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Association of Cardiometabolic Index with Cardiometabolic Continuum Across Healthy, Type 2 Diabetes Mellitus and Cardiovascular Disease Groups in Rural South India.

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ABSTRACT:

Background: The Cardiometabolic index (CMI), a composite marker that combines atherogenic dyslipidemia, mainly triglyceride to high density lipoprotein cholesterol (TG/HDL-C) ratio, with central adiposity, is determined by the waist to height ratio (WHtR). The objective of this study was to examine the diagnostic performance, gender specificity and progressive increase of CMI throughout the cardiometabolic disease continuum (Healthy controls and the study groups).

Methodology: A total of 250 participants were included in this cross-sectional study, categorized into three study groups- Healthy controls (n=50), Type 2 Diabetes mellitus (n=100) and Type 2 diabetes with cardiovascular complications(n=100). Standard biochemical and anthropometrics were recorded. The Kruskal- Walli's test with post hoc pairwise comparison was used to examine the differences in CMI across the study groups. The main and interactive effects of clinical groups and gender on CMI values were assessed by two-way ANOVA. The disease severity was modeled using linear regression and the diagnostic performance of CMI was evaluated using Receiver Operating Characteristic (ROC) curve analysis.

Results: Study participants were grouped into three study categories, across the groups progressive increase in CMI was exhibited, ranging from 1.13 ± 0.56 in healthy controls to 3.29 ± 2.56 and 4.48 ±2.09 in T2DM and T2DM +CVD groups respectively (x^2= 117.9, df=2, $p<0.001$) also significant difference across all groups ($p<0.001$) was observed. A two-way ANOVA demonstrated that clinical group showed significant effect on CMI ($F=10.368$, $p<0.001$), but neither gender nor the group x gender interaction were significant. Linear regression showed an independent positive association between CMI

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and disease severity (β=1.60, p<0.001; R2= 0.244). ROC analysis of controls vs T2DM (AUC=0.908), and T2DM+ CVD vs controls (AUC=0.986), exhibited significant discrimination between the groups. Whereas in T2DM vs T2DM+CVD, CMI demonstrated a moderate degree of discrimination (AUC=0.721).

Conclusion: CMI is progressively rising and gender independent biomarker that effectively mirrors clinical severity across cardiometabolic continuum by providing excellent sensitivity and specificity in detecting diabetic and macrovascular complications. Additionally, further clinical follow up finds uncomplicated T2DM patients at imminent risk of cardiovascular complications, enabling timely, targeted cardioprotective therapeutic interventions.

INTRODUCTION

Type 2 diabetes mellitus primarily marked by insulin resistance and reduced insulin production is a chronic metabolic disorder results in lipid abnormalities by significantly elevating the triglycerides and lowering the high-density cholesterol (HDL) that heighten the risk of cardiovascular complications (1,2). Therefore, assessment of cardiometabolic risk using markers that integrate multiple components of this process provide more comprehensive representation of disease burden than individual anthropometric and biochemical measures (3). Over time, several such indices have been introduced, like Body Mass Index (BMI) which is currently the most widely used in clinical settings. But a certain drawback of BMI is that it provides no information on fat distribution and also fails to distinguish between fat mass and lean mass both of which are key indicators of cardiometabolic risk (4). However, these shortcomings, alternative measurements have been developed, incorporating either anthropometric data solely or combined with lipid profiles.

Cardiometabolic Index (CMI) is one of the alternative indices that integrates indicators of central body fat- specifically the waist to height ratio (WHtR) with markers of atherogenic dyslipidemia measured as the triglyceride to HDL cholesterol ratio (TG/HDL-C), to assess visceral fat dysfunction and overall cardiometabolic risk (5). CMI may be considered the straightforward and low-cost method for detecting various metabolic conditions. Recent studies comparing CM to traditional measures like BMI and waist circumference in predicting multiple cardiometabolic diseases suggest that CMI performs as well as or better than these conventional metrics (6).

CMI frequently exhibits gender specific patterns throughout the nature and magnitude of these associations vary in fat distribution, lipid metabolism, and metabolic traits may affect how anthropometric and biochemical markers relate to later cardiometabolic outcomes (7). Some recent studies have reported stronger correlations in women, particularly for risks such as all cause of mortality, cardiovascular death and diabetes related mortality. In contrast, other research has identified significant links between CMI and conditions like cardiovascular disease in both genders, although the strength of these associations may differ between genders (7). This aligns with growing evidence that newer index such as CMI tend to be more effective than standard anthropometric measurement forecasting adverse health outcomes. Although earlier research studies has exhibited link between CMI and separate cardiometabolic conditions, there is limited evidence on progressive increase of CMI across clinical continuum from metabolically healthy individuals to T2DM and then too T2DM with cardiovascular disease.

METHODS AND METHODOLOGY

Study Design and Participants

This cross-sectional study involved 250 participants aged 35 to 65 years, recruited from the outpatient departments of General Medicine, Endocrinology, at Adichunchanagiri Hospital and Research Centre. Both men and women were included and divided into three groups: 50 controls, 100 individuals with T2DM and 100 with both T2DM and CVD. Patients with T1DM, autoimmune disorders, psychiatric disorders, primary hypertension, pregnant women and those with gestational diabetes (GDM), also individuals suffering from chronic diseases like cancer, end stage renal disease, thyroid disorders and liver diseases were excluded from the study. Anthropometric measurements were recorded, which included information on height, weight, and waist circumference along with demographic data such as age and gender were also documented. Biochemical samples were appropriately managed and preserved. The study has been discussed and approved by the Adichunchanagiri Institute of Medical Sciences Institutional Ethical Committee bearing registration number EC/NEW/INST/2023/KA/0382.

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Data collection

All the study participant's anthropometric measurements; height, weight and waist circumference were recorded by trained medical professionals. BMI and waist circumference were also noted. Venous samples were collected after an overnight fasting to ensure accurate biochemical measurements. Approximately 3 mL of fasting blood sample was collected for biochemical analysis. Serum sample was used for estimation of lipid profile, and plasma was used for glucose estimation by fully automatic Beckman Coulter AU480 Chemistry Analyzer. Another, 3 mL sample was allocated to an EDTA tube for HbA1c estimation using fully automatic CKK A1c- HPLC analyser.

CMI was calculated using the following formula (8):

CMI = TG (mmol/L)/HDL-C (mmol/L) x WHtR. Where, WHtR = waist circumference (cm)/height (cm)

Statistical analysis

The normality of continuous variables was evaluated using the Shapiro-Wilk test. Normally distributed variables were expressed as mean± standard deviations (SD), while non-normally distributed data were reported as medians with interquartile regions (IQR). Study participants were divided into three sub groups; healthy controls, individuals with diabetes and individuals with both diabetes and cardiovascular disease. Using one way ANOVA differences in continuous variables across the study groups was analyzed. While non-normally distributed data were assessed using Kruskal-Walli's test. Post-hoc pairwise comparison was conducted to identify specific group differences, when the overall differences were statistically significant.

Pearson's correlation and Spearman correlation was done to assess the association between CMI and cardiometabolic parameters for normally distributed data and non – normally distributed data respectively. This correlation analyses were performed both in overall study group and separately between genders to evaluate the gender specific pattern of associations. Correlation coefficients (r) and p values were reported. Multinominal logistic regression analysis was performed to evaluate the association between CMI and clinical disease status with the clinical groups. Odds ratio (ORs) with 95% confidence intervals (Cls) and p-values were noted. The discriminatory ability of CMI to distinguish between the clinical groups was performed using receiver operating characteristic (ROC) curve, along with area under the curve (AUC), sensitivity, specificity, and 95% Cl. Youden index was used to determine the optimal cutoff value. A level of significance $p < 0.05$ was used for all data analysis.

RESULTS

Table 1 presents the demographic, anthropometric and laboratory tests data of 50 healthy controls, 100 patients with T2DM and 100 patients with T2DM with CVD. In controls the mean age was 50.6±10.75 years, 55.4±10.99 years in T2DM group and 58.0±11.06 years in the T2DM+CVD group, compared with the healthy controls, both patient groups exhibited higher mean values of WC, HbA1c and TG levels, with the highest values observed in T2DM+CVD groups, whereas HDL-C decreased. Mean CMI increased from 1.13±0.56 in controls to 3.9±2.56 in T2DM and 4.48±2.09 in T2DM+CVD.

Table 1: Baseline characteristics of the study participants

Group/ Variables	Controls (n=50)	T2DM (n=100)	T2DM+CVD (n=100)	Static	p value
Age (Years)	50.6±10.8	55.4±11	58±11.1	F=7.85,df=2	<.001
Weight (Kg)	72.7±7.49	73.3±9.88	75.5±10.6	χ^2=3.99,df=2	0.136
Height (cm)	166±8.6	163±11.9	164±8.01	χ^2=2.2,df=2	0.334
WC (cm)	73.9±8.79	93.2±13.7	98.9±15.3	χ^2=94.44,df=2	<.001
FPG (mg/dl)	98.5±10.6	186±82.9	167±39.4	χ^2=111.13,df=2	<.001
PPPG (mg/dl)	122±14.8	269±99.5	243±52.9	χ^2=118.33,df=2	<.001
HbA1c (%)	5.6±0.49	8.23±1.87	8.58±1.75	χ^2=110.1,df=2	<.001
TC (mg/dl)	162±41.2	192±50.8	215±49.9	χ^2=36.72,df=2	<.001

TG (mg/dl)	115±37.2	213±112	230±77.8	χ^2=77.49,df=2	<.001
HDL-C (mg/dl)	48.3±8.64	41±10.2	32.5±5.78	F=79.87,df=2	<.001
LDL-C (mg/dl)	106±44	117±46.3	134±30.2	F=10.36,df=2	<.001
CMI	1.13±0.56	3.29±2.56	4.48±2.09	χ^2=117.9,df=2	<.001
BMI (kg/m2)	25.7±2.51	28.8±4.51	29.6±3.88	χ^2=35.31,df=2	<.001

Note: Data were analyzed using Kruskal Wallis test for non -parametric data; Welch's ANOVA for parametric data. Values are expressed as Mean ± SD. WC=Waist circumference; FPG= Fasting Plasma Glucose; PPPG= Post Prandial Plasma Glucose; HbA1c= Glycated Haemoglobin; TC= Total Cholesterol; TG= Triglycerides; HDL-C= High Density Lipoprotein Cholesterol; LDL-C= Low Density Lipoprotein Cholesterol; CMI= Cardiometabolic Index; BMI= Body mass index.

Significant differences were observed across the study groups, WC (x2 = 94.44, p<0.001) glycaemic parameters- FPG (x2 = 111.13, p<0.001), PPPG (x2 = 118.33, p<0.001), HbA1c (x2 = 110.10, p<0.001), Lipid parameters- TC (x2 = 36.72, p<0.001), TG (x2 = 35.31, p<0.001). Also, HDL-C decreased significantly across all three groups (ANOVA F (2,118) =79.87, p<0.001). However, weight and height did not show statistically significance between groups.

In control group the median CMI was 1.10 (IQR 0.65), 2.70 (IQR 1.85) in T2DM group and 4.05 (IQR 2.45) in T2DM+CVD group. Kruskal Wallis test generated the result of χ^2=117.9, df=2, p<.001 and effect size= 0.47348 indicating a statistically difference among the study groups. Given the significance difference, Dunn's post hoc analysis with Bonferroni correction was run, revealing all pairwise comparisons were statistically significant among the study groups (p<0.001).

Table 2A: Distribution of CMI across study groups

Group	**Median (CMI)**	**IQR**	**25th Percentile**	**75th Percentile**
Controls	1.10	0.650	0.725	1.37
T2DM	2.70	1.850	1.900	3.75
T2DM+CVD	4.05	2.450	3.000	5.45

Table 2B: Pairwise comparison of CMI across study groups by Dunn's Post hoc analysis

Groups	**z**	**p(unadj)**	**p(Bonferroni)**
Controls vs T2DM	-7.01	<.001	<.001
Controls vs T2DM+CVD	-10.85	<.001	<.001
T2DM vs T2DM+CVD	-4.70	<.001	<.001

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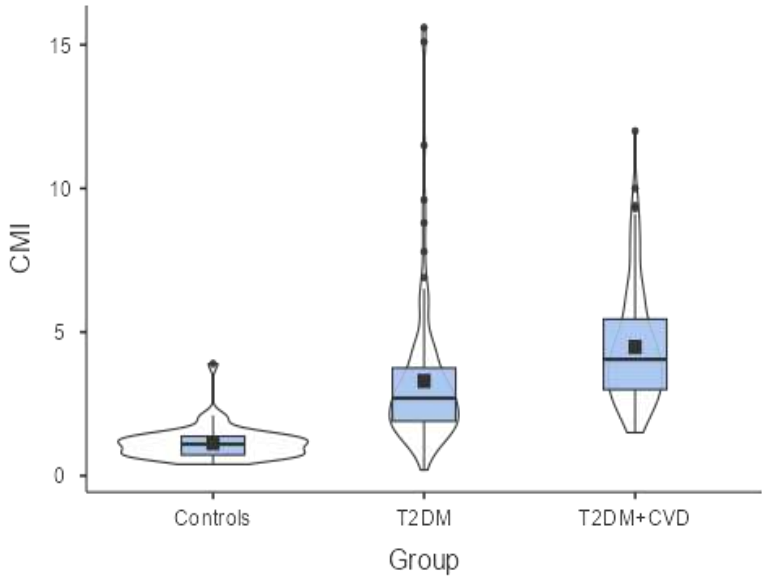

Figure 1: Box plot shows the distribution of CMI among healthy controls, T2DM group and T2DM+CVD group.

Correlation of CMI and cardiometabolic parameters analyzed by Spearman correlation for non-parametric parameters, significant positive correlation was observed with WC (ϱ = 0.579, p<0.001), FPG (ϱ =0.498, p<0.001), HbA1c (ϱ =0.487, p<0.001) and TG (ϱ=0.889, p<0.001). where in Pearson correlation analysis for parametric data CMI showed only strong inverse correlation was demonstrated with HDL-C (r= 0.617, p<0.001), while no significant correlation with age and LDL-C were observed.

Table 3: Correlation of CMI with cardiometabolic parameters

Parameter	Correlation with CMI	p value
WC (cm)	ϱ =0.579	<0.001
FPG (mg/dl)	ϱ =0.498	<0.001
HbA1c (%)	ϱ =0.487	<0.001
TG (mg/dl)	ϱ =0.889	<0.001
HDL-C (mg/dl)	r =-0.617	<0.001
LDL-C (mg/dl)	r =0.030	0.636
Age (Years)	r =0.060	0.346

ϱ= Spearman correlation coefficient; r = Pearson correlation coefficient

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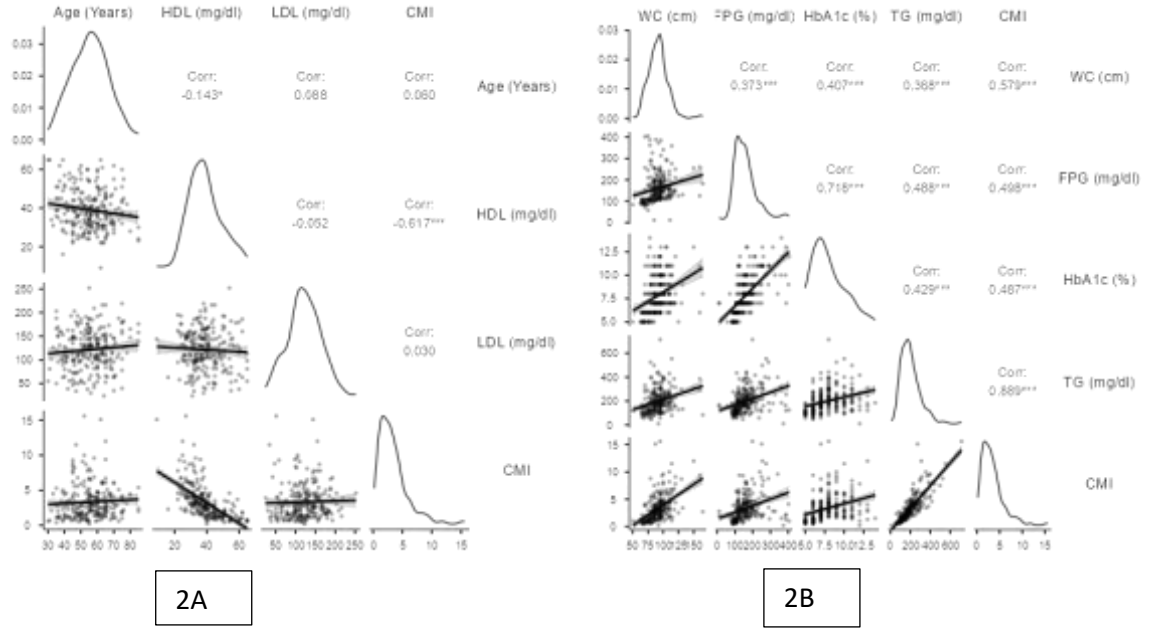

Figure 2A Pearson correlation and Figure 2B spearman correlation of CMI with cardiometabolic parameters.

To examine the association of CMI with disease group, keeping the controls as the reference category multinominal logistic regression was used. Significant association was observed between CMI and patient groups in the unadjusted model. In comparison with control group, for each one-unit increase in CMI was associated with 13.52-fold higher odds of T2DM (OR=13.52, 95%Cl: 5.80- 31.49, p<0.001) and 17.19- fold higher odds of T2DM+CVD (OR=17.19, 95% Cl:7.33-40.27, p<0.001).

After adjusting for age, CMI was significantly associated with T2DM (OR12.53, 95%Cl: 5.43 – 28.64, p<0.001) and T2DM +CVD (OR=16.11, 95% Cl: 6.93- 37.45, p<0.001). When the analysis was further adjusted for both age and BMI, CMI also exhibited strong independent association with T2DM (OR=13.15, 95% Cl: 5.36-32.27, p<0.001) and with T2DM+CVD (OR=16.76, 95% Cl:6.79-41.38, p<0.001).

Table 4: Multinominal logistic regression representing the association of CMI with disease group.

Model	Comparison	Predictor	Odds Ratio	95 % Confidence interval		p value
				Lower	Upper	
Model 1	Unadjusted: T2DM vs Controls	CMI	13.52	5.80	31.49	<0.001
	Unadjusted: T2DM+CVD vs Controls	CMI	17.19	7.33	40.27	<0.001
Model 2	Adjusted for age: T2DM vs Controls	CMI	12.53	5.43	28.94	<0.001
	Adjusted for age: T2DM+CVD vs Controls	CMI	16.11	6.93	37.45	<0.001
Model 3	Adjusted for age+ BMI: T2DM vs Controls	CMI	13.15	5.36	32.27	<0.001
	Adjusted for age+ BMI: T2DM+CVD vs Controls	CMI	16.76	6.79	41.38	<0.001

Two-way ANOVA was used to examine the group and gender effects on CMI. Significant main effect of study group was observed (F= 40.368, p<0.001; partial η2 =0.249), however the main effect of gender was not significant (F= 0.235, p =0.628). The group × gender interaction also did not show any statistical significance (F=2.343, p=0.098), which demonstrates that across study groups the difference in CMI did not vary significantly by gender in this analysis. Also estimated marginal mean comparisons showed significant differences between controls and T2DM, controls and T2DM+CVD, T2DM and T2DM+CVD (all p<0.001).

Table 05: Gender- Related differences in CMI and Cardiometabolic associations

	Sum of Squares	**df**	**Mean Square**	**F**	**p**	**η^2**	**η^2p**	**ω^2**
Overall model	377.78	5	75.56	18.029	<.001	-	-	-
Group	356.08	2	178.04	40.368	<.001	0.245	0.249	0.238
Gender	1.04	1	1.04	0.235	.628	0.001	0.001	-0.002
Group ✻ Gender	20.66	2	10.33	2.343	.098	0.014	0.019	0.008
Residuals	1076.13	244	4.41					

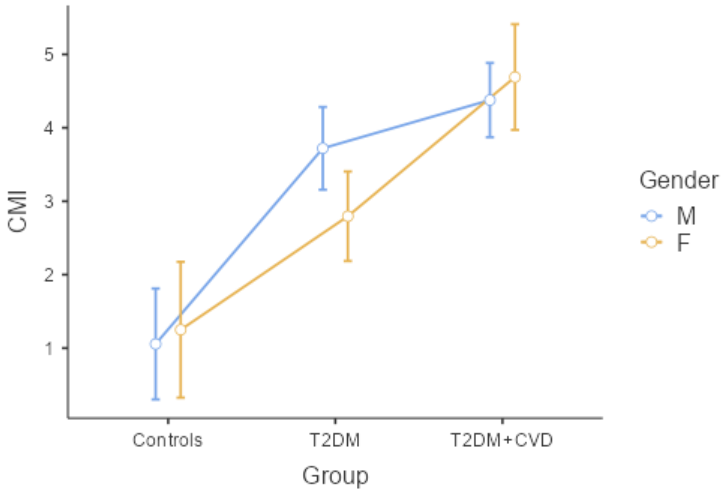

Figure 3: Estimated marginal means of CMI according to study group and gender.

Disease severity of study groups with CMI was demonstrated using Linear regression model, significant positive association was reported between severity code and CMI. The model explained 24.4% of the variance in CMI (R=0.494, R2 =0.244). Severity code was a significant predictor of CMI (estimate=1.60, SE=0.179, t=8.96, p<0.001), this supports that CMI increases with increasing disease severity.

Table 06: Liner regression model – Association of disease severity with CMI

Model Fit Measures		
Model	R	R^2
1	0.494	0.244

Note. Models estimated using sample size of N=250

Model Coefficients – CMI				
Predictor	Estimate	SE	t	p
Intercept	1.41	0.253	5.58	<.001
Severity Code	1.60	0.179	8.96	<.001

To assess the discriminatory performance of CMI for differentiating the study groups Receiver operating characteristic (ROC) analysis was used. In ROC analysis 1, CMI showed strong discriminatory ability, with an area under curve (AUC) of 0.908 (95% CI: 0.859-0.958, p<0.001). The optimal cut-off was 1.65 provided a sensitivity of 83.0 %, 92% specificity, resulting in Youden's index of 0.75, the positive likelihood ratio was 10.375 and negative likelihood ratio was 0.185, with diagnostic accuracy reaching 86%. For ROC analysis 2, CMI exhibited moderate to good discrimination with an AUC of 0.721 (95 % CI: 0.650-0.792, p<0.001). The cut-off according to Youden Index was 2.85, with 80.0% sensitivity and 58.0% specificity. The positive and negative likelihood ratios were 1.905 and 0.345, respectively and an overall diagnostic accuracy of 69.0%. In ROC analysis 3 CMI reached an excellent discrimination, with an AUC of 0.986 (95%CI:0.967-1.00, p<0.001). The most ideal cut-off was 1.65, accomplishing sensitivity of 99.0%, specificity of 92.0%, giving Youden index of 0.910. The positive likelihood ratio was 12.375, while the negative likelihood ratio was 0.0109 and diagnostic accuracy was 96.67%.

Table 7A: Discriminatory performance of CMI in ROC analyses.

ROC Analysis	AUC (95% CI)	Optimal Cut-off	Sensitivity	Specificity	Youden index	Accuracy
ROC 1	0.908(0.859-0.958)	1.65	83.0 %	92.0%	0.750	86.0%
ROC 2	0.721(0.650-0.792)	2.85	80.0 %	58.0%	0.380	69.0%
ROC 3	0.986(0.967-1.00)	1.65	99.0 %	92.0%	0.910	96.67%

Table 7B: Diagnostic accuracy measures at the optimal CMI cut-offs.

Measure	ROC 1	ROC 2	ROC 3
Sensitivity, % (95% CI)	83.0 (74.18- 89.77)	80.0 (70.82- 87.33)	99.0 (94.55-99.97)
Specificity, % (95% CI)	92.0 (80.77- 97.78)	58.0 (47.71- 67.80)	92.0 (80.77-97.78)
Positive likelihood ratio	10.375 (4.036- 26.670)	1.905 (1.483- 2.447)	12.375 (4.833- 31.685)
Negative likelihood ratio	0.185 (0.119- 0.287)	0.345 (0.225- 0.528)	0.0109 (0.00154- 0.0765)
Positive predictive value, %	95.40 (88.98- 98.16)	65.57 (59.73- 70.99)	96.12 (90.62- 98.45)
Negative predictive value, %	73.02(63.52- 80.79)	74.36 (65.45- 81.62)	97.87 (86.72- 99.69)
Accuracy, %	86.00(79.40- 91.12)	69.00 (62.09- 75.33)	96.67 (92.39- 98.91)

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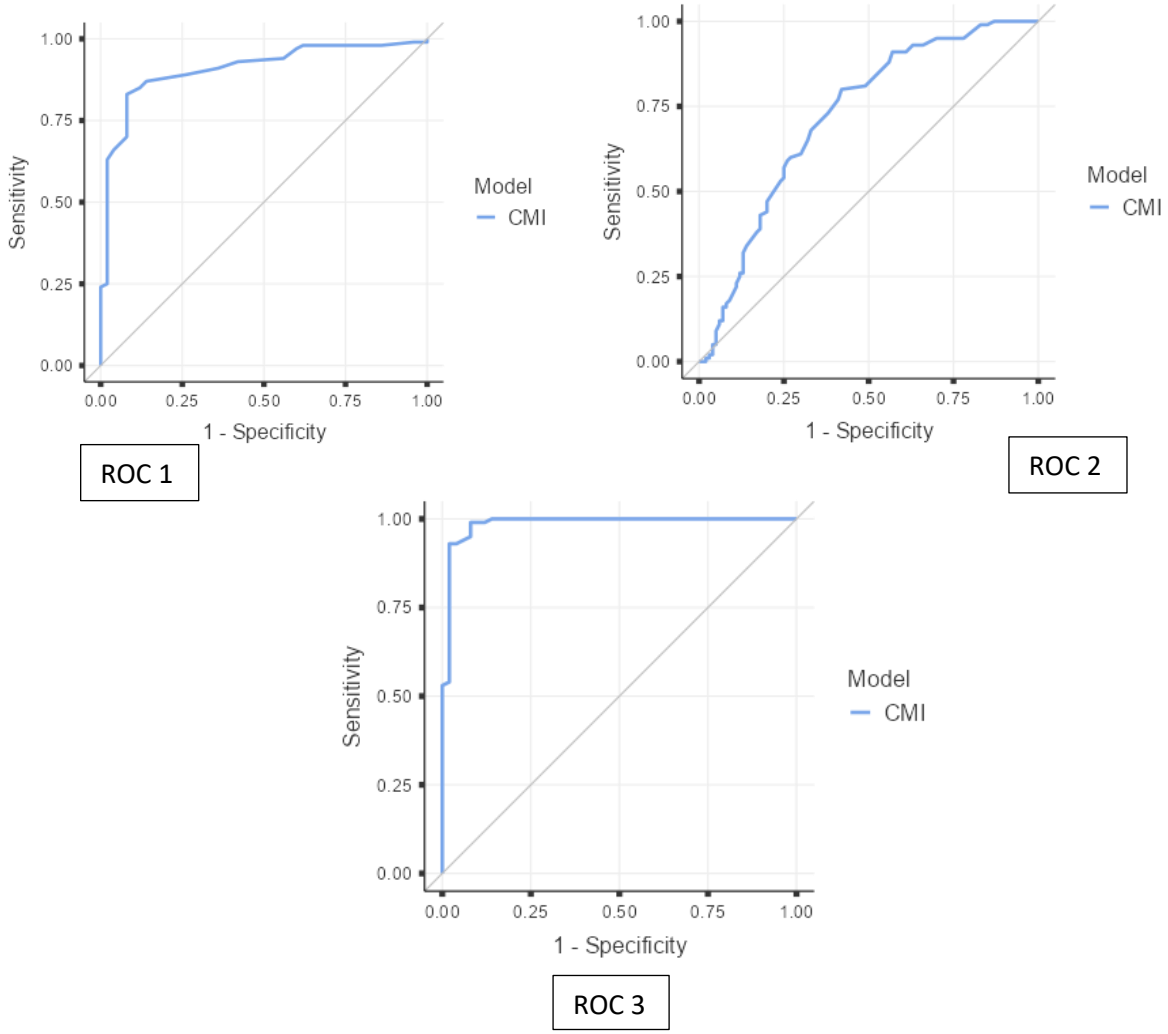

Figure 4: Receiver Operating Characteristic curves demonstrating the discriminatory performance of CMI.

ROC 1- demonstrating discriminative ability of CMI between healthy controls and T2DM participants

ROC 2- demonstrating discriminative ability of CMI between T2DM and T2DM+CVD participants

ROC 3- demonstrating discriminative ability of CMI between healthy controls and patients between T2DM and CVD.

DISCUSSION

A notable strength of our study design is the assessment of CMI across three study groups that represents different stages of cardiometabolic deterioration: Healthy controls, individuals with T2DM, but without clinical macrovascular complications and patients with established T2DM and cardiovascular disease. Although the cross-sectional nature of our study precludes us from establishing causation, comparing T2DM (metabolic dysfunction without macrovascular complications) to T2DM+ CVD (established clinical macrovascular disease) allows us to track the progressive rise of visceral adiposity and lipid dysfunction characteristic of advanced clinical vascular complications. We observe affected, stepwise increase of CMI values across the disease spectrum that is highly statistically significant 1.13 ±0.56 in healthy controls to 3.29 ±2.56 in T2DM and 4.48± 2.09 in T2DM +CVD (overall x2 =117.9, df=2, p<0.001). Notably, Dunn's post hoc pairwise analysis with Bonferroni correction confirms that the transition from CVD-free diabetic state to established macrovascular disease involved, a statistically significant further elevation of CMI values (z= - 0.470, p< 0.001). After adjusting for potential confounding variables such as age and body mass index (BMI), multinominal logistic regression demonstrates that each one unit increase in CMI was associated with

13.15 times higher odds for T2DM (95% CI: 6.79-41.38, p<0.001) compared to healthy controls. Together these results demonstrates that CMI is independently and strongly associated with clinical disease status. Our observation of a significant cardiometabolic gap between T2DM and established T2DM+CVD is highly consistent, with and supported by large scale prospective longitudinal cohort studies. In a 10 year follow up of 6991 middle aged and older adults from China health and retirement longitudinal study (CHARLS) who were initially free of cardiovascular disease, Ren et al. (2026) demonstrates that CMI was independently associated with a significantly increased risk of incident CVD (Quartile 4 vs Quartile 1: HR =1.347, 95 % CI: 1.161 – 1.563, P for trend = 0.0001) (9). Similarly, Zhou et al (2024) followed a national prospective longitudinal cohort and reported that higher CMI levels predicted a significantly increased risk of incident hypertension (HR= 1.05) and diabetes (HR= 1.08). By demonstrating the step wise cross-sectional increase in our cohort, we bridge these findings to suggest that the elevated CMI observed in our T2DM+CVD group is the cross-sectional manifestation of the high risk metabolic state that prospective trials have demonstrated to drive incident vascular events (8).

The physiological mechanism driving the CMI elevation from T2DM to T2DM+CVD involves a synergetic vicious cycle of glucolipotoxicity, visceral adiposity hypertrophy, and vascular endothelial damage (10). T2DM is characterized by insulin resistance that accelerates hepatic de novo lipogenesis, causing elevated TG and diminished HDL -C, this atherogenic dyslipidemia phenotype, represented by the TG, HDL-C component of the CMI, promotes the accumulation of small, dense LDL particles that readily penetrate the vascular walls and undergo oxidation to initiate macrophage foam cell formation (10). Concurrently, central adiposity, represented by the waist to hip ratio (WHtR) component of CMI, drives a persistently low-grade systemic inflammatory state by hyper-secreting pro-inflammatory cytokines such as TNF-alpha and IL-6 (10). When these lipid and visceral obesity derangements converge with severe glucose toxicity-evidences by the elevated FPG and HbA1c in our diabetic cohorts- they accelerate structural vascular damage. In large cohort of 2243 participants with T2DM, Tang et al. (2024) (2) demonstrated that CMI was positively and independently correlated with brachial-ankle pulse wave velocity (baPWV), the clinical gold standard for arterial stiffness (OR = 1.87, 95% CI = 1.66 -2.10, p<0.001). T2DM patients in the highest CMI tertile (> 1.355) exhibited a 5.56-fold times more likely to have active atherosclerosis (OR= 5.56, 95% CI: 4.32- 7.17, p<0.001) compared to those in lowest tertile (2). This clinical evidence strongly supports that tracking CMI in CVD free T2DM patients helps identify the progressive subclinical vascular remodeling that actively bridges the gap between uncomplicated diabetes and clinical macrovascular events. Clinical preventive application and actionable thresholds from a clinical perspective, a progressive CMI marker is highly valuable as it identifies a primary prevention window during which aggressive medical and lifestyle interventions can be deployed before permanent vascular injury occurs (11). Unlike traditional risk scores that rely on complex algorithms or clinical history, CMI is an extremely low, cost, simple metric that can be rapidly calculated in resource- constrained primary care settings using standard anthropometrics and a routine fasting lipid panel (10). To translate this into clinical practice, we performed ROC analysis to establish discriminative thresholds. To distinguish between diabetic patients who had already developed clinical macrovascular complications versus those that did not (ROS analysis 2), CMI showed a moderate- to good discriminative capability (AUC=0.721, 95% CI: 0.650-0.792) with an optimal transitional cut-off of 2.85 (sensitivity= 80.0%, Youden's index =0.380). meanwhile, to discern between diabetic and healthy states (ROC Analysis 1 and 3) the optimum cut-off was 1.65 showing an AUC of 0.908 and 0.986, respectively, with sensitivities up to 99.0 %. These findings correlate remarkably with the biological threshold analyses of Liu et al. (2024) (12), which identified a non-linear, inverse L-shaped relationship between CMI and glucose-lipid abnormalities, finding sharp increases in metabolic risks below inflection point of 1.1 for insulin resistance, 1.45 for prediabetics and 1.6 for clinical diabetes, above which the risk plateaued (12). Our study's lower cut-off of 1.65 represents the threshold at which patients have crossed the metabolic inflection point of cellular insulin resistance, and entered overt glycaemic disease (12). Crucially as the traditional cut-off of 2.85, suggests when a T2DM patients CMI creeps past 2.85, they are escaping the stable diabetic plateau and entering the established CVD risk category. Regular monitoring of CMI in clinical practice and initiating aggressive cardio-protective therapies (such as sodium-glucose cotransporter 2- SGLT 2 inhibitors or glucagon- like- peptide-1 (GLT 1) receptor agonists, specifically targeting patients approaching or exceeding a CMI 2.85 reparents a highly precise and clinically actionable approach to prevent macrovascular complications (11). Even though, CMI exhibited a significant progressive increase from controls to study groups, there was no significant main effect of gender (p=0.628) or group * gender interaction (p=0.098) was observed, which suggests the continuous pattern of elevation of CMI in both males and females. In contrast, previous studies have reported gender-specific CMI cut offs for metabolic syndrome (1.14 in females and 1.47 in males), insulin resistance (0.89 vs 0.77) and MAFLD (0.4319 vs 0.6085) (4,5), also in large scale cohort study, adult female showed 1.49 fold higher risk of cardiovascular mortality, whereas

no statistically significant association was found among men (7,13). This marked that female dimorphism is driven by the post-menopausal shift toward visceral fat accumulation which accelerates systemic insulin resistance and vascular inflammation (4).

CONCLUSION

As an extremely low-cost tool solely constructed from standard anthropometrics and routine fasting lipid profile, CMI represents a highly accessible, practical and accurate preliminary screening marker, while it does not replace comprehensive clinical evaluation or formal risk models, incorporating regular CMI surveillance into routine primary care and public health screening is a powerful strategy to identify, stratify and intercept cardiometabolic decline in its subclinical phase.

Limitations

Some limitation of this cross-sectional study is that the current study limits making any inferences about causality and the findings cannot be generalized because of the small study groups. Hence the findings have to be validated with bigger multicentric population and the longitudinal studies have to be performed to evaluate the disease progression.

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