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Insulin resistance indexes as biomarkers of lifetime cardiovascular risk among adults from Peru

Trabajo de Investigación para obtener el Grado Académico de Bachiller en Medicina Humana

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DECLARACIÓN JURADA DE AUTORÍA DEL TRABAJO DE INVESTIGACIÓN

Salomón Huancahuire Vega, de la Facultad de **Ciencias de la Salud**, Escuela Profesional de **Medicina Humana**, de la Universidad Peruana Unión.

DECLARO:

Que la presente investigación titulada: **"Insulin Resistance Indexes as Biomarkers of Lifetime Cardiovascular Risk among Adults from Peru"** constituye la memoria que presenta el estudiante **Ricardo Josué Rojas Humpire** para obtener el Grado Académico de Bachiller en **Medicina Humana**, cuyo trabajo de investigación ha sido realizado en la Universidad Peruana Unión bajo mi dirección.

Las opiniones y declaraciones en este informe son de entera responsabilidad del autor, sin comprometer a la institución.

Y estando de acuerdo, firmo la presente declaración en la ciudad de **Lima**, a los 15 días del mes de Julio del año 2021

Salomón Huancahuire Vega

Insulin resistance indexes as biomarkers of lifetime cardiovascular risk among adults from Peru

Insulin resistance indexes as biomarkers of cardiovascular risk

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Abstract

Background. Cardiovascular diseases (CVD) are the most prevalent cause of death from disease and disability in the world. Reliable markers are needed to assess and reduce cardiovascular risk. The aim of this study was to determine if insulin resistance indexes, triglycerides to HDL-cholesterol ratio (TG/HDL-c) and triglycerides to glucose index (TGI), are biomarkers for lifetime cardiovascular risk. **Methods.** This analytical cross-sectional study was performed in health workers from the Hospital de Huaycan in Peru. The QRISK model was used to measure lifetime cardiovascular risk. The association and diagnostic accuracy for insulin resistance indexes were determined using Poisson regression models and ROC curves with Youden index, respectively. **Results.** In total 291 adults (207 women and 84 men) were

analyzed. In the multivariable analysis the 3rd tertil of TG/HDL-c (PRa:2.72, CI95% 1.13 - 6.57) and TGI (PRa:4.73, CI95% 1.56 - 14.31) increased significantly the lifetime cardiovascular risk compared to their 1st tertil. The cut-off values of TG/HDL-c was 2.64 (AUC:0.77), 3.90 (AUC:0.80) and 2.64 (AUC:0.74) for the overall population, men and women, respectively. Likewise, the cut-off values of TGI was 9.04 (AUC:0.80), 8.95 (AUC:0.79) and 9.04 (AUC:0.80) for the overall population, men and women, respectively. **Conclusion.** TG/HDL-c and TGI presented significant association with lifetime cardiovascular risk. However, TGI presented a stronger association than TG/HDL-c. Both TG/HDL-c and TGI are shown to be reliable markers for cardiovascular risk in adults.

Keywords: *Cardiovascular diseases, Insulin resistance, Biomarkers, Primary Prevention*

Introduction

Cardiovascular diseases (CVD) are the leading cause of death, disability and also a major public health problem worldwide. [1–3] The World Health Organization (WHO) estimates that 17.7 million people died from a cardiovascular disease in 2015, representing 31% of all deaths recorded in the world. [4] In Peru, the CVD profile presented by the Pan American Health Organization and the WHO (PAHO/WHO) in 2014, showed that about 16% of all premature deaths for people between 30 and 69 years of age were due to CVD. [5] Early detection and prevention of CVD would help reduce the country's high mortality rate regionally. [6]

The discovery and use of cardiovascular risk (CVR) biomarkers during the last few years has led to more sensitive detection methods, bringing favorable clinical outcomes in the population. [7] So far, dozens of CVR markers have been described, such as: Brain Natriuretic Peptide (BNP), Atrial Natriuretic Peptide (ANP), Troponin T, Creatinine Phosphokinase-MB, Galectin-3, C-Reactive Protein, Interleukin 6, Fibrinogen, Monocyte Chemotactic Protein-1, Tumor Necrosis Factor Alpha, Low-Density Lipoproteins, High Density Lipoprotein, Apo b-100, Lipoprotein-Associated Phospholipase A2, Homocysteine, Vitamin D, Fibroblast Growth Factor 23, Adiponectin, Glycated Hemoglobin, Haptoglobin etc. [1,7–9] The detection of most of these biomarkers requires the development of a highly sensitive technological platform.

Certain biomarkers of insulin resistance, such as triglycerides to glucose index (TGI) and triglycerides to HDL-cholesterol ratio (TG/HDL-c), have been shown to be useful in identifying people at high risk of developing a cardiovascular problem at an early stage. [10–12] Elevated plasma triglyceride levels are a CVD risk marker and are associated with impaired fasting glucose, type 2 diabetes, and metabolic syndrome. [13] The TG/HDL-c can help predict patients at increased risk of cardio metabolic disease as well as identify patients who most need intervention. [14,15] Likewise, the TGI has been correlated with the assessment of insulin resistance homeostasis model (HOMA-IR). The detection of apparently healthy individuals with insulin resistance (IR) before the onset of CVD could have clinical relevance in the prevention of cardiovascular disease. [14] Additionally, the direct measurement of these insulin resistance indexes does not require complex techniques, is inexpensive and can be performed in a routine biochemical laboratory.

Patients with CVD usually develop three or more risk factors, so quantifying these factors is essential to understanding the extent of this problem. [16] Different equations and scales make it possible to quantify CVR, their differences being mainly due to the specific parameters established for the calculation. The Framingham equation estimates the risk of presenting a myocardial infarction: fatal or not, symptomatic or silent, and angina, assessing the risk at 10 years. In Peru, using this score it has been shown that 20% of the population is classified with a high CVR with prevalence in males and in a period of 7 years this increases by 3%. [17–19] Recently, the QRISK model was developed, which estimates individualized lifetime CVR, incorporating estimates of the probability that a patient is alive and free of CVD for any age up to 95 years, taking into account individual risk factors, recommended for young adult populations. [20] In the present study, we explored the diagnostic accuracy of TG/HDL-c and TGI to lifetime CVR in adults from a Peruvian hospital.

Methods

Design of the primary study

We conducted a cross-sectional analytical study using data from the Plan for the Prevention and Surveillance of Communicable and Non-Communicable Diseases at the Hospital de Huaycan II-1, Lima, Peru, in 2019. In this prevention plan, clinical evaluation, self-reported questionnaires, medical images and laboratory tests were performed to prevent and diagnose diseases in healthcare workers. Workers were explained that their medical data would be used for future research, and written informed consent was obtained from all participants.

This study was approved by the Ethics Committee of the Universidad Peruana Union (2020-CEUPeU-00021) and authorized by the Hospital de Huaycan (031-2020) to use medical records from health workers.

Inclusion and Exclusion Criteria

We included data of healthcare workers between 20 to 79 years old of both sexes from the Hospital de Huaycan. Participants with a medical record of myocardial infarction, coronary artery disease, cerebrovascular disease, peripheral arterial disease, as well as those who used antihyperlipidemic agents, pregnant women, participants who did not completely fill out the form, those who did not sign informed consent and those who did not do laboratory tests were excluded.

Assessment of Cardiovascular Risk

The American College of Cardiology/American Heart Association (ACC/AHA) risk score was calculated to measure general CVR over 10 years. [21] This score presented the best discrimination (AUC = 0.78) of general CVR in a Latin American population. [22] The population was categorized as low, borderline, intermediate, and high risk according to the ACC/AHA 2019 guideline on the primary care of cardiovascular diseases. [23]

The QRISK model was used to measure the lifetime-CVD [20] in low, borderline and intermediate risk populations based on ACC/AHA risk score, using the QRISK® on-line calculator (https://qrisk.org/lifetime/index.php).

Definition of Variables

Lifetime CVR was categorized into high (≥ 39%) and low (< 39%) risk. [24] Diabetes was defined as, diagnosed by doctor, currently taking anti-diabetic medication, fasting plasma glucose ≥126 mg/dL or HbA1c ≥ 6.5%. Body mass index was categorized as underweight (<18.5 Kg/m2), normal (18.5 - 24.9 Kg/m2), overweight (25 - 29.9 Kg/m2) and obese (>30 Kg/m2). Smoker, antihypertensive medication and alcohol consumption were assessed based on self-reported questionnaires from the Plan for the Prevention and Surveillance of Communicable and Non-Communicable Diseases at the Hospital de Huaycan.

TG/HDL-c and TGI were selected as insulin resistance indexes because they have been shown to be accurate indicators of insulin resistance diagnosis in many populations. [15,25] Additionally, these insulin indexes present accessible alternatives to HOMA-IR or glucose clamp. [26,27] TG/HDL-c was calculated using the following formula: fasting TG (mg/dL) ÷ fasting HDL-cholesterol (mg/dL), and categorized into tertiles Q1 (0.56 - 2.14), Q2 (2.15 - 3.45) and Q3 (3.46 - 12.30). TGI was calculated using the formula: Ln[fasting TG (mg/dL) × fasting plasma glucose (mg/dL)/2], and categorized into tertiles Q1 (6.77 - 8.44), Q2 (8.45 - 8.94) and Q3 (8.95 - 11.20).

Statistical Analysis

Statistical analyses were performed with R program version 4.0.2. Numerical variables were described with mean and standard deviation. Categorical variables were described in absolute and relative frequencies. To assess the association between insulin resistance indexes (TG/HDL-c and TGI) and lifetime CVR, prevalence ratios (PR) and their respective 95% confidence intervals (95% CI) were determined using Poisson regression models with robust variance. The first model examined the bivariate association between insulin resistance indexes and lifetime CVR. The second model of TG/HDL-c was adjusted for sex, HbA1c, LDL-c, uric acid, BMI and alcohol consumption. The second model of TGI was adjusted for sex, LDL-c, uric acid, BMI and alcohol consumption. Receiver operating characteristic (ROC) curve analysis was applied to estimate the accuracy of insulin resistance indexes to lifetime CVR with the calculation of the area under the curve (AUC) with 95% CI. The optimal cutoff value of each marker was estimated using the Youden index. A p value <0.05 was considered statistically significant.

Results

General characteristics of the Participants

We analyzed data from 291 health workers, 84 men (28.9%) and 207 women (71.1%) with an average age of 46 ± 10 years old. Most of the variables of the overall population presented in Table 1 showed average values in normal ranges. Overall, 49.1% of the health workers were overweight, 27.1% obese, 92.8% had low-moderate alcohol consumption, 13.1% had diabetes and 4.8% were smokers.

Characteristics of the participants by lifetime cardiovascular risk

The study population was categorized into high (n = 67) and low (n = 224) lifetime CVR. Most of the variables showed statistically significant differences ($p < 0.01$) between high and low lifetime CVR groups (table 1). Laboratory markers and lipid profile for the high lifetime CVR group showed abnormal values, only uric acid was in the normal interval in both groups.

Table 1: General characteristics of the participants

		Lifetime Cardiovascular risk		
Variables	**Overall (n=291)**	**High (n =67)**	**Low (n =224)**	**P - value**
Sex[a]				
Men	84 (28.9)	38 (57.6)	46 (20.4)	<0.001*
Women	207 (71.1)	29 (43.3)	178 (79.5)	
Age (years)	46 ± 10	49 ± 9	45 ± 10	0.003*
Weight (Kg)	67.8 ± 13.0	78.4 ± 14.2	64.7 ± 10.7	<0.001*
SBP (mmHg)	108 ± 13	116 ± 12	106 ± 12	<0.001*
DBP (mmHg)	69 ± 10	74 ± 11	67 ± 10	<0.001*
Glucose (mg/dL)	95.9 ± 32.8	115.5 ± 60.9	90.0 ± 12.3	<0.001*
HbA1c (%)	6.02 ± 1.03	6.64 ± 1.69	5.84 ± 0.61	<0.001*
Cholesterol (mg/dL)	192.9 ± 36.7	216.7 ± 37.3	185.8 ± 33.4	<0.001*
LDL-c (mg/dL)	114.6 ± 30.2	134.4 ± 33.8	108.3 ± 26.0	<0.001*
VLDL-c (mg/dL)	28.7 ± 12.7	35.8 ± 11.9	26.6 ± 12.2	<0.001*
HDL-c (mg/dL)	49.9 ± 10.3	46.4 ± 9.3	51.0 ± 10.4	0.001*
Triglycerides (mg/dL)	151.1 ± 77.5	201.6 ± 87.0	136.0 ± 67.6	<0.001*
Col/HDL-c	3.99 ± 1.03	4.79 ± 0.97	3.75 ± 0.93	<0.001*
TG/HDL-c	3.20 ± 1.91	4.50 ± 2.07	2.82 ± 1.68	<0.001*
TGI	8.74 ± 0.58	9.19 ± 0.61	8.60 ± 0.49	<0.001*
Uric acid (mg/dL)	3.8 ± 1.0	4.3 ± 1.0	3.7 ± 1.0	<0.001*
Smoker[a]				
Yes	14 (4.8)	6 (9.0)	8 (3.6)	0.139
No	277 (95.2)	61 (91.0)	216 (96.4)	
Diabetes[a]				

Yes	38 (13.1)	31 (46.3)	7 (3.1)	<0.001*
No	253 (86.9)	36 (53.7)	217 (96.9)	
BMI[a]				
Normal	69 (23.7)	5 (7.5)	64 (28.6)	<0.001*
Overweight	143 (49.1)	27 (40.3)	116 (51.8)	
Obesity	79 (27.1)	35 (52.2)	44 (19.6)	
Alcohol consumption[a]				
Low-moderate	270 (92.8)	62 (92.5)	208 (92.9)	1
High	21 (7.2)	5 (7.5)	16 (7.1)	

Data expressed as mean ± standard deviation or number (%). BMI, Body mass index; LDL-c, Low density lipoprotein cholesterol; HDL-c, High density lipoprotein cholesterol; VLDL-c, Very low density lipoprotein cholesterol; Col/HDL, Total Cholesterol to HDL-cholesterol ratio; TG/HDL, Triglycerides to HDL-cholesterol ratio; TGI, Triglycerides Glucose index; HbA1c, Glycosylated hemoglobin; SBP, Systolic blood pressure; DBP, Diastolic blood pressure. [a]Weighted percentage, *p<0.01

Association of insulin resistance indexes and lifetime cardiovascular risk

All regression models were performed with Poisson regression analysis to determine the association between insulin resistance indexes and lifetime CVR (Table 2). The non-adjusted model for tertiles of TG/HDL-c showed more prevalence of high lifetime CVR in Q2 (PR = 2.62, 95%CI: 1.10 - 6.28, p = 0.03) and Q3 (PR = 6.06, 95%CI: 2.72 - 13.49, p<0.001) compared to Q1. Similarly, tertil Q2 (PR = 5, 95%CI: 1.70 - 14.70, p = 0.003) and Q3 (PR = 11.46, 95%CI: 4.12 - 31.89, p<0.001) of TGI showed more prevalence of lifetime CVR compared to Q1.

The adjusted model for tertiles of TG/HDL-c showed high prevalence of lifetime CVR in Q3 (PRa = 2.72, 95%CI: 1.13 - 6.57, p = 0.026) compared to Q1. TGI presented more prevalence of lifetime CVR in Q2 (PRa = 3.08, 95%CI: 1.01 - 9.41, p = 0.048) and Q3 (PRa = 4.73, 95%CI: 1.56 - 14.31, p = 0.006) tertiles compared to Q1. The association of TGI was stronger than TG/HDL-c in all regression models.

Table 2: Prevalence ratio and 95% CIs for Lifetime cardiovascular risk according to insulin resistance indexes tertiles.

	Insulin resistance index tertiles				
Markers	**Q1**	**Q2**	**p-value**	**Q3**	**p-value**
	PR	**PR (95% CI)**		**PR (95% CI)**	
TG/HDL-c					

Model 1[a]	1	2.62 (1.10 - 6.28)	0.030*	6.06 (2.72 – 13.49)	<0.001**
Model 2[b]	1	1.51 (0.60 – 3.78)	0.382	2.72 (1.13 – 6.57)	0.026*
TGI					
Model 1[a]	1	5.00 (1.70 – 14.70)	0.003**	11.46 (4.12 - 31.89)	<0.001**
Model 2[c]	1	3.08 (1.01 – 9.41)	0.048*	4.73 (1.56 - 14.31)	0.006**

Q1, Low tertile; Q2, Middle tertile; Q3, high tertile; CI, Confidence interval; PR, Prevalence ratio; TG/HDL-c, Triglycerides to HDL-cholesterol ratio; TGI, Triglycerides Glucose index. [a]Non adjusted; [b]Adjusted for Sex, HbA1c, LDL-c, Uric acid, BMI and alcohol consumption; [c]Adjusted for Sex, LDL-c, Uric acid, BMI and alcohol consumption; *p<0.05; **p<0.01.

Diagnostic accuracy of insulin resistance indexes

The ROC analysis of insulin resistance indexes and lifetime CVR overall showed that the AUC of TG/HDL-c was 0.77 (sensitivity: 0.86, specificity: 0.60) while the TGI AUC was 0.80 (sensitivity: 0.64, specificity: 0.83). TG/HDL-c in men presented an AUC of 0.80 (sensitivity: 0.66, specificity: 0.87) while their TGI AUC was 0.79 (sensitivity: 0.69, specificity: 0.80). TG/HDL-c in women showed an AUC of 0.74 (sensitivity: 0.86, specificity: 0.60) while their TGI AUC was 0.80 (sensitivity: 0.66, specificity: 0.82) (Figure 1). Each marker presented good diagnostic accuracy to high lifetime CVR in men, women and overall. The optimal cut off point of each marker to predict high lifetime CVR is presented in table 3.

Table 3: Diagnostic accuracy of TG/HDL-col and TGI in predicting Lifetime cardiovascular risk and their optimal cut-off values

Predictors	**Overall**	**Men**	**Women**
	Value (CI 95%)	Value (CI 95%)	Value (CI 95%)
TG/HDL-c			
Optimal Cut-off	2.64	3.90	2.64
AUC	0.77 (0.71 – 0.83)	0.80 (0.70 – 0.90)	0.74 (0.65 – 0.83)
Sensitivity	0.86 (0.76 – 0.94)	0.66 (0.49 – 0.80)	0.86 (0.68 – 0.96)
Specificity	0.60 (0.54 – 0.67)	0.87 (0.74 – 0.95)	0.60 (0.52 – 0.67)
PPV	0.39 (0.33 – 0.60)	0.81 (0.64 – 0.90)	0.26 (0.20 – 0.58)
NPV	0.94 (0.88 – 0.95)	0.75 (0.60 – 0.90)	0.96 (0.90 – 0.97)
TGI			
Optimal Cut-off	9.04	8.95	9.04
AUC	0.80 (0.74 – 0.86)	0.79 (0.69 – 0.89)	0.80 (0.72 – 0.88)

Sensitivity	0.64 (0.51 – 0.76)	0.68 (0.51 – 0.82)	0.66 (0.46 – 0.82)
Specificity	0.83 (0.77 – 0.88)	0.80 (0.66 – 0.91)	0.82 (0.76 – 0.88)
PPV	0.53 (0.44 – 0.66)	0.74 (0.58 – 0.86)	0.38 (0.29 – 0.60)
NPV	0.88 (0.82 – 0.92)	0.76 (0.60 – 0.88)	0.94 (0.87 – 0.96)

AUC, Area under the curve; TG/HDL-c, Triglycerides to HDL-cholesterol ratio; TGI, Triglycerides Glucose index; PPV, positive predictive value; NPV, negative predictive value.

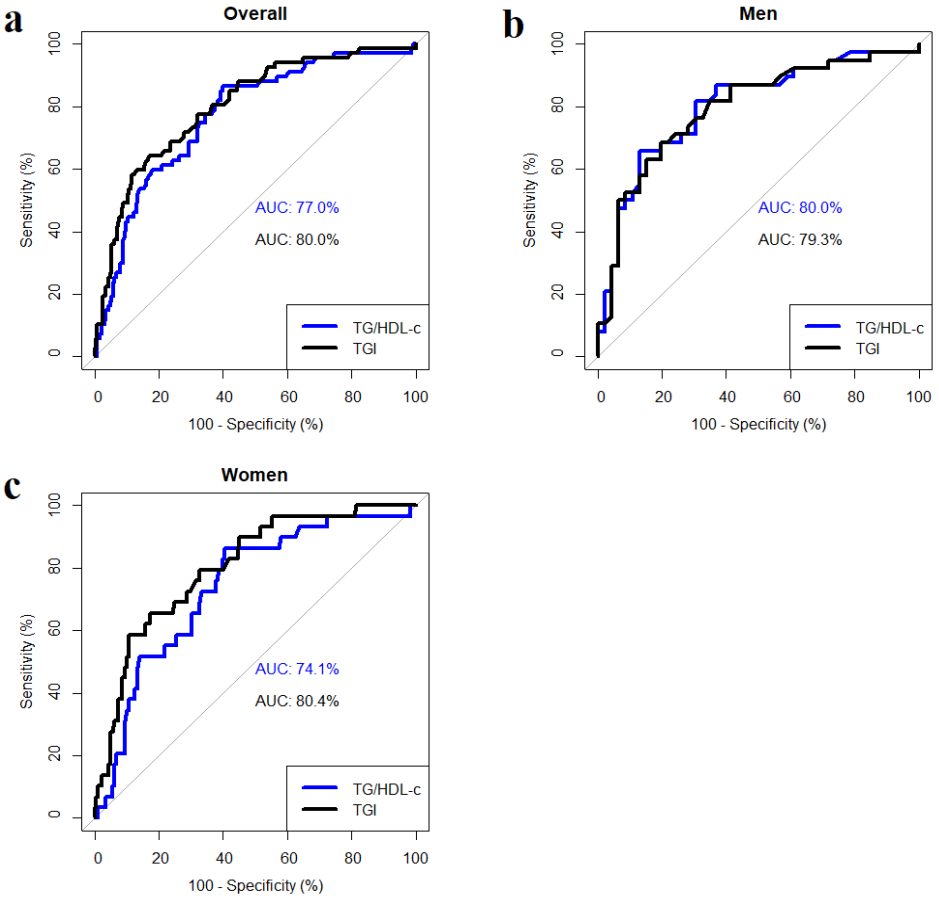

Figure 1: ROC curve of TG/HDL-c and TGI for predicting Lifetime cardiovascular risk. (a) Overall (Cut-offs, TG/HDL-c: 2.64; TGI: 9.04), (b) Men (Cut-offs, TG/HDL-c: 3.90; TGI: 8.95), (c) women (Cut-offs, TG/HDL-c: 2.64; TGI: 9.04).

Discussion

The identification of seemingly healthy people with insulin resistance before the manifestation of cardiovascular diseases is an important step in the prevention of cardiovascular events. Several studies widely use TG/HDL-col and TGI indices as markers of insulin resistance.[26,28–30] Recent studies mention that these indexes could be useful to identify people at high risk of developing some cardiovascular event early. [14,15,31–33] In the present study, TG/HDL-c and TGI indices presented independent association to lifetime CVR and good diagnostic accuracy.

To our knowledge this is the first study to assess the association of insulin indexes to lifetime CVR in a Peruvian population.

Several studies showed that TG/HDL-c is a risk factor for global cardiovascular mortality [25] , calcification of arteries [34] and coronary artery disease [35] in adult and young population. [11,36] For example, a study in adults from the U.S. found that high TG/HDL-c (>2.5 in women or >3.5 in men) increased by 1.5 times the incidence of type 2 diabetes and CVD [14]. Another study showed that high TG/HDL-c increased by 2 times the incidence of events and mortality due to CVD in nondiabetic dialysis patient from Taiwan [37] and in obese type 2 diabetes patients TG/HDL-c ≥ 1.9 presented a 1.6 time increase in the risk of CVD compared with normal weight patients. [36] In this study, the TG/HDL-c ratio increases by 2.72 times the lifetime CVR, according to the adjusted model. The relationship could be explained through increased insulin resistance when TG/HDL-c is high. [25] Additionally, the cutoff values for CVR in our study were similar to other studies [38] but cutoff values for insulin resistance differ from cardiovascular risk [27]. This could be because insulin resistance is the beginning of metabolic changes that predispose many cardiometabolic diseases. [39]

TGI is a surrogate marker of insulin resistance that in different studies was proposed as a predictor of cardiovascular disease. [40] Likewise, a study in patients from Taiwan showed that high levels of TGI increased by 1.5 times the risk of CVD [9]. Another study from Spain found that high levels of TGI increased by 2 times the incidence of CVD in adults and the ROC models integrating TGI were better than Framingham model. [15] In the same way, a study in children and adolescents with normal weight from Mexico showed that the high quintile of TGI was associated with hypertriglyceridemia, hyperglycemia and low HDL-c. [41] We found that the TGI index significantly increases, by 4.73 times, the lifetime CVR, following the adjusted model. The cutoff values of TGI in our study were higher than other populations [41], this fact can be explained through lifestyle and eating habits in Peru which are mainly carbohydrates-based. [42]

Both TG/HDL-c and TGI presented a good AUC for lifetime CVR in our study. Likewise, studies in Asian population showed that the cutoff value of TGI was between 8 to 9 with an AUC of 0.6 to 0.8 for predicting cardiovascular events. [15,40,43] Another study in a Japanese population determined the optimal cutoff values for TG/HDL-c were 2.9 for men and 2.3 for women with an AUC of 0.8 for predicting cardiometabolic risk. [44] However, a population from China reported TG/HDL-c cutoff values of 1.4 for men and 1.0 for women for predicting elevated CVR factors. [45] It is important to determine the optimal cutoff for TGI and TG/HDL-c for predicting cardiovascular events in a Latin American population.

Insulin resistance is a metabolic state that leads to many cardiometabolic diseases. [39] This is caused through defects in the metabolic pathway of insulin receptors, mammalian target of rapamycin (mTOR) and ribosomal protein S6 kinase beta 1 (S6K1) with an increase of proinflammatory proteins, endothelial dysfunction, renin-angiotensin system and dyslipidemia

[45] Additionally, this metabolic state is related to cultural lifestyle factors such as nutrition and physical activity. [17] In our study, we found adults with normal traditional metabolic markers (table 1) but with high lifetime CVR, this fact highlights the necessity of new markers in medical practice and primary prevention in cardiovascular health.

The prediction of lifetime CVR in developing countries such as Peru is very important given all the consequences of CVD in the population and the healthcare system. TG/HDL-c and TGI are inexpensive and accessible markers. In this way, they could aid in the assessment of CVR and establish therapeutic goals in primary prevention care.

This study presents some limitations, notably that it was carried out in health workers from a hospital from Peru and cannot be generalized for the general population. It was not possible to assess causality of variables due to the nature of the cross-sectional study design used. The findings are also limited by the absence of assessment for hypothyroidism, renal and liver diseases. However, no endocrine, renal or liver pathologies were registered in the workers' medical records. In this study, the analysis was adjusted by potential confounders; however, future studies must consider these limitations and include more lifestyle factors.

Conclusions

In conclusion, the TG/HDL-c and TGI showed significant independent association to lifetime CVR after adjusted potential confounders in adults in the healthcare sector from Peru. The association of TGI was stronger than TG/HDL-c in this study. Likewise, diagnostic accuracy of both markers was good in men, women and overall population. These indexes could be practical and reliable markers for CVR and useful tools in primary prevention programs for cardiovascular health.

Data Availability

The datasets used and analyzed for this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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