

Relationship Between Cardiometabolic Index and Insulin Resistance in Patients with Type 2 Diabetes

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Purpose: Cardiometabolic index (CMI) has been suggested as innovative measures for assessing the cardiometabolic status. However, there is a lack of relevant studies on exploring the relationship between CMI and insulin resistance (IR). Consequently, this study aims to examine the relationship between CMI and IR in subjects with type 2 diabetes mellitus (T2DM).

Patients and Methods: A cross-sectional study was performed on 2493 patients with T2DM (including 1505 males and 988 females). IR was measured through the homeostatic model assessment of insulin resistance (HOMA-IR), which was defined as $HOMA-IR \geq 2.69$. The relationship between CMI and IR was evaluated with Spearman's correlation, ROC analysis, multiple logistic regression, generalized smooth curve fitting and subgroup analysis.

Results: CMI was correlated with HOMA-IR in patients with T2DM (Spearman correlation coefficient = 0.391 in females and 0.346 in males, $P < 0.001$). Through the multiple logistic regression analysis, CMI was significantly correlated with IR (OR=1.30, 95% CI=1.15–1.47 in males and OR=1.62, 95% CI=1.32–1.99 in females). In addition, a non-linear correlation between CMI and IR risk was identified. The AUC of CMI (AUC = 0.702 for males and 0.733 for females, all $p < 0.01$) was the largest compared with traditional indexes of adiposity and blood lipids. According to the subgroup analysis, the two had a more significantly positive correlation in females, the elderly and subjects with $HbA1c < 7\%$.

Conclusion: In patients with T2DM, elevated CMI is significantly correlated with IR, as a useful index of IR.

Keywords: high density lipoprotein cholesterol, cardiometabolic index, waist-to-height ratio, insulin resistance, type 2 diabetes mellitus

Introduction

Given that IR is recognized as a prominent factor in various pathological conditions, including diabetes mellitus, atherosclerosis, hypertension and metabolic syndrome (MetS), it is imperative to accurately assess IR. The hyperinsulinemic-euglycemic clamp is considered as a gold standard for measuring IR in studies.¹ However, its practicality is limited for routine clinical use due to issues of replicability, cost and accessibility.^{1–5} As a substitute, HOMA-IR is commonly employed in adults.⁶ Nevertheless, the calculation of HOMA-IR necessitates the measurement of fasting plasma insulin, which is not typically performed in clinical settings. Therefore, an accurate, simple and cost-effective diagnostic test is needed to predict IR.

The correlation between obesity, dyslipidemia and IR has been extensively documented in the literature.^{7,8} Specifically, the TG/HDL-C ratio has emerged as a valuable index for predicting the susceptibility to NAFLD and effectively evaluating IR in NAFLD.^{9–11} The Waist-to-height ratio (WHtR) is a composite measure that incorporates both height and waist circumference (WC). Compared with the conventional single-body measurement index, WHtR demonstrates superior capability in identifying abdominal obesity, assessing cardiac metabolic risk, IR and various noncommunicable diseases.^{12–15} Recently, Wakabayashi et al introduced a novel index known as CMI.¹⁶ CMI is calculated by multiplying WHtR with the TG/HDL-C ratio, thereby integrating lipid and obesity parameters into a straightforward and reproducible marker for the effective detection of NAFLD

and diabetes.^{16,17} Furthermore, a number of recent studies have demonstrated a strong relationship between CMI and various diseases affecting people's health conditions, such as stroke, hypertension, kidney diseases and cardiovascular diseases.^{18–21} These findings suggest that CMI is of great values as an index for metabolic diseases. However, there is currently a lack of relevant studies on exploring potential links between CMI and IR.

Therefore, this study aims to explore the relationship between IR and CMI in patients with T2DM through a comprehensive cross-sectional analysis and to determine whether CMI can be used as a novel and practical biomarker for diagnosing IR.

Materials and Methods

Study Design

In this cross-sectional study, 2493 patients with T2DM admitted to the Department of Endocrinology of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University between January 2020 to August 2022 were included. The study has received the approval from the hospital's ethical review committee (Approval Number: LCKY2020-01), and written consent was obtained from all patients with T2DM following the Declaration of Helsinki. Inclusion criteria encompassed a T2DM diagnosis based on WHO criteria, age of 20 years or older, and the availability of complete clinical and biochemical parameters data. Exclusion criteria included were (1) Patients with acute complications (diabetic ketoacidosis, diabetic hyperosmolar coma, or lactic acidosis); (2) Patients with recent history of surgery, trauma, severe infection, immune diseases, and malignant tumors; (3) Patients with T1DM, pregnancy, previous history of hyperthyroidism, hypothyroidism, cardiovascular diseases, kidney, liver and muscle diseases.

Anthropometric Measurements

The data collected upon admission included a history of hypertension, duration of diabetes mellitus (DD), hypoglycemic drugs, smoking habits, alcohol intake and physical measurements such as blood pressure, height, weight and WC. Specifically, the definitions of hypertension, smoking and alcohol status have been previously described in this study.²² Obesity and overweight were defined as $BMI \geq 28 \text{ kg/m}^2$ and $24 \text{ kg/m}^2 \leq BMI < 28 \text{ kg/m}^2$, respectively.

Biochemical Measurements

Blood samples were collected in patients on an empty stomach and 2h after breakfast on the second day of admission. LDL-C, alanine aminotransferase (ALT), glutamyl transpeptidase (GGT), HbA1c, UA, 2-h PPG, TC, 2-hour postprandial C-peptide (2h PCP), fasting C-peptide (FCP), albumin, TG, creatinine, HDL-C, FPG and aspartate transaminase (AST) were determined as previously described.²² Total number of missing values was less than 2%. Multiple imputation was performed for missing values.

Assessment of IR

HOMA-IR formula was used to evaluate IR. $HOMA-IR = 1.5 + FPG [\text{mmol/L}] \times FCP [\text{pmol/L}] / 2800$.²³ IR was defined as $HOMI-IR \geq 2.69$, based on an epidemiology survey conducted in China.^{24,25}

Cardiometabolic Index

It was worth noting that CMI was considered a continuous variable, and its calculation involved the formula $[WC (\text{cm}) / \text{height} (\text{cm})] \times [TG (\text{mmol/L}) / HDL-C (\text{mmol/L})]$.¹⁶

The non-insulin-based markers of IR were calculated based on previously reported formulas, as follows:²⁶

Visceral Adiposity Index (VAI) was calculated as follows:

For males: $VAI = WC / (39.68 + (1.88 \times BMI)) \times (TG / 1.03) \times (1.31 / HDL-C)$;

For females: $VAI = WC / (36.58 + (1.89 \times BMI)) \times (TG / 0.81) \times (1.52 / HDL-C)$.

Dysfunctional Adiposity Index (DAI) was calculated as follows:

For males: $DAI = WC / (22.79 + (2.68 \times BMI)) \times (TG / 1.37) \times (1.19 / HDL-C)$;

For Females: $DAI = WC / (24.02 + (2.37 \times BMI)) \times (TG / 1.32) \times (1.43 / HDL-C)$. Statistical Analysis

Differences in WhtR and CMI were observed between genders, leading to separate analyses of males and females. The normal distribution of the data were determined through Kolmogorov–Smirnov tests. For continuous variables, normally distributed data were expressed by means and standard deviations (SDs), while asymmetrically distributed data were expressed by medians (interquartile ranges, IQRs). To compare the two groups, the Mann–Whitney *U*-test or *t*-test was adopted for continuous variables, while chi-square test was employed for categorical variables. In addition, Spearman's correlation was utilized to explore the relationship between CMI and metabolic risk factors. Patients were divided into quartiles based on their CMI levels (≤ 0.49 , $0.49–0.79$, $0.79–1.27$, ≥ 1.27 in females, ≤ 0.53 , $0.53–0.86$, $0.86–1.54$, ≥ 1.54 in males), with the first quartile representing the lowest one (as reference group) and the fourth quartile representing the highest. A binary logistic regression model was employed to examine the relationship between CMI quartiles and IR. In Model 1, no covariate was adjusted. Model 2 was adjusted for BMI and age. Based on Model 2, DD, hypoglycemic drugs, SBP, DBP, HbA1c, serum creatinine, serum albumin, uric acid, ALT, AST, GGT, drinking and smoking were added to Model 3. Subgroup analysis was conducted to stratify the patients according to HbA1c, BMI, gender and age. In order to identify the potential non-linear relationship between CMI and IR probabilities, the generalized smooth curve fitting were adopted. The diagnostic efficacy of CMI in detecting IR was evaluated through the ROC curve analysis. The statistical analysis was conducted with EmpowerStats software and R, with the significance determined at $P < 0.05$.

Results

Characteristics of Participants

As depicted in Table 1, the prevalence of IR was found to be 18.1% of males and 21.1% of females. The HOMA-IR, proportion of subjects with hypertension and hypoglycemic drugs, weight, WC, BMI, WhtR, SBP, FPG, ALT, AST, GGT, creatinine, FCP, 2-h PCP, TG, uric acid and CMI levels was observed to be higher in patients with IR compared to those without IR of both genders ($P < 0.001$). Female subjects with IR were found to be significantly older than the non-IR subjects ($P < 0.001$). Additionally, IR subjects exhibited lower levels of LDL-C and HDL-C in comparison to non-IR subjects.

Table 1 Baseline Characteristics of the T2DM Patients Stratified by Insulin Resistance and Gender

	Male		P-value	Female		P-value
	IR positive	IR Negative		IR Positive	IR Negative	
N	231	1274		172	816	
Age, years	54.6±16.6	55.3±14.1	0.526	66.6±13.8	61.3±13.5	<0.001
Duration of diabetes, year	5.0±6.2	4.2±5.6	0.040	8.8±7.0	8.5±7.1	0.117
Hypertension, n (%)	58.6	42.0	<0.001	67.6	48.3	<0.001
Height, cm	169.8±6.3	169.0±7.3	0.113	155.9±6.0	156.8±6.8	0.116
Weight, kg	76.9±15.3	69.6±11.8	<0.001	62.7±10.4	59.0±10.1	<0.001
Body mass index, Kg/m ²	26.6±4.4	24.5±10.5	<0.001	25.7±3.6	24.1±7.3	0.006
Waist circumference, cm	92.7±12.7	88.2±22.2	0.003	88.5±10.5	84.6±11.1	<0.001
Waist-to-height ratio	0.55±0.07	0.52±0.13	0.009	0.57±0.07	0.54±0.08	<0.001
Systolic blood pressure, mmHg	146.4±23.6	139.1±26.7	<0.001	149.4±24.5	141.5±27.8	0.001
Diastolic blood pressure, mmHg	87.4±7.2	84.2±25.0	0.051	82.5±1.7	81.7±7.9	0.264
Current smoking, %	40.2	41.8	1.000	0	1.3	0.601
Current drinking, %	11.3	10.2	0.726	1.8	0	0.504
Metformin, %	53.5	37.4	<0.001	66.7	53.5	<0.001
α-glucosidase inhibitors, %	36.1	26.1	<0.001	49.0	29.1	<0.001
Thiazolidinediones, %	8.8	2.1	<0.001	11.8	5.8	<0.001
Hemoglobin A1c, mmol/L	8.9±2.2	9.5±2.3	0.001	8.6±1.7	9.5±2.3	<0.001

(Continued)

Table 1 (Continued).

	Male		P-value	Female		P-value
	IR positive	IR Negative		IR Positive	IR Negative	
FPG, mmol/L	8.1±2.3	6.3±1.7	<0.001	8.3±2.0	6.8±2.1	<0.001
2-h PPG, mmol/L	16.0±3.8	16.4±3.8	0.222	16.9±4.0	17.2±3.9	0.360
FCP, ng/mL	1.99±0.80	0.66±0.37	<0.001	1.94±0.73	0.65±0.37	<0.001
2-h PCP, ng/mL	4.63±2.51	2.53±1.82	<0.001	4.68±2.54	2.42±1.80	<0.001
HOMA-IR	3.32±0.69	2.00±0.29	<0.001	3.34±0.64	2.02±0.30	<0.001
Albumin, g/dl	41.0±5.5	40.4±4.2	0.081	41.4±6.2	39.8±3.6	<0.001
Creatinine, umol/L	100.9±79.1	74.6±28.9	<0.001	73.1±40.6	57.2±32.8	<0.001
Uric acid, umol/L	421.1±117.3	355.9±98.5	<0.001	377.4±123.8	300.4±89.3	<0.001
ALT, U/L	38.8±45.7	30.7±39.0	0.006	29.6±21.7	23.3±28.0	0.007
AST, U/L	31.9±40.7	25.1±19.6	<0.001	27.6±16.3	22.4±13.6	<0.001
GGT, U/L	66.2±83.9	51.5±117.3	0.076	50.1±60.1	29.6±49.4	<0.001
Total cholesterol, mmol/L	4.60±1.49	4.56±1.36	0.629	4.58±1.37	4.68±1.20	0.315
Triglycerides, mmol/L	2.88±3.24	1.98±1.98	<0.001	2.57±1.98	1.74±1.15	<0.001
HDL-cholesterol, mmol/L	0.94±0.33	0.99±0.28	0.019	1.00±0.29	1.14±0.31	<0.001
LDL-cholesterol, mmol/L	2.65±1.03	2.84±1.08	0.013	2.66±1.15	2.90±1.06	0.007
CMI	1.78±1.68	1.18±1.23	<0.001	1.63±1.42	0.93±0.76	<0.001

Notes: Values are mean±SD or number (%). P<0.05 was deemed significant (comparison between IR positive and IR negative).

Abbreviations: FPG, fasting plasma glucose; HDL-c, High density lipoprotein cholesterol; ALT, alanine aminotransferase; GGT, glutamyl transpeptidase; AST, aspartate transaminase; LDL-c, Low density lipoprotein cholesterol; 2-h PPG, 2-h postprandial plasma glucose; 2h PCP, 2-hour postprandial C-peptide; FCP, fasting C-peptide; HOMA, homeostatic model assessment of insulin resistance; CMI, cardiometabolic index.

Correlation Between CMI and Metabolic Parameters

The correlation between CMI and the metabolic parameters can be seen in [Table 2](#) with Spearman correlation. It was observed that in males, there was a positive correlation between CMI and BMI ($r=0.429$), WC ($r=0.388$), DBP ($r=0.166$), HbA1c ($r=0.094$), TC ($r=0.228$), FPG ($r=0.098$), FCP ($r=0.363$) and HOMA-IR ($r=0.346$). In females, BMI ($r=0.322$), WC ($r=0.344$), SBP ($r=0.076$), DBP ($r=0.141$), TC ($r=0.152$), FPG ($r=0.141$), FCP ($r=0.397$) and HOMA-IR ($r=0.391$) were correlated with CMI (all $P<0.001$) ([Table 2](#)).

Table 2 Spearman's Correlation of CMI Levels with Clinical and Biochemical Parameters

Variable	Male		Female	
	r	P	r	p
BMI	0.429	<0.001	0.322	<0.001
WC	0.388	<0.001	0.344	<0.001
SBP	0.033	0.201	0.076	0.017
DBP	0.166	<0.001	0.141	<0.001
HbA1c	0.094	0.001	0.024	0.503
TC	0.228	<0.001	0.152	<0.001
LDL-C	-0.002	0.946	0.038	0.231
FPG	0.098	<0.001	0.141	<0.001
FCP	0.363	<0.001	0.397	<0.001
HOMA-IR	0.346	<0.001	0.391	<0.001

Abbreviations: BMI, body weight index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; FPG, fasting plasma glucose; FCP, fasting C-peptide; HOMA, homeostatic model assessment of insulin resistance; CMI, cardiometabolic index.

Table 3 Association of the Insulin Resistance with CMI Quartiles

	Crude Model		Model I		Model II	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Male						
Q1	Ref		Ref		Ref	
Q2	1.70 (0.98–2.96)	0.060	1.67 (0.96–2.91)	0.068	1.65(0.89–3.07)	0.112
Q3	2.75 (1.63–4.63)	<0.001	2.72 (1.61–4.58)	<0.001	2.97(1.68–5.25)	<0.001
Q4	4.70 (2.91–7.59)	<0.001	4.67 (2.87–7.61)	<0.001	3.91(2.19–6.98)	<0.001
Female						
Q1	Ref		Ref		Ref	
Q2	2.14 (1.12–4.08)	0.021	1.99 (1.04–3.82)	0.039	1.16(0.59–2.26)	0.668
Q3	4.02 (2.20–7.38)	<0.001	3.54 (1.92–6.54)	<0.001	2.56(1.40–4.68)	0.002
Q4	6.87 (3.82–12.38)	<0.001	6.45 (3.55–11.71)Ⓢ	<0.001	2.87 (1.49–5.52)	0.002

Notes: Crude model: adjusted for none. Model I: adjusted for age and BMI. Model II: adjusted for age, BMI, DD, hypoglycemic drugs, SBP, DBP, HbA1c, serum creatinine, serum albumin, uric acid, ALT, AST, GGT, drinking, smoking.

Abbreviations: BMI, body mass index; DD, duration of diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; ALT, alanine aminotransferase; GGT, glutamyl transpeptidase; AST, aspartate transaminase; CMI, cardiometabolic index.

Correlation Between CMI and IR

Table 3 presents the results of binary logistic analysis examining the relationship between CMI and IR in patients with T2DM. The analysis was adjusted for BMI, age (Model 2), DD, hypoglycemic drugs, SBP, DBP, HbA1c, serum creatinine, serum albumin, uric acid, ALT, AST, GGT, drinking and smoking (Model 3), higher CMI quartiles was correlated with an increased risk of IR ($P < 0.001$). Moreover, a positive correlation was also observed in the non-linear relationship between CMI and IR assessed by smooth curve fittings (Figure 1).

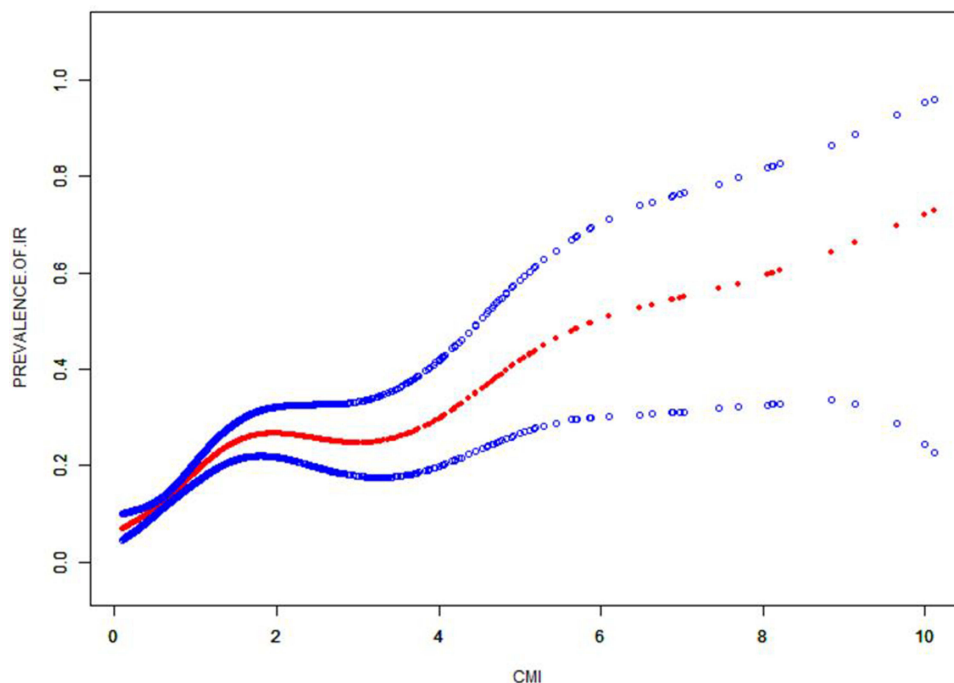


Figure 1 The smooth curve fit for the association between CMI and prevalence of IR. Solid redline represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Adjusted for: age, BMI, DD, hypoglycemic drugs, SBP, DBP, HbA1c, serum creatinine, serum albumin, uric acid, ALT, AST, GGT, drinking and smoking.

Subgroup Analysis to Assess the Relationship Between CMI and IR

To evaluate the impact of subgroups on the relationship between CMI and IR, subgroup analyses were conducted based on age, BMI, HbA1c and gender (Table 4). It was found that the p values for the subgroups were less than 0.005. CMI was independently correlated with IR, and this independently relationship was more obvious in female patients with T2DM, with age \geq 60 years old and HbA1c $<$ 7%. In addition, when the non-linear relationship was characterized by smooth curve fittings, the positive correlation between CMI and IR did survive in most groups (Figure 2).

The Predictive Value of CMI for IR

The ROC of CMI, TG/HDL, WHtR, VAI, DAI, BMI, WC and uric acid to diagnose IR is shown in Figure 3. Table 5 shows that the AUC for CMI in the ROC analysis was 0.702 (95% CI: 0.665–0.738) in males, 0.733 (95% CI: 0.690–0.777) in females, which was considerably higher than that of TG/HDL, WHtR, VAI, DAI, BMI, WC and uric acid ($P < 0.001$), suggesting that CMI may be a better index for IR than traditional indexes of adiposity and blood lipids, although its diagnostic accuracy is still somewhat limited.

Discussion

In this study, compelling evidence were presented supporting a positive correlation between CMI and an increase in HOMA-IR and the risk of IR among a large cohort of patients with T2DM. This relationship remains consistent across various demographic factors, including age, BMI, gender and HbA1c. Furthermore, the findings reveal a non-linear relationship between CMI and the risk of IR.

The analysis on the ROC indicates that CMI outperforms TG/HDL, WHtR, VAI, DAI, BMI, WC and uric acid in detecting IR, suggesting that CMI serves as a highly specific and sensitive marker for IR. CMI represents a novel clinical marker that combines the measurements of TG/HDL-C ratio and WHtR. Wakabayashi et al discovered it for the first time in 2015, which proved its important role in evaluating DM.¹⁶ Subsequent investigations have expanded upon this finding, revealing a strong correlation between CMI and conditions such as cardiovascular disease, hypertension, kidney disease and stroke,^{18–21} which indicates its potential as a metabolic disease index. Nevertheless, there is currently a dearth of data regarding the relationship between CMI and IR. In this sense, this study has successfully confirmed the relationship between CMI and IR in patients with T2DM, utilizing a substantial sample size for the first time.

Table 4 Association Between CMI and Insulin Resistance Stratified by Age, BMI and Hypertension

	OR (95% CI) p Value	P for Interaction
Stratified by gender		0.029
Male	1.30 (1.15–1.47), <0.001	
Female	1.62 (1.32–1.99), <0.001	
Stratified by age		0.016
Age $<$ 60 years old	1.23 (1.08, 1.41), 0.003	
Age \geq 60 years old	1.74 (1.43, 2.12), <0.001	
Stratified by BMI		0.142
BMI $<$ 24kg/m ²	1.65 (1.33, 2.03), <0.001	
BMI \geq 24kg/m ²	1.26 (1.11, 1.42), <0.001	
Stratified by HbA1c		0.020
HbA1c $<$ 7%	2.33 (1.43, 3.80), 0.001	
HbA1c \geq 7%	1.35 (1.21, 1.50), <0.001	

Notes: Gender, age, BMI, hypertension (not adjusted for in the subgroup analyses), DD, hypoglycemic drugs, serum creatinine, serum albumin, uric acid, ALT, AST, GGT, drinking, smoking were adjusted.

Abbreviations: BMI, body mass index; DD, duration of diabetes mellitus; ALT, alanine aminotransferase; GGT, glutamyl transpeptidase; AST, aspartate transaminase; CMI, cardiometabolic index.

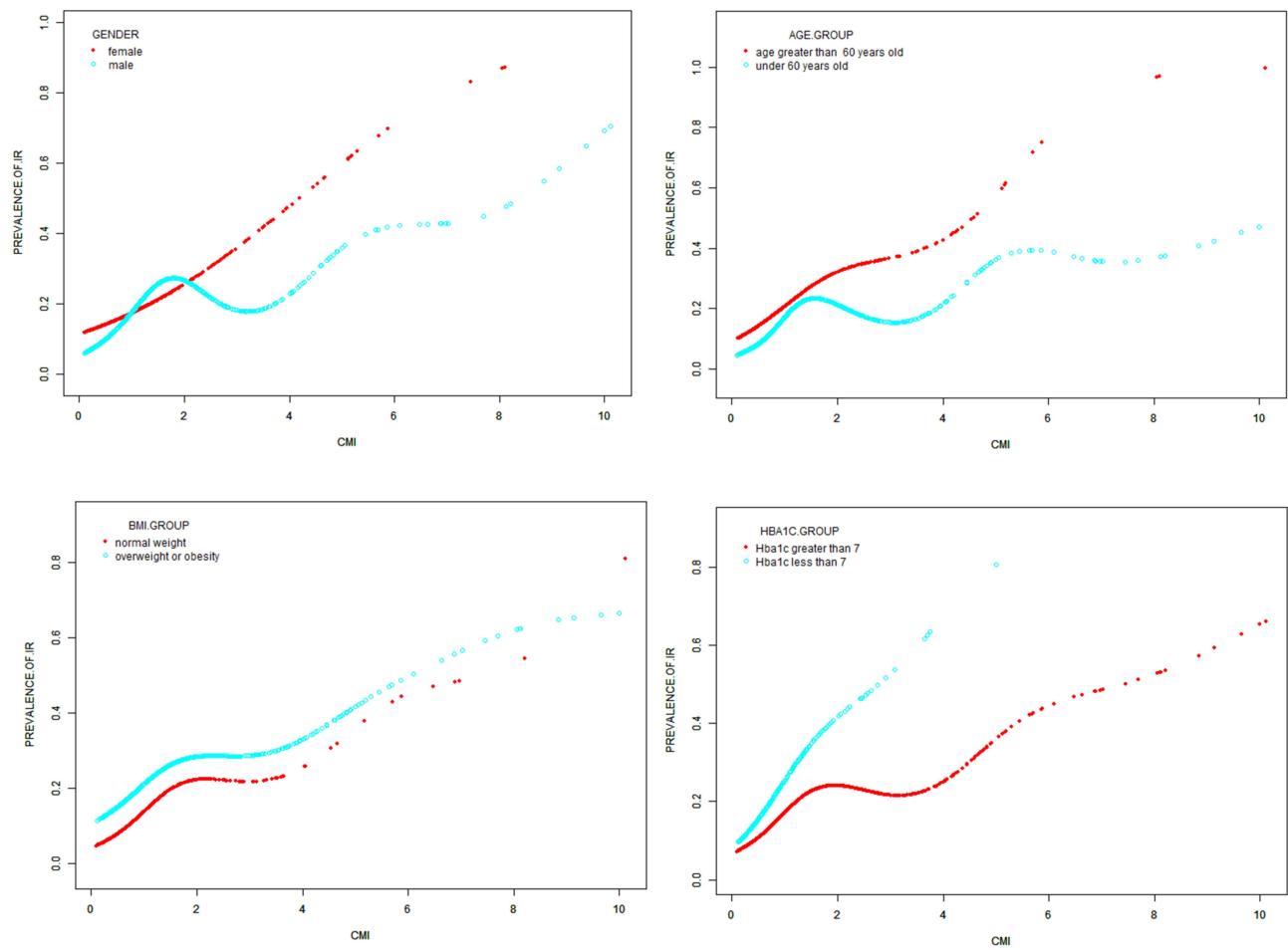


Figure 2 Subgroups analysis for the association between CMI and prevalence of IR by gender, age, BMI and HbA1c level.

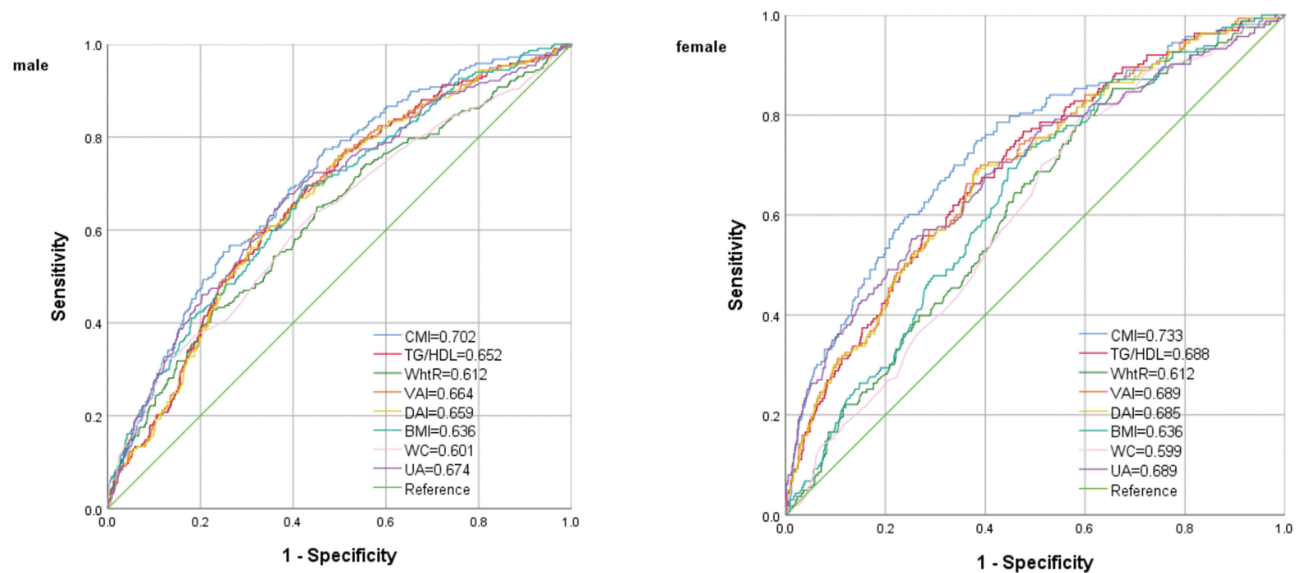


Figure 3 Receiver operating characteristic curves of TG/HDL, WhtR, VAI, DAI, BMI, WC and uric acid to identify IR.

Table 5 The Results of ROC Analysis of CMI, TG/HDL, WHtR, VAI, DAI, BMI, WC and Uric Acid for the Diagnosis of IR

Nutritional Indices	Cut-off	Sensitivity (%)	Specificity (%)	AUC	95% CI
Male					
CMI	0.77	77.5	53.3	0.702	0.665–0.738
TG/HDL	1.49	76.6	48.4	0.652	0.615–0.688
WHtR	0.55	42.4	76.6	0.612	0.571–0.653
VAI	1.93	77.4	48.0	0.664	0.615–0.689
DAI	1.30	76.5	48.3	0.659	0.610–0.684
BMI	24.6	68.0	57.7	0.658	0.620–0.697
WC	98.8	69.3	88.0	0.616	0.574–0.658
UA	368.5	67.7	61.1	0.674	0.634–0.714
Female					
CMI	0.89	74.8	61.9	0.733	0.690–0.777
TG/HDL	1.63	66.3	62.1	0.688	0.645–0.731
WHtR	0.52	79.7	40.4	0.612	0.568–0.656
VAI	3.09	68.6	61.8	0.689	0.642–0.729
DAI	1.79	68.6	61.2	0.685	0.638–0.725
BMI	23.7	73.3	50.6	0.638	0.595–0.681
WC	81.8	79.1	40.7	0.599	0.555–0.643
UA	347.5	55.2	74.7	0.689	0.642–0.737

Abbreviations: CMI, cardiometabolic index; TG/HDL, triglycerides/ high density lipoprotein cholesterol; WHtR, waist-to-height ratio; VAI, visceral Adiposity Index; DAI, dysfunctional Adiposity Index; BMI, body mass index; WC, waist circumference; UA, uric acid.

The distribution of body fat accumulation plays a significant role in the development of DM and progression of IR, as indicated by previous studies.^{27,28} Previous studies have established a robust correlation between various conventional obesity indexes, such as BMI and WC, and IR. Moreover, the WHtR and WC have been proposed as superior measures to BMI in identifying cardiovascular risk factors, including IR and T2DM.^{13,14} The TG/HDL-C ratio is a reliable and simple measurement of IR that has been extensively studied in relation to T2DM.^{13,29,30} In summary, when combined with WHtR and TG/HDL-C, it is believed that CMI can provide a comprehensive assessment of obesity and dyslipidemia, thus making it a practical tool for identifying IR. As shown in Figure 3, the results showed that CMI had the largest AUC compared with TG/HDL, WHtR, BMI and WC, indicating its superior performance in detecting IR.

Previous studies have also highlighted the relationship between CMI and various metabolic-inflammatory diseases. For instance, a study conducted by Ichiro Wakabayashi et al examined a cohort of 10,196 subjects undergoing health check-ups and found a positive correlation between elevated CMI values and hyperglycemia and risk of diabetes.¹⁶ Zou et al discovered that CMI could effectively predict NAFLD in general population in Japanese.³¹ Luo et al found that high CMI values were positively associated with incident cardiovascular disease in patients with obstructive sleep apnea and hypertension.³² Sun et al investigated 11,956 rural residents in China and found that CMI is independently and positively associated with the risk of ischemic stroke.²⁰ Another study by Alleva demonstrated a significant positive correlation between CMI and metabolic syndrome in females suffering from obesity.³³ The findings align with these previous studies, as a correlation between CMI and various factors including BMI, WC, DBP, TC and FPG was observed in patients with T2DM, albeit the correlation is not strong. These results highlight the potential value of CMI in future clinical applications and warrant further promotion.

Age, HbA1c and BMI were significantly correlated with HOMA-IR. Therefore, further subgroup analysis showed a significant interaction between HbA1c levels, age and gender between CMI and IR risk. The study revealed that the correlations were more pronounced in female participants, those who were older, and those with HbA1c levels below 7%. Importantly, for the above population, IR is often neglected. Consequently, CMI should be recognized as a crucial determinant for identifying IR, particularly in this population.

IR was associated with long term damage to organs, especially eyes, kidney, nerves and the heart in patients with T2DM.³⁴ CMI usage is simple and low cost, which has a strong correlation with IR and has some predictive power. This allows clinicians to find IR in a timely manner in clinical work to delay or even prevent the development of diabetes mellitus. It will improve the T2DM patient's life and life treatment and save economic costs.

The specific mechanism through which CMI contributes to IR remains unclear. The observed relationship between abnormal lipid metabolism and subjects with assessed CMI may provide an explanation for these findings. In the case of obese subjects with a high WhtR, an excess of free fatty acids can impede insulin's function in glucose metabolism, thereby leading to the development of IR.³⁵ Additionally, subjects with abdominal obesity may experience a decrease in binding affinity and reduction in the quantity of insulin receptors on target tissues, resulting in a diminished capacity to respond to glucose.^{36,37} Moreover, an elevated triglyceride (TG) status plays a role in the development of IR similar to that of abdominal obesity. Additionally, reduced levels of HDL-C may adversely affect the functioning of beta cells, and lead to decreased insulin output and sensitivity.^{37,38} In summary, there exists a "vicious cycle" between IR and high CMI.

The advantage of this study is that we have well characterized the subjects on a large population basis and tested whether there are differences in CMI and IR among different populations through subgroup analysis, thereby enhancing the dependability of the findings. Nevertheless, certain limitations should be acknowledged. Firstly, the establishment of a causal relationship between CMI and IR is precluded by the utilization of cross-sectional research design. Secondly, the adoption of the HOMA-IR was proposed as an evaluation tool. However, it is important to note that HOMA-IR has been associated with FPG, which exhibits a strong correlation with hepatic IR, but not to muscle IR.³⁹ Additional research is necessary to investigate the relationship between CMI and IR with the gold standard hyperinsulinemic-euglycemic clamp. Moreover, it is important to note that the research population was limited to subjects with T2DM. Consequently, a prospective cohort study involving a larger and more diverse population, including subjects without DM, is needed to validate and promote the current findings, and this correlation with IR that could support further evidence for the treatment of diabetes in primary prevention.

Conclusion

In summary, the extensive cross-sectional study demonstrates that CMI serves as a novel and useful biomarker for biochemical and anthropometric parameters, exhibiting an independent and positive correlation with IR, and appears to have higher IR AUC values than traditional indexes of adiposity and blood lipids.

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Disclosure

The author(s) report no conflicts of interest in this work.

References

1. Tam CS, Xie W, Johnson WD, Cefalu WT, Redman LM, Ravussin E. Defining insulin resistance from hyperinsulinemic-euglycemic clamps. *Diabetes Care*. 2012;35(7):1605–1610. doi:10.2337/dc11-2339
2. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27(6):1487–1495. doi:10.2337/diacare.27.6.1487
3. Espinel-Bermudez MC, Robles-Cervantes JA, Del Sagrario Villarreal-Hernandez L, et al. Insulin resistance in adult primary care patients with a surrogate index, Guadalajara, Mexico. *J Investig Med*. 2012;63(2015):247–250. doi:10.1097/JIM.0000000000000130
4. Borai A, Livingstone C, Ferns GA. The biochemical assessment of insulin resistance. *Ann Clin Biochem*. 2007;44(4):324–342. doi:10.1258/000456307780945778
5. Rudvik A, Mansson M. Evaluation of surrogate measures of insulin sensitivity – correlation with gold standard is not enough. *BMC Med Res Methodol*. 2018;18(1):64. doi:10.1186/s12874-018-0521-y
6. Burke JP, Hale DE, Hazuda HP, Stern MP. A quantitative scale of acanthosis nigricans. *Diabetes Care*. 1999;22(10):1655–1659. doi:10.2337/diacare.22.10.1655
7. Katsiki N, Mikhailidis DP, Mantzoros CS. Non-alcoholic fatty liver disease and dyslipidemia: an update. *Metabolism*. 2016;65(8):1109–1123. doi:10.1016/j.metabol.2016.05.003
8. Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: from pathophysiology to therapeutics. *Metabolism*. 2019;92:82–97. doi:10.1016/j.metabol.2018.11.014

9. Fan N, Peng L, Xia Z, et al. Triglycerides to high-density lipoprotein cholesterol ratio as a surrogate for nonalcoholic fatty liver disease: a cross-sectional study. *Lipids Health Dis.* 2019;18(1):39. doi:10.1186/s12944-019-0986-7
10. Fukuda Y, Hashimoto Y, Hamaguchi M, et al. Triglycerides to high-density lipoprotein cholesterol ratio is an independent predictor of incident fatty liver; a population-based cohort study. *Liver Int.* 2016;36(5):713–720. doi:10.1111/liv.12977
11. Kim-Dorner SJ, Deuster PA, Zeno SA, Remaley AT, Poth M. Should triglycerides and the triglycerides to high-density lipoprotein cholesterol ratio be used as surrogates for insulin resistance? *Metabolism.* 2010;59:299–304. doi:10.1016/j.metabol.2009.07.027
12. Tomas Z, Skaric-Juric T, Zajc Petranovic M, Jalsovec M, Rajic Sikanjic P, Smolej Narancic N. Waist to height ratio is the anthropometric index that most appropriately mirrors the lifestyle and psychological risk factors of obesity. *Nutr Diet.* 2019;76:539–545. doi:10.1111/1747-0080.12520
13. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev.* 2012;13:275–286. doi:10.1111/j.1467-789X.2011.00952.x
14. Correa MM, Thume E, De Oliveira ER, Tomasi E. Performance of the waist-to-height ratio in identifying obesity and predicting non-communicable diseases in the elderly population: a systematic literature review. *Arch Gerontol Geriatr.* 2016;65:174–182. doi:10.1016/j.archger.2016.03.021
15. Sheng G, Xie Q, Wang R, Hu C, Zhong M, Zou Y. Waist-to-height ratio and non-alcoholic fatty liver disease in adults. *BMC Gastroenterol.* 2021;21:239. doi:10.1186/s12876-021-01824-3
16. Wakabayashi I, Daimon T. The “cardiometabolic index” as a new marker determined by adiposity and blood lipids for discrimination of diabetes mellitus. *Clin Chim Acta.* 2015;438:274–278. doi:10.1016/j.cca.2014.08.042
17. Shi WR, Wang HY, Chen S, Guo XF, Li Z, Sun YX. Estimate of prevalent diabetes from cardiometabolic index in general Chinese population: a community-based study. *Lipids Health Dis.* 2018;17:236. doi:10.1186/s12944-018-0886-2
18. Dursun M, Besiroglu H, Otunctemur A, Ozbek E. Association between cardiometabolic index and erectile dysfunction: a new index for predicting cardiovascular disease. *Kaohsiung J Med Sci.* 2016;32:620–623. doi:10.1016/j.kjms.2016.10.003
19. Wang H, Chen Y, Guo X, Chang Y, Sun Y. Usefulness of cardiometabolic index for the estimation of ischemic stroke risk among general population in rural China. *Postgrad Med.* 2017;129:834–841. doi:10.1080/00325481.2017.1375714
20. Wang H, Chen Y, Sun G, Jia P, Qian H, Sun Y. Validity of cardiometabolic index, lipid accumulation product, and body adiposity index in predicting the risk of hypertension in Chinese population. *Postgrad Med.* 2018;130(3):325–333. doi:10.1080/00325481.2018.1444901
21. Wang HY, Shi WR, Yi X, Wang SZ, Luan SY, Sun YX. Value of reduced glomerular filtration rate assessment with cardiometabolic index: insights from a population-based Chinese cohort. *BMC Nephrol.* 2018;19(1):294. doi:10.1186/s12882-018-1098-8
22. Su X, Xu J, Zheng C. The relationship between non-alcoholic fatty liver and skeletal muscle mass to visceral fat area ratio in women with type 2 diabetes. *BMC Endocr Disord.* 2019;19(1):76. doi:10.1186/s12902-019-0404-1
23. Fan H. Influence of islet function on typing and prognosis of new-onset diabetes after intensive insulin therapy. *Med Sci Monit.* 2013;19:787–793. doi:10.12659/MSM.889099
24. Zhou X, Xu J. Association between serum uric acid-to-high-density lipoprotein cholesterol ratio and insulin resistance in patients with type 2 diabetes mellitus. *J Diabetes Investig.* 2023; 2023: 1.
25. Zhou M, Zhu L, Cui X, et al. The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio as a predictor of insulin resistance but not of beta cell function in a Chinese population with different glucose tolerance status. *Lipids Health Dis.* 2016;15(1):104. doi:10.1186/s12944-016-0270-z
26. Jayedi A, Soltani S, Motlagh SZ, et al. Anthropometric and adiposity indicators and risk of type 2 diabetes: systematic review and dose-response meta-analysis of cohort studies. *BMJ.* 2022;376:e067516. doi:10.1136/bmj-2021-067516
27. Wang K, Gong M, Xie S, et al. Nomogram prediction for the 3-year risk of type 2 diabetes in healthy mainland China residents. *EPMA J.* 2019;10(3):227–237. doi:10.1007/s13167-019-00181-2
28. Golubnitschaja O, Costigliola V. General report & recommendations in predictive, preventive and personalized medicine 2012: white paper of the European association for predictive, preventive and personalised medicine. *EPMA J.* 2012;3(1):14. doi:10.1186/1878-5085-3-14
29. Lim TK, Lee HS, Lee YJ. Triglyceride to HDL-cholesterol ratio and the incidence risk of type 2 diabetes in community dwelling adults: a longitudinal 12-year analysis of the Korean genome and epidemiology study. *Diabet Res Clin Pract.* 2020;163:108150. doi:10.1016/j.diabres.2020.108150
30. Zheng D, Li H, Ai F, et al. Association between the triglyceride to high-density lipoprotein cholesterol ratio and the risk of type 2 diabetes mellitus among Chinese elderly: the Beijing longitudinal study of aging. *BMJ Open Diabetes Res Care.* 2020;8(1):e000811. doi:10.1136/bmjdr-2019-000811
31. Zou J, Xiong H, Zhang H, Hu C, Lu S, Zou Y. Association between the cardiometabolic index and non-alcoholic fatty liver disease: insights from a general population. *BMC Gastroenterol.* 2022;22(1):20. doi:10.1186/s12876-022-02099-y
32. Cai X, Hu J, Wen W, et al. Associations of the cardiometabolic index with the risk of cardiovascular disease in patients with hypertension and obstructive sleep apnea: results of a longitudinal cohort study. *Oxid Med Cell Longev.* 2022;2022:4914791. doi:10.1155/2022/4914791
33. Lazzar S, D’Alleva M, Isola M, et al. Cardiometabolic Index (CMI) and Visceral Adiposity Index (VAI) highlight a higher risk of metabolic syndrome in women with severe obesity. *J Clin Med.* 2023;12(9):3055. doi:10.3390/jcm12093055
34. Chawla A, Chawla R, Jaggi S. Microvascular and macrovascular complications in diabetes mellitus: distinct or continuum? *Indian J Endocrinol Metab.* 2016;20(4):546–551. doi:10.4103/2230-8210.183480
35. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature.* 2006;444(7121):840–846. doi:10.1038/nature05482
36. Barazzoni R, Gortan Cappellari G, Ragni M, Nisoli E. Insulin resistance in obesity: an overview of fundamental alterations. *Eat Weight Disord.* 2018;23(2):149–157. doi:10.1007/s40519-018-0481-6
37. Sharma AM, Lau DC. Obesity and type 2 diabetes mellitus. *Can J Diabetes.* 2013;37(2):63–64. doi:10.1016/j.cjcd.2013.03.360
38. Goodpaster BH, Kelley DE. Skeletal muscle triglyceride: marker or mediator of obesity-induced insulin resistance in type 2 diabetes mellitus? *Curr Diab Rep.* 2002;2(3):216–222. doi:10.1007/s11892-002-0086-2
39. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985;28(7):412–419. doi:10.1007/BF00280883

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