide confidence intervals at higher TyG-ALB values indicate lower precision due to fewer participants

Table V. Threshold effect analysis of the association between TyG-ALB and MGUS

TyG-ALB	OR (95% CI)	P-value
TyG-ALB		
< 36.0	Ref.	
≥ 36.0	0.79 (0.75–0.83)	< 0.001
TyG-ALB < 36.0		
T1	Ref.	
T2	0.78 (0.71–0.85)	< 0.001
T3	0.81 (0.73–0.89)	< 0.001
TyG-ALB ≥ 36.0		
T1		
T2	0.65 (0.59–0.71)	< 0.001
T3	0.7 (0.64–0.77)	< 0.001

Age, sex, race, IPR, BMI, education level, smoking status, drinking status, hypertension, diabetes, TC, HDL-C, and eGFR were adjusted; OR – odds ratio, 95% CI – 95% confidence interval.

age, sex, race/ethnicity, educational level, BMI, smoking status, drinking status, hypertension, and diabetes. However, no statistically significant association was observed in participants with higher income levels ($IPR > 3.5$). Notably, a significant interaction was detected in race/ethnicity-stratified analyses, indicating that the inverse association between TyG-ALB and MGUS was more pronounced among racial/ethnic groups other than non-Hispanic White (Figure 4).

Mediation analyses

Exploratory mediation analyses were conducted to assess the potential mediating roles of composite inflammatory markers in the association between TyG-ALB and MGUS. As illustrated in Figure 5, the estimated mediated proportions were 0.93% for PLR, 5.94% for NLR, and 1.85% for PPN. Although NLR showed the largest estimated mediated proportion among the three markers, the overall magnitude of mediation was modest. These findings suggest only limited mediation by systemic inflammatory markers and should be interpreted cautiously.

Discussion

In this population-based study of U.S. adults, we demonstrated that higher TyG-ALB levels were significantly and inversely associated with the odds of MGUS. This association was supported by multiple analytical approaches, including multivariable adjustment, propensity score matching, oversampling analysis, and nonlinear modelling.

We further identified a nonlinear relationship between TyG-ALB and MGUS, characterised by a decline in the odds of MGUS with increasing TyG-ALB values followed by a plateau beyond a specific threshold. This finding suggests that lower TyG-ALB levels may be more strongly associated with MGUS, whereas additional increases above the threshold may be associated with limited incremental change. Such a pattern may reflect a saturation effect, although the underlying explanation remains uncertain. Similar nonlinear associations between metabolic indices and disease outcomes have been reported in previous studies [22, 23]. The inflection point at a TyG-ALB value of 36.0 should be interpreted as a data-derived statistical threshold rather than a clinically validated cutoff.

Subgroup	OR (95% CI)	P-value	P for interaction
Sex			0.526
Male	0.95 (0.94–0.96)	< 0.001	
Female	0.95 (0.94–0.95)	< 0.001	
Age			0.226
≤ 60	0.95 (0.95–0.96)	< 0.001	
> 60	0.94 (0.92–0.95)	< 0.001	
Race			0.028
Non-Hispanic White	0.91 (0.90–0.92)	< 0.001	
Others	0.96 (0.95–0.97)	< 0.001	
Education level			0.125
Less than high school	0.94 (0.93–0.94)	< 0.001	
College or above	0.95 (0.94–0.96)	< 0.001	
Family income–poverty ratio			< 0.001
≤ 3.5	0.93 (0.92–0.93)	< 0.001	
> 3.5	0.99 (0.98–1.01)	0.268	
BMI			0.365
≤ 30	0.94 (0.93–0.95)	< 0.001	
> 30	0.95 (0.94–0.96)	< 0.001	
Smoking status			0.950
Never	0.93 (0.92–0.94)	< 0.001	
Former/Current	0.96 (0.95–0.97)	< 0.001	
Drink status			0.421
Never	0.94 (0.94–0.95)	< 0.001	
Moder/Heavy	0.94 (0.93–0.95)	< 0.001	
Hypertension			0.070
No	0.95 (0.94–0.95)	< 0.001	
Yes	0.94 (0.93–0.95)	< 0.001	
Diabetes			0.671
No	0.95 (0.94–0.96)	< 0.001	
Yes	0.91 (0.89–0.93)	< 0.001	

Figure 4. Subgroup analysis for the association between the TyG-ALB index and the risk of MGUS. Models for MGUS were adjusted for age, sex, race/ethnicity, educational level, smoking status, drinking status, family income-to-poverty ratio, body mass index, hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol, and estimated glomerular filtration rate

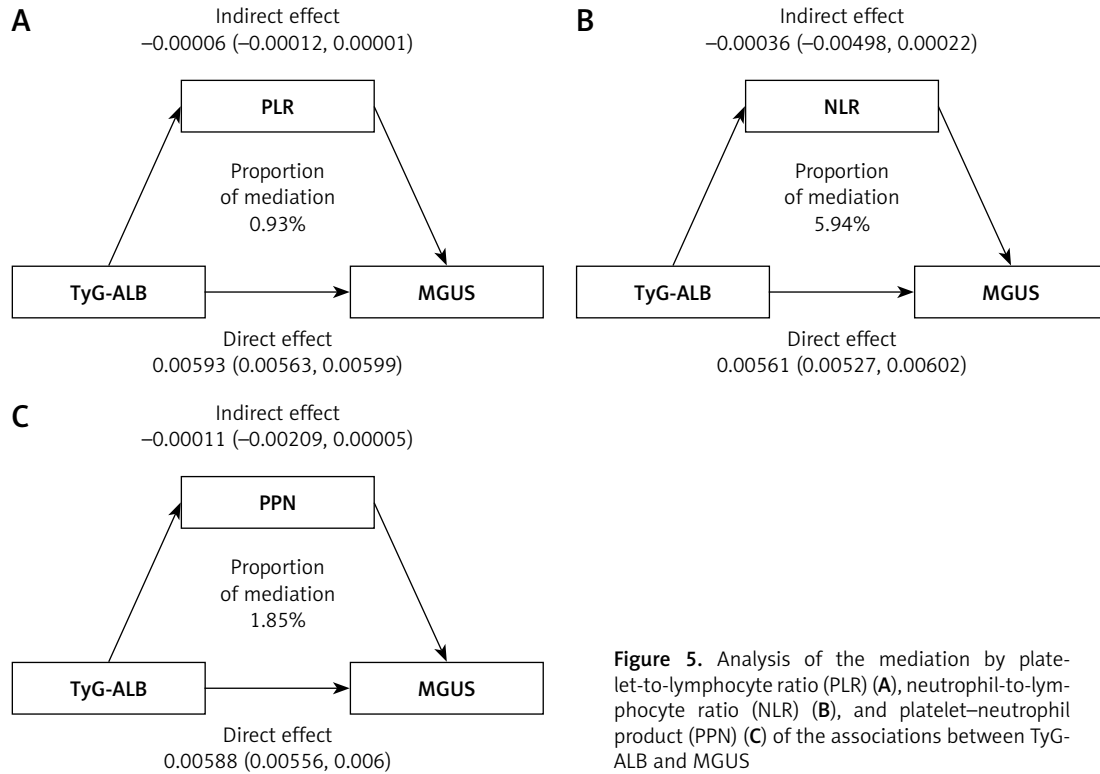


Figure 5. Analysis of the mediation by platelet-to-lymphocyte ratio (PLR) (A), neutrophil-to-lymphocyte ratio (NLR) (B), and platelet–neutrophil product (PPN) (C) of the associations between TyG-ALB and MGUS

Because TyG-ALB integrates both triglyceride–glucose burden and serum albumin, this value may reflect a transition in the combined metabolic–nutritional profile rather than an isolated change in insulin resistance or albumin status alone. Therefore, this threshold helps describe the nonlinear association observed in the present dataset but should not be used as a clinical decision threshold without validation in independent cohorts.

The TyG index, a well-established surrogate marker of insulin resistance, has been associated with a wide range of cardiometabolic conditions. Previous studies have demonstrated that higher TyG levels and related indices are associated with hypertension, diabetes, metabolic syndrome, atrial fibrillation, heart failure, atherosclerosis, stroke, cardiovascular disease, malignancy, and all-cause mortality [24–28]. In our analysis, when TyG was considered alone, its association with MGUS was broadly consistent with prior evidence linking metabolic dysfunction to adverse health outcomes. However, when the composite TyG-ALB index was examined, we observed an inverse association with MGUS. This finding appears counterintuitive and contrasts with previous reports suggesting positive associations between metabolic syndrome and MGUS.

One possible explanation lies in the role of serum albumin. Albumin is the most abundant plasma protein and a key indicator of nutritional status [29]. It plays important roles in maintaining oncotic pressure, transporting endogenous

and exogenous substances, and supporting metabolic homeostasis [30]. Serum albumin has also been recognised as a clinically relevant biomarker in various diseases, including cancer, rheumatoid arthritis, ischaemic diseases, postmenopausal obesity, severe acute graft-versus-host disease, and disorders requiring glycaemic monitoring [29, 31–33]. Previous studies have shown that hypoalbuminaemia is common in patients with chronic diseases and is strongly associated with adverse outcomes [34]. Within the TyG-ALB index, albumin may therefore reflect the importance of nutritional, inflammatory, and immune status [35]. Higher TyG-ALB values generally indicate higher serum albumin levels, suggesting better nutritional reserve and lower systemic inflammation, which is consistent with the observed lower prevalence of MGUS. Conversely, reduced albumin levels, leading to lower TyG-ALB values, may reflect chronic inflammation, malnutrition, or more severe chronic illness, conditions that may be more favourable for clonal plasma cell expansion.

The inverse association between TyG-ALB and MGUS is biologically counterintuitive if TyG-ALB is interpreted as a simple insulin-resistance marker. However, TyG-ALB is a composite index in which serum albumin contributes substantially to the final value. Higher albumin may reflect better nutritional reserve and lower systemic inflammatory burden, whereas lower albumin may indicate chronic illness, inflammation, or poorer nutritional status. Therefore, the observed inverse associa-

tion may be partly related to the albumin-related component rather than to a protective effect of insulin resistance. This interpretation remains speculative because the present cross-sectional analysis cannot establish temporal ordering or formally distinguish the independent contribution of albumin from the TyG component.

Exploratory mediation analyses further suggested that systemic inflammatory markers might partially account for the association between TyG-ALB and MGUS. However, the estimated mediated proportions for PLR, NLR, and PPN were small, ranging from 0.93% to 5.94%. Therefore, these findings should be interpreted cautiously and regarded as hypothesis-generating rather than confirmatory evidence of a causal pathway. Mechanistically, insulin resistance can promote chronic low-grade inflammation by inducing pro-inflammatory cytokines such as tumour necrosis factor- α and interleukin-6, which may support clonal plasma cell survival and proliferation [16]. Meanwhile, hypoalbuminaemia reflects both nutritional deficiency and inflammatory activation, further amplifying a pro-inflammatory milieu. The limited mediation observed for NLR, PLR, and PPN is consistent with the possibility that systemic inflammation may contribute to, but does not fully explain, the association between TyG-ALB and MGUS.

Several strengths of this study should be acknowledged. First, the use of NHANES data provides a large population-based sample of U.S. adults. Second, MGUS was assessed using serum protein electrophoresis, immunofixation, and free light chain assays, improving outcome ascertainment. Third, the application of multiple analytical approaches, including multivariable logistic regression, propensity score matching, oversampling analysis, restricted cubic spline modelling, subgroup analysis, and sensitivity analyses, strengthened the robustness of the findings.

Nevertheless, several limitations should be considered. First, a primary limitation of this study is that the analysis was based on a single, publicly available cross-sectional NHANES dataset and lacked an independent validation cohort. Therefore, although NHANES provides a large population-based sample, the generalisability and reproducibility of the observed associations require confirmation in independent cohorts. In addition, although we performed multiple sensitivity analyses, these approaches cannot replace external validation in an independent prospective cohort. Second, because of the cross-sectional design, causal inference cannot be established, and reverse causation cannot be excluded. Third, TyG-ALB, inflammatory markers, and MGUS status were measured at a single time point; therefore, the temporal sequence required for causal mediation cannot be determined. Although the

albumin-related component provides a plausible explanation for the inverse association, this interpretation remains speculative because no formal component-specific mediation or decomposition analysis was performed to separate the independent contribution of serum albumin from the TyG component. Fourth, although extensive adjustments were made, residual confounding remains possible. In particular, previous studies have reported inconsistent findings regarding the association between diabetes and plasma cell disorders, with several studies reporting no significant relationship [36–38]. Differences in study populations, diabetes definitions, disease duration, glycaemic control, medication use, and adjustment strategies may partly explain these discrepancies. Although diabetes was included as a covariate in our models, detailed information on diabetes severity, duration, and treatment status was limited; therefore, residual confounding related to diabetes cannot be fully excluded. Fifth, potential survey-period heterogeneity in MGUS ascertainment should be considered. Although MGUS testing followed a documented protocol involving serum protein electrophoresis, immunofixation electrophoresis, and serum free light chain testing at Mayo Clinic, NHANES III and NHANES 1999–2004 were conducted during different time periods; therefore, differences in sample collection, storage duration, laboratory implementation, or assay interpretation may have introduced residual heterogeneity. We addressed this issue by conducting period-specific sensitivity analyses in NHANES III and NHANES 1999–2004 separately, which showed generally consistent directions of association. Nevertheless, residual ascertainment heterogeneity remains possible. Finally, the study population consisted primarily of U.S. adults, which may limit the generalisability of the findings to other populations.

In conclusion, higher TyG-ALB levels were inversely associated with the odds of prevalent MGUS in a nationally representative U.S. population. This association was nonlinear and remained generally consistent across multiple sensitivity analyses. However, because this study was cross-sectional and lacked an independent validation cohort, the findings should be interpreted as hypothesis-generating rather than confirmatory and should not be considered evidence of causality or clinical risk stratification. Prospective studies with independent validation cohorts are needed to confirm these findings, establish temporality, and clarify the underlying mechanisms.

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Ethical approval

All survey procedures were reviewed and approved by the Ethics Review Board of the National Center for Health Statistics, and written informed consent was obtained from all participants prior to participation.

Conflict of interest

The authors declare no conflict of interest.

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