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The fibrosis-4 index and its association with carotid atherosclerosis in type 2 diabetes: a cross-sectional study in China

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Abstract

Background The medical community has long been concerned about the cardiovascular disease risk in patients with type 2 diabetes. While liver fibrosis scores were originally designed for application in individuals with liver steatosis, an increasing number of studies have shown that they are also associated with cardiovascular disease risk. However, the association between Fibrosis-4 (Fib-4) in liver fibrosis scores and carotid atherosclerosis (CA) in patients with type 2 diabetes remains unclear.

Objective The aim of this study is to investigate the association between the Fib-4 index and CA in patients with Type 2 diabetes. Additionally, it seeks to determine whether this relationship is influenced by factors including gender, age, body mass index (BMI), hypertension, and other variables.

Methods Screening based on inclusion and exclusion criteria identified 2658 hospitalized patients with type 2 diabetes. Subsequently, patients were divided into three groups according to Fib-4 values (Fib-4 < 1.3, 1.3 ≤ Fib-4 < 2.67, Fib-4 ≥ 2.67). Logistic regression analysis was then applied to evaluate the association between Fib-4 and the presence of CA in type 2 diabetes. Further stratified analyses were conducted considering gender, age (using 60 years as the threshold), hypertension status, smoking, alcohol consumption, and BMI groups (using 24 kg/m2 as the threshold), aiming to investigate potential effect heterogeneity within predefined subgroups. ROC curve analysis was used to evaluate the predictive power of the Fib-4 value for CA, increased CIMT, and carotid plaques.

Results The study encompassed 2658 patients diagnosed with type 2 diabetes, comprising 1441 males and 1217 females, with an average age of 56.71 ± 10.22 years. Among them, 1736 individuals (65.3%) exhibited CA, 1243 (46.8%) had increased carotid intima-media thickness (CIMT), and 1273 (47.9%) manifested carotid plaques. Following adjustments for various factors, the prevalence of CA exhibited a progressive increase in the Fib-4 < 1.3, 1.3 ≤ Fib-4 < 2.67, and Fib-4 ≥ 2.67 groups, with statistically significant differences ($P < 0.05$). Moreover, the prevalence of increased CIMT and carotid plaques in the Fib-4 ≥ 2.67 group remained significantly higher than that in the Fib-4 < 1.3 group after considering various factors ($P < 0.05$). In the 1.3 ≤ Fib-4 < 2.67 group, subsequent to adjustments for gender, smoking, and drinking, the prevalence of increased CIMT and carotid plaques surpassed that in the

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Fib-4 < 1.3 group ($P < 0.05$). Despite further adjustments for multiple factors, the prevalence of increased CIMT and carotid plaques persisted higher than that in the Fib-4 < 1.3 group, yet the difference lacked statistical significance ($P > 0.05$). The results of the ROC curve analysis indicated that the AUC for Fib-4 predicting CA was 0.602 ($P < 0.001$, 95% CI: 0.579–0.625), while the AUC values for increased CIMT and carotid plaques were 0.561 ($P < 0.001$, 95% CI: 0.540–0.583) and 0.580 ($P < 0.001$, 95% CI: 0.558–0.601), respectively.

Conclusion Elevated Fib-4 levels (Fib-4 ≥ 1.3) are positively associated with CA in patients with type 2 diabetes, including increased CIMT and the presence of carotid plaques. As such, Fib-4 may serve as a potential biomarker for the detection of CA in patients with type 2 diabetes. However, its clinical utility needs further validation, particularly in larger sample sizes and multicenter studies.

Keywords Fibrosis-4, Type 2 diabetes, Carotid atherosclerosis, Metabolic dysfunction-associated steatotic liver disease, Liver fibrosis

Introduction

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a prevalent chronic liver condition that affects up to one-third of the global population [1]. Unless specific tests are conducted to identify MASLD, the condition typically remains asymptomatic until advanced stages, potentially leading to irreversible liver damage. Consequently, a significant proportion of MASLD patients are unaware of their underlying serious condition [2]. Formerly recognized as non-alcoholic fatty liver disease (NAFLD), MASLD is characterized by the accumulation of liver fat exceeding 5%, without the influence of excessive alcohol consumption, chronic liver diseases, or other factors causing liver damage [2]. MASLD represents a spectrum of liver disorders, ranging from simple steatosis (fatty liver) to MASLD, marked by liver inflammation and fibrosis [3]. The association between MASLD and metabolic syndrome, along with its components such as obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension, is notably strong [3].

MASLD is not only a liver disease but also a systemic metabolic disorder linked to an elevated risk of cardiovascular disease (CVD), particularly atherosclerosis [3]. The risk of developing atherosclerosis is no longer concentrated in Western countries, and it is instead involved in the majority of deaths worldwide. Atherosclerosis now affects younger people, and more women and individuals from a diverse range of ethnic backgrounds, than was formerly the case [4]. Atherosclerosis represents a chronic inflammatory process characterized by the accumulation of lipids and inflammatory cells within arterial walls, giving rise to plaques that can constrict or block arteries. Common atherosclerotic manifestations encompass coronary heart disease, stroke, carotid atherosclerosis, and peripheral arterial disease (PAD) [4].

Carotid atherosclerosis (CA) emerges as a prevalent complication in individuals with type 2 diabetes, constituting a substantial and potentially preventable contributor to cerebrovascular disease [5]. It serves as a reflection of generalized atherosclerosis and can be noninvasively assessed through carotid ultrasonography [6]. Various parameters, including carotid intima-media thickness (CIMT), carotid plaques, stenosis, and occlusion, as identified by carotid ultrasound, have demonstrated predictive value for assessing the risk of CVD in numerous studies [7]. Therefore, the identification of carotid atherosclerosis risk in patients with type 2 diabetes and the implementation of early intervention hold significant clinical importance.

Liver fibrosis is a fundamental histological characteristic of MASLD and is associated with an increased risk of liver-related morbidity and mortality [8]. Moreover, it is postulated as a potential risk factor for atherosclerosis due to its contribution to chronic inflammation and dyslipidemia. Despite numerous studies exploring the link between liver fibrosis and atherosclerosis, the results have shown inconsistency [9, 10]. To bridge this knowledge gap, we conducted a cross-sectional study to examine the association between the Fibrosis-4 (Fib-4) index and carotid atherosclerosis in patients with type 2 diabetes. Furthermore, our goal was to identify specific population characteristics where the Fib-4 index demonstrates a significant association with carotid atherosclerosis, achieved through comprehensive subgroup analyses.

Methods

Study participants

Figure 1 depicts the process of selecting study participants from the National Metabolic Management Center (MMC) database. After applying the inclusion and exclusion criteria, 2,658 patients with Type 2 diabetes (T2DM), aged 18 to 80 years, were identified from the Endocrinology Department at the Affiliated Hospital of Southwest Medical University between September 2017 and January 2024. These patients were enrolled in the MMC, which provides standardized metabolic disease management under the guidance of Ruijin Hospital, Shanghai. Each participant underwent a comprehensive evaluation, including a standardized questionnaire, anthropometric

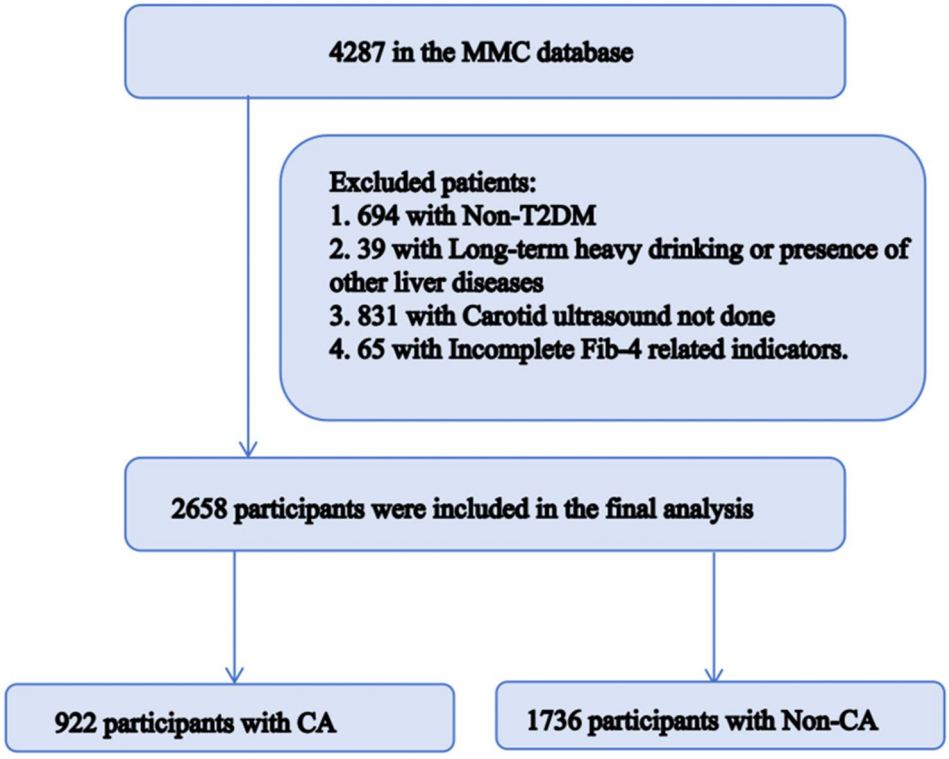

Fig. 1 Flowchart depicting the selection process of the analyzed study sample from the MMC database

measurements, physical examination, laboratory testing, and assessment of diabetes-related complications.

The inclusion criteria were as follows: (1) Age over 18 years; (2) Diagnosis of T2DM according to the American Diabetes Association's "Standards of Medical Care in Diabetes" (2019 edition); and (3) Completion of a carotid ultrasound. Exclusion criteria included: (1) History of alcoholic fatty liver disease; (2) History of hepatitis, cirrhosis, or liver cancer; (3) Chronic heavy alcohol consumption; (4) Diagnosis of Type 1 diabetes, gestational diabetes, or other specific forms of diabetes; (5) Presence of acute diabetic complications, such as diabetic ketoacidosis, hyperglycemic hyperosmolar state, hyperosmolar coma, or hypoglycemia; and (6) Incomplete or missing demographic or clinical data.

Data collection

Trained researchers collected demographic, lifestyle, and medical history data from participants, which included factors such as smoking habits and alcohol consumption. Medical history evaluations considered conditions like hypertension, coronary heart disease, liver diseases, kidney diseases, and other relevant health issues. Additionally, the participants' medication usage was recorded, covering antidiabetic drugs, antihypertensive medications, and antiplatelet agents. Prior to breakfast, participants' weight and height were measured with lightweight clothing and without shoes. Systolic and diastolic blood pressure (SBP and DBP) were measured on the right arm using a standard mercury sphygmomanometer, with three readings taken to calculate the average.

Biochemical data collection included measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum creatinine (Cr), uric acid (UA), blood urea nitrogen (BUN), glycated hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2hPG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG). Hematological parameters assessed included white blood cells (WBC), red blood cells (RBC), and hemoglobin (Hb).

Carotid artery measurements

Participants in our study underwent cervical artery ultrasonography, performed by certified ultrasound technologists. The scans encompassed the bilateral common carotid artery (CCA), internal carotid artery (ICA), external carotid artery (ECA), subclavian artery, and vertebral artery. The measurement of carotid intima-media thickness (CIMT) focused on the far wall of the bilateral common carotid arteries near the bifurcation. An increased CIMT was characterized by an intima-media thickness (IMT) of ≥1.0 mm in either carotid artery. Carotid plaques were identified by an IMT of ≥1.5 mm or the presence of focal structures protruding into the

arterial lumen by at least 0.5 mm or 50% of the surrounding intima-media thickness [11]. Individuals exhibiting increased CIMT, plaques, or carotid stenosis were classified as having carotid atherosclerosis [12].

Definitions

(1) Fib-4 is calculated as follows: Fib-4 = Age (years) × AST (U/L)/[platelets (10^9/L)×$ALT^{1/2}$ (U/L)].The cut-off value for prediction of advanced liver fibrosis was used as established in current literature (≥ 2.67). Additionally, we analyzed the lower cut-off value of Fib-4 (< 1.30) [13].
(2) Insulin resistance was assessed with the HOMA method using the following equation: HOMA-IR = [Fasting insulin (μU/mL) × Fasting glucose (mmol/L)]/22.5 [14].
(3) BMI was calculated on the basis of the weight in kilograms and the height in meters [15].
(4) waist-to-hip ratio(WHR) was calculated as waist circumference (cm)/hip circumference (cm) [16].
(5) waist-to-height ratio(WtHR) was calculated as waist circumference(cm)/height circumference (cm) [17].

Statistical analysis

Participant characteristics were reported as mean (standard deviation) or median (interquartile range), based on the distribution of continuous variables, while categorical variables were summarized as count (percentage). For comparisons of continuous variables, appropriate tests were chosen according to data normality, including Student's t-test, or one-way ANOVA. Chi-square tests were utilized to compare categorical variables between groups. The relationships between Fib-4 and carotid atherosclerosis (CA), increased CIMT, and carotid plaques were evaluated using logistic regression models, with results expressed as odds ratios (OR) and corresponding 95% confidence intervals (CI). Statistical significance was determined using two-tailed p-values, with a threshold set at $p < 0.05$. All analyses were performed using SPSS software (version 26.0), and Forest plots were created with GraphPad Prism (version 9.0.0).

Results

Clinical characteristics

The study included a total of 2658 patients diagnosed with type 2 diabetes, consisting of 1441 males and 1217 females, with an average age of 56.71 ± 10.22 years. Among the participants, 1736 individuals (65.3%) exhibited CA, 1243 (46.8%) had an increased CIMT, and 1273 (47.9%) had carotid plaques. The baseline characteristics of the subjects, categorized by Fib-4, are detailed in Table 1. Significant differences were observed in age, height, WHR, WtHR, and various other parameters across different Fib-4 groups. Moreover, the prevalence of CA increased progressively in the Fib-4 < 1.3 group (60.0%), 1.3 ≤ Fib-4 < 2.67 group (71.4%), and Fib-4 ≥ 2.67 group (73.3%), with statistically significant differences (< 0.001). Similarly, the prevalence of increased CIMT in the Fib-4 < 1.3 group (43.5%), 1.3 ≤ Fib-4 < 2.67 group (49.8%), and Fib-4 ≥ 2.67 group (52.2%) exhibited a gradual rise, with statistically significant differences (< 0.001). Likewise, the prevalence of carotid plaques in the Fib-4 < 1.3 group (43.4%), 1.3 ≤ Fib-4 < 2.67 group (53.3%), and Fib-4 ≥ 2.67 group (53.4%) demonstrated a progressive increase, with statistically significant differences (< 0.001).

Discussion

Several studies have explored the relationship between MASLD and atherosclerosis, with earlier research identifying a strong link between the liver fibrosis index Fib-4 and the severity of coronary artery lesions, as well as its connection to coronary calcification and cardiovascular events [9]. However, other studies present conflicting findings, reporting no association between liver fibrosis and CIMT [10]. To enhance our understanding, it is essential to conduct a more thorough evaluation of the epidemiological relationship between Fib-4 and coronary atherosclerosis (CA) in patients with type 2 diabetes. Our findings indicate that elevated Fib-4 levels are correlated with an increased risk of CA, greater CIMT, and the presence of plaques in patients with type 2 diabetes. Specifically, when Fib-4 levels rise (1.3 ≤ Fib-4 < 2.67), there is a significant increase in the risk of CA, which remains robust even after adjusting for multiple variables. Similarly, higher Fib-4 levels (1.3 ≤ Fib-4 < 2.67) are associated with an increased risk of elevated CIMT and carotid plaques, with this significance persisting after adjustment for confounding factors. In cases of advanced liver fibrosis (Fib-4 ≥ 2.67), the risks of CA, increased CIMT, and carotid plaques are notably higher, and these trends remain significant even after accounting for various confounders. Notably, in the Fib-4 ≥ 2.67 group, the risks of CA, increased CIMT, and carotid plaques exceed those observed in the 1.3 ≤ Fib-4 < 2.67 group and the normal Fib-4 group, highlighting that as Fib-4 levels increase, so do the risks of CA, increased CIMT, and carotid plaques.

Atherosclerosis develops gradually throughout an individual's life, often taking decades before clinical manifestations of atherosclerotic cardiovascular diseases, such as myocardial infarction, stroke, or peripheral ischemic syndromes, become apparent [18]. Previous research has highlighted an increased risk of cardiovascular diseases in individuals with carotid atherosclerosis (CA), leading to the systematic screening of carotid atherosclerosis as part of cardiovascular risk assessments [19]. With aging being a major risk factor for CA, a higher prevalence of

Table 1 Clinical characteristics of study participants stratified by Fib-4 group

Variables	Overall (*n* = 2658)	Fib-4 < 1.3 (*n* = 1524)	1.3 ≤ Fib-4 < 2.67 (*n* = 490)	Fib-4 ≥ 2.67 (*n* = 644)	*p*-value
Gender					0.126
Male(%)	1441(54.2%)	840(55.1%)	274(55.9%)	327(50.8%)	
Age(years)	56.71 ± 10.22	53.09 ± 10.26[bc]	60.14 ± 7.91[ac]	62.68 ± 7.67[ab]	< 0.001
Height(cm)	160.72 ± 8.54	161.05 ± 8.65[c]	160.89 ± 8.28	159.82 ± 8.42[a]	0.008
Weight(kg)	64.21 ± 12.47	64.47 ± 12.47	64.07 ± 11.03	63.69 ± 11.28	0.363
BMI(kg/m2)	24.75 ± 3.57	24.74 ± 3.69	24.67 ± 3.36	24.85 ± 3.46	0.687
Head circumference(cm)	56(55,57)	56(55,58)	56(55,57)	56(55,57)	0.196
Neck circumference(cm)	37(34,39)	37(34,39)	37(34,39)	37(34,39)	0.524
WC(cm)	86.48 ± 10.00	86.15 ± 10.08	86.52 ± 9.88	87.22 ± 9.89	0.075
Hip circumference(cm)	91.17 ± 7.58	91.18 ± 7.71	90.85 ± 7.28	91.41 ± 7.51	0.473
WHR	0.95 ± 0.07	0.944 ± 0.07[c]	0.95 ± 0.08	0.95 ± 0.08[a]	0.009
WtHR	0.54 ± 0.06	0.54 ± 0.06[c]	0.54 ± 0.06	0.55 ± 0.06[a]	0.001
SBP (mmHg)	135.28 ± 20.69	133.65 ± 20.76[bc]	136.85 ± 20.34[a]	137.91 ± 0.47[a]	< 0.001
DBP(mmHg)	79.21 ± 11.36	79.28 ± 1.47	79.43 ± 11.18	78.89 ± 1.26	0.683
Heart rate(beats per minute)	74(67,82)	75(68,84)[bc]	73(66,81)[a]	72(65,81)[a]	< 0.001
FPG(mmol/L)	9.74 ± 3.44	10.04 ± 3.46[bc]	9.54 ± 3.72[a]	9.19 ± 3.09[a]	< 0.001
2hPG(mmol/L)	14.58 ± 4.81	14.92 ± 4.80[bc]	14.21 ± 4.68[a]	14.08 ± 4.89[a]	< 0.001
INS(U/ml)	7.69(4.51,13.22)	7.59(4.35,13.23)	7.30(4.25,2.33)	7.89(5.07,14.56)	0.069
HOMA-IR	3.17(1.80,5.53)	3.20(1.80,5.56)	3.02(1.74,5.02)	3.14(1.88,5.93)	0.722
HbA1c (%)	9.70 ± 2.52	10.07 ± 2.54[bc]	9.37 ± 2.39[a]	9.09 ± 2.39[a]	< 0.001
WBC (*10^9/L)	6.5(5.39,7.81)	6.80(5.73,8.20)	6.22(5.26,7.39)	5.90(4.97,7.08)	0.0155
RBC (*10^{12}/L)	4.57(4.19,4.96)	4.66(4.27,5.06)	4.53(4.15,4.86)	4.42(4.04,4.77)	0.0136
Hb(g/L)	136.19 ± 19.22	137.70 ± 19.36[c]	135.66 ± 8.14	133.00 ± 19.30[a]	< 0.001
PLT(*10^9/L)	204(164,246)	231(200,272)[bc]	187(160,213)[ac]	151(122.25,178.00)[ab]	< 0.001
TG(mmol/l)	1.77(1.21,2.76)	1.78(1.22,2.79)	1.78(1.24,2.82)	1.72(1.18,2.67)	0.489
TC(mmol/l)	4.88 ± 2.00	4.92 ± 1.39	4.97 ± 3.51	4.72 ± 1.58	0.065
HDL-C(mmol/l)	1.17 ± 0.36	1.14 ± 0.33[c]	1.19 ± 0.34	1.21 ± 0.43[a]	< 0.001
LDL-C(mmol/l)	2.87 ± 1.07	2.97 ± 1.07[bc]	2.83 ± 1.06[ac]	2.66 ± 1.05[ab]	< 0.001
ALT(U/L)	21.10(15.70,31.93)	20.40(15.50,30.20)[c]	20.70(15.50,30.53)[c]	23.95(16.40,38.70)[ab]	< 0.001
AST(U/L)	19.50(15.60,5.70)	17.40(14.20,22.00)[bc]	20.25(17.08,6.80)[ac]	4.70(19.93,36.39)[ab]	< 0.001
GGT(U/L)	5.90(17.30,43.50)	26.10(17.33,41.18)[c]	23.40(16.38,40.05)[c]	28.50(17.80,51.80)[ab]	< 0.001
UA (μmol/L)	327.00(267.80,405.23)	322.80(265.25,399.80)	314.30(262.18,403.90)	337.30(277.90,413.30)	0.703
Cr(μmol/L)	62.00(51.05,77.40)	59.85(49.50,4.40)	62.25(53.20,76.35)	67.20(53.60,84.50)	0.077
BUN(mmol/L)	6.42 ± 2.64	6.23 ± 2.47[c]	6.56 ± 2.60	6.77 ± 2.99[a]	< 0.001
Urinary ACR (mg/g)	19.30(9.10,65.30)	19.50(9.30,65.73)	17.00(8.90,52.70)	20.20(9.00,79.00)	0.323
LABI	1.13(1.08,1.19)	1.12(1.07,1.18)[bc]	1.13(1.09,1.19)[a]	1.15(1.08,1.20)[a]	< 0.001
RABI	1.13(1.08,1.18)	1.12(1.07,1.17)	1.14(1.09,1.19)	1.14(1.09,1.19)	0.203
LBAPWV	1695.00(1465.00,1985.00)	1629.00(1414.75,1921.25)[bc]	1771.00(1538.50,2031.00)[a]	1792.00(1556.75,2068.75)[a]	< 0.001
RBAPWV	1697.00(1468.00,1974.00)	1638.00(1423.00,1905.00)[bc]	1740.00(1533.00,2028.00)[a]	1786.00(1549.00,2.54.00)[a]	< 0.001
Hypertension(%)	1431(53.9%)	743(48.8%)[bc]	293(59.8%)[a]	395(61.3%)[a]	< 0.001
Coronary heart disease(%)	146(5.5%)	54(3.5%)[bc]	34(7.0%)[a]	58(9.0%)[a]	< 0.001
Smoking(%)					0.065
Never	1623(61.1%)	913(59.9%)	295(60.2%)	415(64.5%)	
Ever	570(21.5%)	351(23.0%)	99(20.2%)	120(18.7%)	
Current	463(17.4%)	259(17.0%)	96(19.6%)	108(16.8%)	
Drinking(%)					0.898
Never	1459(55.0%)	824(54.2%)	274(55.9%)	361(56.1%)	
Ever	244(9.2%)	134(8.8%)	44(9.0%)	66(10.3%)	
Current	951(35.8%)	563(37.0%)	172(35.1%)	216(33.6%)	
CA					< 0.001
No	922(34.7%)	610(40.0%)[bc]	140(28.6%)[a]	172(26.7%)[a]	
Yes	1736(65.3%)	914(60.0%)[bc]	350(71.4%)[a]	472(73.3%)[a]	

Table 1 (continued)

Variables	Overall (*n* = 2658)	Fib-4 < 1.3 (*n* = 1524)	1.3 ≤ Fib-4 < 2.67 (*n* = 490)	Fib-4 ≥ 2.67 (*n* = 644)	*p*-value
Increased CIMT					< 0.001
No	1415(53.2%)	861(56.5%)[bc]	246(50.2%)[a]	308(47.8%)[a]	
Yes	1243(46.8%)	663(43.5%)[bc]	244(49.8%)[a]	336(52.2%)	
Carotid plaques					< 0.001
No	1385(52.1%)	862(56.6%)[bc]	229(46.7%)[a]	294(45.7%)[a]	
Yes	1273(47.9%)	662(43.4%)[bc]	261(53.3%)[a]	350(54.3%)[a]	

Abbreviations CA, carotid atherosclerosis; CIMT, carotid intima–media thicking; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; WtHR, waist-to-height ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2hPG, postprandial 2-hour plasma glucose; INS, insulin; HbA1c, glycated hemoglobin A1c ; WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; PLT, platelet; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase; UA, uric acid; Cr, serum creatinine; BUN, urea nitrogen; Urinary ACR, the urinary albumin-to- Cr ratio; LABI, left ankle-brachial index; RABI, right ankle-brachial index; LBAPWV, left brachial-ankle pulse wave velocity; RBAPWV, right brachial-ankle pulse wave velocity

"a" represents a statistically significant difference compared to the Fib-4 < 1.3 group ($P < 0.05$), "b" represents a statistically significant difference compared to the 1.3 ≤ Fib-4 < 2.67 group ($P < 0.05$), and "c" represents a statistically significant difference compared to the Fib-4 ≥ 2.67 group ($P < 0.05$)

carotid atherosclerosis is expected as the global population continues to age. Identifying and defining CA in asymptomatic populations remains crucial for those who might benefit from early intervention. The use of serum biomarkers presents a promising strategy to support decision-making in managing carotid vascular burdens.

T2DM and MASLD share some common pathogenic pathways with atherosclerotic disease, including insulin resistance, lipid disorders, and inflammation. Previous studies have identified MASLD as an independent predictor of long-term cardiovascular risk [20]. However, a sensitive and efficient screening tool to identify the risk of CA associated with MASLD in T2DM patients remains elusive. Studies have shown that using ultrasound to evaluate steatosis in MASLD lacks sensitivity [21]. while liver biopsy, though accurate, is invasive and unsuitable for primary cardiovascular risk detection. Additionally, assessing cardiovascular risk in individuals at high risk for MASLD, even without a confirmed diagnosis, is crucial. Non-invasive scoring systems have been proposed as a solution to detect advanced fibrosis and predict liver-related complications [9]. In recent years, various studies have demonstrated that liver fibrosis scores possess significant prognostic value for liver-related outcomes, cardiovascular mortality, and all-cause mortality in both MASLD and the general population [2]. Among these, Fib-4 is a recommended liver fibrosis score in clinical guidelines, recognized for its diagnostic accuracy in identifying patients with advanced fibrosis, showing both high sensitivity and specificity [22]. Chuan Lu et al. found a significant association between elevated Fib-4 scores and coronary artery disease (CAD) in patients with MAFLD. The percentage of patients with high Fib-4 scores was greater in the CAD group than in the non-obstructive and normal groups (5.80%, 4.31%, and 2.24%, respectively; $p < 0.001$), and CA was a significant predictor of CAD. The Fib-4 score remained independently associated with CAD even after adjusting for sex and other established cardiovascular risk factors [9]. Adelaida Solomon et al. reported significantly elevated Fib-4 levels in patients with metabolic syndrome, accompanied by higher CIMT values [23]. A cohort study from Korea, which defined significant fibrosis as a Fib-4 index ≥ 1.45, involved repeated carotid ultrasonography every 1–2 years to monitor carotid atherosclerosis. They observed an increased rate of CA progression in patients with hepatic steatosis and liver fibrosis in T2DM over 6–8 years [24]. In our study, we stratified patients with T2DM into three groups based on their Fib-4 values (< 1.3, ≥ 1.3 and < 2.67, ≥ 2.67) to assess the risk of liver fibrosis. We found that higher Fib-4 values correlated with an increased risk of CA, particularly in patients with high blood pressure and BMI ≥ 24. Our findings contribute additional insights to existing research, further highlighting the link between Fib-4 and CA risk.

The precise mechanisms linking liver fibrosis scores to CA remain unclear. One possible explanation is that the liver in fibrosis may increase the production of prothrombogenic factors, such as fetuin-A, which can promote atherosclerotic plaque formation and accelerate vascular calcium deposition [25, 26]. It is important to note that patients predisposed to MASLD often present with multiple metabolic abnormalities and elevated inflammation levels. Inflamed visceral fat may act as a crucial link between liver disease and atherogenesis, with the liver not only being a target of systemic metabolic disturbances but also serving as a source of proatherogenic factors. MASLD may contribute to cardiovascular disease through the release of inflammatory, prothrombotic, and oxidative stress molecules, while also worsening insulin resistance and promoting atherogenic dyslipidemia [23].

In this study, we examined the relationship between the Fib-4 index and CA in patients with type 2 diabetes. Using univariate analysis and binary logistic regression, we found that elevated Fib-4 levels (Fib-4 ≥ 1.3) were strongly associated with CA, including increased CIMT

and the formation of carotid plaques. These findings suggest that Fib-4 could serve as a potential biomarker for evaluating the risk of carotid atherosclerosis in patients with type 2 diabetes. However, its clinical applicability may be limited due to the AUC value. An AUC value below 0.7 indicates that Fib-4 may not effectively distinguish between diseased and healthy individuals in diagnosis. This limitation explains why Fib-4, as an independent predictive marker, is not yet widely used in clinical practice. Nevertheless, Fib-4 still holds clinical value. In patients with type 2 diabetes, elevated Fib-4 levels could indicate a potential risk of carotid atherosclerosis, particularly when combined with other clinical indicators and imaging assessments. Therefore, Fib-4 may serve as an auxiliary tool to assess the risk of carotid lesions, especially in early screening when integrated with other clinical factors.

This study is the first to explore the association between Fib-4 and CA in a Chinese population with T2DM, offering significant insights for the initial assessment of CA and associated cardiovascular disease risk in these patients. However, our findings should be interpreted with caution due to certain limitations. First, the cross-sectional design of our study prevents us from establishing a causal relationship between Fib-4 levels and CA. Second, future studies could further validate the potential of Fib-4 in predicting carotid atherosclerosis by increasing sample sizes, designing prospective cohort studies, conducting multicenter research, and incorporating additional biomarkers. Despite these limitations, the large sample size of our study strengthens the validity of our results. Additionally, the ease of calculating Fib-4 using routine biochemical markers makes it a practical tool in clinical settings, particularly for widespread screening efforts.

Conclusions

Elevated Fib-4 levels (Fib-4 ≥ 1.3) are positively associated with CA in patients with type 2 diabetes, including increased CIMT and the presence of carotid plaques. As such, Fib-4 may serve as a potential biomarker for the detection of CA in patients with type 2 diabetes. However, its clinical utility needs further validation, particularly in larger sample sizes and multicenter studies.

Association of Fib-4 with carotid atherosclerosis

Univariate analysis was conducted with CA (Supplementary Table 1), defined as the dependent variable (1 = yes, 0 = no), and included gender, age, height, weight, BMI, head circumference, neck circumference, WC, hip circumference, waist-to-hip ratio, waist-to-height ratio, systolic blood pressure, diastolic blood pressure, heart rate, fasting blood glucose, postprandial 2-hour blood glucose, insulin, HOMA-IR, HbA1c, WBC, RBC, Hb, PLT, TG, TC, HDL-C, LDL-C, ALT, AST, GGT, UA, Cr, BUN, Urinary ACR, LABI, RABI, LBAPWV, RBAPWV, hypertension, history of coronary heart disease, smoking, drinking, and Fib-4 grouping. The results indicated that gender, age, BMI, hip circumference, waist-to-hip ratio, systolic and diastolic blood pressure, FPG, RBC, PLT, LDL-C, ALT, UA, Cr, BUN, LBAPWV, RBAPWV, hypertension, history of coronary heart disease, smoking, drinking, and Fib-4 grouping are risk factors influencing carotid atherosclerosis.

The results of the multivariate logistic regression analysis are presented in Table 2 and illustrated in Fig. 2. Fib-4 exhibited a positive association with the prevalence of CA, as well as increased CIMT and carotid plaques. Specifically, concerning the prevalence of CA, the adjusted odds ratios (ORs) (95% confidence intervals, CIs) were 1.450 (1.119, 1.879) and 1.743 (1.315, 2.311) in the

Table 2 Binary logistic regression analyses of the relationship between Fib-4 and CA, increased CIMT, and carotid plaques

	Incident rate (%)	Model 1		Model 2		Model 3	
		OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*
CA							
Fib-4 < 1.3	60.0%	Reference		Reference		Reference	
1.3 ≤ Fib-4 < 2.67	71.4%	1.688(1.337,2.081)	< 0.001	1.682(1.347,2.101)	< 0.001	1.433(1.125,1.826)	0.004
Fib-4 ≥ 2.67	73.3%	1.831(1.496,2.242)	< 0.001	1.893(1.544,2.322)	< 0.001	1.708(1.352,2.159)	< 0.001
Increased CIMT							
Fib-4 < 1.3	43.5%	Reference		Reference		Reference	
1.3 ≤ Fib-4 < 2.67	49.8%	1.288(1.050,1.580)	0.015	1.292(1.051,1.587)	0.015	1.215(0.976,1.513)	0.081
Fib-4 ≥ 2.67	52.2%	1.417(1.178,1.704)	< 0.001	1.467(1.217,1.768)	< 0.001	1.405(1.142,1.730)	0.001
Carotid plaques							
Fib-4 < 1.3	43.4%	Reference		Reference		Reference	
1.3 ≤ Fib-4 < 2.67	53.3%	1.484(1.210,1.821)	< 0.001	1.495(1.217,1.835)	< 0.001	1.225(0.978,1.534)	0.078
Fib-4 ≥ 2.67	54.3%	1.550(1.288,1.866)	< 0.001	1.588(1.318,1.914)	< 0.001	1.351(1.091,1.673)	0.006

Model 1: Unadjusted;

Model 2: Adjusted for sex, smoking, and drinking;

Model 3: Adjusted for sex, smoking, drinking, BMI, hip circumference, WHR, SBP, DBP, FPG, RBC, LDL-C, ALT, UA, Cr, BUN, LBAPWV, RBAPWV, hypertension, and coronary heart disease

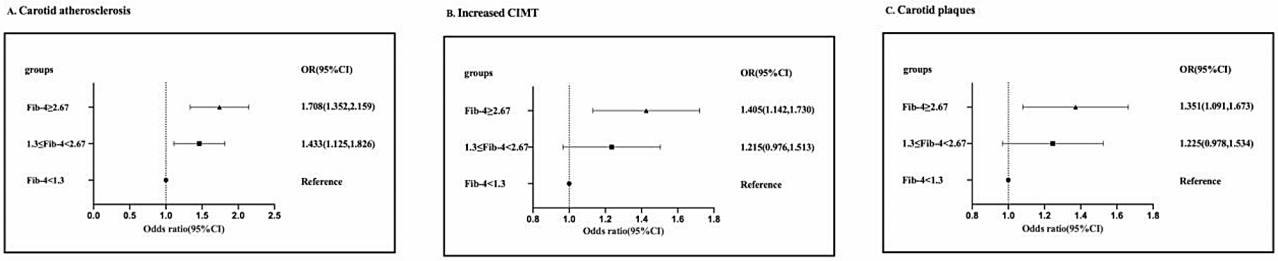

Fig. 2 Logistic regression analyses of the relationship between Fib-4 and CA, increased CIMT, and carotid plaques. Summarized figure of ORs for (**A**) Carotid atherosclerosis, (**B**) Increased CIMT, (**C**) Carotid plaques. OR, odds ratio; CI, confidence interval. CIMT, carotid intima media thickening. Adjusted for sex, smoking, drinking, BMI, hip circumference, WHR, SBP, DBP, FPG, RBC, LDL-C, ALT, UA, Cr, BUN, LBAPWV, RBAPWV, hypertension, and coronary heart disease

1.3 ≤ Fib-4 < 2.67 group and Fib-4 ≥ 2.67 group, respectively, compared to the Fib-4 < 1.3 group, after accounting for traditional risk factors (p for trend < 0.05). Furthermore, compared to the Fib-4 < 1.3 group, the Fib-4 ≥ 2.67 group demonstrated a significant association with a higher prevalence of increased CIMT (OR: 1.440; 95% CI: 1.116–1.857, p for trend < 0.05). Regarding the prevalence of carotid plaques, the adjusted ORs (95% CIs) were 1.280 (1.005, 1.630) and 1.461 (1.124, 1.899) in the 1.3 ≤ Fib-4 < 2.67 group and Fib-4 ≥ 2.67 group, respectively, compared to the Fib-4 < 1.3 group, after controlling for traditional risk factors (p for trend < 0.05).

Subgroup analysis

To comprehensively investigate the association between Fib-4 and CA, we conducted subgroup analyses, stratifying by sex, age, hypertension, smoking, alcohol consumption, and BMI (Table 3; Fig. 3), building upon the Model 3 adjustments presented in Table 2. Notably, in the subgroup analysis by gender, among male patients, the risk of CA exhibited an increasing trend in the 1.3 ≤ Fib-4 < 2.67 group (OR: 1.673, 95% CI: 1.180–2.371) and the Fib-4 ≥ 2.67 group (OR: 1.437, 95% CI: 1.022–2.020), with statistically significant differences ($p < 0.05$). This trend was also observed in increased CIMT and carotid plaques, although the differences were not statistically significant after adjusting for multiple factors. In the female patient subgroup, the risk of CA (OR: 1.949, 95% CI: 1.404–2.704), increased CIMT (OR: 1.629, 95% CI: 1.208–2.198), and carotid plaques (OR: 1.513, 95% CI: 1.115–2.052) demonstrated an increasing trend in the Fib-4 ≥ 2.67 group, with statistically significant differences ($p < 0.05$), while the differences in the 1.3 ≤ Fib-4 < 2.67 group became non-significant after adjusting for multiple factors. In the age-stratified subgroup analysis, among participants aged < 60, the risk of CA increased in the 1.3 ≤ Fib-4 < 2.67 group (OR: 1.437, 95% CI: 1.034–1.998) and the Fib-4 ≥ 2.67 group (OR: 1.428, 95% CI: 1.006–2.027), with statistically significant differences ($p < 0.05$). This trend was also observed in increased CIMT and carotid plaques, although the differences were not statistically significant after adjusting for multiple factors. Among participants aged ≥ 60, there were no statistically significant differences in the risk of CA, increased CIMT, and carotid plaques after multiple-factor regression analysis when Fib-4 ≥ 1.3 and Fib-4 ≥ 2.67. In the subgroup analysis by hypertension, participants with hypertension showed an increased risk of CA in the 1.3 ≤ Fib-4 < 2.67 group (OR: 1.511, 95% CI: 1.072–2.130) and the Fib-4 ≥ 2.67 group (OR: 1.583, 95% CI: 1.154–2.172), with statistically significant differences ($p < 0.05$). The risk of increased CIMT increased in the 1.3 ≤ Fib-4 < 2.67 group, but the difference was not statistically significant. In the Fib-4 ≥ 2.67 group, the risk of increased CIMT showed a significant increase (OR: 1.583, 95% CI: 1.154–2.172, $p < 0.05$), and the risk of carotid plaques increased in both the 1.3 ≤ Fib-4 < 2.67 group and the Fib-4 ≥ 2.67 group, but the differences became non-significant after multiple-factor regression analysis. In the subgroup without hypertension, the risk of CA (OR: 1.780, 95% CI: 1.244–2.547) and carotid plaques (OR: 1.417, 95% CI: 1.103–1.981) increased in the Fib-4 ≥ 2.67 group, with statistically significant differences ($p < 0.05$); other differences were not statistically significant. In the subgroup analysis by smoking, among non-smokers, the risk of CA (OR: 1.974, 95% CI: 1.447–2.636), increased CIMT (OR: 1.641, 95% CI: 1.262–2.133), and carotid plaques (OR: 1.551, 95% CI: 1.187–2.026) increased in the Fib-4 ≥ 2.67 group, with statistically significant differences ($p < 0.05$); other trends existed but were not statistically significant after multiple-factor regression analysis. In the never-drinking subgroup, the risk of CA (OR: 1.877, 95% CI: 1.373–2.567), increased CIMT (OR: 1.443, 95% CI: 1.090–1.911), and carotid plaques (OR: 1.360, 95% CI: 1.020–1.813) increased in the Fib-4 ≥ 2.67 group, with statistically significant differences ($p < 0.05$). In the current-drinking subgroup, the risk of CA increased in the 1.3 ≤ Fib-4 < 2.67 group (OR: 1.727, 95% CI: 1.105–2.697), with statistically significant differences ($p < 0.05$); other differences were not statistically significant. In the subgroup analysis by BMI, among participants with BMI < 24, the risk of CA increased in the Fib-4 ≥ 2.67 group (OR: 1.704, 95% CI: 1.183–2.456), with statistically significant differences ($p < 0.05$). Among participants with BMI ≥ 24, the

Table 3 Subgroup analyses for the association of Fib-4 with CA, increased CIMT and plaques

	Fib-4 < 1.3	1.3 ≤ Fib-4 < 2.67		Fib-4 ≥ 2.67	
		OR(95%CI)	P	OR(95%CI)	P
CA					
Gender					
Male	Reference	1.673(1.180,2.371)	0.004	1.437(1.022,2.020)	0.037
Female	Reference	1.223(0.864,1.731)	0.256	1.949(1.404,2.704)	< 0.001
Age					
< 60	Reference	1.437(1.034,1.998)	0.031	1.428(1.006,2.027)	0.047
≥ 60	Reference	1.052(0.709,1.563)	0.800	1.326(0.922,1.908)	0.128
Hypertension					
Yes	Reference	1.511(1.072,2.130)	0.018	1.583(1.154,2.172)	0.004
No	Reference	1.238(0.869,1.764)	0.237	1.780(1.244,2.547)	0.002
Smoking					
Never	Reference	1.315(0.974,1.776)	0.074	1.974(1.447,2.636)	< 0.001
Ever	Reference	1.593(0.866,2.930)	0.134	1.143(0.646,2.021)	0.647
Current	Reference	1.836(0.987,3.413)	0.055	1.270(0.698,2.311)	0.434
Drinking					
Never	Reference	1.366(0.994,1.876)	0.054	1.877(1.373,2.567)	< 0.001
Ever	Reference	1.052(0.446,2.482)	0.908	1.554(0.682,3.538)	0.294
Current	Reference	1.727(1.105,2.697)	0.016	1.490(0.987,2.248)	0.058
BMI					
< 24	Reference	1.289(0.849,1.860)	0.174	1.704(1.183,2.456)	0.004
≥ 24	Reference	1.571(1.131,2.182)	0.007	1.705(1.251,2.326)	0.001
Increased CIMT					
Gender					
Male	Reference	1.303(0.969,1.752)	0.080	1.227(0.915,1.644)	0.172
Female	Reference	1.085(0.776,1.518)	0.632	1.629(1.208,2.198)	0.001
Age					
< 60	Reference	1.235(0.906,1.684)	0.181	1.167(0.839,1.624)	0.360
≥ 60	Reference	0.933(0.669,1.301)	0.682	1.158(0.857,1.566)	0.340
Hypertension					
Yes	Reference	1.198(0.892,1.609)	0.230	1.520(1.154,2.003)	0.003
No	Reference	1.133(0.808,1.588)	0.470	1.198(0.863,1.664)	0.280
Smoking					
Never	Reference	1.157(0.870,1.539)	0.315	1.641(1.262,2.133)	< 0.001
Ever	Reference	1.167(0.710,1.917)	0.542	1.269(0.780,2.065)	0.337
Current	Reference	1.546(0.917,2.608)	0.102	0.859(0.534,1.502)	0.676
Drinking					
Never	Reference	1.082(0.805,1.445)	0.601	1.443(1.090,1.911)	0.010
Ever	Reference	1.081(0.495,2.361)	0.846	1.452(0.698,3.020)	0.318
Current	Reference	1.443(0.988,2.108)	0.058	1.315(0.916,1.886)	0.138
BMI					
< 24	Reference	1.094(0.783,1.530)	0.599	1.337(0.971,1.843)	0.076
≥ 24	Reference	1.319(0.981,1.773)	0.067	1.429(1.083,1.886)	0.012
Carotid plaques					
Gender					
Male	Reference	1.267(0.932,1.722)	0.130	1.170(0.863,1.587)	0.312
Female	Reference	1.198(0.853,1.681)	0.297	1.513(1.115,2.052)	0.008
Age					
< 60	Reference	1.125(0.817,1.549)	0.472	1.099(0.781,1.547)	0.587
≥ 60	Reference	1.031(0.731,1.456)	0.861	1.104(0.810,1.505)	0.532
Hypertension					
Yes	Reference	1.200(0.890,0.619)	0.232	1.268(0.958,1.677)	0.097
No	Reference	1.169(0.824,1.659)	0.38	1.417(1.103,1.981)	0.042

Table 3 (continued)

	Fib-4 < 1.3	1.3 ≤ Fib-4 < 2.67		Fib-4 ≥ 2.67	
		OR(95%CI)	P	OR(95%CI)	P
Smoking					
Never	Reference	1.266(0.947,1.691)	0.111	1.551(1.187,2.026)	0.001
Ever	Reference	1.082(0.652,1.796)	0.762	1.022(0.621,1.682)	0.932
Current	Reference	1.261(0.733,2.169)	0.403	0.952(0.552,1.641)	0.859
Drinking					
Never	Reference	1.182(0.873,1.599)	0.279	1.360(1.020,1.813)	0.036
Ever	Reference	1.016(0.439,0.354)	0.970	1.195(0.551,2.592)	0.652
Current	Reference	1.383(0.940,2.036)	0.100	1.364(0.945,1.069)	0.097
BMI					
< 24	Reference	1.224(0.869,1.724)	0.249	1.374(0.989,1.908)	0.058
≥ 24	Reference	1.225(0.905,1.659)	0.189	1.315(0.989,1.747)	0.060

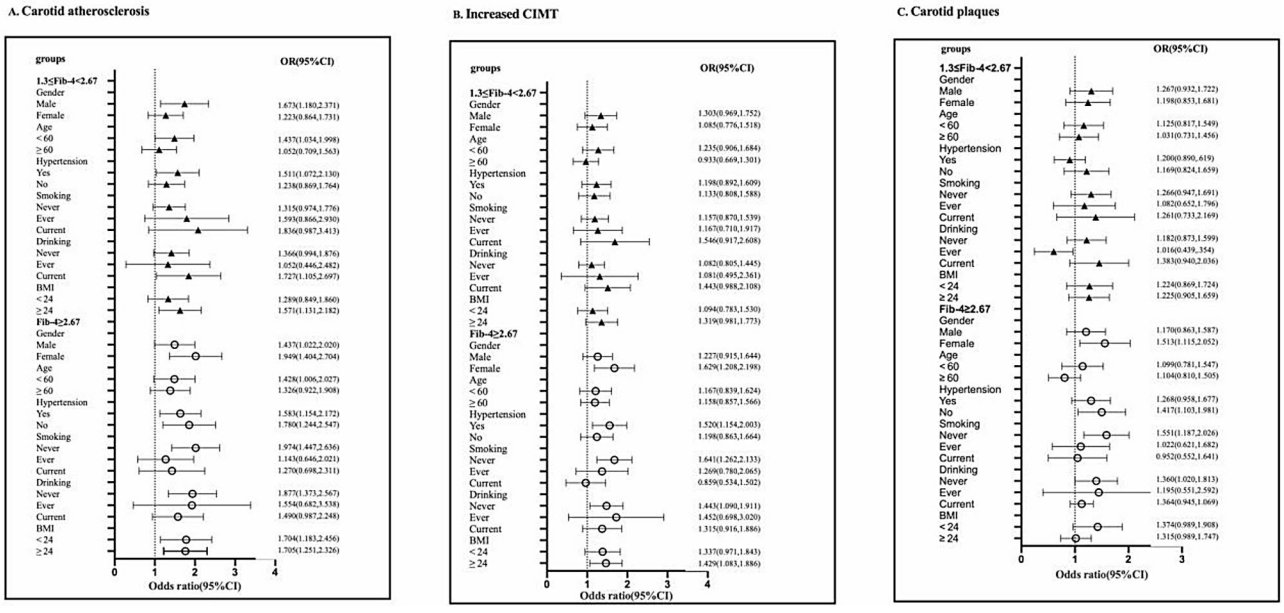

Fig. 3 Subgroup analyses for the association of Fib-4 with CA, increased CIMT and plaques

risk of CA increased in the 1.3 ≤ Fib-4 < 2.67 group (OR: 1.571, 95% CI: 1.131–2.182) and the Fib-4 ≥ 2.67 group (OR: 1.705, 95% CI: 1.251–2.326), with statistically significant differences ($p < 0.05$). The risk of increased CIMT increased in the Fib-4 ≥ 2.67 group (OR: 1.429, 95% CI: 1.083–1.886), with statistically significant differences ($p < 0.05$); other trends existed but were not statistically significant after multiple-factor regression analysis.

Predictive value of Fib-4 in screening for the presence of CA, increased CIMT and carotid plaques

To assess the predictive value of Fib-4 for the presence of carotid atherosclerosis (CA), increased carotid intima-media thickness (CIMT), and carotid plaques, a receiver operating characteristic (ROC) curve analysis was conducted (Fig. 4). The results demonstrated that Fib-4 has modest predictive capability for these conditions. Specifically, the area under the curve (AUC) for Fib-4 in predicting CA was 0.602 ($P < 0.001$, 95% CI: 0.579–0.625), indicating limited discrimination ability. Similarly, the AUC values for predicting increased CIMT and carotid plaques were 0.561 ($P < 0.001$, 95% CI: 0.540–0.583) and 0.580 ($P < 0.001$, 95% CI: 0.558–0.601), respectively, suggesting that Fib-4's predictive power for these markers remains relatively weak.

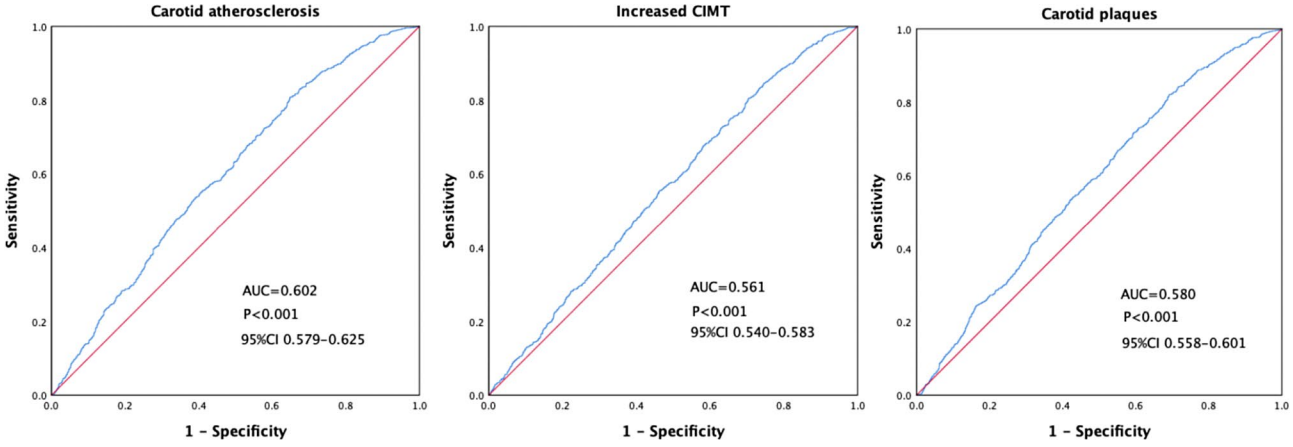

Fig. 4 Receiver Operating Characteristic (ROC) Curve Analysis of Fib-4 for Predicting CA, Increased CIMT, and Carotid Plaques

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04491-4.

Supplementary Material 1

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Author contributions
YM: Conceived the study, conducted data collection, performed data analysis, and drafted the manuscript. YW: Participated in data collection and analysis. QW and NT: Oversaw the study design, data analysis, and manuscript drafting. Provided final approval for the submitted version.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethical approval
The study complied with the ethical standards of the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (ethical approval code: 2018017). Clinical trial number: not applicable. All enrolled participants signed the informed consent form.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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