Cardiology in the Young

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Relationship between homocysteine and chronic total coronary occlusion: a cross-sectional study from southwest China

Kaiyong Xiao[1], Zhe Xv[2], Liang Liu[3], Bin Yang[3], Huili Cao[3], Jianping Wang[1], Yuling Xv[4], Qingrui Li[1], Yulin Hou[1], Feifei Feng[1], Jie Wang[1] and Hui Feng[5]

[1]Department of Cardiology, Guangyuan Central Hospital, Guangyuan, SC, China; [2]Department of Pediatric Medicine, Guangyuan Central Hospital, Guangyuan, SC, China; [3]Department of Cardiology, The Second Hospital of Shanxi Medical University, Taiyuan, SX, China; [4]Sterilization Supply Center, Guangyuan Central Hospital, Guangyuan, SC, China and [5]Medical Laboratory Center, Guangyuan Central Hospital, Guangyuan, SC, China

Original Article

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Corresponding author:
K. Xiao; Email: keyea1@126.com

Abstract

Background: Chronic total coronary occlusion is among the most complex coronary artery diseases. Elevated homocysteine is a risk factor for coronary artery diseases. However, few studies have assessed the relationship between homocysteine and chronic total coronary occlusion. *Methods:* 1295 individuals from Southwest China were enrolled in the study. Chronic total coronary occlusion was defined as complete occlusion of coronary artery for more than three months. Homocysteine was divided into quartiles according to its level. Univariate and multivariate logistic regression models, receiver operating characteristic curves, and subgroup analysis were applied to assess the relationship between homocysteine and chronic total coronary occlusion. *Results:* Subjects in the higher homocysteine quartile had a higher rate of chronic total coronary occlusion ($P < 0.001$). After adjustment, the odds ratio for chronic total coronary occlusion in the highest quartile of homocysteine compared with the lowest was 1.918 (95% confidence interval 1.237–2.972). Homocysteine ≥ 15.2 μmol/L was considered an independent indicator of chronic total coronary occlusion (odds ratio 1.53, 95% confidence interval 1.05–2.23; $P = 0.0265$). The area under the receiver operating characteristic curve was 0.659 (95% confidence interval, 0.618–0.701; $P < 0.001$). Stronger associations were observed in elderly and in those with hypertension and diabetes. *Conclusions:* Elevated homocysteine is significantly associated with chronic total coronary occlusion, particularly in elderly and those with hypertension and diabetes.

Atherosclerosis is a progressive disease that begins already in childhood and usually manifests as subendothelial deposits of lipid, calcium, and fibrous tissue in the arteries. Unstable plaques consisting of an intact lipid core and a thin fibrous cap are most susceptible to rupture or erosion, which is complicated by in situ thrombosis, leading to acute occlusion of the arterial lumen. If the thrombus blocking a coronary artery remains undissolved for more than 3 months, or atherosclerotic plaque continues to progress leading to a complete occlusion, this is defined as chronic total coronary artery occlusion.[1,2] Chronic total coronary occlusion was found in 15–26.4% of individuals who underwent coronary angiography.[3,4] Chronic total coronary occlusion is among the most complex coronary artery diseases, its revascularisation requires more technical experience and instrumentation support, and it is a "stubborn bastion" in the field of percutaneous coronary intervention. Due to unclear alignment, fibrosis, or invisible calcification in the lesion, chronic total coronary occlusion increases the difficulty of passing coronary guidewires, microcatheters, and balloons through the occluded segment, thereby decreasing the success of revascularisation and increasing surgical risk and cost, and chronic total coronary occlusion often requires more contrast and longer radiographic exposure times, which are detrimental to individuals, especially for the elderly.[5]

Homocysteine is a sulfhydryl-containing amino acid synthesised during protein metabolism. It can re-synthesise methionine through methylation or synthesise cysteine and α-ketobutyric acid via transsulfuration pathway.[6] Elevated homocysteine is common in the Chinese population, considering that a study from 31 provinces in mainland China reported elevated homocysteine in 25.9% of participants, with the highest rate reaching 56.8%.[7] Patients with elevated homocysteine have a greater chance of developing severe coronary artery disease. Homocysteine levels are significantly elevated in patients with acute myocardial infarction.[8–10] Homocysteine levels also significantly correlate with increased severity of coronary artery diseases[11] and the number of stenotic coronary arteries.[12]

Gender, age, smoking, hypertension, diabetes, and dyslipidemia are recognised as risk factors for coronary artery disease, and although some studies have shown homocysteine to be another risk factor for coronary artery diseases, few have examined whether homocysteine is associated

with chronic total coronary occlusion. This raises the question of what role these traditional risk factors play in this relationship. To address this, we performed a cross-sectional study to assess the relationship between homocysteine and chronic total coronary occlusion in adults from southwest China. Subgroup analysis was undertaken to dissect the potential impact of cardiovascular risk factors on the relationship between homocysteine and chronic total coronary occlusion.

Methods

Study population

From January 2018 to June 2022, 3346 consecutive patients who underwent percutaneous coronary angiography at Guangyuan Central Hospital for significant stenosis discovered by coronary CT angiogram and/or for angina-like chest pain were included in this study. All of the study subjects were from southwestern China. Exclusion criteria were as follows: (i) living beyond southwestern China; (ii) no homocysteine data; (iii) no height or weight data; (iv) diagnosis of anaemia, abnormal thyroid function, malignancy, chronic kidney disease; or (v) use of folic acid or preparations containing folic acid such as enalapril maleate–folic tablets, multivitamins, or oral contraceptives. Based on these criteria, 1295 individuals were identified to participate in the study (Fig. 1). The study was reviewed by the Medical Ethics Committee of Guangyuan Central Hospital (GYZXLL202118). All procedures were in accordance with the relevant guidelines, and all individuals provided written informed consent. The project was registered with the China Clinical Trials Registry (http://www.chictr.org.cn), registration number ChiCTR2100050519.2.2.

Data collection and measurements

Medical histories and clinical tests of all enrolees were extracted from the electronic medical record system of Guangyuan Central Hospital. Height and weight were measured at admission, and body mass index was calculated by dividing weight in kilograms by the square of height in metres. Individuals who reported using tobacco and alcohol at the time of admission were scored as "yes," while individuals who had never used tobacco and alcohol in their lifetime or had stopped using them at least six months prior to admission were scored as "no." Venous blood samples were collected from the subjects after 8 hours of fasting. Platelets, haemoglobin, total cholesterol, triglycerides, apolipoprotein A, apolipoprotein B, high-density lipoprotein–cholesterol, low-density lipoprotein–cholesterol, lipoprotein a, free fatty acids, glycated haemoglobin A1c, creatinine, cystatin C, uric acid, and homocysteine were measured. All blood samples were analysed at Guangyuan Central Hospital Laboratory Center employing the same automated biochemical analyser (ARCHITECTc16000; Abbott, Chicago, USA). Dyslipidemia was defined as total cholesterol level $\geq$ 5.2 mmol/L, and/or triglycerides level $\geq$ 1.7 mmol/L, and/or low-density lipoprotein–cholesterol level $\geq$ 3.4 mmol/L, and/or high-density lipoprotein–cholesterol level $<$ 1.0 mmol/L. Diabetes was defined as fasting glucose $\geq$ 7.0 mmol/L and/or 2-hour glucose $\geq$ 11.1 mmol/L, and/or glycated haemoglobin A1c $\geq$ 6.5%, and/or a current use of insulin or other glucose-lowering medication. Hypertension was defined as a systolic blood pressure $\geq$ 140 mmHg and/or a diastolic blood pressure $\geq$ 90 mmHg measured more than three times on non-same day and/or a current use of antihypertensive medication.

Definition of chronic total coronary occlusion

All participants underwent percutaneous coronary angiography by one cardiac interventional team at the Department of Cardiology, Guangyuan Central Hospital. Chronic total coronary occlusion was defined as complete occlusion of at least one of the 15 coronary segments described by the American Heart Association, with or without excellent collateralisation, and inferred or definitive evidence of occlusion for more than 3 months. Patients were divided into chronic total coronary occlusion and non-chronic total coronary occlusion groups according to the results of coronary angiography. Individuals with acute total coronary artery occlusion or stenosis $\leq$ 99% were classified as the non-chronic total coronary occlusion group.

Statistical analysis

To investigate the relationship between homocysteine levels and the occurrence of chronic total coronary occlusion, all subjects were divided into four groups according to quartiles of homocysteine (Q1: $<$ 11.2 μmol/L; Q2: from 11.3 to 14.6 μmol/L; Q3: from 14.7 to 19.8 μmol/L; and Q4: $\geq$ 19.9 μmol/L). The basic characteristics of study participants were expressed as numbers and percentages for categorical variables, mean ± standard deviation for normally distributed continuous variables, and median (interquartile spacing) for variables with skewed distribution. Univariate and multivariate logistic regression models were used to calculate odds ratios and 95% confidence intervals for homocysteine and chronic total coronary occlusion, and covariates were adjusted for using a stepwise approach in three models. Model 1 was adjusted for sex and age; model 2 was adjusted for sex, age, body mass index, and tobacco and alcohol use; and model 3 was further adjusted for hypertension, diabetes, total cholesterol, triglycerides, high-density lipoprotein–cholesterol, and low-density lipoprotein–cholesterol on the basis of model 2. To determine the accuracy of homocysteine in detecting chronic total coronary occlusion, we generated receiver operating characteristic curves with an area under the receiver operating characteristic curve $\geq$ 0.6 considered helpful for screening. Then, the relationship between total plasma homocysteine concentration (as a continuous variable) and chronic total coronary occlusion was evaluated. Subgroup analyses were performed according to sex (male or female), age ($<$ 60 or $\geq$ 60 years), current smoking (yes or no), hypertension (yes or no), diabetes (yes or no), and dyslipidemia (yes or no). Finally, the interaction of the groups in relation to homocysteine and chronic total coronary occlusion was examined. All statistical analyses were performed using R (http://www.R-project.org, R Foundation) and Free Statistics Software version 1.6 (http://www.clinicalscientists.cn/freestatistics). $P < 0.05$ was regarded as statistically significant.

Results

Characteristics of the study participants

Table 1 shows demographic characteristics and information according to homocysteine quartiles of the study cohort. Compared with subjects in the Q1 group, subjects with higher homocysteine levels tended to be male, elderly, current smokers, hypertensive, and nondiabetic, and had higher uric acid, creatinine, and cystatin C levels, and were more likely to be diagnosed with chronic total coronary occlusion. Mean plasma total homocysteine levels were markedly elevated in the chronic total coronary occlusion

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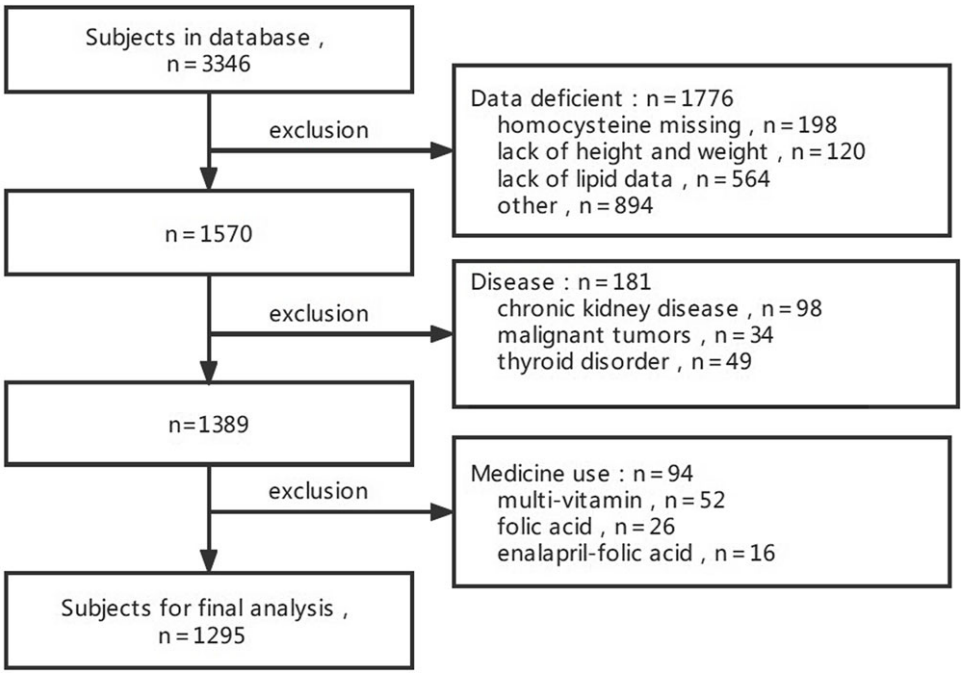

Figure 1. Flow diagram depicting the strategy for the selection of study participants.

group (19.8 ± 12.9 μmol/L) compared with the non-chronic total coronary occlusion group (16.4 ± 10.9 μmol/L).

Relationship between homocysteine and chronic total coronary occlusion

As demonstrated in Table 1, the occurrence of chronic total coronary occlusion increased from Q1 to Q4 of homocysteine levels (Q1: 20.2%; Q2: 21.1%; Q3: 34.4%; Q4: 43.3%). Table 2 shows the multiple-adjusted relationship between the quartiles of homocysteine and chronic total coronary occlusion. In model 1, after adjusting for sex and age, the odds ratio for chronic total coronary occlusion was 2.611 (95% confidence interval 1.809–3.769) for the highest quartile of homocysteine compared with the lowest quartile. After adjusting for sex, age, body mass index, smoking, drinking, hypertension, diabetes, total cholesterol, triglycerides, high-density lipoprotein–cholesterol, and low-density lipoprotein–cholesterol levels, the risk of chronic total coronary occlusion increased across homocysteine quartiles, and the odds ratio for the highest quartile was 1.918 (1.237–2.972) compared with the lowest quartile. Similar results were obtained when homocysteine was included as a continuous variable (per standard deviation increment, Table 2).

The analysis of receiver operating characteristic curves showed that the optimal homocysteine cut-off value for diagnosing chronic total coronary occlusion as determined using the Youden index was 15.2 μmol/L (sensitivity, 68.8%; specificity, 79.4%; area under the receiver operating characteristic curve 0.659 (95% confidence interval, 0.618–0.701; $P < 0.001$) (Fig. 2).

Subgroup analyses

Subgroup analyses indicated that the relationship between homocysteine and chronic total coronary occlusion was in accordance with other results (Fig. 3). Chronic total coronary occlusion was associated with homocysteine in participants that were male (adjusted odds ratio 1.013; 95% confidence interval 1–1.025), aged 60 years or above (adjusted odds ratio 1.025; 95% confidence interval 1.008–1.042), with hypertension (adjusted odds ratio 1.018; 95% confidence interval 1.001–1.036), with diabetes (adjusted odds ratio 1.031; 95% confidence interval 1.001–1.061), and with non-dyslipidemia (adjusted odds ratio 1.02; 95% confidence interval 1.004–1.036). In individuals over 60 years of age, with hypertension or diabetes, the occurrence of chronic total coronary occlusion was associated with homocysteine. In contrast, in individuals under 60 years of age and with dyslipidemia, chronic total coronary occlusion was not associated with increased homocysteine concentrations. Interaction analysis showed no significant interaction between homocysteine quartiles and chronic total coronary occlusion between groups based on sex, age, hypertension, diabetes, and dyslipidemia.

Discussion

In the present cross-sectional study, elevated homocysteine concentrations were positively associated with the occurrence of chronic total coronary occlusion in adults in southwest China. In addition, subgroup analysis showed that older age, hypertension, and diabetes may promote the onset of chronic total coronary occlusion. The association between quartiles of homocysteine and the prevalence of chronic total coronary occlusion was stronger in elderly individuals and those with hypertension and diabetes, whereas interaction analysis showed no interaction between the groups.

Chronic total coronary occlusion is the result of untimely recanalisation of acute coronary occlusion or progression of atherosclerosis. Arteriosclerosis is characterised by unremitting inflammatory damage to the arterial intima with increased permeability to plasma, deposition of plasma lipids, and fibrosis and calcification of so-called plaques.[13] Atherosclerosis is the most common pathological process that leads to cardiovascular disease, including myocardial infarction. The formation of atherosclerotic plaques is closely related to the proliferation of vascular endothelial cells, migration of vascular smooth muscle cells, lipid deposition in arterial walls, and remodelling of the extracellular matrix. Individuals with prior myocardial infarction have a higher mean

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Table 1. Demographic characteristics and baseline laboratory data of the study population.

Variables	Total	Q1 <11.2	Q2 11.3–14.6	Q3 14.7–19.8	Q4 ≥19.9	P value
N	1295	321	317	331	326	
Hcy, Mean ± SD	17.4 ± 11.6	9.1 ± 1.5	12.8 ± 0.9	17.1 ± 1.5	30.3 ± 16.6	<0.001
CTO, n (%)	387 (29.9)	65 (20.2)	67 (21.1)	114 (34.4)	141 (43.3)	<0.001
Male, n (%)	838 (64.7)	149 (46.4)	208 (65.6)	222 (67.1)	259 (79.4)	<0.001
Age (years)	64.4 ± 11.0	62.1 ± 9.9	63.4 ± 10.8	65.4 ± 11.2	66.7 ± 11.6	<0.001
BMI (kg/m^2)	24.4 ± 3.3	24.3 ± 3.1	24.4 ± 3.3	24.6 ± 3.5	24.5 ± 3.3	0.692
Current smoker, n (%)	417 (32.2)	83 (25.9)	96 (30.3)	109 (32.9)	129 (39.6)	0.002
Current drinker, n (%)	156 (12.0)	29 (9)	39 (12.3)	39 (11.8)	49 (15)	0.137
Hypertension, n (%)	741 (57.2)	161 (50.2)	171 (53.9)	205 (61.9)	204 (62.6)	0.002
Diabetes, n (%)	327 (25.3)	91 (28.3)	81 (25.6)	79 (23.9)	76 (23.3)	0.452
Ischaemic stroke, n (%)	87 (6.7)	20 (6.2)	26 (8.2)	22 (6.6)	19 (5.8)	0.648
TC, Mean ± SD	4.2 ± 1.0	4.2 ± 1.0	4.2 ± 1.0	4.2 ± 1.1	4.2 ± 1.1	0.997
ApoA, Mean ± SD	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	<0.001
ApoB, Mean ± SD	0.8 ± 0.3	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.3	0.8 ± 0.3	0.189
HDL-C, Mean ± SD	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	<0.001
LDL-C, Mean ± SD	2.4 ± 0.8	2.4 ± 0.8	2.4 ± 0.8	2.4 ± 0.9	2.4 ± 0.9	0.663
UA, Mean ± SD	325.7 ± 102.6	290.2 ± 85.4	311.0 ± 86.8	330.2 ± 99.4	369.1 ± 117.8	<0.001
PLT, Mean ± SD	161.0 ± 60.0	162.6 ± 58.6	161.1 ± 68.2	157.2 ± 53.7	163.3 ± 58.8	0.570
Hb, Mean ± SD	131.0 ± 19.1	132.2 ± 17.9	129.7 ± 19.7	130.1 ± 19.3	132.0 ± 19.6	0.220
TG, Median (IQR)	1.3 (1.0, 1.9)	1.4 (1.0, 1.9)	1.3 (1.0, 1.8)	1.3 (1.0, 2.0)	1.3 (1.0, 1.9)	0.937
LP(a), Median (IQR)	144.0 (78.0, 303.0)	139.0 (70.2, 301.2)	143.0 (73.0, 271.0)	163.0 (85.5, 321.0)	135.0 (81.5, 279.5)	0.287
FFA, Median (IQR)	0.5 (0.3, 0.7)	0.4 (0.3, 0.7)	0.5 (0.3, 0.7)	0.5 (0.3, 0.6)	0.5 (0.4, 0.7)	0.059
Cr, Median (IQR)	71.0 (59.0, 84.0)	62.0 (53.0, 72.0)	69.5 (58.0, 80.0)	72.0 (61.0, 84.0)	81.0 (69.0, 101.0)	<0.001
Cystatin C, Median (IQR)	1.1 (0.9, 1.4)	1.0 (0.8, 1.1)	1.1 (0.9, 1.2)	1.2 (1.0, 1.4)	1.3 (1.0, 1.6)	<0.001

ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; Hcy = homocysteine; BMI = body mass index; Cr = creatinine; CTO = chronic total coronary occlusion; FFA = free fatty acid; HDL-C = high-density lipoprotein–cholesterol; Hb = haemoglobin; LDL-C = low-density lipoprotein–cholesterol; Lp (a) = lipoprotein a; PLT = platelets; TG = triglyceride; TC = total cholesterol; UA = uric acid.

Table 2. Multivariate logistic regression analysis between homocysteine and chronic total coronary occlusion.

Homocysteine (μmol/L)	n = 1295	Model 1	Model 2	Model 3
Q1 (<11.2)	321.0	1 (Ref)	1 (Ref)	1 (Ref)
Q2 (11.3–14.6)	317.0	0.999 (0.677–1.474)	1.002 (0.679–1.479)	0.87 (0.553–1.368)
Q3 (14.7–19.8)	331.0	1.875 (1.304–2.695)	1.874 (1.303–2.695)	1.544 (1.011–2.357)
Q4 (≥19.9)	326.0	2.611 (1.809–3.769)	2.601 (1.8–3.758)	1.918 (1.237–2.972)
P for trend		<0.001	<0.001	0.0036
Per SD increment	1295.0	1.021 (1.01–1.032)	1.021 (1.01–1.032)	1.012 (1.001–1.024)
P value		0.0002	0.0002	0.0328

CI = confidence interval; OR = odds ratio; SD = standard deviation.
Model 1: Adjusted for sex and age.
Model 2: Adjusted for sex, age, body mass index, smoking, and drinking.
Model 3: Adjusted for sex, age, body mass index, smoking, drinking, hypertension, diabetes, total cholesterol, and triglyceride levels, high-density lipoprotein–cholesterol, low-density lipoprotein–cholesterol, lipoprotein a, uric acid, and Cystatin C.
Per SD increment represents 1 SD increment of homocysteine.

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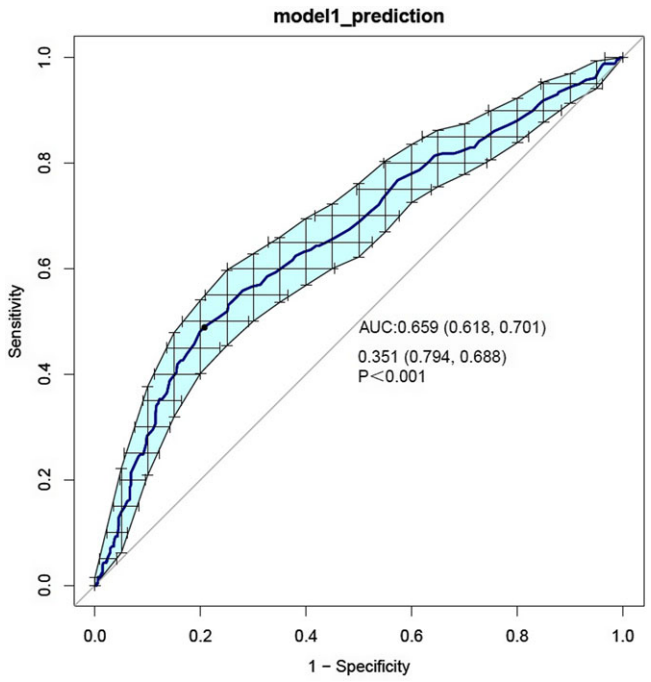

Figure 2. Receiver operating characteristic curves for homocysteine and chronic total coronary occlusion risk. Abbreviations: AUC, area under the receiver operating characteristic curve.

homocysteine concentration than those without coronary artery disease.[14] Homocysteine is a known independent risk factor for atherosclerosis,[15] and is considered a marker for the progression of atherosclerosis.[16–18] Homocysteine may promote atherosclerosis through several mechanisms, such as smooth muscle cell proliferation, endothelial dysfunction, oxidative damage, increased collagen synthesis, decreased high-density lipoprotein–cholesterol synthesis, and deterioration of the elastin of the arterial wall.[11,19,20] Its elevation can contribute to thin fibrous cap atherosclerosis,[21] ischaemia of the arterial wall, endothelial cell apoptosis, haemorrhage, inflammation, and intimal micro-abscesses, ultimately leading to the formation of fragile plaque.[22] Persistent elevation of homocysteine is a predictor of plaque progression.[19] This may lead to unstable plaque rupture and local thrombosis, eventually resulting in chronic total coronary occlusion.[11] Previous studies did not find an association between homocysteine concentration and coronary collateral formation, but elevated homocysteine was noted in individuals with single-vessel chronic total occlusion.[23] These data are consistent with the present findings.

Homocysteine-induced atherosclerosis is associated with multiple cellular molecular mechanisms. The role of homocysteine in endothelial dysfunction is thought to be mediated by oxidative stress, nuclear factor-κB activation, and inhibition of endothelial nitric oxide synthase.[24] Homocysteine binds to N-methyl-D-aspartate receptors, leading to oxidative stress, cytoplasmic calcium influx, apoptosis, and endothelial dysfunction.[17] Homocysteine can produce oxidative stress, contributing to the growth of atherosclerotic vascular lesions by interfering with low concentration endothelial nitric oxide synthase-derived nitric oxide production, mediating the loss of the endothelial antioxidant system, and increasing the concentrations of intracellular reactive oxygen species.[25] Homocysteine stimulates proliferation of endothelial cells by generating reactive oxygen species through the autoxidation of its sulfhydryl group, as well as by inhibiting antioxidant enzymes, activating NADPH oxidase and matrix metalloproteinases, and inducing apoptosis through mitochondrial alterations. Homocysteine can also stimulate the proliferation of smooth muscle cells[26] and damage vascular collagen fibres. In addition, homocysteine can enhance low-density lipoprotein–cholesterol lipid oxidation and promote coagulation, enhance platelet aggregation, and alter the thrombotic properties of endothelial cells, thereby leading to atherosclerosis and thrombosis.[27] Homocysteine inhibits scavenger receptor group B member 1 via the DNMT3b/SP1 pathway[28] and inhibits LXRα-mediated ABCA1/ABCG1-dependent cholesterol efflux from macrophages.[29] Additionally, homocysteine increases the production of inflammatory interleukin-1β in macrophages.[30] Oxidative stress, proinflammatory factor activation, and genomic homocysteine DNA methylation play important roles in the progression of atherosclerosis.[31] Hyperhomocysteinemia promotes atherogenesis by altering histone acetylation patterns and regulating miRNA expression.[31] And finally, homocysteine induces SMAD7 promoter hypermethylation and activates nuclear factor-κB to promote vasculopathy.[32]

Elevated homocysteine is a characteristic feature of ageing. Homocysteine levels are higher in elderly individuals with coronary artery disease than in those without it.[33] Many factors contribute to age-related increase in homocysteine levels, including vegetarian diet,[34] deficiency of vitamins B6 and B12, folic acid and hypertension,[35] and lack of exercise.[36] Age-dependent reduction in cystathionine beta-synthase activity increases serum homocysteine levels.[35,37,38] N-nitration of Trp208, Trp43, and Tyr223, and loss of thiolate coordination inhibit cystathionine beta-synthase activity and lead to age-related hyperhomocysteinemia.[35] Increased homocysteine levels are associated with arteriosclerotic outcomes in elderly individuals and are considered an independent risk for cardiovascular disease.[39]

Hypertension is a recognised contributor to atherosclerosis, causing vascular smooth muscle proliferation, atheromatous plaque, atheroma formation, and luminal narrowing.[40] Renin, catecholamines, and angiotensin that are associated with hypertension can also alter the metabolism of the arterial wall, thereby leading to endothelial damage.[40] Increased arterial stiffness is a warning sign of coronary events in hypertensive patients.[41] Besides an independent effect, a multiplicative effect of hypertension and hyperhomocysteinemia substantially increases the risk of coronary artery disease. Strong interactive effects were observed between homocysteine levels and increasing age or hypertension.[42] These findings suggest a causal link between homocysteine and blood pressure, and elevated blood pressure may mediate some of the cardiotoxic effects of homocysteine.[43] The individuals with hypertension and high levels of homocysteine had more severe coronary atherosclerosis and more diffuse atherosclerosis than those without this association, and the presence of both hypertension and hyperhomocysteinemia was associated with more severe coronary artery disease.[44] Hypertension is a major link between hyperhomocysteinemia and coronary artery disease occurrence.[45] Previous studies have noted increased concentrations of haemostatic or proinflammatory cytokines, growth factors, and heat-shock proteins in the plasma of hypertensive individuals, all of which may promote atherosclerosis.[46,47] Diabetes impairs vascular endothelial function.[48] Insulin resistance leads to less phosphatidylinositol-3-kinase/protein kinase B signalling, impaired endothelial nitric oxide synthase expression, and decreased nitric oxide bioavailability, resulting in endothelial

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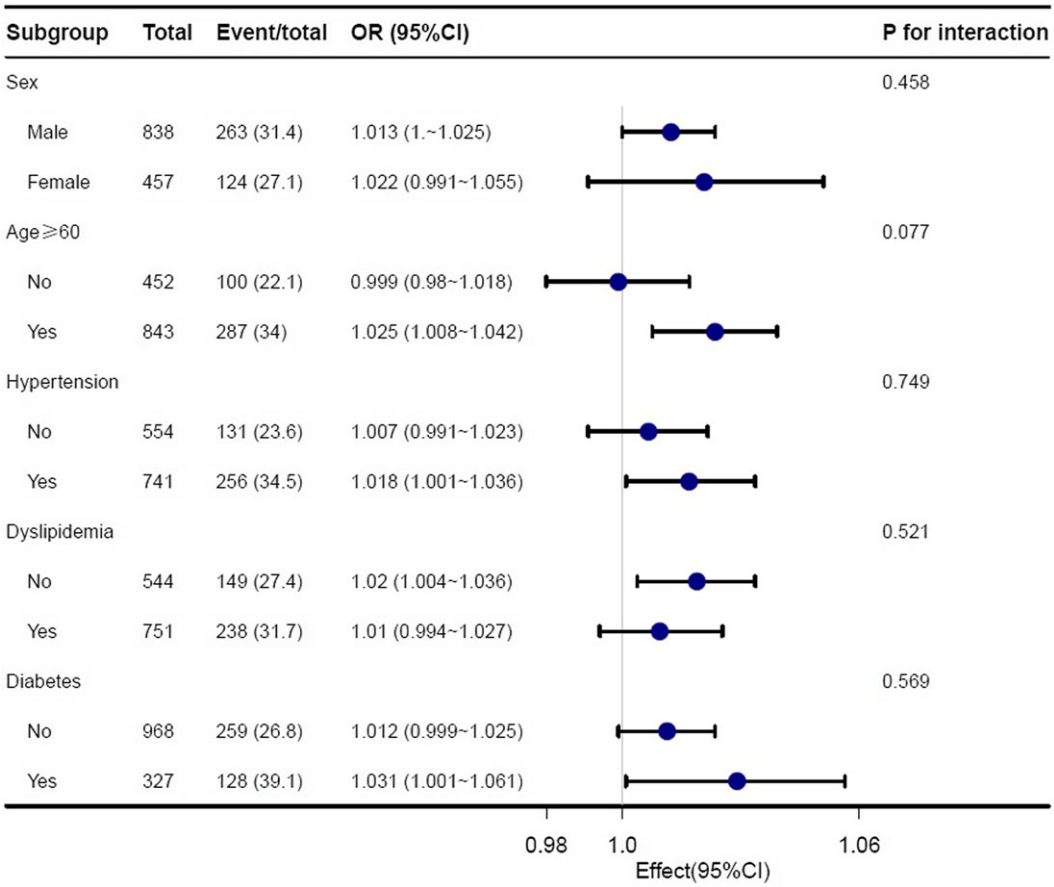

Figure 3. Subgroup analyses of the relationship between homocysteine and chronic total coronary occlusion. Odds ratios were adjusted for variables as in model 4 (Table 2) except for the corresponding stratification variable. Abbreviations: OR, odds ratio; CI, confidence interval.

dysfunction in diabetes individuals with hyperhomocysteinemia.[49] In the combined metabolic state of hyperhomocysteinemia and hyperglycaemia, endothelin 1 synthesis is increased in endothelial cells and mitochondrial reactive oxygen species produced.[50] In addition, homocysteine increases the activity of hydroxymethyleneglycol coenzyme A, which increases cholesterol synthesis, and low-density lipoprotein–cholesterol damages endothelial nitric oxide synthase activity by increasing oxidative stress, which in turn leads to endothelial cell dysfunction.[51] Additionally, in individuals with diabetes and hyperhomocysteinemia, abnormal vascular smooth muscle cell activity thickens the wall of arteries to add to the pathologic changes of atherosclerosis.[52]

The study has several limitations. First, this was a single-centre study performed on a Chinese population, which may have limited the generalisability of the results. The issue needs to be further explored at a larger number of institutions and in a larger number of other ethnic groups. Second, this cross-sectional study only showed an association between elevated homocysteine and the incidence of chronic total coronary occlusion, and a large multicenter prospective study is needed to validate the predictive power of homocysteine on the risk of chronic total coronary occlusion and evaluate whether homocysteine-lowering therapy can reduce the incidence of adverse events in patients with chronic total coronary occlusion who have elevated homocysteine. Third, this study only included subjects who completed coronary angiography, so some populations may have been missed and there may have been selection bias. Fourth, this was a retrospective observational study and responses to medication history may have been inaccurate and folic acid and vitamin B12 levels were not measured, and although we made statistical adjustments for confounders in our multivariate logistic regression model, we may not have completely eliminated their effects. Finally, we did not consider whether any given patient's diagnosis at admission was acute coronary syndrome or chronic coronary ischaemic syndrome, and we did not collect details on the patient's chronic total coronary occlusion lesions, such as site, number, length, whether they were combined with calcification, or collateral circulation, so we were unable to perform an analysis of these relevant conditions.

Conclusions

To our knowledge, this is the first study conducted on the correlation between homocysteine and chronic total coronary occlusion. An elevated homocysteine may be a risk factor for chronic total coronary occlusion. A correlation between plasma homocysteine levels and chronic total coronary occlusion was observed in a single centre in southwest China. This association was especially evident in elderly individuals and those with hypertension and diabetes. Although the value of this finding needs to be further validated in multiple centres, the results suggest that elevated homocysteine may contribute to coronary arterial disease. General awareness of these findings among medical professionals and the public seems warranted.

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Author contribution. K.X. and Z.X. designed the study. Q.L., Y.X., F.F., J.W., and Y.H. collected the data. H.F. and J.W. calibrated the data. K.X. and L.L. analysed the data. K.X. and B.Y. analysed and interpreted the results. B.Y. and H.C. provided statistical consulting. K.X. wrote the manuscript. H.C. and B.Y. provided scientific input and edited the manuscript. All the authors have read and approved the final version of the manuscript for publication.

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Competing interests. None.

Availability of data and materials. All data can be obtained from the corresponding author upon reasonable request.

Ethics approval and consent to participate. This study was approved by the Guangyuan Central Hospital's Medical Ethics Committee. All study participants provided written informed consent. All protocols and procedures were carried out in accordance with the Helsinki Declaration.

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