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# Predicting the presence and severity of coronary artery disease using surrogate markers of insulin resistance: A cross-sectional study

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## Abstract

**BACKGROUND:** The triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio, Metabolic Score for Insulin Resistance (METS-IR), triglyceride-glucose (TyG) index, and triglyceride-glucose body mass index (TyG-BMI) have been associated with the occurrence and severity of coronary artery disease (CAD), although evidence remains limited.

**METHODS:** A total of 1,017 patients undergoing coronary angiography for the first time were included. Insulin resistance (IR) indices were calculated based on patients' laboratory data. Significant CAD was defined as more than 50% stenosis observed in coronary angiography[1].

**RESULTS:** A positive correlation was found between CAD and the TyG index ($\rho = 0.083$, $p = 0.008$). Patients with CAD had a significantly elevated TyG index (9.02 ± 0.62) compared to those with single-vessel disease (SVD) (8.87 ± 0.59) ($p = 0.012$). A strong association was observed between CAD and the TG/HDL-C ratio ($\rho = 0.114$, $p < 0.001$). Patients with multi-vessel disease exhibited a considerably higher index (4.47 ± 2.46) compared to those with SVD (3.77 ± 2.45) ($p = 0.003$). The TyG index cut-off was 9.22 (27.5% sensitivity, 79.3% specificity, 82.2% positive predictive value (PPV), and 23.89% negative predictive value (NPV)), while the TG/HDL-C ratio cut-off was 3.6 (44% sensitivity, 65.2% specificity, 81.5% PPV, and 25.5% NPV).

**CONCLUSION:** Our findings indicate that the TG/HDL-C ratio, with a cut-off point of 3.6, and the TyG index, with a threshold of 9.22, are associated with the presence of CAD. (ClinicalTrials.gov registration number: NCT06237244).

**Keywords:** Coronary Artery Disease; Insulin Resistance Indices

## Introduction

Coronary artery disease (CAD) is a leading cause of mortality worldwide, accounting for more than 9 million deaths in 2020 alone[2]. This disease results from the accumulation of atherosclerotic plaques in the coronary arteries, which impairs myocardial perfusion[3]. Well-established risk factors for CAD include hypertension (HTN), dyslipidemia, family history, smoking, diabetes mellitus (DM), and advanced age; however, research continues to uncover novel contributing factors[4]. Insulin resistance (IR), defined as a decreased physiological response of recipient tissues to insulin stimulation, has emerged as a potential new risk factor. While IR is a key pathophysiologic process underlying type 2 diabetes mellitus (T2DM), evidence suggests that it may promote atherosclerosis independently of established cardiometabolic risk factors[5].

IR is primarily an acquired condition associated with excess adipose tissue, although genetic factors may also play a role[6]. The prevalence of IR has gradually increased, mainly due to changes in lifestyle and diet; approximately 15–46% of the adult population is affected by IR[7,8]. This highly prevalent condition contributes to CAD through various mechanisms, including alterations in circulating lipoproteins and inflammatory responses induced by hyperglycemia-related oxidative stress[9].

Conventional methods for estimating IR rely on insulin levels; however, these measurements are both complex and costly. As a result, evaluating IR in clinical practice often depends on surrogate indices rather than direct measurements. Frequently utilized indices include the ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL-C), the Metabolic Score for Insulin Resistance (METS-IR), the triglyceride-glucose (TyG) index, and the triglyceride-glucose body mass index (TyG-BMI), which serve as reliable and straightforward alternatives to conventional insulin resistance tests.

These indices are computed using standard biochemical blood tests and surpass the limitations of conventional IR assessment methods.

Several studies have examined the utility of surrogate IR indices in predicting CAD presence and severity. In one study, METS-IR demonstrated the highest predictive value among all indices[10]. In another investigation, the TG/HDL-C ratio and METS-IR were identified as independent predictors of CAD occurrence[11]. Furthermore, numerous studies have shown the TyG index to be an independent predictor of multi-vessel CAD, with the strongest correlation observed in individuals with pre-diabetes and diabetes[12,13].

While previous research has explored the link between surrogate IR indices and CAD severity, significant knowledge gaps remain. Earlier studies, though informative, exhibit inconsistencies in their findings, likely due to variations in study populations, methodologies, or analytical approaches. Additionally, while the prognostic value of these indices has been investigated, questions persist regarding their reliability and clinical utility across different populations and settings. Consequently, due to the potential value of these novel IR indices and the lack of conclusive evidence, this study aimed to examine the association of these indices with CAD presence and severity, as well as their predictive values.

## Methods

*Study design*

This cross-sectional research included individuals with suspected CAD who underwent coronary angiography between December 2018 and May 2023. The data were obtained from patients referred to the outpatient cardiovascular clinic (Professor Kojuri Cardiology Clinic, Shiraz, Iran; website: www.kojuriclinic.com). Relevant data were extracted from the Professor Kojuri Cardiology Clinic database, which included patients' clinical history, prior medical history (e.g., HTN, DM, angiography/angioplasty outcomes), and laboratory values. A total of 14,708 individuals who had undergone coronary angiography at least once were evaluated. After applying the exclusion criteria, 1,017 suitable cases were selected for data analysis.

*Inclusion and exclusion criteria*

Inclusion criteria required participants to be aged >18 years and undergoing coronary angiography for the first time. Individuals with missing information, a serum creatinine level >1.4 mg/dL, a history of cirrhosis, malignancy, or chronic kidney disease (CKD), or a history of prior coronary angiography or revascularization (PCI or CABG) were excluded from the study.

*Variables*

Demographic information, past medical history (e.g., DM, HTN), systolic and diastolic blood pressure, height, weight, hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum creatinine (Cr) were recorded for the included patients. Obesity was classified as a BMI ≥30 kg/m², calculated by dividing weight in kilograms by the square of height in meters (kg/m²). Laboratory values were taken from the period prior to angiography or, if unavailable, immediately following angiography. This approach minimized the confounding effects of statin treatment and allowed for the identification of values that most accurately reflected the metabolic status of individuals at the time of angiography.

The findings of coronary angiography determined the existence and severity of CAD. A coronary artery with >50% stenosis was classified as having significant CAD[1]. Minor branches (e.g., diagonal branches) were considered only if their main supplying branch was not blocked. The number of affected vessels was categorized as single-vessel disease (SVD or 1VD), two-vessel disease (2VD), or three-vessel disease (3VD) to define CAD severity. Multi-vessel CAD was defined as having 2VD or 3VD.

The presence of at least one coronary artery with 25–49% stenosis and no additional arteries with significant CAD was classified as mild CAD. In this study, mild CAD was defined as the absence of significant CAD. Coronary arteries with less than 25% stenosis were considered free of CAD. Metabolic syndrome was defined according to the 2005 International Diabetes Federation (IDF) criteria[14].

*Calculations*

The following indices were calculated using the patient's laboratory values and BMI:

Metabolic Score for Insulin Resistance (METS-IR):

$$\frac{\ln(2\times \text{FPG [mg/dL]} + \text{fasting serum TG [mg/dL]}) \times \text{BMI [Kg/m}^2\text{]}}{\ln(\text{HDL-C [mg/dL]})}$$ [15]

Triglyceride-Glucose (TyG) index: $\ln(\text{TG [mg/dL]} \times \text{FPG [mg/dL]} / 2)$[16]

TG/HDL-C ratio: TG [mg/dL] / HDL-C [mg/dL][17,18]

TyG-BMI: TyG × BMI[19].

*Statistical analysis*

The statistical analysis was performed using SPSS for Windows, version 26 (IBM Corp., Armonk, NY, USA). Categorical variables were described using frequencies and percentages, while continuous variables were expressed as mean ± standard deviation (SD). Paired-sample t-tests and one-way ANOVA were used for normally distributed variables. For categorical data, the Kruskal-Wallis test and Pearson's chi-squared test were applied. Following a significant ANOVA result, the Tukey post hoc test was employed to compare results across different categories.

The correlation between categorical and continuous variables was assessed using Spearman's rank correlation coefficient, based on the provided ρ and p-values. The ROC curve was utilized to evaluate the sensitivity and specificity of various indices in predicting the presence of CAD and multi-vessel disease, with the area under the curve (AUC) reported. The diagnostic tool's optimal cut-off point for maximum sensitivity and specificity was determined using Youden's J Index. Statistical significance was defined as a P-value of less than 0.05.

*Ethical considerations*

Confidentiality was maintained and patient data was solely utilized for research. The Ethics Committee of Shiraz University of Medical Sciences accepted this study, which complies with the Declaration of Helsinki (code number: IR.SUMS.MED.REC.1402.252).

## Results

The mean age of the 1,017 patients was 62.8 ± 10.5 years, with 590 men (58%) and 427 women (42%). The patients' average BMI was 27.68 ± 4.77 kg/m². Prevalent risk factors included 518 cases of HTN (50.9%), 315 cases of DM (31%), 262 cases of obesity (25.8%), 212 cases of metabolic syndrome (20.8%), 204 cases of cigarette smoking (20.1%), and 56 cases of opium addiction (5.5%) (Table 1).

There were 790 cases with substantial CAD (77.7%). Significant single-, two-, and three-vessel disease were found in 429 (42.2%), 270 (26.5%), and 91 (8.9%) of the population, respectively. Furthermore, no substantial CAD was present in 227 individuals (22.3%). Table 1 shows that the mean TyG-index, METS-IR, TG to HDL-cholestrol ratio, and TyG-BMI were, respectively, 8.87 ± 0.59, 44.19 ± 8.74, 3.78 ± 2.44, and 245.84 ± 46.00.

**Table 1**. Baseline characteristics of the patients

| **Sex (n, %)** | **Female** | **427 (42)** |
|---|---|---|
| | Male | 590 (58) |
| Age (mean ± SD) | | 62.8 ±10.5 |
| BMI (mean ± SD) | | 27.68 ±4.77 |
| HTN (n, %) | | 518 (50.9) |
| DM (n, %) | | 315 (31) |
| Obesity (n, %) | | 262 (25.8) |
| Metabolic syndrome (n, %) | | 212 (20.8) |
| Cigarette smoking (n, %) | | 204 (20.1) |
| Dyslipidemia (n, %) | | 17 (1.7) |
| Opium addiction (n, %) | | 56 (5.5) |
| CAD (n, %) | No CAD | 227 (22.3) |
| | SVD | 429 (42.2) |
| | 2VD | 270 (26.5) |
| | 3VD | 91 (8.9) |
| FBS (mean ± SD) | | 116.04 ±54.38 |
| HbA1c (mean ± SD) | | 6.43 ±3.74295 |
| Total cholesterol (mean ± SD) | | 144.94 ±41.56 |
| HDL-C (mean ± SD) | | 42.39 ±12.33 |
| LDL-C (mean ± SD) | | 76.97 ±32.01 |
| TG (mean ± SD) | | 145.28 ±73.93 |
| TyG index (mean ±SD) | | 8.87 ±0.59 |
| METS-IR (mean ±SD) | | 44.19 ±8.74 |
| TG/HDL-C ratio (mean ±SD) | | 3.78 ±2.44 |
| TyG-BMI (mean ±SD) | | 245.84 ±46.00 |

*TyG Index*

Patients with 3VD had a significantly higher TyG index (9.01 ±0.63) than those with SVD (8.84 ±0.58) (p=0.05) (Table 2 and Figure 1). Additionally, CAD and the TyG index showed a favourable connection (ρ: 0.083, p=0.008). Among CAD patients, those with multi-vessel disease had a substantially higher TyG index (9.02 ±0.62) than those with SVD (8.87 ±0.59) (p=0.012) (Table 3). According to the Youden index, the TyG index identified CAD with a cut-off value of 9.22, yielding an AUC of 0.522 (95% CI [0.479, 0.564]), 27.5% sensitivity, 79.3% specificity, 82.2% PPV, and 23.89% NPV (Figure 1a). With an AUC of 0.553 (95% CI [0.513, 0.593]), the cut-off point for multi-vessel disease prediction in CAD patients was 8.71, yielding 65% sensitivity, 45.2% specificity, 80.5% PPV, and 27.04% NPV (Figure 1b and Table 4).

*TG/HDL-C ratio*

Table 2 and Figure 2 demonstrate that patients with three-vessel disease (3VD) exhibited a significantly higher TG/HDL-C ratio (4.43 ± 2.48) compared to both those without coronary artery disease (CAD) (3.54 ± 2.37; p=0.016) and those with single-vessel disease (SVD) (3.62 ± 2.29; p=0.019). Furthermore, a significant positive correlation was observed between CAD severity and the TG/HDL-C ratio (ρ=0.114, p<0.001). Among CAD patients, those with multi-vessel disease had a significantly higher TG/HDL-C ratio (4.47 ±2.46) than those with single-vessel disease (3.77 ±2.45) (p=0.003) (Table 3). With a cut-off point of 3.6, this parameter predicted CAD based on the Youden index. This resulted in 81.5% PPV, 25.5% NPV, 44% sensitivity, 65.2%

**Table 2.** Determination and comparison of insulin resistance indices according to different severity of CAD

| | No CAD | SVD | 2VD | 3VD | P-value | Correlation coefficient (spearman) | Correlation p-value |
|---|---|---|---|---|---|---|---|
| FBS | 114.7 ±48 | 115.4 ± 65.1 | 115.8 ±42.4 | 123 ±45.6 | 0.646 | 0.048 | 0.129 |
| HbA1c | 6.64 ±6.8 | 6.2 ±1.63 | 6.57 ±3.54 | 6.72 ±1.54 | 0.41 | 0.101 | **<0.002** |
| HDL | 44.3 ±11.7 | 42.6 ±11.4 | 42 ±14.7 | 37.9 ±9.2 | **<0.001** | 0.077 | **0.014** |
| TG | 140.9 ±68.3 | 141.5 ±73.7 | 151.3 ±78.2 | 156.5 ±74.3 | 0.12 | -0.139 | **<0.001** |
| TyG index (mean, 95% CI) | 8.85 ±0.58 | 8.84 ±0.58 | 8.92 ±0.59 | 9.01 ±0.63 | **0.033** | 0.083 | **0.008** |
| METS-IR (mean, 95% CI) | 44.88 ±9.25 | 43.89 ±8.86 | 43.68 ±7.73 | 45.45 ±9.62 | 0.192 | -0.001 | 0.978 |
| TG/HDL-C ratio (mean, 95% CI) | 3.54 ±2.37 | 3.62 ±2.29 | 4.03 ±2.66 | 4.43 ±2.48 | **0.003** | 0.114 | **<0.001** |
| TyG-BMI (mean, 95% CI) | 252.6 ±48.65 | 244.32 ±47.01 | 242.34 ±40.73 | 246.63 ±48.14 | 0.073 | -0.045 | 0.154 |

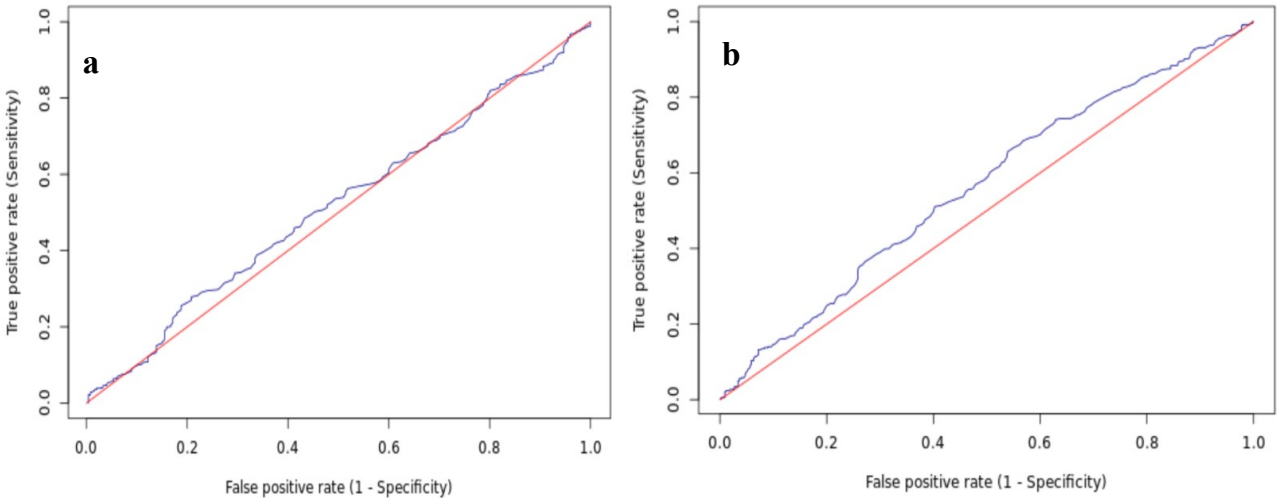


**Figure 1.** ROC curve for the prediction of CAD presence (a) and multi-vessel disease prediction (b) using the TyG index

specificity, and an AUC of 0.539 (95% CI [0.497, 0.582]) (Figure 2a). With an AUC of 0.563 (95% CI [0.523, 0.604]), the cut-off point for multi-vessel disease prediction in CAD patients was 3.73, yielding 82.68% PPV, and 26.53% NPV, 48.9% sensitivity, 64.3% specificity (Figure 2b and Table 4).

*METS-IR and TyG-BMI*

There was no discernible link between CAD and METS-IR. Likewise, there was no discernible correlation between CAD and the TyG-BMI (Tables 2 and 3).

*Predictive values*

The TG to HDL-C ratio and the TyG-index had a high PPV (> 80%) for predicting the existence or severity of CAD, while having relatively poor sensitivity for diagnosing CAD or predicting its severity at the cut-off points mentioned above (Table 4).

## Discussion

This study investigated the predictive values of non-insulin-based insulin resistance (IR) markers and their relationships with the occurrence and severity of CAD. Our primary conclusion was that

**Table 3.** IR indices in CAD patients with single-vessel disease or multi-vessel disease

| | Single-vessel disease | Multi-vessel disease | P-value |
|---|---|---|---|
| FBS | 115.7 ±57.6 | 123 ±45.8 | 0.582 |
| HbA1c | 6.33 ±2.56 | 6.72 ±1.54 | **0.036** |
| HDL | 42.4 ±12.8 | 37.8 ±9.1 | 0.063 |
| TG | 144.8 ±75.6 | 157.8 ±73.7 | **0.038** |
| TyG index (mean, 95% CI) | 8.87 ±0.59 | 9.02 ±0.62 | **0.012** |
| METS-IR (mean, 95% CI) | 43.85 ±8.44 | 45.41 ±9.67 | 0.704 |
| TG/HDL-C ratio (mean, 95% CI) | 3.77 ±2.45 | 4.47 ±2.46 | **0.003** |
| TyG-BMI (mean, 95% CI) | 243.69 ±44.63 | 246.42 ±48.37 | 0.781 |

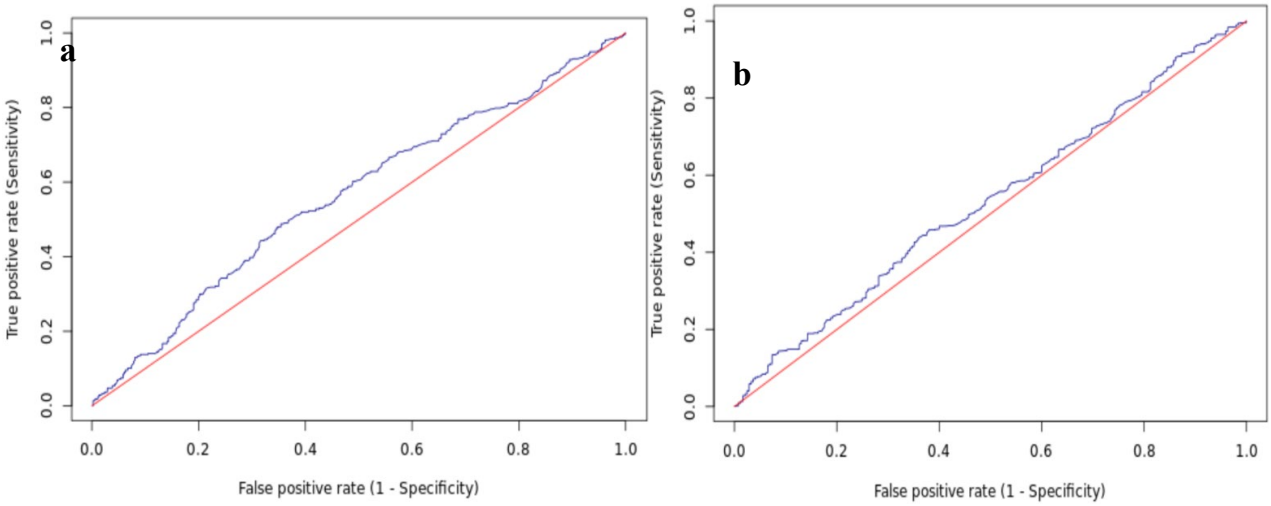


**Figure 2.** ROC curve for the prediction of CAD presence (a) and multi-vessel disease prediction (b) using the TG/HDL-C ratio

**Table 4.** The TyG index and the TG/HDL-C ratio for predicting CAD and multi-vessel disease

| | | Cut-off | Sensitivity (95% CI) | Specificity (95% CI) | AUC (95% CI) | PPV | NPV | P-value |
|---|---|---|---|---|---|---|---|---|
| TyG index | CAD | 9.22 | 27.5 (24.14, 30.46) | 79.3 (73.44, 84,37) | 0.522 (0.479-0.564) | 82.2 | 23.89 | 0.387 |
| | Multi-vessel disease | 8.71 | 65 (61.24, 69.58) | 45.2 (42.75, 49,01) | 0.553 (0.513-0.593) | 80.5 | 27.04 | 0.012 |
| TG/HDL-C ratio | CAD | 3.6 | 44 (41.25, 46.73) | 65.2 (61.39, 68.96) | 0.539 (0.497-0.582) | 81.5 | 25.5 | 0.081 |
| | Multi-vessel disease | 3.73 | 48.9 (43.74, 53.21) | 64.3 (61.75, 67.01) | 0.563(0.523-0.604) | 82.68 | 26.53 | 0.003 |

individuals with CAD had significantly higher TG/HDL-C ratios and TyG indices compared to non-CAD patients. Moreover, those with multi-vessel disease exhibited markedly higher values for these two insulin resistance indicators. Additionally, these indices demonstrated an ideal positive predictive value (PPV) for CAD diagnosis and severity prediction.

Zhang et al. and Wang et al. both categorized the TyG index into tertiles, associating the highest tertile with a substantially increased risk for CAD presence or severity compared to the lowest tertile[10,12]. Zhang et al. used angiography to classify 485 CAD patients into single- and multi-vessel disease groups and divided the TyG index into tertiles: T1 < 8.73, T2 ≥ 8.73 to < 9.57, and T3 ≥ 9.57. The T3 tertile, with the highest TyG values, was significantly associated with more severe (multi-vessel) CAD compared to the T1 group[10]. Similarly, Wang et al. analyzed 2,792

CAD patients and categorized the TyG index into tertiles: T1 < 6.87, T2 ≥ 6.87 to < 7.38, and T3 ≥ 7.38. The T3 group, exhibiting the highest TyG-index levels, showed a 1.496-fold increased risk for more severe CAD compared to the T1 group[12].

A larger prospective cohort study conducted across 22 countries spanning five continents by Lopez-Jaramillo et al., along with a meta-analysis by Liu et al., also linked a higher TyG index with an elevated risk of CAD, myocardial infarction (MI), and the incidence of cardiovascular disease (CVD)[20,21]. Consistent with these findings, our study showed that CAD patients typically had a significantly elevated TyG index, and within the CAD group, those with more severe disease exhibited even higher TyG index values.

Several studies have attempted to establish TyG index cut-off points for specific targets. Wu et al. identified a cut-off point of 8.3 for detecting CAD, with 73% sensitivity and 41.6% specificity. In comparison, Zhang et al. proposed a higher TyG cut-off point of 10.42, with 48% sensitivity and 81.9% specificity for detecting CAD presence[9,10]. Park et al., in a 2020 Korean study, established an ideal TyG cut-off value of 8.44 for CAD prediction in asymptomatic adults without CVD risk factors, yielding 68.5% specificity and 47.9% sensitivity. However, they highlighted the challenges of using the TyG index to detect subclinical CAD[22].

Si et al. defined a cut-off value of 8 as a predictor of CAD in individuals with T2DM, reporting 98.09% PPV, 7.51% NPV, 42.27% sensitivity, and 85.06% specificity[23]. In the current study, we defined a TyG cut-off point of 9.22, with 27.5% sensitivity, 79.3% specificity, and 82.2% PPV for predicting the presence of CAD. Additionally, a cut-off point of 8.71 was established for predicting multi-vessel disease in CAD patients, resulting in 65% sensitivity, 45.2% specificity, and 80.5% PPV.

Numerous studies have demonstrated that a high TG/HDL-C ratio significantly increases the risk of CAD. In 2008, Luz et al. identified this ratio as the most powerful predictor of extensive CAD among all lipid variables. They reported that, while the extent of CAD correlated with all routine lipid indicators, the strongest correlation was observed with this index[24]. Similarly, Islam et al. concluded that utilizing the TG/HDL-C ratio in patients with acute coronary syndrome (ACS) could be beneficial for risk stratification and management[25]. In our study, we also found a significant relationship between this parameter and the occurrence and extent of CAD.

Several studies have attempted to establish TG/HDL-C cut-off points for various purposes. A 2019 study identified threshold values of 2.967 for males and 2.237 for females as indicators of high cardio-metabolic risk[26]. Additionally, Neglia et al. suggested a cut-off point of 2.33 as having predictive importance for CAD[27]. Another study proposed TG/HDL-C thresholds of >1.65 in women and >2.75 in men as highly predictive of metabolic syndrome. Furthermore, this index was found to substantially predict the first coronary incident[28].

According to our research, the TG to HDL-C ratio had a cut-off point of 3.6 for CAD prediction (44% sensitivity, 65.2% specificity, and 81.5% PPV). For predicting multi-vessel disease in CAD patients, the cut-off point was 3.73 (48.9% sensitivity, 64.3% specificity, and 82.68% PPV). Previous studies have suggested lower cut-off points (such as 1.67 or 2.9) for predicting the presence of CAD, with varying sensitivities and specificities[9,10]. Aimo et al. noted that the TG/HDL-C ratio and TyG index, two easily measurable TG-related indices, may have excellent predictive values for CAD in the general population[29]. Sánchez-Íñigo et al. also reported that the TyG index can predict cardiovascular events in seemingly healthy populations[30].

We did not find any significant association between the TyG-BMI or METS-IR and the presence of CAD. This outcome may be attributed to disproportionate weight or height distribution within the population studied, as these indices depend on BMI. These findings suggest that insulin resistance indices that account for factors beyond just height and weight, such as the TyG index, may provide greater utility in assessing insulin resistance and its association with CAD

severity. However, Zhang et al. reported that METS-IR and the TyG-BMI index had greater predictive value compared to other indices[9]. Additionally, Wu et al. claimed that METS-IR exhibited the greatest prognostic significance for assessing the presence and severity of CAD, which contrasts with our findings[10].

Moreover, we observed no discernible relationship between IR indices and CAD in the subset of individuals with metabolic syndrome. Non-weight-based IR indices should always be considered, as they may provide valuable insights about insulin resistance in individuals with relatively average weight. This highlights a limitation of relying solely on BMI-based measures.

This study focused exclusively on patients without a prior history of coronary angiography or revascularization, whereas most previous studies did not clearly define such selection criteria in their methodologies. This approach enabled us to assess the predictive value of IR indices for evaluating primary care CAD. By analyzing only patients undergoing their first angiography, our study offers new insights, particularly for the primary care context.

## Conclusion

Patients with CAD had substantially higher TG/HDL-C ratios and TyG indices than people without CAD. Furthermore, these two indexes were significantly lower in patients with 1VD, indicating that they are reliable indicators of the severity of the illness. These two IR indices offered a flawless PPV (> 80%) for CAD diagnosis and CAD severity prediction, despite their limited sensitivity. This can assist in identifying CAD patients who have more severe conditions and might profit from early treatment.

### *Study limitations*

This study involved 1,017 patients; however, prospective studies with larger sample sizes are needed to achieve more accurate and generalizable results. Additionally, statins are commonly recommended for individuals with suspected CAD prior to undergoing coronary angiography. Since statins alter both TG and HDL levels, they may lead to decreased IR indices if the lipid profile is assessed after their prescription. This could impact the accuracy of the results. Therefore, if these indices are to be utilized as predictors of CAD occurrence and severity in primary care, it is essential that laboratory measurements are conducted before initiating statin therapy to ensure more reliable results.

## Conflict of interests

The authors declare no conflict of interest.

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## Author's Contributions

Study Conception or Design: JK, SJ, SAM, RH
Data Acquisition: NH, MM, HZ, SS, HZ , KA, MY, NH, MM, SS, MS
Data Analysis or Interpretation: SJ, SAM, RH, MY, RGV, KA, SAH, JK
Manuscript Drafting: JK,RH,RG, SAM, SAH
Critical Manuscript Revision: JK, RH, RGV, SAH, SJ, SAM
All authors have approved the final manuscript and are responsible for all aspects of the work.

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