

# Prognostic Impact of Metabolic and Inflammatory Risk for Periprocedural MI and Long-Term Events in Three-Vessel Disease Patients

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**Purpose:** Risk stratification and management of three-vessel coronary artery disease (3VD) remains challenging. Patients with 3VD tolerate greater metabolic and inflammatory burdens than patients with single- and double-vessel coronary artery disease. This study aimed to evaluate the prognostic value of triglyceride-glucose (TyG) index and high-sensitive C-reactive protein (hsCRP), which representing metabolic and inflammatory burdens respectively in a 3VD cohort.

**Patients and Methods:** This is a retrospective observational study, totally 4495 patients with 3VD were enrolled in the study and divided into 4 groups according to TyG ( $\geq$  or  $<8.5$ ) and hsCRP ( $\leq$  or  $>2\text{mg/L}$ ). The primary endpoints were periprocedural myocardial infarction (PMI) following percutaneous coronary intervention (PCI) and major adverse cardiovascular events (MACCEs). Restricted cubic spline (RCS), multivariate Cox proportional hazard models, C-index and net reclassification improvement (NRI) were used for analyses.

**Results:** The median follow-up time was 2.4 years. 3VD patients with TyG $\geq 8.5$  and hsCRP $>2\text{mg/L}$  exhibited 70%-145% increase risk of PMI according to different definitions. Multivariate Cox regression analyses showed that hsCRP $>2\text{mg/L}$  was associated with approximately 30% increased risk of MACCEs in 3VD patients with TyG $\geq 8.5$  (HR: 1.31, 95% CI: 1.02–1.69,  $p = 0.036$ ) and TyG $<8.5$  (HR: 1.31, 95% CI: 1.02–1.68,  $p = 0.034$ ) (both  $p < 0.05$ ). RCS analysis regarding hsCRP as continuous variable found increased hsCRP is positively associated with MACCEs among 3VD patients independent of TyG index (all  $p < 0.05$ ). Finally, the NRI for PMI (0.38,  $p < 0.01$ ) and MACCEs (0.16,  $p < 0.01$ ) were also significantly increased after hsCRP and TyG were added to the baseline model.

**Conclusion:** 3VD patients with TyG $\geq 8.5$  and hsCRP $>2\text{mg/L}$  has significantly increased risks of PMI. HsCRP $>2\text{mg/L}$ , alone or in combination of TyG $\geq 8.5$ , has significantly increased risk of MACCEs among 3VD individuals, highlighting the necessity of managing metabolic and inflammatory burdens simultaneously in 3VD patients.

**Keywords:** three-vessel disease, triglyceride-glucose index, hsCRP, periprocedural myocardial infarction

## Introduction

Three-vessel coronary artery disease (3VD), a severe and prognostically significant form of coronary artery disease (CAD), is defined as more than 50% stenosis in the left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA). Compared to patients with single-vessel or double-vessel CAD, those with 3VD exhibit three key characteristics: a greater atherosclerotic burden, a higher prevalence of cardiovascular risk factors, and more complex coronary lesions (such as chronic total occlusions).<sup>1,2</sup> As an advanced subtype of CAD, 3VD confers an elevated risk of adverse cardiovascular outcomes, particularly in patients with metabolic comorbidities.<sup>3,4</sup>

Triglyceride-glucose (TyG) index, calculated as  $\text{Ln}[\text{fasting triglycerides (mg/dL)} \times \text{fasting glucose (mg/dL)} / 2]$ , is a well-established marker for insulin resistance (IR) and reflects the metabolic burdens of the patients, especially dyslipidemia and hyperglycemia.<sup>5</sup> Accumulating evidence demonstrated that TyG index is associated with coronary artery calcification, atherosclerotic severity and adverse outcomes across diverse populations.<sup>6–8</sup> Moreover, prior studies have linked TyG index to metabolic risk burden and adverse outcomes of 3VD patients.<sup>9</sup>

Metabolic disorders are prevalent among the CVD patients, which is bidirectionally associated with inflammation. Metabolic stress prompts the secretion of pro-inflammatory factors and amplifies inflammatory signaling cascades. In reciprocity, chronic low-grade inflammation exacerbates metabolic dysfunctions by interfering signaling pathways relevant to insulin resistance, lipid metabolism and glucose transport.

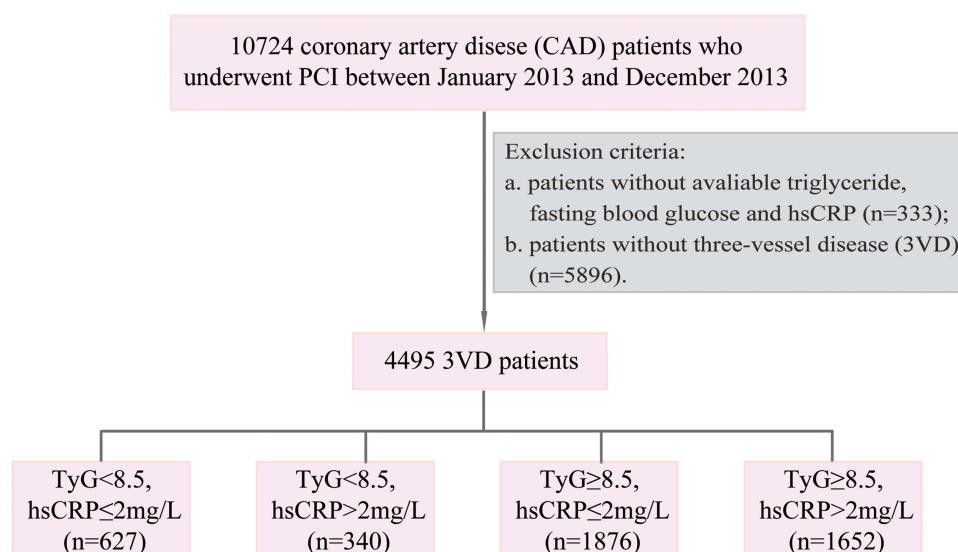
Growing evidence recognized atherosclerosis as a chronic inflammatory disease.<sup>10</sup> High-sensitivity C-reactive protein (hsCRP) is a well-validated surrogate for systemic inflammation. JUPITER trial demonstrated the benefits of anti-inflammatory therapy of statin among populations with  $\text{LDL-C} < 130 \text{ mg/dL}$  and  $\text{hsCRP} \geq 2.0 \text{ mg/L}$ .<sup>11</sup> Subsequent trials, including COLCOT and LoDoCo2, further established that anti-inflammatory therapy (such as colchicine) contributes to lowering the risk of adverse cardiovascular events, particularly in CAD patients already receiving statin therapy.<sup>12,13</sup> The 2024 European Society of Cardiology (ESC) guidelines underscore the importance of targeting inflammation in CVD, reflecting a paradigm shift from purely lipid-lowering strategies to integrated approaches addressing the inflammatory pathophysiology of atherosclerosis.<sup>14,15</sup> HsCRP is identified as an independent prognostic factor for long-term adverse cardiovascular outcomes in 3VD patients with type 2 diabetes (T2DM), but not in nondiabetic individuals.<sup>16</sup> However, it remains unclear whether hsCRP and the TyG index, which reflect inflammatory and metabolic burden respectively, improve risk stratification in 3VD patients.

Prior studies have noticed the predictive values of TyG index and hsCRP among CAD patients for long-term adverse outcomes, however, the predictive value of TyG index and hsCRP among 3VD patients remains unclear. Periprocedural myocardial infarction (PMI) following percutaneous coronary intervention (PCI) is a common complication after PCI, affecting 3.2%-5.5% CAD patients after PCI and independently predicting a significantly increased risk of all-cause death.<sup>17,18</sup> Previous researches mainly focus on the prognostic value of PMI following PCI, few studies investigated the risk factors contributing to PMI following PCI. This study firstly investigated the predictive value of TyG index and hsCRP in combination for short-term PMI following percutaneous coronary intervention (PCI), which is a common complication after PCI, and long-term major adverse cardiovascular events (MACCEs) in a real-world 3VD cohort. By integrating the assessment of metabolic (reflected by the TyG index) and inflammatory (reflected by hsCRP) risk factors, this study addresses a critical gap in previous literature: the absence of systematic investigation into the concurrent predictive role of metabolic and inflammatory biomarkers in the 3VD population.

## Methods

### Study Design and Patient Selection

This is a single-center retrospective observational study, we enrolled 10391 CAD patients with available high-sensitive C-reactive protein (hsCRP) and TyG index and underwent PCI between January 2013 and December 2013. And then enrolled patients with angiographically confirmed three-vessel disease (3VD). Finally, 4495 patients with 3VD were included (Figure 1). 3VD was defined as angiographically confirmed more than 50% stenosis in all three main epicardial coronary arteries, including left anterior descending, left circumflex and right coronary (with or without involvement of the left main artery).  $\text{TyG index} = \text{Ln} [\text{triglyceride (mg/dl)} \times \text{fasting plasma glucose (mg/dl)} / 2]$ .<sup>19</sup> Totally 4495 patients were divided into 4 groups:  $\text{TyG} < 8.5$  and  $\text{hsCRP} \leq 2 \text{ mg/L}$  ( $n = 627$ ),  $\text{TyG} < 8.5$  and  $\text{hsCRP} > 2 \text{ mg/L}$  ( $n = 340$ ),  $\text{TyG} \geq 8.5$  and  $\text{hsCRP} \leq 2 \text{ mg/L}$  ( $n = 1876$ ),  $\text{TyG} \geq 8.5$  and  $\text{hsCRP} > 2 \text{ mg/L}$  ( $n = 1652$ ). Patients with TyG index upper than 8.5 was regarded as insulin resistance, which has been validated in previous studies.<sup>20,21</sup> The cutoff of hsCRP, a sign of inflammation and residual cardiovascular risks, was defined at 2 according to previous study and current guideline.<sup>12,16</sup> This study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Institutional Review Board of the National Center of Cardiovascular Diseases. Written informed consent was obtained from all participants.



**Figure 1** The flowchart of the study design.

**Abbreviations:** 3VD, three-vessel disease; TyG, Triglyceride glucose index; hsCRP, high sensitivity C-reactive protein.

## Clinical Variables

Patient data were systematically abstracted by trained personnel from medical records at participating hospitals. The dataset included admission diagnoses, demographic characteristics, medical history, laboratory test results, vital signs, reperfusion therapy details, pre-hospital medications administered within the preceding 2 weeks, and in-hospital medications prescribed within 24 hours of initial medical contact. Peripheral venous blood specimens were collected following an overnight fasting period (>8 hours) and subsequently processed in a clinical laboratory setting.

## Follow-Up and Study Endpoint

The follow-up of each individual was conducted at 30 days, 6 month and each year after discharge by telephone or outpatient. This study evaluated the predictive value of hsCRP and TyG for in-hospital adverse outcomes and long-term outcomes. The primary endpoint was PMI following PCI and major adverse cardiac and cerebrovascular events (MACCEs), composed of all-cause death, myocardial infarction, stent thrombosis and target vessel revascularization (TVR). Secondary outcomes included all-cause death, myocardial infarction, stent thrombosis and TVR. PMI was defined by the Society for Cardiovascular Angiography and Interventions (SCAI), the third universal definition of myocardial infarction (3<sup>rd</sup>UDMI) criteria, and the fourth universal definition of myocardial infarction (4<sup>th</sup>UDMI) criteria.<sup>22–24</sup> We adopted the following definitions: (1) All-cause death is caused by any causes; (2) myocardial infarction per the fourth universal definition;<sup>22</sup> (3) TVR as any repeat PCI or CABG of the index vessel; (4) stent thrombosis according to ARC classification (definite/probable/possible).<sup>25</sup>

## Statistical Analysis

Kaplan-Meier curves were employed to assess event-free survival, with intergroup comparisons performed by Log rank test. Multivariable Cox proportional hazards models help to evaluate the effect of potential confounders on the relationship between hsCRP level and clinical outcomes. Significant variables ( $p < 0.05$ ) in the univariate analysis and conventional risk factors were included in the multivariate models. Model 1 was adjusted for age. Model 2 was adjusted for age, gender and smoking. Model 3 included adjustment for age, gender, smoking,  $\text{BMI} \geq 25 \text{ kg/m}^2$ , chronic occlusion and hypertension. The Concordance index (C-index) and net reclassification improvement (NRI) were calculated to assess the added prognostic value of hsCRP to a model containing traditional risk factors (including age, gender,  $\text{BMI} \geq 25 \text{ kg/m}^2$ , smoking and  $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$ ). Restricted cubic splines (RCS) analysis was employed to examine the

association between hsCRP and primary/secondary endpoints in the three vessel disease patients with TyG index < and  $\geq$  8.5. P values < 0.05 were considered statistically significant. Analyses were carried out using R 4.2.2.

## Results

### Baseline Characteristics

This study eventually enrolled 4495 3VD patients with available hsCRP and TyG index. 3VD patients were stratified into 4 groups: TyG < 8.5 and hsCRP  $\leq$  2mg/L (n = 627), TyG < 8.5 and hsCRP > 2mg/L (n = 340), TyG  $\geq$  8.5 and hsCRP  $\leq$  2mg/L (n = 1876), TyG  $\geq$  8.5 and hsCRP > 2mg/L (n = 1652) (Figure 1). Table 1 presented the baseline characteristics of all patients. Compared to patients with TyG < 8.5, patients with TyG  $\geq$  8.5 were more likely to be exposed to diabetes mellitus, total occlusion, hypertension and exhibited higher rates of BMI (all  $p$  < 0.05). In patients with TyG  $\geq$  8.5, compared to individuals with hsCRP  $\leq$  2mg/L, patients with hsCRP > 2mg/L were more likely to be male, diabetes mellitus, hypertension, total occlusion, history of MI, IABP use, cardiac shock and exhibited higher BMI. In patients with TyG < 8.5, smoking, prior PCI, history of MI, IABP use, cardiac shock and COPD were more prevalent among patients with hsCRP > 2mg/L in comparison to patients with hsCRP  $\leq$  2mg/L.

### Adverse Outcomes

We recorded a total of 106 (8.6%), 126 (10%) and 216 (17.8%) PMI according to SCAI, 4<sup>th</sup> UDMI and 3<sup>rd</sup> UDMI definition of PMI, respectively. In the 1000 days follow-up, 393 (35.2%) MACCEs, 68 (7.3%) deaths, 302 (26.5%) TVR, 70 MI (5%) and 53 (4.6%) stent thrombosis were recorded. Detailed outcomes were illustrated in Table 2. In the logistic regression, compared to patients with TyG < 8.5 and hsCRP  $\leq$  2mg/L, patients with TyG  $\geq$  8.5 and hsCRP > 2mg/L exhibited 70% (OR: 1.70, 95% CI: 0.90–3.20,  $p$  = 0.1), 145% (OR: 2.45, 95% CI: 1.25–4.80,  $p$  = 0.009) and 75% (OR: 1.75, 95%

**Table 1** Baseline Characteristics

	Total population		TyG < 8.5				TyG $\geq$ 8.5		
	TyG < 8.5 (n=967)	TyG $\geq$ 8.5 (n=3528)	p value	hsCRP $\leq$ 2 (n=627)	hsCRP > 2 (n=340)	p value	hsCRP $\leq$ 2 (n=1876)	hsCRP > 2 (n=1652)	p value
Age (mean $\pm$ SD), year	61.93 $\pm$ 10.01	58.95 $\pm$ 10.04	<0.001	61.71 $\pm$ 9.84	62.33 $\pm$ 10.33	<0.001	58.76 (9.83)	59.16 (10.28)	0.239
Male (%)	791 (81.8)	2662 (75.5)	<0.001	509 (81.2)	282 (82.9)	0.555	1446 (77.1)	1216 (73.6)	0.019
BMI (mean $\pm$ SD)	24.85 (3.28)	26.23 (3.15)	<0.001	24.76 (3.26)	25.01 (3.30)	0.256	25.96 (2.99)	26.54 (3.30)	<0.001
Type of diagnosis			0.095			0.747			<0.001
-Myocardial infarction (%)	231 (23.9)	936 (26.5)		145 (23.1)	86 (25.3)		443 (23.6)	493 (29.8)	
-Unstable angina (%)	705 (72.9)	2510 (71.1)		462 (73.7)	243 (71.5)		1379 (73.5)	1131 (68.5)	
-Stable angina (%)	31 (3.2)	82 (2.3)		20 (3.2)	11 (3.2)		54 (2.9)	28 (1.7)	
Smoking (%)	551 (57.0)	2016 (57.1)	0.957	342 (54.5)	209 (61.5)	0.045	1043 (55.6)	973 (58.9)	0.052
Diabetes mellitus (%)	186 (19.2)	1421 (40.3)	<0.001	132 (21.1)	54 (15.9)	0.063	722 (38.5)	699 (42.3)	0.023
Total occlusions (%)	169 (17.5)	742 (21.0)	0.017	100 (15.9)	69 (20.3)	0.107	356 (19.0)	386 (23.4)	0.002
Hypertension (%)	622 (64.3)	2439 (69.1)	0.005	389 (62.0)	233 (68.5)	0.052	1245 (66.4)	1194 (72.3)	<0.001
Prior PCI (%)	288 (29.8)	1011 (28.7)	0.519	206 (32.9)	82 (24.1)	0.006	558 (29.7)	453 (27.4)	0.137
Prior CABG (%)	62 (6.4)	245 (6.9)	0.61	45 (7.2)	17 (5.0)	0.237	132 (7.0)	113 (6.8)	0.871
Prior cerebrovascular disease (%)	125 (12.9)	429 (12.2)	0.557	71 (11.3)	54 (15.9)	0.055	209 (11.1)	220 (13.3)	0.055
Peripheral artery disease (%)	38 (3.9)	109 (3.1)	0.23	29 (4.6)	9 (2.6)	0.181	68 (3.6)	41 (2.5)	0.063
History of MI (%)	350 (36.2)	1372 (38.9)	0.136	206 (32.9)	144 (42.4)	0.004	621 (33.1)	751 (45.5)	<0.001
IABP use (%)	12 (1.2)	47 (1.3)	0.951	3 (0.5)	9 (2.6)	0.009	16 (0.9)	31 (1.9)	0.012
IVUS use (%)	39 (4.0)	134 (3.8)	0.809	21 (3.3)	18 (5.3)	0.195	72 (3.8)	62 (3.8)	0.965
Cardiac shock (%)	8 (0.8)	39 (1.1)	0.565	1 (0.2)	7 (2.1)	0.006	9 (0.5)	30 (1.8)	<0.001
COPD (%)	23 (2.4)	71 (2.0)	0.563	8 (1.3)	15 (4.4)	0.005	32 (1.7)	39 (2.4)	0.207
Lesion number >3 (%)	14 (1.4)	74 (2.1)	0.246	6 (1.0)	8 (2.4)	0.146	33 (1.8)	41 (2.5)	0.168
Stent number >3 (%)	111 (11.5)	378 (10.7)	0.536	57 (9.1)	54 (15.9)	0.002	199 (10.6)	179 (10.8)	0.870

**Abbreviations:** TyG, Triglyceride glucose index; hsCRP, high sensitivity C-reactive protein; BMI, body mass index; PCI, percutaneous coronary intervention; MI, myocardial infarction; CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump; IVUS, intravenous ultrasound; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

**Table 2** In-Hospital and Long-Term Outcomes of 3VD Patients Stratified According to TyG and hsCRP Status

	TyG<8.5, hsCRP≤2 (n=627)	TyG<8.5, hsCRP>2 (n=340)	TyG≥8.5, hsCRP≤2 (n=1876)	TyG≥8.5, hsCRP>2 (n=1652)	p value
<b>In-hospital events</b>					
Perioperative MI SCAI	12 (1.9)	6 (1.8)	31 (1.7)	53 (3.2)	0.015
Perioperative MI 4 <sup>th</sup> UDMI	10 (1.6)	7 (2.1)	46 (2.5)	63 (3.8)	0.011
Perioperative MI 3 <sup>rd</sup> UDMI	23 (3.7)	13 (3.8)	77 (4.1)	103 (6.2)	0.008
<b>long-term events</b>					
MACCE	39 (6.2)	37 (10.9)	155 (8.3)	162 (9.8)	0.020
All-cause death	8 (1.3)	11 (3.2)	22 (1.2)	27 (1.6)	0.035
TVR	28 (4.5)	27 (7.9)	120 (6.4)	127 (7.7)	0.034
MI	9 (1.4)	5 (1.5)	29 (1.5)	27 (1.6)	0.986
Stent Thrombosis	7 (1.1)	4 (1.2)	25 (1.3)	17 (1.0)	0.869

**Abbreviations:** TyG, Triglyceride glucose index; hsCRP, high sensitivity C-reactive protein; SCAI, Society for Cardiovascular Angiography and Interventions; 3<sup>rd</sup> UDMI, the third universal definition of myocardial infarction criteria; 4<sup>th</sup> UDMI, the fourth universal definition of myocardial infarction criteria; 3VD, three-vessel disease; MI, myocardial infarction; MACCEs, major adverse cardiac and cerebrovascular diseases; TVR, target vessel revascularization.

CI: 1.10–2.77,  $p = 0.018$ ) increased risk of PMI according to SCAI, 4<sup>th</sup> UDMI and 3<sup>rd</sup> UDMI definitions, respectively (Table 3). In the Cox models, compared to individuals with TyG<8.5 and hsCRP≤2mg/L, higher crude hazards of MACCEs (HR: 1.30, 95% CI: 1.01–1.68,  $p = 0.044$ ) and all-cause deaths (HR: 1.80, 95% CI: 1.07–3.03,  $p = 0.028$ ) among patients with TyG≥8.5 and hsCRP>2mg/L in multivariable model 1, 2 and 3 (Table 4). Additionally, patients with TyG<8.5 and hsCRP>2mg/L exhibited a notable increase in the risk of MACCEs, with an HR of 1.32 (95% CI: 1.03–1.70,  $p = 0.03$ ) in multivariable model 1, 2 and 3 (Table 4). Figure 2 reported the Kaplan–Meier curves for primary and secondary outcomes.

We further analyze the relationship between hsCRP, as a continuous variable, and long-term adverse outcomes among individuals with TyG<8.5 and TyG≥8.5. In patients with TyG≥8.5, elevated hsCRP were associated with

**Table 3** Odd Ratios Between hsCRP and PMI in 3VD Patients

	Non-Events	Events	OR	p value
Perioperative MI SCAI				
TyG<8.5, hsCRP≤2	615 (14%)	12 (11.8%)		
TyG<8.5, hsCRP>2	334 (7.6%)	6 (5.9%)	0.92 (0.34–2.47)	$p = 0.870$
TyG≥8.5, hsCRP≤2	1845 (42%)	31 (30.4%)	0.86 (0.44–1.69)	$p = 0.663$
TyG≥8.5, hsCRP>2	1599 (36.4%)	53 (52%)	1.70 (0.90–3.20)	$p = 0.101$
Perioperative MI 4 <sup>th</sup> UDMI				
TyG<8.5, hsCRP≤2	617 (14.1%)	10 (7.9%)		
TyG<8.5, hsCRP>2	333 (7.6%)	7 (5.6%)	1.30 (0.49–3.44)	$p = 0.601$
TyG≥8.5, hsCRP≤2	1830 (41.9%)	46 (36.5%)	1.55 (0.78–3.09)	$p = 0.212$
TyG≥8.5, hsCRP>2	1589 (36.4%)	63 (50%)	2.45 (1.25–4.80)	$p = 0.009$
Perioperative MI 3 <sup>rd</sup> UDMI				
TyG<8.5, hsCRP≤2	604 (14.1%)	23 (10.6%)		
TyG<8.5, hsCRP>2	327 (7.6%)	13 (6%)	1.04 (0.52–2.09)	$p = 0.903$
TyG≥8.5, hsCRP≤2	1799 (42%)	77 (35.6%)	1.12 (0.70–1.81)	$p = 0.629$
TyG≥8.5, hsCRP>2	1549 (36.2%)	103 (47.7%)	1.75 (1.10–2.77)	$p = 0.018$

**Abbreviations:** TyG, Triglyceride glucose index; hsCRP, high sensitivity C-reactive protein; SCAI, Society for Cardiovascular Angiography and Interventions; 3<sup>rd</sup> UDMI, the third universal definition of myocardial infarction criteria; 4<sup>th</sup> UDMI, the fourth universal definition of myocardial infarction criteria.

**Table 4** Association Between hsCRP and Endpoints in 3VD Patients

	Events	Model 1		Model 2		Model 3	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
<b>MACCE</b>							
TyG<8.5, hsCRP≤2	39 (6.2)	Reference		Reference		Reference	
TyG<8.5, hsCRP>2	37 (10.9)	1.31 (1.02–1.68)	0.034	1.33 (1.04–1.71)	0.025	1.32 (1.03–1.70)	0.030
TyG≥8.5, hsCRP≤2	155 (8.3)	0.82 (0.64–1.05)	0.117	0.82 (0.64–1.06)	0.125	0.83 (0.65–1.07)	0.147
TyG≥8.5, hsCRP>2	162 (9.8)	1.31 (1.02–1.69)	0.036	1.30 (1.01–1.68)	0.040	1.30 (1.01–1.68)	0.044
<b>All-cause death</b>							
TyG<8.5, hsCRP≤2	8 (1.3)	Reference		Reference		Reference	
TyG<8.5, hsCRP>2	22 (1.2)	1.14 (0.65–1.98)	0.648	1.21 (0.69–2.12)	0.511	1.22 (0.69–2.16)	0.492
TyG≥8.5, hsCRP≤2	11 (3.2)	0.75 (0.44–1.28)	0.286	0.74 (0.43–1.26)	0.269	0.74 (0.44–1.27)	0.281
TyG≥8.5, hsCRP>2	27 (1.6)	1.76 (1.05–2.96)	0.032	1.80 (1.07–3.04)	0.027	1.80 (1.07–3.03)	0.028
<b>TVR</b>							
TyG<8.5, hsCRP≤2	28 (4.5)	Reference		Reference		Reference	
TyG<8.5, hsCRP>2	120 (6.4)	1.34 (1.00–1.79)	0.050	1.36 (1.01–1.82)	0.040	1.34 (1.00–1.80)	0.052
TyG≥8.5, hsCRP≤2	27 (7.9)	0.82 (0.61–1.10)	0.182	0.82 (0.61–1.10)	0.193	0.83 (0.62–1.12)	0.225
TyG≥8.5, hsCRP>2	127 (7.7)	1.33 (0.99–1.79)	0.056	1.32 (0.98–1.78)	0.064	1.32 (0.98–1.77)	0.069
<b>MI</b>							
TyG<8.5, hsCRP≤2	9 (1.4)	Reference		Reference		Reference	
TyG<8.5, hsCRP>2	5 (1.5)	1.23 (0.71–2.14)	0.458	1.20 (0.69–2.09)	0.528	1.18 (0.67–2.06)	0.573
TyG≥8.5, hsCRP≤2	29 (1.5)	1.01 (0.55–1.86)	0.964	1.01 (0.55–1.85)	0.973	1.01 (0.55–1.86)	0.970
TyG≥8.5, hsCRP>2	27 (1.6)	0.88 (0.45–1.70)	0.701	0.88 (0.45–1.71)	0.710	0.88 (0.46–1.71)	0.714
<b>Thrombosis</b>							
TyG<8.5, hsCRP≤2	7 (1.1)	Reference		Reference		Reference	
TyG<8.5, hsCRP>2	4 (1.2)	1.06 (0.56–2.01)	0.852	1.16 (0.61–2.22)	0.643	1.05 (0.55–2.02)	0.876
TyG≥8.5, hsCRP≤2	25 (1.3)	0.85 (0.43–1.70)	0.649	0.86 (0.43–1.72)	0.678	0.86 (0.43–1.71)	0.660
TyG≥8.5, hsCRP>2	17 (1.0)	0.81 (0.39–1.70)	0.582	0.79 (0.38–1.66)	0.537	0.80 (0.38–1.68)	0.554

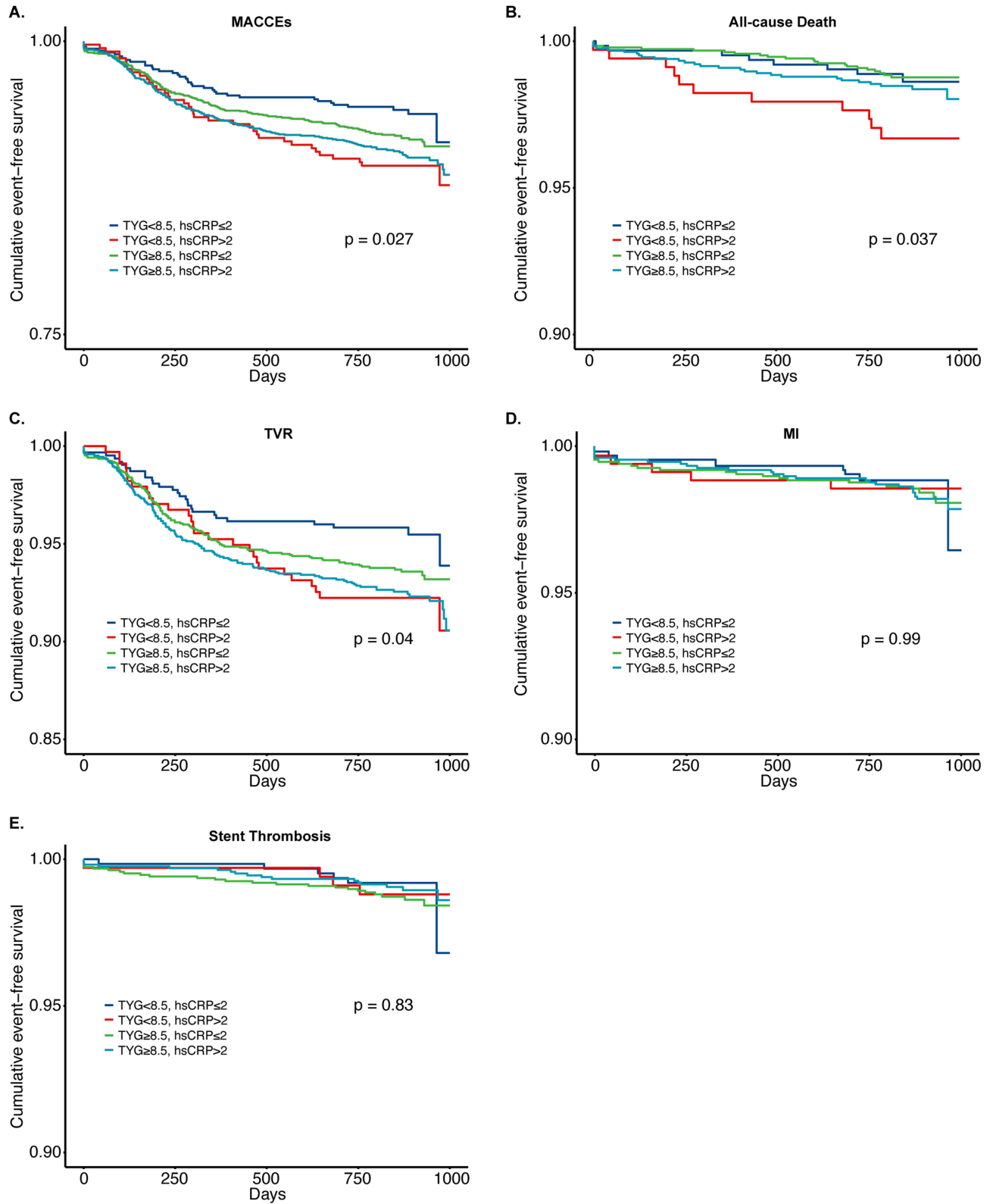
**Notes:** Model 1: covariates were adjusted for age. Model 2: covariates were adjusted for age, gender, smoking. Model 3: covariates were adjusted for age, gender, smoking, BMI ≥25 kg/m<sup>2</sup>, chronic occlusion and hypertension.

**Abbreviations:** TyG, Triglyceride glucose index; hsCRP, high sensitivity C-reactive protein; 3VD, three-vessel disease; MI, myocardial infarction; MACCEs, major adverse cardiac and cerebrovascular diseases; TVR, target vessel revascularization.

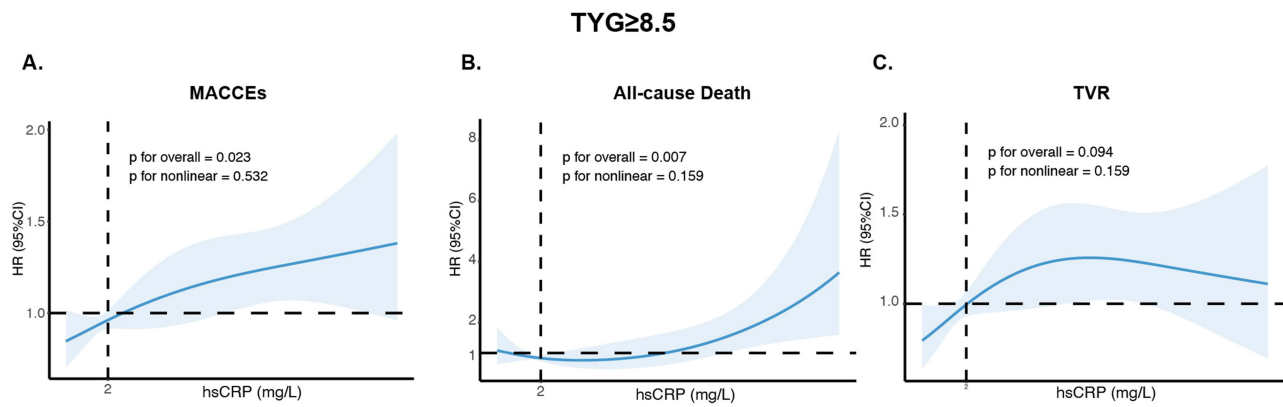
increased risks of MACCEs and all-cause death (both  $p$  for trend<0.05) (Figure 3). In patients with TyG<8.5, elevated hsCRP were linked to the increased risks of MACCEs and TVR (both  $p$  for trend<0.05), but not all-cause death (Figure 4). In order to probe underlying non-linearity association between hsCRP and adverse outcomes, we conducted RCS analysis and found a non-linear association between hsCRP and adverse outcomes (all  $p$  for nonlinear >0.05). Therefore, elevated hsCRP is associated with increased risk of MACCEs among 3VD patients independent of TyG status.

## Adding hsCRP and TyG to the Baseline Model for the Prediction of Outcomes

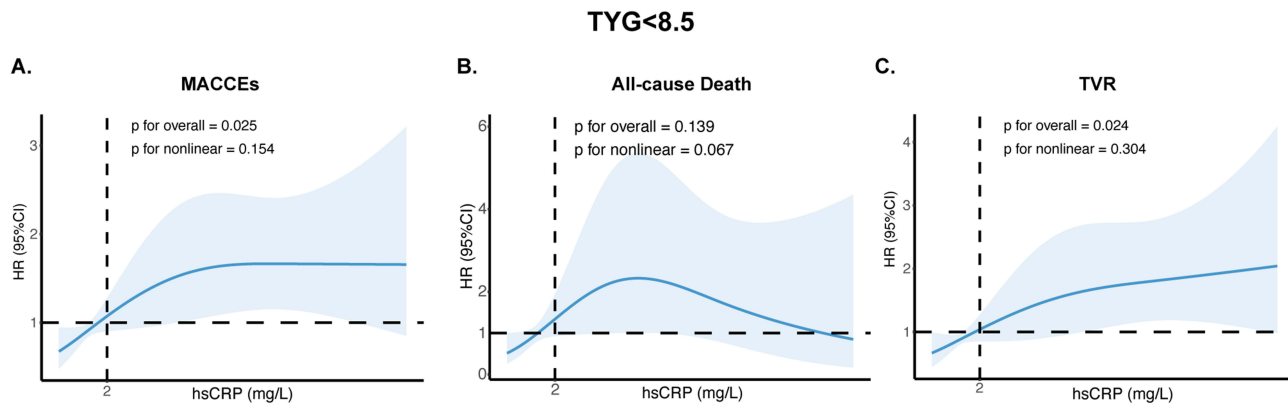
In 3VD patients, PMI reached statistical significance in the C-index when combining hsCRP and TyG with traditional risk factors, with C-index of 0.62 (95% CI: 0.56–0.68,  $p = 0.02$ ), 0.63 (95% CI: 0.58–0.69,  $p = 0.09$ ), 0.60 (95% CI: 0.56–0.64,  $p = 0.04$ ) according to SCAI, 4<sup>th</sup> UDMI and 3<sup>rd</sup> UDMI definitions, respectively. Although the c-index values (0.60–0.63) were relatively modest, our further analysis demonstrated the model incorporating both hsCRP and TyG index demonstrated significantly better discriminative performance for MACCEs compared to the traditional risk factor model alone (C-index improvement,  $p = 0.02$ ). The addition of hsCRP and TyG to the baseline model yielded significant NRI for both PMI (0.38,  $p < 0.01$ ) and MACCEs (0.16,  $p < 0.01$ ) (Table 5).



**Figure 2** The cumulative event-free survival analysis according to the hsCRP and TyG index. **(A)** MACCEs; **(B)** All-cause death; **(C)** TVR; **(D)** MI; **(E)** Stent Thrombosis. **Abbreviations:** MACCE, major adverse cardiac and cerebrovascular event; TVR, target vessel revascularization; MI, myocardial infarction.



**Figure 3** RCS of adverse outcomes and hsCRP in 3VD patients with TyG $\geq$ 8.5. **(A)** MACCEs. **(B)** All-cause death. **(C)** TVR. **Abbreviations:** MACCE, major adverse cardiac and cerebrovascular event; TVR, target vessel revascularization.



**Figure 4** RCS of adverse outcomes and hsCRP in 3VD patients with TyG $<$ 8.5. **(A)** MACCEs. **(B)** All-cause death. **(C)** TVR. **Abbreviations:** MACCE, major adverse cardiac and cerebrovascular event; TVR, target vessel revascularization.

### Sensitivity Analysis

To verify the robustness of our results, sensitivity analyses were further performed on two cohorts: the entire CAD population, and a subset of the CAD population that excluded high-risk patients (individuals who died within 30 days

**Table 5** Evaluation of Predictive Models for Endpoints Using the C-Index and NRI

	C-Index (95% CI)	p value	NRI (95% CI)	p value
<b>Perioperative MI SCAI</b>				
Traditional risk factors	0.55 (0.49–0.61)	Reference	-	Reference
Traditional risk factors + TyG + hsCRP	0.62 (0.56–0.68)	0.02	0.38 (0.17–0.56)	<0.01
<b>Perioperative MI 4<sup>th</sup> UDMI</b>				
Traditional risk factors	0.61 (0.56–0.66)	Reference	-	Reference
Traditional risk factors + TyG + hsCRP	0.63 (0.58–0.69)	0.09	0.24 (0.09–0.42)	<0.01
<b>Perioperative MI 3<sup>rd</sup> UDMI</b>				
Traditional risk factors	0.57 (0.53–0.61)	Reference	-	Reference
Traditional risk factors + TyG + hsCRP	0.60 (0.56–0.64)	0.04	0.17 (0.08–0.33)	<0.01
<b>MACCE</b>				
Traditional risk factors	0.53 (0.51–0.57)	Reference	-	Reference
Traditional risk factors + TyG + hsCRP	0.62 (0.53–0.59)	0.02	0.16 (0.03–0.26)	<0.01

**Notes:** Traditional risk factors included age, gender, BMI, smoking and eGFR  $<60$  mL/min/1.73m<sup>2</sup>.

**Abbreviations:** eGFR, estimated glomerular filter rate; C-index, concordance index; NRI net reclassification improvement; CI, confidence interval; SCAI, Society for Cardiovascular Angiography and Interventions; 3<sup>rd</sup> UDMI, the third universal definition of myocardial infarction criteria; 4<sup>th</sup> UDMI, the fourth universal definition of myocardial infarction criteria; 3VD, three-vessel disease; MI, myocardial infarction; MACCEs, major adverse cardiac and cerebrovascular diseases; TVR, target vessel revascularization.

after PCI). Our results remained robustly consistent in the sensitivity analyses among entire CAD population and CAD population excluded high-risk patients ([Tables S1–6](#)).

## Discussion

This study found that elevated TyG ( $\geq 8.5$ ) and hsCRP ( $> 2$  mg/L) are robust predictors of short-term PMI and long-term MACCEs in 3VD patients. 3VD patients with TyG  $\geq 8.5$  and hsCRP  $> 2$  mg/L showed a significantly increased risk of PMI, and an increased hsCRP level predicts a higher risk of long-term MACCEs in 3VD patients, regardless of TyG levels. TyG index and hsCRP could significantly improve the predictive value of predictive model established with traditional risk factors.

3VD is one of the most severe subtypes of CVD, linking with a significant increased risk of adverse cardiovascular outcomes.<sup>26</sup> Therefore, identifying high-risk patients and giving early interventions are critical to improve the prognosis of 3VD. Previous studies demonstrated that 3VD patients normally tolerate higher inflammatory and metabolic burdens compared to single- and double-vessel disease patients.<sup>27–29</sup> Current guidelines and major clinical trials support lipid-lowering therapy as first-line treatment for 3VD, and the 2024 ESC guidelines strongly emphasize the benefits of anti-inflammatory therapy in CVD patients.<sup>15</sup> HsCRP is prevalently used to evaluate residual inflammatory risk of CVD patients underwent statin treatment.<sup>30</sup> Guo et al reported that hsCRP is an independent predictor for long-term MACCEs in 3VD patients.<sup>16</sup> However, these studies primarily evaluated the predictive value of hsCRP in populations with various lipid levels, neglecting the contribution of hyperglycemia to adverse cardiovascular events. This study used TyG index to evaluate the glycolipid metabolic burden and estimated the risk of adverse outcomes in patients with specific metabolic and inflammatory burdens. In addition, previous studies predominately focused on long-term risks rather than short-term outcomes. This study addresses these research gaps by investigating the predictive value of TyG index and hsCRP in combination for short-term PMI and long-term MACCEs in a real-world 3VD cohort.

Our study found that the TyG index and hsCRP level not only positively associated with short-term adverse cardiovascular outcomes, but also long-term events. Compared with patients who had a TyG  $< 8.5$  and hsCRP  $\leq 2$  mg/L, those with TyG  $\geq 8.5$  and hsCRP  $> 2$  mg/L had a 70% to 145% higher risk of PMI, depending on the definition used, whereas individually elevated TyG index or hsCRP levels were not significantly associated with increased PMI risk. Furthermore, patients with TyG  $\geq 8.5$  and hsCRP  $> 2$  mg/L had a significantly elevated risk of long-term MACCEs and mortality. These findings align with prior studies identifying the TyG index and hsCRP as predictors of adverse cardiovascular outcomes in CVD patients.<sup>7,10,31</sup> Extending previous findings, our study demonstrates for the first time that the co-existence of elevated TyG index ( $\geq 8.5$ ) and high-sensitivity C-reactive protein ( $> 2$  mg/L) levels predicts increased PMI risk in 3VD patients.

In 3VD patients with TyG  $< 8.5$ , individuals with hsCRP  $> 2$  mg/L exhibited a significantly increased risk of MACCEs in comparison to individuals with hsCRP  $\leq 2$  mg/L; and 3VD patients with TyG  $\geq 8.5$  showed similar trend. RCS spine lines showed that elevated hsCRP, as a continuous variable, is positively associated with increased risk of MACCEs and TVR in 3VD patients, independent of TyG index. These evidences indicate that 3VD may benefits anti-inflammatory therapy. Therapeutic strategies specified for metabolic burden are strongly recommended and prevalent among 3VD patients. Given the prognostic impact of hsCRP in 3VD patients, both independently and in combination with TyG index, the therapeutic strategy for 3VD should move beyond LDL-C-centric strategy and promote anti-inflammation therapy in the future.

Our study further found TyG index and hsCRP could significantly improve the predictive value of risk prediction models established with traditional risk factors, including age, gender, BMI, smoking and eGFR  $< 60$  mL/min/1.73m<sup>2</sup>, strengthening the predictive value of TyG index and hsCRP for PMI and long-term MACCEs in 3VD patients. PMI is very severe complication associated with significant mortality.<sup>32,33</sup> HsCRP was also identifies as a predictor of PMI among the CAD patients.<sup>34,35</sup> This study found that elevated TyG index and hsCRP are associated with increased risk of PMI, providing a new and comprehensive insights into the monitor and management of PMI. A large scale of studies has proved that lipid-lowering could reduce cardiovascular-specific morbidity in CAD patients.<sup>36,37</sup> However, adverse cardiovascular events still occur in patients with well-controlled LDL-C levels.<sup>38</sup> Recent major trials and guidelines placed a particular emphasis on the demonstrated benefits of anti-inflammatory therapy for CVD patients.<sup>39</sup> The

landmark CANTOS trial pioneered in demonstrating the efficacy of inhibiting interleukin-1 $\beta$ , IL-6 and hsCRP in patients with prior MI.<sup>40</sup> COLCOT and LoDoCo2 trial subsequently showed the benefits of oral colchicine in reducing ASCVD events in CVD patients. However, few evidences indicated the benefits of anti-inflammatory therapy in the 3VD patients. This study revealed that elevated hsCRP is associated with increased risk of short- and long-term adverse cardiovascular events in 3VD patients with and without well-controlled metabolic burden, indicating that anti-inflammatory therapy has potential benefits for 3VD patients and hsCRP level contributes to guiding risk stratification and therapeutic strategies of 3VD patients.

In conclusion, this study found that 3VD patients with TyG $\geq$ 8.5 and hsCRP>2mg/L has significantly increased risk of PMI. Elevated hsCRP, alone or in combination of TyG $\geq$ 8.5, is significantly associated with an increased risk of long-term MACCEs. These findings underscore that integrating metabolic situation (via TyG) and systemic inflammation (via hsCRP) into 3VD patients risk may contribute to identifying high-risk individuals, guiding personalized preventive and therapeutic strategies.

## Limitations

Limitations of this study should be noticed as well. Firstly, given this is an observational cohort study, the direct causal relationship cannot be addressed. Future prospective interventional studies are needed to make sure whether targeted reduction of both TyG and hsCRP could benefit 3VD patients. Secondly, this is a single-center study, researches including multi-center cohorts or diverse cohorts including comorbidities like chronic kidney disease help to expand the clinical applicability of the TyG-hsCRP risk model. Thirdly, the cutoff of TyG index and hsCRP evaluating insulin resistance and systemic inflammation may be inconsistent among populations with different races, ages or underlying disease, however, this study did not reach this problem, which may require further research.

## Data Sharing Statement

Reasonable requests for access to the study datasets should be directed to the corresponding author.

## Ethics Approval and Consent to Participate

Ethical approval was obtained through Fuwai Hospital Research Ethics Committee. The respective Institutional Review Boards approved the protocol and all patients were provided with information regarding the study and our objectives, before providing informed consent.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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