Original article

Frank's sign associated with the severity of ischemic heart disease in patients under 65 years old

Claudia Elizabeth Velázquez-Sotelo [a,f], María José Fernández-Gómez [b], Annet Cázares-Pérez [c,f], Antonio Covarrubias-Gil [a], Pilar Carranza-Rosales [d], Irma Edith Carranza-Torres [d], Javier Morán-Martínez [e], Nancy Elena Guzmán-Delgado [b,f,*]

[a] Departamento de Cardiología de la Unidad Médica de Alta Especialidad, Hospital de Cardiología No. 34, "Dr. Alfonso J. Treviño Treviño" del Centro Médico Nacional del Noreste, Instituto Mexicano del Seguro Social, Monterrey, Nuevo León, Mexico
[b] División de Investigación en Salud de la Unidad Médica de Alta Especialidad, Hospital de Cardiología No. 34, "Dr. Alfonso J. Treviño Treviño" del Centro Médico Nacional del Noreste, Instituto Mexicano del Seguro Social, Monterrey, Nuevo León, Mexico
[c] Departamento de Cirugía Cardiotorácica de la Unidad Médica de Alta Especialidad, Hospital de Cardiología No. 34, "Dr. Alfonso J. Treviño Treviño" del Centro Médico Nacional del Noreste, Instituto Mexicano del Seguro Social, Monterrey, Nuevo León, Mexico
[d] Centro de Investigación Biomédica del Noreste, Instituto Mexicano del Seguro Social, Monterrey, Nuevo León, Mexico
[e] Facultad de Medicina, Universidad Autónoma de Coahuila, Unidad Torreón, Coahuila, Mexico
[f] Programa de Especialidad Médica de Posgrado, Universidad de Monterrey, San Pedro Garza, García, Nuevo León, Mexico

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ABSTRACT

Background and objective: Frank's sign is the diagonal ear fold which has been associated with ischemic heart disease. The objective of this work was to evaluate the relationship of Frank's sign with severity of ischemic heart disease in adults ≤ 65 years old in the northeast of Mexico.

Patients and methods: A cross-sectional study was conducted in patients ≤ 65 years old who underwent coronary angiography consecutively over a period of 5 months in 2022. Severe coronary artery disease (CAD) was associated with Frank's sign and other common cardiovascular risks. To determine the association, bivariate and multivariate analysis was performed using logistic regression that included variables with a value of $p < 0.05$. Statistical analysis was performed with SPSS version 22.

Results: We included 311 patients ≤ 65 years, of whom 80% were men. The median age was 57 years (range 28–65). Frank's sign was positive in 62% of the population. The main clinical characteristics in patients with Frank's sign were type 2 diabetes mellitus (55%), $p = 0.003$, dyslipidemia (53%), $p = 0.026$ and smoking (68%), $p = 0.002$.

In the multivariate analysis, the independent variables associated with severe CAD were Frank's Sign OR 3.26; 95% CI (1.98–5.38), $p \leq 0.001$, male gender OR 2.28; 95% CI (1.20–4.35), $p = 0.012$, and dyslipidemia OR 1.81; 95% CI (1.11–2.97), $p = 0.017$.

Conclusions: There is an independent association between Frank's sign with the presence of severe CAD in patients ≤ 65 years old, which may be useful for screening and prevention.

Signo de Frank asociado con la gravedad de la cardiopatía isquémica en adultos de edad inferior o igual a 65 años

RESUMEN

Antecedentes y objetivo: El signo de pliegue diagonal de la oreja o signo de Frank se ha asociado con cardiopatía isquémica. El objetivo de este trabajo fue evaluar la relación del signo de Frank con la gravedad de la cardiopatía isquémica en adultos ≤ 65 años en el noreste de México.

* Corresponding author.
  E-mail address: nancyegd@gmail.com (N.E. Guzmán-Delgado).

Pacientes y métodos: Se realizó un estudio transversal en pacientes ≤ 65 años sometidos a coronariografía de manera consecutiva en un periodo de 5 meses en 2022. Se relacionó la enfermedad arterial coronaria (EAC) grave con el signo de Frank y los factores de riesgo cardiovascular tradicionales.

Para determinar la asociación se realizó análisis bivariado y multivariado mediante regresión logística que incluyó las variables con valor de p < 0,05. El análisis estadístico se realizó con el programa SPSS versión 22.

Resultados: Se incluyeron 311 pacientes ≤ 65 años, de los cuales el 80% fueron hombres. La mediana de edad fue 57 años (rango de 28-65 años). El 62% de los pacientes presentó el signo de Frank. Las principales características clínicas en pacientes con signo de Frank fueron diabetes mellitus tipo 2 (55%), p = 0,003, dislipidemia (53%), p = 0,026 y tabaquismo (68%), p = 0,002.

En el análisis multivariado las variables independientes asociadas a EAC grave fueron el signo de Frank (OR: 3,26; IC 95%: 1,98-5,38; p ≤ 0,001), sexo masculino (OR: 2,28; IC 95%: 1,20-4,35; p = 0,012) y dislipidemia (OR: 1,81; IC 95%: 1,11-2,97; p = 0,017).

Conclusiones: Existe asociación independiente del signo de Frank con la presencia de EAC grave en pacientes ≤ 65 años, que puede ser útil para el cribado y la prevención.

Introduction

Cardiovascular diseases are the leading cause of mortality worldwide, of which coronary artery disease (CAD) is the most prevalent manifestation. Globally, more than seven million people die each year because of ischemic heart disease (IHD), which corresponds to 12.8% of all deaths. By 2030, it is predicted that 2.4 million deaths will occur for this cause.[1]

In 2022, heart diseases were the leading cause of death in Mexico, with 105,864 cases. Concretely, in the population ≤ 65 years the main causes of death were cardiovascular disease and type 2 diabetes mellitus (DM).[2]

Premature CAD is defined as a cardiovascular event in women under 65 years old and men 55 years old,[3] which correlates to the economically active population in Mexico,[4] generating a negative impact on health care systems.

In patients under 50 years of age who present acute myocardial infarction (AMI), the most prevalent cardiovascular risk factors are: genetic components (40%), dyslipidemia and smoking.[5]

Frank's sign was first described in 1973 and consists of a 45° angle from the tragus to the lobule and it was originally characterized as bilateral. This first study, that included 20 patients, suggested a positive association of Frank's sign with premature heart disease.[6]

A relationship has been demonstrated between myocardial changes and Frank's sign with arterial myoelastofibrosis, Wallerian degeneration in peripheral nerves, and fibrosis in the deep tissues of the ear fold.[7]

In a systematic review of 13 cross-sectional studies that evaluated 3952 patients, the total prevalence of diagonal ear lobe crease (DELC) was 60.5%, with a wide range varied between 17% and 73%. The reviews included a large ethnic diversity, however the North American and Chinese population prevailed. The prevalence varied from one race to another. The North American population had the highest prevalence of DELC (73%), while the Japanese population had the lowest (17%). None of the studies described the Mexican population.[8]

The association of Frank's sign and the risk of ischemic heart disease have been studied in large cohorts. One of the most remarkable is the Copenhagen City Heart Study that studied 10,885 patients for 35 years. The presence of DELC and other age-related signs were associated with the risk of IHD with a HR 1.4 95% CI (1.2–1.62).[9]

Regardless of technological medical advances, the importance of physical exam cannot be overemphasized.[10]

Early detection of patients with high cardiovascular risk through the Frank's sign would contribute to establishing primary prevention strategies. The objective of this study is to evaluate Frank's sign in population younger than 65 years old and it's relation to severe ischemic heart disease demonstrated by a coronary angiography and to cardiovascular risk factors in a public third-level hospital in the northeast of Mexico.

Patients and methods

This is an observational, cross-sectional study, which was approved by the ethics institutional committee and all participants gave their informed consent.

We studied 311 consecutive patients younger than 65 years old who were hospitalized with a clinical diagnosis of ischemic heart disease and underwent diagnostic coronary angiography in a third-level cardiology hospital in the northeast of Mexico during a 5-month period in 2022.

The age cut-off was ≤ 65 years that was established based on international guidelines for chronic coronary syndrome, which establishes the definition of premature cardiovascular disease as that in men ≤ 65 years and women ≤ 55 years,[3] which also represent the economically active population of our country.[4]

The spectrum of ischemic heart disease studied encompassed chronic stable angina, unstable angina, non-ST-segment elevation AMI and ST-segment elevation AMI.

The patients were examined in a seated position, observing the presence of the obliquely extended diagonal crease of the ear from the external auditory canal towards the edge of the ear lobe. The presence of the diagonal crease of the ear lobe was considered positive if it was unilateral, bilateral, complete or incomplete. Patients where this sign was not assessable, such as those with piercings, expanders or congenital defects, were excluded.

Severe CAD was defined as 2 or more vessels and/or presence of total chronic occlusion (TCO) demonstrated by a coronary angiography. Significant coronary lesion was defined as occlusion of ≥ 70% of the vessel lumen and TCO as 100% occlusion of the vessel lumen for ≥ 3 months.

The following cardiovascular risk factors were identified in the sample: systemic arterial hypertension, described as BP ≥ 130/90 mmHg or using antihypertensive drugs; dyslipidemia, interpreted as LDL levels ≥ 55 mg/dl, total cholesterol ≥ 190 mg/dl or triglyceride levels ≥ 150 mg/dl; smoking, determined as a smoking index ≥10; type 2 DM, diagnosed with one the following criteria: fasting serum glucose ≥ 126 mg/dl, HgA1c ≥ 6.5%, or blood glucose ≥ 200 mg/dl independent of fasting; positive family history defined as a diagnosis of cardiovascular disease in first-degree relatives; sedentary lifestyle was established as the absence of physical activity and/or exercise for less than 150 min per week; chronic kidney disease, classified as glomerular filtration

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rate $\leq 60\,\text{ml/min}/1.73\,\text{m}^2$ or serum creatinine $\geq 2\,\text{mg/dl}$ and finally, obesity was diagnosed with a body mass index $\geq 30\,\text{kg/m}^2$.

The descriptive analysis of qualitative variables was through frequencies and percentages. For quantitative variables measures the median and range was calculated.

The Chi^2 test and the Student's t test were used to compare the categorical and numerical variables with Frank's sign and a multivariate analysis was calculated by binary logistic regression to determine the variables associated with severe CAD that included variables with a value of $p < 0.05$. The OR was used as the association measure. Statistical analysis was performed with SPSS version 22.

The levels of specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of Frank's sign for the diagnosis of coronary artery disease were calculated, using coronary angiography as the gold standard.

Results

A sample of 311 patients ≤ 65 years was obtained, of which 250 (80%) were men and 61 (20%) women. The median age was 57 years, with a wide range that varied form the youngest patient being 28 years and the oldest 65 years.

The number of patients who presented Frank's sign were 193 patients (62%), being mostly male patients (84%), $p = 0.044$. The median age at which the sign appeared was 58 years. The main clinical characteristics in patients with Frank's sign were the diagnosis of type 2 DM (55%), $p = 0.003$, dyslipidemia (53%), $p = 0.026$ and smoking (68%), $p = 0.002$. In Table 1, the baseline clinical characteristics of patients with and without Frank's sign are reported.

Regarding morphology of Frank's sign, 135 patients presented the bilateral DELC, of which 69% had the complete morphology; while 58 patients presented the unilateral DELC, of which 31% had the complete morphology. In Fig. 1, the examples of the different morphologies of Frank's sign (complete and bilateral, complete unilateral and incomplete unilateral) are shown.

Multivessel disease and/or TCO was found in patients from 45 years old, in ascending order. Frank's sign was present in 59% of patients with single-vessel CAD, in 74% of patients with multivessel CAD and in 78% of patients with TCO. Table 2, describes coronary lesions in patients with and without Frank's sign in detail. In Fig. 2, an example of severe coronary angiography in a 62-year-old male patient with DELC of complete and bilateral morphology is represented.

In Table 3, the characteristics of the population according to the presence or absence of severe CAD are displayed. In the bivariate analysis, it was found that the presence of Frank's sign conferred a risk of up to 3.69; 95% CI (2.28–5.98), $p \leq 0.0001$ times more of presenting severe coronary artery disease. The risk factors of male gender, dyslipidemia and smoking also presented a statistically significant risk for severe CAD, obtaining an OR 2.5; 95% CI (1.14–4.45), $p = 0.001$, OR 1.89; 95% CI (1.19–3.003), $p = 0.006$ and OR 1.7; 95% CI (1.07–2.71), $p = 0.023$, respectively. The rest of the risk factors studied for obesity, type 2 DM, systemic arterial hypertension, chronic kidney disease, sedentary lifestyle and family history were not related to the presence of severe CAD. In multivariate analysis using binary logistic regression, 3 variables were persistently associated with the presence of CAD severity: Frank's sign OR 3.26; 95% CI (1.98–5.38), $p \leq 0.0001$; male gender OR 2.28; 95% CI (1.20–4.35), $p = 0.012$ and dyslipidemia OR 1.81; 95% CI (1.11–2.97), $p = 0.017$.

Within the CAD spectrum, the main form of clinical presentation, both severe and non-severe, was in the context of acute coronary syndrome (54% with severe CAD and 60% without severe CAD). In sub analysis, the twenty-three percent of male patients in the age range between 46 and 55 years with severe CAD also presented Frank's sign in the context of acute coronary syndrome, while in the group of male patients between 56 and 65 years old, was found in 33%. Then, the main clinical presentation of male patients over 45 years old was that of acute coronary syndrome, rather than the context of chronic coronary syndrome.

The calculated prevalence of Frank's sign was 85.8% CI (81.8–89.8) in patients with coronary artery disease confirmed by coronary angiography. With a sensitivity of 68%, specificity of 77%, positive predictive value of 94% and negative predictive value of 28%. Regarding the prevalence of Frank's sign in patients with severe CAD was 71%.

Discussion

Our population included patients younger than 65 years old and were mainly made up by male patients with a median age of 57 years. The prevalence of Frank's sign in severe CAD was 71% and 40% in non-severe CAD. This data is greater than that one obtained in a study from Indian population where the prevalence of IHD and DELC all together was 41.2%,[11] but similar to the prevalence reported in other studies up to 80%.[8]

In the metanalysis of Wieckowski et al.,[8] the highest sensitivity and specificity obtained was 81% and 96%, respectively. Being much higher than the data obtained in our study (sensitivity of 68%, specificity of 77%). However, in our study Frank's sign was considered useful to identify patients with CAD than to rule them out.

In this study, the presence of Frank's sign had a significant association with the risk factors for type 2 DM, dyslipidemia, smoking and male gender; unlike a study carried out in patients undergoing preoperative evaluation, where the cardiovascular risk factors for type 2 DM, smoking and hyperlipidemia had no significant association with Frank's sign.[12] Also, we found no significant difference with arterial hypertension, unlike the study by Kumar et al.[11]

It was found that patients younger than 65 years old with a diagonal crease of the ear lobe presented up to 3.26 times a greater risk for presenting multivascular coronary artery disease and/or chronic total occlusion in coronary angiography. The study of Prangenberg et al.[13] found a correlation between Frank's sign and the severity of ischemic heart disease, it was found that the severity of Frank's sign correlated significantly with the severity of ischemic heart disease with an $r = 0.474$ ($p < 0.001$). Contrasting with our study, they classified the severity of Frank's sign as grade 1 (superficial fold), grade 2a (superficial fold that covers 50% of the way between the tragus and the auricle), grade 2b (covering the entire surface of the auricle) and grade 3 (deep fold). The most common morphology of the sign was the grade 3 (the most severe type). In our study, the complete morphology of DELC, that is the most severe type, was the most common too.

The association between Frank's sign and the severity of CAD by coronary angiography is also consistent with the study presented by Wang et al.[14] where Frank's sign was more common in male patients with severe CAD (defined as ≥ 1 vessels with occlusion of >50% of its lumen) ($p \leq 0.001$). The relative risk of CAD among patients with bilateral morphology of Frank's sign was OR 5.6; 95% CI (3.4–9.3), $p \leq 0.001$. Being even a higher risk than that found in our study which was OR 3.7; 95% CI (2.3–5.6).

In addition to the presence of Frank's sign, we established that the risk factors for dyslipidemia, smoking and male gender presented a risk of up to 1.9, 1.7, and 2.5 times for presenting severe coronary artery disease, respectively; all being statistically significant in bivariate analysis. This traditional risk factors have already been described in association with IHD in previous studies[15] and have been associated with IHD in young population too, as is shown in the study of Mathiew-Quirós et al.[16] in the Northeast of Mexico, the risk factors of metabolic syndrome (OR 8; 95% CI 1.73–39.5),

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Table 1
Baseline clinical characteristics of patients with and without Frank's sign.

Characteristics	Total population (n = 311) n (%)	Frank's sign (+) (n = 193) n (%)	Frank's sign (−) (n = 118) n (%)	p
Gender				
Male	250 (80)	162 (84)	88 (75)	0.044
Female	61 (20)	31 (16)	30 (25)	
Age				
Median (min–max)	57 (28–65)	58 (39–65)	55 (28–65)	0.002
Age group				
20–35	2 (1)	0 (0)	2 (2)	0.001
36–45	17 (5)	4 (2)	13 (11)	
46–55	107 (34)	63 (33)	44 (37)	
56–65	185 (60)	126 (65)	59 (50)	
Comorbidities				
Obesity	91 (29)	60 (31)	31 (26)	0.365
Type 2 diabetes mellitus	152 (49)	107 (55)	45 (38)	0.003
Arterial hypertension	209 (67)	132 (68)	77 (65)	0.567
Dyslipidemia	149 (48)	102 (53)	47 (40)	0.026
Chronic renal disease	16 (5)	12 (6)	4 (3)	0.273
Sedentary lifestyle	114 (37)	70 (36)	44 (37)	0.856
Positive family history	131 (42)	83 (43)	48 (41)	0.687
Smoking	190 (61)	131 (68)	59 (50)	0.002
Clinical presentation				
Acute coronary syndrome	176 (57)	109 (56)	67 (57)	0.958
Chronic coronary syndrome	135 (43)	84 (44)	51 (43)	
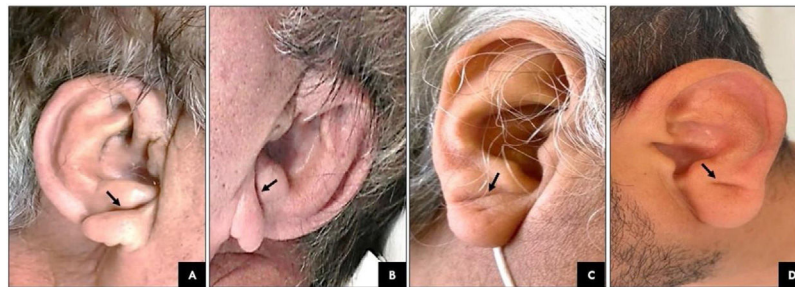
Fig. 1. Diagonal ear lobe crease (Frank's sign) morphology. (A, B) A 65-year-old male patient showing Frank's sign with complete and bilateral morphology, with two-vessel disease, one of them with chronic total occlusion. (C) A 59-year-old female patient with Frank's sign with complete and unilateral morphology and two-vessel disease. (D) A 49-year-old male with Frank's sign with incomplete and unilateral morphology and three-vessel disease. Frank's sign is indicated by the arrow.

Table 2
Coronary angiography findings in patients with and without Frank's sign.

Coronary angiography findings	Frank's sign (+) n = 193 n (%)	Frank's sign (−) n = 118 n (%)	p
Number of vessels and total chronic occlusion (TCO)			
No coronary lesion, n = 42	9 (21)	33 (79)	0.0001
One-vessel disease, n = 98	58 (59)	40 (41)	0.479
With TCO, n = 13	11 (85)	2 (15)	
Two-vessel disease, n = 96	73 (76)	23 (24)	0.001
With TCO, n = 37	30 (81)	7 (19)	
Three-vessel disease, n = 75	53 (71)	22 (29)	0.078
With TCO, n = 48	35 (73)	13 (27)	
Coronary artery disease (CAD)			
Severity of CAD[a], n = 184	137 (75)	47 (25)	<0.0001
Multivessel disease, n = 171	126 (74)	45 (26)	<0.0001
Total chronic occlusion, n = 98	76 (78)	22 (22)	<0.0001

[a] Severity of CAD: defined as multivessel disease and/or presence of TCO.

smoking (OR 7.76; 95% CI 1.27–47.3), positive family history (OR 11.0; 95% CI 2.03–60.4) and sedentary lifestyle (OR 2.26; 95% CI 2.52–9.80) increased the risk for CAD.

While in multivariate analysis, the variables that are persistently associated with severe CAD were Frank's sign, male gender, and

dyslipidemia. Highlighting the importance of nutritional habits as reported by Mathiew-Quirós et al.[16]

Attention is drawn to the fact, that the main form of presentation in the CAD spectrum was acute coronary syndrome (56.6%), both for severe and non-severe CAD. In the study by Moreno[17] the most
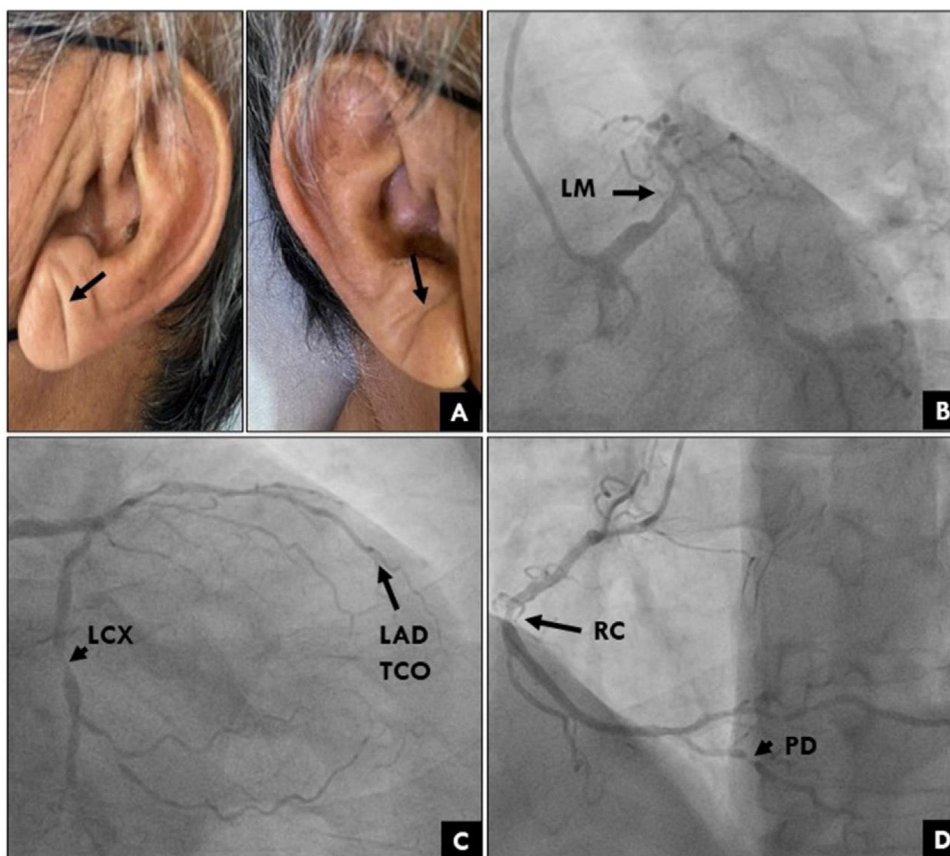
Fig. 2. Representative case of a patient showing Frank's and severe coronary artery disease. (A) A 62-year-old male with complete and bilateral morphology of Frank's sign (arrow). (B) Coronary angiography exhibits distal left main (LM) disease occlusion of 40% (arrow). (C) Left anterior descending (LAD) with total chronic occlusion (TCO) (arrow) and left circumflex artery (LCX) with distal 70% lumen occlusion (arrowhead). (D) Right coronary artery (RC) with a 60% lesion (arrow) and a 90% lesion (arrowhead) in posterior descending artery (PD).

Table 3
Population characteristics associated with and without severity of coronary artery disease.

Characteristics	Coronary artery disease		Bivariate analysis		Multivariate analysis	
	Severe $n=184$ n (%)	Non-severe $n=127$ n (%)	p	OR (95% CI)	p	OR (95% CI)
Gender						
Male	159 (86)	91 (72)	0.001	2.51 (1.42–4.45)	0.012	2.28 (1.20–4.35)
Age group						
46–65	172 (93)	120 (95)	0.715	0.83 (0.31–2.18)		
≤ 45	12 (7)	7 (5)	0.715			
Comorbidities						
Obesity	55 (30)	36 (28)	0.769	1.07 (0.65–1.77)		
Type 2 diabetes mellitus	94 (51)	58 (46)	0.347	1.24 (0.79–1.95)		
Arterial hypertension	125 (68)	84 (66)	0.741	1.08 (0.67–1.75)		
Dyslipidemia	100 (54)	49 (39)	0.006	1.89 (1.19–3.00)	0.017	1.81 (1.11–2.97)
Chronic renal disease	9 (5)	7 (6)	0.808	0.88 (0.32–2.43)		
Sedentary lifestyle	70 (38)	44 (35)	0.541	1.15 (0.72–1.85)		
Positive family history	84 (46)	47 (37)	0.129	1.43 (0.90–2.27)		
Smoking	122 (66)	68 (54)	0.023	1.70 (1.07–2.71)		
Clinical sign						
Frank's sign	137 (75)	56 (44)	<0.0001	3.69 (2.28–5.98)	<0.0001	3.26 (1.98–5.38)
Clinical presentation						
Acute coronary syndrome	100 (54)	76 (60)	0.337	0.79 (0.50–1.26)		
Chronic coronary syndrome	84 (46)	51 (40)	0.337			

common form of presentation of the vulnerable plaque (which is defined as a non-obstructive, asymptomatic, prone to thrombosis lesion) was the acute coronary syndrome in 68.5% and conversely 48% of AMI are the consequence of a non-obstructive plaque,[17] the possible relationship of Frank's sign with the presence of vulnerable plaques cannot not be ruled out.

Frank's sign was also correlated with the severity of CAD relating it to the SYNTAX score with certain phenotypes outlined by

Liu et al.,[18] the phenotype with the highest positive predictive value was the deep ear lobe crease for an intermediate SYNTAX score. Although, in our study, the SYNTAX score for the severity of ischemic heart disease was not applied, the results support the association between Frank's sign and a higher number of injured arteries.

Conclusions

This is the first study in Mexican population that address the prevalence of DELC and its association with severe CAD. Frank's sign is useful for early detection in young patients with a high probability of presenting severe CAD. The main clinical characteristics in patients with Frank's sign established in this study were male gender, type 2 DM, smoking and dyslipidemia.

An independent association of the Frank's sign with the severity of CAD was found, especially in male patients from an early age starting at 45 years and acute coronary syndrome. The main clinical presentation in the condition of acute coronary syndrome could be related to the presence of vulnerable atherosclerotic plaque; however, further studies are required to confirm this association.

The intentional physical exploration for Frank's sign in a first contact clinic scenario can be effortlessly applied and be easily interpreted for screening to suspect the presence of ischemic heart disease more than to rule it out. This may set strategies for primary screening in a younger population and prompt early diagnosis and treatment.

Ethic considerations

This is an observational, cross-sectional study, which was approved by the ethics institutional committee (R-1902-2022-061) and all participants gave their informed consent.

This study was based on provisions of the Declaration of Helsinki and is in accordance with the Regulation of the General Health Law on Research.

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Conflict of interest

The authors of this manuscript declare that they have no conflict of interest.

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