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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Prognostic Value of the H_2FPEF Score in Adults With Repaired Coarctation of Aorta

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ABSTRACT

BACKGROUND Risk stratification is challenging in adults with repaired coarctation of aorta (COA) because of the complex interaction of multiple hemodynamic factors and differences in left ventricular adaptation to these factors. The H_2FPEF score was originally developed for differentiating between heart failure with preserved ejection fraction and noncardiac dyspnea, but it has been shown to be useful for prognostication in other cardiovascular pathologies.

OBJECTIVES The purpose of this study was to assess the prognostic role of the H_2FPEF score in adults with repaired COA.

METHODS This is a retrospective cohort study of adults with repaired COA at the Mayo Clinic (2003-2019). The H_2FPEF score was calculated at baseline and at 5-year follow-up. Cardiovascular events (heart failure hospitalization, transplant, or cardiovascular death) were ascertained from medical records.

RESULTS We identified 712 patients (age 33 years [range 21-45 years]; 419 [59%] males). The baseline H_2FPEF score was 2.2 $\pm$ 1.4. There was a temporal increase in the H_2FPEF score at 5 years (ΔH_2FPEF score 0.34 $\pm$ 0.11) due to the increase in the prevalence of hypertension, obesity, and high filling pressures. The H_2FPEF score correlated with left atrial volume ($r = 0.73$, $P < 0.001$), right atrial volume ($r = 0.41$, $P < 0.001$), right ventricular fractional area change ($r = -0.46$, $P < 0.001$), and left ventricular e' ($r = -0.52$, $P < 0.001$). Both the baseline H_2FPEF score and ΔH_2FPEF score were independently associated with cardiovascular events.

CONCLUSIONS These results suggest that the H_2FPEF score can be used for prognostication in patients with COA. The temporal increase in the H_2FPEF score was due to factors such as hypertension, obesity, and high filling pressures, and hence, it provides potential therapeutic targets to improve outcomes in this population. (JACC Adv 2022;1:100130)

Coarctation of aorta (COA) is characterized by chronic left ventricular (LV) pressure overload resulting from aortic isthmus stenosis, aortic arch hypoplasia, systemic hypertension due to increased aortic stiffness, and associated LV outflow tract lesions such as valvular and subvalvular aortic stenosis.[1-4] Chronic LV pressure overload leads to LV remodeling, and overtime, this results in LV hypertrophy and stiffness, impaired LV compliance, left atrial (LA) remodeling, as well as atrial fibrillation

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

COA = coarctation of aorta

HFpEF = heart failure with preserved ejection fraction

HR = hazard ratio

LA = left atrium

LV = left ventricle

RV = right ventricle

and heart failure.[5-12] Surgical and transcatheter interventions are effective for relieving LV pressure overload and preventing progressive LV remodeling and can sometime lead to LV reverse remodeling if performed prior to the onset of irreversible LV dysfunction.[7,13-16] However, determining the optimal time for such an intervention is challenging because of the complex interaction between multiple hemodynamic factors and differences in LV adaptation to them.[17]

In acquired heart disease, heart failure with preserved ejection fraction (HFpEF) accounts for half of all heart failure-related morbidities and mortality globally, and hence, it is a critical public health problem.[18] In spite of significant differences in the etiology and demographic characteristics between patients with HFpEF and those with COA, both disease conditions share similar hemodynamic characteristics such as abnormal aortic stiffness and hypertension, LV hypertrophy, impaired LV compliance and LA remodeling, and high prevalence of atrial fibrillation and symptomatic heart failure.[5-10,19-21]

Reddy et al[22] proposed the H_2FPEF score as a noninvasive clinical tool for differentiating between patients with HFpEF from those with noncardiac dyspnea, which in turn decreased the number of patients referred for cardiac catheterization. Recent studies have shown that the H_2FPEF score can also be used for prognostication in the outpatient clinic to identify patients at risk of heart failure hospitalization and for prognostication in patients with aortic stenosis undergoing transcatheter aortic valve replacement.[23,24] However, the prognostic role of the H_2FPEF score has not been assessed in adults with congenital heart disease. Considering the hemodynamic similarities between COA and HFpEF (aortic stiffness and hypertension, LV hypertrophy and stiffness, impaired LV compliance and LA remodeling, as well as higher prevalence of atrial fibrillation and symptomatic heart failure), we hypothesized that the H_2FPEF score would be associated with cardiovascular events in this population. The purpose of this study was, therefore, to assess the prognostic role of the H_2FPEF score in adults with repaired COA.

METHODS

STUDY POPULATION. The Mayo Clinic Institutional Review Board approved the study. This is a retrospective cohort study of adults (age ≥18 years) with repaired COA that received care at the Mayo Clinic from January 1, 2003, and December 31, 2019, and had at least 12 months of clinical follow-up. The patients with the following conditions were excluded: 1) concomitant LV inflow disease (Shone complex) defined as having any of the following conditions: mitral valve prosthesis and subvalvular, valvular, or supravalvular mitral stenosis (mean gradient >3 mmHg); 2) ≥moderate mitral regurgitation; and 3) incomplete Doppler indices for estimating Doppler-derived right ventricular (RV) systolic pressure and LV filling pressures needed to calculate the H_2FPEF score.

The study cohort was stratified as follows: 1) age at the time of initial COA repair <18 years vs ≥18 years and 2) isolated COA vs COA with a concomitant LV outflow disease defined as having any of the following conditions: aortic valve prosthesis; subvalvular, valvular, or supravalvular aortic stenosis (mean gradient >20 mmHg); or ≥moderate aortic regurgitation.

The study objectives were: 1) to determine the association between the H_2FPEF score at baseline assessment and the occurrence of cardiovascular events during follow-up; and 2) to determine whether a temporal change in the H_2FPEF score was associated with cardiovascular events independent of the baseline H_2FPEF score.

H_2FPEF SCORE. H_2FPEF score is comprised of 6 weighted variables, and we calculated the H_2FPEF score using the parameters described by Reddy et al.[22] These variables were: 1) Heavy or obesity defined as body mass index >30 kg/m^2 (2 points); 2) Hypertension defined as a clinical diagnosis of hypertension treated with ≥2 antihypertensive medications (1 point); 3) atrial Fibrillation defined as current or prior history of paroxysmal or persistent atrial fibrillation (3 points); 4) Pulmonary hypertension defined as Doppler-derived RV systolic pressure >35 mmHg (1 point); 5) Elderly defined as age >60 years (1 point); and 6) Filling pressure defined as Doppler-derived septal E/e' >9 (1 point). The H_2FPEF score for each patient was calculated as the sum of the points for all 6 variables (range 0-9 points).

The first clinic visit within the study period was considered as the baseline evaluation, and the clinical assessments and cardiac tests performed within 12 months from the baseline evaluation were used to calculate the H_2FPEF score at baseline and to define the baseline characteristics of the cohort. In the subgroup patients that had ≥5 years of follow-up, we also calculated the H_2FPEF score at 5 years of follow-up using the clinical indices obtained 49 to 72 months

from the baseline assessment. A temporal change in the H_2FPEF score was calculated as the H_2FPEF score at 5 years minus the H_2FPEF score at baseline.

ECHOCARDIOGRAPHY. Doppler-derived RV systolic pressure was estimated as: 4 × tricuspid regurgitation peak velocity^2 + estimated right atrial (RA) pressure.[25] RA pressure was estimated based on the size and collapsibility of the inferior vena cava.[25] The LV filling pressure was estimated as the ratio of mitral inflow Doppler early velocity to the septal tissue Doppler early velocity (E/e'). Atrial volumes and ventricular systolic function were assessed using the standard technique.

OUTCOME. The electronic health records and the Accurint mortality database were reviewed to identify cardiovascular events occurring from the baseline clinic encounter to the last clinic encounter. A cardiovascular event was defined as the composite endpoint of heart failure hospitalization, heart transplant, and cardiovascular death. Cardiovascular death was defined as death due to myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular hemorrhage, and cardiovascular procedures.[26]

STATISTICAL ANALYSIS. Data were presented as mean ± SD, median (IQR), and count (%). Between-group comparisons were performed using Wilcoxon rank sum and chi-square tests for continuous variables and categorical variables, respectively. Pearson correlation was used to assess the relationship between continuous variables. The relationship between the H_2FPEF score and cardiovascular events was assessed using a multivariable Cox regression analysis, and the baseline evaluation was considered as time zero. First, we created a univariable Cox model using variables that were chosen a priori based on the known association with clinical outcomes in this population. The covariates with $P < 0.05$ on the univariable analysis were then used to create a multivariable model using stepwise backwards selection with a P value <0.05 as the criterion for a covariate to remain in the model. The associations between covariates and outcomes were expressed using HR and 95% CI, and non-cardiovascular death was modelled as competing risk. Surgical and transcatheter interventions performed during follow-up were modeled as time-dependent covariates.

The assumption of proportionality for all Cox proportional hazard analyses was tested graphically by plotting the logarithm of cumulative hazards with respect to each covariate separately. The proportionality assumption was fulfilled for each model. All statistical analyses were performed with BlueSky Statistics software (version 7.10, BlueSky Statistics LLC), and a P value <0.05 was considered to show statistical significance for all analyses.

RESULTS

BASELINE CHARACTERISTICS. Of 850 patients with COA, 138 patients were excluded because of unrepaired COA (n = 26), concomitant LV inflow disease (n = 58), and missing data (n = 144). Overall, 712 (84%) met the study inclusion criteria. The median age at the time of baseline assessment was 33 (range: 21-45) years, and 419 (59%) were males. **Table 1** shows the baseline characteristics of the cohort.

The baseline median and mean H_2FPEF score were 2 (range: 1-2) and 2.2 ± 1, respectively. Of the 712 patients, 81% (573/712) had a H_2FPEF score of 0 to 3, 17% (124/712) had a H_2FPEF score of 4 to 6, and 2% (15/712) had a H_2FPEF score of 7 to 9 (**Table 2**, **Central Illustration**). The H_2FPEF score was lower in patients with isolated COA vs COA with LV outflow disease (1.9 ± 1.5 vs 2.3 ± 1.7, $P = 0.008$), but there was no significant difference between males vs females (2.2 ± 1.8 vs 2.1 ± 1.7, $P = 0.10$) or between patients that underwent an initial COA repair prior to the age of 18 years vs those undergoing it after 18 years of age (2.2 ± 1.4 vs 2.2 ± 1.5, $P = 0.40$). There was a correlation between the H_2FPEF score and LA volume index (r = 0.73, $P < 0.001$), RA volume index (r = 0.41, $P < 0.001$), RV fractional area change (r = −0.46, $P < 0.001$), and LV e' (r = −0.52, $P < 0.001$), but not with LV ejection fraction (−0.17, $P = 0.30$). There was a correlation between the H_2FPEF score and N-terminal pro-B-type natriuretic peptide (r = 0.64, $P < 0.001$).

The median COA mean gradient was 13 (range: 8-17) mmHg, and of the 712 patients, 601 (84%) had a COA mean gradient <20 mmHg while 111 (16%) had a COA mean gradient ≥20 mmHg. There was no correlation between the H_2FPEF score and COA mean gradient in patients with a COA mean gradient <20 mmHg (r = 0.22, $P = 0.30$) or in patients with a COA mean gradient ≥20 mmHg (r = 0.28, $P = 0.10$). Of the 712 patients, 578 (82%) had available arm-leg pressure gradient data, and of these patients, 454 (79%) had an arm-leg pressure gradient <20 mm Hg while 124 (21%) had an arm-leg pressure

TABLE 1 Baseline Characteristics (N = 712)

Age, y	33 (21-45)
Male	419 (59%)
Age of COA repair, y	3 (1-6)
Age of COA repair <18 y	614 (86%)
Age of COA repair ≥18 y	98 (14%)
Associated lesions	
Isolated COA	531 (75%)
COA + LVOD	181 (25%)
Bicuspid aortic valve	435 (61%)
Comorbidities	
Hypertension	372 (52%)
Diabetes	34 (5%)
Coronary artery disease	46 (7%)
Atrial fibrillation	51 (7%)
Medications	
Beta-blockers	209 (29%)
ACEI/ARB	212 (30%)
Thiazide diuretics	79 (11%)
Spironolactone	18 (3%)
Calcium-channel blocker	97 (14%)
Hydralazine	3 (0.4%)
Laboratory data	
GFR, mL/min/1.73 m^2	95 ± 23
NT-proBNP, pg/mL [N = 314]	215 (61-518)
Echocardiography	
Left heart	
LA volume index, mL/m^2	29 ± 11
Mitral E velocity, m/s	1.1 ± 0.3
Septal e' velocity, cm/s	10 ± 3
Lateral e' velocity, cm/s	12 ± 4
Septal E/e'	10 ± 4
Lateral E/e'	9 ± 5
AV mean gradient, mmHg	10 ± 3
≥Moderate aortic regurgitation	47 (6%)
COA mean gradient, mmHg	13 (8-17)
LV ejection fraction, %	62 ± 8
LV mass index, g/m^2	106 ± 14
Right heart	
RA volume, mL/m^2	24 ± 9
RA pressure, mmHg	6 ± 3
RV systolic pressure, mmHg	34 ± 13
RV fractional area change, %	45 ± 11

Values are median (range), n (%), or mean ± SD.

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin-II receptor blocker; AV = atrioventricular; COA = coarctation of aorta; GFR = glomerular filtration rate; LA = left atrium; LV = left ventricle; LVOD = left ventricular outflow disease; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RA = right atrium; RV = right ventricle.

TABLE 2 H_2FPEF Score (N = 712)

Hypertension	276 (39%)
Heavy (obesity)	125 (17%)
Atrial fibrillation	51 (7%)
Pulmonary hypertension	223 (31%)
Elderly	108 (15%)
Filling pressure	368 (52%)
H_2FPEF score	
0-3	573 (81%)
4-6	124 (17%)
7-9	15 (2%)

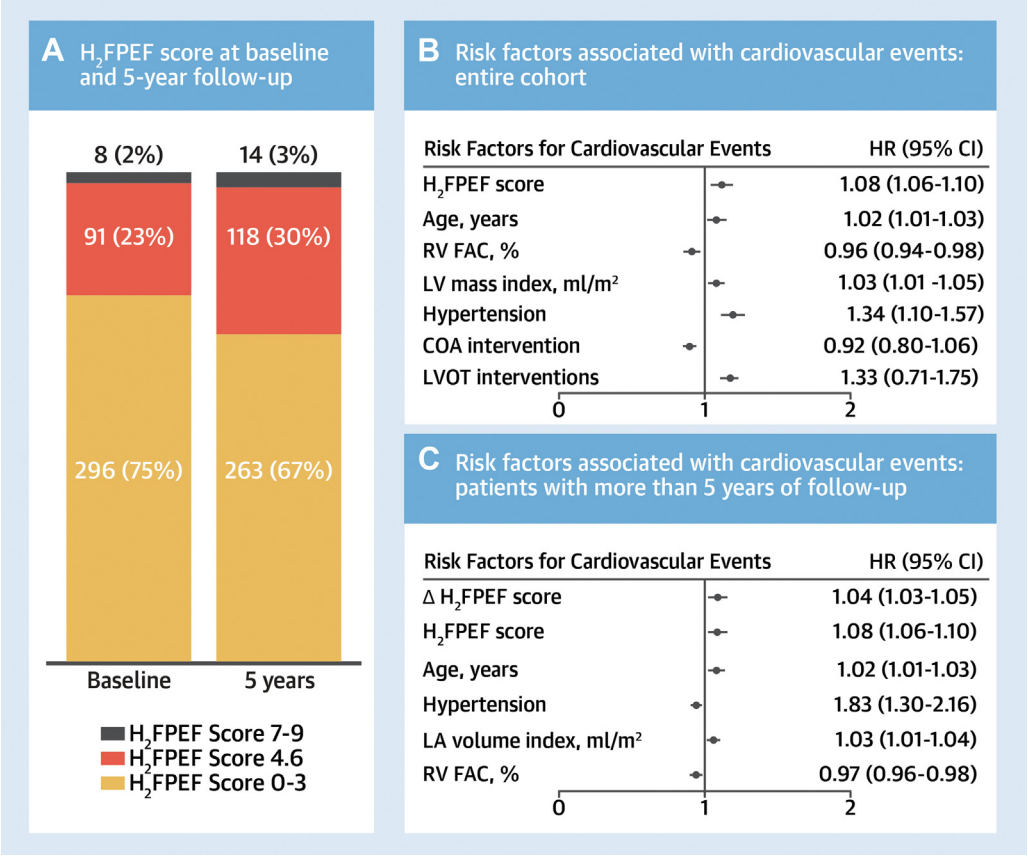
Values are n (%). Heavy defined as a body mass index >30 kg/m^2; Hypertension defined as a clinical diagnosis of hypertension treated with ≥2 antihypertensive medications; atrial Fibrillation defined as current or prior history of paroxysmal or persistent atrial fibrillation; Pulmonary hypertension defined as Doppler echocardiography estimated right ventricular systolic pressure >35 mmHg; Elderly defined as age >60 y; Filling pressure defined as Doppler echocardiography septal E/e' >9.

gradient ≥20 mm Hg. There was no correlation between the H_2FPEF score and arm-leg pressure gradient in patients with an arm-leg pressure gradient <20 mm Hg (r = 0.19, $P = 0.40$) or in patients with an arm-leg pressure gradient ≥20 mm Hg (r = 0.31, $P = 0.09$).

BASELINE H_2FPEF SCORE AND CARDIOVASCULAR EVENTS. The median follow-up duration was 8.1 (range: 4.3-11.5) years, and during this period, 69 (9%) patients were hospitalized for heart failure, 5 (0.7%) patients underwent a heart transplant for end-stage left heart failure, and 75 (11%) died, of which 64 were cardiovascular deaths. The median age at the time of death was 53 (range: 49-57) years. The combined outcome of cardiovascular events occurred in 97 (14%) patients. The clinical and echocardiographic indices associated with cardiovascular events are shown in Table 3. There was a 16% increase in the risk of cardiovascular events for every unit increase in the H_2FPEF score (HR: 1.16; 95% CI: 1.07-1.24; $P = 0.006$) in the overall cohort and a 19% increase in the risk of cardiovascular events for every unit increase in the H_2FPEF score (HR: 1.19; 95% CI: 1.07-1.28; $P = 0.004$) in patients with isolated COA (Table 4, Central Illustration). There was a consistent association between the H_2FPEF score and cardiovascular events in patients that underwent an initial COA repair prior to the age of 18 years (HR: 1.14; 95% CI: 1.05-1.21; $P = 0.01$) and in those who underwent the repair after 18 years of age (HR: 1.20; 95% CI: 1.12-1.29; $P = 0.004$).

TEMPORAL CHANGE IN THE H_2FPEF SCORE AND CARDIOVASCULAR EVENTS. Of the 712 patients, 397 (56%) had an H_2FPEF score at baseline and at 5 years. There was temporal increase in the mean H_2FPEF score from 2.1 ± 1.5 at baseline to 2.4 ± 1.7 ($P = 0.006$) at 5 years (ΔH_2FPEF score 0.34 ± 0.11). Table 5 and Central Illustration show a comparison of the H_2FPEF score at baseline and at 5 years. There was a temporal increase in the proportion of patients with hypertension, obesity, and high LV filling pressures and a trend toward an increase in the proportion of patients with pulmonary hypertension and atrial fibrillation. A temporal change in the H_2FPEF score (ΔH_2FPEF score)

CENTRAL ILLUSTRATION **Prognostic Role of H_2FPEF Score in Coarctation of Aorta**



Egbe AC, et al. JACC Adv. 2022;1(5):100130.

(A) Bar chart showing H_2FPEF score at baseline and 5-year follow-up. There was a temporal increase in the proportion of patients with an H_2FPEF score 0 to 3 ($P = 0.01$) and H_2FPEF score 4 to 6 ($P = 0.02$) but not in patients with an H_2FPEF score 7 to 0. **(B)** Forest plot showing the risk factors associated with cardiovascular events in the overall cohort (n = 712). The H_2FPEF score at baseline and the temporal change in the H_2FPEF score were independently associated with cardiovascular events. **(C)** Forest plot showing the risk factors associated with cardiovascular events in the subset of patients with more than 5 years of follow-up (n = 395). The H_2FPEF score at baseline and the temporal change in the H_2FPEF score (ΔH_2FPEF score) were independently associated with cardiovascular events. COA = coarctation of aorta; LA = left atrium; LV = left ventricle; LVOT = left ventricular outflow tract; RV FAC = right ventricle fractional area change.

by 1 unit was associated with a 4% increase in the risk of cardiovascular events, independent of the baseline H_2FPEF score (Table 6).

DISCUSSION

In this study, we assessed the prognostic role of the H_2FPEF score in adults with repaired COA. We observed that both the H_2FPEF score at baseline and temporal change in the H_2FPEF score were independently associated with cardiovascular events defined as the composite endpoint of heart failure hospitalization, heart transplant, and cardiovascular death.

Although there are safe and effective surgical and transcatheter therapies for treatment of patients with COA, the long-term survival remains significantly less than that of the general population (median survival ~55 years).[14,15,27,28] The morbidity and mortality in this population are attributed to heart failure and atrial/ventricular arrhythmias resulting from cardiac remodeling and dysfunction.[27-29] Risk stratification in this population is challenging and relies on a

TABLE 3 Univariable Cox Model Showing Determinants of Cardiovascular Events (N = 712)

	HR (95% CI)	*P* Value
H_2FPEF score	1.38 (1.23-1.54)	<0.001
Age, y	1.04 (1.02-1.06)	<0.001
Age of COA repair, y	1.03 (0.89-1.22)	0.40
Male	1.01 (0.61-1.67)	0.90
Coronary artery disease	1.91 (1.23-4.11)	0.001
GFR, per 5-unit increment	0.97 (0.96-0.99)	<0.001
COA + LVOD	1.89 (1.26-2.14)	<0.001
COA mean gradient, mmHg	1.26 (0.78-2.54)	0.50
Aortic valve mean gradient, mmHg	1.07 (0.86-1.79)	0.30
≥Moderate aortic regurgitation	0.98 (0.91-1.06)	0.70
LV ejection fraction, %	0.97 (0.95-0.99)	0.006
LA volume index, mL/m^2	1.04 (1.03-1.06)	<0.001
RA volume index, mL/m^2	1.05 (1.03-1.07)	<0.001
RA pressure, mmHg	1.23 (1.17-1.29)	<0.001
RV fractional area change, %	0.93 (0.90-0.97)	0.002
RV systolic pressure, mmHg	1.06 (1.02-1.10)	<0.001
LV mass index, per 10 g/m^2	1.03 (1.01-1.05)	0.02
Hypertension	2.16 (1.54-2.73)	0.005
Atrial fibrillation	1.84 (1.29-2.35)	0.008

COA = coarctation of aorta; GFR = glomerular filtration rate; LA = left atrium; LV = left ventricle; LVOD = left ventricular outflow disease; RA = right atrium; RV = right ventricle.

TABLE 4 Multivariable Cox Model Showing Determinants of Cardiovascular Events

All Patients (N = 712)	HR (95% CI)	*P* Value
H_2FPEF score	1.16 (1.07-1.24)	0.006
Age, y	1.02 (1.01-1.04)	0.005
RV fractional area change, %	0.96 (0.94-0.98)	0.01
LV mass index, per 10 g/m^2	1.03 (1.01-1.05)	0.009
Hypertension	1.34 (1.10-1.57)	0.01
COA intervention*	0.92 (0.80-1.06)	0.40
LVOT intervention*	1.33 (0.71-1.75)	0.60
Isolated COA (n = 531)		
H_2FPEF score	1.19 (1.07-1.28)	0.004
Age, y	1.04 (1.01-1.07)	0.01
LA volume index, mL/m^2	1.04 (1.02-1.06)	0.03
RV fractional area change, %	0.95 (0.93-0.97)	0.02
LV mass index, per 10 g/m^2	1.02 (0.99-1.05)	0.07
Hypertension	1.55 (1.22-1.92)	0.009
COA intervention*	0.94 (0.82-1.09)	0.60

*COA intervention denotes a surgical or transcatheter COA intervention during follow-up; LVOT intervention denotes surgical resection of subaortic stenosis or aortic valve replacement during follow-up. Both COA interventions and LVOT interventions were modeled and time-dependent covariates. Note that the multivariable models were created using stepwise backwards selection with a *P* value <0.05 as the criteria for a covariate to remain in the model. The covariates used in the multivariable models were derived from univariable analysis shown in Table 3.

COA = coarctation of aorta; LA = left atrium; LV = left ventricle; LVOT = left ventricular outflow tract; RV = right ventricle.

TABLE 5 H_2FPEF Score (N = 395)

	Baseline	5 y	*P* Value
Hypertension	127 (32%)	163 (41%)	0.01
Heavy (obesity)	65 (16%)	88 (22%)	0.04
Atrial fibrillation	28 (7%)	41 (10%)	0.07
Pulmonary hypertension	108 (27%)	132 (33%)	0.05
Elderly	46 (12%)	61 (15%)	0.20
Filling pressure	151 (38%)	183 (46%)	0.02
H_2FPEF score			
0-3	296 (75%)	263 (67%)	0.01
4-6	91 (23%)	118 (30%)	0.02
7-9	8 (2%)	14 (3%)	0.20

Values are n (%). Heavy defined as a body mass index >30 kg/m^2; Hypertension defined as a clinical diagnosis of hypertension treated with ≥2 antihypertensive medications; atrial Fibrillation defined as current or prior history of paroxysmal or persistent atrial fibrillation; Pulmonary hypertension defined as Doppler echocardiography estimated right ventricular systolic pressure >35 mmHg; Elderly defined as age >60 years; Filling pressure defined as Doppler echocardiography septal E/e' >9.

combination of indices that provide an assessment of hemodynamic severity of the underlying structural lesions.[17] These indices include aortic size index, Doppler COA gradient, blood pressure, and hypertensive response to exercise. Recent studies have assessed the prognostic role of indices of cardiac remodeling such as LV stiffness and filling pressures, LA function, and pulmonary hypertension.[6,9,11,12,29] However, there are limited data about how these different indices are related to each other and with clinical outcomes.

We observed that the H_2FPEF score correlated with the severity of cardiac remodeling (atrial size, LV diastolic function, and RV systolic function) and with clinical outcomes (heart failure hospitalization, heart transplant, and cardiovascular death). We postulate that is because the H_2FPEF score integrates markers of worse LV afterload (Hypertension, Elderly/age, and Heavy/obesity), left heart remodeling (Filling pressures and atrial Fibrillation), and right heart remodeling (Pulmonary hypertension).[22] Hence, it provides a compressive assessment of the hemodynamic and clinical factors that affect outcomes in this population. Similar to the results of the current study, Suzuki et al[23] and Ludwig et al[24] demonstrated that the H_2FPEF score can be used to predict heart failure hospitalization in stable ambulatory patients and to predict the risk of cardiovascular death in patients with aortic stenosis undergoing transcatheter aortic valve replacement, respectively. Collectively, these findings underscore the robustness of the H_2FPEF score as a prognostic marker.

TABLE 6 Multivariable Cox Model Showing Determinants of Cardiovascular Events in Patients With Longitudinal Assessment of H_2FPEF Score (N = 395)

	HR (95% CI)	*P* Value
ΔH_2FPEF score	1.04 (1.03-1.05)	0.01
H_2FPEF score	1.06 (1.04-1.08)	<0.001
Age, y	1.02 (1.01-1.03)	0.04
Hypertension	1.83 (1.30-2.16)	0.007
LA volume index, mL/m^2	1.03 (1.01-1.04)	0.002
RV fractional area change, %	0.97 (0.96-0.98)	0.001

Note that the multivariable models were created using stepwise backwards selection with a *P* value <0.05 as the criterion for a covariate to remain in the model. The covariates used in the multivariable models were derived from a univariable analysis shown in Table 3.

CI = confidence interval; HR = hazard ratio; LA = left atrium; RV = right ventricle.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS. We observed a temporal increase in the H_2FPEF score and that this change was driven by an increase in the prevalence of hypertension, obesity, and elevated LV pressures. Obesity is a modifiable risk factor, and hence can provide a therapeutic target in this population. In addition, obesity is known to be associated with hypertension, left heart diastolic dysfunction, and atrial fibrillation, and weight loss from diet and exercise has been shown to improve blood pressure and lipid profile, reduce the incidence of atrial fibrillation, and delay the onset of type 2 diabetes in patients with obesity.[30] Perhaps such interventions should be applied to individuals with COA, and further studies are required to determine whether these interventions will improve clinical outcomes in this population. Apart from the H_2FPEF score, other correlates of cardiovascular events observed in this study include hypertension and LV hypertrophy. Since effective screening and treatment of hypertension have been shown to decrease LV hypertrophy and the risk of cardiovascular mortality in patients with an acquired heart disease, we postulate that these interventions can be applied to the COA population. Further studies are also required to determine whether surgical and transcatheter interventions to relieve LV pressure overload in patients with residual LV outflow tract or aortic isthmus obstruction, intensification of antihypertensive therapy in patients with hypertension, and the use of diuretics in patients with increased LV filling pressure would improve outcomes in this population.

STUDY LIMITATIONS. This is a retrospective single-center study, and hence, it is prone to selection and ascertainment biases which may impede the generalizability of the results. Of note, the study cohort comprised of patients with repaired COA that did not have significant residual coarctation (84% of the cohort). Hence, it is unclear whether the H_2FPEF score would have similar prognostic performances in patients with unrepaired COA or patients with repaired COA and significant residual coarctation. Although we adjusted for the effect of surgical and transcatheter interventions performed between the baseline H_2FPEF score and the last follow-up, we did not specifically evaluate the effect of these interventions on the different components of the H_2FPEF score such as systemic hypertension, pulmonary hypertension, and LV filling pressure and the effect of these changes on clinical outcomes.

CONCLUSIONS

The H_2FPEF score at baseline and the temporal change in the H_2FPEF score during follow-up were associated with cardiovascular events in patients with COA, and hence can be used to identify patients at higher risk of adverse events. There was a temporal increase in the H_2FPEF score, and this change was driven by an increase in the prevalence of hypertension, obesity, and left heart filling pressures. Further studies are required to determine whether interventions targeted at these indices would improve clinical outcomes in this population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The H_2FPEF score at baseline and the temporal change in the H_2FPEF score during follow-up were associated with cardiovascular events in patients with COA, and hence can be used to identify patients at higher risk of adverse events. There was a temporal increase in the H_2FPEF score, and this change was driven by an increase in the prevalence of hypertension, obesity, and left heart filling pressures.

TRANSLATIONAL OUTLOOK: Further studies are required to determine whether interventions targeted at these indices would improve clinical outcomes in this population.

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