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Yongjie Yan[1]
Weifang Medical University
Kang Zhang[1]
Weifang Medical University
Hui Song[1]
Weifang Medical University
Fangjie Hou[2]
qdslyyhfj@163.com

Qingdao Municipal Hospital

Research Article

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The Relationship between TyG, AIP, NHR and PIV and Coronary Lesion Burden in Patients with Early-Onset Coronary Heart Disease: A Single-Centre Retrospective Cross-Sectional Study

Yongjie Yan[1], Kang Zhang[1], Hui Song[1], Fangjie Hou[2],*

[1] Shandong Second Medical University, Weifang, Shandong, China.[2] Qingdao Municipal Hospital, Qingdao, Shandong, China.

*Corresponding author:Fangjie Hou

Qingdao Municipal Hospital, Qingdao, Shandong, China.

Email: qdslyyhfj@163.com

Abstract

Background: To compare the associations between the triglyceride-glucose index (TyG), atherogenic index of plasma (AIP), neutrophil-to-high-density lipoprotein cholesterol ratio (NHR) and pan-immune-inflammation value (PIV) with the coronary artery disease burden in patients with early-onset coronary heart disease.

Methods: A retrospective study was conducted involving 781 patients with early-onset coronary heart disease at Qingdao Municipal Hospital between January 2021 and July 2025. Spearman's correlation, the quartile trend test and multivariate linear regression were employed, with the regression outcome defined as ln(Gensini score + 1). All four indicators were standardised; specifically, the natural logarithms of the NHR and PIV were calculated in advance. Regression analysis utilised HC3 robust standard errors, and restricted cubic spline, mutual adjustment, sensitivity and subgroup analyses were conducted.

Results: All four indicators were positively correlated with the Gensini score, which generally increased as the quartiles of the indicators rose. After adjusting for clinical covariates, NHR ($\beta = 0.137$, 95% CI: 0.066–0.208) and PIV ($\beta = 0.154$, 95% CI: 0.086–0.222) showed positive associations in their respective models (both $P < 0.001$), whilst the associations for TyG and AIP were not statistically significant. When NHR and PIV were modelled together, the association with PIV was statistically significant ($\beta = 0.117$, 95% CI: 0.033–0.201, $P = 0.0065$), whilst the association with NHR was not significant. After excluding the top 1% of PIV observations, the effect estimates were similar to those in the primary analysis. Neither the tests for non-linearity nor for subgroup interactions reached statistical significance.

Conclusion: Inflammation-related composite indices are associated with the coronary artery disease burden in patients with early-onset coronary heart disease; PIV shows a consistent positive association across different adjustment frameworks.

Keywords： Early-Onset Coronary Heart Disease; Coronary Artery Burden; Gensini Score; Triglyceride-Glucose Index; Plasma Atherosclerosis Index; Neutrophil-To-Hdl Cholesterol Ratio; Systemic Immune-Inflammatory Markers

1 Introduction

Premature coronary artery disease (PCAD), which occurs in relatively young people, is closely associated with traditional risk factors such as smoking, hypertension, diabetes, obesity, dyslipidaemia and family history; in addition, genetic susceptibility and chronic inflammation also contribute to the early onset and progression of the disease[1, 2].Age carries significant weight in existing cardiovascular risk assessment tools, and the identification of risk in younger patients therefore presents a considerable challenge. Against this backdrop, investigating the relationship between routine biological markers and the burden of coronary artery disease can help to understand the characteristics of lesions in patients with PCAD based on clinical laboratory data[3].Coronary angiography provides a direct visualisation of anatomical lesions in the coronary arteries; the Gensini score, which combines the degree of luminal stenosis with the anatomical weighting of the affected segment, provides a basis for quantifying the coronary lesion burden[4, 5].

Metabolic abnormalities and insulin resistance contribute to the development and progression of atherosclerosis. The triglyceride-glucose index (TyG), calculated from fasting triglyceride and fasting glucose levels, is a simple surrogate marker for insulin resistance. Previous studies have shown that an elevated TyG is associated with multivessel coronary artery disease and a higher Gensini score[6, 7].The atherogenic index of plasma (AIP) is calculated as the logarithm of the molar concentration ratio of triglycerides to high-density lipoprotein cholesterol (HDL-C), and reflects the lipid phenotype associated with atherosclerosis. Large-scale studies and systematic reviews have found that a higher AIP is associated with coronary heart disease, multivessel disease, coronary artery calcification and plaque progression[8, 9].TyG and AIP, which are derived from routine glucose and lipid metabolism tests, provide accessible quantitative indicators for investigating the link between metabolic status and the burden of coronary artery disease.

In addition to metabolic disorders, inflammation and immune responses play a role throughout the formation, progression and development of complications associated with atherosclerotic plaques[10].The neutrophil-to-HDL-C ratio (NHR) combines neutrophil count with HDL-C concentration, providing information on both inflammation and lipid metabolism. Previous studies in patients with stable coronary heart disease have shown that the NHR is not only positively correlated with the Gensini score but is also independently associated with severe coronary artery lesions[11].In recent years, the pan-immune-inflammation value (PIV)—comprising neutrophil, monocyte, platelet and lymphocyte counts—has attracted increasing attention as it integrates information on various blood cell parameters associated with inflammation, immunity and thrombosis. Previous studies have found that the PIV is not only associated with the SYNTAX score in patients with non-ST-elevation myocardial infarction, but is also linked to the severity of coronary artery disease in populations with stable coronary artery disease and other coronary artery conditions[12, 13].

However, existing studies have involved different patient populations, such as those with general coronary heart disease, stable coronary heart disease or acute coronary syndrome, and the methods used to assess lesions have varied in their focus. Although existing studies have begun to examine the diagnostic and prognostic value of TyG and PIV in early-onset coronary heart disease[14],However, within this specific population, there remains a limited number of studies that have systematically evaluated the relationship between TyG, AIP, NHR and PIV and the Gensini score—used as an indicator of coronary lesion burden—in patients with early-

onset coronary heart disease. In this study, the Gensini score was used as a continuous outcome to evaluate the relationship between the four indicators and coronary artery disease burden in the same PCAD cohort. Multivariate regression, restricted cubic spline analysis and mutual adjustment analysis were employed to examine their adjusted associations and the patterns of these associations.

2 Materials and Methods

This study is a single-centre, retrospective, cross-sectional study. Patients who underwent coronary angiography at Qingdao Municipal Hospital between January 2021 and July 2025 were consecutively recruited. Study participants were identified based on predefined age criteria for premature coronary artery disease (PCAD), diagnostic criteria for coronary angiography and exclusion criteria; ultimately, 781 patients were included in the analysis.

The age threshold for early-onset coronary heart disease has not been consistently defined in previous studies[15].For the purposes of this study, men aged ≤55 years and women aged ≤65 years were defined as meeting the age criteria for PCAD. All patients included in the study underwent coronary angiography and had clinical data, laboratory test results and Gensini scores available for analysis in this study. This study adhered to the relevant principles of the Declaration of Helsinki and was approved by the Ethics Committee of Qingdao Municipal Hospital (approval No. 2026-KTLL-045). Informed consent requirements were implemented in accordance with the Ethics Committee's approval.

Inclusion criteria: ① Men aged ≤55 years or women aged ≤65 years; ② Patients undergoing coronary angiography for clinical reasons; ③ Stenosis of ≥50% in the lumen of the left main coronary artery or any of the following major epicardial coronary arteries: the left anterior descending artery, the left circumflex artery or the right coronary artery; ④ Complete coronary angiography data available for calculating the Gensini score; ⑤ Baseline test results, including fasting blood glucose, triglycerides, HDL-C and complete blood count, required for the calculation of TyG, AIP, NHR and PIV. Exclusion criteria: ① Concurrent acute infection or overtly active inflammatory disease; ② Concurrent active malignant tumour; ③ Concurrent haematological disorders or other conditions likely to significantly affect peripheral blood cell counts; ④ Concurrent severe hepatic or renal dysfunction; ⑤ Incomplete key coronary angiography data, rendering it impossible to calculate the Gensini score; ⑥ Missing key laboratory parameters required for the calculation of TyG, AIP, NHR or PIV; ⑦ Other clinical conditions that may significantly affect inflammatory or metabolic markers. The subject selection process is shown in Figure 1.

Baseline patient data were collected via the hospital's electronic health record system, laboratory information system and coronary angiography database. Demographic and clinical data included age, sex, body mass index (BMI), smoking history, history of hypertension, history of diabetes, family history of coronary heart disease and history of chronic kidney disease (CKD). Laboratory and diagnostic test parameters primarily included fasting glucose (Glu), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), neutrophil count, lymphocyte count, monocyte count, platelet count, estimated glomerular filtration rate (eGFR) and left ventricular ejection fraction (LVEF),

amongst others. All laboratory parameters were based on fasting venous blood test results obtained after the patient's initial admission and prior to coronary angiography and interventional procedures. For patients with multiple test results, the result closest in time to the coronary angiography and taken prior to the procedure was used. Gender was categorised as female or male. Variables such as hypertension, diabetes, history of smoking, chronic kidney disease (CKD) and family history of coronary heart disease were determined based on previous confirmed diagnoses, medical records and the diagnosis at the time of the current hospitalisation.

TyG is calculated using the following formula[16]: $TyG = \ln [TG\ (mg/dL) \times Glucose\ (mg/dL) / 2]$. If the original laboratory results are recorded in mmol/L, they must be converted to mg/dL using the appropriate conversion factor before calculation. The AIP was proposed by Dobiásová and Frohlich and is defined as the base-10 logarithm of the ratio of TG to HDL-C molar concentrations[17]:$AIP = \log_{10} (TG / HDL\text{-}C)$, where TG and HDL-C are both expressed in mmol/L. NHR and PIV are calculated using the following formulae respectively: NHR = Neutrophil count / HDL-C; PIV = (Neutrophil count × Platelet count × Monocyte count) / Lymphocyte count.

All patients underwent coronary angiography in accordance with standard clinical practice. The severity of coronary artery disease was quantified using the Gensini score. The Gensini score takes into account both the degree of coronary stenosis and the anatomical significance of the lesion[4].Different base scores are assigned according to the degree of narrowing of the coronary artery lumen: 1 point for 1–25 per cent narrowing, 2 points for 26–50 per cent, 4 points for 51–75 per cent, 8 points for 76–90 per cent, 16 points for 91–99 per cent, and 32 points for complete occlusion. The score for each lesion segment is then multiplied by a weighting factor based on the importance of the coronary artery segment in which the lesion is located, and the scores for all lesion segments are added together to give the patient's final Gensini score. A higher Gensini score indicates a heavier overall coronary artery disease burden.

All study variables were checked for completeness, outliers and distribution. There were no missing values for TyG, AIP, NHR, PIV or the Gensini score; there was one missing value each for eGFR and LVEF. The Gensini score, NHR and PIV exhibited right-skewed distributions, with PIV displaying a pronounced long tail. For the purposes of regression analysis, the following natural logarithmic transformations were applied to the Gensini score, NHR and PIV: $\ln_Gensini = \ln (Gensini\ Score + 1)$; $\ln_NHR = \ln (NHR)$; $\ln_PIV = \ln (PIV)$. TyG and AIP were retained on their original scales. Z-standardisation was performed on TyG, AIP, ln(NHR) and ln(PIV) as follows: $Z = (X - \bar{x}) / SD$. The regression models included standardised TyG, standardised AIP, standardised ln(NHR) and standardised ln(PIV), respectively, with the effect size described in terms of a one-standard-deviation increase in each modelled variable.

All statistical analyses were performed using the R software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables with an approximately normal distribution are expressed as $\bar{x} \pm SD$; continuous variables with a skewed distribution are expressed as Median (P25, P75); and categorical variables are expressed as n (%). As the Gensini score and some core indicators were skewed, Spearman's rank correlation analysis was used to evaluate the monotonic relationship between TyG, AIP, NHR and PIV and the Gensini score, with the Spearman correlation coefficient (ρ) and P-value reported. This analysis utilised the raw

values of the four indicators and the Gensini score. Patients were divided into Q1, Q2, Q3 and Q4 groups according to the quartiles of TyG, AIP, NHR and PIV, respectively. The Kruskal–Wallis test was used to compare the overall differences in Gensini scores across the quartile groups, and the Jonckheere–Terpstra trend test was employed to assess whether the Gensini score exhibited an ordered trend of increase as the indicators progressed from Q1 to Q4; the P-value for the trend test was calculated using 10,000 permutations.

Linear regression models were constructed for TyG, AIP, NHR and PIV, using ln(Gensini score + 1) as the continuous outcome. Model 1 was the unadjusted model; Model 2 was adjusted for age, sex and BMI; Model 3 included, in addition to Model 2, smoking history, hypertension, diabetes, family history of coronary heart disease, CKD, eGFR and LVEF, and served as the primary analysis model. As a sensitivity analysis, NHR and PIV were separately re-evaluated with additional adjustment for clinical presentation.As residual diagnostics indicated a degree of heteroscedasticity, HC3 heteroscedasticity-robust standard errors were used to calculate the 95% confidence intervals and P-values for the regression coefficients. Results are reported as β, 95% CI and P-value, where β represents the mean change in ln(Gensini score + 1) for each one-standard-deviation increase in the corresponding modelled variable. Model 3 employed a complete-case analysis, including a total of 779 patients.

The variance inflation factor (VIF) was used to assess multicollinearity in the model. As both NHR and PIV include neutrophil counts, Spearman's rank correlation analysis was used to assess the correlation between them; in the exploratory analysis, both NHR and PIV were included simultaneously in Model 3 to examine the extent of overlap in the information provided by the two indicators. Restricted cubic spline (RCS) analysis was employed to examine the association patterns between the four indicators and ln(Gensini score + 1). Four knots were set at the 5th, 35th, 65th and 95th percentiles of the respective modelled variables, and P-values for overall associations and non-linearity tests were reported. TyG and AIP were modelled on their original scales, whilst NHR and PIV were modelled using natural logarithm-transformed values.

Given the long-tail distribution of PIV, patients with PIV values above the 99th percentile were excluded; ln(PIV) and its standardised values were then recalculated, and the analysis in Model 3 was repeated to examine the impact of extremely high values on the association estimates. Subgroup analyses were conducted for PIV, with stratification by sex, diabetes status, hypertension status, smoking status and BMI level, with BMI grouped according to the median value in the study population. The association between PIV and ln(Gensini score + 1) was estimated within each subgroup, and the β coefficient and 95% CI were reported. Interaction terms between PIV and the stratification variables were included in the regression models, and interaction tests were used to assess differences in association across subgroups. With the exception of the established ordered trend test, all other statistical tests were conducted as two-sided tests, with $P < 0.05$ taken as the criterion for statistical significance.

3 Results

Based on the inclusion and exclusion criteria, a total of 781 patients with early-onset coronary heart disease were included; the screening process is shown in Figure 1. The mean age of the study participants was

(52.7 ± 7.8) years; 320 were female (41%) and 461 were male (59%), with a mean BMI of (26.8 ± 3.8) kg/m². The prevalence of a history of smoking, hypertension, diabetes, a family history of coronary heart disease and chronic kidney disease was 40%, 66%, 32%, 12% and 3.7%, respectively.

The median (P25, P75) values for TyG, AIP, NHR and PIV were 9.011 (8.585, 9.518), 0.180 −0.003,0.350, 4.333 (2.956, 6.198) and 265.83 (165.41, 491.55); the median Gensini score was 34.0 (14.0, 56.0). The remaining baseline characteristics are shown in Table 1.

Figure 1. Flow diagram of study participant selection.

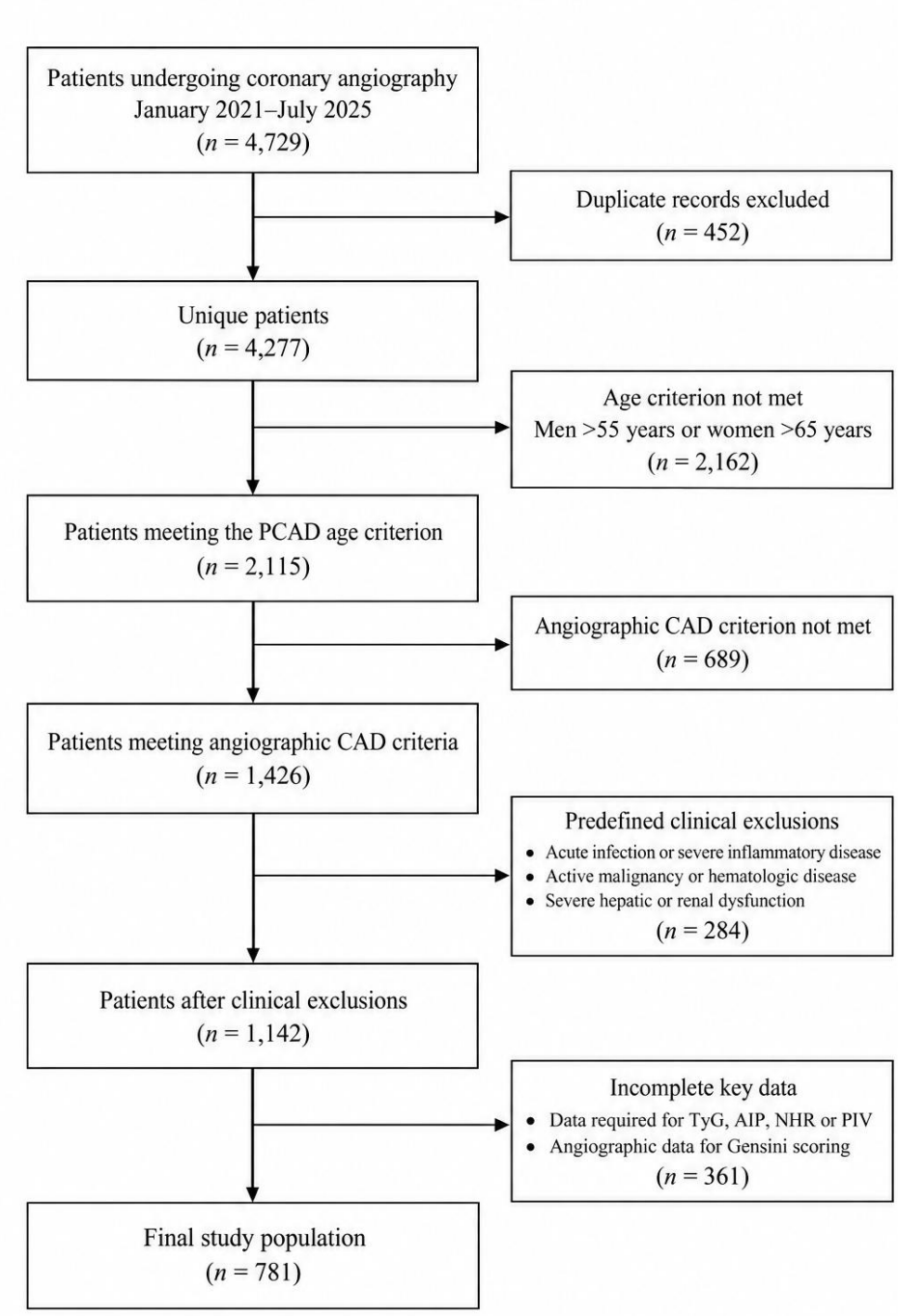

Patients undergoing coronary angiography
January 2021–July 2025
(n = 4,729)
Duplicate records excluded
(n = 452)
Unique patients
(n = 4,277)
Age criterion not met
Men >55 years or women >65 years
(n = 2,162)
Patients meeting the PCAD age criterion
(n = 2,115)
Angiographic CAD criterion not met
(n = 689)
Patients meeting angiographic CAD criteria
(n = 1,426)
Predefined clinical exclusions
Acute infection or severe inflammatory disease
Active malignancy or hematologic disease
Severe hepatic or renal dysfunction
(n = 284)
Patients after clinical exclusions
(n = 1,142)
Incomplete key data
Data required for TyG, AIP, NHR or PIV
Angiographic data for Gensini scoring
(n = 361)
Final study population
(n = 781)

Table 1. Baseline characteristics of the study population

Characteristic	Overall (N = 781)[1]
Age, years	52.7 ± 7.8
Sex	
Female	320 (41%)
Male	461 (59%)
BMI, kg/m²	26.8 ± 3.8
Smoking history	310 (40%)
Hypertension	512 (66%)
Diabetes mellitus	247 (32%)
Family history of CAD	93 (12%)
Chronic kidney disease	29 (3.7%)
eGFR, mL/min/1.73 m²	100.00 (93.00, 106.30)
LVEF, %	60.00 (55.00, 62.00)
Glucose, mmol/L	6.35 (5.30, 8.26)
Total cholesterol, mmol/L	4.68 (3.89, 5.45)
Triglycerides, mmol/L	1.59 (1.11, 2.22)
LDL-C, mmol/L	2.81 (2.28, 3.42)
HDL-C, mmol/L	1.04 (0.88, 1.22)
TyG index	9.011 (8.585, 9.518)
AIP	0.180 (-0.003, 0.350)
NHR	4.333 (2.956, 6.198)
PIV	265.83 (165.41, 491.55)
Gensini score	34.0 (14.0, 56.0)

TyG, AIP, NHR and PIV were all positively correlated with the Gensini score, with Spearman's correlation coefficients of 0.124 ($P < 0.001$), 0.101 P=0.005, 0.327 ($P < 0.001$) and 0.316 ($P < 0.001$), respectively. The correlation coefficients for NHR and PIV were higher than those for TyG and AIP (Table 2).

Table 2. Spearman correlations of TyG, AIP, NHR and PIV with Gensini score

Indicator	Spearman ρ	P value	Direction
TyG	0.124	<0.001	Positive
AIP	0.101	0.005	Positive
NHR	0.327	<0.001	Positive
PIV	0.316	<0.001	Positive

ρ, Spearman rank correlation coefficient.

After grouping by quartiles of TyG, AIP, NHR and PIV, statistically significant differences in Gensini scores were observed between the different quartile groups for each parameter. The median Gensini scores for the TyG Q1–Q4 groups were 30.5, 34.0, 36.0 and 40.0, respectively (Kruskal–Wallis test, P = 0.002); for AIP, they were 27.5, 34.0, 34.0 and 38.0 respectively (P = 0.031); for NHR, they were 18.5, 26.0, 40.0 and 44.0 respectively (P < 0.001); PIV were 20.0, 32.0, 32.0 and 48.0, respectively (P < 0.001). The Jonckheere-Terpstra trend test showed that, as the four parameters progressed from Q1 to Q4, the Gensini scores exhibited a significant overall upward trend; specifically, the P-values for trend were all <0.001 for TyG, NHR and PIV, whilst the P-value for trend for AIP was 0.003 (Table 3, Figure 2).

Table 3. Gensini score across quartiles of TyG, AIP, NHR and PIV

Indicator	Quartile	Range	n	Gensini score, median (IQR)	P value*	P for trend†
TyG	Q1	≤8.585	196	30.5 (10.0, 50.0)	0.002	<0.001
	Q2	8.585–9.011	195	34.0 (14.0, 56.0)		
	Q3	9.011–9.518	195	36.0 (14.0, 56.0)		
	Q4	>9.518	195	40.0 (20.0, 67.0)		
AIP	Q1	≤−0.003	196	27.5 (10.0, 50.2)	0.031	0.003
	Q2	−0.003–0.180	195	34.0 (14.5, 59.5)		
	Q3	0.180–0.350	195	34.0 (16.0, 56.0)		
	Q4	>0.350	195	38.0 (20.0, 58.0)		
NHR	Q1	≤2.956	196	18.5 (8.0, 42.2)	<0.001	<0.001
	Q2	2.956–4.333	195	26.0 (10.0, 50.0)		
	Q3	4.333–6.198	195	40.0 (18.5, 65.0)		
	Q4	>6.198	195	44.0 (30.0, 80.0)		
PIV	Q1	≤165.41	196	20.0 (8.0, 48.0)	<0.001	<0.001
	Q2	165.41–265.83	195	32.0 (11.0, 53.0)		
	Q3	265.83–491.55	195	32.0 (15.5, 50.0)		
	Q4	>491.55	195	48.0 (32.0, 80.0)		

** P values were obtained using the Kruskal–Wallis test.*

† P for trend was calculated using the Jonckheere–Terpstra trend test with 10,000 permutations.

IQR, interquartile range; TyG, triglyceride-glucose index; AIP, atherogenic index of plasma; NHR, neutrophil-to-HDL-C ratio; PIV, pan-immune-inflammation value.

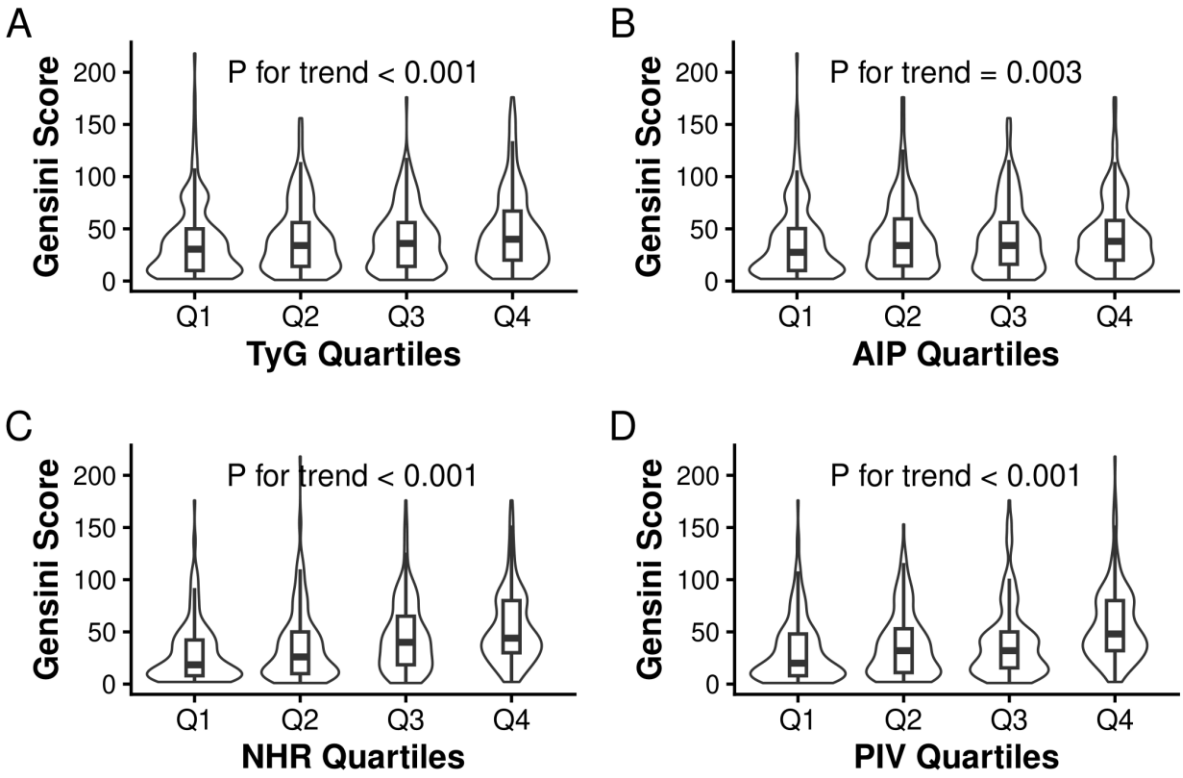


Figure 2. Distribution of Gensini scores across quartiles of TyG, AIP, NHR and PIV.

In the unadjusted model, TyG, AIP, NHR and PIV were all positively correlated with ln(Gensini score + 1). After adjusting for age, sex and BMI, the associations for TyG, NHR and PIV remained statistically significant; the β value for AIP was 0.057 (95% CI: −0.009 to 0.123, P = 0.092). In Model 3, NHR (β = 0.137, 95% CI: 0.066–0.208, P < 0.001) and PIV (β = 0.154, 95% CI: 0.086–0.222, P < 0.001) maintained independent positive associations with ln(Gensini score + 1) in their respective models. The β for TyG was 0.026 (95% CI: −0.040 to 0.092, P = 0.437), and that for AIP was 0.031 (95% CI: −0.031 to 0.093, P = 0.330); neither association reached statistical significance (Table 4). Based on the regression coefficients from Model 3, for every one standard deviation increase in ln(NHR) and ln(PIV), the conditional geometric mean for Gensini+1 is approximately 14.7 per cent and 16.7 per cent higher, respectively..

Table 4. Multivariable associations of TyG, AIP, NHR and PIV with Gensini score

Indicator	Model 1		Model 2		Model 3	
Indicator	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
TyG	0.134 (0.070, 0.198)	<0.001	0.117 (0.054, 0.179)	<0.001	0.026 (−0.040, 0.092)	0.437
AIP	0.110 (0.046, 0.175)	<0.001	0.057 (−0.009, 0.123)	0.092	0.031 (−0.031, 0.093)	0.330
NHR	0.318 (0.254, 0.383)	<0.001	0.276 (0.202, 0.349)	<0.001	0.137 (0.066, 0.208)	<0.001
PIV	0.328 (0.267, 0.390)	<0.001	0.290 (0.227, 0.353)	<0.001	0.154 (0.086, 0.222)	<0.001

Model 1: unadjusted.

Model 2: adjusted for age, sex, and BMI.

Model 3: additionally adjusted for smoking history, hypertension, diabetes mellitus, family history of coronary artery disease, chronic kidney disease, eGFR, and LVEF.

β coefficients represent the change in ln(Gensini score + 1) per 1-SD increase in each index. NHR and PIV were natural-log transformed before standardization.

HC3 heteroskedasticity-robust standard errors were used to calculate 95% confidence intervals and P values.

CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.

After adjusting for Model 3 covariates, the overall associations between NHR and PIV were statistically significant (P overall: 0.001 and <0.001, respectively), whilst the tests for non-linearity were not statistically significant (P for non-linearity: 0.401 and 0.961, respectively). The P-value for the overall association with TyG was 0.419, and the P-value for the non-linearity test was 0.322; the corresponding P-values for AIP were 0.818 and 0.942 (Figure 3).

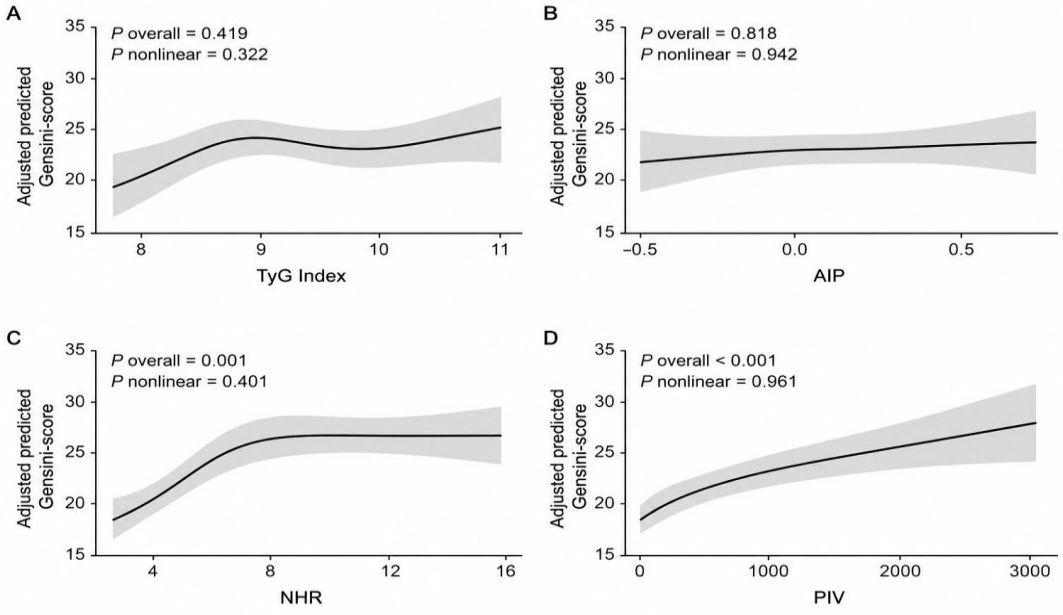


Figure 3. Restricted cubic spline associations of TyG, AIP, NHR and PIV with Gensini score.

NHR showed a strong positive correlation with PIV (Spearman's $\rho = 0.760$, $P < 0.001$). After simultaneously including standardised ln(NHR) and standardised ln(PIV) in Model 3, the VIFs for the two variables were 2.42 and 2.30, respectively. The positive association between PIV and ln(Gensini score + 1) remained statistically significant ($\beta = 0.117$, 95% CI: 0.033–0.201, $P = 0.0065$); the β for NHR was 0.059 (95% CI: −0.027–0.144, $P = 0.179$).In a sensitivity analysis additionally adjusting for clinical presentation (STEMI, NSTEMI, unstable angina, and stable angina), PIV remained significantly associated with ln(Gensini score + 1), whereas the association for NHR was attenuated and was no longer statistically significant.

The 99th percentile of PIV was 3,278.796, with a total of eight patients exceeding this threshold. After excluding these eight patients, recalculating ln(PIV) and its standardised values, and repeating the Model 3 analysis, the β coefficient for PIV was 0.149 (95% CI approximately 0.080–0.218, $P < 0.001$), which was close to the effect estimate from the primary analysis β=0.154.

The effect estimates for PIV and ln(Gensini score + 1) were positive in all subgroups. The β values for the female and male subgroups were 0.216 (95% CI: 0.086–0.346) and 0.097 (95% CI: 0.016–0.178), respectively; for the non-diabetic and diabetic subgroups, they were 0.166 (95% CI: 0.080–0.253) and 0.106 (95% CI: −0.024–0.236), respectively; the subgroups without and with hypertension were 0.209 (95% CI: 0.100–0.317) and 0.115 (95% CI: 0.019–0.211), respectively; The β values for the non-smokers and smokers subgroups were 0.199 (95% CI: 0.100–0.299) and 0.086 (95% CI: approximately −0.0004–0.173), respectively; the lower BMI and higher BMI subgroups were 0.176 (95% CI: 0.088–0.264) and 0.134 (95% CI: 0.020–0.247), respectively. The P-values for the interactions between gender, diabetes, hypertension, smoking and BMI were 0.131, 0.060, 0.053, 0.089 and 0.883, respectively, none of which reached statistical significance (Figure 4).

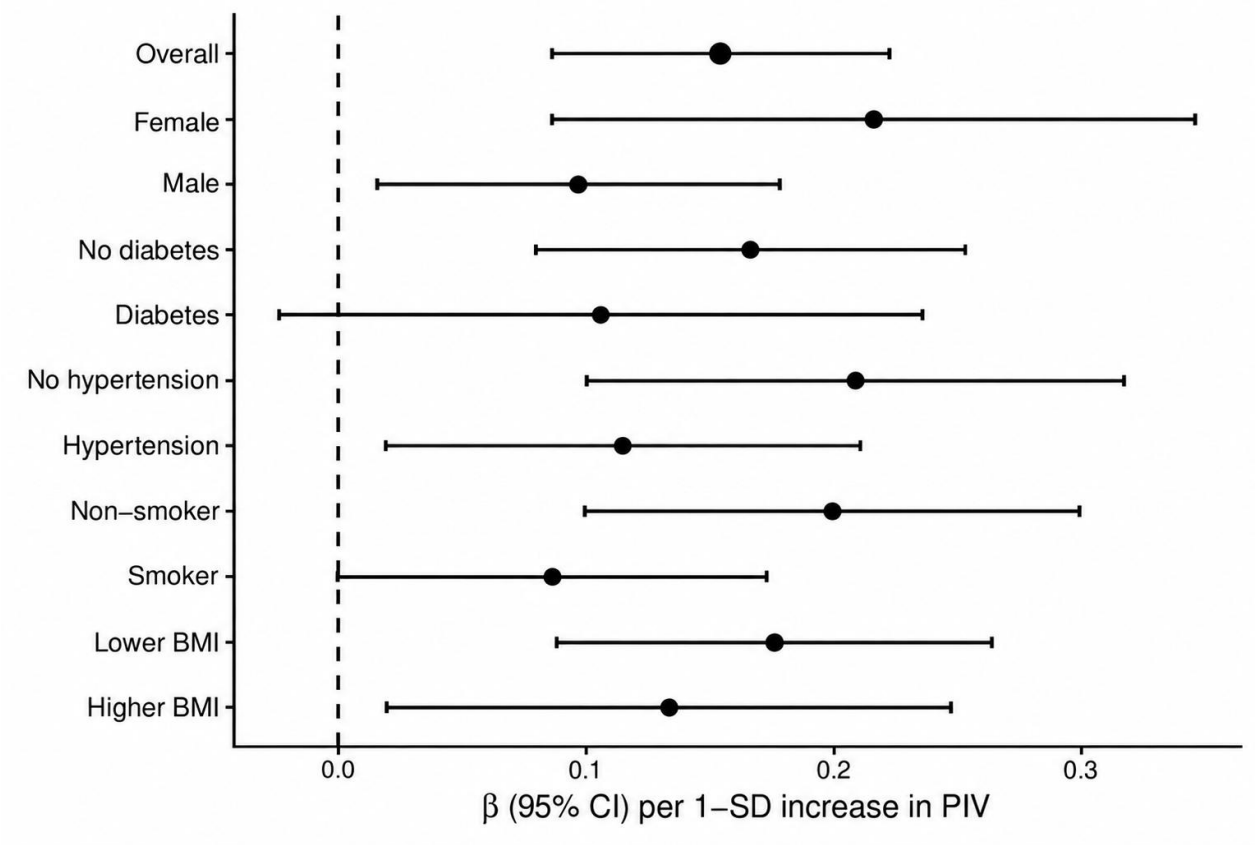


Figure 4. Subgroup analyses of the association between PIV and Gensini score.

4 Discussion

This study compared the associations between TyG, AIP, NHR and PIV and coronary artery disease burden in 781 patients with early-onset coronary heart disease. All four markers were positively correlated with the Gensini score, and quartile analysis also revealed an overall increasing trend. After adjusting for clinical covariates, NHR and PIV maintained a positive association in their respective models, whilst the associations for TyG and AIP were not statistically significant. When both NHR and PIV were included in the model, the association with PIV remained statistically significant; analyses excluding extremely high PIV values yielded similar results. These findings suggest that NHR and PIV exhibit a more stable independent association in the context of inflammatory and immune states, with PIV showing particularly stable results across various analytical frameworks.

The hyperglycaemia, elevated triglyceride levels, oxidative stress and endothelial dysfunction associated with insulin resistance provide a biological explanation for the link between TyG and the burden of coronary artery disease. Wang et al. observed that TyG was independently associated with multivessel coronary artery disease in 2,792 patients with coronary heart disease, and that a dose–response relationship was present.[6];Studies using the Gensini score have also reported a positive association between TyG and lesion burden[7].In this study, TyG was associated with lesion burden in both unadjusted analyses and those adjusted for age, sex and BMI; however, upon inclusion of the remaining clinical covariates, the β coefficient decreased from 0.117 in Model 2 to 0.026 in Model 3, and the association was no longer statistically significant. The

study population, outcome measures and adjustment variables may be the three specific factors contributing to the differences in the above results. The composition of risk factors across different populations and the adjustment strategies employed in different models may both influence the estimated associations. Previous studies have often assessed coronary lesions using categorical outcomes such as multi-vessel disease, whereas this study utilised the continuous Gensini score and focused on patients with early-onset coronary heart disease. Consequently, the fact that the regression coefficient for TyG decreased as covariates were included in this study indicates that the estimated association between TyG and lesion burden is sensitive to the adjustment framework.

Research on AIP has also reported a link between it and the severity of coronary artery disease[8],Some recent systematic reviews and meta-analyses have extended this association to outcomes such as multivessel disease, coronary artery calcification and plaque progression[9].Furthermore, CT angiography studies provide another form of imaging evidence linking AIP to anatomical lesions[13].However, in this study, the β coefficient for AIP decreased from 0.110 (unadjusted) to 0.057 in Model 2 and 0.031 in Model 3; the 95 per cent confidence intervals for both the latter two models spanned zero. When combined with the results for TyG, the association between TyG and AIP was not statistically significant after full adjustment.

In contrast to the above findings, NHR remained positively correlated with lesion burden even after adjusting for clinical covariates. Neutrophils may contribute to endothelial damage, lipid oxidation and plaque inflammation by releasing reactive oxygen species, proteases and inflammatory mediators, as well as by forming neutrophil extracellular traps[18].HDL, on the other hand, is involved in the reverse transport of cholesterol and possesses anti-inflammatory and antioxidant properties; its concentration and function reflect biological information at different levels respectively[19].Consequently, the NHR combines neutrophil count with HDL-C concentration to characterise a patient's condition from the dual perspectives of inflammation and lipid metabolism. In this study, the NHR remained positively correlated with ln(Gensini score + 1) even after adjusting for clinical covariates ($\beta = 0.137$, 95% CI: 0.066–0.208, $P < 0.001$). This finding is consistent with the association between the NHR and the Gensini score as well as severe coronary lesions observed by Gao et al. in patients with stable coronary heart disease[11].This study yielded corresponding results in a cohort of patients with early-onset coronary heart disease, thereby providing population-specific evidence for the association between NHR and coronary lesion burden, and offering insights for further research into the pathological characteristics associated with both inflammation and lipid metabolism.

PIV comprises the counts of neutrophils, monocytes, platelets and lymphocytes; its biological context involves multiple processes, including inflammation, immunity and thrombosis. Modern theories of atherosclerosis suggest that cells of both the innate and adaptive immune systems are involved in plaque formation and progression at different stages of atherosclerosis[20, 21].In addition to their role in thrombus formation, platelets can also influence the pathological process by releasing inflammatory mediators, recruiting white blood cells and interacting with endothelial cells[22].These intercellular connections provide clues as to the mechanism underlying the association between PIV and the burden of coronary lesions. Cetinkaya et al. found that, in patients with non-ST-elevation myocardial infarction, PIV was associated with the SYNTAX

score and a higher degree of coronary lesion complexity[12];Demirtola et al. also observed an association between PIV and more severe coronary lesions in patients undergoing coronary CT angiography[13].Recent studies on early-onset coronary heart disease have investigated the role of PIV and TyG in disease identification and prognostic assessment[14].In this study, the Gensini score was used to characterise the burden of coronary artery disease. It was observed that, after adjusting for clinical covariates, PIV was independently and positively correlated with ln(Gensini score + 1) ($\beta = 0.154$, 95% CI: 0.086–0.222, $P < 0.001$), thereby providing further evidence of the association between PIV and coronary anatomical lesions in patients with PCAD.

It is worth noting that there is a strong correlation between NHR and PIV (Spearman's $\rho = 0.760$); both include neutrophil counts, and there is an overlap in their composition. In the exploratory mutual adjustment model, the association with PIV remained statistically significant ($\beta = 0.117$, 95% CI: 0.033–0.201, $P = 0.0065$), whilst the β for NHR was 0.059 (95% CI: −0.027–0.144, $P = 0.179$). These results indicate that, after adjusting for NHR and established clinical covariates, PIV remains positively associated with disease burden. The information on monocytes, platelets and lymphocytes contained within PIV provides a direction for further research to elucidate this association.

RCS analysis revealed that, after adjusting for Model 3 covariates, the overall association between NHR and PIV was statistically significant, whilst none of the non-linearity tests reached statistical significance. On the logarithmic modelling scale adopted in this study, the results were consistent with a near-linear positive association; quartile analysis also showed that the Gensini score increased overall as the indicator levels rose. After excluding the eight patients with PIV values above the 99th percentile and re-standardising the data, the β coefficient for PIV was 0.149, which is close to the 0.154 observed in the main analysis, and the association remained statistically significant. This result supports the robustness of the association between PIV and disease burden following the exclusion of extremely high values. After stratification by sex, diabetes, hypertension, smoking status and BMI, the estimated effects in each subgroup were positive, whilst none of the interaction tests reached statistical significance.

TyG, AIP, NHR and PIV can all be calculated from routine blood glucose, lipid profile or blood cell count measurements, making them readily available from clinical laboratory data. In the assessment of coronary lesions in patients with PCAD, the metabolic and inflammatory status reflected by routine laboratory parameters can provide information on inter-individual differences in lesion burden. The adjusted associations between NHR and PIV observed in this study provide a basis for further evaluating the application of inflammation-related composite indices in the auxiliary assessment of lesion burden. Moving from observational studies to clinical application requires these indices to be contextualised within specific assessment scenarios. Future studies may incorporate PIV into existing clinical models to examine its incremental discriminatory power, calibration performance and clinical net benefit in identifying high lesion burden, and to validate these findings in independent cohorts.

This study evaluated four composite indices within the same cohort of patients with early-onset coronary heart disease and under a standardised framework for adjusting for covariates, thereby facilitating a comparison of

their association patterns with coronary lesion burden. The use of the continuous Gensini score preserved the gradient information of the lesion burden, whilst mutual adjustment and outlier sensitivity analyses supplemented the main findings by examining both the overlap between indices and the distribution of data. The study population comprised patients from a single centre who underwent coronary angiography; case selection, as well as unmeasured factors such as medication, diet and socioeconomic status, may have influenced the association estimates. Cross-sectional data reflect the relationship between the indices and the burden of coronary lesions at a single point in time and cannot establish a causal sequence. As the indices were based on a single baseline assessment, pharmacotherapy, short-term stress or unrecognised inflammatory states may have influenced the measured values; dynamic changes in the indices require evaluation using longitudinal data. The Gensini score is derived from angiographic interpretation; this study did not quantify inter-observer agreement. The applicability of the above associations to other centres and to coronary heart disease populations of different ages could be further tested using independent samples.

5 Conclusion

Among patients with early-onset coronary heart disease at our centre, TyG, AIP, NHR and PIV were all positively correlated with the Gensini score. After adjusting for established clinical covariates, NHR and PIV maintained an independent positive association in their respective models, whilst the associations for TyG and AIP were not statistically significant. The association with PIV remained statistically significant after further adjustment for NHR and exclusion of outliers, supporting a robust link between PIV and the coronary artery disease burden in patients with early-onset coronary heart disease.

6 Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Qingdao Municipal Hospital (approval number: 2026-KTLL-045). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are not publicly available due to patient privacy and confidentiality considerations. Requests for access to de-identified data should be directed to the corresponding author, Fangjie Hou (qdslyyhfj@163.com), and will be considered in accordance with applicable institutional requirements.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Y.Y. designed the study, performed the statistical analyses, prepared the figures and tables, and drafted and revised the manuscript. K.Z. and H.S. collected and verified the data. F.H. supervised the study, obtained funding, and served as the corresponding author.All authors have read and approved the final manuscript.

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During the preparation of this work, the authors used ChatGPT for language polishing only. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the manuscript.

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