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DIAGNOSTIC VALUE AND PROGNOSTIC ASSESSMENT OF EXERCISE STRESS ECHOCARDIOGRAPHY IN PATIENTS WITH SUSPECTED CORONARY ARTERY DISEASE WITHOUT TYPICAL ANGINA SYMPTOMS

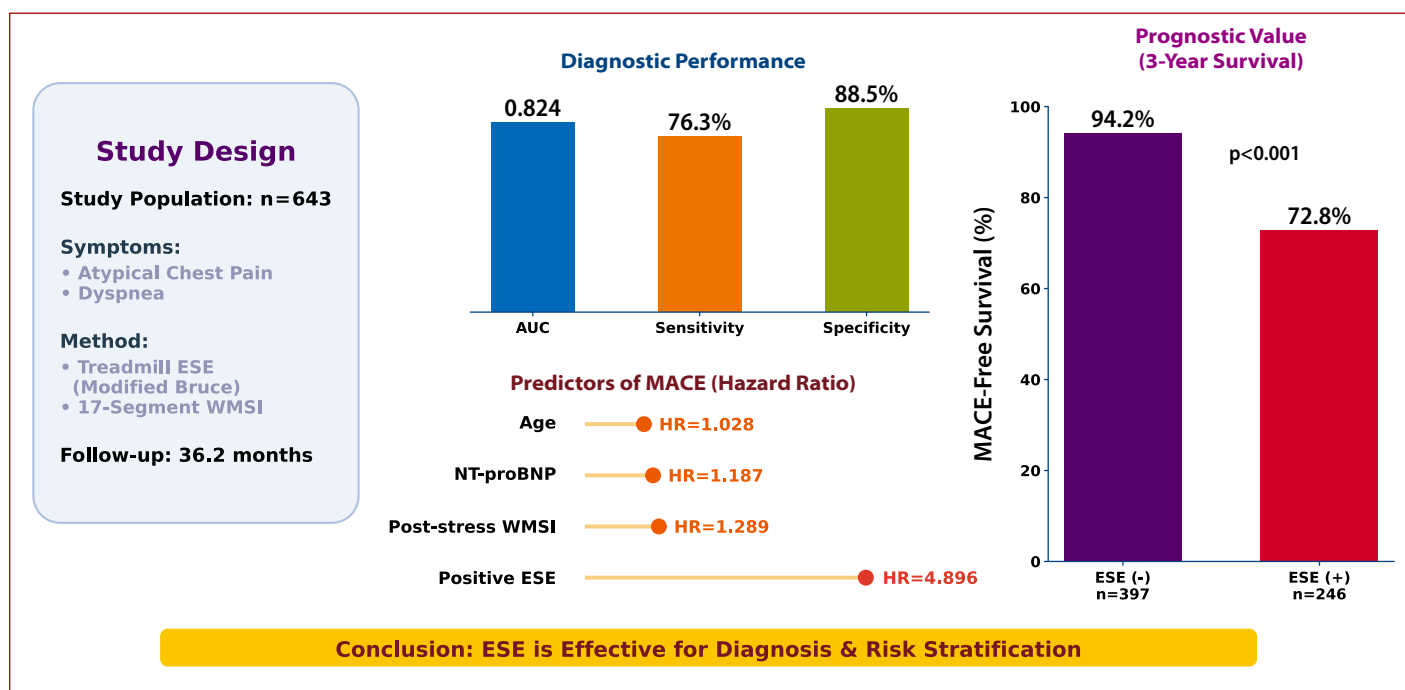
<i>Objective</i>	To evaluate the diagnostic efficacy of exercise stress echocardiography in patients with suspected coronary artery disease (CAD) without typical angina symptoms, and to explore its predictive value for intermediate-term prognosis.
<i>Material and methods</i>	A total of 643 patients aged 45–76 yrs (mean age 58.4±9.7 yrs) with suspected CAD but without typical angina symptoms were retrospectively enrolled in this study. All patients underwent treadmill exercise stress echocardiography using the modified Bruce protocol. Left ventricular wall motion was assessed using the 17-segment scoring method, with coronary angiography or coronary computed tomography angiography (CCTA) as the reference standard for evaluating diagnostic efficacy. The median follow-up time was 36.2 mos. The primary endpoint was a major adverse cardiovascular event (MACE) including cardiac death, non-fatal myocardial infarction, elective revascularization based on objective evidence of myocardial ischemia, and hospitalization for unstable angina. ROC curve analysis was used to evaluate diagnostic efficacy, the Kaplan-Meier method for survival analysis, and a Cox proportional hazards regression model to analyze risk factors for occurrence of MACE.
<i>Results</i>	Of the 643 patients, 253 (39.3%) were diagnosed with severe obstructive CAD (stenosis ≥70%), and 246 (38.3%) had positive results of exercise stress echocardiography. The sensitivity of exercise stress echocardiography for diagnosing severe obstructive CAD was 76.3%, specificity was 88.5%, AUC was 0.824, and diagnostic accuracy was 83.5%. During follow-up, there were 89 cases (13.8%) of MACE. The 3-yr MACE-free survival rate was 72.8% in the positive exercise stress echocardiography group and 94.2% in the negative group ($p<0.001$). Multivariate Cox regression analysis showed that positive exercise stress echocardiography immediately post-stress, wall motion score index, N-terminal pro-B-type natriuretic peptide concentration, and age were independent risk factors for MACE (all $p<0.01$).
<i>Conclusion</i>	Exercise stress echocardiography demonstrated good diagnostic accuracy in patients with suspected CAD but without typical angina symptoms. It had significant predictive value for intermediate-term adverse cardiovascular events. Exercise stress echocardiography can be used for risk stratification and clinical decision-making in this population.
<i>Keywords</i>	Exercise stress echocardiography; coronary artery disease; atypical symptoms; diagnosis; prognosis; wall motion score index; major adverse cardiovascular events
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Introduction

Coronary artery disease (CAD) is a major cardiovascular disease worldwide with continuously rising incidence and mortality rates [1]. Among CAD patients, a considerable proportion lack typical angina symptoms in the early stages of the disease. These patients without typical angina symptoms or with atypical symptoms are often prone to

missed diagnosis or misdiagnosis, and, thus, miss the window for optimal treatment [2]. Traditional resting electrocardiography has limited sensitivity for detecting asymptomatic CAD. The use of coronary angiography, the gold standard for diagnosing CAD, in asymptomatic populations is limited due to its invasiveness, high cost, and potential complications [3].

Central Illustration. Exercise Stress Echocardiography in Suspected CAD Without Typical Angina Symptoms



Exercise stress testing, an important non-invasive examination method for assessing CAD, improves the detection rate of CAD by increasing myocardial oxygen consumption to induce myocardial ischemia during exertion [4]. Exercise stress echocardiography combines echocardiography technology with traditional exercise stress testing to determine the presence of myocardial ischemia by observing changes in left ventricular wall motion before and after exercise. Exercise stress echocardiography has higher sensitivity and specificity for detecting myocardial ischemia than does exercise electrocardiography alone [5]. This technique not only accurately identifies coronary artery stenosis, but it also assesses the extent and severity of myocardial ischemia, thus providing important information for clinical diagnosis and treatment decisions [6]. However, its diagnostic and prognostic performance in patients with suspected CAD who do not present with typical angina symptoms remains insufficiently characterized.

Recent studies have shown that the results of exercise stress echocardiography not only have important diagnostic value but are also closely related to patients' long-term prognosis [7]. Positive results often indicate a significantly increased risk of major adverse cardiovascular events (MACE). This is of great value for risk stratification and treatment strategy formulation in patients without typical CAD symptoms [8].

Large international multicenter prospective studies, such as Stress-Echo 2020 and 2030, and related studies have confirmed the diagnostic and prognostic value of stress echocardiography in assessing left ventricular regional systolic function in various clinical settings [9–13]. However, there are relatively few large-sample cohort studies on the diagnostic accuracy and prognostic value of exercise stress echocar-

diography in patients with suspected CAD without typical angina symptoms [10]. This is particularly true for exercise stress testing in Chinese populations [14].

This retrospective cohort study aimed to systematically evaluate the diagnostic efficacy of exercise stress echocardiography in patients with suspected CAD but without typical angina symptoms. The results permitted an extensive analysis of the predictive value of exercise stress echocardiography for patients' intermediate-term prognosis. The goal was to provide new information for more reliable, evidence-based decisions in clinical cardiology practice and, thus, for optimizing diagnostic and treatment strategies for CAD patients without typical symptoms.

Material and methods

Study design and ethics approval

This study was approved by the hospital ethics committee, and it was compliant with the relevant requirements of the Declaration of Helsinki. Given the retrospective nature of the study, the ethics committee approved waiving informed consent but required strict protection of the patients' personal information.

Study subjects

The inclusion criteria for this study were:

- 1) Age 18–80 yrs;
- 2) Clinically suspected CAD without typical angina symptoms, i.e., with atypical chest pain, exertional dyspnea, or other atypical symptoms;
- 3) Normal resting electrocardiogram or with non-specific changes;

- 4) Exercise stress echocardiography examination with good image quality;
- 5) Coronary angiography or coronary computed tomography angiography (CCTA) within 6 mos after the stress echocardiography examination (patients with interval ACS or revascularization were excluded);
- 6) Complete clinical data, including intermediate-term follow-up data.

Exclusion criteria were (assessed at enrollment, i.e., before stress echocardiography, based on clinical history and medical records):

- 1) Presence of typical angina symptoms or history of myocardial infarction;
- 2) Severe arrhythmia;
- 3) Heart failure (New York Heart Association functional class III–IV);
- 4) Severe valvular disease, e.g., moderate to severe stenosis or regurgitation;
- 5) Hypertrophic cardiomyopathy, dilated cardiomyopathy, or other cardiomyopathies;
- 6) Limited exercise capacity, e.g., joint diseases, neurological diseases;
- 7) Pregnancy;
- 8) Malignant tumor in patients with expected survival less than years;
- 9) Poor echocardiography image quality, i.e., unable to accurately assess wall motion.

According to the 2024 European Society of Cardiology guidelines for chronic coronary syndromes [3], the pre-test probability of CAD in the patients included in this study was in the intermediate-to-low range (10%–50%). Reasons for patients undergoing subsequent coronary angiography or CCTA included:

1. Positive exercise stress echocardiography;
2. Presence of multiple clustering cardiovascular risk factors;
3. Non-specific resting electrocardiogram changes;
4. Abnormalities suggested by other non-invasive examinations, such as ischemic ECG changes, positive stress imaging, or coronary stenosis on CCTA;
5. Comprehensive clinical assessment as high-risk patients.

Patients with negative exercise stress echocardiography findings had coronary angiography or CCTA (n=151) mainly for the following reasons:

1. Clustering of high-risk factors (n=78, 51.7%);
2. Non-specific electrocardiogram changes (n=45, 29.8%);
3. Abnormalities in other imaging examinations (n=18, 11.9%);
4. Comprehensive clinical assessment as high-risk (n=10, 6.6%).

Data collection

Clinical data were retrospectively collected from patients seen in the cardiology outpatient and inpatient departments of the Fourth People's hospital of Kunshan (Kunshan, Jiang-

su Province, China) from January 2019 to December 2022. These patients met the following criteria:

- 1) Complete baseline data, i.e., age, gender, body mass index (BMI), blood pressure, heart rate;
- 2) Presence of CAD risk factors, e.g., hypertension, diabetes mellitus, dyslipidemia, smoking history, CAD family history;
- 3) Results of laboratory tests, including blood lipids (TC, LDL-C, HDL-C, triglycerides), fasting blood glucose, glycated hemoglobin, serum creatinine, NT-proBNP, and hs-CRP;
- 4) Information on medication, including antiplatelet agents, statins, angiotensin-converting enzyme inhibitors (ACEI) / angiotensin receptor blockers (ARB), beta-blockers, and others;
- 5) Presence of symptoms, including atypical chest pain, exertional dyspnea, palpitations, chest tightness, and other non-specific symptoms suggestive of CAD.

Exercise stress echocardiography

Before exercise stress echocardiography, the patients discontinued relevant medications according to drug half-lives, e.g., beta-blockers were stopped for five half-lives (usually 3–5 days), calcium channel blockers for 24–48 hrs, and nitrates for 24 hrs. For patients currently using anti-anginal medications, discontinuation was to avoid drug effects on myocardial ischemia induction and to ensure examination sensitivity. The patients avoided strenuous activity for 24 hrs before the examination, and they fasted for 4 hrs before the examination.

A GE Vivid E95 ultrasound diagnostic system (GE Healthcare, Chicago, IL, USA) equipped with an M5S-D probe (1.5–4.6 MHz frequency) was used. No ultrasound contrast agents were used in any patients, and image quality in all 17 included patients met the requirement for clear visualization. All examinations were performed by cardiac ultrasound physicians with more than five years of experience in exercise stress echocardiography.

The examination protocol included:

- 1) Resting echocardiography with acquisition of parasternal long-axis view, short-axis views (mitral valve level, papillary muscle level, apical level), apical four-chamber, two-chamber, and three-chamber views, with dynamic images of three consecutive cardiac cycles captured for each view;
- 2) Exercise stress test with graded treadmill exercise using the modified Bruce protocol. Target heart rate (THR) was calculated according to age using the following formulas. Age ≤40 yrs, $THR = (220 - age) \times 85\%$; Age = 41–65 yrs, $THR = (207 - 0.7 \times age) \times 85\%$; Age >65 yrs, $THR = (208 - 0.7 \times age) \times 85\%$. Exercise termination criteria:

- 2a) Reaching the target heart rate;
- 2b) Onset of angina symptoms;
- 2c) Abnormal blood pressure elevation ($>250/115$ mmHg), or decrease (systolic blood pressure decrease >10 mmHg from baseline);
- 2d) Severe arrhythmia;
- 2e) Significant ST segment depression >2 mm or elevation >1 mm;
- 2f) Patient request to stop due to fatigue, dyspnea, or other intolerable symptoms;
- 3) Immediate post-stress echocardiography within 30 sec after exercise termination. The same views as during the resting period were acquired, with dynamic images of three consecutive cardiac cycles captured for each view;
- 4) Continuous monitoring during the recovery period until heart rate and blood pressure returned to baseline values or until 15 min after the examination. Electrocardiogram changes and clinical symptoms during exercise and recovery periods were simultaneously recorded.

Echocardiography image analysis and quality control

All images were independently analyzed by two senior physicians (attending physician level or above), each with more than 10 yrs of echocardiography diagnostic experience. In cases with disagreement in interpretation, a third senior physician made the final judgment.

The 17-segment scoring method recommended by the American Society of Echocardiography was used to assess left ventricular wall motion.

Scoring criteria:

- 1) Normal motion, 1 point;
- 2) Hypokinesis, 2 points;
- 3) Akinesis, 3 points;
- 4) Dyskinesis, 4 points.

The left ventricular wall motion score index (WMSI) was calculated. $WMSI = \text{sum of segment score points} / \text{number of assessed segments}$.

Image quality control criteria:

- 1) All 17 segments clearly visible at rest and post-stress;
- 2) Image frame rate ≥ 50 fps;
- 3) No obvious artifacts;
- 4) Clear left ventricular endocardial border.

These quality criteria were assessed at enrollment, and cases not meeting quality requirements were excluded before final analysis.

Positive criteria for exercise stress echocardiography were post-stress WMSI increase ≥ 0.25 compared to rest, or new-onset segmental wall motion abnormality in at least two adjacent segments. Inter-observer agreement was assessed from the kappa value computed after images from

50 randomly selected patients were independently analyzed by two physicians.

Diagnostic criteria for obstructive CAD

Coronary angiography was independently evaluated by two senior physicians (chief physician level) with more than 10 yrs of experience in interventional cardiology using quantitative coronary angiography. In cases of disagreement, the evaluation was made by a third physician.

Diagnostic criteria for severe obstructive CAD:

1. Left main stenosis $\geq 50\%$;
2. Stenosis $\geq 70\%$ in any major epicardial coronary artery (left anterior descending, left circumflex, or right coronary artery);
3. Important branch vessels, such as large diagonal branches, obtuse marginal branches, or posterior descending artery stenosis $\geq 70\%$.

This study used $\geq 70\%$ as the threshold for diagnosing severe obstructive lesions (except for 50% stenosis of left main). These lesions are considered hemodynamically significant, and with these severe lesions composed the Severe Obstructive Lesion Group. Patients with coronary stenosis $<70\%$ composed the Non-Severe Obstructive Lesion Group.

Thirty-four patients had borderline lesions of 50–69%. According to contemporary guideline recommendations [3], these moderately stenotic lesions require functional assessment (such as fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR)) to determine their hemodynamic significance. However, since this was a retrospective study and FFR or iFR measurements were not routinely performed, these patients with borderline lesions were included in the Non-Severe Obstructive Lesion Group ($<70\%$) for analysis.

Coronary computed tomography (CT) angiography was performed using dual-source CT (Siemens Definition Flash) or 256-slice spiral CT (Philips Brilliance, Cleveland, OH, USA), with images independently interpreted by two radiologists (attending physician level and above) with more than five years of experience in cardiovascular imaging diagnosis. The same stenosis degree criteria used for coronary angiography was used for coronary CT angiography.

Patient follow-up and endpoint events

Follow-up information was collected from the date of the exercise stress echocardiography examination by outpatient visits, telephone interviews, medical insurance database queries, and death registry system queries. Follow-up time was defined as the time interval from the examination date to the earliest occurrence of an endpoint event, loss to follow-up information, or study deadline (June 30, 2024). The minimum follow-up time was six months.

The primary endpoint was MACE, which included:

- 1) Cardiac death (determined based on death certificates and clinical records);
- 2) Non-fatal myocardial infarction (meeting the Fourth Universal Definition of Myocardial Infarction) [3];
- 3) Elective revascularization based on objective evidence of myocardial ischemia. Revascularization was performed by percutaneous coronary intervention or coronary artery bypass grafting performed ≥ 90 days after the exercise stress echocardiography;
- 4) Hospitalization for unstable angina requiring intravenous antithrombotic therapy or urgent revascularization. Emergency revascularization for acute coronary syndrome within 90 days after examination was classified as “hospitalization for unstable angina” or “non-fatal myocardial infarction” rather than elective revascularization. Secondary endpoints were:

- 1) All-cause death;
- 2) Hospitalization for heart failure that met the European Society of Cardiology (ESC) guideline criteria for diagnosis of heart failure;
- 3) Composite endpoint of any event (including all-cause death, hospitalization for heart failure, or any MACE component).

All endpoint events were adjudicated by an independent clinical event committee consisting of experts in cardiology, imaging, and emergency medicine, with disputed cases decided by collective discussion.

Statistical analysis

SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R 4.2.0 software (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. Continuous data with normal distributions are expressed as mean $\pm$ standard deviation (SD), and independent sample t-tests were used for comparisons between groups. Non-normally distributed data are expressed as median (interquartile range) (Q1, Q3), and Mann-Whitney U tests were used for group comparisons. Categorical variables are expressed as number (percentage), and chi-square tests were used for group comparisons. Inter-observer agreement was assessed by the intra-class correlation coefficient (ICC), with ICC >0.75 indicating good agreement.

The diagnostic efficacy of exercise stress echocardiography was evaluated using receiver operating characteristic (ROC) curve analysis to determine area under the curve (AUC), sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio [3]. The DeLong test was used to compare the AUCs of different diagnostic indicators [3].

Survival analysis used the Kaplan-Meier method to plot survival curves, with log-rank tests used for comparisons between groups [7]. The Cox proportional hazards re-

gression model was used to analyze risk factors for MACE, with variables having $p < 0.10$ in the univariate analysis included in the multivariate analysis. A Schoenfeld residual test was used to verify the proportional hazards assumption, the Harrell's C-index to assess model discrimination ability, and a Hosmer-Lemeshow test to assess model calibration [7]. A restricted cubic spline function with 3 knots was used to explore dose-response relationships between continuous variables and MACE [3]. All tests were two-sided, with $p < 0.05$ considered statistically significant.

Results

General Data

During the study period, a total of 2247 patients were screened, and finally 643 patients with suspected CAD without typical angina symptoms and meeting the study criteria were included the analysis (Table 1). The patients were 45–76 yrs old, with a mean age of 58.4 ± 9.7 yrs. The study included 379 males (58.9%) and 264 females (41.1%). The median follow-up time was 36.2 (24.8, 48.6) mos, with a loss to follow-up rate of 2.3% (15/643). Clinical manifestations of the patients included atypical chest pain in 312 cases (48.5%), exertional dyspnea in 256 cases (39.8%), palpitations, or chest tightness in 89 cases (13.8%), and other non-specific symptoms in 76 cases (11.8%). Some patients had multiple symptoms.

Inter-observer agreement analysis showed that the ICC for resting WMSI assessment was 0.89 (95% CI: 0.84–0.93), and the ICC for post-stress WMSI assessment was 0.92 (95% CI: 0.88–0.95). These values indicated good agreement among observers.

According to coronary angiography ($n=487$, 75.7%) or CCTA ($n=156$, 24.3%) results, 253 cases (39.3%) were diagnosed with severe obstructive CAD. This group included 142 cases (56.1%) with single-vessel disease, 76 cases (30.0%) with two-vessel disease, and 35 cases (13.8%) with three-vessel disease. Non-severe obstructive lesions were found in 390 cases (60.7%), of which 34 cases (8.7%) had borderline lesions (stenosis 50–69%). Exercise stress echocardiography was positive in 246 cases (38.3%) and negative in 397 cases (61.7%).

Comparison of baseline data between the Severe Obstructive Lesion Group and Non-Severe Obstructive Lesion Group (Table 1) showed that patients in the Severe Obstructive Lesion Group were older, predominately male, and had higher BMI and blood pressure values. The presence of cardiovascular risk factors, the number of patients with hypertension, diabetes, dyslipidemia, smoking history, and CAD family history were all significantly higher in the Severe Obstructive Lesion Group. More patients in this group had abnormal lipid profiles, higher glucose metabolism indicators, and higher NT-proBNP concentrations. The utilization rates of various cardiovascular protective drugs in the Se-

Table 1. Comparison of baseline data between the Severe Obstructive Lesion Group and the Non-Severe Obstructive Lesion Group

Variable	Severe Obstructive Lesion Group (n=253)	Non-Severe Obstructive Lesion Group (n=390)	Test Statistic	P value
General Data				
Age (yrs)	62.8±8.7	55.4±9.9	t=10.21	<0.001
Male	172 (68.0)	207 (53.1)	$\chi^2=14.56$	<0.001
BMI (kg/m ²)	26.5±3.1	25.0±3.7	t=5.42	<0.001
Systolic blood pressure (mmHg)	139.2±16.5	132.1±15.4	t=5.67	<0.001
Diastolic blood pressure (mmHg)	82.8±9.6	79.4±9.2	t=4.58	<0.001
Resting heart rate (bpm) †	69.5±10.5	71.3±10.8	t=-2.12	0.034
Risk Factors				
Hypertension	161 (63.6)	173 (44.4)	$\chi^2=23.78$	<0.001
Diabetes mellitus	81 (32.0)	75 (19.2)	$\chi^2=14.92$	<0.001
Dyslipidemia	180 (71.1)	210 (53.8)	$\chi^2=20.15$	<0.001
Smoking history	122 (48.2)	110 (28.2)	$\chi^2=27.86$	<0.001
CAD family history	69 (27.3)	61 (15.6)	$\chi^2=13.24$	<0.001
Laboratory Tests				
Total cholesterol (mmol/l)	5.21±1.25	4.80±1.14	t=4.42	<0.001
LDL-C (mmol/l)	3.27±0.99	2.87±0.91	t=5.45	<0.001
HDL-C (mmol/l)	1.17±0.33	1.32±0.40	t=-5.12	<0.001
Triglycerides (mmol/l)*	1.82 (1.26,2.48)	1.50 (1.06,2.10)	Z=-3.98	<0.001
Fasting blood glucose (mmol/l)	6.31±1.71	5.65±1.30	t=5.42	<0.001
Glycated hemoglobin (%)*	6.2 (5.7,7.3)	5.7 (5.3,6.2)	Z=-4.89	<0.001
Serum creatinine (μmol/l)	79.1±19.2	74.9±16.5	t=2.98	0.003
NT-proBNP (pg/ml)*	92.7 (54.8,162.4)	65.8 (37.2,110.3)	Z=-5.67	<0.001
Baseline Echocardiographic Parameters				
Left ventricular ejection fraction (%)	62.1±5.9	64.2±5.1	t=-4.78	<0.001
Left ventricular end-diastolic diameter (mm)	49.5±4.7	48.2±4.1	t=3.76	<0.001
Left atrial diameter (mm)	38.1±4.4	36.4±3.8	t=5.23	<0.001
Medication Use				
Antiplatelet agents	142 (56.1)	126 (32.3)	$\chi^2=37.45$	<0.001
Statins	170 (67.2)	164 (42.1)	$\chi^2=41.23$	<0.001
ACEI/ARB	128 (50.6)	112 (28.7)	$\chi^2=32.89$	<0.001
Beta-blockers	89 (35.2)	76 (19.5)	$\chi^2=20.45$	<0.001

Data are mean±SD, mean (Q1, Q3), or n (percentage). † Lower resting heart rate in the Severe Obstructive Lesion Group may be related to higher beta-blocker utilization rate in this group; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

vere Obstructive Lesion Group were significantly higher than in the Non-Severe Obstructive Lesion Group. The resting heart rate of patients in the Severe Obstructive Lesion Group was slightly lower than in the Non-Severe Obstructive Lesion Group, which may have been related to the higher utilization rate of beta-blockers in the Severe Obstructive Lesion Group (most factors, $p<0.05$; for others, $p<0.10$).

Exercise stress test parameters and echocardiographic indicators

Comparisons of the results of exercise stress test parameters and echocardiographic indicators between the Severe Obstructive Lesion Group and Non-Severe Obstructive Lesion Group (Table 2) showed: patients in the Severe Obstructive Lesion Group had poorer exercise tolerance that was manifested as shorter exercise time, lower peak heart rate, and lower proportion that achieved the target heart rate. Echocardiographic indicators showed that patients in the Se-

Table 2. Comparison of exercise stress test parameters and echocardiographic indicators in the two groups

Variable	Severe Obstructive Lesion Group (n=253)	Non-Severe Obstructive Lesion Group (n=390)	Test Statistic	p value
Exercise Stress Test Parameters				
Exercise time (min) *	8.0 (6.3,9.9)	9.8 (7.9,11.7)	Z=-7.56	<0.001
Peak heart rate (bpm)	147.8±18.9	152.5±19.3	t=-3.12	0.002
Peak systolic blood pressure (mmHg)	187.2±24.1	182.4±21.9	t=2.67	0.008
Peak diastolic blood pressure (mmHg)	90.1±12.6	87.7±11.7	t=2.54	0.011
Achieved target heart rate	202 (79.8)	344 (88.2)	$\chi^2=8.23$	0.004
Reason for Exercise Termination			$\chi^2=12.34$	0.015
Achieved target heart rate	202 (79.8)	344 (88.2)	-	-
Chest pain symptoms	28 (11.1)	18 (4.6)	-	-
ECG abnormality	14 (5.5)	13 (3.3)	-	-
Blood pressure abnormality	6 (2.4)	8 (2.1)	-	-
Other reasons	3 (1.2)	7 (1.8)	-	-
Echocardiographic Indicators				
Resting WMSI	1.09±0.13	1.04±0.08	t=6.23	<0.001
Post-stress WMSI	1.36±0.29	1.08±0.11	t=16.78	<0.001
WMSI change value	0.27±0.25	0.04±0.09	t=16.89	<0.001
New-onset segmental wall motion abnormality	179 (70.8)	51 (13.1)	$\chi^2=227.45$	<0.001
Positive exercise stress echocardiography	193 (76.3)	53 (13.6)	$\chi^2=264.12$	<0.001

Data are mean±SD, mean (Q1, Q3), or n (percentage). WMSI: wall motion score index.

vere Obstructive Lesion Group had mildly elevated resting WMSI, significantly elevated post-stress WMSI, significantly increased WMSI change values. The rates of new-onset segmental wall motion abnormality and positive exercise stress echocardiography were significantly higher than in the Non-Severe Obstructive Lesion Group (all $p < 0.05$).

Diagnostic efficacy assessment of exercise stress echocardiography

Coronary angiography or CCTA was used as the reference standard for evaluating the diagnostic efficacy of exercise stress echocardiography for severe obstructive CAD (stenosis $\geq 70\%$) (Table 3). Results showed that the AUC of exercise stress echocardiography for diagnosing severe obstructive CAD was 0.824 (95% CI: 0.793–0.855, $p < 0.001$), demonstrating good diagnostic accuracy. The sensitivity of clinical symptoms, i.e., chest pain, during exercise was 26.8% (95% CI: 21.8–32.3%), specificity was 94.4% (95% CI: 91.4–96.6%), and AUC was 0.606 (95% CI: 0.565–0.647). The sensitivity of positive exercise electrocardiography, i.e., ST segment depression ≥ 1 mm, was 31.4% (95% CI: 26.1–37.1%), specificity was 91.9% (95% CI: 88.5–94.6%), and AUC was 0.617 (95% CI: 0.576–0.657). The diagnostic efficacy of exercise stress echocardiography was significantly superior to clinical symptoms alone ($p < 0.001$) and exercise electrocardiography alone ($p < 0.001$).

The DeLong test was used to compare AUC differences between indicators of wall function. The AUC of the binary stress echocardiography result (positive vs. negative) (AUC=0.824) showed significant differences compared to resting WMSI (AUC=0.681, $p < 0.001$), post-stress WMSI (AUC=0.789, $p = 0.032$), and WMSI change value (AUC=0.793, $p = 0.028$).

Sensitivity analysis was stratified by the degree of vascular disease:

- 1) Single-vessel disease ($n = 142$), sensitivity 70.4% (95% CI: 62.3–77.7%);
- 2) Two-vessel disease ($n = 76$), sensitivity 81.6% (95% CI: 70.9–89.7%);

Table 3. Diagnostic efficacy assessment of exercise stress echocardiography

Diagnostic Indicator	Value	95% Confidence Interval
Sensitivity (%)	76.3	70.6–81.5
Specificity (%)	88.5	85.2–91.3
Positive predictive value (%)	78.5	72.9–83.5
Negative predictive value (%)	86.9	83.3–90.0
Positive likelihood ratio	6.63	5.12–8.58
Negative likelihood ratio	0.27	0.21–0.34
Accuracy (%)	83.5	80.4–86.3
AUC	0.824	0.793–0.855

- 3) Three-vessel disease ($n = 35$), sensitivity 91.4% (95% CI: 76.9–98.2%).

Sensitivity increased with the degree of vascular disease, showing that exercise stress echocardiography has better detection capability for multi-vessel disease.

Sensitivity analysis was stratified by the diseased vessel:

- 1) Left anterior descending artery disease ($n = 180$), sensitivity 80.6% (95% CI: 74.1–86.2%);
- 2) Left circumflex artery disease ($n = 128$), sensitivity 74.2% (95% CI: 65.9–81.4%);
- 3) Right CAD ($n = 115$), sensitivity 71.3% (95% CI: 62.1–79.4%).

Some patients had multi-vessel disease, so the sum of cases for each vessel lesion is greater than the total number patients with severe obstructive CAD.

Prognostic analysis

Follow-up results and endpoint events. During the median follow-up period of 36.2 mos, a total of 89 cases (13.8%) of MACE occurred. Endpoint event statistics used the first event time analysis method, meaning only the first major endpoint event was counted for each patient. Among the 89 MACE patients, cardiac death was the first event in 12 cases (13.5%), non-fatal myocardial infarction was the first event in 21 cases (23.6%), elective revascularization based on objective evidence of myocardial ischemia was the first event in 46 cases (51.7%), and hospitalization for unstable angina was the first event in 10 cases (11.2%). All 46 patients who underwent elective revascularization had the procedure performed more than 90 days after initial examination, with a median time of 156 (112, 234) days.

Regarding secondary endpoints, there were 18 cases (2.8%) of all-cause death and 26 cases (4.0%) of hospitalization for heart failure. Among the 89 patients who experienced MACE, 16 (18.0%) experienced multiple endpoint events during follow-up.

The occurrence of endpoint events in the positive and negative exercise stress echocardiography groups are shown in Table 4. Results showed that the incidence of endpoint events was significantly higher in the positive exercise stress echocardiography group than in the negative group. Similarly, patients with severe obstructive CAD had higher event rates than those without severe obstruction (all $p < 0.05$).

Survival Analysis

Kaplan-Meier survival analysis showed that the 1-, 2-, and 3-yr MACE-free survival rates in the positive exercise stress echocardiography group were 88.6% (95% CI: 84.2–92.3%), 78.5% (95% CI: 72.8–83.6%), and 72.8% (95% CI: 66.7–78.4%), respectively. The corresponding survival rates in the negative group were 97.2% (95% CI: 95.4–98.5%), 94.5% (95% CI: 91.9–96.5%), and 94.2% (95% CI: 91.5–

Table 4. Occurrence of endpoint events in each group

Endpoint Event	Overall (n=643)	Exercise Stress Echocardiography				Coronary Angiography / CCTA Results			
		Positive Group (n=246)	Negative Group (n=397)	χ^2	p value	Severe Obstructive Lesion Group (n=253)	Non-Severe Obstructive Lesion Group (n=390)	χ^2	p value
Primary Endpoint Event									
MACE	89 (13.8)	67 (27.2)	22 (5.5)	53.82	<0.001	71 (28.1)	18 (4.6)	68.45	<0.001
Including: Cardiac death*	12 (1.9)	9 (3.7)	3 (0.8)			10 (4.0)	2 (0.5)		
Non-fatal myocardial infarction*	21 (3.3)	16 (6.5)	5 (1.3)			18 (7.1)	3 (0.8)		
Elective revascularization*	46 (7.2)	35 (14.2)	11 (2.8)			36 (14.2)	10 (2.6)		
Hospitalization for unstable angina*	10 (1.6)	7 (2.8)	3 (0.8)			7 (2.8)	3 (0.8)		
Secondary Endpoint Event									
All-cause death	18 (2.8)	13 (5.3)	5 (1.3)	8.45	0.004	14 (5.5)	4 (1.0)	11.23	0.001
Hospitalization for heart failure	26 (4.0)	19 (7.7)	7 (1.8)	14.52	<0.001	21 (8.3)	5 (1.3)	21.45	<0.001
Composite endpoint of any event	103 (16.0)	76 (30.9)	27 (6.8)	58.14	<0.001	80 (31.6)	23 (5.9)	70.89	<0.001

Data are n (percentage). *Indicates number of cases as first event. MACE statistics based on first event time analysis principle

Table 5. MACE incidence rate stratified by degree of CAD

Degree of CAD	Number of Cases (n)	MACE Occurrence	MACE Incidence Rate (%)	Positive Exercise Stress Echocardiography Rate (%)
Non-severe obstructive lesion (<70%)	390	18	4.6	13.6
Single-vessel disease	142	26	18.3	70.4
Two-vessel disease	76	26	34.2	81.6
Three-vessel disease	35	19	54.3	91.4
p value (trend test)	–	–	<0.001	<0.001

96.3%). Log-rank test detected statistically significant differences between the two groups ($\chi^2 = 50.34$, $p < 0.001$).

When stratified by coronary angiography/CCTA diagnostic results, the 3-yr MACE-free survival rate was 71.9% (95% CI: 66.1–77.2%) in the Severe Obstructive Lesion Group ($\geq 70\%$) and 95.4% (95% CI: 93.1–97.2%) in the Non-Severe Obstructive Lesion Group (<70%), with the log-rank test $p < 0.001$ (Table 5).

Cox hazard regression analysis

Variables with < 0.10 in the univariate Cox hazard regression analysis were included in the multivariate analysis. The Schoenfeld residual test showed that all variables met the proportion-

al hazards assumption ($p > 0.05$). Multivariate Cox regression analysis (Table 6) showed that age (HR=1.028, 95% CI: 1.008–1.049, $p = 0.006$), NT-proBNP level (HR=1.187, 95% CI: 1.086–1.297, $p < 0.001$), positive exercise stress echocardiography (HR=4.896, 95% CI: 3.032–7.905, $p < 0.001$), and post-stress WMSI (HR=1.289, 95% CI: 1.142–1.456, $p < 0.001$) were independent risk factors for MACE.

Model discrimination assessment showed that Harrell's C-index was 0.781 (95% CI: 0.735–0.827), and model calibration according to the Hosmer-Lemeshow test indicated good model fit $p = 0.423$ [3]. Overall proportional hazards assumption test $p = 0.156$, meeting the basic assumptions of the Cox regression model [3].

Table 6. Cox hazard regression analysis of independent risk factors for MACE occurrence

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age (per 1-yr increase)	1.042	1.024–1.061	<0.001	1.028	1.008–1.049	0.006
Male	1.634	1.087–2.455	0.018	1.389	0.901–2.141	0.136
Diabetes mellitus	1.872	1.243–2.820	0.003	1.524	0.995–2.334	0.053
Smoking history	1.756	1.168–2.640	0.007	1.298	0.834–2.021	0.248
LDL-C (per 1 mmol/l increase)	1.287	1.089–1.520	0.003	1.198	0.998–1.439	0.052
NT-proBNP (per 100 pg/ml increase)	1.234	1.132–1.344	<0.001	1.187	1.086–1.297	<0.001
Positive exercise stress echocardiography	6.243	3.921–9.939	<0.001	4.896	3.032–7.905	<0.001
Resting WMSI (per 0.1 increase)	2.145	1.234–3.729	0.007	1.567	0.876–2.805	0.131
Post-stress WMSI (per 0.1 increase)	1.456	1.298–1.633	<0.001	1.289	1.142–1.456	<0.001

HR, hazard ratio; CI, confidence interval; WMSI, wall motion score index.

Non-linear relationship analysis of continuous variables was performed using restricted cubic splines (3 knots at the 10th, 50th, and 90th percentiles). Age and MACE risk showed a significant non-linear association (p for non-linearity = 0.018), with the risk increasing slowly between 45–60 years, accelerating between 60–70 years, and then plateauing after 70 years. NT-proBNP also demonstrated a significant non-linear association with MACE risk (p for non-linearity = 0.009), with a gradual increase below 100 pg/ml, a steeper increase between 100–250 pg/ml, and a plateau above 250 pg/ml. In contrast, post-stress WMSI showed an approximately linear association with MACE risk (p for non-linearity = 0.342), with a 28.9% increase in risk per 0.1-unit increase (HR=1.289).

Discussion

This study found that the sensitivity of exercise stress echocardiography for diagnosing severe obstructive CAD (stenosis $\geq 70\%$) was 76.3%, specificity was 88.5%, and AUC reached 0.824, demonstrating good diagnostic accuracy. These results are basically consistent with the sensitivity of 70–85% and specificity of 85–95% reported in previous meta-analyses [15, 16]. Compared with traditional exercise electrocardiography, the diagnostic accuracy of exercise stress echocardiography was significantly improved, with sensitivity approximately 20–30% higher than exercise electrocardiography alone [17]. In this study, the sensitivity of exercise symptoms and electrocardiographic changes was only 26.8% and 31.4%, respectively, further confirming the incremental diagnostic value of echocardiographic assessment of wall motion.

It is noteworthy that this study showed that exercise stress echocardiography had higher sensitivity for multi-vessel disease, with three-vessel disease sensitivity reaching 91.4%, significantly higher than the 70.4% for single-vessel disease. This finding is consistent with the pathophysiological basis of exercise stress echocardiography. Multi-vessel disease leads to more extensive myocardial ischemia, which more easily induces segmental wall motion abnormalities under exercise stress conditions [18]. This characteristic has important clinical significance for identifying high-risk patients with obstructive CAD.

The specificity of exercise stress echocardiography in this study reached 88.5%, which is consistent with previous reports and higher than the reported specificity range of exercise electrocardiography (70–80%) [19]. This is mainly attributed to the ability of echocardiography to directly observe changes in myocardial contractile function, avoiding common false-positive factors in electrocardiography examinations, such as resting electrocardiogram abnormalities, electrolyte disturbances, and drug effects [20].

However, it should be noted that using anatomical assessment methods, i.e., coronary angiography and CCTA, as the reference standards for functional examinations has inherent limitations. According to the 2024 ESC guidelines for chronic coronary syndromes [3], coronary artery stenosis of 40–90% requires functional assessment, e.g., FFR or iFR, to determine its hemodynamic significance. Since this study used $\geq 70\%$ as the threshold for severe, hemodynamically significant obstructive lesions, it may have undervalued some moderate stenoses with functional significance. Furthermore, the degree of anatomical stenosis does not completely correspond to the degree of functional ischemia. This may lead to underestimation of the true diagnostic efficacy of exercise stress echocardiography.

In this study, a total of 34 patients had borderline lesions of 50–69%, of which 22 (64.7%) had positive exercise stress echocardiography. Although the degree of stenosis in these patients did not reach the $\geq 70\%$ threshold, exercise stress echocardiography showed functional evidence of myocardial ischemia. This finding indicates that exercise stress echocardiography may have value in identifying moderate stenoses with hemodynamic significance. However, due to the lack of invasive functional assessments such as FFR or iFR, we cannot say whether these lesions truly had hemodynamic significance. This factor may have affected the calculation of specificity in this study.

One of the most important findings of this study is that positive exercise stress echocardiography is significantly associated with the rate of intermediate-term MACE. The 3-yr MACE-free survival rate was 72.8% in the positive group and 94.2% in the negative group, with a significant difference ($p < 0.001$). This result is similar to results reported in large foreign cohort studies, confirming the prognostic value of exercise stress echocardiography in patients without typical symptoms [21]. Particularly noteworthy is that the MACE incidence rate of 5.5% (annualized rate $\approx 1.8\%$) among patients with negative exercise stress echocardiography was higher than that reported in some large real-world stress echocardiography follow-up cohorts [7]. This observation is consistent with evidence from the Stress Echo 2020 program and the UK EVAREST cohort [7, 10], indicating that a negative wall motion response on stress echocardiography does not necessarily equate to negligible cardiovascular risk. Subclinical atherosclerosis, non-obstructive CAD, or microvascular dysfunction may still contribute to adverse outcomes; therefore, visual wall motion assessment alone may be insufficient for complete risk exclusion.

Importantly, MACE events in patients with negative exercise stress echocardiography may still be explained by the presence of non-severe obstructive CAD, microvascular

dysfunction, or disease progression with newly developed coronary lesions during follow-up. This suggests:

1. Non-severe obstructive coronary heart disease may still lead to adverse outcomes;
2. Assessment of wall motion alone may not identify microvascular dysfunction;
3. Disease progression.

This finding emphasizes the importance of a multi-parameter assessment that combines coronary flow reserve and other parameters in the ABCDE multidimensional assessment approach advocated by the Stress-Echo 2030 study [13, 22].

Multivariate Cox regression analysis showed that positive exercise stress echocardiography was a strong independent predictor of MACE with predictive value that exceeded traditional clinical risk factors. This finding has important significance for clinical guidance, suggesting that exercise stress echocardiography is not only a diagnostic tool, but that it is also an important prognostic assessment tool [23, 24].

It is noteworthy that this study found post-stress WMSI to be an independent prognostic predictor consistent with previous study reports [10, 25]. WMSI is a quantitative indicator that can reflect the extent and severity of myocardial ischemia, with its elevated value directly related to increased patient prognostic risk. This provides clinicians with an objective, quantifiable tool for risk stratification.

This study confirmed that the NT-proBNP concentration is an independent predictor of MACE, consistent with previously reported findings [26]. Restricted cubic spline analysis showed a non-linear relationship between NT-proBNP and MACE risk, with rapid risk increase in the 100–250 pg/ml range. Age, as a traditional cardiovascular risk factor, also showed independent prognostic value in this study, with restricted cubic spline analysis showing that the relationship between age and MACE risk accelerated in the 60–70 age range. This may be related to accelerated progression of atherosclerosis and decreased cardiovascular reserve [27].

Exercise stress echocardiography has unique advantages compared to other non-invasive examination methods. First, this technique combines the advantages of exercise stress testing and echocardiography, enabling assessment of myocardial ischemia under physiological conditions, while avoiding potential side effects of pharmacological stress testing [28]. Second, the real-time dynamic imaging characteristics of echocardiography allow examiners to directly observe changes in wall motion, providing richer functional information compared to that produced during static imaging examinations [29].

This study demonstrated good inter-observer agreement (ICC >0.89) for resting and post-stress WMSI assessment, supporting the reproducibility of exercise stress echocardiography wall motion interpretation. This was the result of standardized examination protocols and quality control measures. It also reflects the important influence of the tech-

nical ability and professional level of the ultrasound physicians on the examination results [30].

Compared with CCTA, the advantage of exercise stress echocardiography lies in its functional assessment ability. Although CCTA has advantages in anatomical assessment, it has limitations in evaluating the functional significance of vascular stenosis [31]. The results of this study suggest that functional examination may have more important value in prognostic assessment.

Compared with nuclear myocardial perfusion imaging, exercise stress echocardiography has advantages of no radiation, lower cost, and shorter examination time. Previous comparative studies have shown similar diagnostic accuracy between the two, but exercise stress echocardiography has advantages in accessibility and safety [19, 32].

The innovations of this study include:

- 1) Large-sample Chinese population data, providing important reference for Asian populations;
- 2) Use of treadmill exercise stress in contrast to the pharmacological stress or bicycle exercise used in most foreign studies. Thus, the study was more consistent with Chinese clinical practice;
- 3) Focus on intermediate-to-low-risk populations without typical angina symptoms, a population often overlooked in clinical practice but large in number;
- 4) Longer intermediate-term follow-up time (median 36 mos).

This provided additional prognostic evidence from a large Chinese cohort with intermediate-term follow-up, complementing findings from international multicenter studies such as Stress-Echo 2020/2030 [9–13]. Although this study had a single-center design, it validated the diagnostic and prognostic value of stress echocardiography in Chinese populations, providing evidence to inform clinical decision-making in this population.

This study has some limitations. As a single-center retrospective study, the extrapolation of results may be limited. Some patients (24.3%) had CCTA rather than coronary angiography as the reference standard, which may have affected the current assessment of diagnostic accuracy. Anatomical assessment methods (coronary angiography and CCTA) were used as the reference standard for functional examination. This approach has inherent defects, and lack of functional assessment, such as FFR, may have led to misjudgment of some moderate stenoses with functional significance. Borderline lesions of 50–69% were included in the Non-Severe Obstructive Lesion Group (<70%), but 22 of them (64.7%) had positive exercise stress echocardiography, suggesting the possible presence of stenoses with hemodynamic significance. These patients may require invasive functional assessments such as FFR or myocardial blush grade to determine their true hemodynamic significance. This should be explored in future prospective studies. The accuracy of

exercise stress echocardiography largely depends on the examiner's technical ability and clinical experience, which may vary among physicians and medical institutions. In addition, the study follow-up time was median 36.2 mos. Longer observation times, such as 5–10 yrs, are needed for long-term prognostic value. All study subjects were patients with suspected CAD without typical angina symptoms, so results may not be applicable to those patients with typical symptoms or confirmed CAD.

Future research should conduct multicenter prospective cohort studies to validate the diagnostic and prognostic value of exercise stress echocardiography in different populations. Such studies should combine functional assessment methods, such as FFR and iFR, particularly for functional assessment of borderline lesions (50–69% stenosis), to more accurately evaluate the true diagnostic value of exercise stress echocardiography. Future studies could use artificial intelligence technology for automated image analysis sys-

tems. This would improve standardization and reproducibility of examinations. Studies that explore the combined use of data on coronary flow reserve, myocardial strain, and other parameters would further improve diagnostic and prognostic assessment accuracy.

In summary, this study confirmed that exercise stress echocardiography has good diagnostic accuracy and important prognostic predictive value in patients with suspected CAD and without typical angina symptoms. Exercise stress echocardiography provides important information for risk stratification and clinical decision-making in this population.

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