Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Relationships Between Insulin Resistance Surrogate Indicators and Chronic Kidney Disease in Non-Diabetic Individuals: A Retrospective Cross-Sectional Study

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Purpose: This study aimed to investigate the associations between insulin resistance (IR) surrogate indicators and chronic kidney disease (CKD) in non-diabetic individuals.

Methods: A retrospective analysis was conducted on 29625 participants who underwent annual health examinations from January to December 2024. Based on estimated glomerular filtration rate, participants were divided into non-CKD and CKD groups. Univariate and multivariate logistic regression analyses were performed to evaluate the relationships between insulin resistance surrogate indicators, including metabolic score of insulin resistance (METS-IR), triglyceride glucose index (TyG), triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), total cholesterol-high density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (Non-TG/HDL-C), and CKD, adjusting for potential confounders such as age, sex, blood pressure, and metabolic parameters. Receiver operating characteristic (ROC) curves and DeLong tests were used to compare the predictive performances of different indicators.

Results: Among the recruited 29,625 participants, 8.01% (2372/29,625) participants were CKD patients. All insulin resistance surrogate indicators were found to be correlated with the prevalence of CKD. After adjusting for confounding variables, the METS-IR exhibited stronger association with CKD than other insulin resistance surrogate indicators; the odd ratio for CKD in the highest quartile of the METS-IR was 2.360 (95% CI:1.594−3.493). The ROC results showed the area under curve (AUC) of METS-IR were the best, with AUC = 0.681 (0.671−0.691), which was higher than TyG, TG/HDL-C, and NonTG/HDL-C. Results of the DeLong test showed that there was a statistically significant difference between METS-IR and other IR indicators.

Conclusion: IR indicators (METS-IR, TyG, TG/HDL-C, and NonTG/HDL-C) were positively correlated with the prevalence of CKD in the non-diabetic population. The METS-IR had the best predictive ability for CKD in this population. Detection and early intervention of elevated IR indicators may help prevent CKD in non-diabetic individuals.

Keywords: insulin resistance, metabolic score for insulin resistance, triglyceride glucose index, chronic kidney disease

Introduction

Recent data suggest that 9.1%−13.4% of the worldwide population has chronic kidney disease (CKD).[1] In China, the prevalence of CKD was 8.2%.[2] CKD is a major public health problem globally, and with the rising prevalence of diabetes and hypertension (the leading cause of CKD) worldwide, CKD prevalence is projected to continuously increase.[3] Previous studies[4,5] have reported that Metabolic Syndrome (MetS) and its components are closely associated with the early onset, accelerated progression, and deterioration occurring during CKD, with insulin resistance being the core component of MetS.

Received: 11 March 2025
Accepted: 10 June 2025
Published: 17 June 2025

The hyperinsulinemic-euglycemic clamp is widely regarded as the gold standard for quantifying insulin resistance, but it has been limited in epidemiological investigations and large-scale clinical trials because of its complex, invasive, and time-consuming methodology.[6] Studies have shown that IR surrogate indicators, such as the metabolic score of IR (METS-IR),[7] triglyceride glucose index (TyG),[8] triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C),[9] and total cholesterol-high density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (Non-TG/HDL-C)[10] are closely associated with type 2 diabetes, cardiovascular disease, and diabetic kidney disease. However, the association of IR surrogate indicators and CKD without diabetes is unclear. We hypothesize that in non-diabetic populations, IR surrogates are independently associated with the risk of chronic kidney disease (CKD) and demonstrate superior predictive efficacy for CKD. The present study therefore collected data from a population undergoing annual health check-ups, to determine the associations of IR surrogate indicators with CKD in the non-diabetic population.

Methods

Study Population

This retrospective cross-sectional study included participants who underwent annual health check-ups at the Second Hospital of Hebei Medical University, from January 2024 to December 2024. Some participants were excluded based on the following criteria: 1) participants younger than 18 years of age; 2) participants with diabetes; 3) participants with incomplete data; 4) participants with cancer, immune disease, or liver cirrhosis; 5) pregnant women; or 6) participants with acute renal injury. Finally, 29,625 participants were included in the study (Figure 1). This retrospective study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, and received formal approval from the Research Ethics Committee of the Second Hospital of Hebei Medical University (Approval No. 2022-R341). Due to the nature of the retrospective design, obtaining written informed consent from participants was deemed unnecessary. All personal identifiers were removed from the dataset to ensure complete anonymization, and data management complied with strict confidentiality protocols. The study protocol adhered to national and international standards for ethical research involving human subjects.

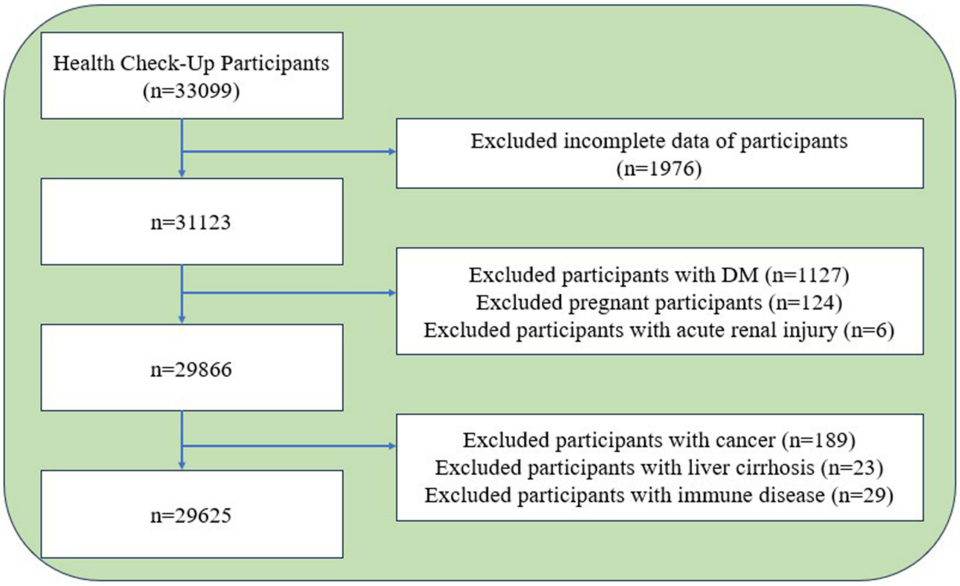

Figure 1 Flowchart of participant selection.

Table 1 Formula of the Different IR Surrogates

IR Indicators	Formula
METS - IR	Ln [2× FPG (mg/dL) + TG (mg/dL)] *BMI (kg/m^2)/Ln [HDL - C(mg/dL)]
TyG	Ln[TG(mg/dL) × FBG/2(mg/dL)]
TG/HDL - C	TG(mg/dL)/HDL - C(mg/dL)
Non-TG/HDL - C	[TC(mg/dL) - HDL - C(mg/dL)]/HDL - C(mg/dL)]

Data Collection and Measurement Methods

The baseline demographic and clinical data of all participants were systematically collected, including sex, age, height, weight, pulse rate, and blood pressure (systolic and diastolic). Prior to measurements, participants were instructed to sit comfortably in a quiet environment for at least 5 minutes to ensure hemodynamic stability. Blood pressure was measured using a validated device, with two consecutive readings taken 1−2 minutes apart. The average of these two values was recorded as the final measurement. Fasting requirements were strictly enforced, with participants refraining from food and caloric beverages for 8−12 hours (overnight) prior to blood collection. This protocol was consistent with standard clinical guidelines to minimize metabolic variabilities. Venous blood samples were collected in the morning following overnight fasting and analyzed for key biochemical indicators, including triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and fasting blood glucose. All procedures adhered to the World Health Organization guidelines for blood sample handling and analysis to ensure data integrity and reliability.

IR Surrogate Indicator Calculations

The IR surrogate indicators were calculated using the following formulas (Table 1).

Diagnostic Criteria

In this study, CKD was defined as the estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73^2.[2]

Statistical Analysis

Statistical analyses were performed using R software (version 4.1.1, www.r-project.org) and MedCalc, version 16.8 (MedCalc Software, Ostend, Belgium). Categorical variables were presented as counts (with percentages) and compared using the χ^2-test. The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. For non-normally distributed data, median values with interquartile ranges (IQR) were represented, and group comparisons were conducted using the Mann–Whitney *U*-test. Multicollinearity among the independent variables was assessed using the variance inflation factor (VIF < 5). To evaluate the discriminatory capacity of insulin resistance surrogates for CKD, receiver operating characteristic (ROC) curve analysis was performed, with the area under the curve (AUC) serving as the metric of performance. Differences in AUC values between models were analyzed using DeLong's test. Statistical significance was defined as $p < 0.05$.

Results

Baseline Participant Characteristics

Among the 29,265 participants in this study, 2372 participants (8.11%) were diagnosed with CKD. Women comprised 56.45%, and the ages ranged from 18−86 years, with the average age being 46.67 average age (years). Compared to non-CKD participants, the CKD participants were more likely to be male, older, with a greater body mass index (BMI), higher systolic blood pressure (SBP), diastolic blood pressure (DBP), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), fasting blood glucose (FPG); lower pulse, high density lipoprotein cholesterol (HDL-C), and

Table 2 Baseline Variables According to the CKD Groups

Variables	Non-CKD (n=27253)	CKD (n=2372)	χ^2/Z	P
Gender, n(%)			2276.593	<0.001
Male	11868(43.55)	2243(94.56)		
Female	15385(56.45)	129(5.44)		
Age, Median(IQR)	43.00(18.00)	59.00(17.00)	−49.271	<0.001
BMI, Median (IQR)	24.30(4.61)	26.07(3.59)	−24.853	<0.001
Pulse, Median (IQR)	79.00(15.00)	76.00(16.00)	−13.098	<0.001
SBP, Median (IQR)	123.00(22.00)	134.00(21.00)	−28.613	<0.001
DBP, Median (IQR)	76.00(15.00)	82.00(14.00)	−22.253	<0.001
Hypertension, n(%)			105.446	<0.001
Yes	1012(3.71)	191(8.05)		
No	26241(96.29)	2181(91.95)		
Dyslipidemia, n(%)			0.204	0.652
Yes	58(0.21)	4(0.17)		
No	27195(99.79)	2368(99.83)		
TG, Median (IQR)	1.17(0.86)	1.48(0.98)	−20.184	0.008
LDL, Median (IQR)	2.88(1.10)	2.96(1.16)	−2.795	0.005
TC, Median (IQR)	4.81(1.23)	4.87(1.34)	−1.081	0.280
HDL, Median (IQR)	1.41(0.40)	1.27(0.35)	−20.965	<0.001
FPG, Median (IQR)	5.01(0.68)	5.25(0.98)	−18.486	<0.001
Smoking, n(%)			1140.467	<0.001
Yes	2720(9.98)	791(33.35)		
No	24533(90.02)	1581(66.65)		
Drinking, n(%)			830.862	<0.001
Yes	2481(9.10)	667(28.12)		
No	24772(80.90)	1705(71.88)		
METS-IR, Median (IQR)	34.68(9.32)	39.14(7.75)	−29.347	<0.001
TyG, Median (IQR)	8.47(0.77)	8.77(0.71)	−23.337	<0.001
TG/HDL-C, Median (IQR)	1.92(1.70)	2.68(2.07)	−24.053	<0.001
Non-TG/HDL-C, Median (IQR)	2.45(1.00)	2.78(0.91)	−21.018	<0.001

higher ratio of hypertension, smoking, and drinking (Table 2). In addition, when compared to the non-CKD participants, all IR surrogate indicators were higher in the CKD participants (all, $p < 0.05$) (Table 2 and Figure 2a–d).

Association Between IR Surrogate Indicators and CKD

Pearson's analyses showed that METS-IR, TyG, TG/HDL-C, and NonTG/HDL-C were all negatively correlated with the level of eGFR (r = −0.393, r= −0.353, r = −0.234, r = −0.331, respectively; all, $p < 0.05$) (Table 3 and Figure 3a–d). Table 4 shows the incidences of CKD in quartiles of the METS-IR, TyG, TG/HDL-C, and Non TG/HDL-C. The incidences of CKD increased per quartile for all parameters, and the chi-square test results were significant (all, p for trend < 0.001). After all confounders (sex, age, BMI, hypertension, smoke, drink, FGP, HDL, LDL, and pulse) were adjusted, all METS-IR, TyG, TG/HDL-C, and NonTG/HDL-C were significantly associated with CKD (all, $p < 0.05$) (Table 5).

Diagnostic Performance of IR Surrogate Indicators for CKD Participants

ROC curve analysis was conducted to evaluate the diagnostic accuracy of IR surrogate indicators (METS-IR, TyG, TG/HDL-C, and NonTG/HDL-C) for identifying CKD participants (Table 6 and Figure 4). The METS-IR was the best predictive indicator

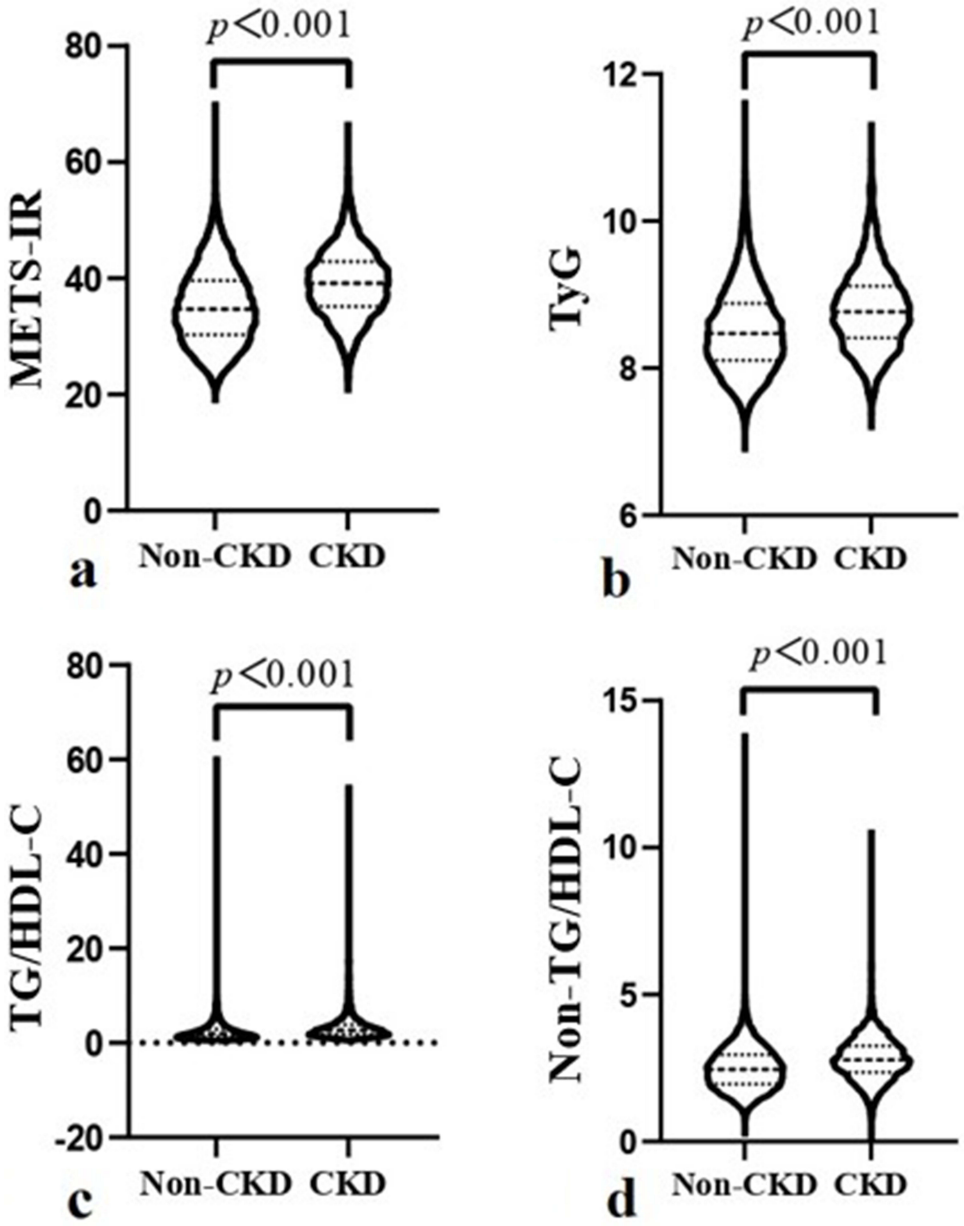

Figure 2 IR surrogates values in CKD group and Non-CKD group. (**a**) Mets-IR values in CKD group and Non-CKD group. (**b**) TyG values in CKD group and Non-CKD group. (**c**) TG/HDL-C values in CKD group and Non-CKD group. (**d**) Non-TG/HDL-C in CKD group and Non-CKD group. The bold dash lines indicate median and thin dash lines indicate quantiles.

(AUC: 0.681, 95% CI: 0.671−0.691), with 80.2% sensitivity and 48.1% specificity; followed by TG/HDL-C (AUC: 0.649, 95% CI: 0.638−0.659), while Non-TG/HDL-C was the worst indicator (AUC: 0.630, 95% CI: 0.619−0.641) (all, $p < 0.05$). The DeLong test showing the difference between METS-IR and other indicators were all significant (all, $p< 0.05$) (Table 7).

Table 3 Pearson's Correlation Analysis of Different IR Indicators and eGFR Levels

IR Indicators	R	*p*
METS-IR	−0.393	<0.001
TyG	−0.353	<0.001
TG/HDL-C	−0.234	<0.001
Non-TG/HDL-C	−0.331	<0.001

https://doi.org/10.2147/DMSO.S527662

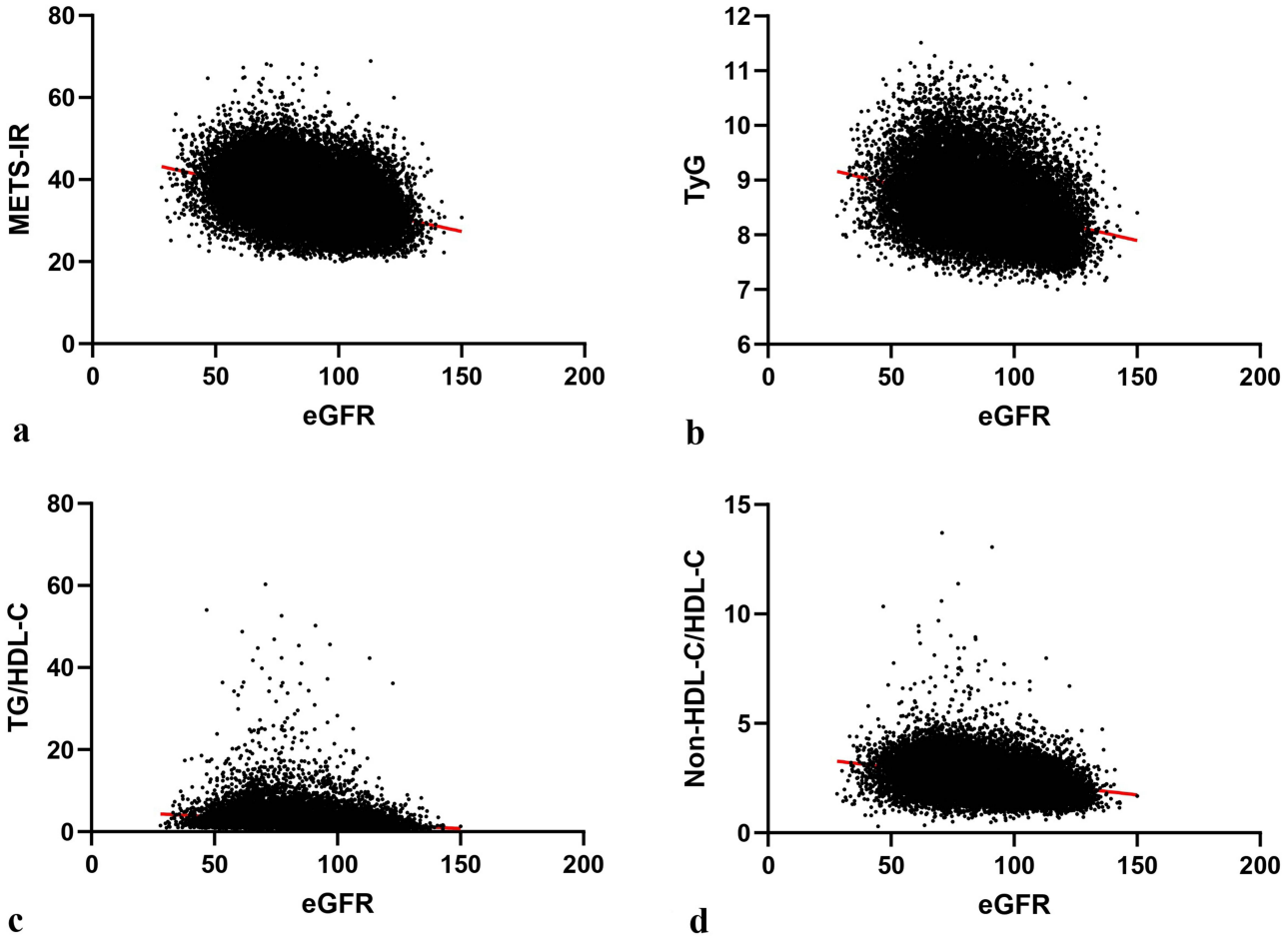

Figure 3 Pearson's analyses of the METS-IR, TyG, TG/HDL-C, and NonTG/HDL-C. (**a**) Pearson's analyses of the METS-IR and eGFR. (**b**) Pearson's analyses of the TyG and eGFR. (**c**) Pearson's analyses of the TG/HDL-C and eGFR. (**d**) Pearson's analyses of the Non-TG/HDL-C and eGFR.

Discussion

This retrospective cross-sectional study, involving 29,265 non-diabetic participants, demonstrated that all IR surrogate markers—including TyG, TG/HDL-C, and Non-TG/HDL-C—were negatively correlated with eGFR and positively associated with CKD incidence.

IR is a critical metabolic feature associated with the progression of CKD.[11] IR disrupts the insulin-dependent activation of the Akt signaling pathway in vascular and renal tissues, impairing endothelial nitric oxide synthase expression and nitric oxide (NO) bioavailability, which are critical for vascular tone regulation. While excessive NO exacerbates vascular inflammation and leukocyte adhesion through enhanced oxidative stress, IR-induced sodium

Table 4 Incidence of CKD Patients in Quartiles of METS-IR, TyG, TG/HDL-C and Non-TG/HDL-C

IR Indicators	Q1	Q2	Q3	Q4	*p* for trend
METS-IR	149(2.01)	423(5.71)	756(10.21)	1044(14.09)	<0.001
TyG	218(2.95)	482(6.58)	741(9.82)	931(12.65)	<0.001
TG/HDL-C	225(3.02)	481(6.56)	704(9.44)	962(13.01)	<0.001
Non-TG/HDL-C	283(3.79)	463(6.29)	705(9.58)	921(12.38)	<0.001

Table 5 Logistic Regression Analysis for the Association Between Insulin Resistance Indicators and CKD

IR Indicators	Q1	Q2		Q3		Q4	
		OR(95% CI)	*p*	OR(95% CI)	*p*	OR(95% CI)	*p*
METS-IR	≤30.60	30.6035.08		35.08~39.98		>39.98	
Model 1	1.00(ref)	2.947(2.438–3.562)	<0.001	5.536(4.630–6.620)	<0.001	7.983(6.702–9.509)	<0.001
Model 2	1.00(ref)	1.340(1.062–1.690)	0.014	1.650(1.283–2.122)	<0.001	1.910(1.411–2.585)	<0.001
Model 3	1.00(ref)	1.443(1.121–1.857)	<0.001	1.890(1.396–2.558)	<0.001	2.360(1.594–3.493)	<0.001
TyG	≤8.13	8.13~8.49		8.49~8.91		>8.91	
Model 1	1.00(ref)	2.317(1.967–2.728)	<0.001	3.585(3.071–4.184)	<0.001	4.768(4.098–5.546)	<0.001
Model 2	1.00(ref)	1.391(1.151–1.681)	0.001	1.507(1.257–1.806)	<0.001	1.681(1.404–2.012)	<0.001
Model 3	1.00(ref)	1.361(1.121–1.653)	0.002	1.452(1.200–1.759)	<0.001	1.709(1.398–2.091)	<0.001
TG/HDL-C	≤1.32	1.32~1.97		1.97~3.07		>3.07	
Model 1	1.00(ref)	2.253(1.917–2.648)	<0.001	3.344(2.868–3.900)	<0.001	4.800(4.136–5.571)	<0.001
Model 2	1.00(ref)	1.237(1.025–1.493)	0.026	1.359(1.134–1.629)	0.0001	1.692(1.414–2.025)	<0.001
Model 3	1.00(ref)	1.181(0.969–1.438)	0.099	1.259(1.028–1.540)	0.026	1.539(1.238–1.914)	<0.001
Non-TG/HDL-C	≤1.99	1.99~2.48		2.48~2.99		>2.99	
Model 1	1.00(ref)	1.704(1.464–1.982)	<0.001	2.690(2.334–3.100)	<0.001	3.585(3.125–4.113)	<0.001
Model 2	1.00(ref)	1.330(1.114–1.587)	0.002	1.596(1.351–1.887)	<0.001	1.702(1.443–2.006)	<0.001
Model 3	1.00(ref)	1.278(1.036–1.578)	0.022	1.485(1.149–1.919)	0.003	1.507(1.082–2.100)	0.015

Notes: Model 1 Crude. Model 2 Adjusted for sex, age, and BMI. Model 3 Adjusted for sex, age, BMI, hypertension, smoke, drink, FGP, HDL, LDL, and pulse.

Table 6 ROC Curve Analysis of Different IR Indicators, Which Were Predictive for CKD

IR Indicators	AUC (95% CI)	Cutoff Value	Sensitivity	Specificity	*p*
METS-IR	0.681(0.671–0.691)	34.355	80.2%	48.1%	<0.001
TyG	0.644(0.634–0.655)	8.535	67.7%	54.5%	<0.001
TG/HDL-C	0.649(0.638–0.659)	2.275	61.6%	60.6%	<0.001
Non-TG/HDL-C	0.630(0.619–0.641)	2.485	68.5%	51.9%	<0.001

retention and vasoconstriction further activate the renin-angiotensin-aldosterone system, exacerbating glomerular hyperfiltration and tubular injury.[4] Furthermore, recent molecular studies have elucidated the intricate physiological mechanisms linking IR to CKD pathogenesis, involving: 1) an enhanced inflammatory response, 2) endoplasmic reticulum stress and dysregulated glycoprotein metabolism, 3) cell-type-specific molecular alterations, and 4) glomerular hyperfiltration and hemodynamic stress.[11]

Our study demonstrates that the METS-IR, a composite index incorporating FPG, TG, HDL-C, and BMI, exhibits superior predictive performance for CKD compared to other IR surrogates (TyG, TG/HDL-C, and Non-TG/HDL-C), as evidenced by ROC curve analysis. These findings align with previous reports[7,12,13] while extending current knowledge through the first comprehensive comparison of these indices specifically in a non-diabetic population. The enhanced predictive capacity of METS-IR derives from its unique ability to simultaneously evaluate multiple metabolic pathways relevant to CKD pathogenesis: (1) visceral adiposity and systemic insulin resistance through BMI and FPG;[14] (2) lipid

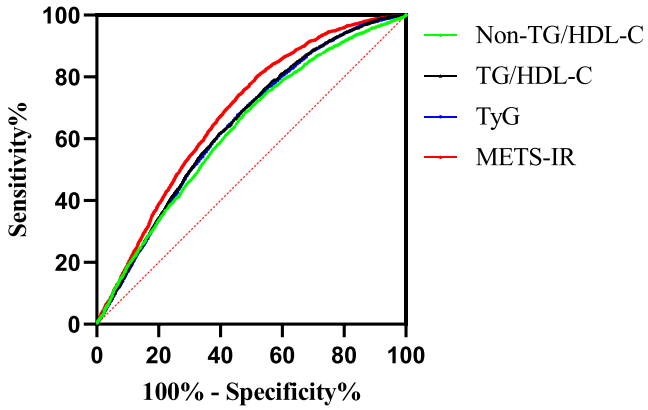

Figure 4 ROC Curves Comparing the Predictive Performance of the METS-IR, TyG TG/HDL-C and Non-TG/HDL-C for Chronic Kidney Disease (CKD) (Cohort: n = 29,265).

metabolism disturbances via TG and HDL-C measurements, capturing both lipid excess and clearance impairment; and (3) the interactive effects of glycolipid metabolism through combined FPG and TG assessment.[15] Importantly, METS-IR's incorporation of adiposity measures also indirectly reflects gut microbiota dysbiosis impacts on renal function,[16,17] a dimension absents in other indices. This comprehensive metabolic profiling contrasts with the more limited scope of TyG (FPG and TG only) or TG/HDL-C derivatives (lipid-focused). Furthermore, METS-IR's established validity for metabolic syndrome detection[18–20] proves particularly relevant given the kidney's established vulnerability to metabolic dysregulation.[12,21,22] Our eGFR-based findings further substantiate prior observations linking elevated METS-IR with accelerated renal function decline,[23,24] underscoring its clinical utility for early CKD risk stratification in at-risk populations.

Previous studies[6,25,26] have reported a nonlinear or U-shaped association between IR surrogate indicators and CKD, which is significantly different from the results of the present study. The possible reasons for this discrepancy may be the following: 1): As a potential mechanism to explain the difference in diabetic patients, the interplay of malnutrition, chronic inflammatory changes, and sarcopenia exacerbates oxidative stress and fibrosis through the synergistic effects of the hyperglycemia-IR axis and advanced glycation end-products. These mechanisms collectively contribute to a U-shaped association between IR surrogate indicators and CKD;[27–29] 2): As a limitation in statistical modeling, many linear studies analyzing the associations between IR surrogate indicators and CKD failed to use nonlinear analytical methods such as restricted cubic splines.[30] This omission may result in overlooking potential threshold effects where IR surrogate indicators initially increase CKD risk but decrease it beyond a certain point, or vice versa; and, 3): The differences among studies could also be attributed to a multitude of other factors, including heterogeneous study populations, divergent inclusion criteria, disparate lifestyle habits, and varying socioeconomic statuses. These discrepancies may also originate from genetic, environmental, or cultural differences among populations, which could influence both the prevalence and expression of diseases, as well as the responsiveness to interventions.

Table 7 DeLong Test for Receiver Operating Characteristic Curve Comparisons of Different Insulin Resistance Indicators

IR Indicators	Z	*p*
METS-IR vs. TyG	7.622	$p < 0.0001$
METS-IR vs. TG/HDL-C	7.678	$p< 0.0001$
METS-IR vs. Non-TG/HDL-C	9.187	$p < 0.0001$
TyG vs TG/HDL-C	1.731	0.0834
TyG vs Non-TG/HDL-C	2.623	0.0087
TG/HDL-C vs Non-TG/HDL-C	3.842	0.0001

The present study has several distinct advantages over prior research. First, it leveraged population-based sample survey data to report findings from real world clinical practice, thereby reflecting authentic clinical scenarios. Notably, the research identified significant associations between IR surrogate indicators and CKD in the non-diabetic population, even after adjusting for confounding variables. The findings suggested that IR surrogate indicators have promise as practical, direct measures for CKD treatment and management. Consequently, clinicians should prioritize the monitoring of both IR and renal function in at-risk populations. However, future studies are needed to establish a safe threshold for IR surrogate indicators, to guide pharmacological therapy in CKD patients, given the complexity of the disease and the presence of multiple comorbid risk factors, which may attenuate the relationships between IR surrogate indicators and CKD outcomes.

However, this study had some limitations. First, the inherent nature of retrospective cross-sectional studies may have resulted in the inability to establish temporal causality, and the results could therefore remain highly susceptible to various biases (selection bias, information bias, and confounding bias, etc). Second, the findings of this study could not be generalized to other populations, due to its restriction to a specific population. Third, prospective, multicenter studies with larger samples and longitudinal follow-ups evaluating multiple IR surrogate indicators are needed to confirm the evidence linking IR and CKD. Last but not least, this study is the lack of inclusion of inflammatory biomarkers such as C-reactive protein and neutrophil-to-lymphocyte ratio, which may influence the eGFR and confound the observed associations between IR surrogates and CKD.

Conclusions

In conclusion, our findings propose the METS-IR as a clinically actionable biomarker for CKD risk stratification in non-diabetic populations. Its superior predictive performance, cost-effectiveness, and operational simplicity support its integration into routine clinical workflows and preventive health strategies, particularly for early identification of high-risk individuals in primary care settings. Future research should focus on validating these findings in diverse populations and exploring the potential of METS-IR to guide personalized prevention strategies.

Acknowledgments

We wish to thank the study participants for their cooperation and participation.

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.

Funding

This study supported by the Medical Science Research Project of Hebei (No.20230505).

Disclosure

The authors report no conflicts of interest in this work.

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