Neuroendocrinology Letters Volume 46 No. 8 2025
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Association between inflammatory biomarkers and type 2 diabetes in adults aged ≥40 years: A cross-sectional study.

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Submitted: 2025-12-01 Accepted: 2025-12-30 Published online: 2025-12-30

Key words: **Diabetes; Inflammation; Biomarkers; Cross-sectional study; Adult; Type 2 Diabetes Mellitus (T2DM); Inflammatory markers; Insulin resistance**

Neuroendocrinol Lett 2025; **46**(8):428–440 **PMID:** 41619294 460801 © 2025 Neuroendocrinology Letters • **www.nel.edu**

Abstract

BACKGROUND: Research confirms that inflammatory responses play a significant role in the pathogenesis of type 2 diabetes mellitus (T2DM). However, existing studies primarily rely on single or traditional inflammatory markers. The diagnostic value of emerging composite inflammatory markers, such as the platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and others, remains unclear in Chinese populations aged ≥40 years. This study aims to investigate the association between these novel inflammatory markers and T2DM in this age group. This study aims to investigate the association between these novel inflammatory markers and T2DM in Chinese adults aged 40 years and older.

METHODS: Data were obtained from the Health Examination Center of the First Affiliated Hospital of Wannan Medical College in Wuhu City, China. Nine inflammatory markers were derived from complete blood counts. Multivariate logistic regression models were employed to assess the association between inflammatory markers and T2DM. Subgroup analyses were conducted to validate the robustness of the findings.

RESULTS: Among 194,348 participants (31,951 with T2DM, 162,397 controls), individuals with T2DM exhibited significantly elevated levels of MHR, NLR, SII, SIRI, AISI, and TyG ($p < 0.001$ for all), while PLR and PNR exhibited inverse associations ($p < 0.001$). In fully adjusted models, the highest tertile versus lowest tertile showed ORs of 7.20 (95% CI: 6.92-7.50) for TyG, 1.71 (1.64-1.79) for AISI, and 0.62 (0.60-0.65) for PNR. LMR showed no linear trend after full adjustment (p for trend = 0.301). Medication data were incomplete, precluding assessment of whether anti-inflammatory drug use (statins, aspirin) influenced these associations. Subgroup analyses revealed effect modification by age, sex, BMI, and hypertension for PLR, PNR, and TyG indices (p for interaction < 0.05).

CONCLUSIONS: Elevated inflammatory markers in patients with T2DM are associated with prevalent diabetes in this cross-sectional analysis. The temporal relationship between inflammation and T2DM development cannot be determined from this study design. These readily available inflammatory markers may hold value for diabetes risk assessment.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common chronic disease clinically characterized by endocrine and metabolic disorders. Since the early 21st century, the number of T2DM patients has been steadily increasing. Current research indicates that by 2045, an estimated 700 million people will be affected by diabetes (Tinajero & Malik 2021). In China, T2DM is the most prevalent chronic metabolic disorder, severely impairing patients' quality of life and imposing a substantial health and economic burden.

T2DM primarily develops from unhealthy lifestyles and dietary habits, characterized by insulin resistance (IR), progressive pancreatic β-cell dysfunction, and chronic low-grade inflammation (Rohm *et al.* 2022). Insulin maintains glucose homeostasis through various physiological responses in tissues such as the liver, skeletal muscle, and adipose tissue. The progression of IR leads to impaired glucose metabolism, causing hyperglycemia and the subsequent onset of diabetes. In severe cases, this may evolve into multi-organ complications, including cardiovascular disease and diabetic nephropathy (Hamblin *et al.* 2025). Chronic low-grade inflammation is central to the development of IR and metabolic dysfunction (Mehdi *et al.* 2023; Lan *et al.* 2025) , thereby playing a crucial role in the pathogenesis of T2DM (Luo *et al.* 2024). Specifically, cytokines and molecular pathways disrupt insulin signalling in the liver, skeletal muscle, and adipose tissue, leading to metabolic dysfunction that significantly impacts disease progression and complications. Persistent inflammation also impairs pancreatic β-cell function, preventing compensation for insulin demand during IR. Thus, systemic inflammation promotes T2DM development through a synergistic pathway involving both impaired insulin action and β-cell destruction (Donath & Shoelson 2011).

Given that systemic inflammation plays a crucial role in the pathogenesis of T2DM, a series of systemic inflammatory markers based on conventional complete blood counts (CBC) has emerged from the aforementioned pathophysiological mechanisms. Compared to traditional single-marker inflammation indicators such as C-reactive protein, white blood cell count, or interleukins, these novel markers not only provide a more comprehensive reflection of interactions among different immune cell subsets and systemic inflammatory states but also serve as reliable surrogate indicators for assessing systemic inflammation. Examples include the platelet-lymphocyte ratio (PLR), monocyte-to-high-density lipoprotein ratio (MHR), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (LMR), platelet-to-neutrophil ratio (PNR), systemic immune inflammation index (SII), acute inflammatory syndrome index (AISI), and systemic inflammatory response index (SIRI). This approach offers a cost-effective method for comprehensively assessing systemic inflammatory status without imposing additional financial burdens on patients, facilitating multidimensional clinical evaluation while demonstrating potential predictive value for cardiovascular events and all-cause mortality risk in diabetic patients.

Although associations between novel inflammatory markers and diabetes have been documented, their clinical significance in middle-aged and older Chinese adults remains understudied.. Therefore, this study investigates the relationship between novel inflammatory markers, including PLR, MHR, NLR, LMR, PNR, SII, SIRI, AISI, and TyG and diabetes in adults aged 40 years and older. The aim is to provide evidence for the prevention, diagnosis, and stratified management of diabetes in clinical practice.

METHODS

Study subjects

This study is a retrospective review, with all participants enrolled between 2011 and 2016 at the Health Examination Centre of the First Affiliated Hospital of Wannan Medical College in Wuhu, China. A total of 194,348 individuals participated in this study, among whom 31,951 had T2DM, accounting for 16.44%. Clinical and demographic information was collected, including age, gender, smoking and drinking habits. The inclusion criteria were as follows: (1) participants aged 18-90 years, (2) available data on their gender, age, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglyceride (TG), fasting plasma glucose (FPG), white blood cells (WBC), neutrophils, lymphocytes, monocytes and platelet (PLT) count. Exclusion criteria include: (1) lack of essential data for analysis; (2) patients with malignant tumors, active infections, or severe hematological diseases. All participants underwent physical examinations, blood biochemistry and blood tests. This research adhered to the Helsinki guidelines of the World Medical Association's Declaration of Helsinki and received approval from the Ethical Committee of a Medical College. Verbal informed consent was obtained from all participants before the survey.

Questionnaire data collection

The research participants' baseline information includes general data, such as gender, age, and occupation. Medical history information includes hypertension, diabetes, abnormal lipid levels or kidney disease,

gout, and cancer. Medication use (antihypertensive, antidiabetic, and lipid-lowering drugs) was assessed via self-reported questionnaires. Sensitivity analyses stratified by anti-inflammatory medication use (statins, aspirin, NSAIDs) were not feasible due to data availability constraints. Additionally, lifestyle habits, such as smoking history and frequency, alcohol consumption history and frequency, dietary habits, and weekly exercise duration, have been collected and organized. Smoking and alcohol consumption were classified as behavioral characteristics using the following categories: (1) never: no use in the past year; (2) occasional: 1-2 days/times per week; (3) frequent: ≥3 days/times per week. Information about severe infections, cardiovascular diseases, major surgeries, medication, and cancer was contained in the column of history of the disease.

Laboratory measurements and inflammatory marker calculation

White blood cell, neutrophil, lymphocyte, monocyte, and platelet counts were extracted from the complete blood count results. Inflammatory markers were calculated as follows: platelet-to-lymphocyte ratio (PLR) = platelet count / lymphocyte count; monocyte-to-high-density lipoprotein cholesterol ratio (MHR) = monocyte count / high-density lipoprotein cholesterol level; neutrophil-to-lymphocyte ratio (NLR) = neutrophil count / lymphocyte count; lymphocyte-to-monocyte ratio (LMR) = lymphocyte count / monocyte count; platelet-to-neutrophil ratio (PNR) = platelet count / neutrophil count; systemic immune-inflammation index (SII) = (platelet count × neutrophil count) / lymphocyte count; systemic inflammation response index (SIRI) = (monocyte count × neutrophil count) /

Tab. 1. Baseline Characteristics of Participants Aged 40 Years and Older, Stratified by T2DM Status

Characteristics	Overall	Non-diabetes	Diabetes	*p* value
N	194,348	162,397(83.56%)	31,951(16.44%)	
Sex (%)				<0.01
Male	115,780(59.27)	92,606(57.02)	22,672(70.96)	
female	79,070(40.73)	69,791(42.98)	9,279(29.04)	
FPG (mmol/L)	5.56±1.25	5.18±1.46	7.50±1.98	<0.01
Age(year)	55.05±10.20	54.22±9.92	59.30±17.94	<0.01
SBP (mmHg)	122.64±17.48	121.23±17.03	129.81±17.94	<0.01
DBP (mmHg)	79.11±10.10	78.56±9.99	81.90±10.21	<0.01
BMI	24.23±3.06	24.00±2.99	25.40±3.15	<0.01
WBC(×10^3/μL)	6.29±1.62	6.22±1.60	6.65±1.67	<0.01
Neutrophil number(×10^3/μL)	3.68±1.23	3.63±1.21	3.94±1.29	<0.01
Lymphocyte number(×10^3/μL)	2.02±1.61	2.00±0.60	2.09±0.65	<0.01
Monocyte number(×10^3/μL)	0.43±0.15	0.42±0.15	0.45±0.16	<0.01
PLT(×10^9/L)	182.57±53.75	183.06±53.71	180.08±53.87	<0.01
TG (mmol/L)	1.68±1.28	1.60±1.15	2.10±1.73	<0.01
HDL-C (mmol/L)	1.39±0.36	1.40±0.36	1.33±0.34	<0.01
Smoke (%)				<0.01
Never	138,508(71.27)	116,771(71.90)	21,737(68.03)	
Occasionally	46,241(23.79)	37,701(23.22)	8,540(26.73)	
Frequently	9,599(4.94)	7,925(4.88)	1,674(5.24)	
Drink (%)				<0.01
Never	125,555(64.60)	107,123(65.96)	18,432(57.69)	
Occasionally	22,404(11.53)	17,493(10.77)	4,911(15.37)	
Frequently	46,389(23.87)	37,781(23.26)	8,608(26.94)	
Operation (%)				<0.01
Yes	38,990(20.06)	31,373(19.32)	7,617(23.84)	
No	155,358(79.94)	131,024(80.68)	24,334(76.16)	

Data are expressed as number (percentage) and mean±SD. Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; PLT, platelet; SBP, systolic blood pressure; TG, triglycerides; WBC, white blood cell count.

Tab. 2. Comparison of blood inflammatory indices between the DM group and the non-DM group

Index	Overall (n = 194,348)	Non-diabetes (n = 162,397)	Diabetes (n = 31,951)	*p* value
log2-PLR	6.51(6.17-6.84)	6.52(6.18-6.85)	6.43(6.09-6.77)	<0.001
log2-MHR	-1.70(-2.15--1.26)	-1.72(-2.18--1.29)	-1.58(-2.0--1.15	<0.001
log2-NLR	0.84(0.49-1.20)	0.83(0.48-1.19)	0.88(0.53-1.25)	<0.001
log2-LMR	2.23(1.91-2.56)	2.24(1.91-2.56)	2.22(1.89-2.55)	<0.001
log2-PNR	5.66(5.27-6.03)	5.68(5.30-6.05)	5.54(5.16-5.91)	<0.001
log2-SII	8.30(7.86-8.74)	8.30(7.86-8.74)	8.31(7.88-8.77)	<0.001
log2-SIRI	-0.44(-0.94-0.07)	-0.46(-0.96-0.04)	-0.33(-0.82-0.18)	<0.001
log2-AISI	7.02(6.42-7.62)	7.01(6.40-7.60)	7.11(6.51-7.70)	<0.001
log2-TyG	3.12(3.05-3.19)	3.10(3.04-3.17)	3.20(3.13-3.26)	<0.001

Data are expressed as median (interquartile range). All inflammatory markers were log2-transformed.

lymphocyte count; aggregate index of systemic inflammation (AISI) = (neutrophil count × monocyte count × platelet count) / lymphocyte count; triglyceride-glucose index (TyG) = ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2], based on previous studies.

Covariates

Based on clinical practice and prior research, we considered the potential influence of covariates on the relationship between inflammatory markers and type 2 diabetes. Included covariates comprised gender, age, BMI, blood pressure levels, smoking, and alcohol consumption. Subsequently, based on clinical experience, the following categories were established: Age (<40 years; ≥40 years); BMI (<28 kg/m^2; ≥28 kg/m^2); Blood Pressure (Normal: SBP <140 mmHg and DBP <90 mmHg; Hypertension: SBP ≥140 mmHg or DBP ≥90 mmHg); Smoking (Yes: smoked at least one day per week; No: no smoking in the past year); Alcohol consumption (Yes: drank alcohol more than once per week; No: no alcohol consumption in the past year); Surgical history (Yes; No).

Physical examination

Under the guidance of the WHO and the International Society of Hypertension (1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee 1999), trained nurses measure height, weight, and blood pressure using standard methods. Participants wore light clothing without shoes for height and weight measurements. Blood pressure was measured using a standardized electronic or mercury sphygmomanometer on the upper arm after participants rested quietly for 5 minutes. The Body Mass Index (BMI) is calculated by dividing the weight (kg) by the square of the height (m).

Biochemical assays

Blood samples are drawn from subjects who have fasted for more than 8 hours by professional nurses to test the following items: fasting plasma glucose (FPG), white blood cells (WBC), triglyceride (TG), neutrophils, lymphocytes, monocytes, platelet (PLT) count and high-density lipoprotein cholesterol (HDL-C).

Statistical analysis

With 31,951 diabetes cases and 162,397 controls, this study achieves >99% statistical power to detect odds ratios ≥1.10 at α = 0.05 (two-tailed), assuming 20% exposure prevalence in controls. This sample size provides robust precision for detecting small-to-moderate associations between inflammatory markers and T2DM. Data are expressed as mean ± standard deviation (SD) and frequency (%). Continuous variables were compared using t-tests, while categorical variables were analyzed using chi-square tests. Due to the skewed distribution of inflammatory markers, they underwent log2 transformation and were categorized into three quantiles (Q1, Q2, Q3) to compare baseline characteristics between the DM and non-DM groups. Multivariate logistic regression was subsequently employed to investigate the relationship between inflammatory markers and DM, adjusting for relevant confounding factors. Subgroup analyses were conducted to assess consistency of associations across different subgroups. All data were analyzed using SPSS 18.0 and R software (V.4.3.1). Given the exploratory nature of examining nine inflammatory markers simultaneously, we report unadjusted *p*-values with $p < 0.05$ considered nominally significant. Bonferroni-corrected significance threshold is $p < 0.0056$ (0.05/9 markers). Markers meeting this stringent threshold demonstrate robust associations less likely attributable to chance. We acknowledge that multiple testing inflates Type I error risk; findings require replication in independent cohorts.

RESULTS

Characteristics of participants

Compared with the non-DM group, the DM group exhibited significantly higher mean age (59.30±17.94

Tab. 3. Association of continuous/categorical inflammatory markers with the risk of DM

Marker	Model1		Model2		Model3	
	OR (95%)	*p*	OR (95%)	*p*	OR (95%)	*p*
log2-PLR						
Q1[<6.29)	REF		REF		REF	
Q2[6.29-6.72)	0.80(0.78-0.83)	<0.001†	0.87(0.85-0.90)	<0.001†	0.91(0.88-0.93)	<0.001†
Q3[>6.72]	0.69(0.67-0.71)	<0.001†	0.79(0.77-0.82)	<0.001†	0.86(0.84-0.90)	<0.001†
p for trend		<0.001†		<0.001†		<0.001†
log2-MHR						
Q1[<-1.99)	REF		REF		REF	
Q2[-1.99--1.42)	1.28(1.24-1.32)	<0.001†	1.17(1.13-1.20)	<0.001†	1.03(0.99-1.06)	0.135
Q3[>-1.42]	1.63(1.58-1.68)	<0.001†	1.36(1.32-1.40)	<0.001†	1.09(1.06-1.13)	<0.001†
p for trend		<0.001†		<0.001†		0.176
log2-NLR						
Q1[<0.62)	REF		REF		REF	
Q2[0.62-1.07)	1.08(1.05-1.11)	<0.001†	1.09(1.06-1.12)	<0.001†	1.08(1.05-1.12)	<0.001†
Q3[>1.07]	1.24(1.20-1.27)	<0.001†	1.17(1.14-1.21)	<0.001†	1.21(1.17-1.25)	<0.001†
p for trend		<0.001†		<0.001†		<0.001†
log2-LMR						
Q1[<2.03)	REF		REF		REF	
Q2[2.03-2.44)	0.90(0.87-0.93)	<0.001†	1.03(1.00-1.06)	0.085	0.97(0.94-1.10)	0.040‡
Q3[>2.44]	0.90(0.88-0.93)	<0.001†	1.11(1.08-1.15)	<0.001†	1.02(0.99-1.05)	0.262
p for trend		<0.001†		<0.001†		0.301
log2-PNR						
Q1[<5.42)	REF		REF		REF	
Q2[5.42-5.90)	0.77(0.75-0.79)	<0.001†	0.84(0.81-0.86)	<0.001†	0.85(0.82-0.87)	<0.001†
Q3[>5.90]	0.57(0.55-0.58)	<0.001†	0.67(0.65-0.69)	<0.001†	0.71(0.69-0.74)	<0.001†
p for trend		<0.001†		<0.001†		<0.001†

vs. 54.22±9.92 years) and BMI (25.40±3.15 vs. 24.00±2.99 kg/m^2, both $p < 0.01$) (Table 1). Significant differences were observed between the two groups in white blood cell count, neutrophil count, and lymphocyte count ($p < 0.01$) (Table 1). Table 2 shows significant differences between the DM and non-DM groups in log2-PLR, log2-MHR, log2-NLR, log2-LMR, log2-PNR, log2-SII, log2-SIRI, log2-AISI, and log2-TyG ($p < 0.001$) (Table 2).

Relationships between inflammatory markers and DM

Table 3 presents inflammatory markers categorized into tertiles (Q1-Q3) based on quantile cutoff points, with Q1 as the reference. Most inflammatory markers demonstrated significant positive associations with diabetes risk, while log2-PLR and log2-PNR exhibited inverse associations. The log2-TyG index demonstrated the strongest positive association. In the fully adjusted model, the middle quartile of log2-TyG showed a significant positive association with DM ($p < 0.001$). This trend was also observed for log2-NLR, log2-SII, log2-SIRI, and log2-AISI ($p < 0.001$). And log2-SII was not significant in Model 1 but became significantly positively correlated after adjusting for confounders (Models 2 and 3), indicating that the observed association may have been obscured by other variables. After full adjustment for confounders including age, BMI, and hypertension, the lymphocyte-to-monocyte ratio (LMR) did not demonstrate a significant linear trend with diabetes risk (p for trend = 0.301), despite elevation in bivariate comparisons (Table 2). This suggests the crude association may be confounded by demographic and metabolic factors rather than representing an independent effect. Although the intermediate risk group showed a slight decrease, the overall association pattern was inconsistent, and the effect was weak. Results demonstrate that LMR is not associated with diabetes as an independent risk factor, and its association with early manifestations may be related to the influence of other metabolic factors. Similarly, this

Marker	Model1		Model2		Model3	
	OR (95%)	*p*	OR (95%)	*p*	OR (95%)	*p*
log2-SII						
Q1[<8.02)	REF		REF		REF	
Q2[8.02-8.59)	1.02(0.99-1.05)	0.177	1.08(1.04-1.11)	<0.001†	1.05(1.02-1.09)	0.001†
Q3[>8.59]	1.09(1.09-1.12)	<0.001†	1.18(1.14-1.21)	<0.001†	1.17(1.14-1.21)	<0.001†
p for trend		<0.001†		<0.001†		<0.001†
log2-SIRI						
Q1[<-0.76)	REF		REF		REF	
Q2[-0.76--0.12)	1.22(1.18-1.25)	<0.001†	1.14(1.11-1.18)	<0.001†	1.10(1.06-1.13)	<0.001†
Q3[>-0.12]	1.46(1.42-1.51)	<0.001†	1.25(1.21-1.28)	<0.001†	1.20(1.16-1.23)	<0.001†
p for trend		<0.001†		<0.001†		<0.001†
log2-AISI						
Q1[<6.64)	REF		REF		REF	
Q2[6.64-7.40)	1.12(1.09-1.15)	<0.001†	1.10(1.07-1.13)	<0.001†	1.05(1.02-1.09)	0.001†
Q3[>7.40]	1.26(1.23-1.30)	<0.001†	1.21(1.17-1.24)	<0.001†	1.14(1.11-1.18)	<0.001†
p for trend		<0.001†		<0.001†		<0.001†
log2-TyG						
Q1[<3.08)	REF		REF		REF	
Q2[3.08-3.16)	2.94(2.82-3.07)	<0.001†	2.72(2.61-2.84)	<0.001†	2.46(2.35-2.57)	<0.001†
Q3[>3.16]	9.10(8.76-9.46)	<0.001†	8.71(8.38-9.06)	<0.001†	7.20(6.92-7.50)	<0.001†
p for trend		<0.001†		<0.001†		<0.001†

† Significant at Bonferroni-corrected threshold ($p < 0.0056$). ‡ Nominally significant at $p < 0.05$ but does not meet multiple testing correction. **Model 1:** Unadjusted; **Model 2:** Adjusted for age and sex; **Model 3:** Adjusted for age, sex, BMI, smoking, drinking, SBP, DBP, TG, HDL-C. **Abbreviations:** AISI, aggregate index of systemic inflammation; CI, confidence interval; LMR, lymphocyte-to-monocyte ratio; MHR, monocyte-to-HDL cholesterol ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; PNR, platelet-to-neutrophil ratio; Q1, first tertile (0–33.3%); Q2, second tertile (33.3–66.7%); Q3, third tertile (66.7–100%); ref, reference group; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; TyG, triglyceride-glucose index.

trend was absent in log2-MHR. Results showed only the highest log2-MHR level had a weak yet statistically significant independent positive association with the study outcome ($p < 0.001$), while the intermediate log2-MHR level did not exhibit such an independent association ($p = 0.135$), indicating that its relationship with diabetes may be affected by complex factors. Both log2-PLR and log2-PNR showed significant negative associations with diabetes risk. In Model 3, the Q3 group of PNR exhibited the greatest risk reduction. As log2-PLR and log2-PNR levels increased, diabetes risk decreased significantly, demonstrating a clear association trend ($p < 0.001$) (Table 3).

Subgroup analysis

To further investigate the heterogeneity of the association between inflammatory markers and diabetes across different populations, we conducted subgroup analyses using the most commonly used clinical indicators or those most frequently reported in previous literature (e.g., NLR, PLR, TyG). We included both types of indicators: those positively correlated with diabetes (e.g., TyG) and those negatively correlated or protective (e.g., PLR, PNR). These three categories of indicators represent distinct inflammatory pathways or hematological characteristics, making them representative.

We grouped log2-PLR, log2-PNR, and log2-TyG into low, medium, and high tertiles. Subgroup analyses were stratified by the following variables: sex, age, BMI, blood pressure, smoking, alcohol consumption, and surgical history. We assessed interactions between subgroup variables and inflammatory markers using likelihood ratio tests. Covariates were adjusted for, excluding subgroup factors. Results showed that after adjusting for confounding factors, the negative correlation between log2-PLR and diabetes remained consistent across all subgroups stratified by age, BMI, and blood pressure. The association strength was more pronounced in individuals aged ≥60 years and those with obesity (BMI ≥ 28 kg/m^2), indicating significant interaction effects (p for interaction < 0.05). The negative correlation of log2-PNR was consistently observed

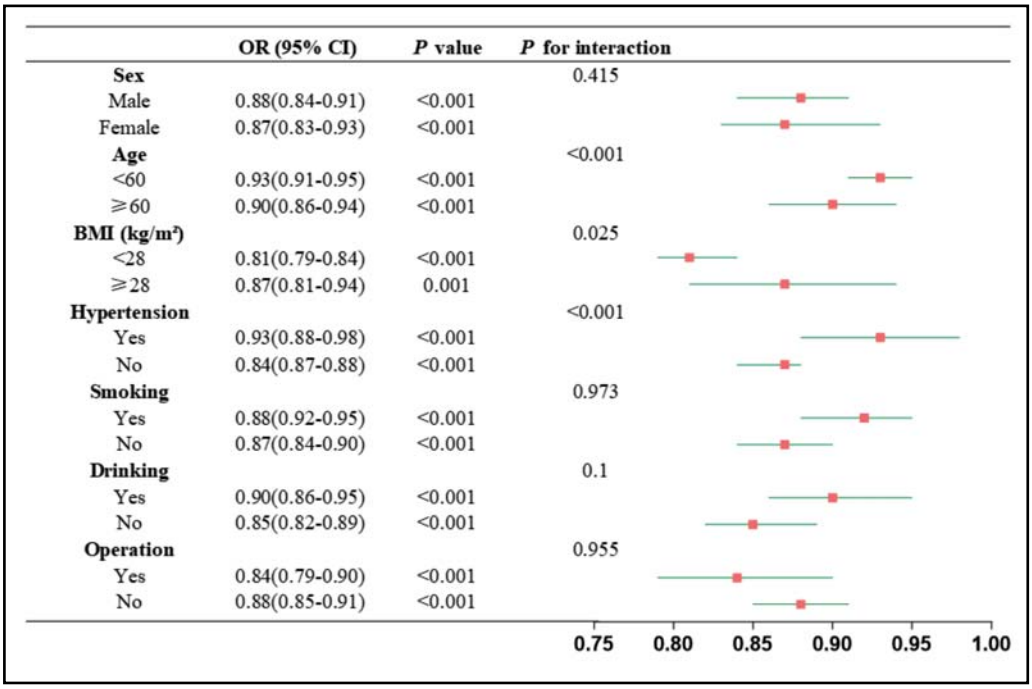

Fig. 1. Subgroup analysis of the association between PLR tertile 3 (T3) and diabetes risk compared with tertile 1 (T1, reference). Forest plots display odds ratios (ORs) and 95% confidence intervals (CIs) for the association between log2-transformed platelet-to-lymphocyte ratio (PLR) and diabetes risk across subgroups stratified by age, sex, BMI, blood pressure, smoking status, alcohol consumption, and surgical history. All analyses adjusted for confounders excluding the stratification variable. *p* for interaction tests heterogeneity of associations across subgroups.

across all subgroups stratified by gender, BMI, blood pressure, and alcohol consumption, with stronger effects in males, current smokers, and obese individuals (p for interaction < 0.05). The negative correlation between log2-TyG and diabetes was consistently observed across all subgroups, with stronger effects in males, current smokers, and obese individuals (p for interaction < 0.05). This correlation was prevalent in BMI, blood pressure, smoking, and alcohol consumption subgroups, with stronger effects in males, current smokers, and obese individuals (p for interaction < 0.05). The positive correlation between log2-TyG and diabetes was consistently observed across all subgroups, with a more pronounced association in females, individuals <60 years old, and those with hypertension (Figures 1-3). Subgroup analyses comparing the middle tertile (T2) versus the lowest tertile (T1) are presented in Figures 4-6.

DISCUSSION

This study aims to analyze differences in various biochemical and hematological indicators between patients with type 2 diabetes mellitus (T2DM) and

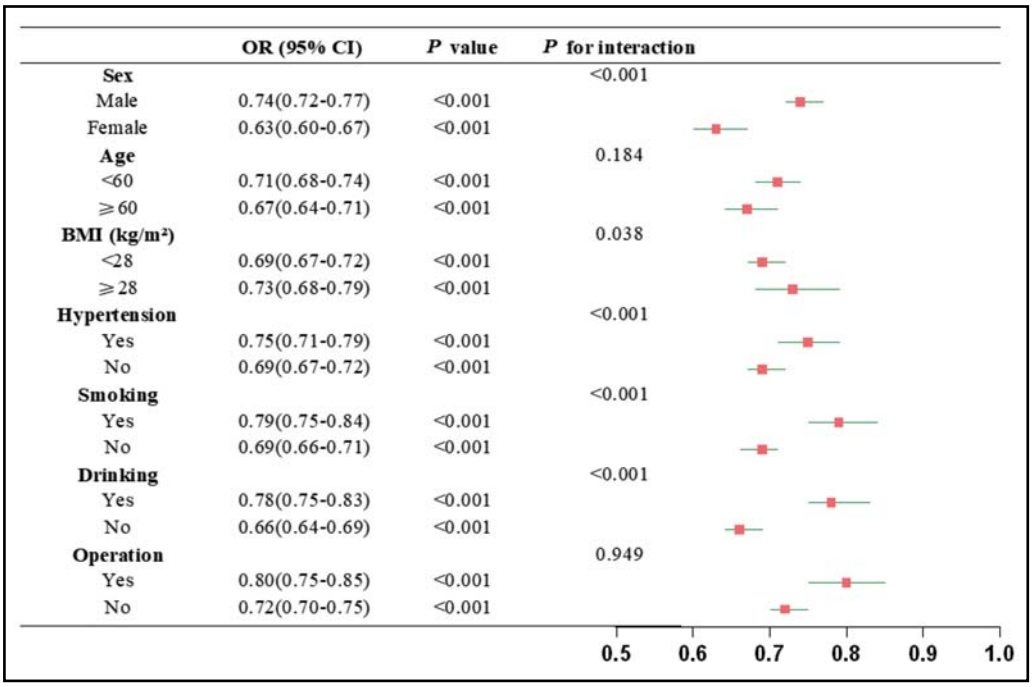

Fig. 2. Subgroup analysis: PNR tertile 3 vs. tertile 1 (reference) and diabetes risk. Forest plots show odds ratios and 95% CIs stratified by demographic and clinical characteristics. *p* for interaction <0.05 indicates effect modification.

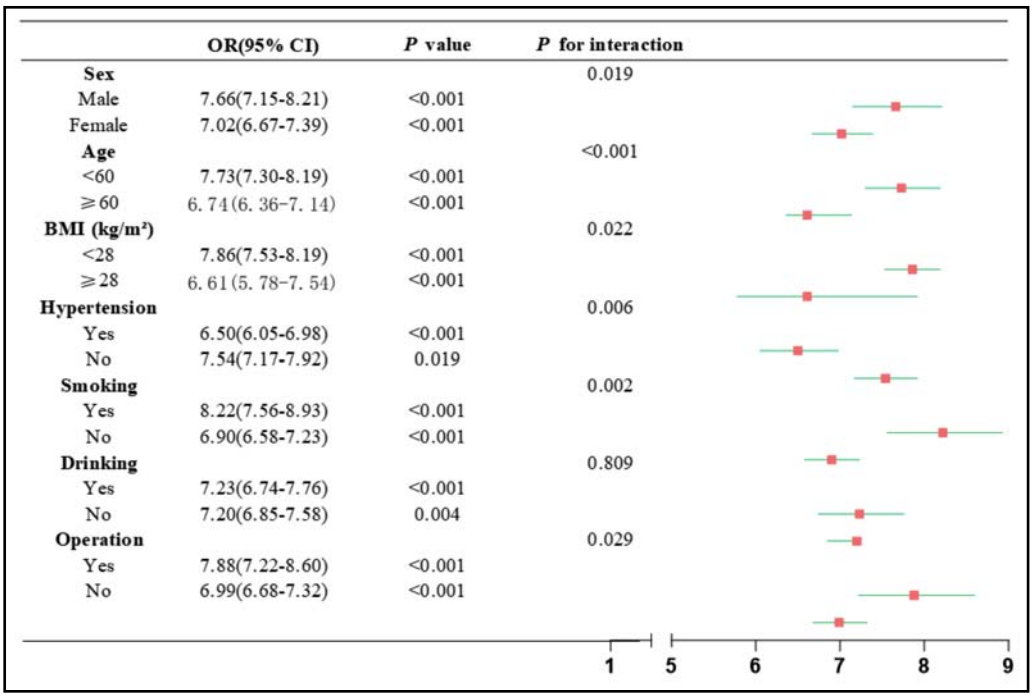

Fig. 3. Subgroup analysis: TyG index tertile 3 vs. tertile 1 (reference) and diabetes risk. Forest plots show odds ratios and 95% CIs stratified by demographic and clinical characteristics. *p* for interaction <0.05 indicates effect modification.

non-diabetic individuals, with a focus on investigating the association between inflammatory markers (PLR, MHR, NLR, LMR, PNR, SII, SIRI, AISI, TyG) and the risk of developing T2DM. Results revealed significant differences in inflammatory and hematological parameters between the T2DM group and the control group, which aligns with the established understanding that T2DM is characterized by a state of chronic low-grade inflammation accompanied by metabolic disorders. Our study identified multiple indicators including MHR, NLR, LMR, SII, SIRI, AISI, and TyG that are positively associated with diabetes risk. This further supports the established perspective that chronic inflammation and insulin resistance are key components involved in the process of diabetes development, consistent with most prior research. Additionally, among individuals aged 40 years and older, PLR and PNR exhibited negative associations with T2DM risk. These findings indicate that inflammatory and metabolic composite indices hold potential value for T2DM risk assessment and for relevant research into its pathophysiological mechanisms.

Our study found that the log2-PLR was significantly lower in patients with type 2 diabetes (6.09±6.77)

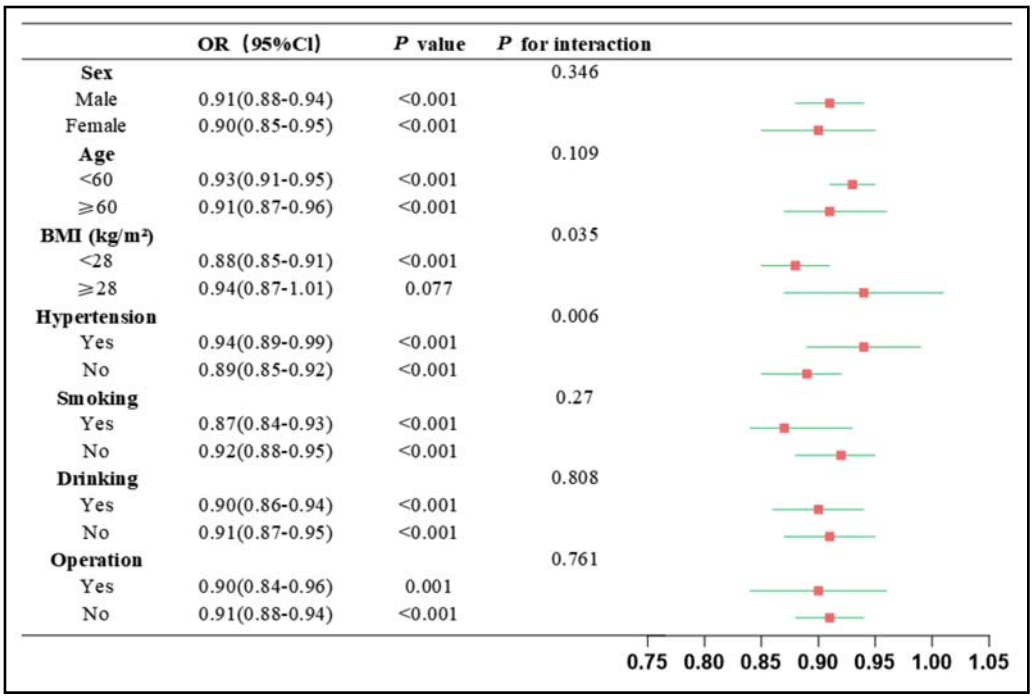

Fig. 4. Subgroup analysis: PLR tertile 2 vs. tertile 1 (reference) and diabetes risk. Forest plots show odds ratios and 95% CIs stratified by demographic and clinical characteristics.

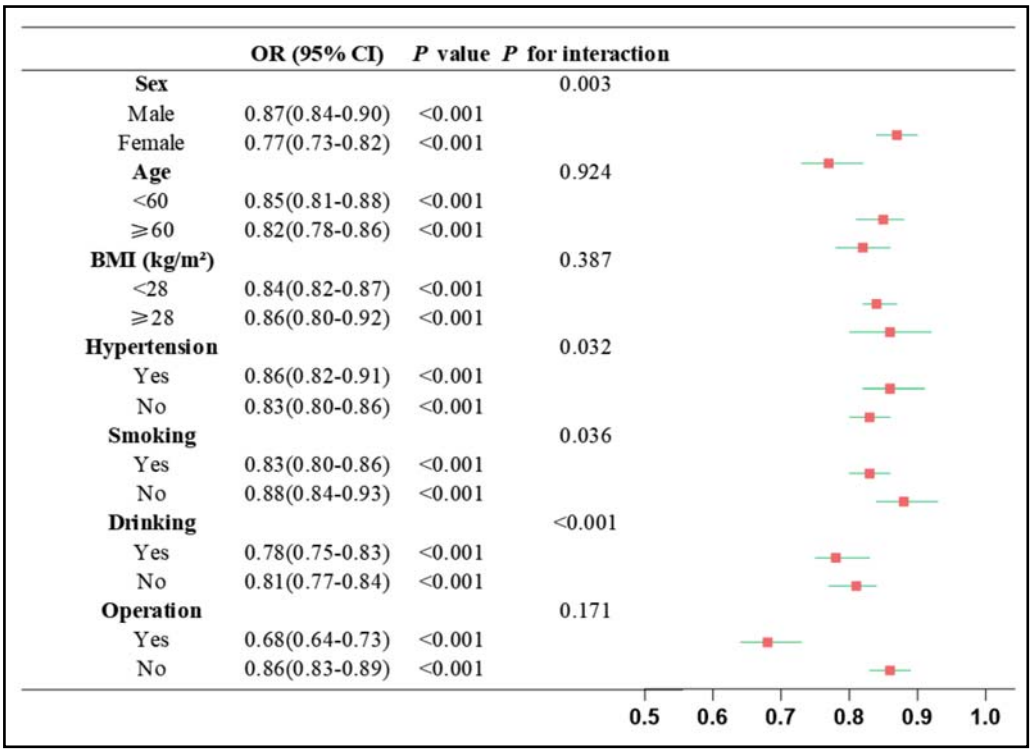

Fig. 5. Subgroup analysis: PNR tertile 2 vs. tertile 1 (reference) and diabetes risk. Forest plots show odds ratios and 95% CIs stratified by demographic and clinical characteristics.

compared to the non-diabetic group (6.18±6.85). This finding differs from several prior studies reporting elevated PLR in diabetic patients (Wang *et al.* 2021; Taban *et al.* 2025; Zhang *et al.* 2022). This discrepancy may reflect characteristics specific to our study population. Several potential explanations exist for this finding. First, statins and aspirin are commonly prescribed in diabetic populations and have demonstrated anti-inflammatory and platelet function-modulating effects (Bikdeli *et al.* 2020; Furuhashi *et al.* 2022; Pedersen *et al.* 2021), which could theoretically attenuate PLR elevations. Second, our non-diabetic control group may have included a substantial proportion of obese or metabolic syndrome individuals, conditions inherently associated with chronic low-grade inflammation, which could have elevated baseline PLR levels in this group. Finally, the diabetic group in this study exhibited relatively well-controlled glycemic levels overall (mean fasting blood glucose: 7.50±1.98 mmol/L). This favorable metabolic control was likely associated with reduced systemic

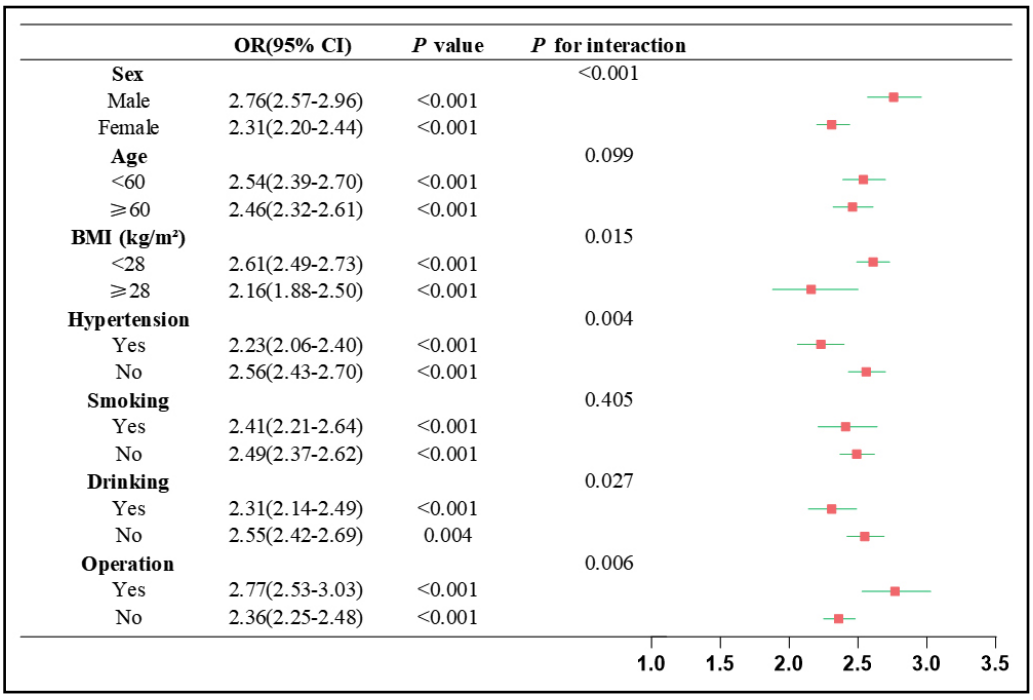

Fig. 6. Subgroup analysis: TyG index tertile 2 vs. tertile 1 (reference) and diabetes risk. Forest plots show odds ratios and 95% CIs stratified by demographic and clinical characteristics.

inflammatory burden. The PNR pattern aligned with the PLR, with both showing a protective association trend against diabetes, consistent with previous findings (Essawi *et al.* 2023; Klisic *et al.* 2022).

Our findings indicate that MHR, NLR, and LMR are significantly elevated in diabetic patients compared to individuals with normal glucose tolerance ($p < 0.001$). MHR, which combines monocytes with HDL-C, serves as an indicator for assessing inflammation and oxidative stress (He *et al.* 2025). Furthermore, studies have demonstrated an association between MHR and insulin resistance (IR) (Okuyan *et al.* 2024; Battaglia *et al.* 2020; Ruan *et al.* 2024). These findings underscore MHR's dual relevance in inflammation and metabolic regulation, positioning it as a potential indicator for assessing T2DM risk.

Additionally, Yu *et al.*'s findings revealed a significant correlation between elevated MHR levels and increased T2DM prevalence (Yu *et al.* 2025), consistent with our study results. NLR is a widely used systemic inflammatory marker reflecting the ratio of neutrophils to lymphocytes (Zhang *et al.* 2022). Previous studies indicate that elevated NLR correlates with poor glycemic control and increased risk of T2DM complications (Adane *et al.* 2023; Bilgin *et al.* 2020). A study by Fonseka *et al.* reported that that elevated interleukin levels during inflammatory states lead to lymphopenia and neutrophilia, along with a subsequent increase in NLR (Fonseka *et al.* 2015).

LMR, composed of the ratio of lymphocytes to monocytes, serves as an inflammatory marker that has been linked to the development of cardiovascular disease. Studies indicate that elevated LMR in pregnant women aged 20–44 years correlates with a higher risk of GDM (OR = 1.82, CI: 1.30–2.56) (Li *et al.* 2025), consistent with our findings. A prior study demonstrated that lymphocyte counts and LMR are associated with a lower risk of the incidence and complications of macrovascular disease-related complications in diabetic patients (Cardoso *et al.* 2021). In another investigation, LMR served as a predictor for the necessity of surgical intervention in diabetic foot infection cases (Demirdal & Sen 2018).

The results of this study indicate that SII, SIRI, and AISI are all significantly positively associated with diabetes risk. This finding collectively confirms the central role of chronic low-grade inflammation in the pathogenesis of diabetes. SII is a comprehensive marker reflecting the body's inflammatory and immune status (Poznyak *et al.* 2020), composed of neutrophils, monocytes, and lymphocytes. Elevated SII levels may indicate worsening inflammatory states, which have been linked to the occurrence of glucose metabolism abnormalities. Previous studies have demonstrated associations between elevated SII levels and increased risks of glucose metabolism abnormalities and diabetic nephropathy (Xu & Jiang 2025; He *et al.* 2025), consistent with our findings. Additionally, research indicates that SII serves as a reliable and profoundly significant biomarker for predicting outcomes in DM patients and assessing mortality risk (Dong *et al.* 2025).

SIRI, a novel and readily accessible biomarker of inflammation and immune system activity, integrates parameters from neutrophils, monocytes, and lymphocytes, typically reflecting the intensity of inflammatory responses. AISI serves as a systemic inflammatory indicator integrating parameters from four cell types: neutrophils, monocytes, platelets, and lymphocytes. Together, platelets, neutrophils, monocytes, and lymphocytes form an inflammatory network that is associated with IR and diabetes progression. Platelets directly drive endothelial dysfunction and atherosclerosis by releasing pro-inflammatory mediators (Al-Mansoori *et al.* 2022). Neutrophils exacerbate endothelial injury and induce pancreatic β-cell apoptosis by secreting cytokines, inducing oxidative stress, and releasing proteases (Dludla *et al.* 2023). Monocyte-derived M1 macrophages secrete abundant proinflammatory cytokines, including IL-1α, IL-1β, and IL-6 (Zhang *et al.* 2025). Overexpression of these cytokines and chemokines leads to inflammation and tissue damage (Xuan *et al.* 2015), accelerating the onset of diabetic complications (Ge *et al.* 2019). In T2DM, elevated levels of neutrophils, monocytes, and platelets alongside relative lymphopenia are common, highlighting the critical role of chronic inflammation in disease onset and progression. These alterations increase SII and SIRI levels, reflecting exacerbated inflammation that mediates insulin resistance.

Our study employed a multivariable-adjusted model to analyze the findings, revealing a significant dose-response relationship between the log2-TyG index and diabetes risk. In the fully adjusted model, compared with the Q1 group, the odds ratios for the Q2 and Q3 groups were 2.46 (2.35–2.57) and 7.20 (6.92–7.50), respectively, with $p < 0.001$. This finding aligns with previous studies, further validating the TyG index's significant value as a diabetes predictor (Rathore *et al.* 2025; Rong *et al.* 2023; Xing *et al.* 2023). From a pathophysiological perspective, the TyG index - derived from fasting triglycerides and glucose - is considered a reliable surrogate marker reflecting insulin resistance (Selvi *et al.* 2021). Moreover, the value of the TyG index extends beyond predicting diabetes onset to encompass its complications. Studies indicate that elevated TyG index significantly correlates with the prevalence and severity of diabetic microvascular complications and macrovascular diseases (Liu *et al.* 2025). This underscores the role of persistent insulin resistance, as reflected by the TyG index, in driving the progression of systemic vascular damage.

Our interaction results indicate that among middle-aged and older adults aged 40 and above, the association between inflammatory and metabolic markers (PLR, PNR, TyG) and diabetes risk is modified by demographic and clinical characteristics such as age,

sex, BMI, and hypertension. First, our data show that the association between PLR and diabetes risk exhibits significant differences across age, BMI, and hypertension status. The age interaction may reflect inflammation associated with aging. Research indicates that immune aging and inflammatory aging form a mutually reinforcing vicious cycle linked to impaired immune function, increased disease risk, and higher susceptibility to infections, cancer, and chronic diseases in the elderly (Fulop *et al.* 2017). Studies also suggest that in older adults (>65 years), type 2 diabetes and inflammation are both associated with damage to the heart's microvascular system and impaired physical function (Dushay *et al.* 2025).

In summary, the specific signals of PLR may be diminished due to widespread immune aging and comorbid inflammation. Furthermore, the interaction between BMI and hypertension collectively points to the relevance of metabolic inflammation. Hypertension and obesity disrupt the balance between vasodilators and vasoconstrictors, amplify oxidative stress, and alter perivascular adipose tissue function, thereby exacerbating vascular dysfunction. These interconnected changes are associated with the progression of atherosclerotic cardiovascular disease and diabetic vascular complications (Młynarska *et al.* 2025). Notably, PNR and TyG indices exhibit broader interaction patterns than PLR, involving behavioral factors such as gender, smoking, and alcohol consumption. This discrepancy indicates that different inflammatory markers may be linked to diabetes through distinct pathophysiological pathways. For instance, fluctuations in estrogen levels may directly affect insulin sensitivity and glucose metabolism (Bian *et al.* 2019; Abu Aqel *et al.* 2024; De Paoli *et al.* 2021); smoking, a risk factor for T2DM (Paz-Graniel *et al.* 2025; Liu *et al.* 2022), may exacerbate insulin resistance by inducing chronic oxidative stress and inflammation (Sia *et al.* 2022; Wronka *et al.* 2022); while the physiological stress and inflammatory response associated with surgical history may alter an individual's metabolic homeostasis over the long term. Furthermore, the association between PNR and diabetes is modified in smokers and drinkers. This may occur because tobacco exposure and alcohol intake directly modulate the activity of immune cells (e.g., neutrophils) and platelet function, thereby disrupting the immune-inflammatory balance represented by PNR (Lee *et al.* 2025). For instance, smoking has been demonstrated to induce neutrophil extracellular traps (NETs) formation and enhance platelet activation (Brembach *et al.* 2023), potentially representing one mechanism altering PNR's predictive value.

LIMITATIONS

This study has several important limitations. First, the cross-sectional design precludes causal inference; we cannot determine whether inflammatory markers precede diabetes onset or result from metabolic dysfunction. Longitudinal studies are needed to establish temporal relationships. Second, selection bias may limit generalizability. Participants from a single tertiary hospital health examination center represent a health-conscious, predominantly urban population that may not reflect the general Chinese population aged ≥40 years or other ethnic groups. Third, we tested nine inflammatory markers without adjusting for multiple comparisons, increasing Type I error risk (family-wise error rate ~37% at $\alpha = 0.05$). Findings should be considered exploratory pending replication in independent cohorts. Fourth, incomplete medication data prevented stratified sensitivity analyses by anti-inflammatory drug use (statins, aspirin, NSAIDs), limiting our ability to distinguish drug-related from disease-related mechanisms. Unmeasured medications or dose variations may also have contributed to residual confounding. "Fifth, data were collected during 2011-2016, and diabetes management practices have since evolved, requiring validation with contemporary data to establish current relevance. Finally, missing data for key variables may introduce bias, though our large sample size provides robustness. Future studies should prospectively collect complete datasets with standardized protocols.

CONCLUSION

This cross-sectional study documented associations between inflammatory markers (PLR, MHR, NLR, LMR, PNR, SII, SIRI, AISI, TyG) and prevalent type 2 diabetes in Chinese adults aged 40 years and above. Compared to non-diabetic individuals, diabetic patients exhibited significantly elevated MHR, NLR, SII, SIRI, AISI, and TyG levels (all $p < 0.001$), while PLR and PNR demonstrated inverse associations (both $p < 0.001$). These patterns persisted across diverse demographic subgroups stratified by age, sex, BMI, and hypertension status. However, the temporal relationship between inflammatory marker elevations and diabetes development cannot be determined from this study design. Prospective cohort studies are required to establish whether these readily available CBC-derived markers predict incident diabetes and whether their monitoring improves clinical outcomes. Until such validation is completed, these associations should inform hypothesis generation rather than routine clinical application.

DECLARATIONS

Ethics approval and consent to participate

This study's protocol has been approved by the Ethics Committee of a Medical College, with data sourced from the Health Management Center at the First Affiliated Hospital of a Medical College in Wuhu, China. Given that participants were hospital visitors for routine medical check-ups, the Medical Ethics Committee deemed verbal informed consent

as sufficient. Therefore, necessary verbal informed consent was obtained from all subjects and/or their legal guardian(s). All methods in this study were conducted in accordance with the guidelines and regulations of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The authors collected participant data and uploaded it to a database. This system conveniently shields irrelevant data and effectively protects participant privacy. The data supporting this study's findings are available from the Health Management Center at the First Affiliated Hospital of Wannan Medical College, Wuhu, China. However, access to these data is restricted as they were used under license for this study and are not publicly available. Data can be provided upon reasonable request and with the Health Management Center's permission. For data requests, please contact Yufeng Wen, the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by several initiatives from the Education Department of Anhui Province: The Teaching Reform and Quality Improvement Plan for the Teaching Team (grant number 2018jxtd153), the Famous Teacher segment of the Teaching Reform and Quality Improvement Plan (grant number 2019jxms066), and the Public Health Collaborative Innovation Project of Provincial Undergraduate Medical Colleges (grant number GXXT-2020-22).

Authors' contributions

Yue Wu and Huan Wu wrote the main text of the manuscript; Xinyu Ma and Tong Wang prepared figures; Wendan Mei conducted the experiments; Yicheng Fang and Chenxu Wang analyzed the data; Yufeng Wen supervised the entire project. All authors reviewed the manuscript.

Acknowledgments

The authors express their gratitude to the staff of the First Affiliated Hospital of a Medical College for their invaluable contributions to this research. We also extend our thanks to the study participants for their collaboration and commitment.

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