# Carotid artery ultrasound for evaluating the degree of stenosis and plaque composition in patients with coronary heart disease

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**Research**

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# Abstract

Background: Early screening, diagnosis, risk assessment, and intervention of intima-media thickness (IMT) and carotid plaques is critical for assessing the risk of coronary heart disease (CHD). The current study aimed to assess carotid IMT and atherosclerotic plaque composition in patients with CHD by carotid artery ultrasound and to determine the associations of various factors with CHD. Methods: 480 patients with suspected CHD underwent a duplex ultrasound of the carotid arteries and coronary angiography or coronary CT. Then, the patients were investigated and evaluated to identify both personal and medical histories of clinical evaluations, and divided into the CHD (n=325) and control (n=155) groups based on clinical symptoms and vessel lesions. Associations of clinical characteristics with ischemic lesions determined by coronary angiography or CT were examined. Screening by B-mode carotid artery ultrasonography was performed the morning after admission prior to any treatment, coronary angiography or CT. Results: Cardiac diagnostic testing was performed in 134 subjects by CT coronary angiography, while the remaining 346 patients underwent coronary angiography. Carotid plaques were mainly distributed in the common carotid artery, with a significant difference between the CHD and control groups. Plaque incidence (80%) and IMT thickness (0.84±0.21) were significantly higher in the CHD group compared with control patients (P=8.92e-12 and P=0.012 respectively). The factors significantly associated with CHD were selected into the multivariate regression model. Male subject (OR=1.569, 95%CI 1.004-2.453; P=0.048) and plaque level (OR=0.457, 95%CI 0.210-0.993; P=0.048) were significant for CHD occurrence. The carotid plaque performed significantly better than IMT and the Framingham CHD risk score for predicting CHD risk (DeLong's correlated AUC test P=5.84e-4 and P=2.52e-5, respectively). Conclusions: The present study demonstrated that carotid artery ultrasound could be an effective method for early detection of atherosclerosis, which would help prevent CHD in asymptomatic patients with advanced atherosclerosis of the carotid artery. Incorporating carotid artery ultrasound plaque composition into screen practice may perform significantly better than the Framingham CHD risk factors for predicting CHD risk.


# 1. Introduction

Atherosclerosis is responsible for coronary heart disease (CHD), which constitutes the leading cause of mortality worldwide [1]. Identifying early predictors of CHD is important in preventing the disease and may potentially help curb the associated health-care expenditure [1]. It is widely accepted that risk assessment in atherosclerosis represents a significant step for the prevention of cardiovascular events, identifying subjects that should undergo more specific diagnostic strategies and medical treatments. Current risk assessment models, for instance, the Framingham risk score, as well as many other risk factors for fatal cardiovascular events, incorporates gender, chronological age, hyperlipidemia, and hypertension [2, 3]. However, they only offer a rough assessment of the individual risk without considering the (pre)diagnosis of atherosclerosis [4].

Currently, an accurate clinical diagnosis of CHD relies on coronary artery computed tomography angiography (CCTA) and coronary arteriography (CAG), which are limited by high cost and other factors

in clinical application[5, 6]. Dalager et al. reported that atherosclerosis distribution is predictable, as plaques are more widely detected in the bifurcation of the carotid and left anterior descending arteries [7]. Interestingly, vulnerable plaques can be observed at the early and active stages of coronary arteriosclerosis, and contain lipids and fibers[8]. Therefore, early detection of vulnerable plaques is a key factor in the prevention and treatment of CHD. Carotid ultrasound is one of the several imaging modalities that allow non-invasive risk assessment of vascular anatomy and function[9]. It has been considered the main modality for assessing carotid wall thickness and allows improved analysis of plaque composition [10].

A critical characteristic of atherosclerosis is that it represents a systemic vascular disorder. Atherosclerotic disorder at a specific location may predict ischemic events at remote locations[11]. The spatial resolution of ultrasound probes is high enough to directly detect early atherosclerosis, e.g. revealing intima-media thickness (IMT) changes in the carotid arteries[12]. IMT is a non-invasively and reproducibly measured marker for evaluating the severity degree of carotid atherosclerosis and considered an independent predictor of CHD[12]. Numerous clinical studies have shown that IMT is an independent risk factor for cardiovascular disorders, incorporating ischemic heart disease and peripheral vascular disease[13] [14].

Such a predisposition to plaque instability attributable to systemic risk factors suggests that plaque composition and instability in the carotid arteries could be associated with stroke as well as other ailments, such as CHD. Carotid plaques have analogous physiologic and pathologic bases as coronary plaques, and their stability is closely related to the development of CHD [15]. Plaque composition analysis as a mean of evaluating vulnerability may complement traditional risk factors and help stratify patients with CHD. However, it is at present unclear whether CHD manifests itself to a similar degree in the carotid artery. In this context, early screening, diagnosis, risk assessment, and intervention of IMT and carotid plaques are of great importance in assessing the risk of CHD. Therefore, this study aimed to assess carotid IMT and atherosclerotic plaques in CHD patients by carotid artery ultrasound and to determine the associations of different factors with CHD.

# 2. Methods

2.1 Study design and subjects

This prospective cohort study was performed at the Department of Cardiology of Northern People's Hospital (Jiangsu, China) between August 2013 and April 2018. Individuals with suspected CHD (chronic angina, dyspnea or positive stress test results) were included. Exclusion criteria included moderate or severe rheumatic heart disease, malignant arrhythmia, congenital coronary artery malformation, carotid artery stenosis, myocarditis, overt renal and liver dysfunction, hematological disease, major mental diseases, allergies and drug allergies, pregnancy or lactation (women), and metabolic diseases such as diabetes and hyperthyroidism. All patients underwent careful investigation and assessment for personal and medical histories of clinical evaluations. Clinical evaluation, echocardiographic scanning,

biochemical tests, and medical treatment were carried out for all participants by two independent study coordinators blinded to carotid ultrasound and coronary angiography data. During the follow-up, all participants maintained their normal living habits and did not change their drug administration. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Northern Jiangsu People's Hospital. Informed consent was obtained from all the patients in the study before the carotid ultrasound examination.

### 2.2 Patient grouping and diagnostic criteria

According to the presence or absence of CHD, we put all the patients into CHD or control group. The control group comprised patients with normal coronary or single-vessel lesion < 50% by coronary angiography or CTA. The CHD group included 285 angina and 40 myocardial infarction (MI) cases. For further analysis, the CHD group was divided into 3 subgroups, including the single, double, and triple lesion groups, based on the diagnostic standards of the American Heart Association [16]. Moderate stenosis of the left main coronary artery (> 50%) was defined as a double branch lesion. The left main coronary artery with a right coronary lesion was defined as a 3 branch lesion [17].

All participants were screened by carotid artery ultrasonography the morning following admission prior to any drug administration, coronary angiography or CT. Demographic information was recorded on gender, age, smoking, along with comorbidities such as Diabetes mellitus, stroke, and hypertension. Levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were obtained at the baseline. Drugs for CHD and hypertension such as aspirin, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonist, statins, and oral anticoagulant therapy of patients were also recorded. Glucose and lipid amounts were measured after a 12-h fast. Serum lipid profiling was carried out by standard laboratory techniques.

Hypertension was diagnosed according to the criteria issued by the World Health Organization/International Society of Hypertension in 1999[18]. Diabetes mellitus was diagnosed according to the Diabetes Diagnosis and Treatment Guideline issued by the American Diabetes Association in 2013[19]. The standards for dyslipidemia were based on the 2007 domestic version of the Dyslipidemia Prevention and Treatment Guideline for Chinese Adults[20]. Current smoking was defined as a self-report of ≥ 1 cigarette in the past 30 days[21]. MI diagnosis was on the basis of a combination of clinical symptoms, electrocardiogram manifestations, and cardiac biomarkers. Stroke was defined as a neurologic event that lasted ≥ 24 hours or until death with a brain imaging finding [22]. The design and selection criteria for the Framingham Heart Study and the Framingham Offspring Study have been detailed elsewhere[23]. The Framingham CHD risk score was calculated from age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, and smoking to predict the 10-year risk of CHD according to the European Task Force Recommendations[24].

### 2.3 Carotid ultrasound examination

Carotid artery measurements were examined as part of a routine inspection by experienced operators, who were blinded to clinical data. These examiners underwent training sessions to standardize image acquisition, evaluation, and collection of the ultrasound data. The carotid artery was examined on both sides as far as could be made visible for plaques on the short and long axes, from the clavicle to the temporomandibular joint in a caudal to cranial direction, by anterior, anterolateral, lateral and posterolateral insonation. High-resolution carotid ultrasonography was performed with an 8–12 MHz transducer and a GE Logiq 8 ultrasound scanner (Aloka, Andover, USA). Patients were imaged in the supine position with the head slightly tilted to either side. Vessel wall changes were deliberately examined in the carotid arteries from diverse longitudinal and transverse views. The images were focused upon the far wall of the artery. The measurements are part of a comprehensive protocol that acquired videotaped images from each side of the neck, and incorporated imaging of the distal common carotid artery (one view on each side) as well as the proximal internal carotid artery and bulb (three projections on each side). The carotid artery includes four segments: common carotid artery (CCA), common carotid artery bifurcation, internal carotid artery (ICA) and external carotid artery (ECA). Details of carotid artery assessment have been previously described [25], and the acquisition protocol was previously used in the Cardiovascular Health Study [26].

### 2.4 IMT quantification

Ultrasound quantitation of carotid IMT has been described previously [27]. Far wall IMT was the mean of the far wall IMT values of both left and right CCAs, which were assessed on both sides of the neck below the bulb, starting at the point at which the outer wall (adventitia) of the artery begins to diverge. Analogously, near-wall IMT was the mean of the values of both left and right CCAs. Mean IMT was obtained by averaging all four CCA IMT values. After identifying a region of ~ 1.0 cm proximal to carotid bifurcation, the IMT of the far wall was assessed as the distance between the luminal-intimal and medial-adventitial interfaces, and triplicate values were averaged. According to data of healthy Chinese subjects, abnormal IMT was defined as a value exceeding 1.0 mm (ultrasound images were provided in Fig. 2).

### 2.5 Carotid plaque assessment

Only carotid artery IMT > 1.5 mm was considered to indicate a plaque. A carotid plaque was identified as an echoic focal projection, or reflected by the presence of focal wall thickening at least 50% greater than that of the surrounding vessel wall, or focal region with carotid IMT greater than 1.5 mm that protrudes into the lumen and is distinct from the adjacent boundary [28]. The plaques were classified on the basis of echo features as follows:[29] (1) soft plaque, hypoechoic intensity relative to the peripheral vascular adventitia with no acoustic shadow (hypoechoic area > 80% of the plaque area); (2) hard plaque, isoechoic or hyperechoic intensity relative to the peripheral vascular adventitia with an acoustic shadow (hyperechoic area > 80% of the plaque area); (3) mixed plaque, no acoustic shadow, with a calcified area of less than 90% of the plaque area, and an anechoic zone of less than 80% of the plaque area[30].

### 2.6 Coronary imaging

CAG was performed through the femoral or radial artery by a standard process according to the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) recommendations [31]. CCTA was used to assess vessel diameters of areas with the worst stenosis (Fig. 4). CCTA was performed on a single-source 64-slice CT instrument (Sensation 64; Siemens Medical Solutions, Forchheim, Germany). Patients with no contraindications to beta-blockers and initial heart rates > 65 bpm took an oral dose of 25 mg of metoprolol 1 hour before CCTA. CCTA was performed according to established guidelines and technical parameters [32]. In general, moderate-to-severe coronary stenosis, or artifact hindering adequate assessment of stenosis on CCTA were identified indications for further assessment by CAG. Coronary angiograms were obtained on a GE Inova 2100 equipment and interpreted visually in two orthogonal views by skilled interventional cardiologists blinded to grouping. Systematic and complete reviews of CCTA findings were performed by expert radiologists. CHD was defined as one or more epicardial coronary arteries showing ≥ 50% angiographic lumen narrowing.

### 2.7 Follow-up and outcome events

All the participants were under continuous surveillance for the development of adverse events and death. Clinical adverse events were defined as a composite of MI, coronary insufficiency, transient ischemic attack, stroke, congestive heart failure, and death. CHD events recorded were angina, MI, resuscitated cardiac arrest and CHD death. Information about clinical follow-up was obtained with the aid of telephone calls, medical histories, physical tests at the study clinic, hospitalization records and communication with personal physicians every 9 to 12 months. All suspected outcome events were reviewed by a panel of 3 experienced investigators who evaluated all pertinent hospital records. We had another independent review committee that included cardiologist adjudicated adverse events, and a heart study cardiologist examined most participants with suspected adverse events[23].

### 2.8 Statistical analysis

Statistical analyses were performed with the SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Continuous data were mean ± standard deviation (SD) and were compared by Student's t-test (group pairs) and one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for pairwise comparison of multiple groups. Categorical variables were presented as count and percentage and compared by the $\chi 2$ test. Logistic regression analysis was performed to determine associations of CHD lesions with various factors. $P < 0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curve and area under the curve (AUC) analysis was used to compare different prediction methods for CHD risk in terms of AUC, sensitivity, and specificity.

# 3. Results

### 3.1 Clinical characteristics

Table 1 summarizes the characteristics of the patients. A total of 480 patients (300 males and 180 females) between the ages of 30 and 95 years were identified as eligible for the study. All the patients were assigned to the CHD group (N = 325) or the control group (N = 155). For further analysis, the CHD group was also divided into 3 groups, including the single group (N = 145), the double group (N = 90) and the triple lesion group (N = 90) according to clinical symptoms and ischemic lesions. Clinical follow-up was achieved for all 480 patients, with a median follow-up duration of 4.8 years. Three patients who accomplished all baseline assessments were lost to follow up because of MI. Follow-up data from all patients (including adverse events) were obtained by telephone from family practitioners and patients, and through hospital records. The investigators adjudicating events during follow-up were blinded for imaging data.

Table 1

Patient characteristics in the four groups (n = 480)

| Variable | Control (n = 155) | CHD | | | P |
|---|---|---|---|---|---|
| | | Single lesion (n = 145) | Two lesions (n = 90) | Three lesions (n = 90) | |
| Gender (male) [n(%)] | 81(52.3) | 91(64.8) | 55(75.6) | 67(74.4) | 0.007 |
| age | 64.41 ± 10.52 | 66.39 ± 10.45 | 68.54 ± 10.12[a] | 71.87 ± 7.88[a] | < 0.001 |
| smoking[n(%)] | 60(38.7) | 62(42.7) | 40(44.4) | 39(43.3) | 0.799 |
| Total cholesterol, mmol/L | 4.21 ± 1.09 | 4.19 ± 1.38 | 4.04 ± 1.00 | 3.96 ± 1.02 | 0.368 |
| Triglyceride, mmol/L | 1.76 ± 1.17 | 1.60 ± 0.92 | 1.65 ± 1.74 | 1.50 ± 0.77 | 0.396 |
| LDL- cholesterol, mmol/L | 2.34 ± 0.89 | 2.40 ± 1.15 | 2.32 ± 0.79 | 2.34 ± 0.87 | 0.651 |
| HDL-cholesterol, mmol/L | 1.18 ± 0.40 | 1.13 ± 0.33 | 1.07 ± 0.35 | 1.06 ± 0.26 | 0.634 |
| Diabetes mellitus[n(%)] | 42(27.1) | 34(23.4) | 24(26.6) | 18(20.0) | 0.605 |
| stroke[n(%)] | 21(16.4) | 21(17.2) | 16(21.1) | 20(22.2) | 0.301 |
| Hypertension[n(%)] | 98(63.2) | 97(66.9) | 61(67.8) | 62(68.9) | 0.798 |

Categorical variables are presented as number (percentages) of patients, continuous variables as mean ± SD. P values reflect differences among the four groups. HDL, high-density lipoprotein; LDL, low density lipoprotein cholesterol; CHD, coronary heart disease.

[a]Significant difference is significant at the 0.05 level when comparing each lesion group with the control group.

Cardiac diagnostic testing was performed in 134 subjects by CT coronary angiography, while 346 subjects were assessed by CAG according to clinical symptoms. The CHD group included 228 male and 97 female patients, with ages of 68.43 ± 9.97 years. The control group included 81 male and 74 female patients, with ages of 64.41 ± 10.52 years. There were significant differences in gender distribution, age among the four groups ($P < 0.05$). There was no statistically significant difference in serum levels of TC, TG, LDL-C and HDL-C among the four groups ($P > 0.05$) (Table 1).

The majority of the patients received aspirin and statins administration and most patients with hypertension received antihypertensives.

3.2 IMT and plaque incidence in various groups

The mean carotid IMT was 0.81 ± 0.20 mm. The mean IMT thickness in the CHD group was 0.84 ± 0.21 mm. Compared with control subjects, CHD patients had higher IMT at the carotid site (P = 0.012). There were also significant differences in the number and incidence of plaques among the various groups (P < 0.001) (Table 2), with control patients showing reduced values compared with all CHD subgroups.

Table 2
Comparison of IMT, plaque in different groups.

| Variable | Control (n = 155) | CHD | | | P |
|---|---|---|---|---|---|
| | | Single lesion (n = 145) | Two lesions (n = 90) | Three lesions (n = 90) | |
| IMT (mean ± SD, mm) | 0.76 ± 0.18 | 0.79 ± 0.19[b] | 0.87 ± 0.21[a] | 0.88 ± 0.21[a] | < 0.001 |
| Plaque(mean ± SD, n) | 1.03 ± 1.41 | 1.52 ± 1.54[b] | 2.57 ± 1.89[a,b] | 3.50 ± 2.13[a,b] | < 0.001 |
| Incidence of plaque [n(%)] | 76(49.0) | 95(65.5)[a,b] | 79(87.8)[a] | 86(95.6)[a] | < 0.001 |
| P values indicate significant differences among the four groups. CHD, coronary heart disease; IMT, intima–media thickness. | | | | | |
| [a]Proportion difference is significant at the 0.05 level when comparing each lesion group with the control group. | | | | | |
| [b]Proportion difference is significant at the 0.05 level when comparing each lesion group. | | | | | |

3.3 Carotid plaque classes in the four groups

The incidence of carotid plaques in the CHD group was much higher than that of the control group. Carotid plaques were mainly distributed in the common carotid artery (Table 3).

Table 3
Carotid plaque distribution in the four groups.

| Variable | Control (n = 76) | CHD | | | P |
|---|---|---|---|---|---|
| | | Single lesion (n = 95) | Two lesions (n = 79) | Three lesions (n = 86) | |
| Common carotid artery | 50(65.8) | 65(68.4) | 56(70.9) | 59(68.6) | 0.927 |
| Common carotid artery bifurcation | 21(27.6) | 23(24.2) | 17(21.5) | 20(23.3) | 0.841 |
| Internal carotid artery | 4(5.3) | 5(5.3) | 5(6.3) | 5(5.8) | 1 |
| External carotid artery | 1(1.3) | 2(2.1) | 1(1.3) | 2(2.3) | 1 |
| P values indicate significant differences among the four groups. | | | | | |

Carotid plaque compositions were compared among the four groups (Fig. 1). There was no significant difference in the four groups of different plaque compositions (P > 0.05). There were 29 soft (30.5%), 34 hard (35.8%) and 32 mixed (33.7%) plaque cases in the single branch lesion group. Meanwhile, 21 (26.6%), 35 (44.3%) and 23 (29.1%) cases showed soft, hard and mixed lesions respectively, in the two branch lesion group; these values were 24(27.9%), 37 (43.0%) and 25 (29.1%), respectively, in the three-branch lesion group. The control group had 27 cases of soft plaques (35.5%), 33 of hard plaques (43.4%) and 16 of mixed plaques (21.1%) (Table 4).

Table 4
Carotid Plaque Compositions in the four Groups

| Variable | Control (n = 76) | Single lesion (n = 95) | Two lesions (n = 79) | Three lesions (n = 86) | P |
|---|---|---|---|---|---|
| Soft plaque[n(%)] | 27 (35.5) | 29 (30.5) | 21 (26.6) | 24(27.9) | 0.634 |
| Hard plaque[n(%)] | 33 (43.4) | 34(35.8) | 35 (44.3) | 37 (43.0) | 0.628 |
| Mixed plaque[n(%)] | 16 (21.1) | 32 (33.7) | 23 (29.1) | 25 (29.1) | 0.337 |

3.4 Associations of CHD with IMT, plaque enhancement intensity, and other factors

Univariate logistic regression analysis was performed to assess the associations of CHD with age, gender, smoking, IMT, plaque, plaque level (< 2 plaques vs. >=2 plaques), dyslipidemia, diabetes mellitus, hypertension, stroke, and the Framingham CHD risk score. We found that CHD occurrence was significantly associated with gender (male vs female OR = 0.521, 95% confidence interval (CI) 0.352–0.770; P = 0.001), age (OR = 1.041, 95% CI 1.022–1.061; P < 0.001), Plaque level (OR = 4.739, 95% CI

3.091–7.266; P < 0.001), plaque (OR = 1.610, 95%CI 1.398–1.854; P < 0.001), IMT (OR = 7.567, 95%CI 2.825–20.268; P < 0.001), the Framingham CHD risk score (OR = 1.039, 95%CI 1.015–1.063; P = 0.001) (Table 5).

Table 5
Associations of CHD with various factors assessed by univariate analysis.

| Variable | OR | 95%CI | P |
|---|---|---|---|
| Age | 1.041 | 1.022–1.061 | < 0.001 |
| Age group (< 65y vs. >= 65y) | 1.418 | 0.956–2.103 | 0.082 |
| Gender(male) | 0.521 | 0.352–0.770 | 0.001 |
| smoking | 0.923 | 0.793–1.075 | 0.303 |
| plaque | 1.610 | 1.398–1.854 | < 0.001 |
| Plaque level(< 2 plaques vs. >=2 plaques) | 4.739 | 3.091–7.266 | < 0.001 |
| IMT | 7.567 | 2.825–20.268 | < 0.001 |
| Framingham CHD risk factors | 1.039 | 1.015–1.063 | 0.001 |
| LDL- cholesterol | 0.988 | 0.802–1.217 | 0.910 |
| Total cholesterol | 0.916 | 0.772–1.086 | 0.312 |
| Triglyceride | 0.882 | 0.743–1.047 | 0.151 |
| HDL-cholesterol | 0.951 | 0.655–1.382 | 0.792 |
| Diabetes mellitus | 1.096 | 0.704–1.707 | 0.686 |
| Stroke | 1.157 | 0.701–1.910 | 0.568 |
| Hypertension | 1.111 | 0.723–1.707 | 0.633 |

CI, confidence interval; OR, odds ratio.

The factors significantly associated with CHD were selected into the multivariate regression model, including gender(male), age, plaque level, plaque, IMT and the Framingham CHD risk score. Male subject (OR = 1.569, 95%CI 1.004–2.453; P = 0.048) and plaque level (OR = 0.457, 95%CI 0.210–0.993; P = 0.048) were significant for CHD occurrence (Table 6).

Table 6
Associations of various factors with CHD occurrence in multivariate analysis.

| Variable | OR | 95%CI | P |
|---|---|---|---|
| Gender(male) | 1.569 | 1.004–2.453 | 0.048 |
| Plaque | 0.823 | 0.648–1.045 | 0.110 |
| Plaque level(< 2 plaques vs. >=2 plaques) | 0.457 | 0.210–0.993 | 0.048 |
| Age | 0.968 | 0.930–1.006 | 0.101 |
| IMT | 0.657 | 0.209–2.063 | 0.472 |
| Framingham CHD risk factors | 1.025 | 0.976–1.077 | 0.324 |
| CI, confidence interval; OR, odds ratio. | | | |

ROC curves of different variables for detecting CHD are shown in Fig. 3. The area under the ROC curve (AUC) for IMT, plaque, plaque level, and the Framingham CHD risk factors was 0.614, 0.709, 0.680, and 0.585 respectively. The sensitivity and specificity of carotid plaque were 59.7% and 76.0%, respectively (cutoff value was 1.5 selected by Youden index). DeLong's test p-value for AUC of correlated ROC curves showed that carotid plaque performed significantly better than IMT and the Framingham CHD risk factors for predicting CHD risk (P = 5.84e-4 and P = 2.52e-5, respectively). There was no significant difference between IMT and the Framingham CHD risk factors for predicting CHD risk (P = 0.358), although the AUC of IMT was greater than the Framingham CHD risk score.

# 4. Discussion

The present study demonstrated that carotid artery ultrasound could effectively detect early atherosclerotic events. In addition, gender and plaque levels were risk factors for CHD. Carotid plaque performed significantly better than IMT and the Framingham CHD risk factors for predicting CHD risk.

Ultrasound can be used by clinician's in-office to assess IMT and plaques. As shown above, carotid atherosclerotic plaque development was significantly associated with CHD. Meanwhile, it is known that patients with different degrees of ischemic heart disease experience long-term morbidity and mortality due to premature atherosclerosis [33]. Since atherosclerosis increases the risk of cardiovascular disease, and measurements can be performed noninvasively by carotid artery ultrasound, this method should be included in screening algorithms for the prevention of cardiovascular events.

The atherosclerotic process is enhanced by diabetes, smoking, hypertension, hyperlipidemia, abdominal obesity (metabolic syndrome), kidney insufficiency, persistent proteinuria and so on [34]. In early atherosclerosis, lipoproteins are retained and modified in the vessel wall, resulting in inflammatory responses in the surrounding cells. IMT is an easy, reproducible and non-invasive measurement for

assessing carotid artery wall thickness, and considered an independent predictor of CHD [35]. Because of its reproducibility, simplicity, cost-effectiveness, and non-invasiveness, IMT measurement of the carotid arteries has been generally used to assess systemic atherosclerosis and cardiovascular risk in adults. For example, in patients with carotid atherosclerosis, an IMT increase of 0.1 mm is relevant to an 11% increase of acute myocardial infarction (AMI) risk [36]. IMT has been consistently associated with CHD in previous research, but its clinical usefulness in predictive risk assessment is limited [37]. Consistent with a previous report[38], the present findings demonstrated that carotid artery IMT was elevated in the CHD group compared with control patients. Plaque quantity and composition were both associated with CHD in high-risk patients for CHD.

As shown above, CHD occurrence was also significantly associated with male gender, age, plaque, plaque level, and IMT. The incidence of plaques was much higher in the CHD group compared with control patients, and carotid plaques were mainly distributed in the common carotid artery. In agreement, Dalager et al. reported that plaques tend to form in the carotid and left coronary arteries more frequently than in other locations [7].

Serious coronary artery stenosis is mostly caused by soft plaques, and moderate stenosis mainly by mixed plaques[38]. Plaque bleeding, rupture, and thrombosis result in more serious stenosis and occlusion. As shown above, coronary plaque composition was related to the degree of stenosis. The number of hard plaques was markedly greater in the CHD group compared with control patients. Assessing plaque development in the carotid artery would be particularly important in evaluating the patient's risk for ischemic disorders. Atherosclerotic development has been demonstrated to be a more clinically useful parameter for measuring cardiovascular risk factors than traditional risk factors, for instance, sex, age, previous medical history and metabolic profile [39].

However, because atherosclerosis is a chronic inflammatory condition with kinds of local and systemic manifestations, plaque instability may be a systemic condition, affected by systemic risk factors [40]. Therefore, the development of a readily inexpensive, available, non-invasive diagnostic tool with high accuracy and no side effects is highly desirable. Ultrasound screening of the carotid artery in patients with multiple cardiovascular risk factors is an easy and inexpensive diagnostic protocol that would promote early treatment. Nearly two-thirds of the current study population was 40–72 years old, while 9.3% were in their eighties. It is likely that a lot of asymptomatic subjects with advanced atherosclerosis (especially male with > = 2 plaques) already have an existing asymptomatic coronary heart condition that would respond favorably to medical therapy. It is widely accepted that a sex-specific multivariable risk factor algorithm can be conveniently used to assess general CHD risk [41]. Our result showed that carotid plaque performed significantly better than IMT and the Framingham CHD risk factors for predicting CHD risk. There was no significant difference between IMT and the Framingham CHD risk factors for predicting CHD risk. Adding carotid plaque and/or IMT information may further improve the accuracy of CHD prediction, which needs more investigation. Coronary CT is recommended for those patients with the

presence of carotid plaques, although there are no vascular lesions. Therefore, further investigation is required to improve preventative medicine and high-risk patients need to be followed up regularly.

The limitations of this pilot study should be mentioned. First, it had a relatively small sample size and was performed in a single center. Therefore, further multicenter studies with large samples are required to confirm our findings. In addition, when using ultrasound to evaluate the carotid artery, reading is usually inadvertently measured in the common carotid artery and not the bifurcation.

# 5. Conclusions

In conclusion, our data convincingly demonstrated that carotid artery ultrasound may be an effective and noninvasive method for early detection of atherosclerosis, which would help prevent CHD in asymptomatic subjects with advanced atherosclerosis of the carotid artery. In addition, gender and plaque levels were confirmed as risk factors for CHD. Carotid plaque performed significantly better than IMT and the Framingham CHD risk factors for predicting CHD risk. Further investigation is required to improve preventative medicine and high-risk patients need to be followed up regularly.

# Abbreviations

CHD: coronary heart disease; CCTA: coronary artery computed tomography angiography; CAG: coronary arteriography; IMT: intima-media thickness; AMI: acute myocardial infarction; CCA: common carotid artery; ICA: internal carotid artery; ECA: external carotid artery; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

# Declarations

Ethical approval and consent to participate

Informed consent was obtained from the subjects involved in the study. The protocol was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethical board of Northern Jiangsu People's Hospital, Jiangsu Province, China.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors had access to the data and a role in writing the manuscript.

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Authors' information

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# Figures

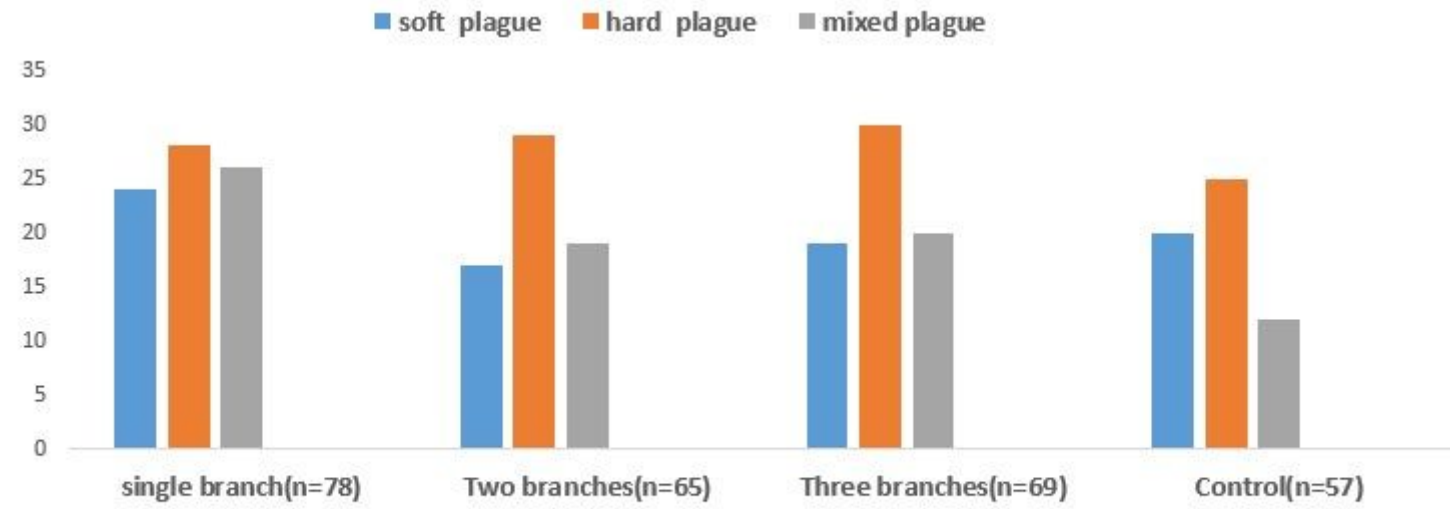
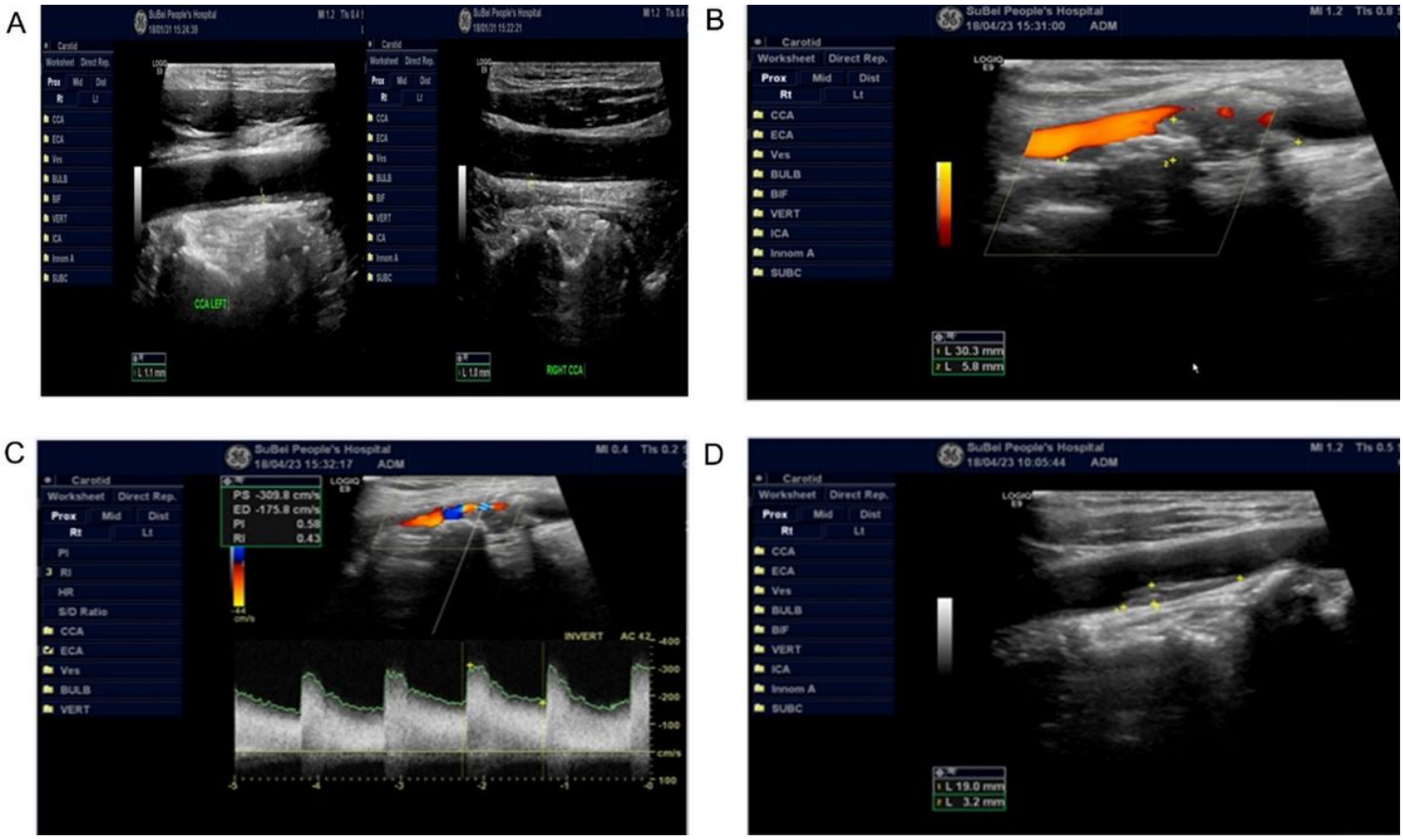



Figure 1 Comparison of Carotid Plaque Compositions between Groups

## Figure 1

Comparison of carotid plaque compositions between groups.




## Figure 2

Ultrasound measurements of thickness. (A)The thickness of the left common carotid artery was 1.1 mm; the thickness of the right common carotid artery was 1.0 mm. (B) Diameter measurements. The diameter

of the proximal section of the right internal carotid artery was 5.2 mm, while the inhomogeneous flat plaque was 30.3 ×5.8 mm in the far wall of the starting section, resulting in local lumen stenosis. The original and residual tube diameters were 9.6 mm and 2.0 mm, respectively, with a section narrowing rate of 309175 cms, RI 0.43. Carotid plaque assessment (C) Severe stenosis at the first segment of the right carotid internal artery. (D) A low echo flat plaque of 9*2.2 mm on the far wall of the right sphere.

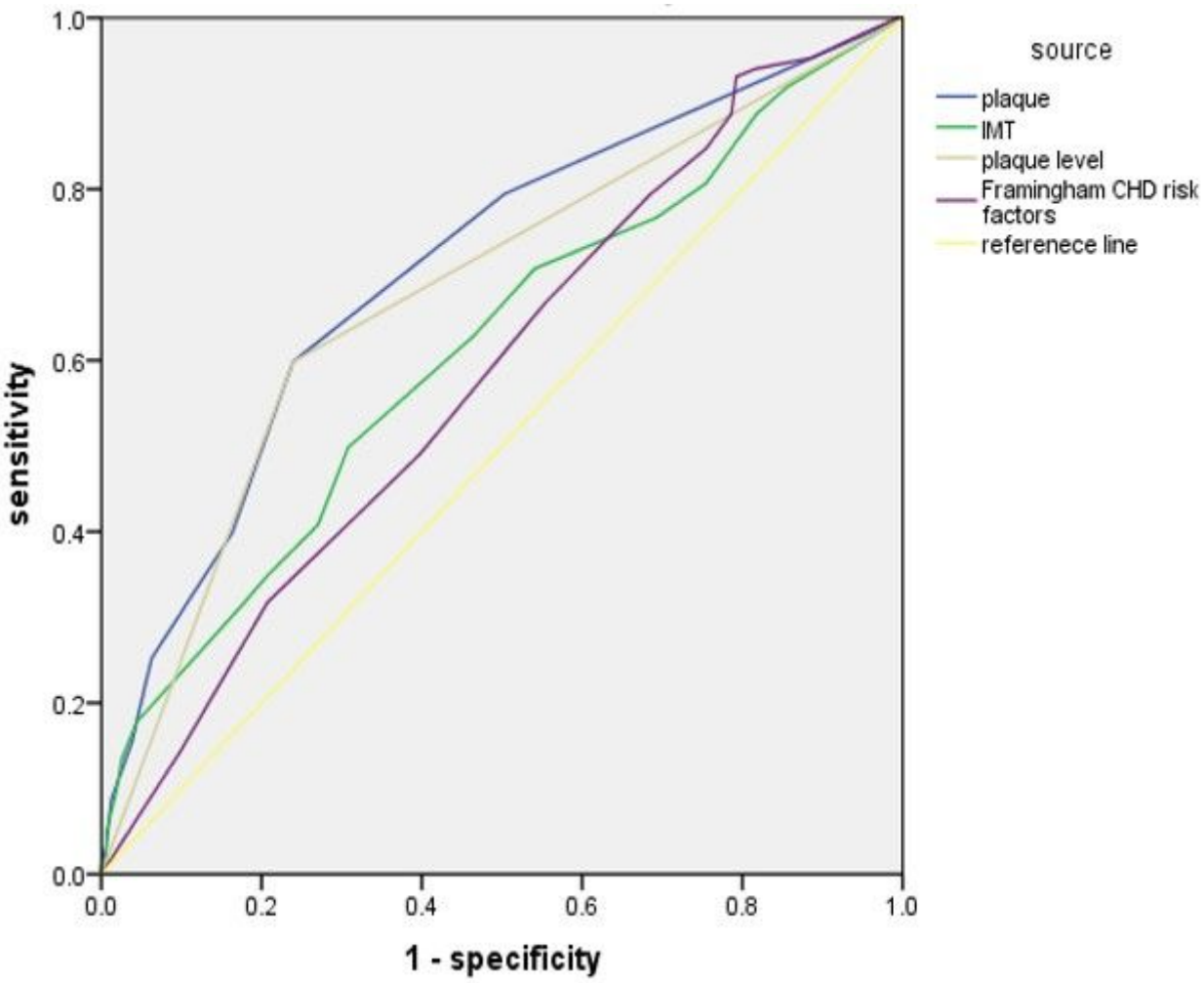
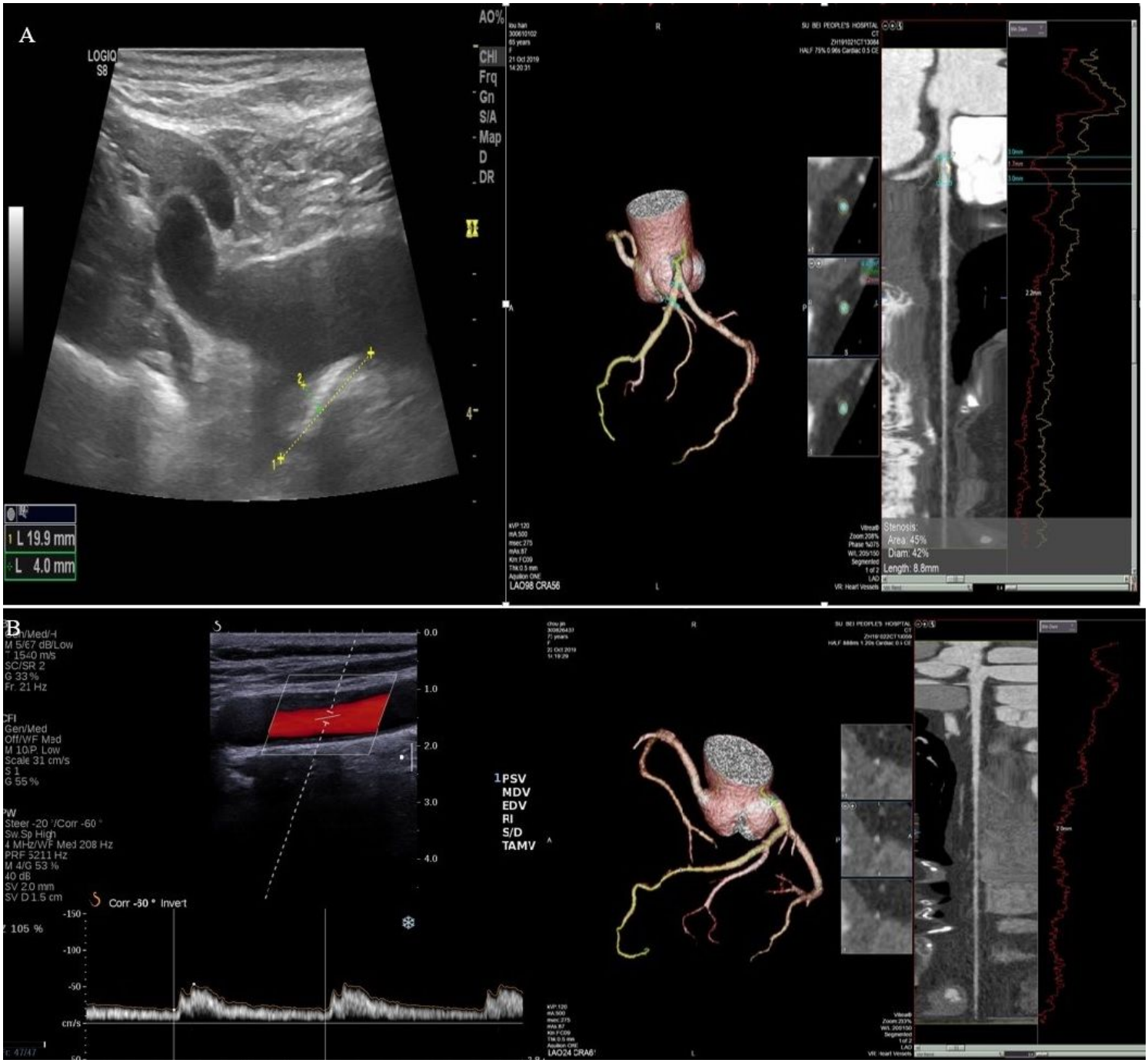



**Figure 3**

ROC curves of different variables for detecting CHD greater than 50% are shown in Fig. 3. The area under the ROC curve (AUC) for IMT, plaque, plaque level, gender, and the Framingham CHD risk factors was 0.614, 0.709, 0.680, 0.585 respectively. The sensitivity and specificity of carotid plaque were 59.7% and 76.0%, respectively (cutoff value was 1.5).




## Figure 4

Left panel: B-mode image showing the right subclavian plaque; Right panel: CTA showing plaque of left anterior descending branch; (B). Left panel: B-mode image showing the normal neck vascular; Right panel: CTA showing the normal coronary artery.