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Original Article

The Prognostic Value of the Triglyceride-Glucose and Fibrosis-4 Indices in Patients Undergoing Coronary Angiography: A Retrospective Cohort Analysis

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ABSTRACT

Background: The triglyceride-glucose (TYG) index, which reflects insulin resistance, and the fibrosis-4 (FIB-4) index, a measure of liver fibrosis, are noninvasive laboratory-based indicators associated with cardiometabolic risk.

Methods: We performed a retrospective analysis of 12,165 patients who underwent coronary angiography, to investigate the association of the TYG and FIB-4 indices with the occurrence of myocardial infarction, stroke, or all-cause death (major cardiovascular events [MACE]), using multivariate Cox proportional hazards models.

Results: The mean age of the study population was 65 ± 10 years; 63% presented with acute coronary syndrome. During a median follow-up period of 6.1 years, the first MACE occurred in 4174 patients. Compared to the TYG index ≤ 50th percentile (≤ 8.81), the multivariable adjusted hazard ratio (95% confidence interval) for MACE was 1.17 (1.10-1.45), 1.32 (1.23-1.43), and 1.72 (1.55-1.99) for TYG index levels ≥ 50th (> 8.81), ≥ 75th (> 9.23), and ≥ 90th (9.66) percentiles, respectively. FIB-4 index levels of 1.3-2.67 and > 2.67 were associated with an adjusted hazard ratio of 1.19 (1.11-1.27) and 1.67 (1.51-1.87), respectively, compared to FIB-4 index levels of < 1.3. Regarding the risk of developing MACE, no significant interaction was detected between TYG or FIB-4 index levels and the presence of diabetes or obesity. In a combined model of both predictive measures, a gradual increase in the incidence rate of MACE was observed, ranging from 3.93 (TYG index ≤ 8.81; FIB-4 index < 1.3) to 8.56 (TYG index > 9.23; FIB-4 index > 2.67) events per 100 patient-years.

Conclusions: The TYG and FIB-4 indices, both individually and when concomitantly elevated, were independently associated with an increased risk of developing MACE in patients undergoing coronary angiography. ,. These simple-to-calculate, noninvasive metabolic biomarkers may aid in the prediction of cardiovascular diseases.

RÉSUMÉ

Contexte : L'indice triglycéride-glucose (TyG), qui indique l'insulinorésistance, et l'indice de fibrose 4 (FIB-4), mesure de la fibrose hépatique, sont des indicateurs biochimiques non invasifs associés au risque cardiométabolique.

Méthodologie : Nous avons mené une analyse rétrospective comptant 12 165 patients ayant été soumis à une coronarographie dans le but d'évaluer le lien entre les indices TyG et FIB-4 et la survenue d'un infarctus du myocarde, d'un AVC ou de décès toutes causes confondues (événements cardiovasculaires indésirables majeurs [ECIM]), au moyen de modèles à risques proportionnels de Cox multivariés.

Résultats : L'âge moyen de la population de l'étude était de 65 ± 10 ans; 63 % ont consulté pour un syndrome coronarien aigu. Sur une période de suivi médiane de 6,1 ans, le premier ECIM est survenu chez 4174 patients. Comparativement à l'indice TyG ≤ 50^{e} percentile (≤ 8,81), le rapport des risques instantanés multivariés (intervalle de confiance à 95 %) pour les ECIM était 1,17 (1,10-1,45), 1,32 (1,23-1,43) et 1,72 (1,55-1,99) pour les niveaux d'indice TyG ≥ 50^{e} (> 8,81), ≥ 75^{e} (> 9,23) et ≥ 90^{e} (9,66) percentiles, respectivement. Des valeurs de l'indices FIB-4 de 1,3-2,67 et > 2,67 ont été associés à un rapport des risques instantanés ajusté de 1,19 (1,11-1,27) et de 1,67 (1,51-1,87), respectivement, comparativement à des valeurs de l'indice FIB-4 < 1,3. Quant au risque d'apparition d'ECIM, aucune interaction notable n'a été décelée entre les valeurs des indices TyG et FIB-4 et la présence de diabète ou d'obésité. Dans un modèle combiné de ces deux mesures prédictives, une hausse graduelle du taux d'incidence d'ECIM a été observée, variant entre 3,93 (indice TyG ≤ 8,81; indice FIB-4 < 1,3) et 8,56 (indice TyG > 9,23; indice FIB-4 > 2,67) événements pour 100 années-patients.

Conclusions : Les indices TyG et FIB-4, lorsqu'ils étaient élevés individuellement ou simultanément, étaient indépendamment associés à une augmentation du risque de survenue d'ECIM chez les patients soumis à une coronarographie. Ces biomarqueurs métaboliques non invasifs et simples à calculer peuvent contribuer à prédire les maladies cardiovasculaires.

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See page 471 for disclosure information.

The rate of metabolic syndrome is increasing worldwide with the rise in the prevalence of obesity, diabetes, and dyslipidemia.[1,2] These risk factors are closely related to metabolic dysfunction–associated fatty liver disease (MAFLD), which

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may develop into liver fibrosis.[3] Noninvasive serum biomarkers have been developed for the initial assessment of hepatic fibrosis; among them is the fibrosis-4 (FIB-4) index, simply calculated using a formula comprised of age, platelet count, and level of aminotransferases.[4] FIB-4 levels were shown to be not only an indicator of liver impairment and fibrosis, but also an index associated with all-cause mortality in chronic disease states.[5,6] As patients with fatty liver disease have an increased prevalence of cardiovascular events, the FIB-4 index was examined further in relation to cardiovascular diseases, including ischemic heart disease and heart failure, particularly in patients with diabetes.[7,8]

Insulin resistance is a key factor in the metabolic derangement associated with fatty liver disease[9]; it is closely related to not only type 2 diabetes, but also the development of cardiovascular diseases.[10] The triglyceride-glucose (TYG) index indirectly assesses insulin resistance without requiring measurement of circulating insulin concentrations, through a simple laboratory calculation of the natural logarithm of the product of fasting plasma triglyceride and glucose levels.[11] The TYG index has been shown to be a reliable surrogate marker of insulin resistance and to have significant prognostic value.[12] The index has also been suggested to be a useful predictive marker for fatty liver disease, because of the association of MAFLD with insulin resistance and dyslipidemia.[13,14] In the current study, we aimed to investigate the association of the FIB-4 and TYG indices with future adverse cardiovascular events and mortality in patients undergoing coronary angiography. We also sought to determine whether the predictive value of these indices is dependent on the presence of obesity and diabetes, and assess their combined predictive capacity.

Methods

Study population

This study was a single-centre analysis of prospectively collected data from the Cardiac Catheterization Laboratory at Lady Davis Carmel Medical Center, in Haifa, Israel. All patients were members of Clalit Health Services (CHS), the largest non-for-profit healthcare provider in Israel, for whom we had full access to the outcome data during the follow-up period. Patients who underwent coronary angiography between January 2010 and December 2022 were included. Only the first procedure performed on each patient during the study period was included. The analysis was restricted to patients aged 45-85 years who underwent catheterization for the assessment and treatment of coronary artery disease. We excluded patients who lacked data on the main laboratory parameters during the 6-month period prior to the index hospitalization. The final study population was comprised of 12,165 patients. An outline of this study is presented in Figure 1. The study database was approved by the Carmel Medical Center Ethics Committee, which waived the need for individual patient consent, owing to the retrospective nature of the study.

Study variables and definitions of terms

Demographic data, clinical variables, laboratory tests, comorbidities, and risk factors were most often collected prospectively from the patients' medical records at the time of their undergoing coronary angiography. Data that were not collected originally were retrieved from the computerized CHS database. The 2 main study predictors of interest were as follows: (i) the TYG index—an indirect surrogate of insulin resistance, calculated by multiplying values for fasting plasma triglyceride and glucose concentrations, and (ii) the FIB-4 index—a marker of hepatic fibrosis. The TYG index was calculated according to the following formula Ln [triglycerides (mg/dL) × plasma glucose (mg (dL)/2].[11], The FIG-4 index was calculated according to the following formula: age [years] × aspartate transaminase [U/L]/[platelet count (10^9/L) × alanine transaminase (U/L)$^{1/2}$].[15] Laboratory tests were performed in a single laboratory using a COBAS analyzer (Roche Diagnostics, Rotkreuz, Switzerland) for clinical chemistry assays, and an ADVIA 2120i Hematology analyzer (Siemens Healthcare Diagnostics, New York, NY) for automatic complete blood count sample results. Both the TYG and FIB-4 indices were analyzed for their association with the primary study endpoint, defined as major adverse cardiovascular events (MACE)—that is, the occurrence of myocardial infarction (MI), ischemic stroke, or all-cause death during the long-term follow-up period. Data on MI and ischemic stroke were retrieved from the CHS hospitalization database and defined as primary discharge diagnosis with International Classification of Diseases, 9th edition (ICD-9) codes 410.xx and 433.x1 (MO) and 434.x1 and 436 (ischemic stroke). Vital status data were retrieved from the Israel Ministry of Interior. The cohort participants received follow-up evaluation until the first occurrence of the study outcome (MACE) or the end of the follow-up period on June 30, 2024.

Data analysis

Continuous data are reported as mean and standard deviation, or as median and interquartile range (IQR). Categorical variables are reported as number and percentage. Comparisons of continuous variables between the 2 groups were performed using the Independent-samples t test or the Mann-Whitney U test, and the χ^2 test was used to compare categorical variables. Histograms were used to visually display the distribution of the TYG and FIB-4 indices in the study population. Descriptive statistics, crude events, incidence rates per 100 patient-years, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model for the association of the TYG and FIB-4 indices with the development of MACE during the follow-up period. Predictor variables were analyzed as both categorical and continuous variables. The TYG index was classified according to percentiles, with the group of patients with TYG $\leq$ 50th percentile ($\leq$ 8.81) serving as the reference category. The FIB-4 index was categorized into 3 groups according to the customary classification, as follows: $<$ 1.3; 1.3-2.67; and $>$ 2.67.[16] Adjustments were made for age, sex, smoking, obesity, diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, cerebrovascular disease, peripheral artery disease, and MI. FIB-4 was not adjusted for age, as age is a component of the FIB-4 formula, and both variables had a significant interaction with the risk of MACE ($P = 0.001$). Subgroup analysis was performed by calculating the P-values for

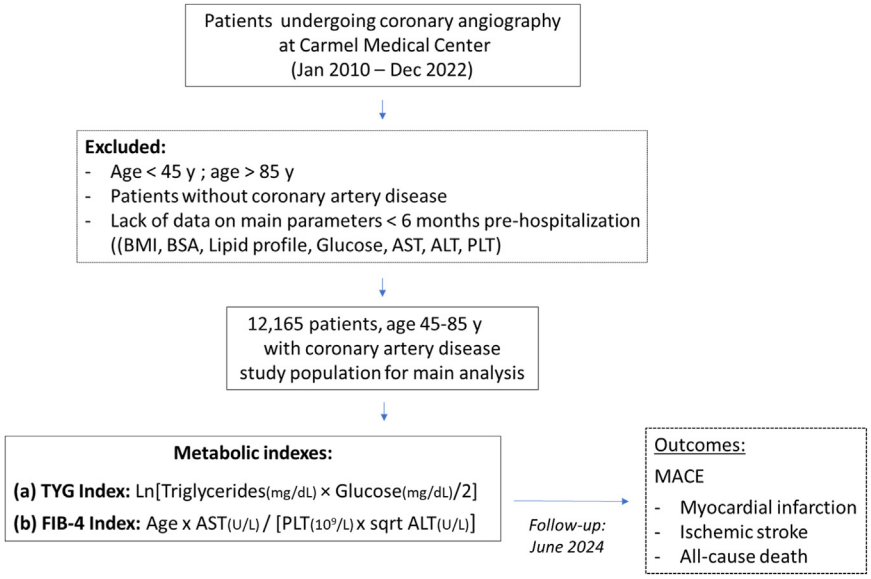

Figure 1. Study outline. ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BSA, body surface area; Dec, December; FIB-4 index, fibrosis-4 index, a marker of hepatic fibrosis, calculated as follows: age [years]×AST [U/L]/[platelet count (10^9/L) × ALT (U/L)$^{1/2}$]; Jan, January; MACE, major adverse cardiovascular events; PLT, platelet; TYG index, triglyceride-glucose index, indirect surrogate of insulin resistance, calculated by multiplying values for fasting plasma triglyceride and glucose concentrations, calculated as: Ln [triglycerides (mg/dL) × plasma glucose (mg (dL)/2.

interactions, and a graphical presentation of results was made using forest plots. The Kaplan—Meier method was used to depict the distribution of time to MACE and its individual components (MI, ischemic stroke, and all-cause death), according to the TYG and FIB-4 groups, and comparisons between categories were performed using the log-rank test. To assess the combined effect of the TYG and FIB-4 indices on MACE, the incidence rates of MACE per 100 patient-years were presented graphically, according to a 3 × 3 contingency table comprising the TYG and FIB-4 categories.

Statistical analyses were considered significant when the 2-sided *P*-value was < 0.05. All statistical analyses were performed using SPSS, version 25.0 (IBM, Armonk, NY) and MedCalc, version 16.8.4 (MedCalc Software, Ostend, Belgium).

Results

Of the 12,165 study patients who underwent coronary angiography, 63% presented with acute coronary syndrome (ACS), and the remainder had stable coronary artery disease. The mean age of the patients was 65 ± 10 years, and 26% were women. Overall, 42.8% of the study patients had diabetes, and 10.3% had previous MI. The TYG index values that were above, vs below, the median level (8.81) were associated with younger age and more significant rates of comorbidities, including obesity, diabetes, hypertension, hyperlipidemia, active smoking, and chronic kidney disease (Table 1). In contrast, FIB-4 levels ≥ 1.3 (evident in approximately half of the study cohort) were associated with older age and lower rates of obesity, diabetes, and active smoking, whereas rates of hypertension, hyperlipidemia, and chronic kidney disease were higher. The distribution of the TYG index and FIB-4 levels in the study population, according to sex, is presented in Supplemental Figure S1.

During a median follow-up period of 6.1 years (IQR, 3.2-9.5), acute MI was evident in 1501 patients (12.3%), ischemic stroke occurred in 495 patients (4.1%), and 2945 patients (24.2%) died. Overall, the first incidence of MACE occurred in 4174 patients (34.3%). The crude events and incidence rates of MACE per 100 patient-years progressively increased with the percentiles of the TYG and FIB-4 indices in the study population (Table 2). The cumulative probability over time for the occurrence of MACE was significantly higher in patients with a TYG index above the median level, and across FIB-4 categories (< 1.3; 1.3-2.67; > 2.67), as graphically presented in Figure 2, A and B (log rank $P < 0.001$ for both predictive measures). In comparison to individuals with a TYG index at ≤ 50th percentile (≤ 8.81; reference group), those with a TYG index at > 50th (> 8.81), > 75th (> 9.23), or > 90th (> 9.66) percentile had an HR (95% CI) for MACE of 1.17 (1.10-1.45), 1.32 (1.23-1.43), and 1.72 (1.55-1.99), respectively, after multivariable adjustment (Table 2). Similarly, compared to a FIB-4 index level < 1.3 (reference), FIB-4 index levels of 1.3-2.67, and > 2.67 were associated with an adjusted HR (95% CI) for MACE of 1.19 (1.11-1.27) and 1.68 (1.51-1.87), respectively. An increase in the risk of MACE was observed in the adjusted models when the TYG and FIB-4 indices were analyzed as continuous variables, including in the subgroup of patients presenting with ACS (Table 2). In addition, no significant interaction was detected between the presence of diabetes or obesity and the TYG or FIB-4 indices, regarding the adjusted risk of developing MACE (nonsignificant interaction for each comparison, as shown in Supplemental Fig. S2).

Analysis of the association between the predictive variables and the individual components of MACE revealed that an increase in TYG percentiles in the study population was

Table 1. Patients' baseline characteristics

Variable	Overall (n = 12,165)	TYG Index		P	FIB-4 index		P
		≤ 8.81 (n = 6095)	> 8.81 (n = 6070)		< 1.3 (n = 6047)	≥ 1.3 (n = 6118)	
Age, y	65.3 ± 10.3	66.6 ± 10.2	64.1 ± 10.3	< 0.001	61.1 ± 9.8	69.5 ± 9	< 0.001
Sex (female)	3142 (25.8)	1550 (25.4)	1592 (26.2)	0.315	1586 (26.2)	1556 (25.4)	0.317
Body mass index, kg/m^2	28.4 ± 4.7	27.7 ± 4.6	29.2 ± 4.7	< 0.001	28.8 ± 4.8	28 ± 4.6	< 0.001
Obesity	3298 (27.1)	1308 (21.5)	1990 (32.8)	< 0.001	1830 (30.3)	1468 (24)	< 0.001
Diabetes mellitus	5210 (42.8)	1726 (28.3)	3484 (57.4)	< 0.001	2687 (44.4)	2523 (41.2)	< 0.001
Insulin therapy	1316 (10.8)	402 (6.6)	914 (15.1)	< 0.001	753 (12.5)	563 (9.2)	< 0.001
Hypertension	9082 (74.7)	4338 (71.2)	4744 (78.2)	< 0.001	4273 (70.7)	4809 (78.6)	< 0.001
Hyperlipidemia	9506 (78.1)	4501 (73.8)	5005 (82.5)	< 0.001	4642 (76.8)	4864 (79.5)	< 0.001
Active smoking	3067 (25.2)	1399 (23)	1668 (27.5)	< 0.001	1925 (31.4)	1142 (18.7)	< 0.001
Former smoking	2376 (19.5)	1100 (18)	1276 (21)	< 0.001	1078 (17.8)	1298 (21.2)	< 0.001
Cerebrovascular disease	259 (2.1)	122 (2)	137 (2.3)	0.329	137 (2.3)	122 (2)	0.300
Peripheral artery disease	498 (4.1)	212 (3.5)	286 (4.7)	0.001	222 (3.7)	276 (4.5)	0.019
Chronic kidney disease	1272 (10.5)	566 (9.3)	706 (11.6)	<0.001	527 (8.7)	745 (12.2)	< 0.001
Hemoglobin, mg/dL	13.6 ± 1.7	13.5 ± 1.6	13.6 ± 1.7	0.06	13.7 ± 1.7	13.5 ± 1.6	< 0.001
Previous MI	1248 (10.3)	615 (10.1)	633 (10.4)	0.539	588 (9.7)	660 (10.8)	0.053
ACS	7629 (62.7)	3831 (62.9)	3797 (62.6)	0.731	3899 (64.5)	3729 (61)	< 0.001

Values are mean ± standard deviation, or n (%), unless otherwise indicated.

ACS, acute coronary syndrome; ALT, alanine transaminase; AST, aspartate transaminase; FIB-4, a marker of hepatic fibrosis, calculated as follows: age [years]× AST [U/L]/[platelet count (10^9/L) × ALT (U/L)$^{1/2}$]; MI, myocardial infarction; TYG, TYG index, indirect surrogate of insulin resistance, calculated by multiplying values for fasting plasma triglyceride and glucose concentrations, calculated as: Ln [triglycerides (mg/dL) × plasma glucose (mg (dL)/2].

associated with a progressive rise in the crude incidence rates and cumulative probability of MI, ischemic stroke, or all-cause death (Supplemental Figs. S3a and S4). On the other hand, an increase in the FIB-4 index categories was associated significantly with higher rates of all-cause death, but not with the incidence of MI or ischemic stroke events (Supplemental Figs. S3b and S5).

Combining the 2 predictive measures (the TYG and FIB-4 indices) using a 3 x 3 contingency table showed that the incidence rates of MACE tended to increase progressively across subgroups, ranging from 3.93 events per 100 patient-years in those in the lowest TYG and FIB-4 group (≤ 8.81 and < 1.3, respectively), to up to 8.56 events per 100 patient-years in the highest TYG and FIB-4 group (≥ 9.24 and > 2.67, respectively; Fig. 3).

Discussion

In the current study, we examined the association of the TYG and FIB-4 indices with the risk of developing MACE in patients undergoing coronary angiography during a median follow-up period of 6 years. Both metabolic indices demonstrated a stepwise increase in the risk of composite adverse outcome events that remained significant after multivariable adjustment for risk factors, comorbidities, and the presence of atherosclerotic cardiovascular disease. Notably, no significant interaction was found between the presence of diabetes or obesity and the TYG or FIB-4 index in relation to the risk of experiencing MACE. Combining the data on the TYG and FIB-4 indices showed that a progressive increase occurred in the incidence of MACE when the 2 measures were elevated concomitantly.

Substantial evidence supports use of the TYG and FIB-4 indices as reliable surrogate markers for insulin resistance and MAFLD.[7,8,11] Both are associated with altered glucose and lipid metabolism that may result in chronic inflammation and oxidative stress, leading to endothelial dysfunction, cellular damage, and eventually, accelerated atherosclerosis.[17-19] Persistent insulin resistance may induce the development of chronic disease states, including type 2 diabetes and cardiovascular disease.[20,21] Supporting evidence demonstrates a positive correlation between the TYG and FIB-4 indices and the severity of coronary heart disease, as evaluated by cardiac computed tomography angiography.[22,23] A significant association between the TYG index and plaque burden was reported, including a correlation with vulnerable plaque characteristics, such as positive remodelling and low-attenuation plaque sign.[24] Similarly, MAFLD was reported to be associated with both non-calcified and mixed coronary plaques, as well as multivessel coronary artery stenosis, as demonstrated by cardiac computed tomography angiography.[25] According to these findings, the TYG and FIB-4 metrics may have a potential role in assessing cardiometabolic risk and predicting coronary artery disease.

Several previous studies have demonstrated the prognostic significance of the TYG and FIB-4 indices in predicting cardiovascular outcomes.[15,26-28] Chen et al. reported a significant association between the TYG index and all-cause and cardiovascular mortality in the general population.[29] Moreover, both the TYG and FIB-4 indices were reported to be associated independently with future cardiovascular events, regardless of other traditional cardiovascular risk factors, suggesting that they may be useful predictors of clinical outcomes.[15,28,30] Our study findings are consistent with previous data and they strengthen the importance of these data by reporting on a large cohort of patients undergoing coronary angiography for the assessment and treatment of coronary artery disease, with approximately two-thirds presenting with an ACS. Given that the TYG and FIB-4 indices serve as surrogate markers for insulin resistance and MAFLD, individuals with elevated TYG and FIB-4 levels are more vulnerable to metabolic disturbances and their associated consequences, including cardiovascular

Table 2. Descriptive statistics, incidence rates, and hazard ratios (HRs) for the association between baseline TYG (triglyceride-glucose) index, fibrosis 4 (FIB-4) index, and future major adverse cardiovascular events (MACE)

		MACE		
Variable	Events / patients (%)	Incidence rate per 100 person-y	Age- & sex- adjusted HR* (95% CI); *P*	Multivariable† adjusted HR (95% CI); *P*
TYG Index, percentile (value)				
≤ 50 (≤ 8.81)	1853/6095 (30.4)	4.68	1 (reference)	1 (reference)
> 50 (> 8.81)	2321/6070 (38.2)	5.92	1.45 (1.36−1.54); < 0.001	1.17 (1.10−1.45); < 0.001
> 75 (> 9.23)	1328/3055 (43.5)	6.88	1.74 (1.62−1.87); < 0.001	1.32 (1.23−1.43); < 0.001
≥ 90 (> 9.66)	617/1211 (50.9)	8.67	2.35 (2.14−2.58); < 0.001	1.72 (1.55−1.99); < 0.001
TYG Index (per SD increase)	All patients		1.30 (1.26−1.34); < 0.001	1.15 (1.11−1.19); < 0.001
	Patients with ACS		1.31 (1.27−1.36); < 0.001	1.14 (1.10−1.19); < 0.001
FIB-4 index				
< 1.3	1836/6047 (30.4)	4.60	1 (reference)	1 (reference)
1.3−2.67	1935/5204 (37.2)	5.79	1.26 (1.18−1.34); < 0.001	1.19 (1.11−1.27); < 0.001
> 2.67	403/914 (44.1)	7.47	1.64 (1.47−1.82); < 0.001	1.68 (1.51−1.87); < 0.001
FIB-4 index (per SD increase)	All patients		1.10 (1.07−1.12); < 0.001	1.09 (1.07−1.12); < 0.001
	Patients with ACS		1.06 (1.04−1.09); < 0.001	1.07 (1.04−1.10); < 0.001

ACS, acute coronary syndrome; ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; FIB-4 index, fibrosis-4 index, a marker of hepatic fibrosis, calculated as follows: age [years]×AST [U/L]/[platelet count (10^9/L) × ALT (U/L)$^{1/2}$]; SD, standard deviation; TYG index, triglyceride-glucose index, indirect surrogate of insulin resistance, calculated by multiplying values for fasting plasma triglyceride and glucose concentrations, calculated as: Ln [triglycerides (mg/dL) × plasma glucose (mg (dL)/2].

*The FIB-4 index was not adjusted for age, as age is part of the FIB-4 formula (*P* for interaction = 0.001 between FIB-4 groups and age regarding the risk of MACE).

†Multivariable adjustment for age (TYG index only), sex, hyperlipidemia, hypertension, obesity, diabetes mellitus, smoking status, chronic kidney disease, previous myocardial infarction, peripheral artery disease, cerebrovascular disease.

disease.[7,8,11] As is often seen in cohorts of patients with metabolic syndrome, we observed a high burden of traditional cardiovascular risk factors in our patient population cohort.[31,32] Nevertheless, even after multivariable adjustment for cardiometabolic comorbidities, an increased risk of MACE was noted in all adjusted models with a continuous rise in both TYG and FIB-4 levels. Moreover, we did not observe an interaction between obesity or diabetes and TYG or FIB-4 levels regarding the risk of MACE, emphasizing the independent prognostic value of these metabolic indices. Sánchez-Íñigo et al. similarly reported that the TYG index was correlated positively with an increased risk of developing

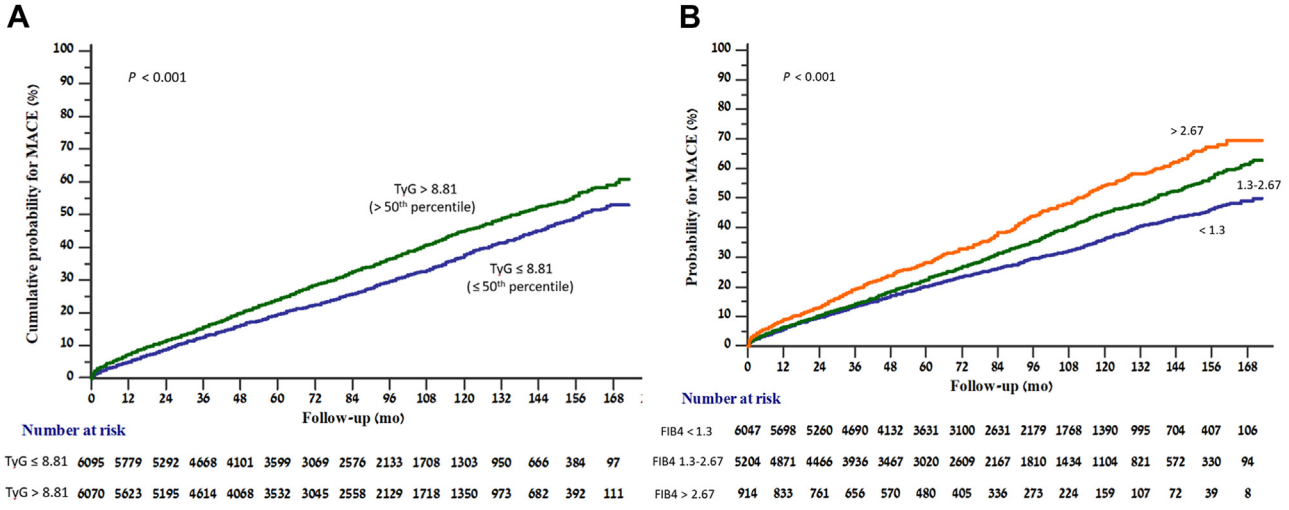

Figure 2. Cumulative probability for major adverse cardiovascular events (MACE), according to TYG index and FIB-4 index categories. (**A**) TYG index above or below median level (8.81); (**B**) FIB-4 index categories: < 1.3; 1.3-2.67; > 2.67. ALT, alanine transaminase; AST, aspartate transaminase; FIB-4 index, fibrosis-4 index, a marker of hepatic fibrosis, calculated as follows: age [years]×AST [U/L]/[platelet count (10^9/L) × ALT (U/L)$^{1/2}$]; TYG index, triglyceride-glucose index, indirect surrogate of insulin resistance, calculated by multiplying values for fasting plasma triglyceride and glucose concentrations, calculated as: Ln [triglycerides (mg/dL) × plasma glucose (mg (dL)/2].

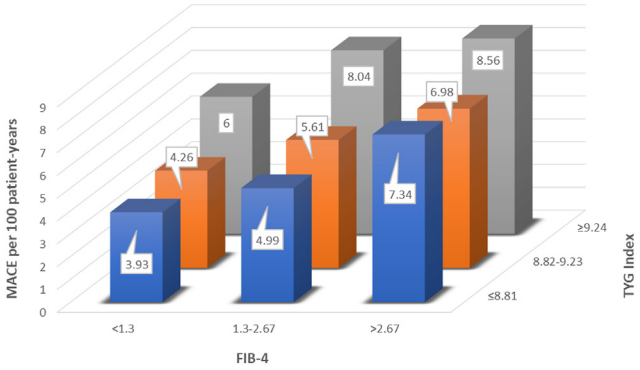

Figure 3. The association between FIB-4 and TYG index categories, with the incidence rates of major adverse cardiovascular events (MACE). ALT, alanine transaminase; AST, aspartate transaminase; FIB-4 index, fibrosis-4 index, a marker of hepatic fibrosis, calculated as follows: age [years]× AST [U/L]/[platelet count (10^9/L) × ALT (U/L)$^{1/2}$]; TYG index, triglyceride-glucose index, indirect surrogate of insulin resistance, calculated by multiplying values for fasting plasma triglyceride and glucose concentrations, calculated as: Ln [triglycerides (mg/dL) × plasma glucose (mg (dL)/2.

cardiovascular disease, after adjusting for both body mass index and diabetes, noting that a lack of information on the use of lipid-lowering therapy and antidiabetic drugs may have influenced their results.[33]

Although multiple studies have been published regarding the prognostic value of both TYG and FIB-4 indices, no consensus has been reached regarding the optimal cutoff levels for defining increased cardiometabolic risk.[4,34] We observed a stepwise increase in the risk of MACE, with a TYG index value above 8.81, the cohort median level. A TYG index cutoff value of 8.26 was reported previously to be predictive of the occurrence of insulin resistance in a young Korean population, with a sensitivity and specificity of 66% and 65%, respectively.[35] Another study established a higher cutoff of 9.2, with a lower predictive capacity.[36] Regarding the FIB-4 index, a cutoff value of > 3.25 is often used in clinical trials and consensus documents to define high risk, although it was validated originally to predict liver fibrosis in patients with viral hepatic infections.[4,34] As only 4% of our patient population had FIB-4 levels > 3.25, we selected a lower cutoff of 2.67 to define elevated levels, as this value was shown to be associated with high risk for hepatic fibrosis and cardiovascular events in patients with MAFLD.[16] In addition, we used an intermediate FIB-4 cutoff value of 1.3, a level that approximates the median level in our cohort and is used regularly in the literature for defining intermediate risk for hepatic fibrosis.[16]

Strengths and limitations

The strengths of the present study include the large sample size of patients undergoing coronary angiography and a significant representation of patients admitted with ACSs. In addition, unlike most previous reports, we included an analysis of the combined effect of the TYG and FIB-4 indices. Our study also has some limitations that should be noted. First, because coronary angiography was performed for the evaluation and treatment of ischemic heart disease, a selection bias may have affected our analysis. Second, the MACE rates were driven mainly by an excess in the incidence of all-cause mortality. Further studies evaluating the cardiovascular causes of death should be conducted to further support our findings. Third, the association between FIB-4 and adverse outcomes was not adjusted for age, as age is an inherent component of the FIB-4 formula. The increase in MACE associated with the FIB-4 index was driven by all-cause mortality and may be linked to the confounding effects of aging. This link may be related to a reduced specificity of this index in elderly patients. Indeed, the performance of the FIB-4 index in patients aged $\geq$ 65 years evaluated for liver disease was previously reported to be associated with higher false-positive rates.[37] Fourth, although multivariable adjustment was performed, including for multiple comorbidities with an impact on the incidence of MACE, the potential effect of competing risks factors and residual confounders in patients with coronary artery disease—such as left ventricular ejection fraction, degree of cardiorespiratory fitness, and adherence to drug therapy—could not be ruled out.

Conclusions

Insulin resistance and MAFLD are associated with obesity and diabetes, which are the cardinal features of metabolic syndromes. Their prevalence is increasing worldwide, affecting morbidity and mortality with a growing burden on public health.[38] The TYG and FIB-4 indices are simple to calculate and reflect these metabolic disorders, and they are associated with an increased risk for developing MACE in patients undergoing coronary angiography. The indices are easy to determine in clinical practice without additional costs or the need for imaging or invasive techniques, and they may be useful surrogate biomarkers for early identification of those patients at high risk of developing cardiometabolic disease.

Ethics Statement

The study was approved by the Ethics Committee of the Carmel Medical Center Haifa, Israel (protocol no. 0108-24-CMC).

Patient Consent

This study did not require patient consent because of the retrospective cross-sectional nature of the study without the use of patient identification data.

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Disclosures

The authors have no conflicts of interest to disclose

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2025.01.005.