

Joint Associations of Anthropometric Indices and the Cholesterol–High-Density Lipoprotein–Glucose Index with Collateral Circulation Formation in Patients with Chronic Total Occlusion of Coronary Arteries: A Cross-Sectional Study

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Abstract

Background

Coronary collateral circulation (CCC) is an important adaptive response in chronic total occlusion (CTO), yet the capacity for collateral formation varies substantially among patients. Whether the cholesterol-high-density lipoprotein-glucose (CHG) index and CHG-modified anthropometric indices are associated with poor CCC in CTO remains unclear.

Methods

This single-center cross-sectional study included 841 patients with angiographically confirmed CTO from January 2024 to January 2026. CCC was assessed by the Rentrop classification. Associations of CHG, anthropometric indices, and CHG-modified indices with poor CCC were examined using multivariable logistic regression, restricted cubic splines, receiver operating characteristic curves, DeLong tests, mediation analyses, subgroup analyses, and sensitivity analyses after multiple imputation.

Results

Poor CCC was observed in 298 patients (35.4%). CHG and all CHG-modified indices were independently associated with poor CCC. In the fully adjusted model, CHG-ABSI and CHG-WWI showed the strongest associations, with odds ratios of 3.39 (95% CI 2.69–4.27) and 3.27 (95% CI 2.61–4.09) per 1-SD increment, respectively. CHG-ABSI and CHG-WWI also had the highest discriminatory ability, with AUCs of 0.770 and 0.769, and significantly outperformed CHG alone. Restricted cubic spline analyses suggested mainly nonlinear risk-increasing patterns, except for CHG-CVAI. CHG statistically mediated the associations between anthropometric indices and poor CCC, with mediated proportions ranging from 8.17% to 47.72%. Findings were consistent across subgroup and sensitivity analyses.

Conclusions

CHG-modified anthropometric indices, particularly CHG-ABSI and CHG-WWI, were strongly associated with poor CCC in patients with CTO. These accessible composite indices may help identify patients with an adverse metabolic-adiposity phenotype who are at increased risk of inadequate collateral formation.

Background

Chronic total occlusion (CTO) is a complex and high-risk lesion in coronary artery disease. Under the condition of long-term occlusion, the ischemic myocardium relies on the establishment of coronary collateral circulation (CCC) to compensatorily maintain blood perfusion[1]. Good CCC not only reduces the extent of myocardial infarction but is also a critical factor determining the prognosis of patients with CTO[2–4]. However, there is significant individual heterogeneity in the capacity for collateral vessel formation among patients. Therefore, identifying the key predictive factors affecting CCC formation holds significant clinical value for the risk assessment of patients with CTO[2, 5].

Obesity has been proven to be one of the high-risk factors for CTO. Clinically, body mass index (BMI) is commonly used to evaluate obesity in patients, but this index cannot accurately reflect the accumulation of visceral fat[6]. Visceral fat, as one of the key factors in cardiometabolic risk, differs from subcutaneous fat in that it is a highly active endocrine organ. It secretes a large number of pro-inflammatory cytokines (such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6)) and reduces the secretion of adiponectin, which has cardiovascular protective effects, thereby leading to a state of chronic low-grade inflammation and local insulin resistance (IR) in the human body[7]. To more accurately assess an individual's central obesity and fat distribution characteristics, various novel anthropometric indices have been introduced in recent years, including the waist-to-hip ratio (WHR), body roundness index (BRI), weight-adjusted waist index (WWI), a body shape index (ABSI), and the Chinese visceral adiposity index (CVAI)[8–10]. Some of the aforementioned indices have been proven to have good value in predicting the state of CCC in patients with CTO[11]; however, a single index of visceral fat accumulation may not fully explain the true pathological state of impaired endothelial function and angiogenesis in an individual.

Collateral angiogenesis is highly dependent on endothelial cell homeostasis, and oxidative stress triggered by lipid and glucose metabolism disorders and IR is a key pathway leading to endothelial dysfunction and the inhibition of angiogenesis[7, 12]. The hyperinsulinemic-euglycemic clamp (HEC) technique is the gold standard for evaluating IR, but it is expensive and requires multiple venipunctures[13]. Based on previous studies, the cholesterol-high-density lipoprotein-glucose (CHG) index proposed by Ruan et al. integrates three core parameters of lipids and blood glucose, which can comprehensively quantify the body's metabolic burden and the degree of IR better than a single

indicator[14]. Although existing studies have confirmed that a high level of the CHG index is closely related to adverse cardiovascular events[15–17], its independent role in evaluating the quality of CCC formation has not yet been systematically reported.

Previous studies exploring the influencing factors of CCC have mostly considered human visceral fat measurement indices and metabolic parameters as isolated variables. However, in actual pathological mechanisms, an individual's morphological phenotype is closely related to their internal metabolic microenvironment, and complex interactions exist[6, 7]. The pressure effect of obesity stems not only from mechanical load but is also closely linked to chronic low-grade inflammation and IR. Inflammatory factors secreted by visceral fat not only directly damage vascular endothelial function, thereby inhibiting the vascular endothelial growth factor (VEGF) pathway, but also induces IR through the phosphorylation of insulin receptor substrate-1 (IRS-1) to further promote endothelial dysfunction[7, 12]. To date, there is a lack of systematic clinical verification regarding the joint associations of anthropometric indices and the CHG index, as well as their impact on CCC formation in patients with CTO. Based on the above background, this cross-sectional study hypothesizes that there is an interaction between anthropometric indices and the CHG index in affecting angiogenesis, and aims to systematically evaluate the clinical predictive value of their joint association for poor CCC formation in patients with CTO.

Methods

Study design and participants

This study enrolled 4865 patients, and a total of 841 patients with CTO in one or more major coronary branches were included as illustrated in Fig. 1. Given the single-center, observational, and cross-sectional characteristics of this study, all patients included were confirmed via coronary angiography at the Affiliated Hospital of Qingdao University from January 2024 to January 2026. The specific exclusion criteria for all included patients were as follows: (1) Acute coronary episodes, percutaneous interventions, or open-chest revascularization procedures occurring during the preceding ninety days. (2) Profound cardiac decompensation, ventricular emptying capabilities below thirty percent, significant valve abnormalities, or inborn heart defects. (3) Profound liver dysfunction or diminished renal filtration metrics (defined as transaminase levels > 5 times the upper normal limit or estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m²). (4) Active viral or bacterial contagions, autoimmune anomalies, ongoing neoplastic growths, or severe blood-related abnormalities. (5) Current immune-suppressing pharmacological regimens, hormonal therapies, or recent major physical injuries and invasive operative procedures.

Data collection and definitions

Information on patient demographics (age and sex), cardiovascular risk factors (hypertension, diabetes mellitus, and smoking status), and prescribed medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [ACEIs/ARBs], beta-blockers, mononitrates, and antidiabetic agents) was obtained from the hospital's electronic medical record system. In addition, baseline laboratory parameters—such as neutrophil count, lipid profiles, creatinine (Cr), urea, eGFR, and uric acid (UA), among others—were measured from fasting venous blood samples collected within 24 hours prior to the CTO revascularization. Then we calculated the CHG index, BRI, WWI, WHR, ABSI, CVAI, and CHG-modified indices. The baseline anthropometric and metabolic indices were defined and calculated using the following standardized formulas:

$$CHG = \ln \left(\frac{TC_{mg/mL} \times FBG_{mg/mL}}{2 \times HDL - C_{mg/mL}} \right)$$

;

$$BRI = 364.2 - 365.5 \times \sqrt{1 - \frac{(WC_{cm}/2\pi)^2}{(0.5 \times Height_{cm})^2}}$$

;

$$WWI = \frac{WC_{cm}}{\sqrt{Weight_{kg}}}$$

;

$$WHR = \frac{WC_{cm}}{Hip\ circumference_{cm}}$$

;

$$ABSI = \frac{WC_m}{BMI^{2/3} \times Height_m^{1/2}}$$

;

for males:

$$CVAI = -267.93 + 0.68 \times Age_{years} + 0.03 \times BMI + 4.00 \times WC_{cm} + 22.00 \times \log_{10}TG_{mmol/L} - 16.32 \times HDL - C_{mmol/L}$$

;

for females:

$$CVAI = -187.32 + 1.71 \times Age_{years} + 4.32 \times BMI + 1.12 \times WC_{cm} + 39.76 \times \log_{10}TG_{mmol/L} - 11.66 \times HDL - C_{mmol/L}$$

.

CHG-modified indices were calculated as follows:

$$CHG - CVAI = CHG \times CVAI$$

;

$$CHG - ABSI = CHG \times ABSI$$

;

$$CHG - WHR = CHG \times WHR$$

;

$$CHG - WWI = CHG \times WWI$$

;

$$CHG - BRI = CHG \times BRI$$

.

Diagnostic criteria

The major coronary branches evaluated included the left anterior descending (LAD), left circumflex (LCX), and right coronary arteries (RCA). CTO was angiographically defined as a 100% luminal narrowing with Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow for an estimated duration of at least 3 months[18]. All angiograms were independently evaluated by two experienced interventional cardiologists who were blinded to the patients' laboratory findings. Any disagreements were resolved by a third senior interventional cardiologist. To assess the development of collateral blood flow, we applied the Rentrop scoring system, categorizing it into four distinct levels: grade 0, no collateral vessels were filled with contrast; grade 1, collateral vessels were filled with contrast but did not perfuse the epicardial arteries; grade 2, the epicardial arteries were partially filled with contrast through the collateral vessels; and grade 3, the epicardial arteries were completely filled with contrast through the collateral vessels[19]. For individuals presenting with several affected vessels, the specific branch exhibiting the maximum Rentrop score served as the primary analytical target. Based on these established criteria, the study population was subsequently bifurcated into a poor CCC cohort (encompassing scores of 0 or 1) alongside a good CCC cohort (representing scores of 2 or 3).

Handling of missing data

Overall, incomplete data were present in 13.2% of the patients (111 of 841), with the missing rates for individual covariates ranging from 0.12% to 6.66% (detailed patterns of missing data are provided in Table S1). The missingness was assumed to be missing at random (MAR). To minimize potential bias, we employed multiple imputation by chained equations (MICE) based on Markov chain Monte Carlo (MCMC) sampling. Twenty imputed datasets were generated, and final parameter estimates were pooled according to Rubin's rules.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normality of continuous data. Normally distributed variables were expressed as mean $\pm$ standard deviation (SD), non-normally distributed variables as median and interquartile range (IQR), and categorical variables as frequencies and percentages (n, %). Intergroup differences were evaluated using the independent-samples t-test, Mann-Whitney U test, or Chi-square test, as appropriate.

To evaluate the independent and joint associations of the anthropometric indices and CHG with the risk of poor CCC, a parallel modeling strategy was implemented. For each primary biomarker (CHG, CVAI, ABSI, WHR, WWI, and BRI) and CHG-modified indices (CHG-CVAI, CHG-ABSI, CHG-WHR, CHG-WWI, and CHG-BRI), three distinct logistic regression models were constructed: Model 1 was unadjusted; Model 2 was adjusted for baseline demographic and risk factors (including sex, age, and smoking status); Model 3 was further adjusted for history of diabetes, history of hypertension, low-density lipoprotein cholesterol (LDL-C), high-sensitivity C-reactive protein (hs-CRP), UA, eGFR, Cr, and LAD artery involvement. All regression analyses were performed across the 20 imputed datasets, and the results were pooled using Rubin's rules to estimate the overall odds ratios (ORs) and their 95% confidence intervals (CIs). Additionally, the fraction of missing information (FMI) was extracted from the fully adjusted models (Model 3) to quantify the statistical uncertainty introduced by the multiple imputation process. To address the challenges in interpreting regression coefficients and the potential inflation of ORs caused by vast differences in the original measurement scales, all continuous core predictors were standardized using Z-score transformation prior to model entry. Thus, the final reported ORs represent the risk of poor CCC per 1-standard deviation (1-SD) increase in each index, ensuring the horizontal comparability of predictive performance across different indicators. Furthermore, multicollinearity diagnostics (Table S2) indicated that all variance inflation factors (VIFs) were below 5, confirming the absence of significant multicollinearity among the covariates.

Restricted cubic spline (RCS) analysis was employed to characterize the dose-response relationship. Furthermore, receiver operating characteristic (ROC) curves and the area under the curve (AUC) were utilized to evaluate the sensitivity and specificity of the CHG index and its modified indices in predicting poor CCC formation. DeLong's test was subsequently applied to statistically compare the differences in AUCs among these indices. Mediation analysis was performed to assess the direct and indirect associations of anthropometric indices with the risk of poor CCC through the CHG index. Specifically, anthropometric indices were treated as the exposure variables (X), the CHG index as the mediator (M), and poor CCC as the outcome (Y). Before modeling, six anthropometric indices were Z-transformed so that effect estimates are expressed per 1-standard deviation (SD) increase, ensuring cross-index comparability. Within the mediation framework, a linear regression model was fitted for the continuous mediator (CHG index) and a logistic regression model for the binary outcome (poor CCC). The average causal mediation effect (ACME), average direct effect (ADE), total effect, and proportion mediated were estimated using nonparametric bootstrapping with 1,000 resamples, and robust 95% confidence intervals were derived. All models were mutually adjusted for the following potential confounders: age, sex, smoking status, diabetes, hypertension, LDL-C, CRP, UA, eGFR, creatinine, and LAD artery involvement. Of note, these analyses estimate statistical mediation based on observational data and do not establish biological causality; any potential causal relationship warrants further experimental validation.

Subgroup and interaction analyses were performed to evaluate the robustness of the associations between the CHG index (and its modified indices) and poor coronary collateral circulation across various clinical strata, and to explore potential effect modifiers. These different subgroups were set according to age (< 60 or ≥ 60 years), eGFR (< 60 or ≥ 60 ml/min/1.73m²), diabetes status (Yes or NO), hypertension status (Yes or NO), smoking status (Yes or NO), CTO related artery (LAD or LCX or RCA), and BMI (< 25 or ≥ 25 kg/m²). To enhance the robustness of our findings, we conducted a series of sensitivity analyses. First, the dataset was reanalyzed after excluding all cases with missing values. Second, we redefined the outcome variable: only patients with a Rentrop grade of 3 were classified into the good CCC group, while those with Rentrop grades 0–2 were classified into the poor CCC group, and the analysis was subsequently repeated. All statistical analyses were implemented using R software (version 4.3.0). All tests were two-tailed, with a significance level set at $p < 0.05$; results yielding p -values below this threshold were considered statistically significant.

Results

Population characteristics

This study included 841 subjects, where 298 (35.4%) presented impaired coronary collateral circulation (CCC). The median age reached 64.00 (55.00, 71.00) years, comprising predominantly males (76.58%, $n = 644$). Initial clinical profiles varied significantly between the favorable and poor CCC groups (Table 1). Relative to patients possessing adequate CCC, the impaired cohort exhibited elevated BMI, TG, TC, hs-CRP, FBG, neutrophils, smoking status, β -blocker usage, and all CHG-modified indices (CHG, CHG-CVAI, CHG-ABSI, CHG-WHR, CHG-WWI, CHG-BRI). Conversely, they showed reduced age, SBP, HDL-C, and creatinine concentrations. Table 1 provides comprehensive baseline characteristics.

Table 1
Baseline characteristics of the study participants

Characteristics	Total (n = 841)	Good CCC (n = 543)	Poor CCC (n = 298)	p value
Demographics				
Age, years	64.00 (55.00, 71.00)	65.00 (56.00, 72.00)	62.00 (54.00, 70.00)	0.011
Gender				0.069
Female	197 (23.42%)	116 (21.36%)	81 (27.18%)	
Male	644 (76.58%)	427 (78.64%)	217 (72.82%)	
BMI, kg/m ²	26.00 (24.00, 28.00)	25.80 (23.90, 27.70)	26.30 (24.50, 28.40)	0.002
SBP (mmHg)	131.10 ± 17.85	133.40 ± 17.31	126.93 ± 18.09	< 0.001
DBP (mmHg)	77.00 (70.00, 85.00)	78.00 (70.00, 84.00)	76.00 (69.25, 85.00)	0.274
Current smoking	276 (32.82%)	164 (30.20%)	112 (37.58%)	0.035
Co-morbidities (n, %)				
Diabetes	406 (48.28%)	255 (46.96%)	151 (50.67%)	0.338
Hypertension	470 (55.89%)	310 (57.09%)	160 (53.69%)	0.381
Medical history (n, %)				
Antidiabetic drugs	301 (35.88%)	185 (34.13%)	116 (39.06%)	0.178
β-receptor blocker	457 (54.47%)	276 (50.92%)	181 (60.94%)	0.007
ACEI/ARB	470 (56.02%)	299 (55.17%)	171 (57.58%)	0.549
Nitrates	362 (43.15%)	245 (45.20%)	117 (39.39%)	0.121
Laboratory measurements				
CHG	5.12 (4.87, 5.38)	5.04 (4.77, 5.25)	5.26 (5.05, 5.60)	< 0.001
CHG-CVAI	583.17 (428.84, 718.11)	521.73 (374.82, 661.27)	677.47 (555.87, 802.76)	< 0.001
CHG-ABSI	0.39 (0.36, 0.42)	0.38 (0.35, 0.40)	0.42 (0.39, 0.45)	< 0.001
CHG-WHR	4.60 (4.30, 4.90)	4.53 (4.22, 4.79)	4.80 (4.45, 5.16)	< 0.001
CHG-WWI	52.00 (47.52, 56.42)	49.97 (46.07, 53.70)	55.80 (51.97, 60.71)	< 0.001
CHG-BRI	18.99 (14.74, 23.49)	17.01 (13.64, 21.10)	22.75 (18.38, 26.41)	< 0.001
TG, mmol/L	1.21 (0.91, 1.80)	1.16 (0.90, 1.69)	1.33 (0.95, 2.06)	< 0.001
TC, mmol/L	4.19 (3.55, 5.12)	3.94 (3.47, 4.78)	4.65 (3.83, 5.40)	< 0.001
LDL-C, mmol/L	2.44 (1.79, 3.11)	2.38 (1.78, 3.08)	2.52 (1.89, 3.15)	0.177
HDL-C, mmol/L	1.29 (1.14, 1.48)	1.30 (1.14, 1.49)	1.26 (1.11, 1.46)	0.041
hs-CRP, mg/L	1.25 (0.34, 5.68)	0.83 (0.31, 4.14)	2.21 (0.52, 7.92)	< 0.001
Creatinine, μmol/L	91.00 (76.00, 102.25)	92.00 (77.50, 103.00)	86.00 (74.00, 101.00)	0.024
FBG, mmol/L	5.52 (4.89, 6.74)	5.33 (4.65, 6.50)	5.98 (5.29, 7.21)	< 0.001
Uric acid, mmol/L	340.00 (282.00, 407.00)	336.50 (279.50, 396.75)	343.00 (282.50, 419.50)	0.247
Urea nitrogen, mmol/L	6.09 (4.96, 7.62)	6.04 (4.95, 7.48)	6.13 (4.99, 7.87)	0.618
Neutrophils, ×10 ⁹ /L	4.22 (3.25, 5.64)	4.00 (3.14, 5.25)	4.80 (3.63, 6.42)	< 0.001

Abbreviations: ABSI, a body shape index; ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; BMI, body mass index; BRI, body roundness index; CCC, coronary collateral circulation; CHG, cholesterol-high-density lipoprotein-glucose; Cr, creatinine; CVAI, Chinese visceral adiposity index; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglycerides; UA, uric acid; WHR, waist-to-hip ratio; WWI, weight-adjusted waist index.

Characteristics	Total (n = 841)	Good CCC (n = 543)	Poor CCC (n = 298)	p value
eGFR, mL/min/1.73m ²	72.92 (61.70, 87.61)	71.80 (62.03, 85.90)	76.41 (61.63, 91.61)	0.090
Angiographic results				
CTO related artery				
LAD	377 (44.83%)	256 (47.15%)	121 (40.60%)	0.080
LCX	372 (44.23%)	234 (43.09%)	138 (46.31%)	0.409
RCA	446 (53.03%)	284 (52.30%)	162 (54.36%)	0.617
Abbreviations: ABSI, a body shape index; ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; BMI, body mass index; BRI, body roundness index; CCC, coronary collateral circulation; CHG, cholesterol-high-density lipoprotein-glucose; Cr, creatinine; CVAI, Chinese visceral adiposity index; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglycerides; UA, uric acid; WHR, waist-to-hip ratio; WWI, weight-adjusted waist index.				

Association of CHG and CHG-modified indices with CCC

Table 2 delineates the multivariable logistic regression analysis assessing the associations between the standardized biomarker indices and the risk of poor CCC. Across all three models, both the primary anthropometric indices and their CHG-modified indices emerged as robust, independent risk factors for poor CCC (all $p < 0.05$, with the vast majority < 0.001). In the fully adjusted model (Model 3), each 1-SD increment in these variables was consistently associated with a substantially elevated risk of impaired collateralization. Notably, combining CHG with morphological indices yielded a pronounced synergistic effect. CHG-ABSI and CHG-WWI demonstrated the highest predictive magnitudes, with the risk of poor CCC increasing by more than threefold per 1-SD increment (OR = 3.39, 95% CI: 2.69–4.27; and OR = 3.27, 95% CI: 2.61–4.09, respectively). Other indices, including CVAI (OR = 2.50, 95% CI: 1.76–3.55) and ABSI (OR = 2.48, 95% CI: 2.03–3.02), also exhibited strong independent predictive values. Furthermore, the fraction of missing information (FMI) remained consistently low across all evaluated indices (ranging from 0.0101 to 0.2399, Table S3), confirming that the multiple imputation process introduced minimal simulation uncertainty to these robust estimates.

Table 2

Multivariable logistic regression analysis for the associations of CHG and CHG-modified anthropometric indices with the risk of poor CCC.

Biomarker	Model 1		Model 2		Model 3	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
CHG index	2.00 (1.65–2.44)	< 0.001	1.94 (1.59–2.36)	< 0.001	2.24 (1.77–2.84)	< 0.001
CVAI index	2.62 (1.88–3.67)	< 0.001	2.54 (1.80–3.58)	< 0.001	2.50 (1.76–3.55)	< 0.001
ABSI index	2.41 (1.99–2.92)	< 0.001	2.48 (2.04–3.01)	< 0.001	2.48 (2.03–3.02)	< 0.001
WHR index	1.23 (1.07–1.43)	0.005	1.44 (1.21–1.70)	< 0.001	1.45 (1.22–1.72)	< 0.001
WWI index	2.37 (1.97–2.85)	< 0.001	2.40 (1.99–2.89)	< 0.001	2.39 (1.98–2.89)	< 0.001
BRI index	2.16 (1.81–2.59)	< 0.001	2.13 (1.77–2.56)	< 0.001	2.12 (1.76–2.56)	< 0.001
CHG-CVAI index	2.27 (1.86–2.75)	< 0.001	2.24 (1.83–2.73)	< 0.001	2.26 (1.84–2.79)	< 0.001
CHG-ABSI index	3.02 (2.45–3.71)	< 0.001	2.97 (2.41–3.65)	< 0.001	3.39 (2.69–4.27)	< 0.001
CHG-WHR index	1.94 (1.62–2.32)	< 0.001	2.10 (1.73–2.55)	< 0.001	2.34 (1.88–2.91)	< 0.001
CHG-WWI index	2.98 (2.43–3.64)	< 0.001	2.92 (2.38–3.59)	< 0.001	3.27 (2.61–4.09)	< 0.001
CHG-BRI index	2.41 (2.01–2.89)	< 0.001	2.38 (1.98–2.86)	< 0.001	2.40 (1.98–2.90)	< 0.001
Model 1: Unadjusted.						
Model 2: Adjusted for age, sex, and smoking status.						
Model 3: Further adjusted for history of diabetes, history of hypertension, LDL-C, hs-CRP, UA, eGFR, Cr, and LAD artery involvement.						
Abbreviations: ABSI, a body shape index; BRI, body roundness index; CCC, coronary collateral circulation; CHG, cholesterol-high-density lipoprotein-glucose; CI, confidence interval; Cr, creatinine; CVAI, Chinese visceral adiposity index; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LAD, left anterior descending; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SD, standard deviation; UA, uric acid; WHR, waist-to-hip ratio; WWI, weight-adjusted waist index.						

RCS analyses revealed the dose-response relationships between the CHG index, its five modified indices, and the risk of poor CCC. After adjusting for confounders, all six evaluated indices demonstrated a highly significant positive association with the incidence of poor CCC (all P overall < 0.001 , Fig. 2). Notably, the CHG-CVAI index exhibited a typical linear dose-response trajectory (P non-linearity = 0.220, Fig. 2-B), indicating that the risk of impaired collateralization escalates proportionally as CHG-CVAI levels rise. Conversely, the remaining indices (CHG, CHG-ABSI, CHG-WHR, CHG-WWI, and CHG-BRI) displayed significant non-linear associations with the risk of poor CCC (all P non-linearity ≤ 0.002 , Figs. 2-A, C, D, E, F).

To further evaluate and compare the diagnostic performance of these biomarker indices for predicting poor CCC, ROC curve analysis was performed (Fig. 3). Among the evaluated parameters, CHG-ABSI and CHG-WWI demonstrated the highest discriminatory capacity, yielding the largest AUC of 0.770 and 0.769, respectively. Other composite indices, including CHG-BRI (AUC = 0.733) and CHG-CVAI (AUC = 0.715), also showed moderate diagnostic utility. Conversely, the traditional CHG-WHR (AUC = 0.676) and the singular baseline CHG index (AUC = 0.693) exhibited relatively weaker performance. Subsequent pairwise comparisons using DeLong's test (Table S4) confirmed that the diagnostic efficacies of both CHG-ABSI and CHG-WWI were significantly superior to the diagnostic efficacy of the CHG index alone (both $P < 0.001$), and no statistical difference was observed between the diagnostic performance of CHG-ABSI and CHG-WWI ($P = 0.860$). Furthermore, CHG-ABSI significantly outperformed CHG-CVAI ($P = 0.002$), CHG-WHR ($P < 0.001$), and CHG-BRI ($P = 0.020$).

Mediation analysis

Figure 4 summarizes the potential mediating effect of the CHG index in the association between anthropometric indices and the risk of poor CCC. Following covariate adjustments, this metabolic marker significantly bridged all morphological parameters with adverse collateralization. Explained fractions varied widely, from 8.17% (ABSI) to 47.72% (BMI). Specifically, conventional scales (BMI) showed substantial mediated overlaps, whereas modern centralized fat indicators (ABSI, WWI) exhibited marginal bridging ratios. The wide variation in mediation proportions across different anthropometric indices suggests that the extent to which lipid-glucose metabolic pathways explain these associations differs by body composition phenotype. Crucially, these observational findings reflect mathematical bridging, not definitive physiological causation.

Subgroup and sensitivity analyses

To further assess the robustness and generalizability of our findings, we performed comprehensive subgroup analyses stratified by demographic characteristics, baseline clinical profiles, and angiographic features (Fig. 5). Across all evaluated subgroups, there was no interaction effect of the optimal composite indices (e.g., CHG-ABSI and CHG-WWI) on the risk of poor CCC (P for interaction > 0.05). However, when evaluating the singular CHG index, there was an interaction effect with age strata and diabetes status (both P for interaction < 0.05 , Fig. 5-A). During the sensitivity analyses, after excluding all cases with missing values, CHG-ABSI and CHG-WWI maintained their predictive dominance (OR = 3.66 and 3.45, respectively) and non-linear associations, indicating that the results were robust to the missing data imputation process. Furthermore, applying a stricter criterion for good CCC (exclusively Rentrop grade 3) eliminated the statistical significance of traditional indices like CVAI and WHR. In contrast, all CHG-modified composite indices sustained robust predictive values. Under this broader impairment definition, their trajectories shifted to a linear pattern, indicating proportional risk accumulation for any incomplete collateralization (Table S5–S6, Figure S1–S2).

Discussion

To our knowledge, this is the first large-scale clinical study to investigate the relationship between the CHG index, its modified indices, and the formation of CCC in patients with CTO. Our findings demonstrated that CHG and all its modified indices were associated with poor CCC formation in CTO patients, with CHG-ABSI and CHG-WWI exhibiting the most pronounced associations. Subsequent RCS analyses revealed that, aside from the linear dose-response trajectory of CHG-CVAI, the remaining indices exhibited significant non-linear risk-increasing trajectories. Furthermore, CHG-ABSI and CHG-WWI demonstrated the strongest predictive capacities for poor CCC. Additionally, as a crucial metabolic mediator, CHG played a bridging role between morphological phenotypes and impaired collateralization, although the magnitude of this mediation effect varied across different anthropometric indices.

The presence and adequacy of CCC are fundamental determinants of prognosis in patients with CTO. Collateral vessels provide an alternative source of perfusion to the myocardium distal to the occlusion, thereby limiting ischemic burden, preserving left ventricular function, reducing infarct size, and influencing clinical outcomes after CTO recanalization[20–23]. Previous studies have identified several clinical, angiographic, inflammatory, and metabolic determinants of collateral development, including diabetes, metabolic syndrome, insulin resistance, systemic inflammation, angiogenic mediators, and other cardiometabolic risk markers[24–30]. In line with these observations, our data showed that CHG, CVAI, ABSI, WHR, WWI, BRI, and all CHG-modified indices were positively associated with poor CCC. More importantly, the composite

indices, especially CHG-ABSI and CHG-WWI, outperformed CHG alone and other modified indices in ROC analyses, suggesting that integrating metabolic and body-shape information may capture a broader risk phenotype than either domain in isolation.

The superior performance of CHG-ABSI and CHG-WWI may be biologically plausible. Unlike BMI, which mainly reflects general body mass and cannot distinguish fat distribution from lean mass, ABSI and WWI are more closely related to central body shape, visceral adiposity, and cardiometabolic risk[6, 9, 31–33]. In patients with CTO, visceral obesity-related indices have been directly associated with coronary collateralization, supporting the relevance of adiposity distribution to collateral vessel formation[8]. When combined with CHG, these indices may jointly characterize two complementary dimensions of risk: adverse lipid-glucose metabolism and unfavorable fat distribution. Recent evidence also suggests that the CHG index and related lipid-glucose composite markers are associated with cardiovascular and cardiometabolic outcomes, and may provide information beyond traditional single metabolic parameters[13, 34]. This may explain why each 1-SD increase in CHG-ABSI and CHG-WWI was associated with more than a threefold higher risk of poor CCC after full adjustment, and why these two indices achieved the highest AUC values. The nonlinear associations observed for CHG, CHG-ABSI, CHG-WHR, CHG-WWI, and CHG-BRI further indicate that the detrimental effect of metabolic-adiposity burden may accelerate beyond specific risk ranges rather than increasing uniformly across the entire distribution. By contrast, the linear dose-response pattern for CHG-CVAI suggests a more proportional accumulation of risk with increasing cardiometabolic-visceral adiposity burden.

Several mechanisms may link the combined metabolic and adiposity phenotype to impaired collateralization. Insulin resistance and dysregulated glucose metabolism can reduce nitric oxide bioavailability, promote oxidative stress, impair endothelial progenitor cell function, and attenuate angiogenic signaling, all of which are essential for arteriogenesis and collateral vessel maturation[24, 35, 36]. Visceral adipose tissue is also an active endocrine and paracrine organ that secretes pro-inflammatory cytokines and adipokines, contributing to vascular inflammation, endothelial dysfunction, and adverse vascular remodeling[6, 37–39]. Consistent with this mechanism, inflammation-related biomarkers such as the systemic immune-inflammation index and pan-immune-inflammation value have been associated with CCC status in CTO patients[29, 40, 41]. Although the CHG index and its modified indices do not directly measure circulating cytokines, they may serve as accessible surrogates of the metabolic-inflammatory milieu that is unfavorable for collateral growth. In this context, the mediation analysis provides quantitative support for a statistical bridging role of CHG between anthropometric phenotypes and poor CCC. The mediated proportions ranged from 8.17% for ABSI to 47.72% for BMI, indicating that lipid-glucose metabolism explains part, but not all, of the relationship between body composition and collateral impairment.

The subgroup and sensitivity analyses further strengthen the credibility of the findings. The associations of the best-performing composite indices, particularly CHG-ABSI and CHG-WWI, were consistent across strata defined by age, renal function, diabetes, hypertension, smoking, culprit CTO artery, and BMI, with no significant interaction detected. Although CHG alone showed interactions with age and diabetes status, the combined indices remained stable, supporting their potential applicability across heterogeneous CTO populations. The complete-case analysis produced similar results, indicating that the findings were not driven by the multiple-imputation procedure. Moreover, when a stricter definition of good CCC was applied, traditional anthropometric indices such as CVAI and WHR lost statistical significance, whereas the CHG-modified indices retained robust associations. This pattern suggests that combined indices may be more resilient than single-domain markers when collateral status is defined under different clinical thresholds.

These findings may have practical implications. CHG and anthropometric indices are inexpensive, noninvasive, and easily derived from routine clinical measurements, making CHG-modified indices attractive tools for preliminary risk stratification in patients with CTO. Evidence from contemporary cohort studies indicates that ABSI, WWI, BRI, CVAI, and other body-shape indices can provide clinically meaningful information for cardiovascular risk assessment[10, 33, 42, 43]. Similarly, recent CHG-related studies support the value of this lipid-glucose composite index in predicting cardiovascular and cardiometabolic outcomes[13, 34]. Identifying patients with a high metabolic-adiposity burden before coronary angiography or revascularization may help clinicians recognize individuals who are more likely to have inadequate collateral protection and who may require closer assessment, more intensive cardiometabolic management, and individualized procedural planning. Nevertheless, the moderate AUC values indicate that these indices should not be used as stand-alone diagnostic tools. Rather, they may complement established clinical, laboratory, and angiographic information in a multidimensional evaluation of collateral circulation.

Several limitations should be acknowledged. First, this was a single-center cross-sectional study; therefore, causal relationships between CHG-modified indices and poor CCC cannot be inferred. Second, although we adjusted for multiple potential confounders and performed sensitivity analyses, residual confounding from unmeasured factors, such as the exact duration of occlusion, physical activity, dietary pattern, medication adherence, and inflammatory cytokine levels, may remain. Third, CCC was assessed angiographically using the Rentrop classification, which is widely used but semi-quantitative and may not fully reflect functional collateral flow. Fourth, the study population consisted of Chinese patients with CTO from one hospital, which may limit generalizability to other ethnic groups and healthcare settings. Finally, the proposed composite indices require external validation in prospective multicenter cohorts, and future studies should determine whether interventions that improve metabolic health or visceral adiposity can enhance collateral development or improve clinical outcomes.

Conclusions

CHG and CHG-modified anthropometric indices were independently associated with poor CCC formation in patients with CTO. Among them, CHG-ABSI and CHG-WWI showed the strongest associations and the best discriminatory performance, while CHG partially mediated the relationship between anthropometric phenotypes and impaired collateralization. These results highlight the importance of considering the joint metabolic and body-shape burden when evaluating collateral circulation in CTO and provide a basis for future prospective studies and risk-stratification models.

Abbreviations

ABSI
A body shape index

Declarations

Ethical approval and consent to participate

This research obtained approval from the Ethics Committee of the Affiliated Hospital of Qingdao University (Approval Number: QYFY WZLL 50293) and adhered strictly to the Declaration of Helsinki. Given that this study adopts a cross-sectional research design, the Ethics Committee referenced above has waived the requirement to obtain informed consent from participants. All personal identifying information of the patients was fully anonymized to protect privacy.

Consent for publication

Not applicable.

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Author Contribution

Xueyu Lv and DL initiated the study's design. Analysis and preparation of the datasets were conducted by Xueyu Lv, ZHD and JQY, while Xueyu Lv and Xiaoyan Lu composed the original text. DL, Xiaoyan Lu and JQY contributed to the review of findings and subsequent edits. The completed manuscript was formally checked and authorized by every author.

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Data Availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Figures

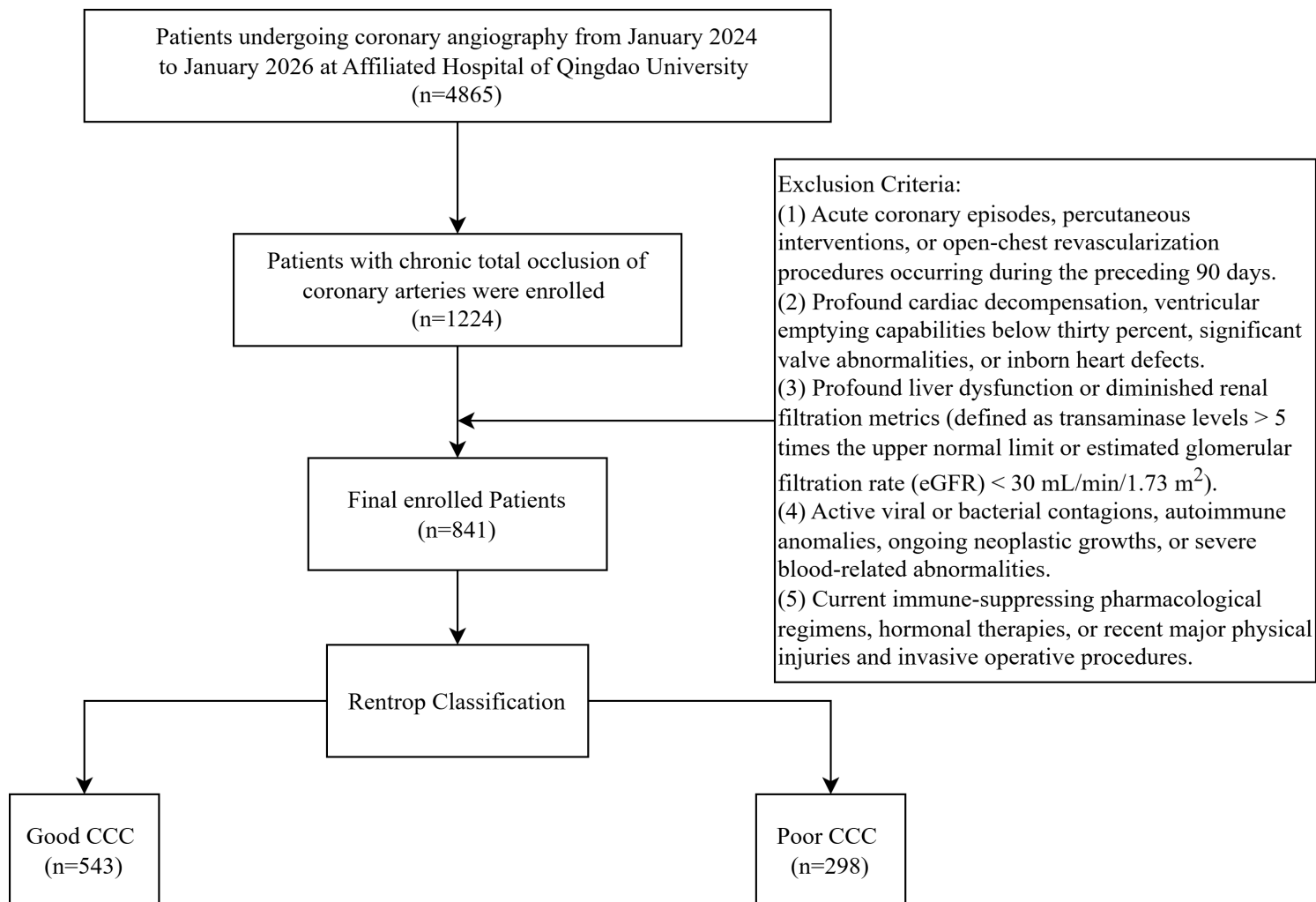


Figure 1

Flow diagram of the study population selection process. CABG, coronary artery bypass grafting; CCC, coronary collateral circulation; CTO, chronic total occlusion; PCI, percutaneous coronary intervention.

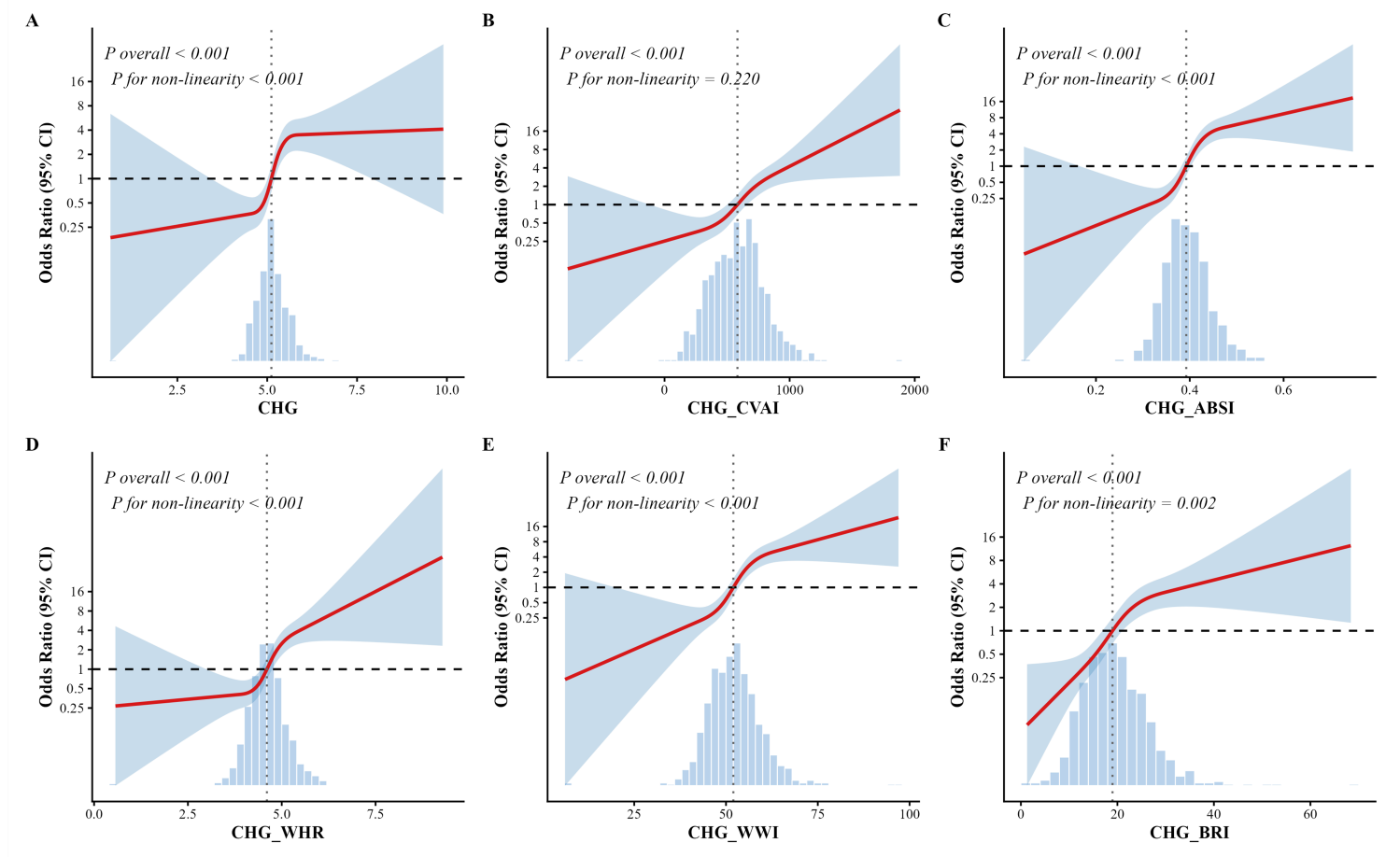


Figure 2

Restricted cubic spline curves for CCC by CHG (A), CHG-CVAI (B), CHG-ABSI (C), CHG-WHR (D), CHG-WWI (E) and CHG-BRI (F), after covariate adjustment. Heavy central line represents the estimated adjusted hazard ratio, with shaded ribbons denoting 95% confidence interval. The model is adjusted for sex, age, smoke, DB, HB, LDL, CRP, UA, eGFR, LAD, and Cr. CCC Coronary collateral circulation; CHG Cholesterol-high-density lipoprotein-glucose; ABSI A body shape index; BRI Body roundness index; CVAI Chinese visceral adiposity index; WHR Waist-to-hip ratio; WWI Weight-adjusted waist index; CI Confidence interval; Cr Creatinine; CRP C-reactive protein; DB Diabetes mellitus; eGFR Estimated glomerular filtration rate; HB Hypertension; HR Hazard ratio; LAD Left anterior descending artery; LDL Low-density lipoprotein cholesterol; UA Uric acid.

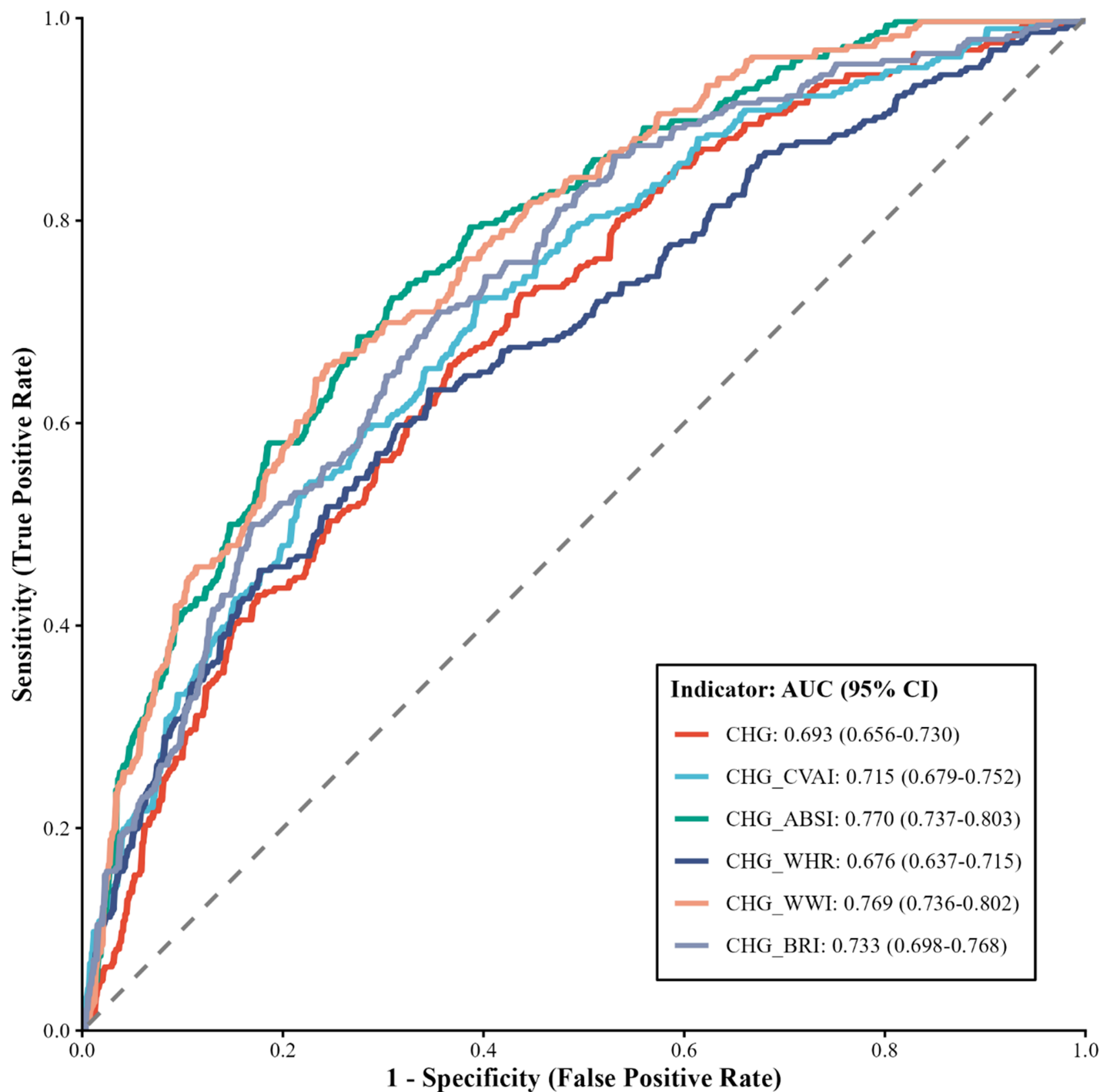
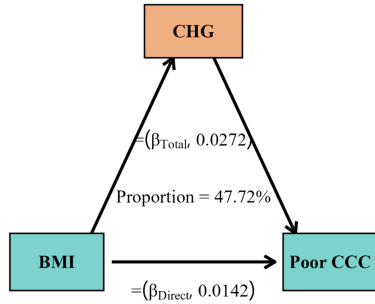
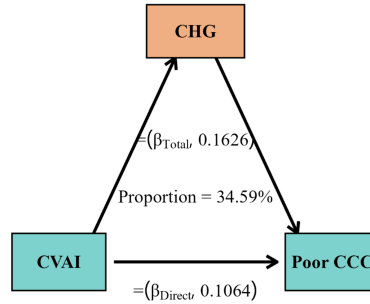
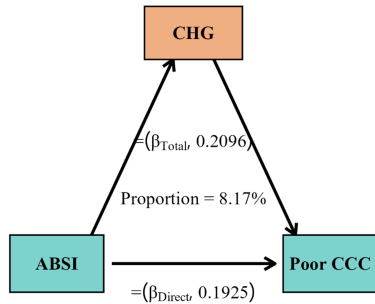
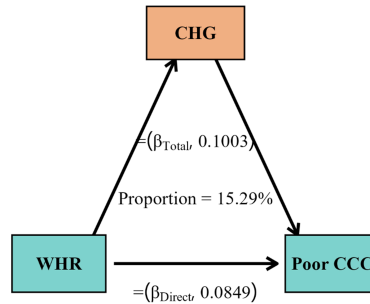
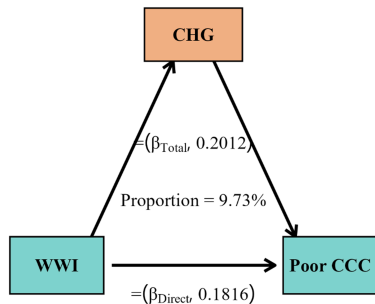
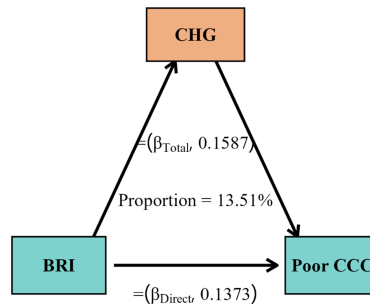


Figure 3

Dose-response associations of the CHG index and CHG-modified anthropometric indices with the risk of poor CCC. ABSI, a body shape index; BRI, body roundness index; CCC, coronary collateral circulation; CHG, cholesterol-high-density lipoprotein-glucose; CVAI, Chinese visceral adiposity index; WHR, waist-to-hip ratio; WWI, weight-adjusted waist index.

A**B****C****D****E****F****Figure 4**

Mediation analysis of CHG on the association between anthropometric indices and the risk of poor CCC. Adjusted for sex, age, smoke, DB, HB, LDL, CRP, UA, eGFR, LAD, and Cr. ABSI, a body shape index; BRI, body roundness index; BMI body mass index; CCC, coronary collateral circulation; CHG, cholesterol-high-density lipoprotein-glucose; CVAI, Chinese visceral adiposity index; WHR, waist-to-hip ratio; WWI, weight-adjusted waist index.

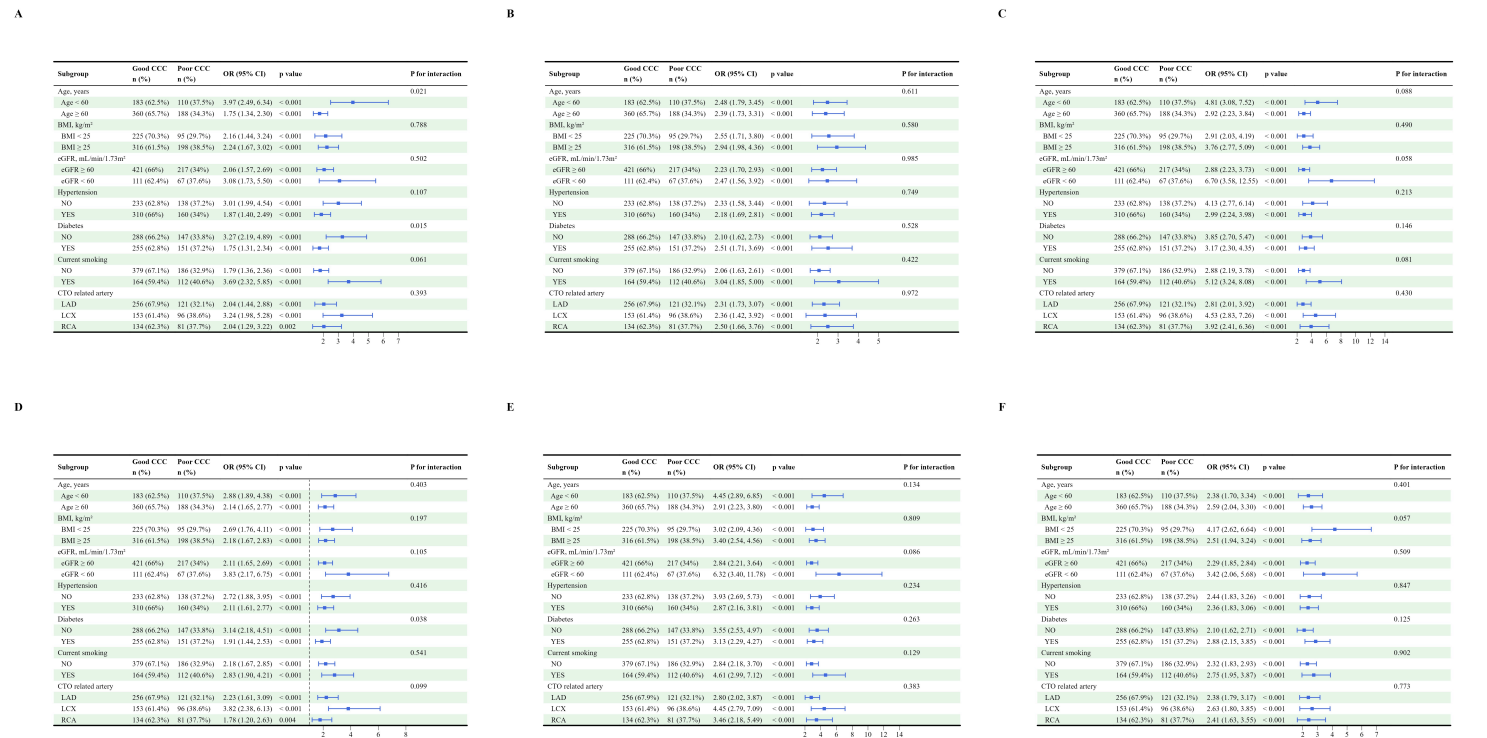


Figure 5

Forest plot showing the subgroup analyses of the multivariable-adjusted association between CHG index and CHG-modified anthropometric indices and the risk of poor CCC. Multivariate models were adjusted for sex, age, smoke, DB, HB, LDL, CRP, UA, eGFR, LAD, and Cr. ABSI, a body shape index; BRI, body roundness index; BMI body mass index; CCC, coronary collateral circulation; CHG, cholesterol-high-density lipoprotein-glucose; CVAI, Chinese visceral adiposity index; WHR, waist-to-hip ratio; WWI, weight-adjusted waist index.

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