Predictive Value of ABI, baPWV, and FMD Combined with apoB/apoA-1 for Blood Stasis Syndrome in Young and Middle-Aged Patients with Coronary Heart Disease: Postprint

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Abstract

Background Coronary heart disease falls under the category of "chest bi-syndrome and heart pain" in Traditional Chinese Medicine, among which blood stasis syndrome represents the most common pattern. Compared with elderly patients, the incidence of blood stasis syndrome is higher in young and middle-aged individuals. Expanding upon our team' s previous research, this study is the first to employ combined arterial elasticity and vascular endothelial function testing together with apolipoprotein ratios for diagnosing blood stasis syndrome in young and middle-aged coronary heart disease patients, aiming to provide novel insights for early detection and serve as a reference for optimizing diagnostic criteria.

Objective To investigate the correlation and diagnostic predictive value of ankle-brachial index (ABI), brachial-ankle pulse wave velocity (baPWV), flow-mediated dilation (FMD), and the apolipoprotein B to apolipoprotein A-1 ratio (apoB/apoA-1) with blood stasis syndrome in young and middle-aged coronary heart disease patients.

Methods Baseline clinical data were compared between 127 young and middle-aged coronary heart disease patients with blood stasis syndrome and 79 without blood stasis syndrome from China-Japan Friendship Hospital. ABI, baPWV, FMD, and apoB/apoA-1 measured prior to the first percutaneous coronary intervention (PCI) were incorporated into a Logistic regression analysis to construct a predictive model for blood stasis syndrome in young and middle-aged coronary heart disease patients. The model' s accuracy was evaluated using receiver operating characteristic (ROC) curve analysis.

Results Logistic regression analysis demonstrated that ABI, baPWV, FMD, and apoB/apoA-1 were all independently associated with blood stasis syndrome in young and middle-aged coronary heart disease patients, showing statistically significant differences (P=0.001, P<0.001, P<0.001, P=0.035). The predictive regression equation for blood stasis syndrome in young and middle-aged coronary heart disease patients was P=1/[1+e-(5.519-0.599×ABI+0.297×baPWV -0.515×FMD+0.172×apoB/apoA-1)]. ROC curve analysis revealed that when patients exhibited ABI$ 1.19, baPWV\ 14.93m \cdot s-1, FMD\ 8.33 $0.72, the diagnostic value for blood stasis syndrome in young and middle-aged coronary heart disease was substantial. The areas under the curve (AUC) for ABI, baPWV, FMD, apoB/apoA-1, and predicted probability P were 0.647, 0.680, 0.676, 0.606, and 0.807, respectively. The AUC of predicted probability P was the largest (P<0.001), with sensitivity of 0.740 and specificity of 0.734.

Conclusion ABI, baPWV, FMD, and apoB/apoA-1 demonstrate independent correlations with the diagnosis of blood stasis syndrome in young and middle-aged coronary heart disease and possess independent predictive capability. The predictive value is enhanced when the four parameters are combined, which can provide a basis for early clinical identification of young and middle-aged coronary heart disease patients with blood stasis syndrome.

Full Text

Preamble

The Diagnostic Predictive Value of ABI, baPWV, and FMD Combined with apoB/apoA-1 Ratio for Blood Stasis Syndrome in Young and Middle-Aged Coronary Heart Disease Patients

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Abstract

Background: Coronary heart disease (CHD) falls under the category of "chest bi-syndrome and heart pain" in traditional Chinese medicine, with blood stasis syndrome being the most common pattern. Compared with elderly patients, the incidence of blood stasis syndrome is higher among young and middle-aged individuals. Building upon our team' s previous research, this study is the first to combine arterial elasticity and vascular endothelial function testing with apolipoprotein ratios for the combined diagnosis of blood stasis syndrome in young and middle-aged CHD patients. The aim is to provide new approaches for early detection of blood stasis syndrome in this population and to offer references for optimizing and supplementing the diagnostic criteria for CHD with blood stasis syndrome.

Objective: To investigate the correlation between ankle-brachial index (ABI), brachial-ankle pulse wave velocity (baPWV), flow-mediated vasodilation (FMD), and apolipoprotein B to apolipoprotein A-1 ratio (apoB/apoA-1) with blood stasis syndrome in young and middle-aged CHD patients, and to evaluate their diagnostic and predictive value.

Methods: We compared baseline clinical data between 127 young and middle-aged CHD patients with blood stasis syndrome and 79 without blood stasis syndrome at China-Japan Friendship Hospital. ABI, baPWV, FMD, and apoB/apoA-1 measured before patients' first percutaneous coronary intervention (PCI) were included in logistic regression analysis to construct a predictive model for blood stasis syndrome in young and middle-aged CHD patients. The model' s accuracy was evaluated using receiver operating characteristic (ROC) curve analysis.

Results: Multivariate logistic regression analysis revealed that ABI, baPWV, FMD, and apoB/apoA-1 were all independently associated with blood stasis syndrome in young and middle-aged CHD patients ($P=0.001$, $P<0.001$, $P<0.001$, and $P=0.035$, respectively). The predictive regression equation was: P=1/[1+e^(-(5.519-0.599×ABI+0.297×baPWV-0.515×FMD+0.172×apoB/apoA-1))]. ROC curve analysis showed that when ABI$ 1.19, baPWV 14.93m · s^{-1}, FMD 8.33 $0.72, the diagnostic value for blood stasis syndrome in young and middle-aged CHD patients was substantial. The area under the curve (AUC) values for ABI, baPWV, FMD, apoB/apoA-1, and the predicted probability P were 0.647, 0.680, 0.676, 0.606, and 0.807, respectively. The predicted probability P demonstrated the largest AUC ($P<0.001$), with a sensitivity of 0.740 and specificity of 0.734.

Conclusion: ABI, baPWV, FMD, and apoB/apoA-1 are independently correlated with the diagnosis of blood stasis syndrome in young and middle-aged CHD patients and possess independent predictive capability. The combined diagnostic approach yields higher predictive value and can provide a basis for early clinical identification of young and middle-aged CHD patients with blood stasis syndrome.

Keywords: young and middle-aged; coronary heart disease; blood stasis syndrome; apoB/apoA-1 ratio; arterial elasticity; vascular endothelial function; predictive value

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Introduction

Coronary heart disease (CHD), caused by coronary atherosclerosis leading to luminal stenosis or occlusion resulting in myocardial ischemia, hypoxia, or necrosis, affects approximately 11.39 million people in China, with increasing incidence and mortality rates [1,2]. Notably, the age of CHD onset has been trending younger in recent years [3]. Compared with elderly patients, young and middle-aged CHD patients often present without warning signs, with acute onset, frequently seeking medical care due to acute myocardial infarction, and experiencing higher rates of sudden death outside the hospital [4], warranting heightened attention.

In traditional Chinese medicine, CHD is classified as "chest bi-syndrome and heart pain," characterized by a pattern of root deficiency and branch excess, with blood stasis being the primary excess pattern [5]. Epidemiological studies demonstrate that blood stasis syndrome is the most common TCM pattern in CHD patients [6-8], with even higher incidence in young and middle-aged populations compared with the elderly [9]. The "Diagnostic Criteria for Blood Stasis Syndrome in Coronary Heart Disease" established by Academician Chen Keji in 2016 provides a reliable foundation for objective diagnosis integrating Chinese and Western medicine [10].

This study selected simple, non-invasive, and highly reproducible indicators—including brachial-ankle pulse wave velocity (baPWV), ankle-brachial index (ABI), flow-mediated vasodilation (FMD), and serum apolipoprotein B to apolipoprotein A1 ratio (apoB/apoA1)—to investigate the correlation between arterial elasticity, vascular endothelial function, and lipid parameters with blood stasis syndrome in young and middle-aged CHD patients. Our objective is to provide evidence for early detection of blood stasis syndrome in this population and to offer references for further refinement of diagnostic criteria.

Methods

Study Design and Participants

This retrospective study included young and middle-aged (<50 years) CHD patients hospitalized in the Department of Integrative Cardiology at China-Japan Friendship Hospital between December 2016 and December 2021. Patients were divided into blood stasis syndrome and non-blood stasis syndrome groups. Diagnosis of CHD with blood stasis syndrome required fulfillment of both the

CHD diagnostic criteria from the "2019 ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes" [11] (coronary angiography showing $ $50% stenosis in at least one major coronary artery or its main branch) and the "Diagnostic Criteria for Blood Stasis Syndrome in Coronary Heart Disease" [10] (blood stasis syndrome score $ $19). Baseline information and relevant indicators including blood glucose, lipids, arterial elasticity, and vascular endothelial function were collected before patients' first coronary angiography. This study was approved by the Clinical Research Ethics Committee of China-Japan Friendship Hospital (2021-139-K97) with a waiver of informed consent.

Inclusion Criteria

Young and middle-aged (<50 years) hospitalized patients meeting CHD diagnostic criteria, regardless of geographic region, ethnicity, or gender.

Exclusion Criteria

Patients with incomplete primary observation indicator data that could not be supplemented; those with recent acute infection, severe hepatic or renal dysfunction, hematological or endocrine system diseases, or those whose data were affected by mental or language factors.

Data Collection

Basic Information Data were extracted from the electronic medical record system and Hospital Information System (HIS) at China-Japan Friendship Hospital. Dual simultaneous data entry with cross-checking was implemented to ensure accuracy. Young patients (<50 years) were screened from the Department of Integrative Cardiology medical record system. General patient information and medical history were recorded, including body mass index (BMI). Laboratory indicators were collected from the HIS system: fasting blood glucose (FBG), glycated hemoglobin (HbA1c), total cholesterol (CHO), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein B (apoB), and apolipoprotein A-1 (apoA-1). The apoB/apoA-1 ratio was calculated.

Arterial Elasticity and Vascular Endothelial Function Measurements Arterial elasticity (ABI, baPWV) and vascular endothelial function (FMD) indicators were collected from the medical record system. Arterial elasticity measurements were performed using a vascular stiffness detector (OMRON, Japan), while endothelial function was assessed using an endothelial function detector (UNEX, Japan). Both examinations were conducted before coronary angiography, after 8-12 hours of fasting, between 8:00 and 10:00 AM.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics 26.0 and MedCalc 20.0 software. For continuous variables, independent samples t-test was used for normally distributed data and Mann-Whitney U test for non-normally distributed data. Categorical variables were analyzed using ^{2} test. Normally distributed continuous data were expressed as mean±standard deviation (x±s), non-normally distributed data as median (quartiles) [M(Q1, Q3)], and categorical data as number (percentage). ABI, baPWV, FMD, and apoB/apoA-1 were included in multivariate logistic regression analysis to examine their independent association with blood stasis syndrome in young and middle-aged CHD patients and to construct a predictive probability model. ROC curves were generated to calculate area under the curve (AUC). Optimal cutoff points were determined at maximum Youden index. Sensitivity and specificity of the predictive probability P were evaluated. AUC values of 0.5-0.7 indicated low accuracy, 0.7-0.9 moderate accuracy, and \$ \$0.9 high accuracy. P<0.05 was considered statistically significant.

Results

Comparison of Baseline Clinical Characteristics

A total of 206 young and middle-aged CHD patients were included, comprising 127 in the blood stasis syndrome group and 79 in the non-blood stasis syndrome group. As shown in Table 1 , no significant differences were observed in baseline clinical characteristics between the two groups (P>0.05).

Table 1 Baseline clinical characteristics of young and middle-aged CHD patients with and without blood stasis syndrome

Clinical baseline indicator	Blood stasis syndrome (n=127)	Non-blood stasis syndrome (n=79)	t or ^{2}
Gender, male (%)	115 (90.6)	68 (86.1)	
Height/cm	1.71\$±0.06|1.71±0.06|||Weight/kg| m^{-2}\$	77.84\$±3.48|28.19±3.96||| 1}\$	57(42.49)||BMI/kg{- [4.97, 7.51]
CHO/mmol · L^{-1}	4.15\$±1.21|4.21±1.21|||TG/mmol· L^{-1}\$	2.31\$±1.52|2.15±1.76|||LDL− c/mmol · L^{-1}\$	2.56\$±0.90|2.63±0.86|||HDL−c/mmol· L^{-1}\$
apoA1/mg · dL^{-1}	1.21\$±0.20|1.17±\$0.21		

Analysis of Primary Diagnostic Indicators

As shown in Table 2 , among the primary observation indicators, ABI and FMD levels were significantly lower in the blood stasis syndrome group, while baPWV and apoB/apoA-1 values were significantly higher compared with the non-blood stasis syndrome group (t_{ABI}=4.623, P<0.001; t_{baPWV}=17.982, P<0.001; t_{FMD}=5.103, P<0.001; t_{apoB}/apoA-1=6.565, P=0.010).

Table 2 Characteristics of main diagnostic variables between two groups

Variable	Blood stasis syndrome (n=127)	Non-blood stasis syndrome (n=79)	t	P
ABI	1.05$±0.11\|1.13±0.10\|4.623\|<0.001\|\|baPWV/m · s^{-1}$	15.88 [14.49, 17.76]	14.51 [13.55, 16.32]	17.982
FMD/%	8.07$±1.39|9.16±$1.63	5.103	<0.001	
apoB/apoA-1	0.73 [0.61, 0.94]	0.70 [0.57, 0.81]	6.565	0.010

Note: ABI=ankle-brachial index; baPWV=brachial-ankle pulse wave velocity; FMD=flow-mediated vasodilation (same for Tables 3 and 4).

Multivariate Logistic Regression Analysis of Primary Diagnostic Indicators

Multivariate logistic regression analysis including ABI, baPWV, FMD, and apoB/apoA-1 is presented in Table 3 . The results demonstrated that ABI (P=0.001), baPWV (P<0.001), FMD (P<0.001), and apoB/apoA-1 (P=0.035) all showed statistically significant differences in Wald tests (P<0.05). The optimal diagnostic model equation was: Logit(P)=ln[P/(1-P)]=5.519-0.599×ABI+0.297×baPWV-0.515×FMD+0.172×apoB/apoA-1. The predictive probability regression equation for blood stasis syndrome in young and middle-aged CHD patients was: P=1/[1+e^(-(5.519-0.599×ABI+0.297×baPWV-0.515×FMD+0.172×apoB/apoA-1))]. Model stability was validated using maximum likelihood ratio and Hosmer-Lemeshow test, yielding a likelihood ratio of 209.755 and ^{2}=3.448 (P=0.903), indicating good model fit.

Table 3 Multivariate logistic regression analysis of main diagnostic indexes

Variable	P	95% CI
ABI	0.001	[0.385, 0.783]
baPWV	<0.001	[1.143, 1.583]
FMD	<0.001	[0.469, 0.762]
apoB/apoA-1	0.035	[1.013, 1.394]

ROC Curve Evaluation of Diagnostic Model Performance

Using ABI, baPWV, FMD, apoB/apoA-1, and predicted probability P as test variables, ROC curves were plotted (Figure 1 [Figure 1: see original paper]).

Figure 1 ROC curve of ABI, baPWV, FMD, apoB/apoA-1, and predicted probability P for diagnosing blood stasis syndrome in young and middle-aged CHD patients

The AUC values for ABI, baPWV, FMD, apoB/apoA-1, and predicted probability P were 0.647, 0.680, 0.676, 0.606, and 0.807, respectively. The predicted probability P showed the largest AUC and maximum Youden index ($P<0.001$). When using predicted probability $P=0.60$ as the cutoff value, the diagnostic model achieved optimal performance with sensitivity of 0.740 and specificity of 0.734 (Table 4).

Table 4 Optimal critical values of different diagnostic indicators and predictive value for blood stasis syndrome in young and middle-aged CHD patients

Indicator	Cutoff value	AUC	95% CI	Youden index
ABI	1.19 (1/0.84)	0.647	[0.578, 0.712]	0.294
baPWV	14.93 $m \cdot s^{-1}$	0.680	[0.607, 0.739]	0.307
FMD	8.33% (1/0.12)	0.676	[0.612, 0.743]	0.312
apoB/apoA-1	0.72	0.606	[0.536, 0.673]	0.212
Predicted probability P	0.60	0.807	[0.746, 0.858]	0.474

Note: Cutoff=cutoff value; SE=standard error; +LR=positive likelihood ratio; -LR=negative likelihood ratio; AUC=area under the curve; 95% CI=95% confidence interval for AUC; all P<0.001; 1) Reciprocal of cutoff value.

Discussion

Hemorheological abnormalities, manifested as increased blood viscosity and aggregation, can be observed in CHD patients of all TCM pattern types, which aligns with the pathological essence of blood stasis syndrome and confirms that blood stasis obstructing the heart vessels represents the key pathological mechanism [12,13]. The fundamental pathogenesis of CHD involves impaired blood flow and obstruction of heart vessels by blood stasis, which remains central throughout disease progression. With the 年轻化 of CHD onset, incidence among young and middle-aged populations has increased annually [14]. Compared with elderly patients, CHD in young and middle-aged individuals is more closely associated with smoking, physical inactivity, and dyslipidemia [4,15]. These interacting factors cause vascular wall and endothelial injury, leading to decreased vascular elasticity, enhanced platelet aggregation, and potentially acute thrombosis or plaque rupture [16]. Early diagnosis and intervention based on these characteristics are therefore crucial for long-term prognosis.

Analysis of 206 young and middle-aged CHD patients revealed that males predominated in both groups (90.6% in the blood stasis syndrome group vs. 86.1% in the non-blood stasis group), consistent with previous findings and likely related to estrogen' s protective effects in premenopausal women [17]. Regarding primary diagnostic indicators, the blood stasis syndrome group exhibited significantly higher baPWV and apoB/apoA-1 but lower ABI and FMD levels compared with the non-blood stasis group (all P$ 0.05), *indicatingworsevascularelasticity, endothelialfunction, andlipidstatus.Logisticregressionanalysis* *1levelswereindependentlyassociatedwithbloodstasissyndromeinyoungandmiddle−agedCHDpatients.ROCcurveanalysisidentifiedoptimalcutoffvaluesofbaPWV* 14.93*m*· *s*^{-1}, *ABI* 1.19, *FMD* 8.33 $0.72 for predicting blood stasis syndrome. The combined diagnostic model using predicted probability P achieved the largest AUC of 0.807, with sensitivity of 0.740 and specificity of 0.734, demonstrating moderate diagnostic accuracy compared with the gold standard.

As stated in the *Jin Gui Yao Lue*: "When meridians and collaterals are affected by pathogenic factors and extend to the viscera···the nine orifices and four limbs, with blood vessels communicating, become obstructed and blocked." Blood stasis syndrome severely impacts the "collateral-vessel system," as qi and blood fail to nourish the meridians and orifices, ultimately leading to obstruction of heart vessels and collateral disease affecting the heart [18]. Clinically, ABI, baPWV, and FMD are commonly used non-invasive indicators for evaluating peripheral arterial elasticity and endothelial function. Studies have shown that all three correlate with blood stasis syndrome, with baPWV positively and ABI/FMD negatively associated with blood stasis syndrome scores [19-22]. While ABI$ 0.9*istheclinicalgoldstandardfordiagnosingperipheralarterialdisease*[23], *ourstudyfoundABI* $1.19 more predictive for blood stasis syndrome–a higher threshold likely attributable to our specific population characteristics. The high proportion of male patients, elevated BMI, and suboptimal glycemic and lipid control in our young and middle-aged CHD cohort may have resulted in more severe coronary lesions and more prominent blood stasis syndrome, necessitating a higher diagnostic threshold. This broader criterion may facilitate earlier identification of suspected cases for timely intervention.

baPWV accurately reflects large artery stiffness, with values $ 18*m*/*sindicatinghighcardiovascularrisk*[24].*Our* *s*^{-1}$ for predicting blood stasis syndrome in young and middle-aged CHD patients, likely because age significantly influences baPWV values. Older age correlates with higher arterial stiffness and faster baPWV. Our middle-aged cohort, having better baseline arterial elasticity, exhibited lower baPWV values than elderly patients, potentially affecting the results. FMD is commonly used to assess endothelial function, with FMD<11.3% associated with a 2.93-fold increase in long-term cardiovascular events [25-27]. Our identified cutoff of 8.33% for predicting blood stasis syndrome reflects that our cohort comprised

CHD patients rather than healthy individuals, likely exhibiting more severe endothelial dysfunction.

Lipid and apolipoprotein levels directly correlate with CHD onset and progression. As stated in *Xue Zheng Lun*: "Qi is what transports blood." Qi deficiency causes sluggish blood flow, forming blood stasis that combines with turbid phlegm in vessels, covertly promoting atherosclerosis [28]. Dyslipidemia is more prevalent in young and middle-aged CHD patients than in the elderly, warranting particular attention [29]. The apoB/apoA-1 ratio is unaffected by statin therapy [30] and may better predict CHD risk than traditional lipid markers [31]. Our study found apoB/apoA-1 independently predicted CHD events in young and middle-aged patients, with optimal predictive value at apoB/apoA-1$ $0.72, further defining a diagnostic threshold for clinical reference.

Our research team emphasizes using standardized physical and chemical indicators to evaluate TCM patterns, reducing subjectivity in syndrome differentiation. We previously investigated the diagnostic value of vascular elasticity indicators (baPWV, ABI, FMD) for CHD blood stasis syndrome [32], examined their combined diagnostic efficacy in postmenopausal women [33], and explored the TyG index combined with vascular function indicators [34]. Despite variations, these studies confirmed the good diagnostic predictive value of baPWV, ABI, and FMD for CHD blood stasis syndrome. This study builds upon previous work by adding the lipid metabolism indicator apoB/apoA-1 and focusing specifically on young and middle-aged populations. For the first time, we combined arterial elasticity and endothelial function testing with apolipoprotein ratios for diagnosing blood stasis syndrome in young and middle-aged CHD patients, providing reference for developing simple, practical combined diagnostic methods. The selected indicators offer new approaches for early detection and can supplement the optimization of diagnostic criteria for CHD blood stasis syndrome.

Limitations: First, as a retrospective study, information bias during data entry cannot be completely excluded. Second, the study was limited to young and middle-aged CHD patients (<50 years), and missing data for primary indicators resulted in a relatively small sample size, requiring further validation in large-scale clinical studies. Finally, this study only examined correlations between diagnostic indicators and blood stasis syndrome in young and middle-aged CHD patients using a combined predictive model, without further analysis of coronary stenosis severity or lesion number, and without incorporating other characteristics of young populations such as sleep duration, work stress, or TCM pathological factors. Our team will continue to explore these aspects to develop more comprehensive clinical prediction models that better reflect the characteristics of young populations and incorporate more distinctive TCM features.

Author Contributions

CHEN Ying proposed the research direction, collected and organized clinical case data, and drafted the manuscript; WANG Zi-han assisted with clinical data collection, figure/table preparation, and data verification; XUE Chong-xiang was responsible for manuscript revision and refinement; TAO Shi-yi and SUN Zi-yi assisted with figure/table preparation; HUANG Li provided guidance on study design, quality control, and final approval, taking overall responsibility for the article. All authors confirmed the final manuscript.

Conflict of Interest: All authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.