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Carotid atherosclerosis in the first five years since rheumatoid arthritis diagnosis: a cross sectional study

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Abstract

Background Systemic inflammation, documented before rheumatoid arthritis (RA) diagnosis, is associated with accelerated atherosclerosis. We aimed to compare the prevalence of carotid plaque (CP) in RA patients in the first five years since diagnosis and healthy controls, and to determine disease characteristics associated with the presence of subclinical atherosclerosis in RA patients.

Methods This was a cross-sectional study. We recruited 60 RA patients in the first five years since diagnosis and 60 matched healthy controls. Carotid ultrasound was performed to detect the presence of CP and measure carotid-intima media thickness (cIMT). Subclinical atherosclerosis was considered as the presence of CP and/or increased cIMT. Distribution was evaluated with the Kolmogorov-Smirnov test. Comparisons were made with Chi-square or Fisher's exact test for qualitative variables and Student's t or Mann-Whitney's U test for quantitative variables. A p-value < 0.05 was considered significant.

Results There were no differences in the demographic characteristics between RA patients and controls. The mean disease duration was 2.66 ± 1.39 years. A higher prevalence of CP (30.0% vs. 11.7%, $p = 0.013$), bilateral CP (18.3% vs. 3.3%, $p = 0.008$), increased cIMT (30.0% vs. 6.7%, $p = 0.001$), and subclinical atherosclerosis (53.3% vs. 18.3%, $p = < 0.001$) was found in RA patients. RA patients with subclinical atherosclerosis were older (56.70 years vs. 50.00 years, $p = 0.002$), presented a higher prevalence of dyslipidemia (53.1% vs. 14.3%, $p = 0.002$), and higher prevalence of classification in moderate-high disease activity category measured by DAS28-CRP (68.8% vs. 35.7%, $p = 0.010$). The latter variable persisted independently associated with subclinical atherosclerosis in the binary logistic regression (OR 6.11, 95% CI 1.51–24.70, $p = 0.011$).

Conclusions In the first five years since diagnosis, higher prevalence of subclinical atherosclerosis, including CP was found in RA patients. Carotid ultrasound should be considered part of the systematic CVR evaluation of RA at the time of diagnosis.

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Keywords Cardiovascular risk, Carotid plaque, Carotid ultrasound, Disease activity, Rheumatoid arthritis, Subclinical atherosclerosis

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory joint disease associated with increased cardiovascular morbidity. Patients who suffer from RA have greater cardiovascular disease (CVD) mortality than the general population [1, 2]. Major adverse cardiovascular events (MACE) are the leading cause of death in RA patients, and subclinical atherosclerosis has an elevated incidence in this population [3, 4]. Atherosclerosis is a multifactorial, widely present pathogenic process in RA patients linked to chronic systemic inflammation [5].

The updated recommendations for cardiovascular risk (CVR) management in RA patients of the European League Against Rheumatism (EULAR) propose that all patients with RA be evaluated at least once every five years [6]. The use of CVR algorithms is recommended for cardiovascular (CV) evaluation of RA patients; however, these scales have been proven to overestimate or underestimate the actual risk of this population [3]. Carotid ultrasound is useful for screening asymptomatic atherosclerotic plaques and reclassifying the CVR of patients with inflammatory joint diseases [7, 8]. The presence of carotid plaque (CP) is a strong predictor of future MACE, and the initiation of statin therapy is therefore recommended [9].

Traditional CVR factors are partly involved in RA patients CVR; however, systemic inflammation plays a role in atherosclerotic disease [10]. Patients with RA present elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and inflammatory cytokines, which have a proatherogenic role in the disease [11]. Systemic inflammation also contributes to endothelial damage, a dysfunctional lipid pattern, and a pro-thrombotic state [12].

RA patients present elevated inflammatory biomarkers before having symptoms; thus, the accelerated proatherogenic process related to inflammation may start at the early stages of the disease [13]. Patients with early RA have higher carotid-intima media thickness (cIMT) values than controls [14]; however, no studies have reported higher incidence of CP, which is a stronger predictor of myocardial infarction (MI) and ischemic stroke [15, 16], in RA patients at early stages of the disease. Therefore, we aimed to compare the prevalence of CP detected by carotid ultrasound in RA patients in the first five years after diagnosis and controls, and to determine the disease characteristics associated with the presence of subclinical atherosclerosis in RA patients.

Materials and methods

Patients

This was a cross-sectional study. We recruited 60 consecutive patients aged 40–75 years diagnosed with RA in the previous five years or less according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria and 60 matched controls without RA. Patients were recruited at an outpatient Cardio-Rheumatology clinic of a tertiary-care hospital in Monterrey, Mexico.

Patients with a previous MACE (MI, cerebrovascular event, or peripheral artery disease), another connective tissue disease, or pregnancy were excluded. Control subjects from the community without RA were invited to participate in the study through social media, and via posters and flyers distributed in surrounding areas of the hospital, applying the same exclusion criteria. A total of 102 subjects were interested to participate in the study. After demographic data evaluation, we selected a total of 60 controls that were matched by age (±5 years), gender, and traditional CVR factors (type 2 diabetes mellitus, hypertension, dyslipidemia, obesity and active smoking) to RA patients.

The Institutional Research Board and Ethics Committee approved this study with registration number MI14-006. It was conducted following the ethical standards outlined in the Declaration of Helsinki and its subsequent amendments. All study subjects provided written informed consent.

Data collection

A medical history was obtained from all study subjects, including age, gender, comorbidities, and traditional CVR factors. Type 2 diabetes mellitus and hypertension were considered in patients that referred a previous diagnosis performed by a physician. For dyslipidemia we considered patients with a previous diagnosis and those with total cholesterol levels ≥ 200 mg/dl, low density lipoprotein-cholesterol (LDL-c) levels ≥ 130 mg/dl, high density lipoprotein-cholesterol (HDL-c) levels < 40 mg/dl or triglycerides levels ≥ 150 mg/dl. We also collected information about disease characteristics in RA patients, such as duration (disease and symptoms) and current treatment, including disease-modifying antirheumatic drugs (DMARD), synthetic and/or biological. The beginning of the disease was considered as the first medical evaluation applying the 2010 ACR/EULAR classification criteria for RA diagnosis. Disease activity was evaluated using the 28-joint Disease Activity Score based on C-reactive protein (DAS28-CRP). Classification was performed using

common cut-off values: remission (<2.6), low disease activity (≥2.6 to <3.2), moderate disease activity (≥3.2 to ≤5.1), and high disease activity (>5.1) [17]. Anthropometric measures including weight, height, and body mass index (BMI) were also collected. Blood pressure was measured according to current guidelines.

A blood sample was drawn for laboratory studies, including C-reactive protein and erythrocyte sedimentation rate; rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies were considered positive with values >20.0 U/mL and >5 U/mL by ELISA, respectively.

Carotid ultrasound evaluation

All study subjects underwent a high-resolution B-mode carotid ultrasound with a linear 10 Mhz transductor and a Logiq E9 ultrasound system (GE Healthcare, Milwaukee, WI, USA) performed by a certified radiologist blinded to clinical information. Subjects were placed in a supine position according to the American Society of Echocardiography guidelines [18]. CP was defined as a focal narrowing ≥0.5 mm of the surrounding lumen or a cIMT ≥1.2 mm. Increased cIMT was considered as a value ≥75th percentile, which in our population was 0.8 mm. Subclinical atherosclerosis was considered as the presence of CP and/or increased cIMT.

Sample size calculation

Sample size was calculated from comparing two independent means using expected values of cIMT, based from a previous study, where RA patients with recent disease onset had a mean cIMT of 0.64 ± 0.13 mm compared to controls with a mean cIMT of 0.58 ± 0.09 mm [19]. Fifty-five patients were required in each group to have a power of 80% and a significant $\alpha = 0.05$.

Statistical analysis

For quantitative variables the distribution of normality was evaluated using visual (histograms and probability plots) and analytical (Kolmogorov-Smirnov test) methods. Descriptive analysis was done using frequencies (%), mean ± SD, and median (IQR), accordingly. For comparisons, the Chi-square or Fisher's exact test was used for qualitative variables, Student's t-test was used to compare means of parametric continuous variables and the Mann-Whitney U test was used to compare medians of non-parametric continuous variables. A p-value <0.05 was considered significant. Statistical analysis was performed utilizing SPSS version 25 (IBM Corp., Armonk, NY, USA).

Results

We found no significant differences between RA patients and controls regarding age, gender, traditional cardiovascular risk factors (type 2 diabetes mellitus, hypertension, dyslipidemia, obesity, active smoking), and BMI. Most RA patients were women (93.3%) with a mean disease duration of 2.66 ± 1.39 years, a median symptoms' duration of 3.41 (2.58-5.00) years, 70.0% with RF positivity, and 45.0% with anti-CCP antibody seropositivity. Median disease activity assessed with DAS28-CRP was 3.36 (2.00-4.20). Most patients were classified in the moderate disease activity category (43.3%). When evaluating RA treatment, we found that 44 (73.3%) patients were on MTX therapy, only 4 (6.7%) patients were on bDMARD, and 34 (56.7%) patients were on glucocorticoids treatment, with a median dosage of 5.00 (5.00-8.12) mg and a mean duration of 1.68 ± 1.40 years. Demographic and clinical characteristics are shown in Table 1.

We compared the lipid profile [total cholesterol, HDL-c, LDL-c, very low-density lipoprotein-cholesterol (VLDL-c) and triglycerides] between RA patients and controls and found no significant differences between both groups. Lipid profile comparisons are shown in Table 2.

When evaluating the carotid ultrasound findings, we found that RA patients had a higher prevalence of CP (30.0% vs. 11.7%, $p = 0.013$), a higher prevalence of bilateral CP (18.3% vs. 3.3%, $p = 0.008$), a higher prevalence of increased cIMT (30.0% vs. 6.7%, $p = 0.001$), higher cIMT as a continuous variable [0.75 (0.60–1.03) mm vs. 0.60 (0.50–0.70) mm, $p = <0.001$], and a higher prevalence of subclinical atherosclerosis (53.3% vs. 18.3%, $p = <0.001$) than the control group. Analyzing patients eligible for statin therapy initiation according to the presence of CP, after excluding those who were already receiving such treatment, a significantly higher proportion of patients with RA were found to have this indication compared to the control group (20.0% vs. 3.3%, p = 0.008). Carotid ultrasound findings are shown in Table 3.

We compared demographic and clinical characteristics between RA patients with and without subclinical atherosclerosis and we found that patients with subclinical atherosclerosis were older [56.70 (51.55–65.92) years vs. 50.00 (45.25–55.08) years, $p = 0.002$], with a higher prevalence of dyslipidemia (53.1% vs. 14.3%, $p = 0.002$) and a higher prevalence of being classified in the moderate-high disease activity category (68.8% vs. 35.7%, $p = 0.010$). Comparisons between patients with and without subclinical atherosclerosis are shown in Table 4.

A binary logistic regression was performed to evaluate the influence of disease activity in subclinical atherosclerosis, including variables with a p-value <0.05, which were age, dyslipidemia, and disease activity. This analysis showed that a higher classification of disease

Table 1 Demographic and clinical characteristics

Characteristic	RA patients (n = 60)	Controls (n = 60)	*p*-value
Age years, mean ± SD	54.37 ± 8.88	54.83 ± 6.62	0.750
Female, n (%)	56 (93.3)	56 (93.3)	1.000
T2DM, n (%)	10 (16.7)	9 (15.0)	0.803
Hypertension, n (%)	20 (33.3)	20 (33.3)	1.000
Dyslipidemia, n (%)	21 (35.0)	21 (35.0)	1.000
Obesity, n (%)	25 (41.7)	24 (40.0)	0.853
BMI, median (IQR)	28.90 (26.39–33.78)	27.99 (24.90-32.87)	0.187
Active smoking, n (%)	4 (6.7)	5 (8.3)	1.000
Antidiabetic treatment, n (%)	10 (16.7)	8 (13.3)	0.609
Antihypertensive treatment, n (%)	16 (26.7)	18 (30.0)	0.685
Statins, n (%)	13 (21.7)	13 (21.7)	1.000
Disease duration, mean ± SD	2.66 ± 1.39	-	-
Symptom duration, median (IQR)	3.41 (2.58-5.00)	-	-
DAS28-CRP, median (IQR)	3.36 (2.00-4.20)	-	-
DAS28-CRP, n (%)			
Remission	21 (35.0)	-	-
Low disease activity	7 (11.7)	-	-
Moderate disease activity	26 (43.3)	-	-
High disease activity	6 (10.0)	-	-
CRP, median (IQR)	0.79 (0.46–1.36)	-	-
ESR, median (IQR)	20.00 (13.00–37.00)	-	-
Seropositivity, n (%)			
RF	42 (70.0)	-	-
Anti-CCP antibodies	27 (45.0)	-	-
MTX, n (%)	44 (73.3)	-	-
bDMARD, n (%)	4 (6.7)	-	-
Glucocorticoids, n (%)	34 (56.7)	-	-
Dosage mg, median (IQR)	5.00 (5.00-8.12)	-	-
Duration years, mean ± SD	1.68 ± 1.40	-	-

RA, rheumatoid arthritis; T2DM, type 2 diabetes mellitus; BMI, body mass index; DAS28-CRP, 28-joint disease activity score and C-reactive protein; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; MTX, methotrexate; bDMARD, biological disease modifying anti-rheumatic drugs

activity (moderate-high DAS28-CRP) was an independent risk factor for the presence of subclinical atherosclerosis in RA patients with an OR 6.11, 95% CI 1.51–24.70, $p=0.011$.

Discussion

We found that RA patients in the first five years since diagnosis had a higher prevalence of CP, increased cIMT, and subclinical atherosclerosis overall than non-RA controls. Subclinical atherosclerosis is associated with a higher prevalence of MACE, including MI and stroke, and a higher rate of CV mortality [20]. There is controversy on whether atherosclerosis begins in the early stages of the disease. Our results concur with previous studies that found a difference in cIMT measurements, being higher in RA patients at early stages of the disease than matched controls [14, 19], but differ from the results of Björsenius et al., where no difference was found in cIMT between RA patients and controls at the time of diagnosis and 5-year follow-up, and the results of Södergren et al., where patients with early RA did not have a significantly higher cIMT than controls; however, these patients were newly diagnosed and with symptom duration less than 12 months, and in the 18-months follow-up, the cIMT was significantly increased in RA patients, inferring an important role of inflammation in CVR at early stages of the disease [21, 22].

Systemic inflammation starts years before RA diagnosis, as elevated proinflammatory cytokines, such as IL-1, IL-2, IL-6, and tumor necrosis factor-α, as well as cytokine receptors and chemokines levels, have been reported in RA patients before the diagnosis of the disease compared to non-RA controls [13]. A proinflammatory state

Table 2 Lipid profile comparison

Characteristic	RA patients (n = 60)	Controls (n = 60)	*p*-value
Total cholesterol, median (IQR)	176.0 (161.0-196.0)	180.5 (161.2-205.2)	0.534
HDL-c, median (IQR)	46.3 (41.3–62.5)	50.0 (42.3–57.5)	0.695
LDL-c, median (IQR)	99.8 (81.1-111.4)	101.9 (82.8-126.8)	0.317
VLDL-c, median (IQR)	26.0 (20.2–32.3)	23.8 (17.1–33.0)	0.409
Triglycerides, median (IQR)	130.0 (101.2-161.5)	118.3 (82.0-163.5)	0.280

RA, rheumatoid arthritis; HDL-c, high density lipoprotein-cholesterol; LDL-c, low density lipoprotein-cholesterol; VLDL-c, very low density lipoprotein-cholesterol

Table 3 Carotid ultrasound findings

Characteristic	RA patients (n = 60)	Controls (n = 60)	*p*-value
Carotid plaque, n (%)	18 (30.0)	7 (11.7)	0.013
Unilateral carotid plaque, n (%)	7 (11.7)	5 (8.3)	0.743
Bilateral carotid plaque, n (%)	11 (18.3)	2 (3.3)	0.008
Increased cIMT, n (%)	18 (30.0)	4 (6.7)	0.001
Unilateral increased cIMT, n (%)	11 (18.3)	4 (6.7)	0.095
Bilateral increased cIMT, n (%)	7 (11.7)	0 (0.0)	0.013
cIMT mm, median (IQR)	0.75 (0.60–1.03)	0.60 (0.50–0.70)	< 0.001
Subclinical atherosclerosis, n (%)	32 (53.3)	11 (18.3)	< 0.001
Statin therapy initiation, n (%)	12 (20.0)	2 (3.3)	0.008

RA, rheumatoid arthritis; cIMT, carotid intima media thickness

Table 4 Comparisons between rheumatoid arthritis patients with and without subclinical atherosclerosis

Characteristic	RA patients with subclinical atherosclerosis (n = 32)	RA patients without subclinical atherosclerosis (n = 28)	*p-value*
Age years, median (IQR)	56.70 (51.55–65.92)	50.00 (45.25–55.08)	0.002
Female, n (%)	29 (90.6)	27 (96.4)	0.616
T2DM, n (%)	7 (21.9)	3 (10.7)	0.312
Hypertension, n (%)	14 (43.8)	6 (21.4)	0.067
Dyslipidemia, n (%)	17 (53.1)	4 (14.3)	0.002
Obesity, n (%)	14 (43.8)	11 (39.3)	0.726
BMI, mean ± SD	30.03 ± 4.80	29.47 ± 4.65	0.668
Active smoking, n (%)	2 (6.3)	2 (7.1)	1.000
Disease duration, mean ± SD	2.87 ± 1.41	2.41 ± 1.34	0.210
Duration of symptoms before diagnosis, median (IQR)	0.49 (0.11–1.83)	0.77 (0.12–1.58)	0.888
DAS28-CRP, median (IQR)	3.60 (2.58–4.14)	2.63 (1.80–4.31)	0.116
DAS28-CRP, n (%)			
Moderate-high disease activity	22 (68.8)	10 (35.7)	0.010
CRP, median (IQR)	0.98 (0.51–1.38)	0.64 (0.25–1.45)	0.133
ESR, median (IQR)	20.00 (13.25–44.25)	19.00 (12.00–29.00)	0.257
Seropositivity, n (%)			
RF	21 (65.6)	21 (75.0)	0.429
Anti-CCP antibodies	13 (40.6)	14 (50.0)	0.466
MTX, n (%)	22 (68.8)	22 (78.6)	0.391
bDMARD, n (%)	4 (12.7)	0 (0.0)	0.116
Glucocorticoids, n (%)	17 (53.1)	17 (60.7)	0.554

RA, rheumatoid arthritis; T2DM, type 2 diabetes mellitus; BMI, body mass index; DAS28-CRP, 28-joint disease activity score and C-reactive protein; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; MTX, methotrexate; bDMARD, biological disease modifying anti-rheumatic drugs

is associated with an accelerated process of atherosclerosis [10]; therefore, since systemic inflammation begins years before RA onset, the atherosclerosis process may also begin years before the clinical diagnosis of the disease.

Studies have shown that RA patients have a higher incidence of MACE before the time of diagnosis and in the early stages of the disease. Nikiphorou et al. found that at the time of RA diagnosis, patients had a higher prevalence of stroke and heart failure than controls, especially in the five years preceding the diagnosis [23]. A higher prevalence of coronary heart disease at the time of diagnosis in RA patients [24] and a higher incidence of MI shortly after RA diagnosis [25] have also been reported. In a study of two Swedish cohorts, there was no increase in the incidence of ischemic heart disease in the two years before the RA diagnosis; however, a higher prevalence of MI in the 1 to 4-year follow-up was later observed [25, 26].

Additionally, a higher prevalence of bilateral CP was found, which is associated with a worse CV prognosis than patients with unilateral CP. RA patients are reported to have two times more risk of bilateral CP than matched controls [4, 27]. Bilateral CP was associated with a four-fold risk of coronary events compared to a two-fold risk in patients with unilateral CP [27]. The identification of patients with CP allows opportune initiation of statin therapy, which is proven to prevent the development of MACE and even the reduction of the plaque [28].

A high proportion of RA patients (56.7%) were on glucocorticoids therapy at the time the study was conducted. Glucocorticoids are known to increase the cardiovascular risk, as a higher prevalence of cardiovascular events, including myocardial infarction, heart failure and death, have been observed in patients with higher cumulative exposure, higher average daily dosage, and recent use of glucocorticoids [29]. These medications may promote the development of atherosclerosis by altering lipid and glucose metabolism and increasing blood pressure levels [30].

Current CVR guidelines for RA state that a carotid ultrasound may be considered as part of the CVR evaluation of RA patients [6]. Furthermore, our findings reinforce this recommendation, as a higher prevalence of subclinical atherosclerosis was observed in RA patients. The inclusion of the carotid ultrasound as part of the systematic CV evaluation of RA patients would allow the identification of high-risk patients who could benefit from preventive CV treatment.

Prior studies investigating the impact of biological disease-modifying antirheumatic drugs (bDMARDs) on CV disease in patients with RA have shown a beneficial effect. The mechanism behind these findings is believed to be the improvement of systemic inflammation and achieving disease control through the use of this therapy [31, 32]. It is important to notice that in our population only 6.7% of RA patients had access to bDMARDs, as this study was conducted in a public hospital. More prospective studies are needed to evaluate the effect of this therapy in Hispanic RA.

We found that RA patients with subclinical atherosclerosis were older, with a higher prevalence of dyslipidemia, and were classified in a higher disease activity category by DAS28-CRP, which was found to be independently associated with the presence of subclinical atherosclerosis. An association between disease activity and

CVR has been previously described, finding that patients whose disease activity improved from the high category to remission presented a 53% reduction in MACE [33]. Low disease activity is considered a protective cardiovascular factor in RA [34]. This emphasizes the importance of tight disease control as part of the CV prevention strategy for RA.

The clinical relevance of our findings relies on the fact that patients with recent RA diagnosis may have atherosclerotic disease, including CP and increased cIMT. The presence of CP is a stronger predictor of MI and ischemic stroke than cIMT [15, 16]; thus, initiation of statin therapy is recommended in this group of patients [9]. According to the 2015 EULAR recommendations, CVR should be evaluated at least once every five years [6], but there is no specification on when the first evaluation should be performed. We found that 30% of patients had CP with a mean disease duration of 2.49 years. Therefore, an early cardiovascular evaluation with the inclusion of a carotid ultrasound may benefit RA patients who were recently diagnosed, especially those with higher disease activity.

Some strengths of this study should be highlighted. To our knowledge, this is the first study to report a higher prevalence of CP in patients with RA at the early stages of the disease. Patients were matched with controls by age, gender, and traditional CVR factors; thus, the influence of these factors is reduced, and the impact of the disease itself can be further evaluated. Among the limitations of this study are the number of patients, that they were recruited from a single center which was a public hospital where most patients lack access to biologic therapy, the high proportion of patients receiving glucocorticoids therapy and the cross-sectional design that does not allow us to know the exact time of atherosclerosis development and the evaluation of the long-term implications of these findings.

Conclusions

RA patients in the first five years since diagnosis have a higher prevalence of subclinical atherosclerosis, including CP and bilateral CP. The performance of a carotid ultrasound as part of the systematic CVR evaluation at the time of diagnosis of RA patients, especially those with high disease activity, may help identify high-risk patients who would benefit from timely statin therapy.

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Authors' contributions
All authors had access to the data and a role in writing the manuscript. Dionicio A. Galarza-Delgado, Jose R. Azpiri-Lopez, Iris J. Colunga-Pedraza, Natalia Guajardo-Jauregui and Jesus A. Cardenas-de la Garza contributed to the study conception and design. Data collected by Natalia Guajardo-Jauregui, Andrea N. Garza-Cisneros, Mario A. Balderas-Palacios and Alexis García-Heredia. Statiscal analyses and interpretations were performed by Natalia Guajardo-Jauregui and Jesus A. Cardenas-de la Garza. Writing of the first draft was performed by Natalia Guajardo-Jauregui, Jesus A. Cardenas-de la Garza, Andrea N. Garza-Cisneros, Mario A. Balderas-Palacios, and Alexis García-Heredia. All authors commented on posterior versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability
The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional research and ethics committee of the University Hospital "Dr. Jose E. Gonzalez" from the Universidad Autonoma de Nuevo Leon, with registration number MI14-006 and was therefore conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained before the inclusion.

Consent for publication
Not required.

Competing interests
None of the authors of this study has any financial interest or conflict with industries or parties.

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