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Original Article

Sex Differences in Outcomes of Adults With Isolated Coarctation of the Aorta

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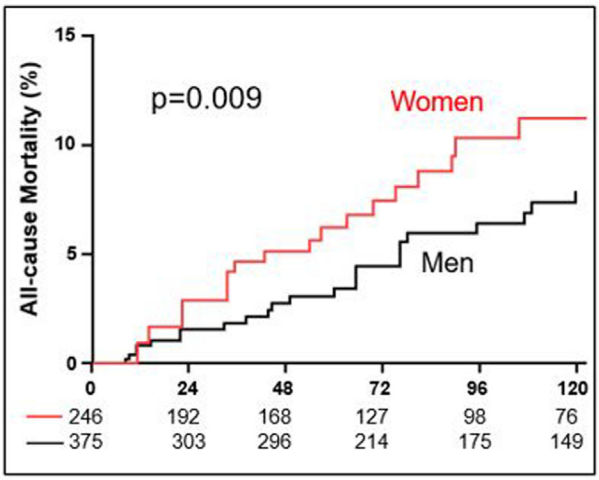

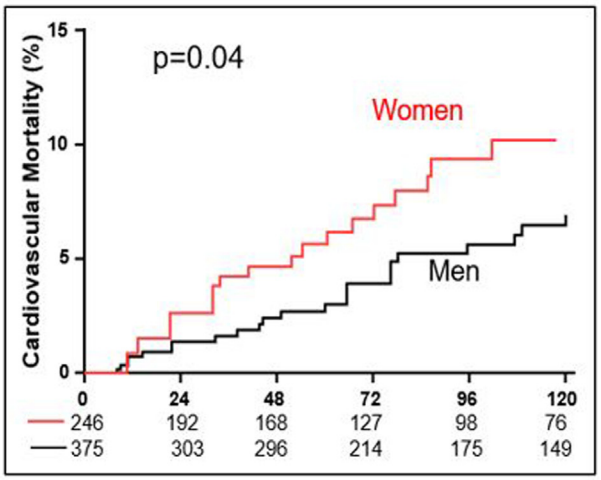

ABSTRACT

Background: Data are limited about the effect (or lack thereof) of sex on clinical outcomes in adults with coarctation of the aorta (COA). The purpose of this study was to compare atherosclerotic cardiovascular disease (ASCVD) risk profile, blood pressure (BP) data, echocardiographic indices, and mortality between men and women with COA.

Methods: Retrospective study of adults with COA, and no associated left-sided obstructive lesions, who received care at Mayo Clinic (2003-2022). ASCVD risk profile was assessed as the prevalence of hypertension, hyperlipidemia, type 2 diabetes, obesity, smoking history, and coronary artery disease. A 24-hour BP monitor was used to assess daytime and nighttime BP and calculate nocturnal dipping.

Results: Of 621 patients with isolated COA, 375 (60%) were men, and 246 (40%) were women. Women had similar ASCVD risk profile and daytime BP as men. However, women had less nocturnal dipping (7 ± 5 mm Hg vs 16 ± 7 mm Hg, $P < 0.001$), higher pulmonary artery mean pressure (23 mm Hg [interquartile range: 16-31] vs 20 mm Hg [interquartile range: 15-28], $P = 0.04$), and higher pulmonary vascular resistance index (3.41 ± 1.14 WU · m^2 vs 3.02 ± 0.76 WU · m^2, $P =$

RÉSUMÉ

Contexte : Il existe peu de données sur l'issue clinique en fonction du sexe chez les adultes présentant une coarctation de l'aorte (CoA). Le but de cette étude consistait donc à comparer le profil de risque de maladie cardiovasculaire athéroscléreuse (MCVAS), les données relatives à la pression artérielle (PA), les indices échocardiographiques et le taux de mortalité chez des hommes et des femmes présentant une CoA.

Méthodologie : Il s'agissait d'une étude rétrospective réalisée chez des adultes présentant une CoA en l'absence de lésions obstructives gauches, soignés à la clinique Mayo entre 2003 et 2022. Le profil de risque de MCVAS a été évalué en fonction de la prévalence de l'hypertension, de l'hyperlipidémie, du diabète de type 2, de l'obésité, des antécédents tabagiques et de la coronaropathie. Une surveillance sur 24 heures a été utilisée pour évaluer la PA diurne et nocturne, en plus de calculer la chute nocturne de la PA.

Résultats : Parmi les 621 patients présentant une CoA isolée, 375 (60 %) étaient des hommes et 246 (40 %) étaient des femmes. Les femmes présentaient une PA diurne et un profil de risque de MCVAS

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0.006). Female sex was associated with all-cause mortality (adjusted hazard ratio 1.26, 95% confidence interval 1.04-1.94) and cardiovascular mortality (adjusted hazard ratio 1.38, 95% confidence interval 1.09-2.18).

Conclusions: Women had a higher risk of both cardiovascular mortality and all-cause mortality compared to the risks in men. This difference may be related to the higher-than-expected ASCVD risk factors, abnormal nocturnal blood pressure, and pulmonary hypertension observed in women in this cohort. Further studies are required to identify optimal measures to address these risk factors.

semblables aux hommes. Elles présentaient néanmoins une chute nocturne de la PA moins prononcée (7 ± 5 mmHg *vs* 16 ± 7 mmHg, $p < 0{,}001$), une pression artérielle pulmonaire moyenne plus haute (23 mmHg [max.-min. : 16-31] *vs* 20 mmHg [max.-min. : 15-28], $p = 0{,}04$) et un indice de résistance vasculaire pulmonaire plus élevé (3,41 ± 1,14 UW · m^2 *vs* 3,02 ± 0,76 UW · m^2, $p = 0{,}006$). Le sexe féminin a été associé à un plus fort taux de mortalité toutes causes confondues (rapport de risques ajusté : 1,26; intervalle de confiance à 95 % : 1,04-1,94) et de mortalité cardiovasculaire (rapport de risques ajusté : 1,38; intervalle de confiance à 95 % : 1,09-2,18).

Conclusions : Les femmes sont exposées à un risque de mortalité cardiovasculaire et de mortalité toutes causes confondues plus élevé que les hommes. Cette différence pourrait être attribuable au rôle plus important que prévu joué par les facteurs de risque de MCVAS ainsi qu'à la pression artérielle nocturne anormale et à l'hypertension pulmonaire chez les femmes de cette cohorte. D'autres études sont nécessaires pour savoir quels seraient les paramètres optimaux qui permettraient d'évaluer ces facteurs de risque.

Coarctation of the aorta (COA) is the primary diagnosis in 8%-10% of adults with congenital heart disease.[1-3] In spite of significant improvements in medical, transcatheter, and surgical therapies for COA, adults with COA have a significantly shorter lifespan, compared to that in the general population, with a life expectancy of approximately 55 years in the current era.[1,3-5] The suboptimal long-term outcome in this population is attributed to the high prevalence of comorbidities, such as hypertension and coronary artery disease, in patients with COA.[6-10]

Several studies have described the hemodynamics, comorbidities, risk stratification models, and outcomes of adults with COA.[4,5,11] However, whether clinical outcomes in patients with COA differ between men and women is unknown. This knowledge gap is important, because identifying sex-related differences in disease pathophysiology and outcomes would improve risk stratification, and allow tailoring of interventions to address the risk profile of the different groups. The purpose of this study was to compare clinical characteristics, cardiac remodelling indices, and outcomes between men and women presenting with isolated COA.[12]

Methods

Study population

This retrospective study is of adults (age ≥ 18 years) with isolated COA who received care at Mayo Clinic, Rochester, Minnesota, between January 1, 2003, and December 31, 2022. Isolated COA was defined as the absence of concomitant left ventricular (LV) outflow tract disease or LV inflow disease. Similar to definitions in previous studies,[13] LV outflow tract disease was defined as presence of any of the following conditions: aortic valve prosthesis, subvalvular and/or valvular and/or supravalvular aortic stenosis (aortic valve Doppler-derived peak velocity > 3 m/s) or ≥ moderate aortic regurgitation. LV inflow disease was defined as presence of any of the following conditions: mitral valve prosthesis, subvalvular and/or valvular and/or supravalvular mitral stenosis (mean gradient > 3 mm Hg) or ≥ moderate mitral regurgitation. The rationale for excluding these patients was to control for the confounding effect of concomitant left-sided structural heart disease on cardiac remodelling and outcome.

The first clinical ncounterr in the adult congenital heart disease clinic within the study period was considered the baseline encounter. Clinic notes, echocardiograms, cross-sectional imaging, exercise tests, and cardiac catheterization reports obtained within 12 months from the baseline encounter were reviewed and were used to define the baseline characteristics of the cohort. The COA cohort was further categorized as having either repaired or native COA, depending on whether they had an initial COA repair prior to the baseline encounter.

Study objectives

The 5 study objectives were as follows: The first was to compare the atherosclerotic cardiovascular disease (ASCVD) risk profile between men and women. ASCVD risk profile was assessed as the prevalence of hypertension, hyperlipidemia, type 2 diabetes, obesity, smoking history, and coronary artery disease. The second was to compare blood pressure (BP) data (office BP, ambulatory BP, and exercise BP) between men and women. Nocturnal dipping, which is the expected nocturnal decrease in nighttime systolic BP, was calculated as the average daytime systolic BP minus the average nighttime systolic BP on a 24-hour ambulatory BP measurement.[14] Exercise-induced hypertension was defined as systolic BP at peak exercise > 210 mm Hg in men or > 190 mm Hg in women.[15] The third objective was to compare invasive (cardiac catheterization) and noninvasive (echocardiographic) indices between men and women. The fourth was to compare thoracic aorta indices between men and women. Thoracic aorta indices were derived

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See page 766 for disclosure information.

Table 1. Baseline characteristics

Characteristic	All (N = 621)	Men (n = 375; 60%)	Women (n = 246; 40%)	*P*
Demographic/anatomic indices				
Age, y	33 (22−46)	33 (20−48)	33 (21−47)	0.7
Bicuspid aortic valve	378 (61)	243 (65)	135 (55)	0.004
Body mass index, kg/m^2	27.0 ± 5.6	27.2 ± 5.3	26.6 ± 5.9	0.06
Body surface area, m^2	1.93 ± 0.27	2.04 ± 23	1.74 ± 0.22	< 0.001
Native COA at baseline encounter	62 (10)	44 (11)	18 (7)	0.07
Repaired COA at baseline encounter	559 (90)	331 (88)	228 (93)	0.07
Age of initial COA repair, y	4.5 (0.8−9.4)	4.5 (0.8−9.7)	4.1 (0.7−9.2)	0.5
# COA interventions prior to baseline	1 (1−3)	1 (1−3)	1 (1−2)	0.8
Atrial arrhythmias				
Atrial fibrillation	47 (8)	34 (9)	13 (5)	0.08
Atrial flutter and/or tachycardia	11 (2)	6 (2)	5 (2)	0.7
Medications				
Beta-blockers	255 (41)	155 (41)	100 (41)	0.9
Calcium-channel blockers	101 (16)	70 (19)	31 (13)	0.05
Diuretics	85 (14)	48 (13)	37 (15)	0.9
ACEI/ARB	241 (39)	168 (45)	73 (30)	< 0.001
Mineralocorticoid antagonist	14 (2)	5 (1)	9 (4)	0.06
Antiplatelet therapy	172 (28)	111 (30)	61 (25)	0.2
NYHA functional class				0.8
I	494 (80)	300 (80)	194 (79)	
II	87 (14)	54 (14)	33 (13)	
III−IV	40 (11)	21 (9)	19 (3)	
Exercise data	(n = 334; 54%)	(n = 191; 51%)	(n = 143; 58%)	
Exercise time, min	7.9 ± 2.6	8.5 ± 2.6	6.8 ± 2.3	< 0.001
Peak VO_2, mL/kg/min	26.9 ± 8.7	28.5 ± 7.4	23.3 ± 7.4	< 0.001
Predicted peak VO_2, %	70 ± 17	72 ± 16	69 ± 16	0.7

Values were expressed as mean ± standard deviation for continuous variables with normal distribution, median (interquartile range) for continuous variables with skewed distribution, and count (%) for categorical variables. The *P* values were derived from between-group comparisons using the unpaired *t* test for continuous variables with normal distribution, the Wilcoxon rank-sum test for continuous variables with skewed distribution, and the χ^2 test for categorical variables.

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; COA, coarctation of the aorta; NYHA, New York Heart Association; VO_2, volume of oxygen consumption.

from cross-sectional imaging. The aortic isthmus ratio was defined as the ratio of aortic isthmus dimension to descending aorta dimension at the level of the diaphragm.[9,16] Hypoplastic aortic arch was defined as the ratio of the distal transverse arch dimension to descending aorta measured at the level of the diaphragm ≤ 0.5.[9,16] The fifth objective was to compare the risk of all-cause mortality and cardiovascular mortality between men and women. Cardiovascular mortality was defined as death due to heart failure, myocardial infarction, arrhythmic and/or sudden cardiac death, cardiovascular hemorrhage and/or stroke, or cardiovascular procedures.[17] Mortality was assessed as a time-to-event outcome using the time of the baseline encounter as time zero. Mortality events were obtained from the medical records, and they were verified using the Accurint database (Mayo Clinic, Rochester, MN), an institutional approved mortality reporting system. The patients who were alive throughout the study period were censored on December 31, 2022.

Statistical analysis

Data were presented as mean ± standard deviation, median (interquartile range [IQR]), or count (%). Between-group comparisons were performed using the unpaired *t* test for continuous variables with normal distribution, the Wilcoxon rank-sum for continuous variables with skewed distribution, and the χ^2 test for categorical variables. The 10-year cumulative incidence of all-cause and cardiovascular mortality was estimated using the Kaplan-Meier method, and comparisons were made using the log-rank test. The relationship between sex and mortality was assessed using Cox regression. The Cox models were adjusted for the following: demographic indices (age, bicuspid aortic valve, COA repair status, age of initial COA repair, and subsequent COA intervention after baseline evaluation); ASCVD risk profile; atrial arrhythmia history; office BP (systolic and diastolic BP); echocardiographic indices (COA Doppler mean gradient, LV mass index, LV global longitudinal strain, right ventricular [RV] free wall strain, and RV systolic pressure); and use of cardiac medications (renin-angiotensin-aldosterone system antagonist and calcium-channel blockers). The final covariate selection was based on stepwise backward selection, and only the covariates with $P < 0.1$ remained in the final model. All statistical analyses were performed with BlueSky Statistics (Chicago, IL) software (version. 7.10) and JMP Statistical Discovery (SAS Institute Inc., Cary, NC) software (version 17.1.0). A *P* value < 0.05 was considered to be statistically significant for all analyses.

Results

Baseline characteristics

Of the 621 patients with isolated COA, 559 (90%) had COA repair prior to the baseline encounter, and 378 (61%) had bicuspid aortic valve. A total of 375 of the patients (60%) were men, and 246 (40%) were women. Table 1 shows a

Table 2. Atherosclerotic cardiovascular disease (ASCVD) and blood pressure (BP) data

ASCVD risk factors	All (N = 621)	Men (n = 375; 60%)	Women (n = 246; 40%)	*P*
Hypertension	342 (55)	218 (58)	124 (50)	0.06
Coronary artery disease	43 (7)	26 (7)	16 (7)	0.8
Diabetes	30 (5)	21 (6)	9 (4)	0.3
Hyperlipidemia	124 (20)	81 (22)	43 (18)	0.1
Obesity	175 (28)	110 (29)	65 (26)	0.4
Current and/or prior smoker	100 (16)	69 (18)	31 (13)	0.06
BP data, mm Hg	**All (N = 621)**	**Men (n = 375; 60%)**	**Women (n = 246; 40%)**	***P***
Office BP				
Systolic BP	129 ± 22	132 ± 21	124 ± 18	0.1
Diastolic BP	73 ± 13	74 ± 13	72 ± 14	0.2
Pulse pressure	56 ± 19	58 ± 21	53 ± 18	0.2
ULE systolic BP gradient	12 (2−21)	11 (0−22)	10 (2−26)	0.3
Heart rate, bpm	72 ± 14	73 ± 23	76 ± 15	0.3
Ambulatory BP				
Daytime systolic BP	138 ± 29	141 ± 31	136 ± 22	0.1
Daytime diastolic BP	78 ± 12	79 ± 15	78 ± 12	0.7
Daytime pulse pressure	60 ± 24	63 ± 29	58 ± 21	0.1
Nighttime systolic BP	127 ± 18	125 ± 16	129 ± 11	0.3
Nighttime diastolic BP	69 ± 12	65 ± 10	71 ± 8	0.1
Nighttime pulse pressure	58 ± 26	60 ± 22	58 ± 29	0.5
24-h systolic BP	130 ± 22	133 ± 25	128 ± 15	0.1
Nocturnal dipping*	11 ± 6	16 ± 7	7 ± 5	< 0.001
24-h diastolic BP	74 ± 9	74 ± 8	73 ± 9	0.7
24-h pulse pressure	56 ± 17	59 ± 20	54 ± 16	0.08
Exercise BP				
Systolic BP at rest	124 ± 18	126 ± 17	120 ± 19	0.8
Diastolic BP at rest	74 ± 11	74 ± 10	73 ± 11	0.9
Pulse pressure at rest	50 ± 14	52 ± 13	47 ± 12	0.7
Systolic BP at peak exercise	180 ± 54	187 ± 63	164 ± 39	< 0.001
Diastolic BP at peak exercise	67 ± 14	67 ± 13	66 ± 14	0.8
Pulse pressure at peak exercise	113 ± 56	120 ± 59	94 ± 51	0.006
Exercise-induced hypertension†	149 (24)	92 (26)	57 (23)	0.2

Values are expressed as mean ± standard deviation for continuous variables with normal distribution, median (interquartile range) for continuous variables with skewed distribution, and count (%) for categorical variables. The *P* values were derived from between-group comparisons using the unpaired *t* test for continuous variables with normal distribution, the Wilcoxon rank-sum test for continuous variables with skewed distribution, and the χ^2 test for categorical variables.

bpm, beats per minute; ULE, upper-to-lower extremity.

*Nocturnal dipping was defined as the difference between the averaged daytime systolic BP and the averaged nighttime systolic BP.

†Exercise-induced hypertension was defined as systolic BP at peak exercise > 210 mm Hg (for men) or > 190 mm Hg (for women).

comparison of the baseline characteristics between men and women. Women had smaller body surface area than did the men (1.74 ± 0.22 vs 2.04 ± 23 m^2, $P < 0.001$), and they were less likely to have bicuspid aortic valve (55% vs 65%, $P = 0.004$). No significant between-group difference was present in atrial arrhythmia history, or New York Heart Association functional class (Table 1). Although women had a shorter exercise time (6.8 ± 2.3 vs 8.5 ± 2.6 minutes, $P < 0.001$), both groups had similar aerobic capacity (predicted peak oxygen consumption of 69% ± 16% vs 72% ± 16% for women and men, respectively, $P = 0.7$; Table 1).

Outcomes

ASCVD risk profile and BP data. Table 2 shows a comparison of ASCVD risk profile and BP data between men and women. No significant between-group differences were present in ASCVD risk factors and office BP data between men and women. Although no significant between-group difference was present in daytime or nighttime BP data, women had less nocturnal dipping than men (7 ± 5 mm Hg vs 16 ± 7 mm Hg, $P < 0.001$). Systolic BP at peak exercise was higher in men than in women (187 ± 63 mm Hg vs 164 ± 39 mm Hg, respectively, $P < 0.001$), but the proportions of patients with exercise-induced hypertension were similar in the 2 groups (26% vs 23%, for men and women, respectively, $P = 0.2$; Table 2).

Hemodynamic indices. Table 3 shows the invasive and noninvasive hemodynamic indices for the cohort. Compared to women, men had larger LV end-diastolic volume (65 ± 27 mL/m^2 vs 53 ± 16 mL/m^2, $P < 0.001$), LV end-systolic volume (25 ± 17 mL/m^2 vs 20 ± 11 mL/m^2, $P < 0.001$), and LV stroke volume (50 ± 14 mL/m^2 vs 44 ± 12 mL/m^2, $P = 0.04$). Although LV mass index was higher in men than in women (108 ± 26 g/m^2 vs 90 ± 22 g/m^2, $P < 0.001$), the prevalence of LV hypertrophy was similar in the 2 groups (31% vs 30%, for men and women, respectively, $P = 0.7$). Women had a higher estimated RV systolic pressure (37 ± 11 mm Hg vs 31 ± 9 mm Hg, $P = 0.02$) and a lower absolute value of RV free wall strain (-26 ± 4 mm Hg vs -29 ± 5 mm Hg, $P = 0.01$).

Of the 621 patients, 133 (21%) underwent cardiac catheterization. Compared to men, women had higher pulmonary artery pressures (pulmonary artery mean pressure 23 mm Hg [IQR 16-31] vs 20 mm Hg [IQR 15-28], $P = 0.04$) and a higher pulmonary vascular resistance index (3.41 ± 1.14 WU · m^2 vs

Table 3. Echocardiographic, thoracic aorta, and invasive hemodynamic data

Echocardiography	All (N = 621)	Men (n = 375; 60%)	Women (n = 246; 40%)	*P*
Left heart indices				
LA reservoir strain, %	39 ± 13	40 ± 13	38 ± 14	0.2
LA volume index, mL/m^2	29 ± 11	28 ± 11	28 ± 22	0.7
LV end-diastolic volume index, mL/m^2	60 ± 24	65 ± 27	53 ± 16	< 0.001
LV end-systolic volume index, mL/m^2	23 ± 15	25 ± 17	20 ± 11	< 0.001
LV ejection fraction, %	62 ± 8	62 ± 9	63 ± 7	0.4
LV global longitudinal strain, %	21 ± 3	21 ± 3	21 ± 2	0.9
LV mass index, g/m^2	101 ± 27	108 ± 26	90 ± 22	< 0.001
LV hypertrophy	191 (31)	74 (30)	117 (31)	0.7
Septal E/e'	11.5 ± 5.6	11.3 ± 5.7	11.7 ± 5.3	0.2
Lateral E/e	8.8 ± 4.2	8.5 ± 4.1	9.0 ± 4.3	0.09
LV stroke volume index, mL/m^2	48 ± 14	50 ± 14	46 ± 12	0.04
Cardiac index, L/min/m^2	3.29 ± 0.84	3.32 ± 0.84	3.24 ± 0.81	0.2
Aortic valve mean gradient, mm Hg	8 ± 4	8 ± 4	8 ± 3	0.7
COA Doppler mean gradient, mm Hg	14 (9–21)	14 (9–20)	14 (10–22)	0.5
COA Doppler peak gradient, mm Hg	19 (10–31)	19 (10–30)	19 (11–36)	0.5
Right heart indices				
RA pressure, mm Hg	6 ± 2	6 ± 2	7 ± 3	0.5
RA volume index, mL/m^2	24 ± 10	25 ± 10	22 ± 9	0.3
RA reservoir strain, %	45 ± 16	46 ± 15	44 ± 14	0.4
RV free wall strain, %	-28 ± 6	-29 ± 5	-26 ± 4	0.01
RV fractional area change, %	45 ± 8	46 ± 7	43 ± 9	0.1
RV end-diastolic area, cm^2/m^2	11.8 ± 2.8	11.3 ± 1.8	10.9 ± 2.1	0.06
RV end-systolic area, cm^2/m^2	6.2 ± 2.4	6.4 ± 2.2	5.8 ± 2.1	0.07
≥ Moderate tricuspid regurgitation	20 (3)	11 (3)	9 (4)	0.6
RVSP, mm Hg	33 ± 13	31 ± 9	37 ± 11	0.03
CT/CMRI: Thoracic aorta indices	(n = 482; 78%)	(n = 298; 80%)	(n = 184; 76%)	
Aortic root diameter, mm	35 ± 6	37 ± 6	31 ± 6	< 0.001
Proximal aorta diameter, mm	32 ± 6	33 ± 7	31 ± 6	0.01
Mid aorta diameter, mm	31 ± 7	32 ± 6	30 ± 6	0.02
Distal aorta diameter, mm	25 ± 8	25 ± 9	23 ± 7	0.5
Proximal arch diameter, mm	26 ± 6	27 ± 6	25 ± 5	0.2
Distal arch diameter, mm	19 ± 4	19 ± 4	19 ± 3	0.7
Aortic isthmus diameter, mm	14 ± 3	15 ± 4	13 ± 3	0.01
Desc aorta at level of diaphragm, mm	21 ± 5	22 ± 6	19 ± 4	0.009
Aortic isthmus ratio*	0.67 ± 0.19	0.68 ± 0.22	0.67 ± 20	0.8
Hypoplastic aortic arch†	37 (6)	23 (6)	14 (6)	0.9
Invasive hemodynamic indices	(n = 133; 21%)	(n = 86; 23%)	(n = 47; 19%)	
RA mean pressure, mm Hg	8 ± 4	8 ± 4	9 ± 5	0.3
PA mean pressure, mm Hg	22 (17–29)	20 (15–28)	23 (16–31)	0.04
PA wedge pressure, mm Hg	13 (10–17)	13 (9–17)	13 (11–17)	0.3
LV end-diastolic pressure, mm Hg	16 (13–20)	16 (14–20)	15 (12–20)	0.7
Ascending aorta systolic pressure, mm Hg	130 ± 27	132 ± 26	127 ± 21	0.4
Ascending aorta mean pressure, mm Hg	83 ± 13	84 ± 12	79 ± 15	0.2
Ascending aorta diastolic pressure, mm Hg	65 ± 12	66 ± 9	63 ± 16	0.2
Descending aorta systolic pressure, mm Hg	102 ± 19	103 ± 18	102 ± 5	0.9
COA peak-to-peak gradient, mm Hg	27 ± 9	29 ± 8	25 ± 14	0.1
Cardiac index, L/min/m2	2.85 ± 0.86	2.89 ± 94	2.82 ± 1.01	0.8
PVR index, WU · m^2	3.14 ± 0.92	3.02 ± 0.76	3.41 ± 1.14	0.006
SVR index, WU · m^2	21.4 ± 4.3	20.8 ± 5.3	22 ± 4.6	0.4

Values are expressed as mean ± standard deviation for continuous variables with normal distribution, median (interquartile range) for continuous variables with skewed distribution, and count (%) for categorical variables. The *P* values were derived from between-group comparisons using the unpaired *t* test for continuous variables with normal distribution, the Wilcoxon rank-sum test for continuous variables with skewed distribution, and the χ^2 test for categorical variables. LV hypertrophy was defined as LV mass index > 115 g/m^2 in men and > 95 g/m^2 in women.

COA, coarctation of the aorta; CT/CMRI, computer tomography/cardiac magnetic resonance imaging; Desc, descending; E/e', ratio of mitral inflow pulse wave Doppler early velocity to tissue Doppler early velocity; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle; RVSP, right ventricular systolic pressure; SVR, systemic vascular resistance.

*Theaortic isthmus ratio was defined as the ratio of aortic isthmus dimension to descending aorta dimension at the level of the diaphragm.

†Hypoplastic aortic arch was defined as the ratio of the distal transverse arch dimension to descending aorta measured at the level of the diaphragm ≤ 0.5. N signifies the total number of patients; n signifies the number of patients with available data.

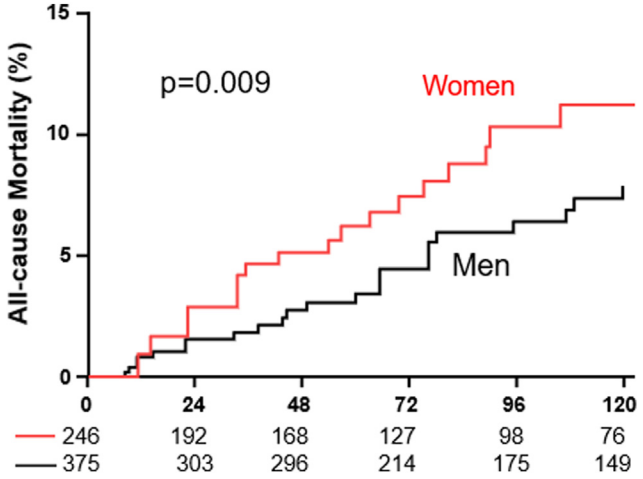

Figure 1. Kaplan-Meier curves comparing all-cause mortality in women (**red**) vs men (**black**). The *P* value was derived from the log-rank test.

3.02 ± 1.72 WU · m^2, $P = 0.006$). Other invasive hemodynamic indices were similar between the 2 groups (Table 3).

Thoracic aortic indices. Compared to women, men had a larger aortic root diameter (37 ± 6 mm vs 31 ± 6 mm, $P < 0.001$), a larger proximal ascending aorta diameter (33 ± 6 mm vs 31 ± 6 mm, $P = 0.01$), and a larger mid ascending aorta diameter (32 ± 6 mm vs 30 ± 6 mm, $P = 0.02$; Table 3). However, these between-group differences were no longer significant after adjusting for body surface area (aortic root diameter 18.5 ± 2.9 mm/m^2 vs 18.2 ± 3.1 mm/m^2, $P = 0.2$; proximal ascending aorta diameter 16.5 ± 2.9 mm/m^2 vs 17.2 ± 3.1 mm/m^2, $P = 0.1$; and mid ascending aorta diameter 16.4 ± 2.7 mm/m^2 vs 16.7 ± 2.9 mm/m^2, $P = 0.2$; Table 3). Similarly, no significant between-group differences were present in the aortic isthmus ratio (0.68 ± 0.22 vs 0.67 ± 20, $P = 0.8$, for men and women, respectively), or in the proportion of patients with hypoplastic aortic arch (6% vs 6%, $P = 0.8$, for men and women, respectively; Table 3).

Cardiovascular and all-cause mortality. Of the 621 patients, 56 patients (9%) died during a median follow-up of 8.3 years (range: 5.9-11.4), of whom 49 died from cardiovascular causes (end-stage heart failure, n = 36; myocardial infarction, n = 2; arrhythmic and/or sudden cardiac death, n = 4; endocarditis and/or sepsis, n = 4; cardiovascular hemorrhage and/or stroke-related deaths, n = 3; and postoperative death, n = 2). The median age at the time of death was lower in women compared to that in men (58 years [IQR 49-72] vs 66 years [IQR 59-78], $P = 0.02$).

The annual incidence of all-cause mortality was 1.16% per year (95% confidence interval [CI] 0.97%-1.32%). Women had a higher annual incidence of all-cause mortality than that of men (1.32% per year [95% CI 1.18%-1.46%] vs 0.93% per year [95% CI 0.91%-1.08%], $P = 0.006$), and a higher 10-year cumulative incidence of all-cause mortality (13% vs 9%, $P = 0.01$; Fig. 1). Similarly, women had a higher annual incidence of cardiovascular mortality (1.12% per year [95% CI 0.98%-1.22%] vs 0.79% per year [95% CI 0.83%-

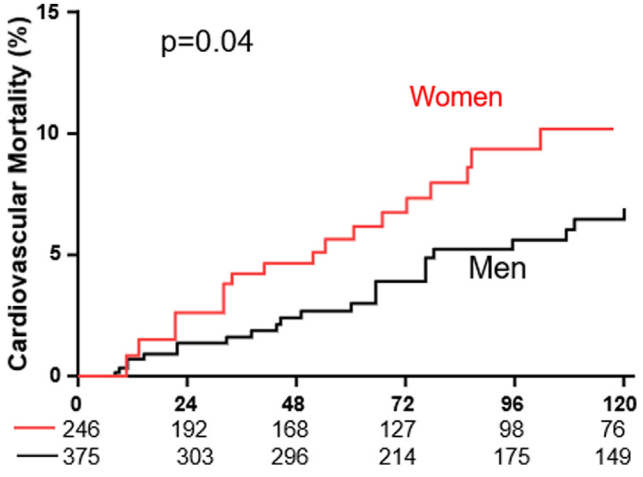

Figure 2. Kaplan-Meier curves comparing cardiovascular mortality in women (**red**) vs men (**black**). The *P* value was derived from the log-rank test.

Table 4. Multivariable Cox regression models for all-cause and cardiovascular mortality

	HR (95% CI) for all-cause mortality					
	Model A	Model B	Model C	Model D	Model E	Model F
Female sex	1.33 (1.14−1.92)	1.42 (1.16−2.03)	1.38 (1.10−1.91)	1.31 (1.09−1.86)	1.29 (1.08−2.06)	1.24 (1.02−1.85)
	HR (95% CI) for cardiovascular mortality					
	Model A	Model B	Model C	Model D	Model E	Model F
Female sex	1.49 (1.12−2.32)	1.47 (1.13−2.31)	1.45 (1.22−2.01)	1.42 (1.14−1.88)	1.36 (1.19−1.92)	1.33 (1.07−2.04)

Model A: unadjusted model. model B: Model adjusted for age, coarctation of aorta (COA) repair (native vs repaired), age of initial COA repair,* subsequent COA intervention during follow-up.† Model C: Models adjusted for covariates in model B + atherosclerotic cardiovascular disease (ASCVD) risk profile + Office blood pressure. Model D: Models adjusted for covariates in model C + atrial arrhythmia history. Model E: Models adjusted for covariates in model D + New York Heart Association (NYHA) functional class. Model F: Models adjusted for covariates in model E + echocardiographic indices (COA Doppler mean gradient, left ventricle (LV) global longitudinal strain, LV mass index, right ventricle (RV) free wall strain, RV systolic pressure) + use of renin-angiotensin-aldosterone system antagonist + use of calcium-channel blockers.

CI, confidence interval; HR, hazard ratio; LV, left ventricle; RV, right ventricle.

*The age of initial COA repair was coded as the age at the time of baseline evaluation for the patients that presented with native COA.

†Subsequent COA intervention during follow-up was modelled as a time-dependent covariate.

0.96%], $P = 0.01$), and a higher 10-year cumulative incidence of cardiovascular mortality (11% vs 8%, $P = 0.04$; Fig. 2). Overall, female sex was associated with incidence of all-cause mortality (adjusted hazard ratio 1.26, 95% CI 1.04-1.94) and cardiovascular mortality (adjusted hazard ratio 1.38, 96% CI 1.09-2.18; Table 4; Supplemental Tables S1 and S2).

Discussion

In this study, we compared the clinical characteristics and outcomes between men and women with COA, and assessed the relationship between sex and mortality in this population. The main findings are as follows: (i) Both groups had similar ASCVD risk profiles. (ii) Women had less nocturnal dipping on ambulatory BP measurement, but other BP indices were similar between the 2 groups. (iii) Women had worse right heart indices (RV systolic function, pulmonary artery pressures, and pulmonary vascular resistance). (iv) Women had higher adjusted risks of all-cause mortality and cardiovascular mortality.

Previous studies have described the incidence and risk factors associated with mortality in adults with COA.[3-5,18,19] Lee at al. reported a 5% mortality incidence in a cohort of 834 COA patients, and the average age at the time of death was 56 years.[5] Choudhary et al. reported a 6% mortality incidence in a cohort of 151 COA patients, and the average age at the time of death was 60 years.[4] Verheugt et al. reported a 1% mortality incidence in a cohort of 756 COA patients, and the average age at the time of death was 43 years.[20,21] In the current study, we observed a 9% mortality incidence, and the average age at the time of death was 63 years. We postulate that the higher mortality incidence in the current study may be related to the older age of the cohort, as evidenced by the lowest mortality incidence being observed in the studies with the youngest cohorts.[4,5,20,21] the current study also provides new insight into sex-based differences in outcomes in adults with COA. The higher risk of mortality observed in women can be explained by some of the findings from this study.

First, we observed a similar ASCVD risk profile for men vs women, and this similarity is different from the situation in the general population, in which the incidences of comorbidities such as hypertension and coronary artery disease are expected to be higher in men.[22] Hence, the higher-than-expected ASCVD risk factors in women in the current cohort may contribute to the higher risk of mortality observed in the current study. Furthermore, a smaller proportion of women were treated with renin-angiotensin-aldosterone system antagonists, compared to the proportion of men, even though the prevalence of hypertension was similar between the 2 groups. This observation is important, as renin-angiotensin-aldosterone system antagonists are associated with a lower risk of cardiovascular adverse events.[23] However, even after adjusting for differences in medical therapy, the current study showed a higher risk of both cardiovascular mortality and all-cause mortality in women, compared to those in men

Second, we observed less nocturnal BP dipping in women. The 24-hour ambulatory BP measure is not monophasic, but rather measures BP across 2 distinct phases of the circadian cycle, with daytime BP showing response during activities of daily living, and nighttime BP showing the expected nocturnal decrease during sleep.[24,25] The absence or blunting of nocturnal decline in systolic BP is associated with cardiovascular and all-cause mortality in the general population.[26,27] The cause of abnormal nocturnal dipping is not fully understood, but the dipping is attributed to arterial smooth muscle and endothelial dysfunction, and previous studies have shown that vascular dysfunction is more common in women.[26-28] We postulate that the blunted nocturnal dipping observed in women may contribute to the worse outcome in this group, as blunted nocturnal dipping has been shown to have a stronger correlation with cardiac remodelling and cardiovascular adverse events, as compared to daytime BP in the COA population.[14] This finding supports the guideline recommendation for routine ambulatory BP monitoring in patients with COA.

Third, women had higher RV systolic pressure and lower RV systolic function compared to those in men. The prevalence and prognostic implication of pulmonary hypertension and RV systolic dysfunction in adults with COA have been described.[13,29,30] Oliver et al. reported that 19% of adults with COA had pulmonary hypertension (defined in that series as Doppler-derived estimated RV systolic pressure > 40 mm Hg), and that pulmonary hypertension was associated with

mortality.[30] Previous studies based on the Mayo Clinic cohort yielded similar findings about the prevalence and prognostic implications of pulmonary hypertension and right heart dysfunction in COA.[13,29] The invasive hemodynamic indices presented in the current study suggest that the higher burden of pulmonary hypertension in women was more likely due to precapillary pulmonary hypertension, given the higher pulmonary vascular resistance index observed in women. We postulate that pulmonary hypertension and RV systolic dysfunction (both of which are known risk factors for mortality) may contribute to the adverse outcomes observed in women in the current study. Perhaps, a lower threshold for cardiac catheterization should be used in women with abnormal Doppler-derived RV systolic pressure, given the higher risk of precapillary pulmonary hypertension in this population. Further studies are required to determine whether these patients would benefit from pulmonary vasodilators.

Limitations

This is a single-centre retrospective study, and it is therefore prone to selection and ascertainment bias, and this may limit generalizability of the results. We did not have invasive hemodynamic data, ambulatory BP data, or data about the socioeconomic status of the patients, and hence, we could not adjust for these factors. Furthermore, although we adjusted for surgical history (native COA vs repaired COA), age of COA repair, and COA reintervention during follow-up, other residual confounders may be present that were not accounted for in the model.

Conclusions

Women had a higher risk of both all-cause mortality and cardiovascular mortality, compared to the risks in men, and this may be related to the higher-than-expected ASCVD risk factors in women, blunted nocturnal dipping in ambulatory BP, and worse pulmonary hypertension and RV systolic dysfunction in women. Further studies are required to determine whether preventive interventions, such as intensive ASCVD risk-factor modification, and use of pulmonary vasodilators for precapillary pulmonary hypertension, would improve clinical outcomes in this population.

Ethics Statement

The research adhered to relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. The study was based on a retrospective chart review.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2024.01.008.