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Beyond traditional metrics: evaluating the triglyceride-total cholesterol-body weight index (TCBI) in cardiovascular risk assessment

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Abstract

Background Cardiovascular disease (CVD), a non-communicable condition, stands as the primary cause of death globally. This study seeks to evaluate the predictive power of atherogenic indices, which are recognized for their influence on CVD, alongside a newly developed index encompassing all three principal risk factors for CVD, referred to as the triglyceride-total cholesterol-body weight index (TCBI). The primary outcomes evaluated include both the incidence and mortality rates associated with CVD.

Methods A prospective cohort study was conducted on Mashhad stroke and heart atherosclerotic disorder (MASHAD) study data, involving 9704 healthy participants. Baseline variables were measured, and TCBI, Atherogenic Index of Plasma (AIP), Atherogenic Coefficient (AC), Castelli risk index I and II (CRI-I & II) were calculated using specific formulas.

Results Following a 10-year follow-up period, a significant positive relationship was observed between TCBI (HR: 1.078, 95% CI: 1.012–1.15), CRI-I (HR: 1.16, 95% CI: 1.007–1.337), and CRI-II (HR: 1.199, 95% CI: 1.001–1.437) with CVD mortality. However, no significant relationship was identified between TCBI and atherogenic indices related to CVD incidence, and neither AIP nor AC was associated with CVD mortality.

Conclusion In conclusion, TCBI, in contrast to AC and AIP, was linked to increased CVD mortality. However, the more substantial predictive capabilities of CRI-I and CRI-II compared to TCBI emphasize the importance of traditional atherogenic indices for accurate risk assessment. These findings underscore the necessity of enhancing the TCBI formula to improve its effectiveness in assessing CVD risk.

Keywords CVD, Mortality, TCBI, Atherogenic indices, AC, CRI-I, CRI-II, AP

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. According to the World Health Organization (WHO), CVD accounts for approximately 17.9 million deaths each year [1]. In Iran, CVD is identified as the primary cause of death, responsible for 46% of all fatalities and 20-23% of the overall disease burden [2].

Lipid disorders are major risk factors for CVD, typically characterized by elevated levels of low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and triglycerides (TG), along with decreased levels of high-density lipoprotein (HDL) [3]. The ratios of these lipids provide insight into the balance between atherogenic and anti-atherogenic lipoproteins, which is crucial for assessing atherosclerosis risk. Research indicates that a one standard deviation increase in the atherogenic index of plasma (AIP) is associated with a 110% increase in the risk of coronary artery disease (CAD) [4]. Other significant indicators include the Castelli Risk Index I and II (CRI-I & II) and the atherogenic coefficient (AC) [5–7]. However, these indices primarily focus on lipid profiles and overlook body weight's influence. Recent studies have demonstrated that weight loss can improve lipid parameters, reducing TG and LDL-C while increasing HDL-C levels [8].

There are several tools available for screening CVD, including the Framingham Risk Score, the Estudio de Riesgo Cardiovascular en España (ERICE), the Registre Gironí del Cor (REGICOR), and the Atherosclerotic Cardiovascular Disease Risk Assessment Tool (ASSING). However, many of these tools are complex and difficult to calculate [9]. A new and more straightforward index called the triglyceride-total cholesterol-body weight index (TCBI) has recently been introduced as a prognostic indicator for CVDs [10]. Research has shown a significant relationship between TCBI and various conditions such as heart failure (HF) [11], cardiomyopathy [12], and CAD [13].

Most research has concentrated on TCBI's ability to predict mortality in specific patient populations, such as those with sepsis [14], individuals undergoing trans-catheter aortic valve replacement [15], and HF patients [16]. Although a limited number of studies have examined its association with CVD mortality in the general population [17], there has yet to be a comprehensive investigation into its predictive value across this broader demographic. Furthermore, existing comparative studies have primarily focused on comparing TCBI with malnutrition indicators like the geriatric nutritional risk index (GNRI), prognostic nutritional index (PNI), and controlled nutritional score (CONUT) [18–20]. Given the similar lipid profile characteristics of traditional atherogenic indices and TCBI, more extensive research would be beneficial to evaluate TCBI's predictive power alongside established traditional indices. To address this research gap, we conducted a 10-year cohort study to assess and compare the predictive capabilities of TCBI and atherogenic indices for forecasting CVD incidence and mortality within the Iranian general population.

Methods

Study population and follow-up period

The research involved 9704 individuals who were part of the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) cohort study. As outlined in previous literature, the objective of the MASHAD study was to determine the risk and occurrence of cardiovascular events [21]. Participants with incomplete anthropometric and biochemical data, as well as those who died from causes not related to cardiovascular events, were excluded.

The MASHAD study collected data on biochemical parameters (such as fasting blood glucose and lipid profiles), demographic information (including education level, gender, age, marital status, and occupation), medical history, lifestyle factors (including smoking habits), and anthropometric measurements (such as body mass index, weight, and height) through trained nursing staff [22]. The methods for biochemical measurements using an automated analyzer and blood pressure assessments using a standard mercury sphygmomanometer are detailed elsewhere [23]. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg [23]. Diabetes was defined as FBG ≥ 126 mg/dl or receiving oral hypoglycemic agents or insulin [23].

The study evaluated outcomes using two primary endpoints: morbidity and mortality during the follow-up period, CVD incidence, and CVD mortality. In total, 1060 CVD events were documented, with 875 individuals surviving the events and 185 succumbing. The events were classified based on the International Classification of Diseases (ICD-10). The presence of CAD was determined using the individual's history (myocardial infarction or angina pectoris, or the presence of a definitive Q wave in an electrocardiogram using the Minnesota Code).

Calculation of indices

We calculated AIP, AC, CRI-I, CRI-II and TCBI with specific formulas below:

$\text{AIP} = \log\left(\frac{TG\left(\frac{mg}{dl}\right)}{HDL\left(\frac{mg}{dl}\right)}\right)$ [24].

$\text{AC} = \frac{\text{TC} - HDL\left(\frac{mg}{dl}\right)}{LDL\left(\frac{mg}{dl}\right)}$ [25].

$\text{CRI-I} = \frac{TC\left(\frac{mg}{dl}\right)}{HDL\left(\frac{mg}{dl}\right)}$ [26].

$\text{CRI-II} = \frac{LDL\left(\frac{mg}{dl}\right)}{HDL\left(\frac{mg}{dl}\right)}$ [26].

$\text{TCBI} = TG\left(\frac{mg}{dl}\right) \times \text{TC}\left(\frac{mg}{dl}\right) \times \text{Body weight (kg)}$ [10].

Table 1 Demographic characteristics according to CVD event in study population

variables	Healthy (*N* = 8644)	CVD-Survivor (*N* = 875)	CVD-mortality group (*N* = 185)	*P* value
Age (y)	47.59 (8.19)	51.50 (7.59)	54.79 (7.58)	**< 0.001**
Sex (male)	3371 (39.0%)	398 (45.5%)	116 (62.7%)	**< 0.001**
Marriage status				
Single	56 (0.6%)	1 (0.1%)	2 (1.1%)	**0.014**
Married	8055 (93.2%)	809 (92.5%)	174 (94.1%)	
Divorced	127 (1.5%)	6 (0.7%)	1 (0.5%)	
Widow	405 (4.7%)	59 (6.7%)	8 (4.3%)	
Occupation status				
Employee	3217 (37.2%)	321 (36.7%)	67 (36.2%)	**< 0.001**
Unemployed	4638 (53.7%)	423 (48.3%)	84 (45.4%)	
Retried	785 (9.1%)	131 (15.0%)	34 (18.4%)	
Smoking status				
Non smoker	5996 (69.4%)	560 (64.0%)	98 (53.0%)	**< 0.001**
Ex-smoker	826 (9.6%)	100 (11.4%)	32 (17.3%)	
Current smoker	1822 (21.1%)	215 (24.6%)	55 (29.7%)	
FBG				
≥ 126 mg/dl	1051 (12.3%)	247 (28.6%)	71 (39.2%)	**< 0.001**
< 126	7469 (87.7%)	616 (71.4%)	110 (60.8%)	
HTN	2488 (28.9%)	436 (49.9%)	111 (60.0%)	**< 0.001**
Obesity	2544 (29.5%)	317 (36.2%)	56 (30.3%)	**< 0.001**
PAL	1.6 (0.28)	1.52 (0.3)	1.59 (0.28)	**< 0.001**
Energy intake	1901.51 (666.78)	1956. 61 (676.64)	1822.7 (650.64)	**0.045**

Data presented as N (percentage) or mean (standard division); One-Way ANOVA or Chi-Square test has been done

FBG: Fasting blood glucose, HTN: Hypertension, PAL: Physical activity level,

Statistical analysis

After a decade-long follow-up, participants were classified into three groups: healthy, event-alive (incidence of CVDs), and event-dead (CVD mortality). Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were presented as numbers and percentages. Baseline differences among the groups were evaluated using One-way ANOVA with post-hoc analysis using the Tukey test, chi-squared test, or Fisher's exact test. The predictive value of the variables was assessed through Cox proportional hazards regression analysis. Cox regression models were constructed to determine the independent prognostic significance of the variables and survival. Kaplan-Meier curves were used to display survival and mortality based on TCBI and atherogenic indices. Confounders were selected based on clinical judgment and significance in univariate analysis, including age, sex, occupation status, marriage status, smoking, DM, HTN, physical activity, energy intake, and social level. Statistical analyses were performed using SPSS software version 26 (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp, 2019.), and statistical significance was set at a two-tailed P value < 0.05.

Table 2 Anthropometric features, lipid profile, TCBI and atherogenic indices according to CVD event in study population

variables	Healthy (*N* = 8644)	CVD-Survivor group (*N* = 875)	CVD-mortality group (*N* = 185)	*P* value
Weight	71.53 (12.88)[a, b]	73.88 (12.52)	73.46 (13.61)	**< 0.001**
BMI	27.81 (4.75) [a]	28.69 (4.53)	27.87 (4.82)	**< 0.001**
Cholesterol	190.42 (38.56) [a, b]	198.96 (42.56)	199.55 (44.56)	**< 0.001**
TG	139.93 (90.36) [a, b]	163.66 (103.18)	167.48 (117.23)	**< 0.001**
HDL	43.03 (9.97) [a, b]	41.55 (9.56)	40.92 (9.74)	**< 0.001**
LDL	116.03 (34.83) [a, b]	120.54 (39.05)	121.16 (37.50)	**< 0.001**
FBG	90.46 (35.98) [a, b]	108.92 (53.32)	122.72 (71.13)	**< 0.001**
TCBI	2041.21 (1796.36) [a, b]	2541.22 (2105.59)	2644.04 (2359.79)	**< 0.001**
AIP	0.45 (0.27) [a, b]	0.54 (0.27)	0.54 (0.29)	**< 0.001**
CRI-I	4.58 (1.15) [a, b]	4.96 (1.27)	5.04 (1.27)	**< 0.001**
CRI-II	2.79 (0.93) [a, b]	3.00 (1.04)	3.07 (1.03)	**< 0.001**
AC	3.58 (1.15) [a, b]	3.96 (1.27)	4.04 (1.27)	**< 0.001**

Data presented as mean (standard division); One-Way ANOVA

a: Survivor group vs. healthy; b: mortality group vs. healthy

BMI: body mass index, TG: triglyceride, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, FBG: fasting blood sugar, TCBI: triglyceride-total cholesterol-body weight index, AIP: Atherogenic Index of Plasma, CRI-I: Castelli risk index I, CRI-II: Castelli risk index II, AC: Atherogenic Coefficient

Results

Baseline demographic data, as shown in Table 1, revealed significant differences among the three groups. The study involved a total of 9,704 individuals, with 8,644 healthy subjects (39% male), 875 CVD-Survivor participants (45.5% male), and 185 CVD-Mortality cases (62.7% male). The mean age of participants in the three groups was 47.59 ± 8.19 in the healthy group, 51.50 ± 7.59 in the CVD-Survivor Group, and 54.79 ± 7.58 in the CVD-Mortality Group. The percentage of obesity in the CVD-Survivor and CVD-Mortality Groups was higher than in the healthy group (36.2% and 30.3% vs. 29.5%). Also, cholesterol, TG, and LDL levels were higher in the CVD-Mortality Group (P-value < 0.001). Unlike these factors, HDL-C levels are higher in the healthy group than in the CVD-Survivor Group (P-value < 0.001).

According to Table 2, the healthy group participants' mean weight was 71.53 ± 12.88 Kg, 73.88 ± 12.52 kg in the CVD-Survivor Group, and 73.46 ± 13.61 kg in the CVD-Mortality Group. CVD-Survivor Group individuals have the highest BMI (28.69 ± 4.53 kg/m²) (P-value < 0.001). Regarding FBG, the highest FBG level (122.72 ± 71.13 mg/dl) was seen in CVD-Mortality cases (P-value < 0.001), and FBG increased gradually from the healthy to the CVD-Mortality Group. Also, TCBI and atherogenic indices are higher in CVD groups than the healthy ones (P-value < 0.001), and numbers are higher, especially in

the CVD-Mortality Group. (TCBI: 2644.04 ± 2359.79, AIP: 0.54 ± 0.29, CRI-I: 5.04 ± 1.27, CRI-II: 3.07 ± 1.03 and AC: 4.04 ± 1.27).

The results of the Cox regression analysis are presented in Table 3. After adjusting for confounding variables, it was found that for every unit increase in TCBI, the risk of CVD mortality increased by 7.8% (HR: 1.078, 95% CI: 1.012–1.15). In contrast, CRI-I and CRI-II showed a more significant association; with each additional unit increase in CRI-I and CRI-II, the risk of CVD mortality rose by 16% (HR: 1.16, 95% CI: 1.007–1.337) and 19.9% (HR: 1.199, 95% CI: 1.001–1.437), respectively. Neither AC nor AIP showed any association with CVD mortality. Furthermore, TCBI and all atherogenic indices were not linked to CVD incidence.

Table 4 and Figure 1 presents the median survival time and 95% CI in months based on various atherogenic indices and the TCBI. The indices were categorized into two groups: those with values below the median and those equal to or above the median. With the exception of the CRI-II, the avarage survival time in the second group (values equal to or above the median) was lower than in the first group (values below than the median).

Discussion

In this cohort study, we aimed to compare the predictive value of TCBI with various atherogenic indices, including AIP, CRI-I, CRI-II, and AC, with CVD incidence and mortality. Our findings indicated that TCBI, in contrast to AC and AIP, was linked to increased CVD mortality. Additionally, CRI-I and CRI-II showed more substantial predictive capabilities compared to TCBI. Furthermore, none of these indicators were associated with CVD incidence.

CRI, consisting of CRI-I (Total Cholesterol/HDL-C ratio) and CRI-II (LDL-C/HDL-C ratio), serves as predictors of CVD risk [26]. Higher CRI values indicate an unfavorable lipid profile, characterized by increased cholesterol levels and reduced protective HDL-C levels. These imbalances accelerate coronary plaque formation and intima-media thickness in the carotid arteries, leading to a higher incidence of CVD mortality [27, 28]. In the context of CRI-II, research has concentrated on all-cause mortality, focusing on the predictive value of the LDL-C/HDL-C ratio in several populations. In line with our study, it has been demonstrated that an elevated LDL-C/HDL-C ratio can predict mortality in elderly hypertensive patients [29] and those with intracerebral hemorrhage [30]. Additionally, this ratio has emerged as a risk factor for sudden cardiac death [31]. However, conflicting findings have been reported in a study examining the relationship between the LDL-C/HDL-C ratio and prognosis in Chinese patients who have experienced their first ischemic stroke. Contrary to our results, a higher LDL-C/

Table 3 Cox regression model for predicting role of TCBI and atherogenic indices according cardiovascular events

Variables	Healthy* (*N* = 8644)	CVD-Survivor (*N* = 875)		CVD-mortality (*N* = 185)	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
TCBI	Ref	1.027 (0.994, 1.062)	0.21	1.078 (1.012, 1.15)	0.021
AIP	Ref	1018 (0.926, 1.119)	0.71	1.806 (0.971, 3.357)	0.062
CRI_I	Ref	1.009 (0.986, 1.031)	0.45	1.16 (1.007, 1.337)	0.039
CRI_II	Ref	1.022 (0.996, 1.049)	0.095	1.199 (1.001, 1.437)	0.049
AC	Ref	1.081 (0.992, 1.178)	0.077	1.082 (0.911, 1.418)	0.065

Cox regression model has been done; data adjusted by age, sex, occupation status, marriage status, smoking, DM, HTN, physical activity, energy intake, and social level

*Reference level

TCBI: triglyceride-total cholesterol-body weight index, AIP: Atherogenic Index of Plasma, CRI-I: Castelli risk index I, CRI-II: Castelli risk index II, AC: Atherogenic Coefficient, TCBI: Triglyceride-total cholesterol-body weight index

Table 4 Median survival time and 95% confidence intervals (CI) in months according to atherogenic indices and TCBI

Indices	Estimate mean time for event, 95% CI *P*-value CVD-Survivor group	Estimate mean time for event, 95% CI *P*-value CVD-mortality group
AIP		
< 0.46	140.42 (139.66, 141.18)	146.18 (145.94, 146.42)
≥ 0.46	136.76 (135.94, 137.58)	144.12 (143.66, 144.57)
CRI-I		
< 4.5	140.54 (139.76, 141.33)	146.07 (145.79, 146.35)
≥ 4.5	135.65 (134.92, 136.37)	142.34 (141.95, 142.74)
CRI-II		
< 2.8	136.78 (135.61, 137.96)	-
≥ 2.8	138.71 (138.11, 139.30)	-
TCBI		
< 1623	140.87 (140.12, 141.62)	146.00 (145.71, 146.28)
≥ 1623	136.34 (135.52, 137.17)	144.30 (143.86, 144.73)
AC		
< 3.5	140.54 (139.76, 141.33)	146.07 (145.79, 146.35)
≥ 3.5	135.65 (134.92, 136.37)	142.34 (141.95, 142.74)

Kaplan-Meier has used to estimate mean event time

All indices are categorized based on the median

AIP: Atherogenic Index of Plasma, CRI-I: Castelli risk index I, CRI-II: Castelli risk index II, AC: Atherogenic Coefficient, TCBI: Triglyceride-total cholesterol-body weight index

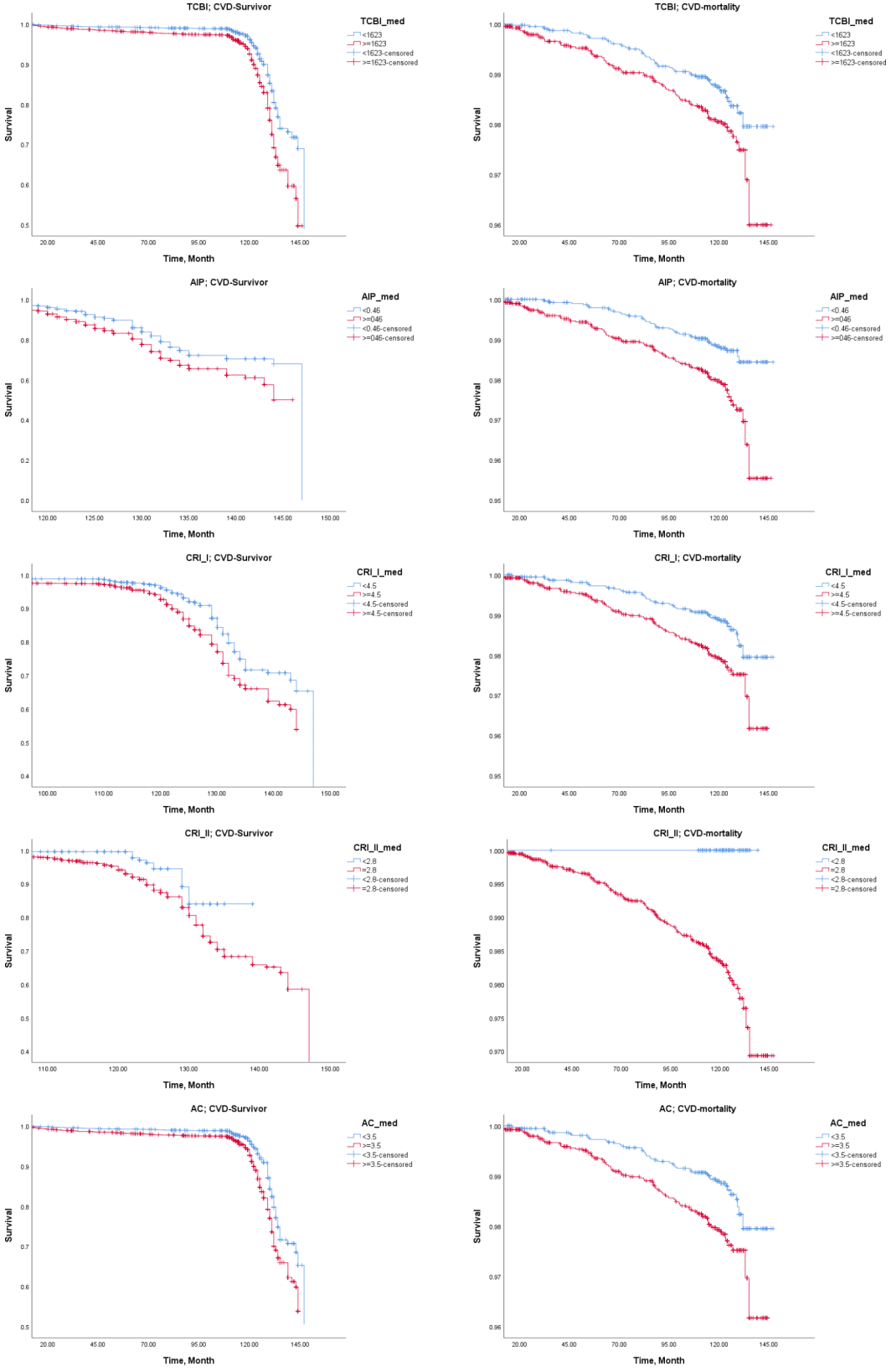

Fig. 1 Kaplan-Meier survival function of study participants with CVD surviving and CVD mortality based on TCBI and atherogenic indices. Caption-Triglyceride-total cholesterol-body weight index (TCBI), Atherogenic index of plasma (AIP), Castelli Risk Index I (CRI-I) and II (CRI- II), Atherogenic coefficient (AC)

HDL-C ratio was found to offer protection against death within 3 and 12 months following stroke onset [32]. Other studies support our findings regarding CRI-I. For instance, Zhou investigated the Total Cholesterol/HDL-C ratio in the general population and observed that it predicted CVD mortality [33]. Furthermore, other studies have associated the Total Cholesterol/HDL-C ratio with hospital mortality and all-cause mortality [34, 35].

AIP is a marker reflecting the balance between atherogenic and anti-atherogenic lipoproteins. A higher AIP indicates a more atherogenic lipid profile, characterized by elevated TG and HDL-C levels [24]. This imbalance may contribute to the formation of atherosclerotic plaques, thereby increasing the risk of CVD mortality [36]. However, similar to our findings, some studies have reported no significant association between AIP and CVD mortality [37, 38]. For example, research by Bendzala et al. indicated a negative correlation between AIP and all-cause mortality in women, but no such correlation was found in men [37]. Additionally, a population-based study in the United States reported no association between AIP and all-cause or CVD mortality [38]. Duiyimuhan's cohort study identified a U-shaped relationship between AIP and CVD mortality, where both low and high AIP levels were associated with increased hazard ratios. At the same time, average values corresponded with a lower CVD mortality rate [39]. Therefore, the lack of association between AIP and CVD mortality in our current study may be explained by these established scientific findings related to this index.

AC is a metric used to evaluate the atherogenic potential of lipoproteins. It is calculated as the ratio of non-HDL cholesterol to HDL-C [25]. An imbalance in this ratio indicates an abnormal lipid profile, which has been associated with slow coronary flow [40]. Similar to the AIP, evidence suggests a U-shaped relationship between non-HDL cholesterol and all-cause and CVD mortality within the general adult population [39, 41]. Consequently, the association between AC and CVD mortality may diminish based on the average levels of non-HDL cholesterol in the general population. While specific research on the link between AC and CVD mortality in the general population is lacking, associations have been noted in patient populations, such as those with sepsis [42] or end-stage renal disease [43].

While the role of atherogenic indices in the development of atherosclerosis has been thoroughly investigated [44, 45], it is noteworthy that relatively few studies have explored their relationship with the incidence of CVD. A recent study by Kim et al. found that the AIP is associated with a 28% increase in CVD events, contrasting our findings [46]. Additionally, there is a notable lack of research examining the association of other indicators, such as the AC, CRI-I, CRI-II, and TCBI, with the development of CVDs in the general population.

The TCBI differs from traditional atherogenic indices by including body weight in its calculation, making it relevant alongside lipid profiles as a risk factor for CVD mortality [47]. In 2018, Doi introduced a novel index and utilized it as a prognostic indicator for mortality across various cardiac conditions [10]. Specifically, it has been employed in predicting mortality in patients with HF [11], Cardiac Critical Patients [48], CAD [13], and dilated cardiomyopathy [12]. Notably, research has identified a distinct inverse relationship between TCBI and the incidence of stroke, particularly among hypertensive individuals [49]. However, limited studies have explored the application of this index in the general population and its efficacy in predicting mortality. One study revealed that TCBI was significantly linked to 42% increasing the risk of all-cause mortality but did not show a significant association with CVD mortality [17]. Evidence indicates there are genetic, cultural, and environmental differences in the causes of CVD among various races and ethnicities. For example, elevated fasting glucose levels and high blood pressure are more prevalent in lower-middle-income countries, such as Iran. In comparison, higher-income nations tend to have higher rates of high cholesterol and obesity [50]. Therefore, research conducted in different countries can help improve the predictive indicators of CVD risk.

While our study found an association between TCBI and CVD mortality, this link was weaker compared to CRI-I and CRI-II. Despite its simplicity and accessibility, TCBI has certain limitations. Specifically, TCBI's lipid profile component relies solely on TG and total cholesterol levels for its calculations [10]. In contrast, other atherogenic indices incorporate HDL or LDL levels, potentially offering a more comprehensive evaluation of CVD risk [51]. Moreover, TCBI was mainly designed to predict severe outcomes in the patients [14–16, 52], making its application to the general population potentially inconvenient. Therefore, it is recommended that future studies explore modifications to enhance the relevance of TCBI for broader populations. Given our findings that indicate TCBI is less effective than CRI-I and CRI-II in predicting CVD mortality risk, one significant suggestion for improvement is to include additional important lipid profile components, such as HDL and LDL, in its calculations.

Strength and limitation

This study represents the first comprehensive examination comparing the newly introduced TCBI index's predictive potential with atherogenic indices concerning the occurrence and mortality of CVDs. The research is robust, utilizing a cohort design, a substantial sample

size, and a decade-long follow-up. However, its focus on the Iranian population may limit the generalizability of the findings to other demographics. Given the recent emergence of the TCBI index, additional studies are warranted to validate and assess its screening efficacy for CVD. Identifying some cardiovascular events and mortality through ICD-10 codes may lead to misclassification and reduced accuracy. Finally, while no significant association was found between the TCBI, atherogenic indices, and CVD incidence, the study highlights the need for further research to enhance our understanding of the predictive value of these markers in CVD development.

Conclusion

The TCBI has primarily been studied to predict health outcomes in patients, but this research highlights its potential preventive role in the general population. While TCBI can predict CVD mortality events better than AIP and AC, this study revealed that its association is notably weaker than that of CRI-I and CRI-II. Conversely, none of the indicators assessed showed a significant link to CVD incidence, emphasizing a critical gap in our understanding. This finding underscores the necessity for further research to validate the effectiveness of the newly developed TCBI index in predicting CVD outcomes. Future studies could also consider modifications to this index, such as incorporating LDL, HDL, or VLDL values into its calculation.

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Author contributions
Farzam Kamrani was responsible for conceptualizing the study and writing the manuscript. Mobina Imannezhad also contributed to writing the manuscript. Hamed Hashemi Shahri, Waleed Khaled Saihood, Alireza Rezvani, Parsa Mearaji Far, and Hanie Mahaki gathered the data for the study. Susan Darroudi conducted the statistical analysis. Habibollah Esmaily, Mohammad Shariati, and Mohsen Moohebati provided scientific consultation. Susan Darroudi and Majid Ghayour-Mobarhan served as the corresponding authors.

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Data availability
Data is available upon request from the corresponding author, Prof. Majid Ghayour-Mobarhan.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
The study protocol was approved by the Mashhad university of medical sciences ethical committee (grant number: 4021804). Written informed consent was obtained from all participants prior to their participation in the study.

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