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Characterization of clinical and anatomical profile of patients with anomalous aortic origin of coronary arteries and their association with major cardiovascular outcomes: the experience of a Latin American third-level center

Caracterización del perfil clínico y anatómico de los pacientes con origen aórtico anómalo de las arterias coronarias y su asociación con eventos cardiovasculares mayores. La experiencia de un centro de tercer nivel en Latinoamérica

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ABSTRACT

Introduction: coronary artery abnormalities are a rare condition but one associated with a potentially serious outcome. **Objectives:** characterization of clinical and anatomical profiles of patients with Anomalous Aortic Origin of Coronary Arteries (AAOCA) and their association with any pre-specified Major Cardiovascular Events (MACE). **Material and methods:** a retrospective study was conducted among patients with AAOCA in a tertiary care center, from January 2000 to June 2022. We analyzed the association between clinical and anatomical characteristics of patients and pre-specified MACE (Acute Coronary Syndrome [ACS], surgical revascularization, or cardiovascular death). **Results:** fifty patients were included. The mean age was 52 ± 15 years, and most patients were male (68%). Systemic hypertension was the most frequent comorbidity (38%). Only five patients (10%) had congenital heart disease. ACS was the most frequent initial clinical presentation (42%). Most AAOCA affected solely the right coronary artery (60%), and nearly half of all individuals (44%) had at least a high-risk characteristic. MACE was recorded in 14 patients (28%) with a median follow-up of 1,636 days [IQR 626-2,345]. Cumulative

RESUMEN

Introducción: las anomalías de las arterias coronarias son una patología rara pero relacionada a un posible desenlace ominoso. **Objetivos:** caracterización de los perfiles clínicos y anatómicos de pacientes con origen aórtico anómalo de las arterias coronarias (AAOCA por sus siglas en inglés) y su asociación con cualquier evento cardiovascular mayor (MACE por sus siglas en inglés) preespecificado. **Material y métodos:** se realizó un estudio retrospectivo en pacientes con AAOCA en un centro de atención terciaria, desde enero de 2000 hasta junio de 2022. Se analizó la asociación entre las características clínicas y anatómicas de los pacientes y los MACE preespecificados (síndrome coronario agudo [SCA], revascularización quirúrgica o muerte cardiovascular). **Resultados:** se incluyeron cincuenta pacientes. La edad media fue de 52 ± 15 años y la mayoría de los pacientes fueron hombres (68%). La hipertensión arterial sistémica fue la comorbilidad más frecuente (38%). Solo cinco pacientes (10%) tenían cardiopatía congénita. El SCA fue la presentación clínica inicial más frecuente (42%). La mayoría de las AAOCA se dieron únicamente en la arteria coronaria derecha (60%) y casi la mitad de todos los individuos (44%)

Keywords:
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anomalies, anomalous
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congenital artery
disease, high-risk
features in coronary
artery anomalies,
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events, congenital
heart disease.

Palabras clave:
anomalías de las
arterias coronarias,
origen aórtico
anómalo de las
arterias coronarias,
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probability of MACE was higher in the high-risk group (log-rank $p = 0.04$). **Conclusions:** this study highlights the importance of identifying high-risk profiles in such patients, given their association with adverse outcomes.

*presentaban al menos una característica de alto riesgo. Se registraron MACE en 14 pacientes (28%) durante un tiempo mediano de seguimiento de 1,636 días [RIC 626-2,345]. La probabilidad acumulada de MACE fue mayor en el grupo de alto riesgo (log-rank $p = 0.04$). **Conclusiones:** este estudio destaca la importancia de identificar perfiles de alto riesgo en estos pacientes, dada su asociación con desenlaces adversos.*

Abbreviations:

AAOCA = Anomalous Aortic Origin of a
Coronary Artery

ACS = Acute Coronary Syndromes

CAAs = Coronary Artery Anomalies

CCTA = Coronary Computed

Tomography Angiography

ICA = Invasive Coronary Angiography

MACE = Major Cardiovascular Events

MRI = Magnetic Resonance Imaging

RCA = Right Coronary Artery

SCD = Sudden Cardiac Death

INTRODUCTION

First described by Galen and Vesalius,¹ Coronary Artery Anomalies (CAAs) may involve alterations in origin, structure, and course. Although most CAAs are incidental findings with a benign clinical course, a subset of patients might develop a series of clinical manifestations (e.g., myocardial ischemia, ventricular arrhythmias, acute coronary syndromes, ventricular dysfunction, or even Sudden Cardiac Death [SCD]).²⁻⁴ These adverse outcomes have been attributed to several mechanisms such as morphological and functional alterations that can predispose to ischemia, hypoxemia, and an increased arrhythmogenic substrate.

Among these anomalies, Anomalous Aortic Origin of a Coronary Artery (AAOCA) represents one of the most clinically important entities due to its potential association with major cardiovascular outcomes, particularly in younger patients and during physical exertion. However, their risk stratification might be difficult to assess, since many individuals remain asymptomatic during their lifetime, whereas others might truly experience a major cardiovascular event without a final diagnosis (e.g., SCD). As expected, the true impact

of CAAs in the general population remains unclear, ranging from 0.2 to 5.6%;¹ this variation depends on the diagnostic method employed and the diagnostic criteria used to report them. Most data are derived from registries, and, particularly in Latin America, available information is scarce, with a similar prevalence.^{5,6}

Therefore, this study aimed to obtain the clinical and anatomical profile of patients diagnosed with AAOCA and the association with Major Cardiovascular Events (MACE) in a specialized tertiary center in Latin America.

MATERIAL AND METHODS

A longitudinal, retrospective, and analytic study was conducted. Epidemiological data from a Mexican specialized cardiology center were scrutinized using the terms «coronary artery anomalies» and «coronary artery malformations», coded as Q24.5 in the 10th International Disease Classification (ICD-10). All patients evaluated from January 2000 to July 2022 with a confirmed diagnosis of AAOCA were included; the diagnosis was established by Invasive Coronary Angiography (ICA) or Coronary Computed Tomography Angiography (CCTA). Minor CAAs (e.g., myocardial bridge), coronary fistulae, and CAAs arising from the pulmonary arteries were excluded. Clinical data consisted of general information such as age, sex, and cardiovascular and non-cardiovascular comorbidities. Anatomical and functional data were obtained through a multimodal imaging approach (ICA, CCTA, stress echocardiography, nuclear perfusion imaging, stress Magnetic Resonance Imaging [MRI], or treadmill exercise testing), specifically from the official study report and, if necessary, after re-examination by an independent expert. Every imaging test

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was acquired according to a pre-specified protocol in accordance with the international recommendations available at the time of acquisition. Patients were stratified according to the presence or absence of high-risk features (slit-like ostium, an intramural or interarterial course, acute take-off angle [$< 45^\circ$], high take-off orifice, and proximal significant stenosis [$< 50\%$ normal lumen]) (Figure 1). The above-mentioned features were not mutually exclusive; therefore, their individual frequencies could exceed the total number of patients. Follow-up time was calculated from diagnosis to the last known contact with the patient. MACE was defined as Acute Coronary Syndromes (ACS), surgical revascularization, or cardiovascular death, whichever occurred first. ACS could represent the initial presentation in some patients; therefore, only the occurrence of a new ACS during follow-up was considered a MACE event. These variables were selected

to construct the primary outcome because their occurrence was considered reliable and definitive. Although other hard endpoints were also explored, their occurrence could have been underestimated for multiple reasons; therefore, a robust and reliable composite outcome was constructed using these variables.

Numerical data were presented as mean and standard deviation or median and interquartile range, depending on their distribution. Categorical variables were presented as absolute and relative frequencies. Initial comparisons were performed using an unpaired Student's t test or a Mann-Whitney U test, as appropriate, whereas categorical variables were compared using the χ^2 test or Fisher's exact test. Kaplan-Meier curves were constructed for survival analysis to depict cumulative MACE-free survival according to the presence or absence of high-risk features, and these were compared using the log-rank

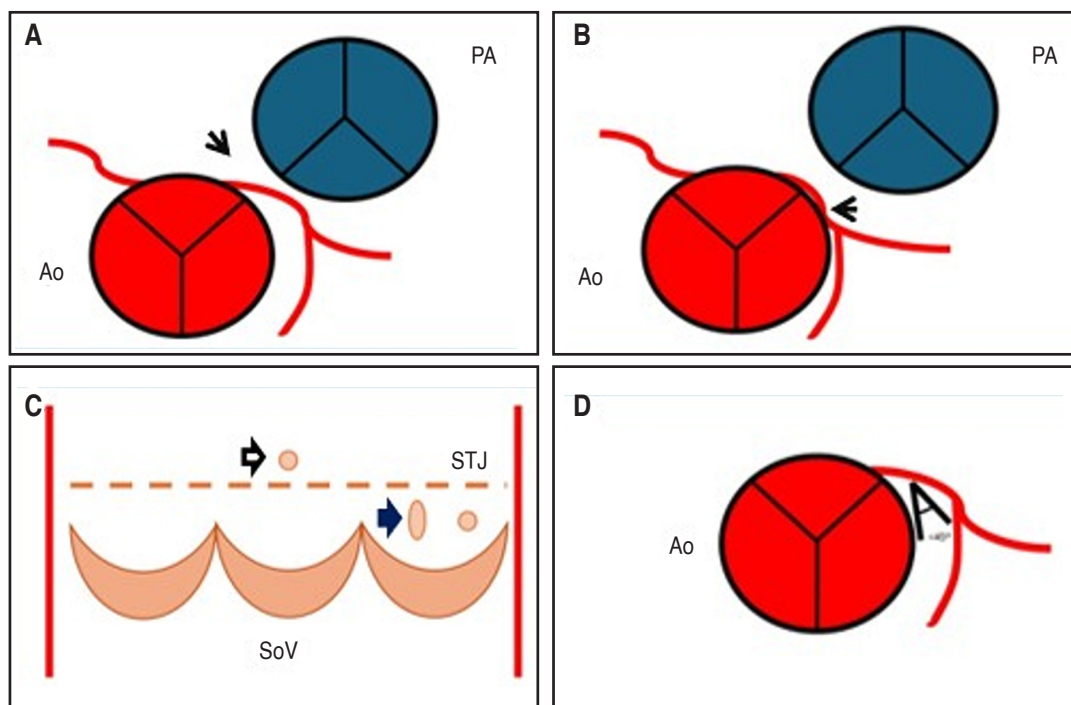


Figure 1: Depiction of high-risk characteristics. Schematic representation of the different anatomical characteristics related to worse outcomes. Anomalous course is seen between the aorta and the pulmonary artery (black arrows), **A)** interarterial and **B)** intramural. **C)** Slit-like ostium (blue solid arrow) and high take-off orifice origin (white filled arrow). **D)** Acute take-off angle ($< 45^\circ$). Finally, proximal lumen narrowing ($< 50\%$), not represented. Ao = Aorta. PA = Pulmonary Artery. SoV = Sinus of Valsalva. STJ = Sinotubular Junction.

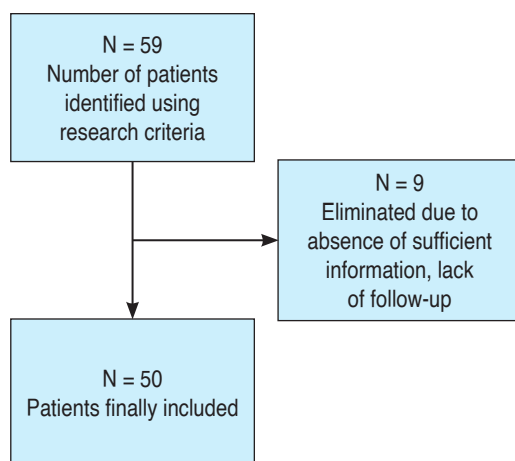


Figure 2: Patient selection flowchart.

test. Additionally, Kaplan-Meier curves were generated based on the number of high-risk characteristics present. For all statistical tests, a p -value < 0.05 was considered statistically significant. The study was conducted in accordance with the ethical standards of the local institutional research committee and the 1964 Declaration of Helsinki and its later amendments. The final protocol was reviewed by the institution's Directorate of Medical Education, and, given its retrospective, non-interventional nature, approval from the local Ethics Committee was obtained. No identifiable personal data were collected or used; therefore, patient confidentiality was strictly maintained. Statistical analyses were performed using RStudio 2024.09.0 + 375 for Windows 11. The study was conducted in accordance with the STROBE guidelines.

RESULTS

Fifty-nine patients were identified with AAOCA after initial exploration. Further review resulted in the exclusion of nine patients, leaving a total of 50 individuals, as shown in [Figure 2](#). Baseline characteristics are summarized in [Table 1](#). Among the 50 included patients, coronary anatomy was evaluated by invasive coronary angiography alone in 29 patients (58%), by coronary CT angiography alone in one patient (2%), and by both imaging modalities in 20 patients (40%).

The mean age was 52 ± 15 years, and the vast majority were male ($n = 34$, 68%). Among the comorbidities, the most frequent was systemic hypertension ($n = 19$, 38%). A small proportion of patients had congenital heart disease.

Nearly half of the patients ($n = 21$, 42%) presented with ACS at diagnosis. Non-ST-segment elevation myocardial infarction was the most frequent subtype, followed by ST-segment elevation myocardial infarction and unstable angina. However, the etiology of these events was not specified. Most hospitalizations and emergency department visits were related to ischemic syndromes or arrhythmic manifestations.

Most anomalies involved coronary artery origin, and the Right Coronary Artery (RCA) was the most frequently affected vessel ($n = 30$, 60%). Only 10% ($n = 5$) of patients had two or more coronary arteries affected. More than half of the anomalous RCAs originated from the opposite coronary sinus. Coronary artery stenosis was described in 30 patients (60%); however, only eight had significant stenosis ($> 50\%$ luminal narrowing). In addition to coronary artery stenosis, several anatomical characteristics associated with a worse prognosis were identified, as shown in [Figure 1](#). Overall, 22 patients (44%) exhibited at least one high-risk anatomical feature.

Patients with positive ischemia testing had a significantly higher incidence of MACE than those without ischemia; however, the anatomical correlation with the anomalous vessel could not be consistently established. Ventricular arrhythmias and syncope were documented in a subset of patients, most of whom were symptomatic at presentation, predominantly with angina or functional limitation.

[Table 1](#) also summarizes the comparison according to MACE status. No significant differences were observed for most baseline characteristics, except for the presence of high-risk anatomical features ($p < 0.01$). The median follow-up was 1,636 days [IQR, 626-2,345]. The primary outcome occurred in 21 patients (42%). Among the components of MACE, six patients (12%) experienced a new ACS during follow-up, five (10%) underwent surgical

Table 1: Distribution of patients according to MACE (N = 50).

Parameter	Total N = 50 n (%)	MACE		p
		No N = 29 n (%)	Yes N = 21 n (%)	
Characteristic				
Age (years), mean $\pm$ SD	52 $\pm$ 15	53 $\pm$ 16	50 $\pm$ 14	0.30
Female	16 (32.0)	11 (37.9)	5 (23.8)	0.81
Systolic arterial hypertension	19 (38.0)	13 (44.8)	6 (28.6)	0.28
Diabetes mellitus	6 (12.0)	4 (13.8)	2 (9.5)	0.99
Dyslipidemia	16 (32.0)	10 (34.5)	6 (28.6)	0.76
Atrial fibrillation	5 (10.0)	3 (10.3)	2 (9.5)	0.99
Ventricular tachycardia	4 (8.0)	2 (6.9)	2 (9.5)	0.99
Congenital cardiopathy				0.06
None	45 (90.0)	26 (89.7)	19 (90.5)	
Post-tricuspid valve defect	1 (2.0)	0 (0.0)	1 (4.8)	
Other types	4 (8.0)	3 (10.3)	1 (4.8)	
Concomitant cardiopathy				0.05
None	41 (82.0)	24 (80.0)	18 (85.7)	
Left-sided valve disease	7 (14.0)	5 (20.0)	1 (4.8)	
Others	2 (4.0)	0 (0.0)	2 (9.5)	
Symptoms				0.23
Asymptomatic	5 (10.0)	4 (13.8)	1 (4.8)	
Angina	33 (66.0)	19 (65.5)	14 (66.7)	
Dyspnea	7 (14.0)	5 (17.2)	2 (9.5)	
Syncope	2 (4.0)	1 (3.4)	1 (4.8)	
Palpitations	3 (6.0)	0 (0.0)	3 (14.3)	
Initial clinical presentation				0.69
Acute coronary syndrome	21 (42.0)	13 (44.8)	8 (47.6)	
Unstable angina	4 (8.0)	3 (10.3)	1 (4.8)	
Non-ST elevation AMI	10 (20.0)	4 (13.8)	6 (28.6)	
ST elevation AMI	7 (14.0)	6 (20.7)	1 (4.8)	
Chronic angina	12 (24.0)	7 (24.1)	5 (23.8)	
Others	17 (34.0)	9 (31.0)	8 (38.0)	
ACS related to AAOCA	21 (42.0)	11 (37.9)	10 (50.0)	
Functional and anatomic findings				
LVEF 2D (%), mean $\pm$ SD	52 $\pm$ 14	52 $\pm$ 12	53 $\pm$ 16	0.81
Specific location of the anomaly				
LMCA	4 (8.0)	3 (10.3)	1 (4.8)	
LAD	1 (2.0)	1 (3.4)	0 (0.0)	
LCx	5 (10.0)	4 (13.8)	1 (4.8)	
RCA	30 (60.0)	15 (51.7)	15 (71.4)	
Single coronary artery (single ostium)	5 (10.0)	3 (10.3)	2 (9.5)	
Two or more affected coronary arteries	5 (10.0)	3 (10.3)	2 (9.5)	

Continue Table 1: Distribution of patients according to MACE (N = 50).

Parameter	Total N = 50 n (%)	MACE		p
		No N = 29 n (%)	Yes N = 21 n (%)	
RCA origin*				
Left coronary sinus	20 (54.1)	11 (61.1)	9 (47.4)	
High take-off orifice	11 (29.7)	4 (22.2)	7 (36.8)	
From a coronary artery	6 (16.2)	3 (16.7)	3 (15.8)	
LMCA origin*				
Right coronary sinus	1 (14.3)	1 (16.7)	0 (0.0)	
Non-coronary sinus	2 (28.6)	2 (33.3)	0 (0.0)	
High take-off orifice	3 (42.9)	2 (33.3)	1 (100.0)	
From a coronary artery	1 (14.3)	1 (16.7)	0 (0.0)	
LAD origin*				
Right coronary sinus	2 (50.0)	2 (66.7)	0 (0.0)	
Left coronary sinus	1 (25.0)	0 (0.0)	1 (100.0)	
Non-coronary sinus	1 (25.0)	1 (33.3)	0 (0.0)	
Single coronary artery (single ostium)				0.71
Left coronary sinus	3 (80.0)	2 (66.7)	2 (100.0)	
Right coronary sinus	1 (20.0)	1 (33.3)	0 (0.0)	
LCX origin*				0.23
Right coronary sinus	6 (66.7)	5 (83.3)	1 (33.3)	
Left coronary sinus	1 (11.1)	0 (0.0)	1 (33.3)	
From a coronary artery	2 (22.2)	1 (16.7)	1 (33.3)	
Other characteristics				
High take-off orifice	15 (30.0)	5 (33.3)	10 (66.7)	0.05
Acute angle take-off	10 (20.0)	2 (20.0)	8 (80.0)	0.06
Slit like/oval orifice	5 (10.0)	1 (20.0)	4 (80.0)	0.20
Patients with high-risk features	–	8 (27.6)	14 (66.7)	0.01
Coronary artery course				< 0.01
Intramural	3 (6.0)	0 (0.0)	3 (14.3)	
Retroaortic	22 (44.0)	18 (62.1)	4 (19.0)	
Interarterial	21 (42.0)	9 (31.0)	12 (57.1)	
Prepulmonic	4 (8.0)	2 (6.9)	2 (9.6)	
Stenosis of the AAOCA	30 (60.0)	12 (41.4)	18 (85.7)	0.01
Stenosis etiology				
Atherosclerotic	9 (30.0)	7 (58.3)	2 (11.1)	
Both congenital and atherosclerotic	21 (70.0)	5 (41.7)	16 (88.9)	
Degree of stenosis				0.71
> 90%	4 (13.3)	1 (8.3)	3 (16.7)	
70-89%	4 (13.3)	1 (8.3)	3 (16.7)	
50-69%	9 (30.0)	5 (41.7)	4 (22.2)	

Continue Table 1: Distribution of patients according to MACE (N = 50).

Parameter	Total N = 50 n (%)	MACE		p
		No N = 29 n (%)	Yes N = 21 n (%)	
Diagnostic and therapeutic approach				
Functional performed test				
Perfusion myocardial imaging	22 (64.7)	12 (66.7)	10 (62.5)	
Treadmill stress	2 (5.9)	2 (11.1)	0 (0.0)	
Dobutamine-stress MRI	8 (23.5)	3 (16.7)	5 (31.3)	
Stress echocardiography	2 (5.9)	1 (5.6)	1 (6.3)	
Positive for ischemia**	15 (44.7)	20 (69.0)	16 (76.2)	
Follow-up				
Days, median [IQR1-IQR3]	1,636 [626-2,345]	1,379 [451-1,957]	1,904 [1,284-2,647]	0.20
Comparisons were made with: Continuous variables were compared using the unpaired Student's <i>t</i> test or the Mann–Whitney U test, as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Paired post-hoc analysis showed differences between retroaortic and interarterial (non-adjusted p value 0.008, adjusted 0.12) and interarterial and prepulmonic (non-adjusted p value 0.04, adjusted value 0.63). * Anatomical characteristics were not mutually exclusive; therefore, patients could be included in more than one category, and percentages may not sum to 100%. ** The percentage of positive ischemia tests was calculated among patients who underwent functional testing. ACS = Acute Coronary Syndrome. AMI = Acute Myocardial Infarction. AAOCA = Anomalous Aortic Origin of the Coronary Artery. IQR = InterQuartile Range. LAD = Left Anterior Descending artery. LCx = Left Circumflex Artery. LMCA = Left-Main Coronary Artery. LVEF = Left Ventricle Ejection Fraction. MACE = Major Adverse Cardiovascular Events. MRI = Magnetic Resonance Imaging. PY12i = Inhibitor of Surface Platelet P2Y12 Receptor. RCA = Right Coronary Artery. SD = Standard Deviation.				

revascularization during follow-up, and three (6%) died from cardiovascular causes.

Kaplan-Meier analysis demonstrated a lower MACE-free survival probability among patients with high-risk anatomical features (log-rank $p = 0.04$), as shown in [Figure 3A](#). Likewise, patients with a greater number of high-risk anatomical features exhibited a higher cumulative incidence of MACE (log-rank $p = 0.049$), as shown in [Figure 3B](#).

DISCUSSION

This retrospective study in patients with AAOCA found that most coronary anomalies involved the coronary artery origin and course, predominantly affecting the RCA. Furthermore, a substantial proportion of patients exhibited at least one high-risk anatomical feature,

which was associated with a lower cumulative probability of MACE-free survival over time. Moreover, stratification by the number of high-risk anatomical features showed a progressively higher cumulative incidence of MACE with increasing risk-feature burden.

Our cohort included 50 patients, like previous studies.^{5,6} Although larger cohorts have been reported,⁷⁻⁹ these studies invariably required extended recruitment periods, often spanning several years or even decades, likely reflecting the low prevalence of this condition.¹⁰ This also explains the heterogeneity in age and other baseline characteristics observed across published series.^{7,11} Nearly all our patients were symptomatic, most commonly presenting with angina or other clinically relevant cardiovascular manifestations.

The high-risk anatomical profile has been widely associated with adverse cardiovascular

outcomes.¹²⁻¹⁴ Although an interarterial course is the most frequently reported high-risk anatomical variant in previous series,^{8,15,16} the retroaortic course was the most common anatomical variant in our cohort. Nevertheless, a substantial proportion of patients exhibited an interarterial course, consistent with previous reports.⁸ Similarly, we observed an association between high-risk anatomical features and the occurrence of MACE, in agreement with previous reports. Furthermore, patients with a greater number of high-risk anatomical features exhibited a lower MACE-free survival probability and a higher cumulative incidence of events, suggesting that the accumulation of these anatomical characteristics may identify individuals at progressively higher cardiovascular risk.

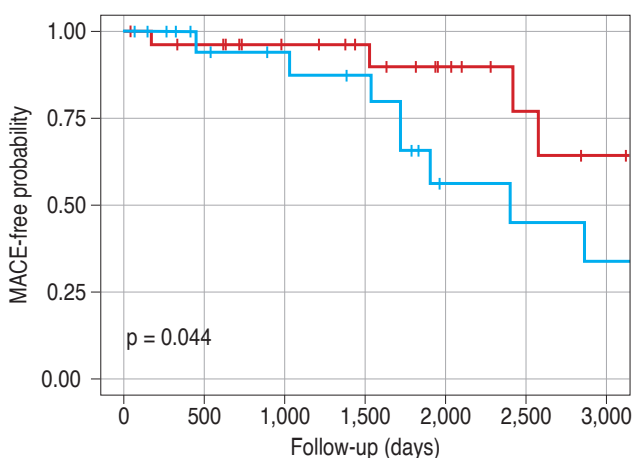
Current recommendations regarding the evaluation and management of patients with coronary artery anomalies are largely based on the identification of high-risk anatomical features. Our findings support the importance of systematically identifying these characteristics during the diagnostic evaluation of patients with AAOCA.

Functional assessment revealed that a significant proportion of patients had evidence of myocardial ischemia. Some of these patients subsequently underwent surgical revascularization and later experienced MACE during follow-up. However, because the available data did not allow us to determine whether these procedures were directly related to AAOCA or whether subsequent events were influenced by prior coronary interventions, no definitive association could be established.

Limitations

A key limitation of this study is its retrospective, single-center design, which may introduce selection bias and limit how broadly the findings can be applied. The relatively small sample size and low number of events, particularly acute coronary syndromes and arrhythmic events, limit the statistical power to establish robust associations between AAOCA and clinical outcomes. In addition, attributing outcomes

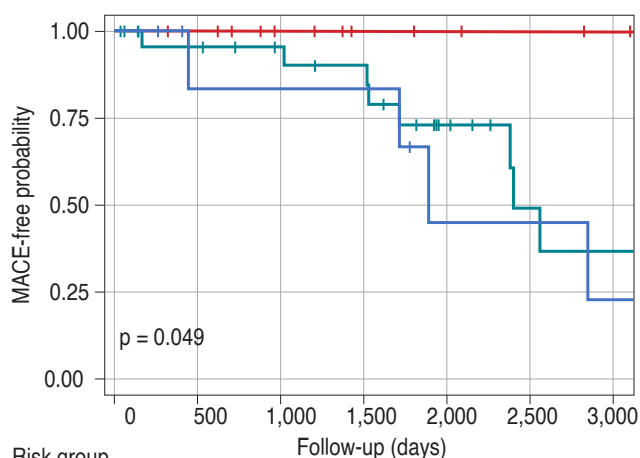
A) By high-risk anatomy



Strata
 + No high risk + High risk

Strata	Number at risk						
No high risk	28	25	19	15	10	6	4
High risk	22	16	14	12	5	4	3
	Follow-up (days)						

B) By grouped number of risk factors



Risk group
 + 0 factor + 1-2 factors + 3-5 factors

Risk group	Number at risk						
0 factors	17	15	10	6	5	4	3
1-2 factors	25	21	18	16	8	4	3
3-5 factors	8	5	5	5	2	2	1
	Follow-up (days)						

Figure 3: Cumulative MACE-free occurrence depicted in Kaplan-Meier curves. Proportion of patients free of MACE throughout observation time distributed according to high-risk factors profile (A) and when patients were stratified according to the number of high-risk factors (B).

such as ACS or cardiovascular death to AAOCA is inherently challenging, as these events may be influenced by comorbid conditions and may not be directly related to the congenital anomaly. Moreover, none of the MACE components could be definitively attributed to AAOCA. The heterogeneity in clinical presentation and management, including the limited number of patients undergoing surgical correction despite high-risk features such as inducible ischemia, further complicates the interpretation of the results and may introduce treatment bias. Additionally, detailed anatomical characterization and functional assessment (e.g., standardized ischemia testing) were not uniformly available for all patients, which may have affected risk stratification. Finally, given the observational nature of the study, causal inferences cannot be established, and the findings should be interpreted as hypothesis-generating, warranting confirmation in larger, prospective, multicenter cohorts.

CONCLUSIONS

In this cohort of patients with AAOCA, high-risk anatomical features were associated with the occurrence of MACE. Moreover, patients with a greater number of high-risk anatomical features exhibited a lower MACE-free survival probability and a higher cumulative incidence of adverse cardiovascular events.

This study also provides a description of the clinical and anatomical characteristics of patients with AAOCA in our setting. Given the rarity of this condition and the heterogeneity of its presentation, larger prospective studies are needed to better define the prognostic significance of high-risk anatomical features and to optimize risk stratification and management.

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