Predictive value of Frank's sign for obstructive coronary artery disease confirmed by coronary computed tomography angiography

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ABSTRACT

Numerous studies have suggested a link between Frank's sign and coronary artery disease (CAD); however, there is limited data available from Southeast Asia, and no previous studies have been conducted in Vietnam to evaluate this association. This cross-sectional study examined 124 consecutive Vietnamese individuals who underwent coronary computed tomography angiography at our center. Differences in patient characteristics and the association between Frank's sign and CAD were analyzed using Chi-square and *t*-tests. Multivariate regression was performed to adjust for confounding variables, and receiver operating characteristic curve analysis was utilized to evaluate the predictive accuracy of Frank's sign for CAD. In this study, 124 patients with a mean age of 58.5±12.4 years, predominantly male, were included. Frank's sign was present in 84% of the participants. Among these, males and older individuals had significantly higher rates compared to those without the sign. Obstructive CAD was observed in 48 patients (38.7%). The prevalence of obstructive CAD was significantly higher in those with Frank's sign (52.5%) compared to those without it (13.6%), with p<0.001. Multivariate analysis identified Frank's sign [odds ratio (OR) 3.79; 95% confidence interval (CI) 1.33-10.82] and age (OR 1.06; 95% CI 1.01-1.10) as independent risk factors for CAD. Frank's sign demonstrated an area under the curve of 0.69, with 88% sensitivity and 50% specificity in predicting CAD. This study highlights a significant association between Frank's sign and CAD, independent of established risk factors, in a Vietnamese population.

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Key words: coronary artery disease, Frank's sign, CCTA.

Contributions: all the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: this study was approved by the Ethics Committee of the University of Medicine and Pharmacy, Ho Chi Minh City on January 2, 2024, with approval code 10/HĐĐĐ-ĐHYD and study code 23103-ĐHYD

Informed consent: participants gave informed consent to participate in the study before taking part.

Patient consent for publication: obtained.

Availability of data and materials: data and materials are available from the corresponding author upon request.

Funding: none.

Acknowledgments: this study was conducted at the University Medical Center of Ho Chi Minh City. The authors would like to thank the medical staff who helped with the data collection.

Received: 18 November 2024.
Accepted: 18 November 2024.

Licensee PAGEPress, Italy
Italian Journal of Medicine 2025; 19:1863
doi:10.4081/itjm.2025.1863

Introduction

Cardiovascular diseases (CVDs) account for 32% of global annual deaths, equivalent to 17.9 million lives lost.[1] This trend is projected to escalate, with an estimated more than 23 million CVD-related deaths by 2030.[2,3] The burden is particularly heavy on low- and middle-income countries (LMICs), contributing to 75% of CVD-related deaths worldwide.[1]

In Vietnam, an LMIC, CVDs are causing severe consequences. In 2016, CVDs were the leading cause of death, responsible for 31% of all deaths equating to over 170,000 cases.[4] Coronary artery disease (CAD), one of the most common manifestations of CVD, contributes significantly to this burden.[5,6] The impact of CAD extends beyond healthcare, profoundly affecting socio-economic aspects by causing poverty due to high medical costs and reducing national labor productivity.[7,8] In this context, early detection and effective management of CAD have become more urgent than ever. However, LMICs like Vietnam face considerable challenges in deploying advanced diagnostic methods due to limited resources and healthcare infrastructure. Therefore, the need for a simple, ef-

fective CAD screening tool suitable for local conditions is pressing.

Frank's sign, also known as a diagonal earlobe crease, has been shown in numerous international studies to have a strong correlation with CAD.[9-13] This characteristic has the potential to become an ideal screening tool for LMICs due to its simplicity, non-invasiveness, and low cost. However, there is currently no specific date on Frank's sign in the Vietnamese population, nor any evaluation of the correlation between Frank's sign and early-stage CAD using coronary computed tomography angiography (CCTA).

In this study, we aim to investigate the correlation between Frank's sign and CAD in its early stages, as well as determine the diagnostic accuracy of Frank's sign for CAD in the Vietnamese population. The study promises to bring new insights and high practical value in improving strategies for early detection and management of CAD in Vietnam, help to reduce the disease burden, and improve the quality of life for the population.

Materials and Methods

Study design and participants

This was a descriptive cross-sectional study conducted on patients diagnosed with obstructive CAD at the University Medical Center in Ho Chi Minh City between January 2024 and June 2024. Obstructive CAD was diagnosed by CCTA. The study population included both inpatient and outpatient cases who underwent CCTA at the Department of Diagnostic Imaging. The study excluded cases where the earlobe could not be clearly observed due to keloid scars, ulcers, absence of earlobes, wearing of earrings, or patients who had undergone coronary artery bypass grafting, stent placement, or cases where the CCTA results were inconclusive.

CCTA was performed using a 512-slice computed tomography scanner, and the images were independently analyzed by two radiologists who were blinded to the patients' Frank's sign status. Obstructive CAD was diagnosed based on CCTA, defined by the presence of atherosclerotic plaques causing luminal diameter stenosis of ≥50% in one or more epicardial coronary arteries (including the left main artery, left anterior descending artery, left circumflex artery, or right coronary artery) (Figure 1).

The study also collected anthropometric variables such as age and gender; clinical variables including medical history, vital signs, and body mass index; and laboratory variables such as hemoglobin A1C, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, total cholesterol, triglycerides, and serum creatinine.

Assessing Frank's sign

The earlobe was evaluated with the patient in a seated position, and a complete Frank's sign was identified when a diagonal crease extended from the tragus to the outer border of the earlobe, covering its entirety. The evaluation was independently conducted by two physicians who were blinded to the patient's CAD status, and they later reached a consensus on the presence of Frank's sign (Figure 2).[14]

Statistical analysis

Data were entered and analyzed using Stata 17.0 software for Windows. Continuous variables were described as mean±standard deviation or median (interquartile range), while nominal variables were presented as counts (percent-

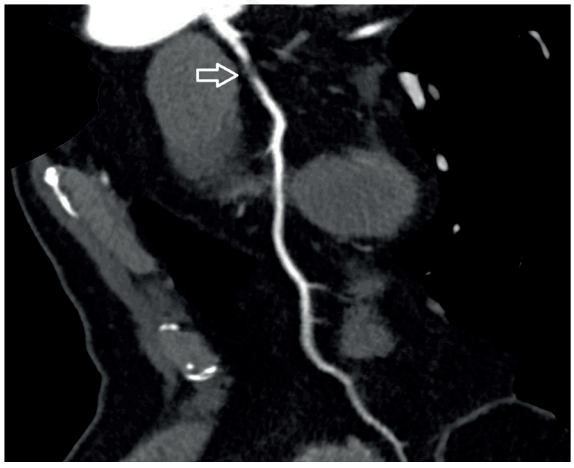

Figure 1. Coronary computed tomography angiography of a severe stenosis of 90% in the left anterior descending artery.

Figure 2. A patient in this study. The presence of a diagonal ear lobe crease is defined as a deep crease or wrinkle present on the earlobe, running from the lower pole of the external meatus, diagonally backward to the edge of the lobe at approximately 45 degrees without discontinuity covering at least two-thirds of its path.

ages). Univariate and multivariate regression analyses were applied to evaluate the correlation between clinical and laboratory variables and Frank's sign in predicting obstructive CAD. The receiver operating characteristic curve was used to assess the predictive ability of Frank's sign only, and a model combining Frank's sign with other factors for obstructive CAD. The area under the curve (AUC) of the two models was compared using the bootstrap method. Statistical significance was considered when $p<0.05$.

Ethic considerations

The written informed consent of all participants was collected. This study was approved by the Ethics Committee of the University of Medicine and Pharmacy, Ho Chi Minh City on January 2, 2024, with approval code 10/HĐĐĐ-ĐHYD and study code 23103-ĐHYD.

Results

A total of 124 patients meeting the inclusion criteria were enrolled in the study, with a mean age of 58.5±12.4 years. Male patients predominated, with a male-to-female ratio of 2.4. The study recorded that 84% of patients had Frank's sign (comprising 64.5%), with a near-equal distribution between those with bilateral and unilateral Frank signs (*Supplementary Figure 1*).

The clinical and paraclinical characteristics of the study population are shown in Table 1. Among patients with Frank's sign, males had a significantly higher proportion, and the mean age was significantly greater compared to patients without Frank's sign. In addition, smoking status was significantly more prevalent in patients with Frank's sign compared to those without, with rates of 50.0% and 20.5%, respectively, p=0.002.

Among the 124 patients, 48 were found to have obstructive CAD, accounting for 38.7%. The proportion of patients with obstructive CAD accompanied by Frank's sign was 52.5% (42 out of 80 cases), which was significantly higher than in patients with obstructive CAD without Frank's sign, at 13.6% (4 out of 44 cases), with $p<0.001$. *Supplementary Figure 2* illustrates the distribution of coronary artery lesion characteristics according to the presence of Frank's sign.

Compared to patients without obstructive CAD, the mean age and the proportion of smokers were significantly higher in patients with obstructive CAD (Table 2). The prevalence of Frank's sign was also significantly higher in patients with obstructive CAD (87.5% compared to 50.0%). Additionally, there were no significant differences in other

Table 1. Comparison of clinical characteristics between patients with or without Frank's sign.

Variables	Total (n=124)	Frank's sign + (n=80)	Frank's sign - (n=44)	p
Male, n (%)	88 (71.0)	65 (81.3)	23 (52.3)	0.001
Age, years	58.5±12.4	62.5±10.8	51.3±12.1	<0.001
BMI, kg/m^2	23.4±2.7	23.3±2.6	23.5±3.0	0.676
Systolic BP, mmHg	132±17	134±17	129±17	0.191
Diastolic BP, mmHg	78±10	78±10	78±9	0.910
Heart rate, bpm	75±11	75±10	77±12	0.298
Symptoms				
Chest pain, n (%)	63 (50.8)	39 (48.8)	24 (54.6)	0.577
Dyspnea, n (%)	40 (32.3)	26 (32.5)	14 (31.8)	0.552
Palpitation, n (%)	8 (6.5)	4 (5.0)	4 (9.1)	0.453
Hypertension, n (%)	74 (59.7)	52 (65.0)	22 (50.0)	0.127
Diabetes mellitus, n (%)	18 (14.5)	15 (18.8)	3 (6.8)	0,108
Dyslipidemia, n (%)	93 (75.0)	62 (77.5)	31 (70.5)	0.395
Chronic kidney disease, n (%)	5 (4.0)	4 (5.0)	1 (2.3)	0.655
Smoking, n (%)	49 (39.5)	40 (50.0)	9 (20.5)	0.002
Sedentary lifestyle, n (%)	13 (10.5)	9 (11.3)	4 (9.1)	1.000
Family history of premature CAD, n (%)	5 (4.1)	3 (3.8)	2 (4.5)	1.000
Hemoglobin, G/L	134.3±31.1	133.1±31.7	136.5±30.1	0.564
White blood cell, G/L	7.9±2.6	8.0±2.9	7.6±2.0	0.391
Uric acid, mg/dL	7.3±8.2	7.2±10.2	6.5±1.5	0.435
Creatinine, mg/dL	0.88±0.17	0.90±0.17	0.85±0.17	0.155
Glucose, mg/dL	103.1±24.3	103.3±26.4	102.6±20.4	0.869
HBA1c, %	5.84±0.97	5.86±0.75	5.80±1.29	0.752
Total cholesterol, mg/dL	179.6±50.8	178.7±50.4	181.1±52.1	0.806
LDL-C, mg/dL	113.2±42.3	113.3±42.3	112.81±42.7	0.948
HDL-C, mg/dL	47.1±9.5	46.3±9.4	48.5±9.5	0.226
Triglycerides, mg/dL	156.6±72.8	156.4±66.5	157.0±83.8	0.964

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; HBA1c, hemoglobin A1c; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.

variables such as gender, systolic and diastolic blood pressure, or medical history, including hypertension, diabetes, or dyslipidemia, between the two groups of patients with and without obstructive CAD.

Association between Frank's sign and diagnosis of coronary artery disease

Using CAD as the dependent variable, logistic regression was used to evaluate whether the following factors were significant predictors: Frank's Sign, age, and smoking status. Multivariate analysis revealed that independent risk factors for CAD included Frank's sign and age (Table 3 and *Supplementary Figure 3*).

The variance inflation factor (VIF) values for the predictors in the combined model are as follows: Frank's sign - VIF=1.34; smoking - VIF=1.10; year - VIF=1.24. The VIF for each factor was less than 10, and there was no multicollinearity. The AUCs of Frank's sign alone (model 1) and the combined model for CAD (model 2) are shown in *Supplementary Figure 4*. The AUCs of models 1 and 2 were 0.69 [95% confidence interval (CI): 0.61 to 0.76] and 0.77 (95% CI: 0.68 to 0.85), respectively, indicating fair discriminatory ability. The sensitivity of model 1 was 88%, and the speci-

Table 2. Comparison of clinical characteristics between patients with or without obstructive CAD.

Variables	Total (n=124)	CAD + (n=48)	CAD - (n=44)	p
Male, n (%)	88 (71.0)	37 (77.1)	51 (67.1)	0.310
Age, years	58.5±12.4	64.1±9.9	54.9±12.6	<0.001
BMI, kg/m^2	23.4±2.7	23.7±2.5	23.1±2.8	0.278
Systolic BP, mmHg	132±17	134±17	130±17	0.215
Diastolic BP, mmHg	78±10	78±11	78±9	0.839
Heart rate, bpm	75±11	76±10	75±11	0.784
Chest pain, n (%)	63 (50.8)	26 (54.2)	37 (48.7)	0.584
Dyspnea, n (%)	40 (32.3)	15 (31.2)	25 (32.9)	1.000
Palpitation, n (%)	8 (6.5)	3 (6.3)	5 (6.6)	1.000
Hypertension, n (%)	74 (59.7)	32 (66.7)	42 (55.3)	0.260
Diabetes mellitus, n (%)	18 (14.5)	10 (20.8)	8 (10.5)	0.125
Dyslipidemia, n (%)	93 (75.0)	35 (77.9)	58 (76.3)	0.676
Chronic kidney disease, n (%)	5 (4.0)	4 (8.3)	1 (1.3)	0.073
Smoking, n (%)	49 (39.5)	25 (52.1)	24 (31.6)	0.025
Sedentary lifestyle, n (%)	13 (10.5)	8 (16.7)	5 (6.6)	0.129
Family history of premature CAD, n (%)	5 (4.1)	1 (2.1)	4 (5.3)	0.648
Hemoglobin, G/L	134.3±31.1	138.6±16.1	131.6±37.5	0.222
White blood cell, G/L	7.9±2.6	8.2±3.3	7.7±2.1	0.283
Uric acid, mg/dL	7.3±8.2	6.5±1.3	7.8±10.5	0.393
Creatinine, mg/dL	0.88±0.17	0.91±0.17	0.86±0.17	0.092
Glucose, mg/dL	103.1±24.3	103.9±18.5	102.5±27.5	0.757
HbA1C, %	5.8±1.0	5.9±0.7	5.8±1.1	0.864
Total cholesterol, mg/dL	179.6±50.8	180.8±51.9	178.8±50.5	0.831
LDL-C, mg/dL	113.2±42.3	114.7±44.0	112.2±41.4	0.748
HDL-C, mg/dL	47.1±9.5	48.0±9.8	46.5±9.3	0.394
Triglycerides, mg/dL	156.6±72.8	155.0±63.4	157.6±78.5	0.843
Frank's sign, n (%)	80 (64.5)	42 (87.5)	38 (50.0)	<0.001

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; HBA1c, hemoglobin A1c; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.

Table 3. The univariate and multivariate logistic regression of the characteristics of coronary artery disease (CAD) and non-CAD.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.07 (1.03-1.11)	<0.001	1.06 (1.01-1.10)	0.008
Smoking	2.36 (1.12-4.96)	0.02	1.80 (0.78-4.15)	0.171
Frank's sign	7.0 (2.66-18.4)	<0.001	3.79 (1.33-10.82)	0.013

OR, odds ratio; CI, confidence interval.

ficity was 50%. The sensitivity of model 2 was 65%, the specificity was 74%. The bootstrap method shows a p-value of 0.995, indicating that there is no statistically significant difference between the AUCs of Frank's sign-only model and the combined model. Overall, model 2 showed a slightly better performance.

Discussion

Our study on the role of Frank's sign in predicting obstructive CAD has yielded significant findings. This study used CCTA to assess coronary artery obstruction and evaluated the presence of Frank's sign to explore its diagnostic utility in CAD. In multivariate regression analysis, the presence of Frank's sign is an independent predictor for CAD with an odds ratio (OR) of 3.79. Frank's sign alone has a fair predictive ability for CAD with an AUC of 0.69 (95% CI 0.61-0.76).

Our results align with previous research demonstrating a strong correlation between Frank's sign and CAD.[9,15,16] Studies in populations from China and Mexico have shown that Frank's sign is independently associated with CAD, even after adjusting for traditional risk factors such as age, hypertension, and diabetes.[17] For instance, a Chinese study reported that the prevalence of Frank's sign was 46.2% in those without CAD and 75.2% in those with CAD.[10] Similarly, our study confirms a robust relationship between Frank's sign and the severity of CAD diagnosed *via* CCTA. The study by Liu *et al.* demonstrated a statistically significant positive correlation between Frank's sign and the SYNTAX score (r=0.457).[12] Another study conducted on a Chinese population reported an AUC of 0.693 for Frank's sign in predicting CAD, with a sensitivity and specificity of 78% and 61%, respectively.[18] The results in our study are similar to those of the aforementioned authors, with an AUC of 0.69 for Frank's sign but with a higher sensitivity of 88% and a lower specificity of 50%. When we used a combined model incorporating Frank's sign along with two CAD-related factors, age and smoking status, the diagnostic ability for CAD slightly improved, with an AUC of 0.77. Wu *et al.* also reported an AUC of 0.645 for Frank's sign in predicting CAD, which increased to 0.722 when combined with other clinical factors related to the disease.[18]

One key difference between our study and previous studies is that, in this study, CAD was diagnosed using CCTA rather than invasive coronary angiography, as in prior studies. CCTA is a recommended tool by cardiovascular societies for diagnosing CAD in patients with a low to intermediate pretest probability.[19] This is a non-invasive tool that is more accessible in the current healthcare context compared to invasive coronary angiography. If a patient presents with Frank's sign as the sole indicator of CAD, an approach using CCTA might be more appropriate than invasive coronary angiography. Kuri *et al.* assessed the value of the diagonal earlobe crease as an indicator of CAD in a group of 530 Japanese patients over the age of 40, all scheduled for elective surgery. Their findings suggested that Frank's sign could serve as a helpful marker for identifying CAD in patients with minimal or no prior history and limited diagnostic information available.[20]

The exact mechanism linking Frank's sign to CAD is not fully understood, but several hypotheses have been proposed.[9,14] Frank's sign is believed to result from microvascular damage in the earlobe, which shares similar pathological mechanisms with atherosclerosis. The earlobe is primarily supplied by terminal arteries, making it more susceptible to ischemic changes caused by vascular disease. Histopathological studies suggest that the crease is related to elastin and collagen degradation, as well as fibrosis, which are also observed in atherosclerotic vessels.[21] Additionally, the hypoxia-reoxygenation injury hypothesis suggests that the tissues of the earlobe may be vulnerable to chronic microvascular ischemia due to underlying atherosclerotic processes. This theory is further supported by studies showing a strong association between Frank's sign and cardiovascular conditions characterized by systemic vascular injury, such as hypertension, diabetes, and dyslipidemia. Moreover, some studies propose that Frank's sign might be an external marker of peripheral microangiopathy, which reflects more widespread endothelial dysfunction in the body. This suggests that Frank's sign may not only be a cosmetic or age-related phenomenon but also a manifestation of systemic vascular pathology, closely tied to CAD progression.[22,23]

Our study also confirmed that traditional cardiovascular risk factors such as age, male, and smoking are associated with Frank's sign, consistent with global findings. The combination of Frank's sign with these risk factors can enhance the prediction of CAD severity.[24] In our study, the presence of Frank's sign was linked to ≥50% stenosis on CCTA, reinforcing its potential as an early marker for CAD. Although Frank's sign is an easily identifiable and non-invasive physical marker, its diagnostic accuracy for CAD remains debated. Some studies report high sensitivity but low specificity, potentially limiting its stand-alone clinical utility.[18,25] In our study, Frank's sign was useful in identifying patients at higher risk for CAD, but it should be used in conjunction with traditional risk factors and advanced diagnostic tools like CCTA for optimal accuracy. Frank's sign examination is the most suitable option for CAD screening in countries with limited resources and healthcare facilities. It is simple, cost-effective, and useful as a diagnostic marker for CAD[26].

While our study adds to the growing body of evidence supporting the association between Frank's sign and CAD, there are limitations. First, the study is descriptive and limited to a single center with a relatively small sample size. Additionally, we were unable to control for potential confounders like smoking habits, obesity, or family history. Future large-scale, multi-center studies are needed to confirm these findings and further investigate the clinical utility of Frank's sign as a non-invasive marker for early CAD detection.

Conclusions

Our study confirmed a strong association between Frank's sign and obstructive CAD. Although Frank's sign alone cannot be used as a definitive diagnostic tool, when combined with other risk factors and modern diagnostic methods, it can be a useful indicator for early detection of CAD.

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Online supplementary material:

Supplementary Figure 1. Distribution of Frank's sign in this study.
Supplementary Figure 2. Distribution of coronary artery lesion characteristics according to the presence of Frank's sign.
Supplementary Figure 3. Forest plot regarding the analysis of influencing factors for coronary artery disease.
Supplementary Figure 4. The receiver operating characteristic curve of Frank's sign model and the combined model for predicting obstructive coronary artery disease.