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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Cardiometabolic Risk Factors in Mexican Adults With Congenital Heart Disease

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ABSTRACT

BACKGROUND In recent decades, adults living with congenital heart disease (ACHD) have improved their survival, thus increasing their predisposition to the onset of cardiometabolic risk factors and chronic health conditions.

OBJECTIVES The purpose of this study was to describe cardiometabolic risk profiles in the ACHD population and their relationship to congenital heart disease (CHD) lesion complexity.

METHODS We performed a cross-sectional study from ACHD in a third-tier referral center in Mexico City. The association between cardiometabolic risk factors and CHD complexity was estimated using logistic regression models.

RESULTS Our study cohort included 1,171 ACHD patients (median age: 31 [IQR: 23.2-42.7] years, male 63.6%). Cardiac diagnosis was classified as mild (44.9%), moderate (37.8%), and severe (17.2%) CHD complexity. Low high-density lipoprotein cholesterol (55%) was the most common cardiometabolic risk factor; followed by insulin resistance (54.5%) and prediabetes (52.4%). Patients with mild and moderate CHD had a higher prevalence of obesity and metabolic syndrome, while patients with severe CHD had a higher prevalence of hyperuricemia and subclinical hypothyroidism. In the logistic regression analysis, the severity of CHD was associated with higher odds of hyperuricemia (moderate CHD, OR: 1.87; 95% CI: 1.20-2.93; $P = 0.010$; severe CHD, OR: 2.75; 95% CI: 1.64-4.62; $P < 0.001$) and lower risks of metabolic syndrome (OR: 0.61; 95% CI: 0.41-0.91; $P = 0.010$), prediabetes (OR: 0.58; 95% CI: 0.42-0.81; $P < 0.001$), and arterial hypertension (OR: 0.49; 95% CI: 0.33-0.74; $P < 0.001$) compared with mild CHD complexity.

CONCLUSIONS We observed high rates of cardiometabolic risk factors in Mexican ACHD patients and these risk profiles varied by CHD lesion complexity. These results highlight the need for ongoing metabolic health surveillance in the ACHD population. (JACC Adv 2023;2:100596) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACHD = adults living with congenital heart disease
BMI = body mass index
CHD = congenital heart disease
CVD = cardiovascular disease
DBP = diastolic blood pressure
HDL = high-density lipoprotein
SBP = systolic blood pressure
T2D = type 2 diabetes

Worldwide, congenital heart disease (CHD) affects 9 per 1,000 live births in industrialized countries.[1] Despite efforts to understand the prevalence of CHD in Latin America, the estimated number of adults living with CHD (ACHD) in South America was only 1.8 million in 2020, with an annual growth rate of 5% to 6%.[2] Over the past few decades, advancements in surgical and interventionist techniques have led to approximately 90% of children with CHD reaching adulthood, resulting in a 3:2 ratio between adults and pediatric patients.[3,4] As a result, the ACHD population has increased, facing standardized conditions that lead to cardiovascular diseases (CVDs) and chronic health complications associated with aging and congenital disabilities. Studies have shown significantly higher rates of noncardiac comorbidities, such as type 2 diabetes mellitus (T2D) and kidney disease, in ACHD patients compared to the general population.[5,6]

Additionally, coronary artery disease is as prevalent in ACHD as it is in the general population and has become a leading cause of mortality. In numerous instances, coronary artery disease in the ACHD population is driven by traditional CVD risk factors like hypertension, obesity, and lack of physical activity, which are common among both pediatric and adult patients with CHD.[7,8] Nevertheless, there is a lack of information concerning clinical characterization or cardiovascular risk factors among ACHD and their impact on CHD-related complexity in Latin America. In this context, low- and middle-income countries face a significant burden of cardiometabolic diseases, including obesity, T2D, dyslipidemias, and arterial hypertension.[9,10] These conditions pose a particular challenge for the ACHD population, as they often coexist.[11-13] Therefore, comprehensive evaluation of ACHD patients should consider metabolic factors that increase the risk of CVD and mortality, an aspect that has not been extensively studied in Mexico.

In light of these considerations, the objectives of this study are: 1) to describe the prevalence of 11 cardiometabolic risk factors; and 2) to explore the association between the severity of CHD and cardiometabolic risk factors in a sample of 1,171 ACHD patients who were studied at a third-tier referral center in Mexico City.

MATERIAL AND METHODS

STUDY DESIGN. We performed a cross-sectional study of ACHD registered at the National Institute of Cardiology Ignacio Chávez outpatient clinic in Mexico City. The institute serves as a national third-tier referral center and maintains an intern registry of over 3,500 patients with ACHD in Mexico. Using our clinical registry, we screened and included ACHD patients, regardless of their repair or palliative status, from October 2021 to January 2022. Patients older than 90 years or without any registered laboratory analyses in Their electronic medical records were excluded. No additional exclusion criteria regarding atherosclerotic cardiovascular disease risk factors were used to avoid selection bias. The study was approved by the National Institute of Cardiology Ethics Committee (protocol number INCAD-DG-DI-CI-234-2021). This work complies with the strengthening the reporting of observational studies in epidemiology guidelines for cross-sectional studies.

DATA COLLECTION. During a normal patient's visit at the clinic, sociodemographic, clinical, and biochemical data are collected from the medical visit and the electronic medical records. This information is then pooled on a designed medical card created to enhance data management and storage, named: "Carnet" (Supplemental Figure 1). Then, all the information is pooled in an internal database of the ACHD outpatient clinic. After the patient screening, data for this study were retrospectively gathered from the "Carnet'' and the internal database. This information was compared with the electronic medical records, designed to mitigate any potential biases or discrepancies that might have imperceptibly surfaced during the acquisition of data.

VARIABLES INCLUDED.

a) *Sociodemographic variables:* These included sex, age, address of residence, institutional registry number, and contact information. Only age and sex are displayed in our results.
b) *Clinical variables:* We recorded systolic blood pressure (SBP) and diastolic blood pressure (DBP), both measured in mmHg, self-reported physical activity and smokers, antiplatelet medication, exercise, and anticoagulant medication. A smoker

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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was defined as an adult who has smoked >100 cigarettes in his or her lifetime and who currently smokes cigarettes.[14] Exercise was defined as physical activity that is planned, structured, repetitive, and purposefully focused on the improvement or maintenance of one or more components of physical fitness. The patient should do at least 150 to 300 (30 minutes daily for at least 5 days a week) minutes of moderate-intensity aerobic physical activity.[15]

c) *Biochemical variables:* These included fasting plasma glucose (mg/dL), triglycerides (mg/dL), total cholesterol (mg/dL), serum albumin (g/dL), serum creatinine (mg/dL), ferritin (ng/mL), hemoglobin (g/dL), and hematocrit (%). The measurement of glycated hemoglobin is reported in percentage (%).

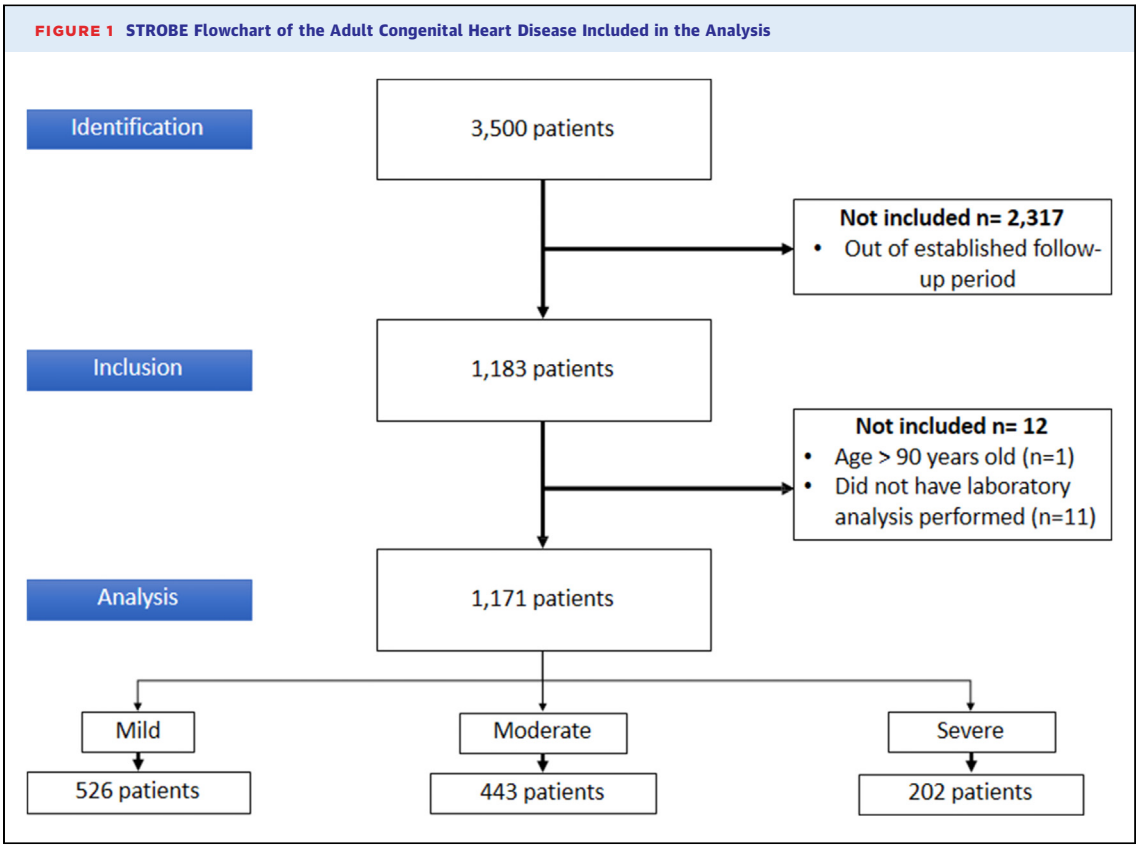
d) *Complexity of CHD:* Patients were divided into 3 groups according to the complexity of their heart disease into mild, moderate, or severe. This classification was based on the "2020 European Society of Cardiology Guidelines for the management of adult CHD."[1]

DEFINITION OF VARIABLES. Our study centered on describing and studying 11 cardiometabolic risk factors related to the onset of CVD. These are the factors that encompass the global risk of CVD and T2D associated with traditional risk factors, while also taking into consideration the potential additional contribution of abdominal obesity and/or insulin resistance and other related metabolic markers (to be identified) to global CVD risk.[16] Each definition is stated as follows:

1. *Arterial hypertension*: as a SBP or DBP ≥130 or ≥80 mm Hg, respectively, according to the 2017 "American Heart Association Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults."[17] The blood pressure measurement protocol consisted of 3 measurements with 1 minute between them and calculate the average of the last 2 measurements. The measurement of blood pressure was made by a trained nurse to treat adults with CHD after a 5-minute rest.
2. *Hypertriglyceridemia*: as a plasmatic triglyceride >150 mg/dl, according to the "2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease."[18]
3. *Hypercholesterolemia*: as a total cholesterol >200 mg/dl, according to the "2006 Prevalence of Dyslipidemias in the Mexican National Health and Nutrition Survey."[19]
4. *Low high-density lipoprotein (HDL) cholesterol:* <40 mg/dL in males or <50 mg/dL in females.[18]
5. *Insulin resistance:* we used as a proxy of insulin resistance the triglyceride/HDL ratio. We used the threshold of >2.75 to define insulin resistance according to the European Society of Cardiology article "triglycerides (TG)/HDL ratio as a surrogate marker for insulin resistance."[20]
6. *Type 2 diabetes:* fasting plasmatic glucose >126 mg/dL or a glycated hemoglobin ≥6.5% considering the "American Diabetes Association Standards of Medical Care in Diabetes 2021."[21]
7. *Prediabetes*: defined as a patient without T2D and glycated hemoglobin ≥5.7% and <6.5%, according to the "American Diabetes Association Standards of Medical Care in Diabetes 2021."[21]
8. *Obesity*: classified as body mass index (BMI) >30 kg/m^2 according to the "American Association of Clinical Endocrinologists/American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity."[22]
9. *Metabolic syndrome*: defined as patients with 3 or more of the following criteria: fasting glucose >100 mg/dL, SBP >130 mm Hg and/or DBP >85 mm Hg, triglycerides >150 mg/dL, HDL <40 mg/dL (male) or <50 mg/dL (female), and BMI >30 kg/m^2.[18] We used BMI as an equivalent measure to capture the increased accumulation of adipose tissue intended to be captured by waist circumference.
10. *Subclinical hypothyroidism:* this was defined as patients with thyroid stimulating hormone (TSH)>4.5 μIU/mL and normal values of total T4 (6.5-12 μIU/mL) according to our institutional laboratory.[23]
11. *Hyperuricemia*: we used a uric acid level threshold of >6 mg/dL in women and >7 mg/dL in men, according to the 2021 paper, "Uric Acid and Risk of Cardiovascular Disease", published *Hypertension*.[24]

STATISTICAL ANALYSIS. Qualitative variables were described in frequencies and percentages. Quantitative variables were described with mean ± SD or with median (IQR) according to their normal distribution assessed by the Anderson-Darling test. A Kruskall-Wallis test and a chi-square test were used to evaluate the parameters between the severity of heart disease. All statistical analyses were performed in

FIGURE 1 STROBE Flowchart of the Adult Congenital Heart Disease Included in the Analysis



R Studio (version 4.1). A value of $P < 0.05$ was considered as the statistical significance threshold.

Missing variables assessment. We carefully assessed and imputed missing values of the biochemical variables to ensure the robustness and accuracy of our analysis. We used the multiple imputation algorithm based on the wholly conditional specification technique proposed by Van Buuren and Groothuis-Oudshoorn, which assumes that the missing data are completely at random. The *mice* package (version 3.14.0)[25] in R software was utilized to perform the imputation. Detailed results of imputed variables are presented in Supplemental Figure 2.

Prevalence estimations of cardiometabolic risk factors. To estimate the prevalence at a 95% CI for the cardiometabolic risk factors, we used the Wilson approach from the *epiR* package.[26] Then, we visualized our prevalence estimations using bar plots created with the *ggplot2* package.[27]

Association of CHD complexity and cardiometabolic risk factors. We fitted binomial logistic regression models to estimate the association between our cardiometabolic risk factors and the complexity of CHD. We fitted each of our cardiometabolic risk factors as our independent variable, and the complexity of the CHD was determined to be the independent variable. Covariates of adjustment were age and sex. These models were performed using individual models for each comparison, thus, not requiring adjustment for multiple comparisons within the final analyses. OR plots were created using the *jtools* package (Version 2.1.4).[27]

RESULTS

STUDY POPULATION. According to medical archives, 3,500 adult patients have attended the CHD outpatient clinic in our institute, of which 1,183 attended the clinic in the established period for this analysis. After exclusion criteria, 11 patients were excluded due to missing laboratory analyses, and 1 patient was older than 90 years. Therefore, 1,171 patients were included in our main analysis (**Figure 1**). The complete characteristics of our population are displayed in **Table 1**. Briefly, our study population had a male predominance (63.6%), with a median age of 31 years (IQR: 23.2-42.7 years). Our subclassification by type of CHD delineated that the 5 most frequent CHD were

TABLE 1 Clinical Characteristics, Biochemical Measurements, and Metabolic Impairments Among CHD Patients

	All (N = 1,171)	Mild CHD (n = 526)	Moderate CHD (n = 443)	Severe CHD (n = 202)	*P* Value
Male	745 (63.6)	370 (70.3)	258 (58.2)	117 (57.9)	<0.001[a]
Age (y)	31 (23.25-42.75)	34 (25-47)	30 (23-40)	28 (22-37)	<0.001[a]
Clinical characteristics					
SBP (mm Hg)	120 (100-130)	120 (110-130)	118 (100-130)	110 (100-120)	<0.001[a]
DBP (mm Hg)	70 (70-80)	80 (70-80)	70 (70-80)	70 (60-80)	<0.001[a]
Physical activity (%)	400 (34.2)	189 (36.1)	150 (33.9)	61 (30.2)	0.320
Smoking (%)	54 (4.6)	30 (5.7)	19 (4.3)	5 (2.5)	0.170
Antiplatelet medication (%)	34 (9.3)	13 (9.6)	9 (5.7)	33 (16.7)	0.029[a]
Anticoagulant medication (%)	133 (11.4)	37 (7.1)	59 (13.3)	37 (18.3)	<0.001[a]
Cyanosis	123 (10.50)	12 (2.31)	27 (6.14)	84 (41.79)	<0.001
Biochemical measurements					
Glucose (mg/dL)	93 (86-101)	93.85 (87-101.75)	93 (86-102)	91 (82.92-98.62)	0.002[a]
HbA1c (%)	5.95 (5.64-6.27)	6 (5.66-6.27)	5.89 (5.62-6.22)	5.97 (5.61-6.27)	0.150
Triglycerides (mg/dL)	117 (88.4-161)	124.5 (93-166)	114 (84.7-153.5)	113 (87.25-154.75)	0.009[a]
Total cholesterol (mg/dL)	167 (142-190)	172 (147-193)	164 (139.5-186.5)	159 (136.25-183.98)	0.002[a]
Albumin (g/dL)	4.7 (4.4-4.87)	4.7 (4.4-4.83)	4.7 (4.4-4.87)	4.7 (4.4-4.89)	0.199
Creatinine (mg/dL)	0.7 (0.6-0.83)	0.7 (0.6-0.8)	0.7 (0.6-0.83)	0.72 (0.6-0.9)	0.002[a]
Uric acid (mg/dL)	5.44 (4.45-6.51)	5.25 (4.24-6.15)	5.54 (4.57-6.61)	6.29 (4.99-7.45)	<0.001
Ferritin (ng/mL)	22.4 (11.3-59.8)	22.4 (11.3-61.2)	22.4 (11.3-47.75)	22.4 (12.8-41.6)	0.859
Hemoglobin (g/dL)	15.1 (13.93-16.8)	14.6 (13.75-16)	15.5 (14-16.9)	16.65 (14.5-19.9)	<0.001[a]
Hematocrit (%)	46 (42.5-50.5)	44.6 (41.9-48.4)	46 (42.5-51)	50.6 (45.18-60.17)	<0.001[a]
TSH (μIU/ml)	3.25 (2.05-4.85)	3.00 (1.96-4.85)	3.29 (2.0-4.92)	3.68 (2.33-5.31)	<0.001[a]
Prevalence of cardiometabolic risk factors					
Arterial hypertension (%)	357 (30.5)	190 (36.1)	127 (28.6)	40 (19.6)	<0.001
Hypertriglyceridemia (%)	353 (30.1)	175 (33.3)	118 (26.6)	60 (29.7)	0.083
Hypercholesterolemia (%)	227 (19.4)	113 (21.5)	81 (18.3)	33 (16.3)	0.225
Low HDL cholesterol (%)	644 (55.0)	301 (57.3)	232 (52.5)	111 (54.9)	0.683
Insulin resistance (%)	638 (54.5)	297 (56.4)	233 (52.7)	108 (53.5)	0.041
Type 2 diabetes (%)	246 (21)	118 (22.4)	83 (18.7)	45 (22.3)	0.352
Undiagnosed diabetes (%)	166 (14.2)	71 (13.5)	53 (14.2)	32 (15.8)	0.725
Prediabetes (%)	614 (52.4)	283 (53.9)	229 (51.6)	102 (50.5)	0.966
Obesity (%)	122 (10.4)	63 (12.0)	40 (9.0)	19 (9.4)	<0.001
Metabolic syndrome	282 (24.3)	153 (29.2)	98 (22.3)	31 (15.6)	<0.001
Subclinical hypothyroidism (%)	295 (25.1)	120 (22.9)	116 (26.12)	57 (28.2)	0.259
Hyperuricemia (%)	123 (10.5)	38 (7.23)	53 (11.93)	32 (15.84)	<0.001

Values are n (%) or median (IQR). [a]*P* value < 0.05.

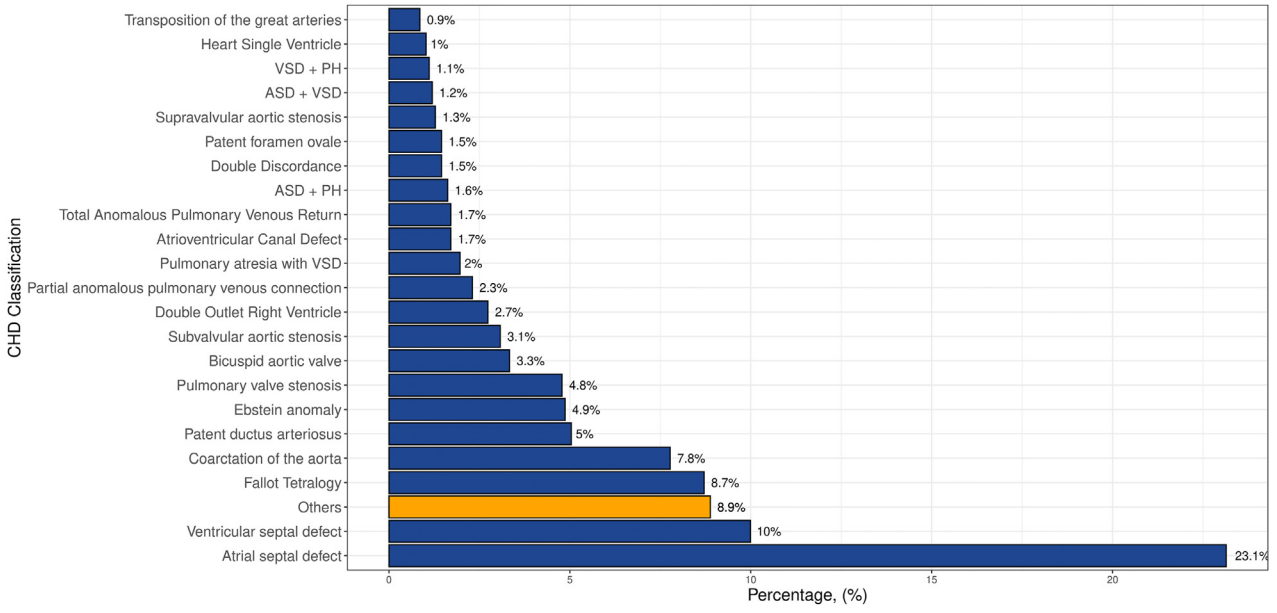
CHD = congenital heart disease; DBP = diastolic blood pressure; HDL = high-density lipoprotein; SBP = systolic blood pressure; TSH = thyroid stimulating hormone.

atrial septal defect (23.1%), ventricular septal defect (10%), tetralogy of Fallot (8.7%), coarctation of the aorta (7.8%), and patent ductus arteriosus (5%) (Figure 2). According to the European Society of Cardiology 2020 ACHD Guidelines,[1] we classified the complexity of congenital heart defects as follows: 44.9% mild, 37.8% moderate, and 17.2% severe.

CLINICAL, BIOCHEMICAL, AND METABOLIC CHARACTERIZATION OF THE OVERALL STUDY POPULATION. Regarding clinical variables, the median SBP was 120 mm Hg (IQR: 100-130 mm Hg) and the median DBP was 70 mm Hg (IQR: 70-80 mm Hg). Of the total population, 34.2% reported physical activity, and 4.6% referred to having active smoking status. Regarding biochemical parameters, the median fasting serum glucose was 93 mg/dL (IQR: 86-101 mg/dL) with median glycated hemoglobin of 5.95% (IQR: 5.64%-6.27%). In the lipid profile, the median triglyceride value was 117 mg/dL (IQR: 88.4-161 mg/dL), and the median total cholesterol value was 167 mg/dl (IQR: 142-190). According to metabolic impairments, we observed that low HDL cholesterol (55%) was the highest cardiometabolic risk factor; followed by insulin resistance (54.5%) and prediabetes (52.4%). Of the patients not known to have type 2 diabetes, 166 (14.2%) were diagnosed at the medical visit (Table 1, Figure 3A).

CLINICAL PARAMETERS ACCORDING TO CHD SEVERITY. Stratifying by complexity, we observed that adults with mild CHD complexity tended to be

FIGURE 2 Bar-Plot of the Percentage of Congenital Heart Disease in Our Population



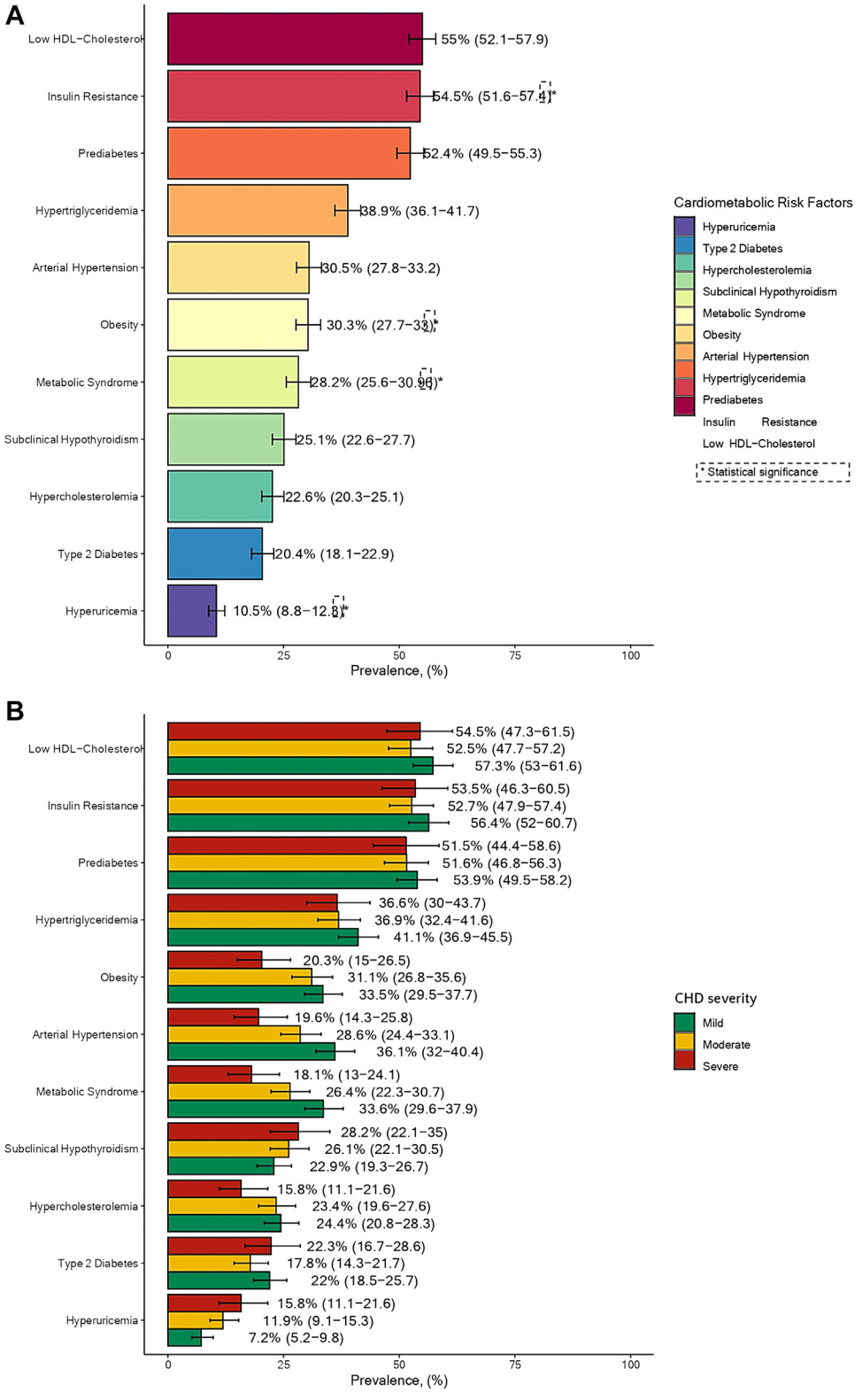
ASD + PH = atrial septal defect with pulmonary hypertension; ASD + VSD = atrial septal defect with ventricular septal defect; VSD = ventricular septal defect; VSD + PH = ventricular septal defect with pulmonary hypertension.

older men compared with patients classified with moderate and severe disease. The prevalence of patients with cyanosis in the mild, moderate, and severe CHD groups was 2.31%, 6.14%, and 41.79%, respectively. The severe CHD group more commonly used antiplatelet (16.7%) and anticoagulant medication (18.3%). SBP and DBP were lower in the severe CHD group (**Table 1**). Furthermore, there was a significant increase in uric acid levels as the complexity of CHD increased (Supplemental Figure 3A). Upon further analysis, we stratified the association and found that the effect related to CHD complexity was specifically attributable to polycythemia and cyanosis (Supplemental Figures 3B and 3C). To confirm and strengthen this association, we fitted adjusted logistic regression models, which allowed us to control for potential confounding factors (Supplemental Table 1). Both cyanosis and polycythemia were found to contribute to the underlying mechanism between CHD complexity and hyperuricemia.

BIOCHEMICAL MEASUREMENTS AND PREVALENCE OF CARDIOMETABOLIC RISK FACTORS. Regarding biochemical parameters, patients with mild and moderate complexity had higher fasting glucose, triglycerides, and total cholesterol levels than patients with severe heart disease. Conversely, patients with severe CHD have greater hemoglobin, hematocrit, TSH levels, creatinine, and uric acid than those in the mild group (**Table 1**). According to metabolic disorders, patients with severe CHD had a higher proportion of hyperuricemia (15.8%) and T2D (22.3%). Subclinical hypothyroidism tended to have a higher proportion (28.2%) but did not reach a statistically significant difference. Finally, a higher proportion of obesity and metabolic syndrome was observed in mild and moderate CHD (**Table 1**, **Figure 3B**).

CARDIOMETABOLIC RISK FACTORS RELATED TO CHD COMPLEXITY. We fitted logistic regression models to explore the association with cardiometabolic risk factors related to the complexity of CHD. Complete models are presented in **Table 2**. We observed that patients with moderate and severe CHD had increased odds for hyperuricemia (moderate CHD OR: 1.87; 95% CI: 1.20-2.93; $P < 0.010$); severeCHD OR: 2.75; 95% CI: 1.64-4.62; $P < 0.001$) compared with mild CHD presentation after adjusting for covariates. Conversely, patients with severe CHD had lower odds of having metabolic syndrome (OR: 0.61; 95% CI: 0.41-0.91; $P = 0.010$) and arterial hypertension (OR: 0.49; 95% CI: 0.33-0.74; $P < 0.001$) compared with mild CHD complexity.

FIGURE 3 **Distribution of Cardiometabolic Risk Factors Stratified by CHD Complexity**



(A) Frequency of risk factors. (B) Frequency of risk factors by CHD severity classification. CHD = congenital heart disease; HDL = high-density lipoprotein.

TABLE 2 Binomial Logistic Regression Models to Assess the Metabolic Impairments Related to CHD Severity

		OR (95% CI)			
Cardiometabolic Risk Factor (Outcome)	Mild	Moderate	*P* Value	Severe	*P* Value
Subclinical hypothyroidism	Reference	1.21 (1.63-1.26)	0.210	0.80 (1.70-0.78)	0.430
Insulin resistance		0.92 (0.71-1.18)	0.500	0.98 (0.70-1.37)	0.900
Metabolic syndrome		0.77 (0.58-1.02)	0.070	0.61 (0.41-0.91)	0.010
Hypertriglyceridemia		0.79 (0.61-1.03)	0.090	0.94 (0.67-1.31)	0.700
Hypercholesterolemia		1.07 (0.78-1.47)	0.690	1.18 (0.78-1.76)	0.440
Prediabetes		0.79 (0.61-1.02)	0.070	0.58 (0.42-0.81)	<0.001
Type 2 diabetes		0.98 (0.69-1.38)	0.900	1.67 (1.11-2.51)	0.010
Obesity		0.78 (0.51-1.20)	0.260	0.84 (0.49-1.46)	0.540
Hyperuricemia		1.87 (1.20-2.93)	<0.010	2.75 (1.64-4.62)	<0.001
Low HDL cholesterol		1.04 (0.79-1.37)	0.770	1.17 (0.82-1.67)	0.390
Arterial hypertension		0.77 (0.57-1.03)	0.070	0.49 (0.33-0.74)	<0.001

CHD = congenital heart disease; HDL = high-density lipoprotein.

DISCUSSION

This study examines the clinical and metabolic characteristics of Mexican patients with ACHD with variable lesion complexity. We found a high prevalence of cardiometabolic risk factors among ACHD patients, with distinct risk profiles based on lesion complexity. It is noteworthy that longer survival in those with mild to moderate forms of ACHD, likely contribute to that higher levels of cardiometabolic risk factors, such as hypertension, T2D, and dyslipidemias that are linked with CVD.[28] This association is consistent with prior research outside of Mexico, reinforcing the necessity for a multidisciplinary management approach to enhancing cardiovascular and metabolic health.

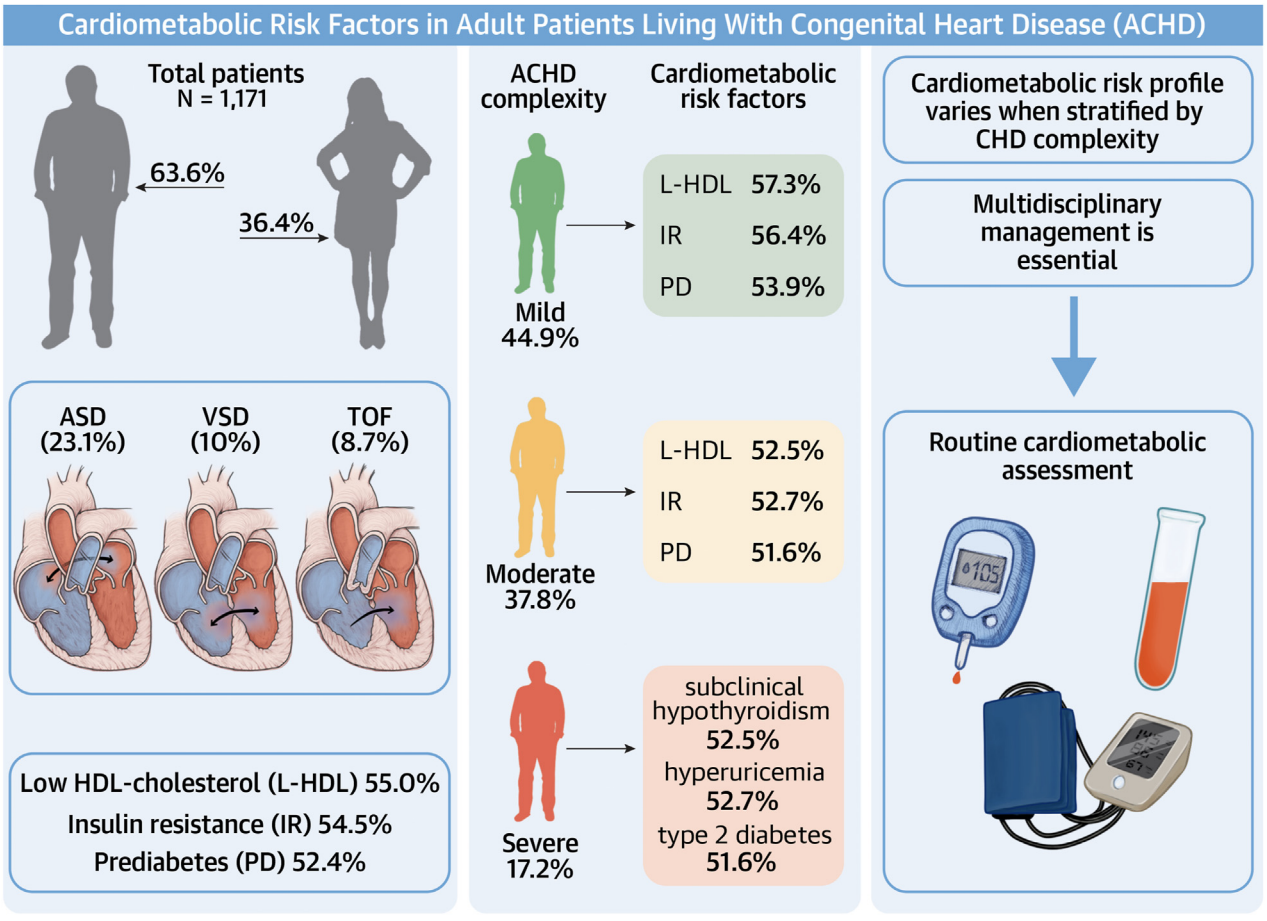
THE UNIQUE PROFILE OF MEXICAN ACHD PATIENTS. ACHD in our population displayed unique trends. Male prevalence and a median age of 31 were observed, aligning with findings from previous research. Epidemiologically, the presentation of CHD in our cohort mirrored those observed in other ACHD populations.[12,17] Interestingly, our population demonstrated a significantly higher prevalence of severe CHD compared to global reports (10%-15%).[1]

In terms of lifestyle habits, only a third of the patients reported regular physical activity, likely due to the traditionally prescribed physical activity restriction for CHD patients. Despite this, previous studies underline the positive outcomes of physical rehabilitation programs for such patients.[12,28] Notably, our study exhibited lower smoking incidence compared to others, largely attributed to resource scarcity affecting over 90% of our patient population.[29] This underlines the substantial influence socioeconomic factors hold over health behaviors.

CARDIOMETABOLIC RISK FACTORS RISK FACTORSIN MEXICAN ACHD PATIENTS. Assessing CVD risk factors has witnessed a steady rise over the past 3 decades.[30] Mexico is among the nations severely afflicted, with T2D prevalence progressively increasing from 14.4% in 2006,[31] 16.8% in 2018, to 15.7% in 2020.[32] When comparing metabolic disorders in ACHD patients with the broader Mexican population, we found an unexpected 20.4% prevalence of T2D in ACHD, surpassing previous reports. Additionally, our study detected a strikingly high prevalence of undiagnosed T2D (14.2%) compared to other studies,[33-35] possibly attributable to the significantly higher prediabetes rate (52.4%) detected in our cohort.

The higher prevalence of prediabetes and diabetes observed in our study compared to other countries may be attributed to several factors. These include a carbohydrate-rich diet, lack of physical activity, and a greater propensity to accumulate dysfunctional adipose tissue among Mexicans.[35,36] In line with these findings, insulin resistance levels were significantly higher in our overall population (54.5%) compared to the reported prevalence in the general Mexican population (39.7%).[37] This suggests a potential association between CHDs and an increased risk of insulin resistance. However, further studies are needed to confirm this relationship. In our study, the TG/HDL index was utilized as a surrogate marker of insulin resistance, as it has been previously used in the Mexican population.[38] Bello-Chavolla et al[39] reported on the diagnostic performance of the TG/HDL index

CENTRAL ILLUSTRATION **Cardiometabolic Risk Factors in 1,171 Mexican Adult Patients Living With Congenital Heart Disease**



García-Cruz E, et al. JACC Adv. 2023;2(8):100596.

ACHD = adult congenital heart disease; CHD = congenital heart disease; HDL = high-density lipoprotein.

for detecting impaired insulin sensitivity, further supporting its utility in assessing insulin resistance in Mexican population. It is important to note that the predictability of the TG/HDL-C ratio as a surrogate marker for insulin resistance is influenced by ethnic and genetic variations in the TG/HDL-C ratio.[40] Nevertheless, studies conducted in the Mexican population have consistently shown that a cutoff value >2.5 is associated with metabolic syndrome, obesity, insulin resistance, and prediabetes.[41]

Our study revealed a higher prevalence of obesity (30.3%) in ACHD patients compared to prior studies.[42] However, this figure is marginally higher when compared to the general population as reported by ENSANUT 2018.[9] Also, it was found that metabolic syndrome was diagnosed in 28.2% of our patients, which is more frequent in patients with mild CHD and higher than other studies but lower than the overall Mexican population.[9,12,43] Similarly, the occurrence of subclinical hypothyroidism in our patients was significantly higher (25.1%) than that reported in the literature (10%), especially in those with moderate and severe complexity.[33,44,45] These patients have been observed to have improved functional classes and decreased cardiovascular risk with the early initiation of treatment.[23,33,44,45]

ACHD LESION COMPLEXITY AND CARDIOMETABOLIC RISK FACTORS. When stratifying cardiometabolic risk factors according to CHD complexity, it was observed that patients with mild CHD have a higher prevalence

of obesity and metabolic syndrome, likely due to their longer life expectancy.[36,46] In CHD of moderate and mild complexity, an apparent increase in odds of developing metabolic syndrome and arterial hypertension was observed. However, this finding could be biased toward the higher life expectancy observed in these patients, while patients with severe CHD do not achieve these complications because of earlier mortality. Furthermore, an additional analysis was performed, unveiling the main driving factors of this association, benign hypoalphalipoproteinemia the first, followed by hypertriglyceridemia and arterial hypertension. Conversely, we found that patients with moderate and severe CHD were more likely to develop hyperuricemia, which correlates with chronic cyanosis and reduced renal elimination of uric acid. It has been mentioned that hyperuricemia is considered a biomarker of severity in these patients and correlates negatively with the cardiac index.[47] Overall, ACHD living with chronic cyanosis often experience multisystemic disease, with kidney injury being a common complication associated with CHD.[48] Nevertheless, our results show no significant association between increased CHD complexity and kidney disease.

STRENGTHS AND LIMITATIONS. This study is a pioneering effort in Latin America, providing a large, pragmatic, and comprehensive analysis of a large sample of ACHD patients living in Mexico, setting it apart from previous studies relying on estimations from systematic reviews. However, there are some limitations to consider. First, being a cross-sectional study, it is subject to inherent biases. Secondly, using BMI as a proxy for waist circumference in diagnosing metabolic syndrome may introduce limitations, as it may not capture the ectopic accumulation of dysfunctional adiposity. A third limitation is the variation in blood pressure measurements due to different operators and instruments used, potentially leading to measurement bias. Fourth, a survival bias could also influence the association between severe CHD and arterial hypertension and metabolic syndrome, potentially portraying severity as a protective factor. Fifth, the study's diagnostic protocol for subclinical hypothyroidism using a single measurement of TSH without repeated measurements or anti-thyroperoxidase antibody determination is a limitation. Finally, our study was conducted in a third-tier referral center which could derive in a lack of generalizability to other sociocultural contexts in Mexico and Latin America, which should be acknowledged as another limitation.

CONCLUSIONS

In this cross-sectional study of Mexican ACHD patients, we observed a high prevalence of low HDL cholesterol, insulin resistance, and prediabetes. Obesity, metabolic syndrome, and insulin resistance were more frequent in our subgroup of patients with ACHD lesions of mild complexity, while hyperuricemia and subclinical hypothyroidism were more prevalent in patients with moderate and severe ACHD lesion complexity. While survival in the ACHD population has progressively improved, this has resulted in older patients and the development of cardiovascular risk factors. As exposed in the **Central Illustration**, ongoing surveillance and management is necessary in order to improve cardiovascular and metabolic health in this population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: An ACHD specialized cardiologist should be proficient in diagnosing and effectively managing additional comorbidities that may accompany the primary diagnosis, such as T2D, HTN, metabolic syndrome, and other related conditions.

TRANSLATIONAL OUTLOOK: With the increased lifespan of individuals with CHD, it is imperative to take into account the potential complications arising from both the underlying heart condition and its treatment, as well as the added risk factors related to cardiometabolic health.

WHAT IS NEXT? Considering the significant proportion of metabolic disorders in this population, we should focus on prospective studies on prevention, prompt detection, treatment, and cardiovascular outcomes in ACHD.

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KEY WORDS adult congenital heart disease, cardiometabolic risk factors, hyperuricemia, insulin resistance, type 2 diabetes

APPENDIX For supplemental tables and figures, please see the online version of this paper.