Received: 27 October 2022 | Revised: 25 December 2022 | Accepted: 26 December 2022

DOI: 10.1111/jch.14639

ORIGINAL ARTICLE

WILEY

Association between triglyceride-glucose index and arterial stiffness reflected by carotid pulse-wave velocity in stage 1 hypertension and individuals with normal/elevated blood pressure

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Funding information
National Natural Science Foundation of China, Grant/Award Numbers: U21A20387, 81871373

Abstract

Evidence of the triglyceride-glucose (TyG) index as an independent predictor of arterial stiffness in stage 1 hypertension patients is scarce. This study aimed to explore the association between TyG index and arterial stiffness in this population. A total of 1041 individuals from 32 centers with normal/elevated blood pressure (BP, <130/80 mmHg; 345 men (33%); median age, 37 years) and 585 stage 1 hypertension patients (BP ≥130/80 and <140/90 mmHg; 305 men (52%); median age, 47 years) were prospectively enrolled. Arterial stiffness was determined by measuring carotid ultrafast pulse-wave velocity (ufPWV). TyG index was calculated as ln (fasting triglyceride (TG) × fasting blood glucose/2). Patients with a higher TyG index tended to have higher ufPWV. The TyG index was positively associated with ufPWV at the end of systole in stage 1 hypertension patients after adjusting for confounding factors (β for per unit .48), and restricted cubic spline analysis confirmed a linear association. Subgroup analyses in terms of age, sex, and body mass index yielded similar results. However, no significant relationship was observed between the TyG index and ufPWV in the population with normal/elevated BP. The fully adjusted β between ufPWV and the TyG index was higher than the TG/high-density lipoprotein cholesterol ratio, TG, and pulse pressure. In conclusion, patients with a higher TyG index had greater arterial stiffness, and the TyG index independently and positively correlated with arterial stiffness in stage 1 hypertension patients. The TyG index may provide a simple and reliable marker to monitor arterial stiffness in hypertensive patients.

KEYWORDS
arterial stiffness, stage 1 hypertension, triglyceride-glucose index, ultrafast pulse-wave velocity

1 | INTRODUCTION

Hypertension is the most common risk factor for cardiovascular diseases (CVD). In 2019, the global number of patients with hypertension reached 1.28 billion, which was double the number observed 20 years prior.[1] Owing to the increasing prevalence of hypertension, the morbidity and mortality of hypertension-related CVD have increased in recent decades, making hypertension a major public health concern. Several studies have confirmed that arterial stiffness is a common vascular complication that plays a pivotal role in the development of hypertension-related CVD.[2–4] Therefore, there is an urgent need for a reliable marker to monitor early arterial stiffness and provide a basis for CVD risk stratification and timely formulation of preventive strategies.

A growing number of studies have demonstrated insulin resistance (IR) as a reliable marker of arterial stiffness because IR is linked to hypertension and frequently accompanies abnormal glycolipid metabolism, which greatly enhances the progression of arterial stiffness.[5–7] The glucose clamp technique is the gold standard for measuring IR.[8] However, this method is complicated, expensive, and limited in its wide clinical applications.[8] In recent years, the triglyceride-glucose (TyG) index has been suggested as a reliable surrogate marker for IR.[9–11] As the TyG index is calculated using fasting blood glucose (FBG) and triglyceride (TG) levels, it has the advantages of convenience, cost-effectiveness, and efficiency. Recent studies have confirmed that TyG index is independently associated with hypertension, arterial stiffness, and vascular damage.[12–14] Moreover, it can predict coronary artery disease and adverse cardiovascular events.[15,16] Taken together, we speculate that the TyG index may be a rapid, easily available, and reliable marker for early monitoring of arterial stiffness in patients with hypertension.

Recent studies have found that the TyG index independently and positively correlated with arterial stiffness detected using brachial-ankle pulse-wave velocity in patients with hypertension.[17] However,

the study population mainly included patients with stage 2 hypertension, and it is unclear whether TyG index can also reflect arterial stiffness in patients with stage 1 hypertension. Ultrafast ultrasound imaging is a novel approach for measuring pulse-wave velocity. This method can track and capture pulse waves in real time at extremely high sampling rates (>10 000 frames/s), and visually display and accurately measure the local ultrafast pulse-wave velocity (ufPWV) using the Doppler tissue imaging principle.

Thus, this study aimed to compare the associations between the TyG index and arterial stiffness reflected by ufPWV in patients with stage 1 hypertension and individuals with normal/elevated blood pressure (BP), based on a prospective and multicenter cohort. Moreover, we compared the associations between the TyG index and arterial stiffness with other previously reported indicators, such as the TG/high-density lipoprotein (HDL) cholesterol ratio, TG, and pulse pressure.

2 | METHODS

2.1 | Study population

Participants were enrolled from the carotid pulse wave velocity study cohort between January 2017 and May 2019, which was registered with the North American Clinical Trials Network (NCT03351127). This prospective, open-label, observational, multicenter study was conducted at Shengjing Hospital of China Medical University and Sichuan Provincial People's Hospital. A total of 32 hospital ultrasound laboratories accredited by the Chinese Society of Ultrasound in Medicine participated in this study.

The methods of participant recruitment and inclusion and exclusion criteria were described in detail in a previous study.[18] Briefly, the study included participants from the physical examination center of each participating institution that is, Han Chinese individuals aged >18 years and without stage 2 hypertension (BP ≥ 140/90 mmHg),[19] any abnormalities on physical examination of the cardiovascular and respiratory systems, or cardiovascular medication history. Medical checkups included physical, laboratory, and imaging assessments. The participants were excluded based on the following criteria: history of coronary artery disease, abnormal electrocardiographic findings, any pathological abnormalities of structure or function on echocardiography, acute or chronic respiratory disease, diabetes mellitus (FBG > 7.0 mmol/L), obesity (body mass index [BMI] > 30 kg/m2), anemia, abnormal liver and kidney function, total cholesterol > 190 mg/dl, connective tissue disease, malignancy, and abnormal carotid ultrasound results (abnormal intima-media thickness, presence of carotid plaques, or congenital variations). Professional athletes, pregnant or nursing women, alcoholics, and participants with inadequate ultrasound image quality were excluded.

Among the 1740 participants who met the criteria, we further excluded 114 with missing ufPWV and TyG index data, and 1626 participants were finally analyzed (Figure 1). The included participants had slightly lower BMI, diastolic BP, FBG, and intima-media thickness, and higher pulse pressure than that of the excluded participants owing to missing ufPWV and TyG index data (Table S1).

The study protocol was approved by the Ethics Committee of the Shengjing Hospital of China Medical University (2017PS342K). Written informed consent was obtained from all participants. This study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

2.2 | Characteristics collection and definition

Trained physicians systematically collected and measured demographic and anthropometric data. The demographic data included age, sex, and smoking history. Participants were categorized into two subgroups according to age: young (18–40 years) and middle-aged/elderly (>40 years) adults. Smoking history was defined as participants who smoked at least 100 cigarettes in a lifetime based on the 2011 Center of Disease Control and Prevention Criteria and previous studies.[20,21] Anthropometric data included weight, height, BMI, body surface area, BP, and heart rate. Weight and height were measured with the participants wearing light clothes and bare feet. The BMI (kg/m2) was calculated as weight (kg)/height2 (in meters squared). Overweight was defined as a BMI ≥25.0 kg/m^2 as per the World Health Organization criteria. The body surface area (m^2) was calculated using the formula proposed by Du Bois.[22] Brachial BP and heart rate were measured using an OMRON electronic BP monitor (Dalian, China) on the upper arm at the same level as the right atrium within 3 min before the carotid scans. As per the guidelines for prevention, detection, evaluation, and management of high BP, the values were measured after the participant had relaxed in a chair for at least 5 min.[19] The average of two careful measurements was used to evaluate participants' systolic and diastolic BP and heart rate. Pulse pressure is the difference between the systolic and diastolic BP. Based on the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) criteria for defining hypertension,[19] participants were categorized into two groups: stage 1 hypertension (BP ≥130/80 mmHg and <140/90 mmHg) and normal/elevated BP (<130/80 mmHg).

Peripheral venous blood samples were obtained from the antecubital vein in the morning after at least 12 h of fasting. The blood was temporarily stored in a vacuum tube containing ethylenediaminetetraacetic acid, and measured within 4 h of centrifugation in each participating laboratory. Laboratory evaluation parameters, including hemoglobin, white blood cell count, platelet count, FBG, total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, TG, alanine transaminase, and creatinine levels, were measured using an autobiochemical analyzer. FBG levels were measured using the hexokinase/glucose-6-phosphate dehydrogenase method, and TG levels were measured using an enzymatic colorimetric method. TyG index was calculated using the following formula: TyG index = ln [TG (mg/dl) × FBG (mg/dl)/2]. The participants were divided into three groups according to tertiles of the TyG index (tertile 1, 5.16–6.47;

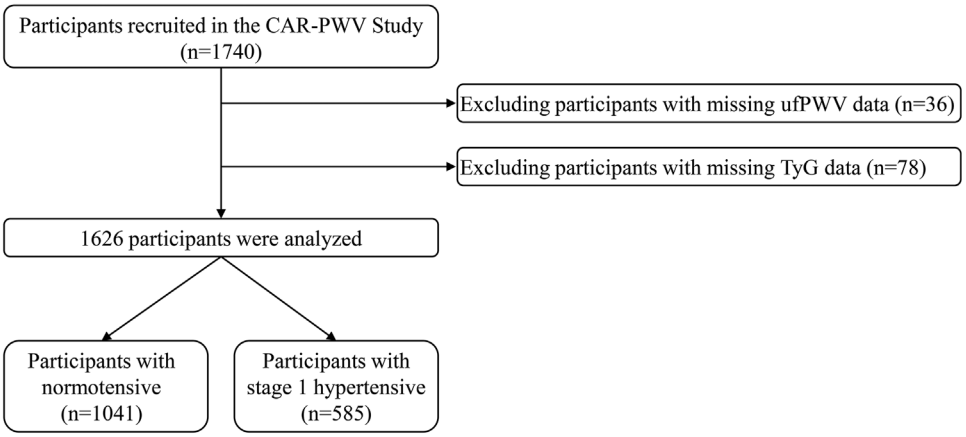

FIGURE 1 Flow chart of the study population. *TyG* triglyceride-glucose, *ufPWV* ultrafast pulse-wave velocity

tertile 2, 6.48–6.83; tertile 3, 6.84–6.94). The TG/HDL cholesterol ratio was calculated as the TG level (mmol/L) divided by the HDL cholesterol level (mmol/L).

2.3 | ufPWV measurement

Ultrasound image acquisition, ufPWV measurement, and related quality controls were described in detail in a previous study.[18] Briefly, an experienced doctor who had received intensive training in the core laboratory performed the standardized carotid ultrasonography and ufPWV measurements. All data and ufPWV images were transmitted to the core laboratory for quality control and statistical analyses.

Carotid ultrasonography was performed in vascular pulse-wave velocity mode using the Aixplorer ultrasound system (SuperSonic Imagine, France) with an SL10-2 or SL15-4 probe. The view was adjusted to clearly show the intima of the distal common carotid artery. The imaging parameters were set as follows: Map 8, dynamic range of 60 dB, low persistence, frame rate of 60 Hz, depth of 4.0 cm. The intima-media thickness of common carotid artery was measured 1.0–1.5 cm below the carotid bifurcation at the end-systole. The probe should be as parallel to the arterial wall as possible. While holding the probe stationary, the ufPWV at the beginning of systole (BS) and end of systole (ES) was measured using a single keystroke with breath held for 5 s. Ultrafast ultrasound imaging tracked pulse waves in the anterior wall of the common carotid artery based on the tissue Doppler imaging principle. The software automatically calculated ufPWV, and a corresponding color bar image was formed, which could visually display the ufPWV. The ufPWV at the BS corresponded to the slope of the brightest line in the red bar, and the ufPWV at the ES corresponded to the slope of the brightest line on the blue bar. The detailed measurement process and principles are presented in Supplementary methods. The ufPWV on each side of the common carotid artery was measured three times and the mean values were calculated. The average ufPWV values of both carotid arteries were calculated for the data analysis.

2.4 | Statistical analysis

Categorical variables were presented as frequencies (percentages). The Shapiro–Wilk method was used to test the normal distribution of continuous variables. Normally distributed continuous data were expressed as mean ± standard deviation, and skewed distributed continuous data were expressed as medians (quartiles).

The independent samples *t*-test or Mann–Whitney *U* test was used to compare the continuous clinical characteristics of participants with stage 1 hypertension and normal/elevated BP, and the chi-square test was used for categorical characteristics. One-way analysis of variance or Kruskal–Wallis test was used for linear trends of continuous clinical characteristics across tertiles of the TyG index, and chi-square test was used for linear trends of categorical characteristics. The correlation between the TyG index and cardiometabolic risk factors was presented using Pearson's coefficient.

A general and generalized linear model was used to analyze the independent association of the TyG index with ufPWV while adjusting for major covariables. Associations were expressed as beta coefficients (β) and 95% confidence intervals (CI). In regression models, covariables refer to factors that have great significance based on previous literature and clinical knowledge, which have statistical significance in the univariate analysis, or that change the estimated confounding effect individually by ≥10%. No additional adjustments were made to Model 1. Model 2 was adjusted for age, sex, BMI, systolic and diastolic BP, heart rate, and smoking history. Model 3 was further adjusted for hemoglobin, white blood cell count, platelet count, total cholesterol, LDL cholesterol, HDL cholesterol, alanine transaminase, and creatinine. Moreover, we used restricted cubic spline models fitted for ordinary least squares models with three knots at the 10th, 50th, and 90th percentiles to investigate the association between the TyG index and ufPWV, after adjusting for potential confounders. Participants were categorized into two groups based on sex, age, and BMI, and the associations between TyG index and ufPWV were analyzed in different subgroups. The associations between the TG/HDL cholesterol ratio, TG, pulse pressure, and ufPWV were also explored.

Inter- and intra-observer repeatability of ufPWV measurement was tested by a blinded second measurement by a second observer and the same observer in a subset of randomly selected 20 participants from the entire population. The repeatability was evaluated by calculating the intra-class correlation coefficient and coefficient of variation.

Statistical analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org) and SPSS software (version 26.0; IBM Corp, Armonk, NY, USA). Two-tailed $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics

The final data analysis included 1626 participants, 585 (35.98%) of whom had stage 1 hypertension and 1041 (64.02%) had normal/elevated BP. Patients with stage 1 hypertension were older and had higher BMI, body surface area, BP, heart rate, hemoglobin, FBG, TG, total cholesterol, LDL cholesterol, TyG index, TG/HDL cholesterol ratio, alanine transaminase, creatinine, intima-media thickness, ufPWV at BS and ES, and lower HDL cholesterol values than that of participants with normal/elevated BP. Additionally, the stage 1 hypertension population included more men and participants with a smoking history (Table 1).

3.2 | TyG index and clinical characteristics

The trends in clinical characteristics according to the tertiles of the TyG index in the populations with stage 1 hypertension and normal/elevated BP are shown in Table 2 and Table S2. Compared with patients in the lowest tertile of the TyG index, those with a higher TyG index tended to be men, were older, and had higher BMI, body surface area, systolic BP, pulse pressure, hemoglobin, FBG, TG, total cholesterol, LDL cholesterol, TyG index, TG/HDL cholesterol ratio, alanine transaminase, and creatinine in both groups. The TyG index positively correlated with BMI, systolic BP, pulse pressure, hemoglobin, total cholesterol, and LDL cholesterol, and inversely associated with HDL cholesterol in both groups (Figure 2). Similar results were obtained after adjusting for age and sex (Table S3).

3.3 | TyG index and ufPWV

Patients with a higher TyG index scores tended to have a higher ufPWV at both the BS and ES than patients with the lowest tertile of the TyG index (Table 2). The TyG index positively correlated with ufPWV at both BS and ES, with no adjustment. Each one-unit increment of the TyG index was related to a change in ufPWV at ES of approximately .50 (95% CI, .27–.73) m/s in the population with normal/elevated BP and.97 (95% CI, .56–1.38) m/s in the stage 1 hypertension population, and a change in ufPWV at BS of approximately .21 (95% CI, .05–.36) m/s in the population with normal/elevated BP and .44 (95% CI, .20–.68) m/s in the stage 1 hypertension population (Table 3). A similar significant positive association between the TyG index and ufPWV at ES was observed after adjusting for age, sex, BMI, BP, heart rate, smoking history, hemoglobin, white blood cell count, platelet count, total cholesterol, LDL cholesterol, HDL cholesterol, alanine transaminase, and creatinine in the stage 1 hypertension population; however, this association was not observed in the population with normal/elevated BP. Moreover, in the fully adjusted model (Model 3), the adjusted β of ufPWV at ES for participants in the second and third tertile of the TyG index were .34 (95% CI, .03–.66) m/s and .48 (.15–.81) m/s, respectively, with the first tertile of the TyG index as a reference (P for trend = .007) in the stage 1 hypertension population. However, the association between the TyG index and ufPWV at BS in both groups was not statistically significant after adjusting for different confounders (Table 3). In addition, restricted cubic spline analysis showed a positive and linear association between the TyG index and ufPWV at ES in the stage 1 hypertension population than in the population with normal/elevated BP (Figure 3 and Figure S1).

3.4 | Subgroup analysis

Stratified analysis of the association between the TyG index and ufPWV at the ES in stage 1 hypertension was further performed in subgroups of sex, age, and BMI (Table 4 and Figure 4). Similar independent and positive associations were observed in the following subgroups: sex (women vs. men, P for interaction = .24), age (≤40 years vs. > 40 years, P for interaction = .37), and BMI (<25.0 kg/m2 vs. ≥25.0 kg/m2, P for interaction = .56).

3.5 | Other arterial stiffness indicators with ufPWV

We further investigated the relationships between other arterial stiffness indicators, such as the TG/HDL cholesterol ratio, TG, pulse pressure, and ufPWV at ES (Tables S4–S6, and Figure 3). The TG/HDL cholesterol ratio, TG, and pulse pressure also positively associated with ufPWV at ES, and each one-unit increment was related to a change of ufPWV at ES of approximately .32, .44, .45, and .02 m/s, respectively, in the population with normal/elevated BP (all $P < .05$) and .52, .75, .59, and .04 m/s, respectively, in the stage 1 hypertension population (all $P < .05$). However, the association between the TG/HDL cholesterol ratio and pulse pressure with ufPWV at ES was not observed after adjusting for different confounders in the populations with both normal/elevated BP and stage 1 hypertension. Nonetheless, an association between TG and ufPWV at ES was still observed in the stage 1 hypertension population. The fully adjusted β of ufPWV at ES by confounders for participants in the third tertile of TG was .37 (95% CI, .04–.70) m/s, with the first tertile of TG as a reference (P for trend = .02), in the stage 1 hypertension population, which was lower than the adjusted β for participants in the third tertile of the TyG index (adjusted β, .37 vs. .48).

TABLE 1 Comparison of clinical characteristics between populations with normal/elevated BP and stage 1 hypertension

	All subjects ($n = 1626$)	Normal/elevated BP ($n = 1041$)	Stage 1 hypertensive ($n = 585$)	*P* value
Age, years[a]	41.0 (3.0;54.0)	37.0 (28.0;5.0)	47.0 (34.0;6.0)	<.001
Sex, *n* (%)[b]				<.001
Men	650 (39.98)	345 (33.14)	305 (52.14)	
Women	976 (6.02)	696 (66.86)	280 (47.86)	
Body mass index (kg/m^2[a])	22.03 (2.25;23.46)	21.50 (19.90;23.14)	22.72 (21.14;24.22)	<.001
Body surface area (m^2[c])	1.63 (.16)	1.60 (.16)	1.68 (.16)	<.001
Systolic BP (mmHg[a])	118.0 (11.0;124.0)	114.0 (108.0;12.0)	124.0 (12.0;13.0)	<.001
Diastolic BP (mmHg[a])	74.5 (69.0;8.0)	7.0 (65.0;74.0)	8.0 (8.0;84.0)	<.001
Pulse pressure (mmHg[a])	42.0 (38.0;5.0)	43.0 (38.0;5.0)	41.0 (37.0;5.0)	.20
Heart rate (beats/min[a])	71.0 (66.0;78.0)	7.00 (65.0;78.0)	72.0 (67.0;79.0)	.001
Smoking history, *n* (%)[b]				.008
No	1554 (95.57)	1006 (96.64)	548 (93.66)	
Yes	72 (4.43)	35 (3.36)	37 (6.34)	
Hemoglobin (g/L[a])	137.00 (128.00;147.00)	136.00 (128.00;146.00)	138.00 (128.00;149.00)	.006
White blood cell count (109/L[a])	5.62 (4.80;6.67)	5.52 (4.73;6.65)	5.76 (4.93;6.72)	.009
Platelet count (109/L[a])	231.00 (196.00;268.00)	231.00 (196.00;268.00)	232.00 (195.00;268.00)	.68
FBG (mmol/L[a])	4.94 (4.58;5.30)	4.88 (4.55;5.22)	5.06 (4.67;5.44)	<.001
TG (mmol/L[a])	.99 (.73;1.27)	.95 (.69;1.23)	1.05 (.81;1.32)	<.001
Total cholesterol (mmol/L[a])	4.31 (3.80;4.80)	4.29 (3.78;4.73)	4.34 (3.87;4.94)	.01
LDL cholesterol (mmol/L[a])	2.54 (2.14;2.96)	2.51 (2.13;2.88)	2.61 (2.15;3.02)	.02
HDL cholesterol (mmol/L[a])	1.36 (1.19;1.56)	1.40 (1.23;1.58)	1.29 (1.12;1.51)	<.001
TyG index[a]	6.66 (6.35;6.94)	6.62 (6.29;6.88)	6.75 (6.46;7.02)	<.001
TyG index tertiles, *n* (%)[b]				<.001
Tertile 1 (5.16–6.47)	542 (33.33)	392 (37.66)	151 (25.81)	
Tertile 2 (6.48–6.83)	542 (33.33)	343 (32.95)	198 (33.85)	
Tertile 3 (6.84–6.94)	542 (33.33)	306 (29.39)	236 (4.34)	
TG/HDL cholesterol ratio[a]	.73 (.49;1.01)	.67 (.46;.94)	.81 (.57;1.08)	<.001
Alanine transaminase (U/L[a])	16.95 (13.00;23.67)	16.00 (12.00;22.00)	19.00 (14.00;26.00)	<.001
Creatinine (mmol/L[a])	62.90 (54.80;74.50)	61.00 (54.00;73.00)	65.55 (55.00;76.90)	<.001
Intima-media thickness (mm[a])	.50 (.42;.59)	.48 (.41;.58)	.52 (.44;.62)	<.001
ufPWV at BS (m/s[a])	5.25 (4.58;6.08)	5.13 (4.50;5.86)	5.49 (4.83;6.37)	<.001
ufPWV at ES (m/s[a])	6.48 (5.50;7.80)	6.20 (5.40;7.40)	7.10 (5.85;8.72)	<.001
Elevated ufPWV[*,b])	82 (5.04%)	32 (3.07%)	50 (8.55%)	<.001

Abbreviations: BP, blood pressure; BS, beginning of systole; ES, end of systole; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TyG, triglyceride-glucose; ufPWV, ultrafast pulse-wave velocity.

*Elevated ufPWV was defined as ufPWV at ES ≥95th percentile (1.57 m/s).

[a]Median (interquartile range), and the variables were tested by the Mann–Whitney *U* test.

[b]Number (percentage), and the variables were tested by Chi-square test or Fisher exact test.

[c]Mean (standard deviation), and the variables were tested by the independent Student's *t* test.

3.6 | Measurement repeatability of ufPWV

Both ufPWV at BS and ES have high intra- and inter-observer measurement repeatability. For ufPWV at BS and ES, the intra-observer intra-class correlation coefficients were .97 and .97, and coefficient of variations were 3.72% and 2.95%, respectively; the inter-observer intra-class correlation coefficients were .96 and .95, and coefficient of variations were 4.61% and 5.27%, respectively.

TABLE 2 Comparison of clinical characteristics according to TyG index in stage 1 hypertension population

	Tertile 1 ($n = 151$)	Tertile 2 ($n = 198$)	Tertile 3 ($n = 236$)	*P* for trend
Age (years)[a]	42.0 (31.0;54.0)	45.5 (32.0;6.0)	5.0 (38.0;61.0)	<.001
Sex, *n* (%)[b]				.014
Men	70 (46.36)	97 (48.99)	138 (58.47)	
Women	81 (53.64)	101 (51.01)	98 (41.53)	
Body mass index (kg/m2)[a]	21.93 (2.01;23.37)	22.86 (21.06;24.00)	22.93 (21.80;24.52)	<.001
Body surface area (m2)[c]	1.65 (.16)	1.66 (.15)	1.71 (.17)	.001
Systolic BP (mmHg)[a]	12.0 (117.0;13.0)	121.5 (118.0;13.0)	129.0 (12.0;132.0)	<.001
Diastolic BP (mmHg)[a]	8.0 (8.0;83.0)	8.0 (8.0;84.0)	8.0 (8.0;84.0)	.492
Pulse pressure (mmHg)[a]	4.0 (34.5;46.5)	4.0 (35.0;46.0)	46.0 (4.0;5.3)	<.001
Heart rate (beats/min)[a]	72.0 (68.0;78.5)	72.0 (67.0;79.0)	72.5 (67.0;8.0)	.624
Smoking history, *n* (%)[b]				.321
No	143 (94.70)	187 (94.44)	217 (92.34)	
Yes	8 (5.30)	11 (5.56)	18 (7.66)	
Hemoglobin (g/L)[a]	135.00 (125.00;144.00)	138.00 (128.00;15.00)	141.00 (131.00;152.00)	<.001
White blood cell count (109/L)[a]	5.35 (4.70;6.41)	5.74 (5.02;6.68)	6.00 (5.01;6.92)	.001
Platelet count (10^9/L)[a]	232.00 (195.00;264.00)	234.50 (196.00;269.75)	229.00 (196.50;27.00)	.647
FBG (mmol/L)[a]	4.81 (4.45;5.10)	5.00 (4.66;5.31)	5.27 (4.90;5.67)	<.001
TG (mmol/L)[a]	.66 (.58;.75)	.98 (.89;1.07)	1.38 (1.26;1.60)	<.001
Total cholesterol (mmol/L)[a]	3.98 (3.44;4.58)	4.30 (3.90;4.87)	4.62 (4.19;5.02)	<.001
LDL cholesterol (mmol/L)[a]	2.22 (1.73;2.69)	2.56 (2.15;3.00)	2.86 (2.45;3.08)	<.001
HDL cholesterol (mmol/L)[a]	1.40 (1.21;1.63)	1.28 (1.12;1.51)	1.23 (1.09;1.43)	<.001
TyG index[a]	6.26 (6.06;6.38)	6.67 (6.59;6.76)	7.07 (6.96;7.20)	<.001
TG/HDL cholesterol ratio[a]	.46 (.38;.57)	.75 (.64;.90)	1.13 (.94;1.31)	<.001
Alanine transaminase (U/L)[a]	17.00 (12.92;24.00)	19.00 (14.40;25.60)	2.50 (15.00;28.00)	<.001
Creatinine (mmol/L)[a]	63.80 (54.00;73.30)	64.00 (56.00;76.00)	68.00 (55.00;8.07)	.008
Intima-media thickness (mm)[a]	.47 (.40;.56)	.52 (.45;.63)	.56 (.47;.65)	<.001
ufPWV at BS (m/s)[a]	5.14 (4.53;6.27)	5.36 (4.78;6.19)	5.73 (5.15;6.52)	<.001
ufPWV at ES (m/s)[a]	6.36 (5.40;7.74)	7.07 (5.81;8.83)	7.54 (6.34;9.05)	<.001

P for trend, *P* value for trend across the tertiles of TyG index. Abbreviations as Table 1.
[a]Median (interquartile range).
[b]Number (percentage).
[c]Mean (standard deviation).

4 | DISCUSSION

In the present study, we explored the association between the TyG index and arterial stiffness reflected by ufPWV in patients with stage 1 hypertension based on a prospective study with 32 participating laboratories. The results showed that the TyG index independently and positively associated with arterial stiffness in patients with stage 1 hypertension but not in the population with normal/elevated BP. Subgroup analyses of age, sex, and BMI yielded similar results. Moreover, the TyG index was more closely associated with arterial stiffness reflected by ufPWV than those of the TG/HDL cholesterol ratio, TG, and pulse pressure. These findings suggest that TyG index may be a simple and reliable marker of arterial stiffness in patients with stage 1 hypertension. This study further reinforces evaluating arterial stiffness using the TyG index, expands its clinical application, and provides a basis for CVD risk stratification and guidance for antihypertensive treatment in patients with stage 1 hypertension.

Hypertension has become a major public health concern owing to its increasing prevalence. Before the publication of the 2017 ACC/AHA hypertension guidelines, the recommended target BP for antihypertensive therapy was 140/90 mmHg in the general population.[23] The Systolic Blood Pressure Intervention Trial study revealed that lowering systolic BP to 120 mmHg lowered the incidence of CVD and all-cause mortality compared with a threshold of 140 mmHg.[24] Given these results, the 2017 BP guidelines lowered the BP thresholds of hypertension from 140/90 mmHg to 130/80 mmHg and defined elevated BP

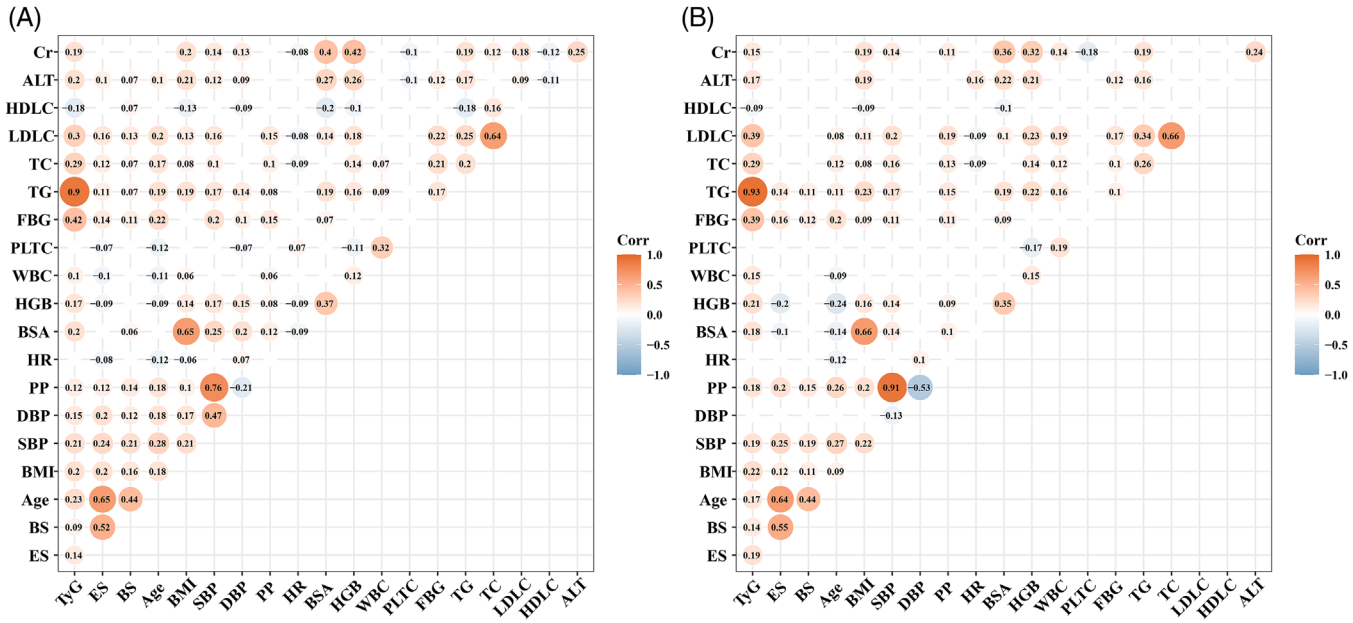

FIGURE 2 Correlation of TyG index with cardiometabolic risk factors in population with normal/elevated BP (A) and stage 1 hypertension (B). The red and blue bubbles respectively represent the positive and negative correlation, and the size and color intensity of the bubbles represent the magnitude of correlation coefficients. Only the correlation with $P < .05$ was showed. *ALT*, alanine transaminase; *BS*, beginning of systole; *BMI*, body mass index; *Cr*, creatinine; *DBP*, diastolic blood pressure; *ES*, end of systole; *FBG*, fasting blood glucose; *HDLC*, high-density lipoprotein cholesterol; *HR*, heart rate; *HGB*, hemoglobin; *IMT*, intima-media thickness; *LDLC*, low-density lipoprotein cholesterol; *PLTC*, platelet count; *PP*, pulse pressure; *SBP*, systolic blood pressure; *TG*, triglyceride; *TyG*, triglyceride-glucose; *WBC*, white blood cell count; *ufPWV*, ultrafast pulse-wave velocity

as systolic BP ≥120 and <130 mmHg, diastolic BP < 80 mmHg, and stage 1 hypertension as BP ≥130/80 mmHg and <140/90 mmHg.[19] Even with a lower threshold, patients with stage 1 hypertension have a significantly higher risk of CVD than do those with normal BP.[25,26] Therefore, exploration of a reliable marker for stratifying the risk of CVD in patients with stage 1 hypertension has vital clinical value. Accumulating evidence suggests that arterial stiffness is a major marker of hypertension risk and is strongly associated with target organ damage, adverse events, and mortality.[27] Arterial stiffness may increase pulsatile loads within the microvascular bed and affect the function of target organs, such as the brain and kidney, as well as increase the systolic load of the heart and decrease coronary artery perfusion. Moreover, arterial stiffness can promote vascular remodeling and increase peripheral vascular resistance and BP, which in turn increases arterial stiffness and generates a vicious cycle.[28] In light of the interaction between arterial stiffness and hypertension, the measurement of arterial stiffness may play an important role in cardiovascular risk stratification and therapy guidance in patients with stage 1 hypertension.

Recently, there has been a tremendous increase in the interest of the TyG index usage as a novel and reliable indicator for detecting arterial stiffness and CVD, owing to its advantages of high cost-effectiveness, efficiency, and convenient application in large-scale clinical screening. Several studies revealed that higher TyG index was associated with a higher prevalence of increased arterial stiffness.[14,29] Wu et al.[30] extended these findings and showed that an elevated TyG index was more likely to indicate a higher risk of arterial stiffness in a longitudinal follow-up. Moreover, the TyG index can predict coronary artery calcification progression and future adverse cardiovascular events.[16,31] These studies indicate that TyG index is a promising marker for monitoring arterial stiffness in clinical practice.

However, evidence regarding the value of the TyG index in assessing arterial stiffness in patients with hypertension is scarce. Li et al.[32] demonstrated that TyG index independently and positively correlated with arterial stiffness in patients with hypertension; however, this study was mainly based on stage 2 hypertension patients (≥140/90 mmHg). Whether these findings can be extrapolated to patients with stage 1 hypertension remains unclear. Wu et al.[17] demonstrated a similar relationship in patients with stage 2 hypertension; however, the TyG index did not correlate with arterial stiffness in prehypertensive patients (≥120/80 mmHg and <140/90 mmHg). We found consistent results in the prehypertensive population according to the seventh criterion of the Joint National Commission (JNC) (Table S7). Interestingly, the present study also revealed that the TyG index independently and positively associated with arterial stiffness, which was reflected by ufPWV after adjusting for potential confounding factors in stage 1 hypertension patients. These results may further expand the clinical application of TyG index based on previous findings.

The TyG index was first introduced as a surrogate biomarker for IR by Simental-Mendía et al. in 2008.[11] Our findings imply an interaction between the hypertension status, IR, and arterial stiffness. Hypertension is often accompanied by hyperglycemia and dyslipidemia, and IR plays a key role in this link.[33] Although the underlying mechanisms are not completely elucidated, they are complex.[34] First, IR causes

TABLE 3 Association between TyG index and ufPWV in normal/elevated BP and stage 1 hypertension populations

	Model 1		Model 2		Model 3	
TyG index	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***
ufPWV at ES						
Normal/elevated BP						
Per 1 unit increase	.50 (.27–.73)	<.001	−.12 (−.31–.06)	.20	−.10 (−.30–.11)	.35
Per SD	.21 (.11–.30)	<.001	−.05 (−.13–.02)	.20	−.04 (−.12–.05)	.35
Tertiles						
T1 (5.16–6.47)	Reference		Reference		Reference	
T2 (6.48–6.83)	.22 (−.01–.45)	.06	−.16 (−.34–.02)	.07	−.15 (−.33–.03)	.10
T3 (6.84–6.94)	.49 (.26–.73)	<.001	−.12 (−.31–.07)	.22	−.08 (−.28–.12)	.43
P for trend		<.001		.19		.38
Stage 1 hypertensive						
Per 1 unit increase	.97 (.56–1.38)	<.001	.37 (.04–.70)	.03	.48 (.11–.84)	.01
Per SD	.40 (.23–.57)	<.001	.15 (.02–.29)	.03	.20 (.05–.35)	.01
Tertiles						
T1 (5.16–6.47)	Reference		Reference		Reference	
T2 (6.48–6.83)	.51 (.11–.91)	.01	.26 (−.05–.57)	.09	.34 (.03–.66)	.03
T3 (6.84–6.94)	.91 (.52–1.29)	<.001	.38 (.08–.69)	.01	.48 (.15–.81)	.005
P for trend		<.001		.02		.007
ufPWV at BS						
Normal/elevated BP						
Per 1 unit increase	.21 (.05–.36)	.008	−.12 (−.26–.03)	.11	−.08 (−.23–.08)	.34
Per SD	.09 (.02–.15)	.008	−.05 (−.11–.01)	.11	−.03 (−.10–.03)	.34
Tertiles						
T1 (5.16–6.47)	Reference		Reference		Reference	
T2 (6.48–6.83)	.13 (−.03–.28)	.10	−.08 (−.22–.06)	.29	−.06 (−.20–.08)	.42
T3 (6.84–6.94)	.24 (.08–.40)	.003	−.08 (−.23–.07)	.29	−.03 (−.19–.13)	.73
P for trend		.004		.28		.69
Stage 1 gypertensive						
Per 1 unit increase	.44 (.20–.68)	<.001	.15 (−.09–.38)	.22	.06 (−.19–.32)	.63
Per SD	.18 (.08–.28)	<.001	.06 (−.04–.16)	.22	.02 (−.08–.13)	.63
Tertiles						
T1 (5.16–6.47)	Reference		Reference		Reference	
T2 (6.48–6.83)	.16 (−.07–.40)	.18	.05 (−.17–.26)	.67	.01 (−.20–.23)	.90
T3 (6.84–6.94)	.36 (.13–.59)	.002	1.11 (−.10–.32)	.31	.05 (−.18–.28)	.68
P for trend		.001		.24		.67

Per SD, beta coefficient (*β*) for per standard deviation (.41) change in TyG index. *P* for trend, *P* value for trend across the tertiles of TyG index. Model 1, no adjustment. Model 2, adjusted for age, sex, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, and smoking history.
Model 3, adjusted for age, sex, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, smoking history, hemoglobin, white blood cell count, platelet count, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, alanine transaminase, and creatinine.
Abbreviations as Table 1.

hyperinsulinemia, which may enhance sympathetic nervous system activity and secretion of epinephrine and norepinephrine. Moreover, IR leads to the development of hypertension by activating the renin-angiotensin-aldosterone system and increasing endothelin synthesis, which leads to an increase in cardiac output, contraction of blood vessels, and peripheral vascular resistance. Additionally, IR interferes with insulin signaling at the cellular level in endothelial and vascular smooth muscle cells, promoting the impairment of endothelial function and development of dyslipidemia and vascular inflammation. All of these interactions greatly enhance the likelihood of the

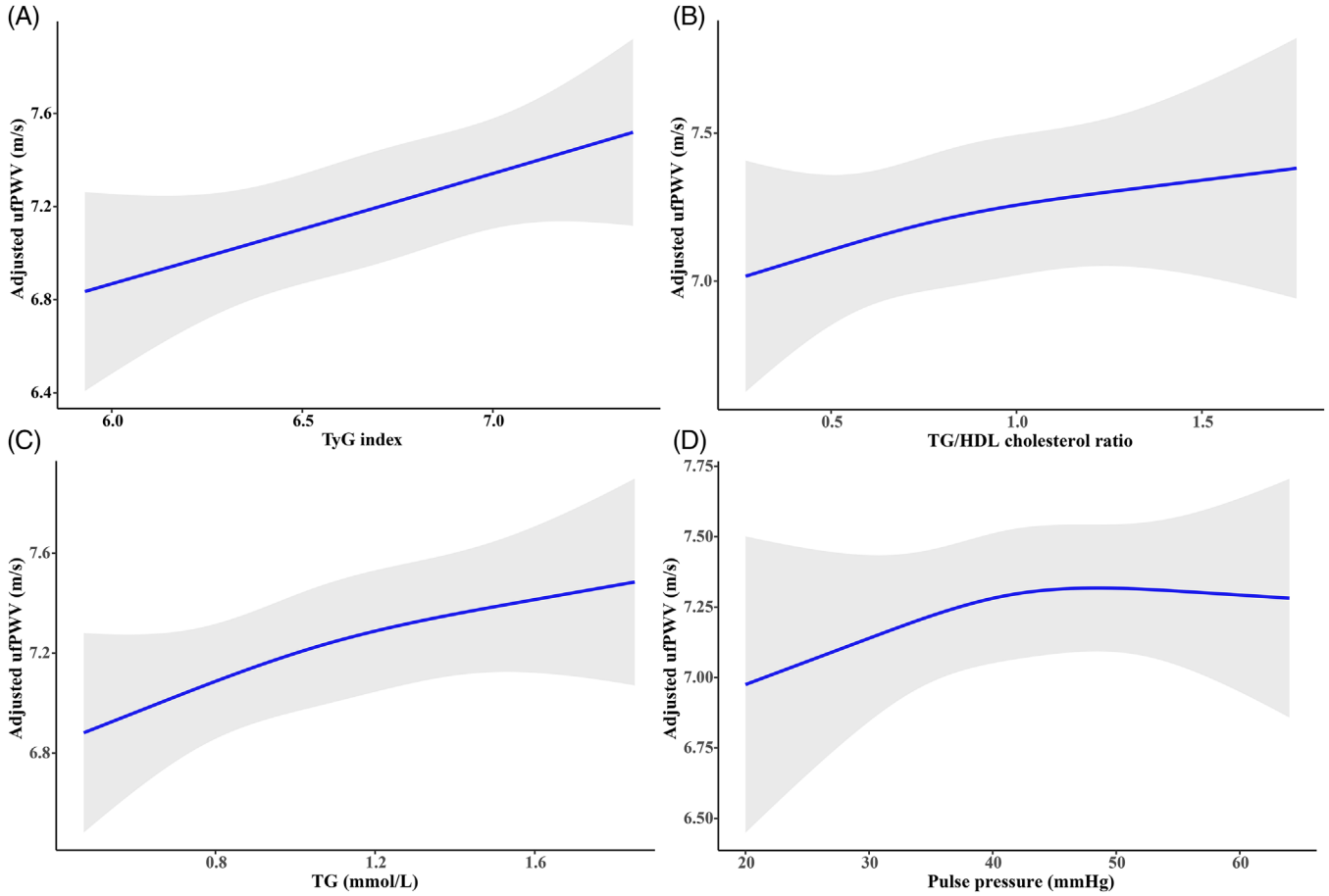

FIGURE 3 Associations of TyG index (A), TG/HDL cholesterol ratio (B), TG (C), and pulse pressure (D) with ufPWV at ES in stage 1 hypertension patients. Data were fitted using the linear regression models with ordinary least squares of the restricted cubic spline with three knots at the 10th, 50th, and 90th percentiles of atrial stiffness indicator. The models were adjusted for age, sex, BMI, systolic BP (exception in Fig. d), diastolic BP (exception in Fig. d), heart rate, smoking history, hemoglobin, white blood cell count, platelet count, fasting blood glucose (exception in Fig. a), total cholesterol, LDL cholesterol, HDL cholesterol (exception in Fig. b), triglycerides (exception in Fig. a and b), ALT, and creatinine. The blue solid line represents the point estimation of the association between TyG index and ufPWV, and the shaded part represents the 95% confidence interval estimation. *ALT*, alanine transaminase; *BP*, blood pressure; *BMI*, body mass index; *ES*, end of systole; *TG*, triglyceride; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *FBG*, fasting blood glucose; *TyG*, triglyceride-glucose; *ufPWV*, ultrafast pulse-wave velocity

development of arterial stiffness and hypertension-related CVD. Our findings also underscore the clinical significance of dynamically monitoring IR and arterial stiffness in hypertensive patients. The TG/HDL cholesterol ratio is another surrogate biomarker of IR. However, our results did not show a significant relationship between the TG/HDL cholesterol ratio and arterial stiffness reflected by ufPWV in stage 1 hypertension patients, further suggesting the advantages of the TyG index.

TyG index was calculated from FBG and TG levels. TG and FBG levels were closely related. Previous studies have shown that TG can stimulate the formation of atherosclerotic plaques, whereas FBG is associated with endothelial cell dysfunction and plaque instability.[35,36] These findings suggest that the TyG index may integrate the values of TG and FBG as a whole, and may provide incremental value for identifying potential risks in individuals. The specific mechanisms by which the TyG index exerts the synergistic value of TG and FBG in assessing arterial stiffness should be further investigated in future studies. However, an arising additional hint is that clinicians may miss some potential risk groups if a single indicator was paid more attention, especially when TG or FBG values are in the borderline ranges in hypertensive patients.

Pulse-wave velocity is used as the gold standard for the noninvasive evaluation of arterial stiffness because of its direct association with Young's modulus.[37,38] Ultrafast ultrasound imaging is a novel and noninvasive technology that has been developed in recent years. This novel method can track and capture pulse waves in real time with extremely high sampling rates (> 10,000 frames/s) and accurately measure local ufPWV. It is worth mentioning that unlike ufPWV at ES, there were no significant associations between TyG index and ufPWV at BS in stage 1 hypertensive patients. These results were consistent with those of a previous study, which showed that ufPWV at ES is a superior pattern for early diagnosis and quantification of arterial stiffness than that at BS.[18,39,40] The potential reasons for this finding may be related to the greater susceptibility of ufPWV at BS to early peripheral reflections,

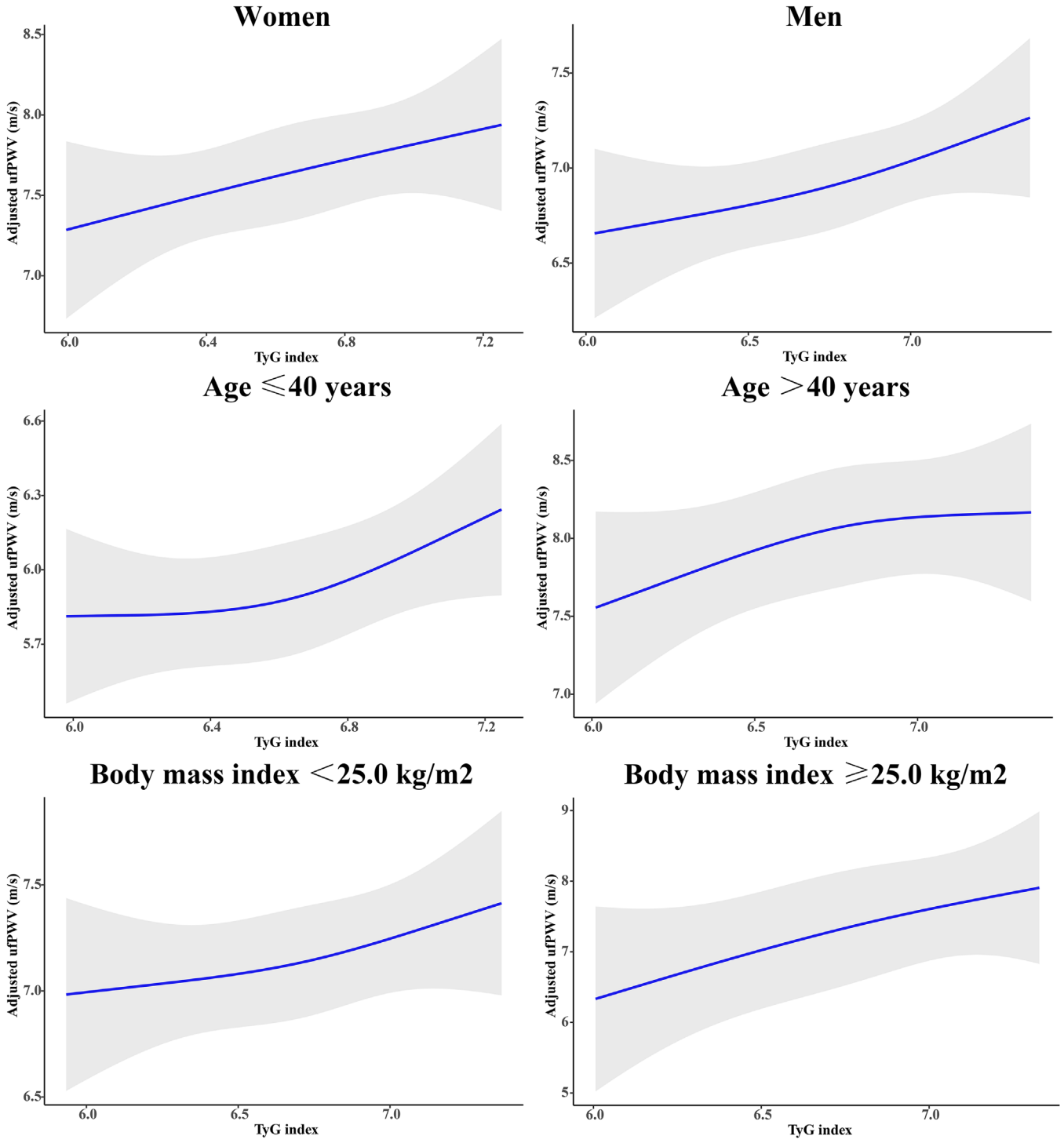

FIGURE 4 Subgroup analysis of association between TyG index and ufPWV at ES in stage 1 hypertension population. Data were fitted using the linear regression models with ordinary least squares of the restricted cubic spline with three knots at 10, 50, and 90th percentiles of TyG index. The models are adjusted for age, sex, BMI, systolic BP, diastolic BP, heart rate, smoking history, hemoglobin, white blood cell count, platelet count, total cholesterol, LDL cholesterol, HDL cholesterol, ALT, and creatinine. The blue solid line represents the point estimation of the association between TyG index and ufPWV, and the shaded part represents the 95% confidence interval estimation. *ALT*, alanine transaminase; *BMI*, body mass index; *BP*, blood pressure; *ES*, end of systole; *TyG*, triglyceride-glucose; *ufPWV*, ultrafast pulse-wave velocity; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein

TABLE 4 Subgroup analysis of association between TyG index and ufPWV at ES in stage 1 hypertension population

	Sex		Age		Body mass index	
Group	Women	Men	≤40 years	>40 years	<25.0 kg/m2	≥25.0 kg/m2
N	280	305	221	364	520	65
Per 1 unit increase						
β	.55	.46	.52	.54	.44	1.12
95% CI	−.05–1.15	.02–.91	.10–.93	−.03–1.11	.05–.83	−.07–2.30
P value	.07	.04	.02	.06	.03	.06
Tertiles						
T1 (5.16–6.47)	Reference	Reference	Reference	Reference	Reference	Reference
T2 (6.48–6.83)						
β	.39	.28	.18	.66	.26	1.82
95% CI	−.09–.87	−.14–.69	−.15–.52	.16–1.17	−.07–.59	.67–2.97
P value	.12	.19	.29	.01	.12	.002
T3 (6.84–6.94)						
β	.48	.52	.44	.72	.41	1.48
95% CI	−.04–1.00	.10–.94	.08–.81	.21–1.23	.06–.76	.53–2.44
P value	.07	.01	.01	.006	.02	.002
P for trend	.09	.02	.03	.02	.03	.03
P for interaction	.24		.37		.56	

The model is adjusted for age, sex, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, smoking history, hemoglobin, white blood cell count, platelet count, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, alanine transaminase, and creatinine (except for interaction with the corresponding variables). Abbreviations as Table 1.

and the more pronounced effect of reflections at older ages compared with ufPWV at ES.

The strength of this study is that it is the first to investigate the usefulness of the TyG index for assessing arterial stiffness in stage 1 hypertension patients, using a prospective cohort from a large number of participating centers and accurate arterial stiffness parameters such as ufPWV. However, this study has some limitations. First, this study analyzed the association between the TyG index and ufPWV based on an observational cross-sectional study design without longitudinal follow-up, and the value of the TyG index for predicting the progression of arterial stiffness and the risk of CVD in stage 1 hypertension should be confirmed in future studies. Second, this study did not collect data on serum insulin levels or a direct indicator of IR for comparison with the TyG index in stage 1 hypertension patients. Third, although we adjusted for most of the available demographic and clinical variables in our model, other possible confounding factors such as dietary habits, activity level, and environmental factors were not routinely collected, and we could not examine their modifying effects on the association between TyG index and arterial stiffness. Fourth, this study was based on a Han Chinese population; therefore, the findings should be validated across multiple geographies and races. Furthermore, the measurement of ufPWV was dependent on local pressure. In the study, the measurements of blood pressure were taken within 3 min before the carotid scans, rather than at the same time that the carotid scans are done. This may be also a limitation in the present study. Finally, the car-PWV study was designed before the issue of the ACC/AHA BP guidelines, and the study enrolled healthy people without other CVDs, diabetes mellitus, dyslipidemia, or hypertension according to the seventh JNC criterion; thus, the correlation between TyG and TG and ufPWV may be due to the high correlation between TyG and TG. Therefore, the advantage of using TyG instead of the conventional TG may not be fully explained in the current study. To conclude, these findings should be further validated in other clinical settings.

5 | CONCLUSION

Patients with stage 1 hypertension and a higher TyG index had higher levels of arterial stiffness, and the TyG index independently and positively correlated with arterial stiffness. The TyG index may provide a simple and reliable marker for the early and dynamic monitoring of arterial stiffness in stage 1 hypertension patients.

ACKNOWLEDGEMENT

This work was supported by the National Natural Science Foundation of China (numbers U21A20387 and 81871373) in the design of the study and collection, analysis, and interpretation of data.

CONFLICT OF INTEREST

The authors have nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wang Y, Wang S, Pan X, et al. Association between triglyceride-glucose index and arterial stiffness reflected by carotid pulse-wave velocity in stage 1 hypertension and individuals with normal/elevated blood pressure. *J Clin Hypertens*. 2023;25:199–212. https://doi.org/10.1111/jch.14639

APPENDIX

The following hospitals (investigators) participated in this study: The Fifth Affiliated Hospital of Southern Medical University (Jianmin Qiu); Huadu Hospital Affiliated to Southern Medical University (Hongyan Zeng); Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology (Youbin Deng); Hangzhou Hospital of Traditional Chinese Medicine (Meilin Tu); Wuchang Hospital of Hubei Province (Wen Wang); Ningbo First Hospital (Shengmin Zhang); Central Hospital Affiliated to Shenyang Medical College (Minghui Xiang); The First Affiliated Hospital of Zhengzhou University (Ruifang Zhang); The First Affiliated Hospital of Dalian Medical University (Ying Che); The First Affiliated Hospital of Jinzhou Medical University (Yuhong Li).