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ORIGINAL RESEARCH

Comparison of TyG and Newly TyG Related Indicators for Chronic Kidney Diseases Estimation in a Chinese Population

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Background: Obesity and insulin resistance (IR) are positively associated with chronic kidney disease (CKD). Previous studies have identified triglyceride-glucose index (TyG) as a valuable surrogate of insulin resistance. Recently, new indicators combining TyG and simple anthropometric indices have emerged, The objective of this study was to assess the diagnostic accuracy of TyG and newly TyG related indicators in detecting CKD and explore which indices were superior in associating with CKD in Chinese population.

Methods: Correlation test, logistic regression analysis, and receiver operating characteristic (ROC) analyses were used to evaluate the optimal cut-off and value of TyG, TyG-body mass index (TyG-BMI), TyG-waist circumference (TyG-WC), TyG-waist to height ratio (TyG-WHtR) for predicting CKD.

Results: TyG-WHtR, TyG-WC, and TyG-BMI correlated with several risk factors for CKD. After adjusting for confounders, TyG-WHtR and TyG-WC remained significantly associated with CKD, while TyG-BMI did not. The highest quartiles of TyG-WHtR and TyG-WC had 1.95- and 1.91-fold increased risk of CKD than the lowest quartiles ($P<0.05$). TyG-WHtR had the largest AUC (0.687) for CKD detection, followed by TyG-WC (0.669), TyG (0.652), and TyG-BMI (0.648). A united model that involved TyG-WHtR and other risk variables had higher predictive performance (AUC=0.791) than a single TyG related indicator. However, TyG had the highest OR (2.713, 95% CI, 1.446–5.090) for reduced eGFR in the fully adjusted model. A united model that involved TyG and WHtR separately had stronger predictive ability (AUC: 0.794) than the model that involved TyG-WHtR individually (AUC:0.791).

Conclusion: This study found that TyG-WHtR had a better diagnostic value in the diagnosis of CKD, compared to other TyG related indicators, but none of the TyG related indicators showed a stronger association with CKD than TyG. Further research and more refined algorithms are needed to verify these new indicators.

Keywords: chronic kidney disease, insulin resistance, obesity, TyG related indicators

Introduction

Chronic kidney disease (CKD) is a condition that causes gradual loss of kidney function and has become a global public health burden over time. CKD can lead to various complications such as anemia, bone disease, cardiovascular disease, and kidney failure. A systematic review and analysis estimated that the global prevalence of CKD was 9.1% in 2017, affecting about 700 million adults.[1] In China, the prevalence of CKD was 10.8% in 2018–2019, affecting about 82 million adults.[2] CKD poses

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a major public health challenge in China, as it is associated with increased mortality, morbidity, and health care costs. Therefore, it is necessary to prevent and control the progression of CKD.

Insulin resistance (IR) is a potential pathophysiological factor involved in the progression of CKD. IR is a state of reduced sensitivity and response to the action of insulin. It is well known that IR predisposes individuals to several metabolic disorders, such as hyperglycemia, dyslipidemia, and hypertension, all of which are strongly associated with poor outcomes of CKD.[3] Additionally, previous studies have shown that IR is an early metabolic alteration in CKD patients.[4,5] These pieces of evidence suggest that IR may play a critical role in the progression of renal impairment. The current gold standard for IR measurement is the hyperinsulinemic euglycemic clamp test, however, this test is rarely performed in large-scale populations because of its high costs and laborious, time-consuming and complex process.[6] Another widely used index is the homeostasis model assessment estimated insulin resistance (HOMA-IR), but it also has some limitations. HOMA-IR requires the measurement of endogenous insulin, which is not involved in basic and routine blood tests.[7] Thus, a simple, low-cost, and convenient index of IR is particularly needed.

Recently, the triglyceride-glucose (TyG) index has been developed and shown to be superior to HOMA-IR in assessing IR in individuals.[8] It is calculated by a natural logarithm function of fasting blood glucose and fasting blood triglycerides. The TyG is a quick and feasible method because it only requires basic and widely used blood tests.[9] Some studies have shown that the TyG index has a significant correlation with IR assessed by the gold standard, hyperinsulinemic-euglycemic clamp test, and could be useful for identifying subjects with decreased insulin sensitivity.[10–12] Previous studies have also investigated the significant correlation between the TyG index and CKD.[13,14] Furthermore, several cross-sectional and longitudinal evidence have demonstrated that the TyG index is positively associated with a higher prevalence of CKD.[15–17]

Following the development of the triglyceride-glucose (TyG) index, new indicators that combine TyG and simple anthropometric indices have emerged, such as TyG-body mass index (TyG-BMI), TyG-waist circumference (TyG-WC), and TyG-waist to height ratio (TyG-WHtR). These anthropometric indices (BMI, WC, WHtR) are often used to assess lipid over-accumulation and visceral adiposity.[18] Visceral fat accumulation can lead to the secretion of adipocytokines. Oversecretion of proinflammatory adipocytokines and hyposecretion of defensive adipocytokines might be the main mechanism of IR.[19] The relationship between these newly proposed TyG-related indicators and various metabolic diseases has been investigated, such as hypertension,[20] metabolic syndrome,[21] diabetes,[22,23] and nonalcoholic fatty liver disease (NAFLD).[24,25] However, few studies have compared the different predictive values of TyG and TyG-related indicators (TyG-BMI, TyG-WC, TyG-WHtR) for CKD, especially in the southern Chinese population. The objective of this study was to explore which indices were superior in associating with CKD.

Materials and Methods

Study Population

This cross-sectional survey was conducted in Wanzhai community, Zhuhai City, on the southern coast of China, from December 2017 to March 2018. It included a random sample of nearly 3000 community residents. Participants were selected by a multi-stage stratified random method. First, our team randomly selected two communities from Wanzhai Town. Second, from the two selected communities, we randomly chose 500 families as the sample families. Third, we included and sampled all the residents aged 18 to 75 from these families. After excluding participants with missing clinical data, 2713 individuals were analyzed in this study. The details of this cross-sectional survey have been previously described.[13] The study was approved by the ethics committee of the Third Affiliated Hospital of Southern Medical University, and participants provided written informed consent in accordance with the Declaration of Helsinki. The informed consent documents were collected and securely stored after the subjects agreed and signed them.

Data Collection

Participants' socio-demographic data were collected using a structured questionnaire, which included information on age, gender, current education, physical activity, current smoking, current alcohol consumption, history of hypertension, and history of diabetes. Anthropometric indices (height, weight, waist circumference) were measured by trained researchers, and BMI [BMI= weight(kg)/height(m)^2] and WHtR [WHtR=waist(cm)/height (cm)] were calculated. Systolic blood pressure

(SBP) and diastolic blood pressure (DBP) were measured in sitting position after 5 min of rest by a mercury desk-top sphygmomanometer. The resting blood pressure was measured three times and the mean blood pressure was calculated. All participants fasted for at least 10 hours at night. The staff collected fresh morning urine and venous blood using coagulation separation gel tubes (Shanghai Kehua, China). The blood samples were gently inverted three times to mix the blood and left undisturbed for 20–30 minutes. Then, the blood samples were centrifuged at a speed of 3200–4000 rpm for 10 minutes. Subsequently, all the samples (urine and blood) were sent to the central laboratory of the Third Affiliated Hospital of Southern Medical University for examination. Total cholesterol (TC), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and very low-density lipoprotein (VLDL-C) were measured by a colorimetric method (apparatus: Roche cobas6000, Penzberg, Germany). The level of high-sensitivity C-reactive protein (hs-CRP) was measured by immunotransmission turbidimetry. Serum creatinine (Scr), fasting blood glucose (FBG), and triglycerides (TG) were measured by a standard enzymatic method. Fasting insulin was measured by an electrochemical luminescence method. The Homoeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated using the formula:$\mathrm{HOMA-IR} = \text{fasting blood glucose}(\mathrm{mmol/L}) \times \text{fasting insulin}(\mathrm{mU/L})/22.5$. The visceral adiposity index (VAI) score was calculated as follows: (1) In male population,$\mathrm{VAI} = [\mathrm{WC}/(39.68 + 1.88 \times \mathrm{BMI})] \times (\mathrm{TG}/1.03) \times (1.31/\mathrm{HDL})$. (2) In females, the$\mathrm{VAI} = [\mathrm{WC}/(36.58 + 1.89 \times \mathrm{BMI})] \times (\mathrm{TG}/0.81) \times (1.52/\mathrm{HDL})$. Urinary albumin concentration was measured using immunoturbidimetric tests (Audit Diagnostics, Cork, Ireland), while urinary creatinine concentration was evaluated using Jaffe's kinetic method (Audit Diagnostics, Cork). The urinary albumin to creatinine ratio (ACR) value was calculated based on the recorded concentrations of urinary albumin and urinary creatinine.

Definitions of CKD, Insulin Resistance and Triglyceride-Glucose Related Parameters

The CKD was diagnosed by following criteria: estimated glomerular filtration rate (eGFR) <60 (mL/min/1.73m^2) or urinary albumin-to-creatinine ratio (ACR) >30 mg/g. A formula from the Chinese-Modification of Diet Renal Disease (C-MDRD) study was used to calculate the estimated glomerular filtration rate (eGFR): $\mathrm{eGFR}\left(\mathrm{mL/min/1.73m^2}\right) = 175 \times (\mathrm{Scr})^{-1.234} \times (\mathrm{Age})^{-0.179} \times (\text{if female}, \times 0.79)$.[26]

IR is a condition where the body does not respond well to insulin, which is a hormone that regulates blood sugar levels. IR can lead to various metabolic problems, such as type 2 diabetes and cardiovascular disease. One way to measure IR is by using the homeostatic model insulin resistance index, also known as HOMA-IR. Based on the review of previous epidemiological literature, this study establishes a cut-off point for defining IR as HOMA-IR > 2.69 mmol/L.mU/L.[27]

Triglyceride-glucose related indicators were calculated according to the following formulas: 1. $\mathrm{TyG} = \mathrm{Ln}[\mathrm{TG(mg/dL)} \times \mathrm{FPG(mg/dL)}/2]$.[21] 2. $\mathrm{TyG-BMI} = \mathrm{TyG} \times \mathrm{BMI}$.[21] 3. $\mathrm{TyG-WC} = \mathrm{TyG} \times \mathrm{WC}$.[21] 4. $\mathrm{TyG-WHtR} = \mathrm{TyG} \times \mathrm{WHtR}$.[21]

Statistical Analysis

Statistical Method: We used SPSS, version 20.0, for the statistical analysis. The data were divided into two types: numerical and categorical. Numerical data that followed a normal distribution were presented as mean ± standard deviation, and the *t*-test was used to compare the means between groups. Numerical data that did not follow a normal distribution were presented as median (25% quantile, 75% quantile), and the non-parametric rank sum test was used to compare the medians among groups. Categorical data were presented as absolute values (percentage), and the chi-square test was used to compare the proportions between groups. When the categorical data did not meet the assumptions for the chi-square test, Fisher's exact test was used instead. Pearson's correlation test was used to measure the correlation between numerical variables that followed a normal distribution. Spearman's correlation test was used to measure the correlation between numerical variables that did not follow a normal distribution. The strength of association was categorized as very weak (r<0.1), weak (0.1–0.39), moderate (0.40–0.69), strong (0.70–0.89), and very strong (r > 0.90). Binomial logistic regression models were used to examine the relationship between CKD and the TyG related indicators. To enhance the association between these indicators and CKD, we divided the subjects into four subgroups based on quartiles of TyG, TyG-BMI, TyG-WC, and TyG-WHtR. The subjects in the first quartile were considered as the reference group in the binomial logistic regression analysis. A two-sided test with a significance level of 0.05 was used to determine statistical significance. A receiver operating characteristic (ROC) curve analysis was conducted to evaluate the predictive value of TyG related indicators for CKD. The analysis quantified the area under the ROC curve (AUC). The AUCs

were compared to assess the performance of the indicators. Additionally, Youden's index was calculated using the formula: Youden's index = sensitivity + specificity - 1.

Results

The study population comprised 2713 subjects, of which 434 were patients with CKD. As depicted in Table 1, the mean age and education status, history of hypertension and diabetes, physical inactivity were higher in CKD patients. In comparison of physical examination, those in the CKD group were more likely to have higher values of weight, WC, BMI, WHtR, SBP, DBP, VAI and lower value of height. Additionally, subjects in CKD group generally had higher levels of FPG, TG, TC, LDL-C, VLDL-C, insulin, HOMA-IR index, Scr, uric acid, ACR, hs-CRP, but lower values of HDL-C

Table 1 Baseline Characteristics of the Study Population

Parameters	Non-CKD (2279)	CKD(434)	P
Age (years)	53.18 (14.05)	63.78 (13.16)	<0.001
Education (high school or above, n (%))	906 (41.6%)	100 (24.6%)	<0.001
Physical activity, n (%)	1259 (56.4%)	174 (40.1%)	0.005
Current smoking, n (%)	282 (12.5%)	53 (12.5%)	0.989
Current alcohol use, n (%)	124 (5.5%)	25 (5.9%)	0.934
History of hypertension, n (%)	485 (21.3%)	234 (54.0%)	<0.001
History of diabetes, n (%)	146 (6.4%)	78 (18.0%)	<0.001
Height (cm)	159.37 (8.171)	157.64 (8.710)	<0.001
Weight (kg)	60.30 (10.56)	62.35 (11.35)	<0.001
Waist circumference (cm)	83.38 (10.08)	88.30 (10.25)	<0.001
BMI (kg/m^2)	23.69 (3.37)	25.04(3.86)	<0.001
WHtR (cm/cm)	0.52(0.06)	0.56(0.07)	<0.001
Systolic blood pressure (mmHg)	130.55 (29.88)	145.34(20.663)	<0.001
Diastolic blood pressure (mmHg)	80.37(10.85)	85.19(11.81)	<0.001
visceral adiposity index	1.37(0.91–2.15)	1.84(1.17–2.89)	<0.001
Fasting plasma glucose, mmol/L	5.09(1.03)	5.89(2.01)	<0.001
Triglyceride, mmol/L	1.48(0.87)	1.81(1.04)	<0.001
Total cholesterol, mmol/L	5.36(1.03)	5.65(1.12)	<0.001
HDL-C, mmol/L	1.51(0.33)	1.46(0.35)	<0.001
LDL-C, mmol/L	3.17(0.90)	3.37(0.99)	<0.001
VLDL-C mmol/L	0.67(0.38)	0.82(0.47)	<0.001
Insulin (mU/mL)	8.67(6.30–12.37)	10.85(7.31–15.40)	<0.001
HOMA-IR (μU/mL ·mmol/mL)	1.89(1.34–2.86)	2.68(1.71–4.07)	<0.001
Serum creatinine (μmol/mL)	74.32(14.77)	90.12(42.47)	<0.001
eGFR (mL/min/1.73 m^2)	96.46(19.76)	81.10(26.36)	<0.001

(*Continued*)

Table 1 (Continued).

Parameters	Non-CKD (2279)	CKD(434)	P
ACR (mg/g)	8.83(5.83–13.42)	47.53(33.97–90.82)	<0.001
Serum uric acid (μmol/L)	344.51(87.86)	380.49(102.77)	<0.001
hypersensitive C-reactive protein, mmol/L	1.19(0.45–2.35)	1.89(0.87–3.75)	<0.001
Triglyceride-glucose related parameters			
TyG	8.55(0.55)	8.87(0.60)	<0.001
TyG-BMI	203.33(35.80)	222.79(40.40)	<0.001
TyG-WC	715.66(113.74)	785.64(118.96)	<0.001
TyG-WHtR	4.49(0.70)	4.99(0.76)	<0.001

and eGFR. Furthermore, significant differences were found in the TyG and TyG related indicators (TyG, TyG-BMI, TyG-WC, TyG-WHtR) in CKD group and these indicators were all higher than subjects without CKD.

The participants were divided into quartiles based on TyG and TyG related indicators (TyG, TyG-BMI, TyG-WC, TyG-WHtR). According to Figure 1, the results indicated that there was a positive association between TyG and TyG related indicators with the risk of IR and CKD in participants. As the TyG related indicators increased, the prevalence of IR and CKD also increased. Those in the fourth quartile were more likely to have a significantly higher prevalence of IR than those in the lower quartile. The same trend was observed in the prevalence of CKD as well.

Table 2 presented the correlations between TyG and TyG-related indicators with other risk factors, using either Pearson's correlation analysis or Spearman correlation analysis as the analytical method. TyG demonstrated a strong correlation with VAI (r=0.898) and VLDL-C (r=0.88) and showed a moderate correlation with HDL-C, insulin, and HOMA-IR. On the other hand, other indicators (TyG-BMI, TyG-WC, TyG-WHtR) also exhibited a moderate correlation with VAI, HDL-C, VLDL-C, insulin, HOMA-IR, and hs-CRP. Furthermore, the correlation coefficients between combined indicators of TyG and anthropometric markers (TyG-BMI, TyG-WC, TyG-WHtR) with insulin, HOMA-IR, and hs-CRP were higher compared to TyG alone. All TyG-related indicators demonstrated a weak correlation with blood pressure, TC, Scr, eGFR, ACR, and uric acid. Our results revealed that combined indicators of TyG and anthropometric markers were more strongly associated with insulin resistance and inflammation than TyG alone, but TyG also was more strongly associated with visceral adiposity. Additionally, all TyG-related indicators and renal function may be relevant to some extent.

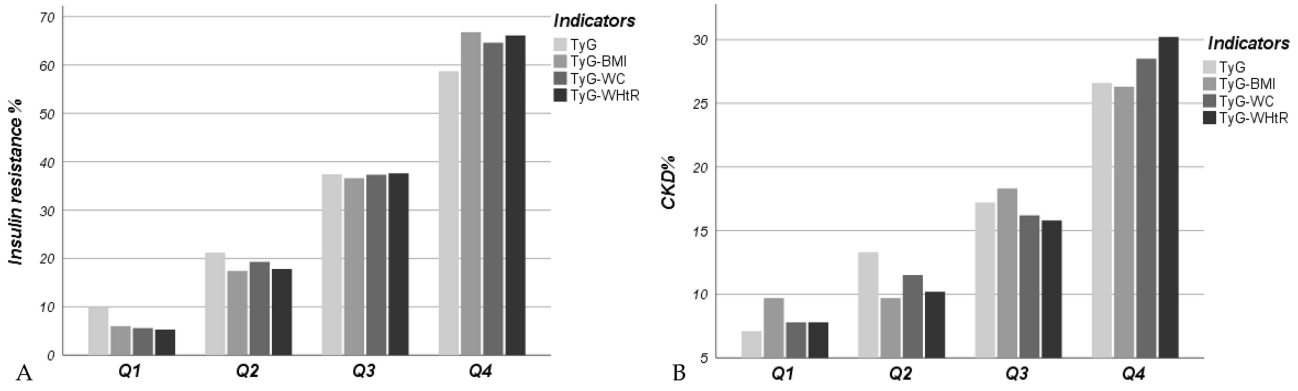

Figure 1 The incidence rate of IR (**A**) and CKD (**B**) stratified by quartiles of TyG and TyG related indicators. The results indicated a positive association between TyG-related indicators and the risk of IR and CKD. As TyG-related indicators increased, the prevalence of IR and CKD also rose. Participants in the fourth quartile had a significantly higher prevalence of IR and CKD compared to those in the lower quartiles.

Table 2 Correlation Between TyG and TyG Related Indicators with Metabolic Risk Factors

risk Factors	TyG		TyG-BMI		TyG-WC		TyG-WHtR	
	r	P	r	P	r	P	r	P
Systolic blood pressure (mmHg)	0.221	<0.001	0.237	<0.001	0.271	<0.001	0.299	<0.001
Diastolic blood pressure (mmHg)	0.305	<0.001	0.355	<0.001	0.374	<0.001	0.347	<0.001
Visceral adiposity index	0.898	<0.001	0.635	<0.001	0.692	<0.001	0.707	<0.001
Total cholesterol, mmol/L	0.288	<0.001	0.187	<0.001	0.211	<0.001	0.257	<0.001
HDL-C, mmol/L	−0.432	<0.001	−0.377	<0.001	−0.429	<0.001	−0.357	<0.001
LDL-C, mmol/L	0.097	<0.001	0.113	<0.001	0.130	<0.001	0.167	<0.001
VLDL-C mmol/L	0.886	<0.001	0.538	<0.001	0.604	<0.001	0.581	<0.001
Insulin (mU/mL)	0.414	<0.001	0.561	<0.001	0.531	<0.001	0.537	<0.001
HOMA-IR (μU/mL ·mmol/mL)	0.508	<0.001	0.617	<0.001	0.605	<0.001	0.614	<0.001
Serum creatinine (μmol/mL)	0.159	<0.001	0.138	<0.001	0.219	<0.001	0.125	<0.001
eGFR (mL/min/1.73 m2)	−0.216	<0.001	−0.191	<0.001	−0.250	<0.001	−0.228	<0.001
ACR (mg/g)	0.162	<0.001	0.185	<0.001	0.184	<0.001	0.263	<0.001
Serum uric acid (μmol/L)	0.282	<0.001	0.317	<0.001	0.385	<0.001	0.297	<0.001
Hypersensitive C-reactive protein, mmol/L	0.291	<0.001	0.428	<0.001	0.432	<0.001	0.456	<0.001

Binary logistic regression models were used to analyze the association between TyG and TyG-related indicators quartiles with CKD. Table 3 showed the results of the unadjusted model (model 1), which revealed that individuals in the Q4 of TyG, TyG-BMI, TyG-WC, and TyG-WHtR quartiles had a 4.756, 3.301, 4.693, and 5.111-fold increased risk of CKD, respectively, compared to those in the Q1 quartiles (P<0.001). After adjusting for age, gender, education, physical activity, smoking, drinking, systolic pressure, diastolic pressure, VLDL-C, LDL-C, HDL-C, and TC (model 2), the highest quartile of TyG and

Table 3 Binary Logistic Regression Analysis Showing Independent Predictors of CKD

	Model 1		Model 2		Model 3	
	OR(95% CI)	P	OR(95% CI)	P	OR(95% CI)	P
TyG						
Q1(Ref)	1		1		1	
Q2	2.019(1.398–2.917)	<0.001	1.594(1.053–2.413)	0.028	1.269(0.781–2.063)	0.336
Q3	2.721(1.910–3.878)	<0.001	1.782(1.154–2.753)	0.009	1.274(0.760–2.136)	0.359
Q4	4.756(3.386–6.681)	<0.001	3.352(1.956–5.720)	<0.001	2.713(1.446–5.090)	0.002
P for trend		<0.001		<0.001		<0.001
TyG+BMI						
Q1(Ref)	1		1		1	
Q2	0.998(0.697–1.430)	0.993	0.727(0.486–1.089)	0.122	0.726(0.442–1.193)	0.206
Q3	2.075(1.507–2.858)	<0.001		0.342		0.766
Q4	3.301(2.430–4.484)	<0.001	1.203(0.822–1.761)	0.015	1.075(0.667–1.732)	0.201
P for trend		<0.001	1.654(1.101–2.484)	<0.001	1.415(0.831–2.441)	0.033

(*Continued*)

Table 3 (Continued).

	Model 1		Model 2		Model 3	
	OR(95% CI)	**P**	**OR(95% CI)**	**P**	**OR(95% CI)**	**P**
TyG+WC						
Q1(Ref)	1		1		1	
Q2	1.533(1.063–2.212)	<0.001	1.001(0.664–1.509)	0.996	1.112(0.674–1.834)	0.678
Q3	2.280(1.612–3.225)	<0.001	1.118(0.736–1.699)	0.600	1.039(0.614–1.758)	0.888
Q4	4.693(3.386–6.503)	<0.001	2.057(1.319–3.209)	0.001	1.913(1.076–3.403)	0.027
P for trend		<0.001		<0.001		0.014
TyG+WHtR						
Q1(Ref)	1		1		1	
Q2	1.336(0.918–1.944)	<0.001	0.846(0.559–1.281)	0.430	0.956(0.574–1.594)	0.864
Q3	2.206(1.557–3.125)	<0.001	0.942(0.621–1.429)	0.779	0.889(0.522–1.512)	0.663
Q4	5.111(3.694–7.072)	<0.001	1.868(1.208–2.887)	0.005	1.957(1.070–3.398)	0.028
P for trend		<0.001		<0.001		0.006

Notes: Model 2 adjust for age, gender, education, physical activity, smoking, drinking, systolic pressure, diastolic pressure, VLDL-C, LDL-C, HDL-C, TC. Model 3: adjusted for model 2 covariates plus Serum creatinine, Serum uric acid, eGFR, log hs-CRP and log insulin.

TyG related indicators still had a significantly higher risk of developing CKD. Furthermore, after further controlling for serum creatinine, serum uric acid, eGFR, log hs-CRP, and log insulin (model 3), only TyG-BMI lost its significant correlation with CKD. However, TyG (OR: 2.713, 95% CI, 1.446–5.090), TyG-WHtR (OR: 1.957, 95% CI, 1.070–3.398) and TyG-WC (OR: 1.913, 95% CI, 1.076–3.403) still showed significant odds ratios for the presence of CKD when comparing the top quartile with the bottom quartile. Overall, TyG exhibited the strongest association with CKD in the multivariable-adjusted model.

The abilities of TyG-related indicators to identify patients with CKD were compared in Table 4 and Figure 2. The highest AUC was achieved by TyG-WHtR (AUC=0.687), followed by TyG-WC (AUC=0.669), TyG (AUC=0.652), TyG-BMI (AUC=0.648) and HOMA-IR (AUC=0.642). The sensitivity, specificity, optimal cut-off value, Youden index of each TyG-related indicator were presented in Table 4, respectively. After careful evaluation, the united models for predicting CKD were built in participants. The united model 1 involved TyG and other common and accessible risk factors related to CKD (including age, gender, history of hypertension, history of diabetes, WHtR, systolic blood pressure, diastolic blood pressure, VLDL-C, serum creatinine). The united model 2 was similar to the model 1, but we

Table 4 The Areas Under ROC Curve (AUC), Sensitivity and Specificity by the Optimized Cut-off Points for TyG and TyG Related Indicators in Predicting CKD

Characteristic	AUC	Cut-off	Youden Index	Sensitivity	Specificity
TyG	0.652(0.624–0.679)	8.58	0.234	0.671	0.563
TyG-BMI	0.648(0.619–0.678)	211.79	0.257	0.631	0.626
TyG-WC	0.669(0.640–0.697)	768.09	0.268	0.574	0.694
TyG-WHtR	0.687(0.659–0.715)	4.66	0.292	0.687	0.605
HOMA-IR	0.642(0.613–0.672)	2.14	0.218	0.637	0.581
United predictive model 1	0.794(0.767–0.820)	0.15	0.460	0.752	0.708
United predictive model 2	0.791(0.765–0.816)	0.17	0.459	0.711	0.748

Notes: United predictive model 1 includes TyG, age, gender, history of hypertension, history of diabetes, WHtR, systolic blood pressure, diastolic blood pressure, VLDL-C, Serum creatinine. United predictive model 2 includes TyG-WHtR, age, gender, history of hypertension, history of diabetes, systolic blood pressure, diastolic blood pressure, VLDL-C, Serum creatinine.

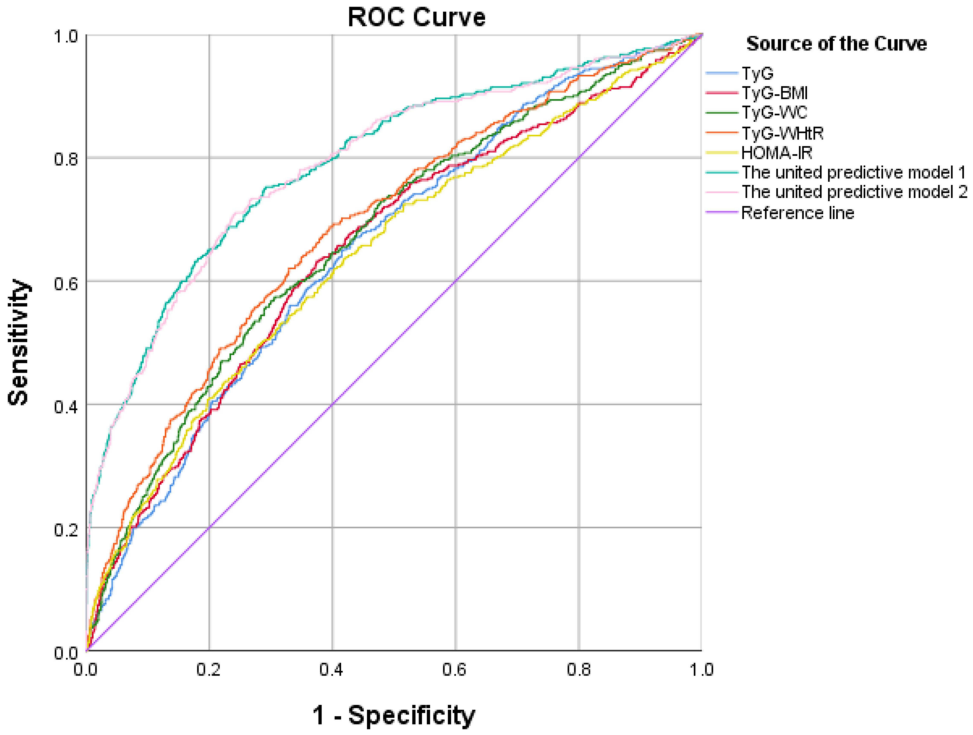

Figure 2 Receiver operator characteristic curves analysis of the value of TyG and TyG related indicators, united predicted model for predicting CKD. The highest AUC was achieved by TyG-WHtR (0.687), followed by TyG-WC (0.669), TyG (0.652), TyG-BMI (0.648), and HOMA-IR (0.642). Two unified models for predicting CKD were developed. Model 1 included TyG and common CKD risk factors. Model 2 replaced TyG and WHtR with TyG-WHtR. Model 1 had a higher predictive ability (AUC: 0.794) than Model 2 (AUC: 0.791).

removed TyG and WHtR and added TyG-WHtR to the model. The ability of the united model 1 for predicting CKD (AUC: 0.794) was stronger than model 2 (AUC:0.791), which suggested that incorporating TyG and WHtR in the model separately was better than incorporating TyG-WHtR in the model individually. Furthermore, the diagnostic value of a single TyG-related indicator was limited. These results suggested that uniting TyG-related indicator and other common risk factors of CKD could improve the accuracy for predicting CKD.

Discussion

In this population-based cross-sectional study, we explored the potential association between TyG and TyG related indicators with CKD in the southern Chinese population. TyG and TyG related indicators were significantly different between non-CKD and CKD groups, and correlation analysis showed that all TyG related indicators were associated with obesity, blood pressure, blood lipid, inflammation, and renal function. Moreover, this study directly compared the predictive value of TyG, TyG-BMI, TyG-WC, TyG-WHtR, and HOMA-IR. Our results were consistent with previous studies that TyG related indicators had a better capability to identify individuals with CKD than HOMA-IR. This study also found that TyG, TyG-BMI, TyG-WC, and TyG-WHtR all had a strong positive relationship with CKD. After adjustment for age, gender, lifestyle, history of diseases, blood pressure, blood lipid, inflammation, insulin, and renal function indicators, TyG, TyG-WC, and TyG-WHtR remained significantly correlated with CKD. To our knowledge, this study was the first to confirm and compare a significant correlation between TyG and TyG related indicators with CKD in the southern Chinese population.

IR is an early metabolic complication of CKD that is associated with worsening cardiovascular outcomes.[28,29] Previous studies have found that IR exists in different stages of CKD, even in the early stage of mild renal function impairment.[30–32] The kidney has various insulin-sensitive cells that express insulin receptors. Animal studies have demonstrated that podocyte-specific deletion of insulin receptor in mice resulted in albuminuria, together with histological features that recapitulate diabetic kidney disease (DKD), even in a normoglycemic environment.[33] Another study

also showed that podocyte-specific and proximal tubule-specific knockout of the insulin receptor resulted in albuminuria, DKD pathological changes, and the development of hyperglycemia, respectively.[34] Furthermore, many patients with diabetes mellitus (DM) develop CKD despite low HbA1C levels and relatively good metabolic control, stressing the importance of enhancing insulin sensitivity and not simply lowering glucose in the early phase of CKD.[35] On the other hand, several clinical studies indicated that IR was associated with the occurrence and development of type 2 DKD.[36,37] Hence, identification of IR and its severity can have great clinical value to stratify the risk of renal function damage.

Dyslipidemia and hyperglycemia are two basic hallmarks of IR.[38,39] IR leads to increased lipolysis and fatty acids, which further impair insulin's anti-lipolytic effect, creating a vicious circle.[40] Excess fatty acids in the liver increase hepatic triglyceride synthesis and hypertriglyceridemia.[41] Insulin resistance also causes increased glucose absorption in the intestine, increased glucose reabsorption in the kidney, and decreased glucose uptake in the peripheral tissues.[42,43] This results in hyperglycemia. High glucose levels increase reactive oxygen species, which damage b cells.[44] Excess TG impair b-cell function, reduce insulin secretion, and cause fat accumulation and IR.[45] According to the above evidence, the TyG index, a combination of both glucose and TG, becomes a valuable index to detect IR. Several cross-sectional and prospective studies have proven the positive and independent association between TyG and CKD.[16–18] A recent high-value publication reported that higher TyG indices are associated with increased in-hospital and 1-year mortality rates among CKD patients. The TyG index is a crucial prognostic indicator for in-hospital and 1-year mortality rates in HF and CKD patients. This finding suggest that assessing the TyG index could play a key role in developing novel therapeutic strategies to improve outcomes for this high-risk population.[46]

Previous research has indicated that obesity is related to the onset of CKD, the progression of renal disease in CKD patients, and the occurrence of cardiovascular disease in CKD patients.[47–49] Obesity affects the kidney through various mechanisms, such as chronic inflammation, hypoxia-induced oxidative stress, glomerular hyperfiltration, increased renal blood flow, activation of the renin-angiotensin-aldosterone system, focal segmental glomerulosclerosis, and kidney hypertrophy.[50–52] Obesity may also induce hypertension, dyslipidemia, impaired glucose tolerance, insulin resistance, and diabetes, which are well-known risk factors for CKD.[53,54] Therefore, obesity may cause renal damage through direct or indirect pathways. Consequently, timely measurement of body fat content and distribution, and early assessment of the impact of obesity, are essential for preventing the development of CKD.

Imaging methods such as CT, MRI, etc., are the gold standard for evaluating body fat content and distribution, but they are not widely used in clinical practice due to their high cost and the need for special equipment. Therefore, anthropometric indices, which are simple, cheap, and highly reproducible, are the most widely used indicators for assessing fat mass in clinical practice. There are three common anthropometric indices: BMI, WC, and WHtR, each with its own strengths and weaknesses. BMI is the most widely used method for assessing fat mass, but it uses two body indicators (weight and height), which cannot distinguish other components that make up weight, such as bones, muscles, viscera, etc., nor can it reflect the fat distribution status.[55] WC is an indicator of abdominal fat content, which is more strongly associated with insulin resistance and metabolic disorders than subcutaneous fat, as it has larger adipose cells and more free fatty acids.[56] These fatty acids reach the liver through the portal vein and cause hepatic insulin resistance. However, the accuracy of WC in reflecting abdominal fat content may decrease in people who are too tall or too short.[57] WHtR is another indicator of abdominal fat, which has been shown to be a good indicator of abdominal fat content measured by CT.[58] Moreover, systematic reviews and meta-analyses support the use of WHtR as a body measurement index for predicting cardiovascular and metabolic risk factors.[59] This meta-analysis of 78 studies using WHtR, WC, or BMI to predict cardiovascular and metabolic outcomes found that WHtR and WC were better than BMI in predicting cardiovascular and metabolic outcomes, based on 22 prospective studies and 57 cross-sectional studies. In addition, Lin et al's study suggested that WHtR was the best body measurement index for predicting CKD.[60] In summary, both insulin resistance and obesity, especially abdominal obesity, play critical roles in the development and progression of CKD.

Recently, several TyG related indices that combine TyG and anthropometric indices have been proposed (TyG-WHtR, TyG-WC, TyG-BMI) and have been expected to have a stronger association with metabolic diseases than TyG. For example, a cohort study on pre-diabetes suggested that a higher TyG-BMI significantly increased an individual' s risk of pre-diabetes, and this risk was significantly correlated with women and non-obese individuals.[23] Another study conducted by Raimi et al showed that TyG-WHtR had the largest AUC for metabolic syndrome detection, followed by TyG-

WC, TyG-BMI, and TyG index.[61] In the study by Lim et al, the combinations of TyG and obesity indices showed better insulin resistance prediction performance than TyG alone.[62] Recent study showed that elevated levels of TyG-related indices, particularly the TyG-BMI and TyG-WC indices, are significantly associated with all-cause mortality, cardiovascular mortality, and diabetes-related mortality in non-alcoholic fatty liver disease (NAFLD), surpassing the predictive power of the TyG index alone.[63]

Based on the above theory and evidence, we hypothesized that the newly proposed TyG related indices, which combine TyG and anthropometric indices, would also have a greater impact on the risk of impaired renal function and would have value to refine the risk stratification and prevention of CKD. The results partly confirmed our hypothesis. In correlation test, TyG-WHtR, TyG-WC, and TyG-BMI were all significantly associated with blood pressure, VAI, TC, LDL-C, VLDL-C, HDL-C, HOMA-IR, eGFR, ACR, and hypersensitive C-reactive protein. Univariate logistic regression showed that, after adjusting for age, gender, lifestyle, blood pressure, VLDL-C, LDL-C, HDL-C, TC, insulin, inflammatory factors, serum creatinine, serum uric acid, and eGFR (model 3), TyG-WHtR and TyG-WC were still independently and significantly associated with CKD, while TyG-BMI lost its significance. The population in the fourth quartile of TyG-WHtR and TyG-WC had 1.95- and 1.91-fold increased risk of CKD than those in the first quartile ($P<0.05$). Furthermore, in ROC curve analysis, TyG-WHtR had the largest AUC for CKD detection (AUC=0.687), followed by TyG-WC (AUC=0.669), TyG (AUC=0.652), and TyG-BMI (AUC=0.648), indicating that TyG-WHtR could be an important marker for detecting the risk of reduced eGFR. Additionally, we found that the united model that involved TyG-WHtR and other risk variables related to CKD had higher predictive performance (AUC=0.791), indicating that combining TyG related and other traditional readily accessible factors such as age, blood pressure, history of diseases, VLDL-C, and serum creatinine could substantially improve the accuracy for predicting CKD. However, in the fully adjusted binary logistic regression model (model 3), we observed the highest OR (OR: 2.713, 95% CI, 1.446–5.090) for reduced eGFR when comparing the top quartile with the bottom quartile in the TyG subgroup, followed by the TyG-WHtR subgroup (OR: 1.957, 95% CI, 1.070–3.398) and the TyG-WC subgroup (OR: 1.913, 95% CI, 1.076–3.403). Moreover, we observed an intriguing result that the predictive ability of the united model that involved TyG and WHtR separately (AUC: 0.794) was stronger than the model that involved TyG-WHtR individually (AUC:0.791).

This observation raises the question of whether the products of TyG and anthropometric indices are more associated with CKD than TyG. We cannot compare the results of our study with other studies because of the lack of relevant studies. In fact, in other metabolic diseases, it is still controversial which TyG related indices are superior in associating with metabolic diseases. In a comparative study, Mirr et al compared the diagnostic accuracy of indirect insulin resistance indicators in detecting metabolic syndrome in a Caucasian population.[21] The results showed that all indexes achieved significant diagnostic accuracy, with the highest AUC for TyG, suggesting that TyG seemed to be the most useful among eight insulin resistance indexes (TG/HDLc, METS-IR, TyG, TyG-BMI, TyG-WC, TyG-WHtR, TyG-NC, TyG-NHtR). This study also indicated that TyG had a better diagnostic value than its products with anthropometric indices. Another study in a Chinese elderly population found that TyG index had higher predictive ability than TyG-related indicators for prediction of type 2 diabetes mellitus,[64] while other studies suggested that TyG related indicators were significantly better than TyG index in predicting the risk of T2DM in a Korean population[22] and a Chinese population.[65] The specific reasons for this discrepancy remain unknown so far. Ethnic disparities might be one of the reasons for these differences. Another reason could be that the formula is too simple to fully realized the effect of TyG and anthropometric indices. Simply multiplying the two indicators may not achieve the desired results. Therefore, more scientific and rigorous formulas are needed, for which more and further relevant studies are required.

This study had several limitations. First, this was a retrospective single-center cross-sectional study, which limited the analysis of the causal effect of TyG related indicators on CKD. However, a substantial body of previous longitudinal cohort studies have confirmed the causal relationship between insulin resistance, visceral adipose accumulation, and the progression of CKD. Second, this study lacked information about the drug use of the subjects. Therefore, we were unable to perform some subgroup analyses of comorbidities and drug therapy. Third, the sample size of this study was relatively small and the study was conducted on a Chinese population, so the generalizability of the TyG related indicators to other populations should be carefully evaluated.

In conclusion, this study found that TyG-WHtR had a better diagnostic value in the diagnosis of CKD, compared to other TyG related indicators, but none of the TyG related indicators reached a sufficiently high diagnostic power (AUC<0.7) or showed a stronger association with CKD than TyG. Therefore, combining TyG related indicators and other common, readily available risk factors to establish a united predictive model is a more valuable way for evaluating CKD. Further research is needed to verify these new indicators and to develop more refined algorithms to amplify the effect of IR and anthropometric indicators on the progression of CKD.

Data Sharing Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Third Affiliated Hospital of Southern Medical University. Written informed consent forms were signed by all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interest in this work.

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