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Predictive Performance of Triglyceride-Glucose Index on Asymptomatic Multiple Organ Damage in Patients with Newly Diagnosed Hypertension

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ABSTRACT

Background: Insulin resistance (IR) contributes to the development of hypertension and mediated organ damage (HMOD) through various mechanisms. **Objectives:** The objective of the study was to assess the diagnostic performance of the triglyceride-glucose (TyG) index, a surrogate marker of IR, in predicting the presence and severity of HMOD in newly diagnosed untreated hypertensive patients from an academic training and research hospital. **Methods:** The study included 438 patients with newly diagnosed, untreated hypertension. The control group comprised normotensive individuals matched on a 1:1 ratio based on age, gender, body mass index, and smoking using the nearest neighbor method. The presence of HMOD was defined by renal damage (microalbuminuria > 30 mg/day or proteinuria > 150 mg/day), vascular damage (carotid intima-media thickness > 0.9 mm or presence of plaque), or cardiac damage (left ventricular mass index > 95 g/m^2 in women and > 115 g/m^2 in men). The severity of HMOD was considered as single-, two-, or triple-organ damage. **Results:** TyG index values were higher in the hypertensive group than the normotensive group. An increased TyG index was independently associated with HMOD (OR: 1.33, p < 0.001). The TyG index exhibited gradually increasing threshold values for distinguishing patients with single-organ HMOD (> 8.8 with 77.8% sensitivity and 74.3% specificity), two-organ HMOD (> 9.1 with 77.6% sensitivity and 71.4% specificity), and triple-organ HMOD (> 9.4 with 71.5% sensitivity and 87.7% specificity). **Conclusions:** In newly diagnosed hypertensive patients, the TyG index exhibits significant diagnostic performance in predicting multiple-organ damage beyond the presence of HMOD. Since the detection of multiple-organ HMOD requires a multidisciplinary approach, the TyG index can serve as a simple and inexpensive screening tool. (REV INVEST CLIN. 2023;75(5):221-32)

Keywords: Atherosclerosis. Hypertensive organ damage. Insulin resistance. Triglyceride-glucose index

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INTRODUCTION

Hypertension-mediated organ damage (HMOD) is caused by high blood pressure (BP) damaging the cardiac, renal, and vascular tissues and leading to atherosclerosis[1]. Because hypertension is often asymptomatic, many patients are diagnosed late and may have asymptomatic HMOD when they are first admitted to the hospital[2,3]. Late diagnosis due to the lack of specialized imaging and laboratory tests in some medical centers may worsen the prognosis and increase the risk of cardiovascular events[4], especially in cases of multiple-organ damage, which indicates HMOD severity[5]. Therefore, there is a need for easily measurable biomarkers at each medical center to predict the presence and severity of HMOD.

Hypertensive patients are prone to impaired glucose and lipid homeostasis, which significantly increase the risk of organ damage[6]. Insulin resistance (IR) plays a role in elevating BP through various mechanisms, including impaired vasodilation, increased activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), and induction of oxidative stress[7]. These mechanisms lead to the development of an inflammatory milieu and abnormal lipid metabolism, which are shared characteristics of both atherosclerosis and IR[8]. Besides, IR is characterized by hypertriglyceridemia[9]. Therefore, triglyceride-based indices such as the triglyceride-glucose (TyG) index and triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio have been developed for predicting IR. Although these indices exhibit similar diagnostic performance in predicting IR or metabolic syndrome[10-13], it has been shown that the TyG index exhibits a better diagnostic performance in predicting patients with prediabetes, hypertension, and subclinical atherosclerosis[13-15].

Although limited studies have suggested that the TyG index may serve as indicators of HMOD[16-18], its diagnostic accuracy in predicting the severity of HMOD has not been evaluated. Therefore, we hypothesized that the TyG index could serve as practical screening tools for predicting the presence and severity of HMOD. This study aimed to assess the diagnostic performance of the TyG index in predicting the presence and severity of HMOD in newly diagnosed untreated hypertensive patients.

MATERIALS AND METHODS

Following the principles set forth in the Declaration of Helsinki, this retrospective study was conducted at the Dışkapı Yıldırım Beyazit Training and Research Hospital Cardiology Clinic from January 2017 to December 2021. The study received approval from the local Ethics Committee (Approval Date: 18 April 2022, Decision No. 135/14). The need for informed consent was waived under the approval of the local Ethics Committee due to the retrospective design.

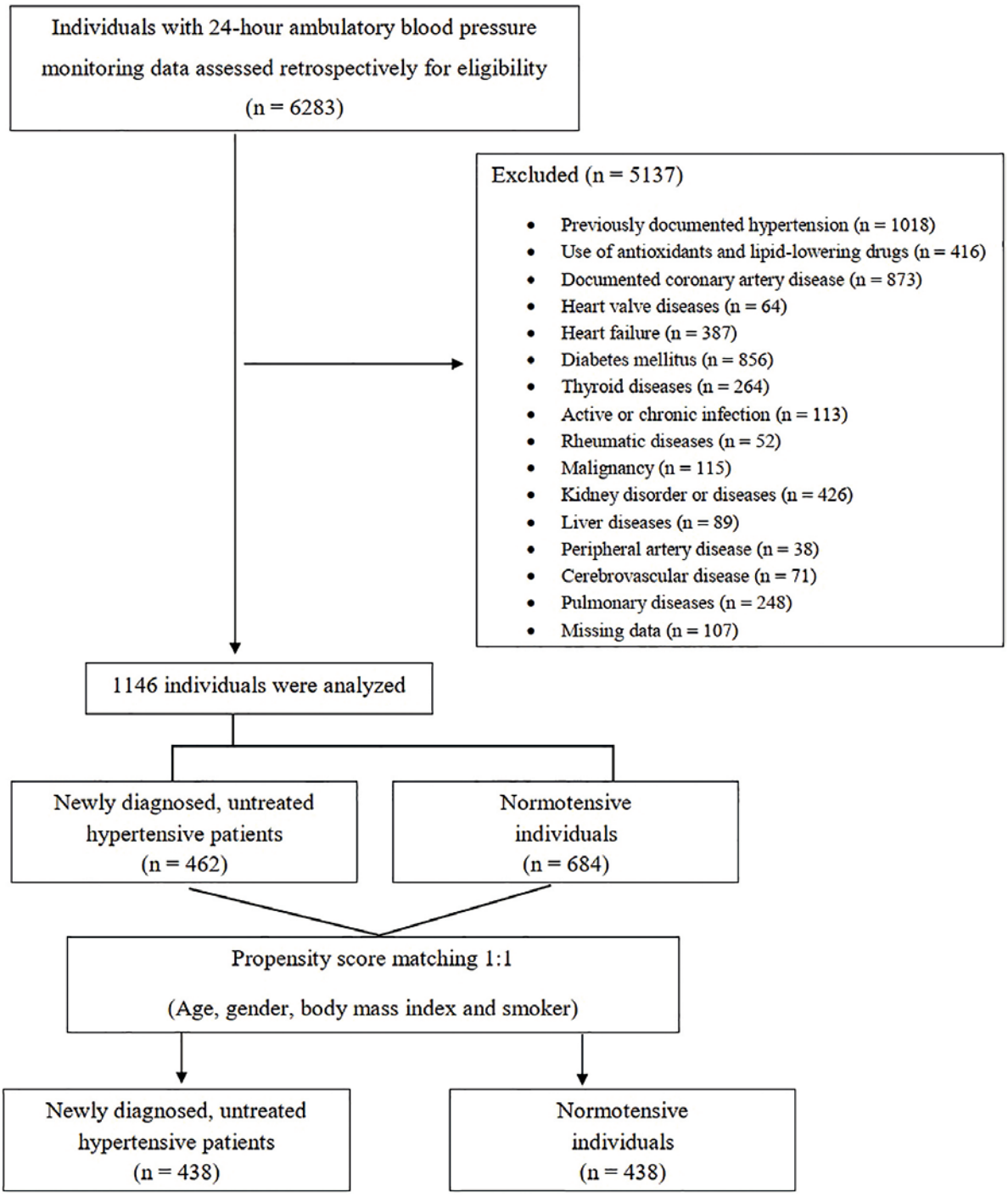
Study population

A total of 7820 individuals who underwent 24-h ambulatory BP monitoring (ABPM) during the study period were evaluated retrospectively. The inclusion criteria were normotensive individuals or newly diagnosed, untreated hypertensive patients between the ages of 18 and 65 who had all indicators of HMOD (microalbuminuria, proteinuria, left ventricular [LV] mass index [LVMI], and carotid intima-media thickness [CIMT]), along with complete demographic and laboratory data and no comorbidities. Exclusion criteria were previously documented hypertension, use of antioxidants or lipid-lowering drugs, active or chronic infection, any additional diseases, and missing data. After the exclusion process, 462 newly diagnosed primary hypertensive patients and 684 normotensive individuals remained. To address the imbalance in covariates (age, gender, body mass index [BMI], and smoking) between the hypertensive and normotensive individuals, propensity score matching analysis was performed. The analysis involved 1:1 matching with the nearest neighbor matching method, using calipers (0.2) with a width equal to 0.25 of the standard deviation of the logit[19] (Supplementary Fig. 1). Individuals who did not have a match were excluded from the statistical analysis. As a result, the analysis included 438 hypertensive patients and an equal number of normotensive individuals in the control group (Fig. 1).

Study protocol

The demographic, clinical, and imaging data were extracted from the electronic records of the patients. Biochemical parameters were analyzed using venous blood samples collected during outpatient evaluations after a 12-h fasting period. All samples were analyzed

Figure 1. Flow diagram of the study.



in a single laboratory using the same methodology as described below.

Hypertension was defined as having systolic BP (SBP) of 135 mmHg or higher and diastolic BP (DBP) of 85 mmHg or higher while awake based on ABPM records[20]. Renal damage was defined by micro albuminuria of > 30 mg/day or proteinuria of > 150 mg/day, while vascular damage entailed CIMT of > 0.9 mm or presence of plaque in the carotid. Cardiac damage was considered as the presence of LV hypertrophy (LVMI of > 95 g/m^2 in women and > 115 g/m^2 in

men)[20]. The presence of HMOD included the presence of any organ damage, while the severity of HMOD was categorized as single-, two-, or triple-organ damage[5]. BMI was calculated as body weight (kg)/height^2 (m^2). The TyG index was calculated with the following formula: Ln[triglyceride (mg/dL) × glucose (mg/dL)/2]. The TG/HDL-C ratio was computed as triglyceride (mg/dL) / HDL-C (mg/dL).

Biochemical analysis

A Beckman Coulter LH 780 device (Mervue, Galway, Ireland) and Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., Indianapolis, IN, USA) were used to evaluate patients' venous blood samples and 24-h urine samples. Levels of 24-h urine protein (microalbumin turbidimetric method), total protein (albumin colorimetric method), hemoglobin (photometrically method), leukocytes (optical laser scattering method), platelet count (impedance method), C-reactive protein (CRP) (immunoturbidimetric method), albumin (bromocresol green method), fasting blood glucose (FBG), and lipid parameters (enzymatic colorimetric method) were measured. The Friedewald formula was used to determine low-density lipoprotein cholesterol (LDL-C)[21].

Blood pressure measurement

After admission to the hospital, all participants underwent a 5-min rest period before their in-office BP measurements were taken. The BP levels were then measured three times at 5-min intervals using an Omron M6 sphygmomanometer (Omron Healthcare, Japan). The average of the three measurements was recorded. Following the office BP measurements, 24-h ABPM was conducted using the Bravo HR ABP device (Sun Tech Medical Inc., Morrisville, NC, USA). The device recorded BP measurements at 15-min intervals during the daytime (6:00 am to 10:00 pm) and at 30-min intervals during the nighttime (10:00 pm to 6:00 am). Patients with fewer than 80% valid measurements were excluded from the analysis.

Echocardiographic examination

Echocardiography was conducted by cardiologists who were blinded to the patients' clinical status using the Philips Epic 5 (Philips Healthcare, Andover, MA, USA) equipped with a 1-5 MHz transducer. Calculation of the LVMI was performed using the Devereux formula, which is given as LV mass = 1.04 × ([interventricular septal thickness + posterior wall thickness + LV end-diastolic dimension]^3 – [LV end-diastolic dimension]^3) – 13.6, and it was indexed to the patient's body surface area[22].

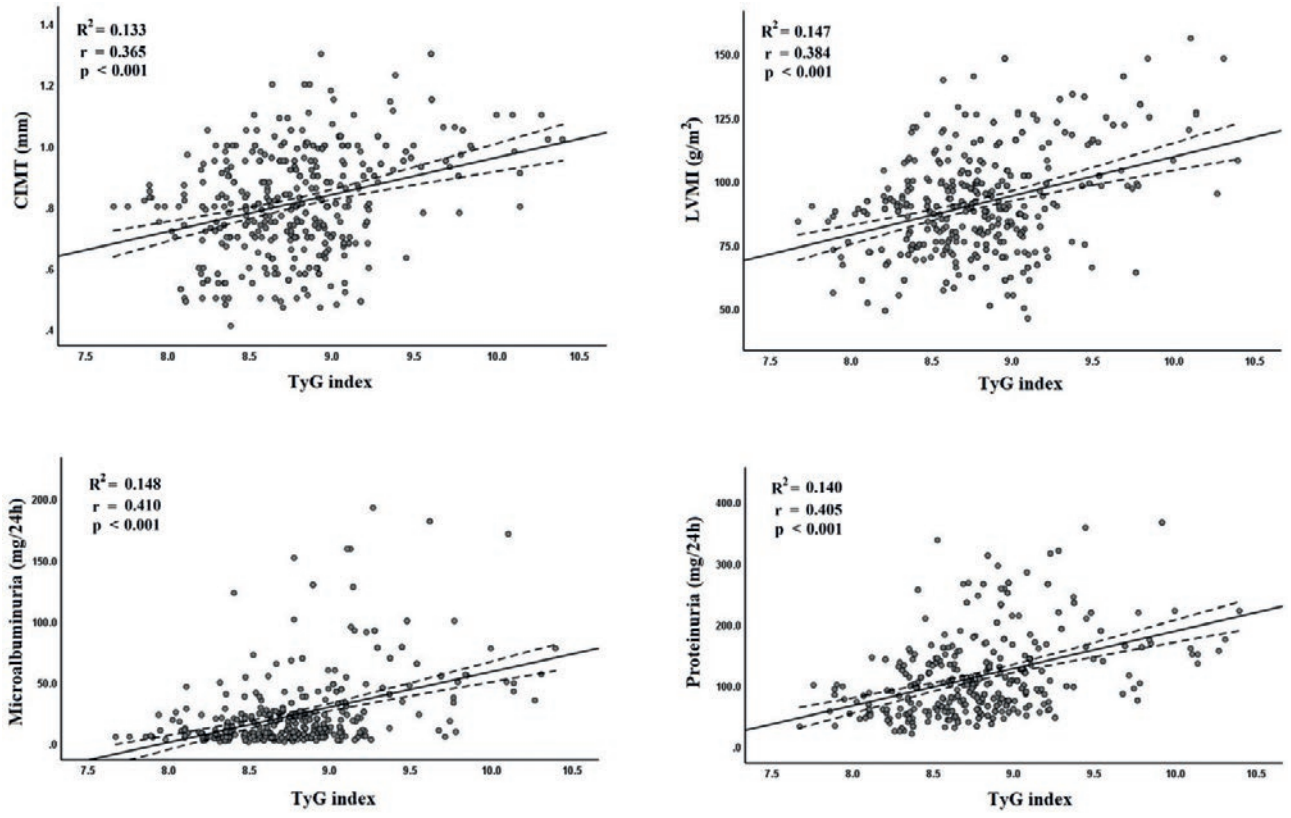
Carotid ultrasonography evaluation

The measurements were conducted by a radiologist who was blinded to the patients' clinical status. CIMT was measured with the patient in supine position and both hands under the head, using a high-resolution ultrasound device (EUB 7000 HV, Hitachi, Tokyo, Japan) equipped with a 13 MHz linear array transducer. The definition of CIMT included the distance between the blood-intima and media-adventitia boundaries in B-mode imaging. Measurements were taken from the posterior wall by performing three measurements 1 cm proximal to both main carotid artery bifurcations. The average CIMT was determined by calculating the mean of three measurements for both carotid arteries. The presence of plaque in the carotid was assessed and documented.

Statistical analysis

All data were analyzed with STATA/MP v.16 software (StataCorp LLC, Texas, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean ± standard deviation values, while non-normally distributed variables are given as median (25^{th}-75^{th} quartiles) values. Accordingly, Student t-test and Mann-Whitney U test were used for comparisons between two groups. ANOVA test (post-hoc: Bonferroni test) or Kruskal–Wallis H test (*post-hoc:* Dunn's test) were used for comparisons between more than two groups. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using Chi-square and Fisher exact tests. Pearson's and Spearman's correlation analyses were used to assess the associations between numerical variables. Multivariable logistic regression analysis with the backward Wald method was performed to identify any possible independent predictors of HMOD. The issue of multicollinearity among variables included in the multivariate regression models was assessed using the Variance Inflation Factor (VIF). A VIF value greater than 2.5 was considered indicative of multicollinearity[23]. The performance of this regression

Figure 2. Relationship between TyG index and indicators of hypertension-mediated organ damage.



CIMT: carotid intima media thickness; LVMI: left ventricular mass index; TyG: triglyceride-glucose index.

model was compared with the Leave-One-Out Cross-Validation (LOOCV) method. LOOCV is a model validation technique. This method works by sequentially leaving out each instance in the dataset, training the model on the remaining instances, and then measuring how well the model predicts the left-out instance. This process is repeated for each instance in the dataset, resulting in an estimate of the model's generalization performance[24]. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance, and the results of area under the curve (AUC), standard error (SE), and sensitivity and specificity are reported. The optimal threshold value of the TyG index in predicting HMOD was determined by the Youden index method. Significance was accepted at $p < 0.05$ (*) for all statistical analyses.

RESULTS

The hypertensive and normotensive groups, the majority of whom were female, had similar mean ages, BMIs, and rate of smoker. The levels of HMOD indicators and mean TyG index (9.0 ± 0.4 *vs.* 8.4 ± 0.4, $p < 0.001$) were higher in the hypertension group than the normotensive group. In both groups, there was a positive correlation between blood pressure levels and the TyG index, but it was stronger in the hypertensive group. In the hypertension group, TyG index was positively correlated with the levels of CIMT ($r = 0.365$; $p < 0.001$), and LVMI ($r = 0.384$; $p < 0.001$), and microalbuminuria ($r = 0.410$; $p < 0.001$), and proteinuria ($r = 0.405$; $p < 0.001$) (Fig. 2 and Table 1).

Vascular damage was detected in 158 cases (36.1%), renal damage in 142 cases (32.4%), and cardiac damage in 144 cases (32.9%). The prevalence of HMOD among hypertensive patients was 59.1%, and single-HMOD was more prevalent (28.8%). The mean TyG index (9.2 ± 0.4 *vs.* 8.6 ± 0.3, $p < 0.001$), as well as age, leukocytes, neutrophils, platelets, FBG, cholesterol, triglycerides, and CRP levels, were higher in the HMOD group than in the group without HMOD (Table 2).

Table 1. Demographic and laboratory findings of study population and their relationship with the TyG index

Variables	Normotensive group	Hypertensive group	p	Normotensive group TyG index		Hypertensive group TyG index	
	n = 438	n = 438		r	p	r	p
Female gender, n (%)	283 (64.6)	292 (66.7)	0.522	–0.091	0.056	–0.015	0.912
Age, years	51.9 ± 13.8	52.4 ± 11.7	0.519	0.205	0.480	0.212	0.462
BMI, kg/m^2	28.9 ± 7.2	29.3 ± 4.9	0.337	0.308	< 0.001*	0.352	< 0.001*
Smoker, n (%)	115 (26.3)	122 (27.9)	0.594	0.019	0.852	0.042	0.796
SBP, mm Hg	121.1 ± 8.1	154.8 ± 19.4	< 0.001*	0.284	0.043*	0.345	< 0.001*
DBP, mm Hg	76.5 ± 8.9	96.8 ± 9.6	< 0.001*	0.278	0.048*	0.330	< 0.001*
CIMT, mm	0.6 ± 0.1	0.8 ± 0.2	< 0.001*	0.018	0.876	0.365	< 0.001*
LVMI, g/m^2	74.1 ± 10.2	91.2 ± 20.1	< 0.001*	0.052	0.711	0.384	< 0.001*
Microalbuminuria, mg/24h	13.5 (5.6-19.8)	11.8 (5.3-25.8)	< 0.001*	0.091	0.646	0.410	< 0.001*
Proteinuria, mg/24h	57.4 (31.1-98)	99.5 (65.2-142.7)	< 0.001*	0.069	0.692	0.405	< 0.001*
Hemoglobin, g/dL	14.1 ± 1.8	14.0 ± 1.5	0.372	–0.103	0.631	–0.136	0.556
Leukocytes, × 10^9/L	7.2 ± 2.0	7.4 ± 2.1	0.149	0.020	0.680	0.186	0.448
Neutrophils, × 10^9/L	3.9 ± 1.6	4.3 ± 1.5	< 0.001*	0.011	0.811	0.282	0.046*
Lymphocytes, × 10^9/L	2.4 ± 0.8	2.3 ± 0.7	0.105	–0.041	0.808	–0.219	0.365
Platelets, × 10^9/L	249.8 ± 59.3	283.2 ± 62.6	0.049*	0.053	0.701	0.279	0.048*
FBG, mg/dL	90.2 ± 8.6	93.6 ± 8.1	< 0.001*	0.719	< 0.001*	0.768	< 0.001*
Cholesterol, mg/dL	193.9 ± 45.5	203.0 ± 39.9	0.002*	0.281	0.046*	0.293	0.039*
LDL-C, mg/dL	116.4 ± 37.4	122.1 ± 34.6	0.017*	0.208	0.517	0.214	0.458
HDL-C, mg/dL	52.8 ± 13.7	49.2 ± 13.7	< 0.001*	–0.289	< 0.001*	–0.295	0.036*
Triglyceride, mg/dL	100 (75-155)	145 (115-205)	< 0.001*	0.807	< 0.001*	0.809	< 0.001*
TyG index	8.4 ± 0.4	9.0 ± 0.4	< 0.001*	–	–	–	–
TG/HDL ratio	2.0 (1.3-3.2)	2.9 (2.0-4.8)	< 0.001*	0.743	< 0.001*	0.796	< 0.001*
Albumin, g/dL	4.6 ± 0.5	4.5 ± 0.6	0.175	-0.083	0.683	-0.258	0.116
CRP, mg/dL	1.6 (1-3)	3.2 (1.6-6.1)	< 0.001*	0.059	0.690	0.325	< 0.001*

Data are mean ± standard deviation or median (IQR), or number (%).
*p < 0.05 indicates statistical significance.
BMI: body mass index; CIMT: carotid intima media thickness; CRP: C-reactive protein; DBP: diastolic blood pressure; FBG: fasting blood glucose: HDL-C: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; LVMI: left ventricular mass index; SBP: systolic blood pressure; TyG: Triglyceride to HDL ratio.

The TyG index was similar in patients with vascular, renal and cardiac damage (9.2 ± 0.5 *vs.* 9.3 ± 0.4 *vs.* 9.2 ± 0.4, p = 0.296; respectively).

The mean age was similar in the two- and triple-HMOD groups (55.8 ± 11.7 *vs.* 56.4 ± 12.4 years, p > 0.05), while it was lower in the single-HMOD group compared to the two- and triple-HMOD groups (*vs.* Single-HMOD: 52.4 ± 10.1, p < 0.05). The mean CIMT, mean LVMI, median microalbuminuria, and median proteinuria levels were higher in the triple-HMOD group compared to the other groups, while they were higher in the two-HMOD group compared to the single-HMOD group. The mean leukocyte count, mean neutrophil count, mean platelet count, mean cholesterol level, and median CRP level were higher in the triple-HMOD group compared to the other groups, while mean HDL-C level was lower. While the median triglyceride level did not differ significantly between the two-HMOD and triple-HMOD groups (194 *vs.* 214 mg/dL, p > 0.05), it was higher than in the single-HMOD group (*vs.* 140 mg/dL, p < 0.05). An increase in the TyG index level was associated with an increase in the number of organs damages (Single-HMOD: 8.8 ± 0.3 *vs.* Two-HMOD: 9.1 ± 0.3 *vs.* Triple-HMOD: 9.5 ± 0.6, p < 0.001) (Table 2).

Parameters associated with the presence of HMOD and the number of organs damaged were included in the multivariable regression analysis with the backward-Wald method. There was multicollinearity between the TyG index and triglyceride (VIF = 2.9) and FBG (VIF = 2.8) levels, as well as the TG/HDL-C ratio (VIF = 2.7). In addition, multicollinearity was found between leukocyte and neutrophil (VIF = 3.1) or platelet (VIF = 2.8) counts. Therefore, triglyceride, glucose, TG/HDL-C ratio, and leukocyte parameters were not included in the multivariable regression model. Regression analysis showed that the TyG index was an independent predictor of both the presence of HMOD (OR = 1.33, p < 0.001 *vs.* without HMOD), and the number of organs damaged (OR = 1.23, p < 0.001 for single-HMOD *vs.* without HMOD; OR = 1.37, p < 0.001 for two-HMOD *vs.* single-HMOD; OR = 1.10, p < 0.001 for triple-HMOD *vs.* two-HMOD) (Table 3). The performance of the multivariable regression model with the backward-Wald method to predict HMOD was compared with the Leave-One-Out Cross-Validation method. According to the results, the diagnostic performance of both models was similar (Supplementary table 1).

In predicting the presence of HMOD, the TyG index exhibited superior diagnostic discrimination compared to its components, TG/HDL ratio, other predictors (Supplementary Table 2), and HMOD indicators (Fig. 3A). Threshold value of TyG index for the presence of HMOD was determined as >8.8 with 82.1% sensitivity and 81.0% specificity (AUC ± SE = 0.893 ± 0.02, +PV = 86.1%, -PV = 74.7%, p < 0.001). The TyG index exhibited gradually increasing threshold values in distinguishing patients with single-HMOD (> 8.8 with 77.8% sensitivity and 74.3% specificity *vs.* without HMOD), two-HMOD (> 9.1 with 77.6% sensitivity and 71.4% specificity *vs.* single-HMOD), and triple-HMOD (> 9.4 with 71.5% sensitivity and 87.7% specificity *vs.* two-HMOD) (Fig. 3B). The sensitivity, specificity, positive predictive value, and negative predictive value for different threshold values of the TyG index are shown in Supplementary table 3.

DISCUSSION

This is the first study to reveal the correlation between elevated TyG index values and the severity of HMOD based on the number of damaged organs in newly diagnosed treatment-naive hypertensive patients. The TyG index was positively correlated with indicators of renal, vascular, and cardiac damage. The TyG index was higher in patients with multiple-organ HMOD compared to single-organ HMOD. Furthermore, it exhibited gradually increasing threshold values in distinguishing patients with single-, two, and triple-organ damage.

A positive correlation was found between the TyG index and BP levels in both normotensive and hypertensive individuals. However, this relationship was more prominent among patients with hypertension. Population-based studies report that incident hypertension is associated with increased TyG index values[25-27]. Similar findings were supported by other indicators of IR, such as the TG/HDL-C ratio and waist-to-hip ratio[28,29]. IR may affect the synthesis of endothelin or vasodilator prostaglandins involved in the contraction or dilation of vessels, leading to BP elevation[30]. IR-induced hyperinsulinemia may elevate SNS activity, trigger the release of adrenaline and norepinephrine, and ultimately raise both cardiac output and peripheral vascular resistance. The increased concentration of catecholamine may

Table 2. Demographic and laboratory findings associated with hypertension-mediated organ damage

Variables	HMOD		p	Number of HMOD			p
	Without (n = 179)	With (n = 259)		Single (n = 126)	Two (n = 81)	Triple (n = 52)	
Female gender, n (%)	112 (62.6)	180 (69.5)	0.131	88 (69.8)	54 (66.7)	38 (73.1)	0.423
Age, years	**49.8 ± 11.9**	**54.3 ± 11.4**	< 0.001*	**52.4 ± 10.1**	55.8 ± 11.7	56.4 ± 12.4	< 0.001*
BMI, kg/m²	28.8 ± 4.5	29.6 ± 5.2	0.082	29.1 ± 5.5	30.4 ± 4.0	29.7 ± 5.9	0.105
Smoker, n (%)	46 (25.7)	76 (29.3)	0.403	35 (27.8)	24 (29.6)	17 (32.7)	0.755
SBP, mm Hg	154.1 ± 21.2	155.3 ± 18.2	0.526	154.5 ± 17.9	156.9 ± 20.6	154.6 ± 14.7	0.752
DBP, mm Hg	96.1 ± 10.1	97.3 ± 9.2	0.204	97.9 ± 6.9	96.6 ± 11.9	96.8 ± 9.2	0.449
CIMT, mm	**0.7 ± 0.1**	0.9 ± 0.2	< 0.001*	**0.8 ± 0.2**	**0.9 ± 0.1**	**1.0 ± 0.1**	< 0.001*
LVMI, g/m²	**79.2 ± 12.6**	99.1 ± 20.2	< 0.001*	**90.1 ± 14.0**	**100.0 ± 20.9**	**120.0 ± 16.2**	< 0.001*
Microalbuminuria, mg/24h	**7 (4-13)**	22 (8-42)	< 0.001*	**13 (6-24)**	**21 (11.2-33)**	**55 (40-79)**	< 0.001*
Proteinuria, mg/24h	**74 (55-102)**	125 (79-175)	< 0.001*	**101 (68-145)**	**125 (100-175)**	**166 (155-219)**	< 0.001*
Hemoglobin, g/dL	14.1 ± 1.6	13.9 ± 1.4	0.120	13.9 ± 1.4	13.8 ± 1.3	13.9 ± 1.7	0.444
Leukocytes, × 10^9/L	7.2 ± 2.0	**7.6 ± 2.1**	0.046*	7.2 ± 1.8	7.4 ± 1.5	**8.1 ± 2.3**	0.024*
Neutrophils, × 10^9/L	**3.9 ± 1.4**	4.6 ± 1.4	< 0.001*	4.3 ± 1.2	4.5 ± 1.1	**5.6 ± 1.9**	< 0.001*
Lymphocytes, × 10^9/L	2.3 ± 0.7	2.2 ± 0.7	0.499	2.3 ± 0.8	2.3 ± 0.5	2.2 ± 0.8	0.846
Platelets, × 10^9/L	275.6 ± 61.7	**288.5 ± 62.9**	0.034*	279.8 ± 54.6	279.1 ± 63.4	**324.3 ± 78.2**	< 0.001*
FBG, mg/dL	**92.1 ± 8.1**	94.5 ± 8.0	< 0.001*	94.2 ± 8.0	94.8 ± 8.5	94.6 ± 7.4	0.050*
Cholesterol, mg/dL	198.5 ± 37.8	**207.2 ± 41.0**	0.050*	202.7 ± 37.5	201.9 ± 43.6	**220.8 ± 42.5**	0.005*
LDL-C, mg/dL	120.7 ± 33.1	123.2 ± 35.7	0.458	121.2 ± 31.7	122.6 ± 36.4	128.5 ± 41.6	0.568
HDL-C, mg/dL	**51.7 ± 14.7**	47.4 ± 12.8	0.001*	48.3 ± 13.7	48.1 ± 11.0	**43.7 ± 13.0**	0.003*
Triglyceride, mg/dL	**120 (90-165)**	155 (135-220)	< 0.001*	**140 (120-195)**	194 (145-245)	214 (150-307)	< 0.001*
TyG index	**8.6 ± 0.3**	9.2 ± 0.4	< 0.001*	**8.8 ± 0.3**	**9.1 ± 0.3**	**9.5 ± 0.6**	< 0.001*
TG/HDL ratio	**2.5 (1.8-3.8)**	3.5 (2.6-5.8)	< 0.001*	**3.0 (2.1-4.5)**	**3.9 (2.7-4.8)**	**4.5 (2.9-5.2)**	< 0.001*
Albumin, g/dL	**46.2 ± 3.1**	45.9 ± 3.4	0.272	46.1 ± 2.7	45.8 ± 3.2	45.2 ± 4.8	0.367
CRP, mg/dL	**2.5 (1.1-4.5)**	3.6 (1.8-5.6)	0.004*	3.3 (2.1-6.2)	3.5 (2.4-6.5)	**4.8 (2.6-9.4)**	< 0.001*

Data are mean ± standard deviation or median (IQR), or number (%).
*p < 0.05 indicates statistical significance. Parameters were compared between the number of HMOD groups plus the group without HMOD. Differences between groups are highlighted in bold characters.
BMI: body mass index; CIMT: carotid intima media thickness; CRP: C-reactive protein; DBP: diastolic blood pressure; FBG: fasting blood glucose: HDL-C: high-density lipoprotein cholesterol; HMOD; hypertension-mediated organ damage; LDL-C: low-density lipoprotein cholesterol; LVMI: left ventricular mass index; SBP: systolic blood pressure; TyG: Triglyceride to HDL ratio.

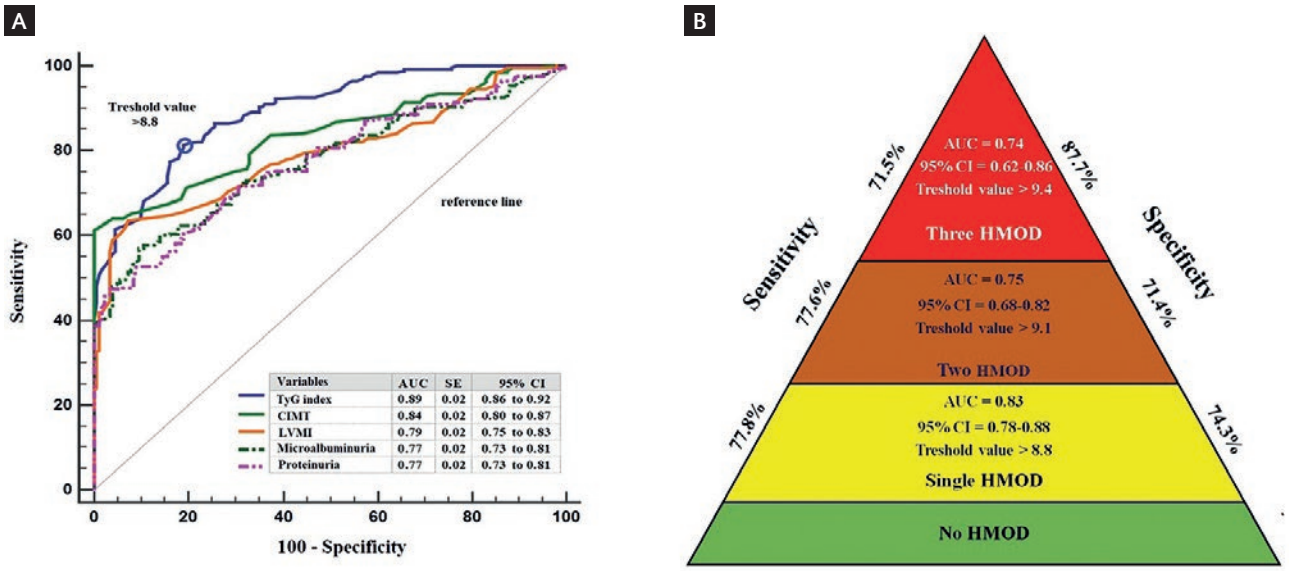
Table 3. Independent predictors of presence and severity of hypertension-mediated organ damage

Variables	Univariable regression			VIF	Multivariable regression		
	OR	95% CI	p		OR	95% CI	p
HMOD (*vs.* without HMOD)							
Age	1.04	1.02-1.06	< 0.001	1.16	1.03	1.01-1.05	0.025
Neutrophils	1.49	1.27-1.76	< 0.001	1.12	1.50	1.25-1.80	< 0.001
Platelets	1.03	1.01-1.06	0.038	1.07	–	–	–
Cholesterol	1.05	1.01-1.10	0.050	1.25	–	–	–
HDL-C	0.97	0.96-0.99	0.001	1.18	0.97	0.96-0.99	0.045
TyG index	1.33	1.24-1.43	< 0.001	1.18	1.33	1.23-1.43	< 0.001
CRP	1.04	1.01-1.08	0.004	1.20	–	–	–
					Nagelkerke R^2 = 0.587		
Single-HMOD (*vs.* without HMOD)							
Age	1.02	1.01-1.04	0.046	1.06	–	–	–
Neutrophils	1.24	1.03-1.48	0.020	1.03	1.28	1.06-1.56	0.031
HDL-C	0.97	0.95-0.99	0.042	1.14	–	–	–
TyG index	1.22	1.12-1.32	< 0.001	1.13	1.23	1.13-1.34	< 0.001
CRP	1.03	1.01-1.06	0.040	1.09	–	–	–
					Nagelkerke R^2 = 0.364		
Two-HMOD (*vs.* single-HMOD)							
Age	1.03	1.01-1.06	0.031	1.01	1.02	1.01-1.05	0.048
TyG index	1.38	1.21-1.56	< 0.001	1.01	1.37	1.20-1.55	< 0.001
					Nagelkerke R^2 = 0.325		
Triple-HMOD (*vs.* two-HMOD)							
Neutrophils	1.66	1.27-2.16	< 0.001	1.04	1.63	1.18-2.26	0.003
Platelets	1.03	1.01-1.06	0.001	1.03	1.03	1.01-1.08	0.012
Cholesterol	1.04	1.02-1.08	0.018	1.49	–	–	–
HDL-C	0.96	0.93-0.99	0.024	1.14	–	–	–
TyG index	1.13	1.04-1.23	< 0.001	1.12	1.10	1.02-1.19	0.002
CRP	1.04	1.02-1.09	0.006	1.05	–	–	–
					Nagelkerke R^2 = 0.481		

CI: confidence interval; CRP: C-reactive protein; HDL-C: high-density lipoprotein cholesterol; HMOD; hypertension-mediated organ damage; OR: odds ratio; TyG: Triglyceride to HDL ratio; VIF: variance inflation factor.

contribute to the thickening of vascular smooth muscle, leading to luminal narrowing and hypertension[31]. Furthermore, IR can augment the RAAS activity, leading to water and sodium retention, as well as increased vascular reactivity mediated by noradrenaline and angiotensin II, resulting in hypertension[32]. These mechanisms are also involved in the pathogenesis of HMOD[7]. Therefore, newly diagnosed hypertensive patients may be at risk of HMOD.

Figure 3. Diagnostic performance assessment of TyG in predicting the presence **(A)** and severity **(B)** of hypertension-mediated organ damage.



AUC: area under the curve; CI: confidence interval; CIMT: carotid intima media thickness; HMOD; hypertension-mediated organ damage; LVMI: left ventricular mass index; SE: standard error; TyG: triglyceride-glucose index.

The prevalence of HMOD among newly diagnosed hypertensive patients was approximately 60%, with multiple-organ HMOD observed in about 30% of cases. These rates are consistent with those reported in previous studies[2,3], indicating that the hypertensive cohort was likely unaware of their HMOD statuses during their initial hospital visits. In hypertensive patients, who are often diagnosed late because of their asymptomatic presentations, overt HMOD may evolve silently before its clinical manifestation becomes apparent. In general, the assessment of HMOD indicators, which were also employed in the current study, necessitates specialized equipment and trained professionals in clinical practice[4]. Therefore, HMOD evaluation may not be performed at the time of admission to hospitals with limited resources. The TyG index and TG/HDL-C ratio, serving as surrogate markers for IR, are derived from blood parameters that are readily available, cost-effective, and accessible in any healthcare facility. Therefore, they may have the potential to serve as a universally applicable screening tool for assessing HMOD during the diagnosis of hypertensive patients.

Higher quartiles of the TyG index have been associated with LV dysfunction, atherosclerosis, and susceptibility to LV hypertrophy[33]. Histochemical examinations conducted on insulin-treated rats in an *in vivo* study showed the presence of myocyte hypertrophy and an increase in interstitial fibrosis[34]. A study of two different cohorts showed that the TyG index was an independent predictor of carotid atherosclerosis and had better diagnostic performance compared to the homeostatic model assessment of IR[35]. Several population-based studies have demonstrated that the TyG index is associated with a higher risk of arterial stiffness and nephric microvascular damage, even after adjustment for traditional cardiovascular risk factors[36-38]. In hypertensive cohorts, it was reported that there was a positive correlation between the TyG index and both albuminuria, which is an indicator of renal damage, and arterial stiffness, which is an indicator of vascular damage[17,18]. Similar findings were also demonstrated for the TG/HDL-C ratio[39,40]. The outcomes of the present study both support and broaden the current literature on this subject. Consistent with these studies, there was a positive correlation between the TyG index and indicators of renal, vascular, and cardiac damage in patients with newly diagnosed treatment-naive hypertension. However, patients with vascular, cardiac, and renal damage had similar TyG index values. This may be associated with

accelerated atherosclerotic processes as a result of the various mechanisms of IR in the development of HMOD[41].

Although the TyG index exhibits a high correlation with the TG/HDL-C ratio, consistent with the previous studies, it has been shown that the TyG index is a better predictor of atherosclerosis[13,42]. In addition, the relationship between the progression of arterial stiffness and the TyG index was more pronounced compared to the TG/HDL-C ratio[43]. In the present study, the TyG index exhibited better diagnostic performance in predicting HMOD compared to the TG/HDL-C ratio. A previous study that included cardiac, vascular, and renal damage indicators concluded that the TyG index had a high diagnostic performance in predicting HMOD, with sensitivity of 79.0%, specificity of 77.1%, and a threshold value of > 8.85[16]. However, that study included patients who had previously been diagnosed with hypertension and the vast majority were taking antihypertensive therapy. Such confounding factors may affect the levels of metabolic abnormalities, including IR[44,45], resulting in lower or higher diagnostic performances of the TyG index. Given that newly diagnosed hypertensive patients have not received any treatment, they may be more likely to have impaired glycolipid metabolism and higher blood pressure[6]. In this context, the TyG index may exhibit better sensitivity and specificity in predicting HMOD in newly diagnosed hypertensive patients compared to patients with a known history of hypertension[16]. On the other hand, the TyG index demonstrated a high true-positive rate in distinguishing patients with two-organ HMOD from those with single-organ HMOD and patients with triple-organ HMOD from those with two-organ HMOD. To the best of our knowledge, these findings are reported here for the first time in the literature. The TyG index, which is readily available, inexpensive, and calculable at every center, may serve as a screening tool for predicting multiple-organ HMOD beyond subclinical atherosclerosis in newly diagnosed, treatment-naive hypertension patients.

The retrospective design of this study was its most significant limitation. Another limitation was the inability to compare the diagnostic performance of the TyG index to the homeostatic model assessment of IR for predicting multiple-organ HMOD.

In conclusion, High TyG index values independently predict the presence and severity of HMOD in patients with newly diagnosed treatment-naive hypertension. Given the potential mechanism of IR in hypertension, the TyG index exhibits a gradual increase in the severity of HMOD according to the number of organs involved. It also exhibits significant diagnostic performance in differentiating patients with more extensive organ involvement. Since the detection of multiple-organ HMOD requires a multidisciplinary approach, the TyG index can serve as a simple and inexpensive screening tool.

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SUPPLEMENTARY MATERIAL

Supplementary data are available at DOI: 10.24875/RIC.23000113. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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