ORIGINAL RESEARCH ARTICLE

Heart failure related to adult congenital heart disease: prevalence, outcome and risk factors

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Abstract

Aims   Information on the prevalence, outcome and factors associated with heart failure in patients with adult congenital heart disease (CHD) (ACHD-HF) is lacking. We aimed at assessing the prevalence and outcome of ACHD-HF, the variables associated with ACHD-HF, and the differences between major anatomical/pathophysiological ACHD subgroups.
Methods and results   We included 3905 patients (age 35.4 ± 13.2 years) under active follow-up in our institution (last visit >2010). Outcome of ACHD-HF cases was compared with sex- and age-matched cases. Univariable and multivariable binary logistic regression with ACHD-HF diagnosis as a dependent variable was performed. Overall prevalence of ACHD-HF was 6.4% (mean age 49.5 ± 16.7 years), but was higher in patients with cyanotic CHD (41%), Fontan circulation (30%), and a systemic right ventricle (25%). All-cause mortality was higher in ACHD-HF cases when compared with controls (mortality rate ratio 4.67 (2.36–9.27); *P* = 0.0001). In multivariable logistic regression analysis, age at latest follow-up [per 10 years; odds ratio (OR) 1.52; 95% confidence interval (CI) 1.31–1.77], infective endocarditis (OR 4.11; 95%CI 1.80–9.38), history of atrial arrhythmia (OR 3.52; 95%CI 2.17–5.74), pacemaker implantation (OR 2.66; 95% CI 1.50–4.72), end-organ dysfunction (OR 2.41; 95% CI 1.03–5.63), New York Heart Association class (OR 9.28; 95% CI 6.04–14.25), heart rate (per 10 bpm; OR 1.27; 95% CI 1.08–1.50), ventricular dysfunction (OR 3.62; 95% CI 2.54–5.17), and pulmonary hypertension severity (OR 1.66; 95% CI 1.21–2.30) were independently related to the presence of ACHD-HF. Some variables (age, atrial arrhythmia, pacemaker, New York Heart Association, and ventricular dysfunction) were related to ACHD-HF in all anatomical/physiological subgroups, whereas others were not.
Conclusions   ACHD-HF is prevalent especially in complex CHD and is associated with poor prognosis. Our data provide insight in the factors related to ACHD-HF including differences between specific anatomical and physiological subgroups.

Introduction

As a result of a significant increase in the survival of patients with congenital heart disease (CHD), 88% of children with CHD nowadays survive into adulthood.[1] There are now more adults than children with CHD with a rapidly expanding cohort of survivors with complex lesions and even a new group of patients with 'geriatric' ACHD.[2,3] Even repaired, the hearts of adult patients with CHD (ACHD) remain abnormal, making them vulnerable to the development of heart failure (HF).[4,5] Unsurprisingly, ACHD-HF has become a rapidly growing reason for hospitalization,[6] is associated with a high mortality rate,[7] and has become the leading cause of death for ACHD patients.[8] The associated increase in ACHD-HF-related

admissions and procedures poses a significant burden on the health care system.[6,9,10] Simultaneously, the number of ACHD patients assessed for orthotopic heart transplantation increases, although few are listed with those unsuitable for transplantation having a poor prognosis.[11]

Despite this, precise data on the prevalence of ACHD-HF remain elusive. Detailed information on the factors associated with ACHD-HF is needed in order to recognize patients at risk, trigger further investigations for modifiable structural and electrical issues and/or refer patients for consideration of advanced HF therapies.[12] Fundamental differences in anatomy and pathophysiology between subgroups need to be taken into account to understand similarities and differences in the ACHD-HF phenotype. Therefore, this study aimed at evaluating the prevalence and outcome of ACHD-HF, examining variables associated with ACHD-HF and identifying differences between major anatomical/pathophysiological ACHD groups in a contemporary cohort of ACHD patients followed in a tertiary care centre.

Methods

Study population

All adult patients with CHD (ACHD) under active follow-up at the University Hospitals Leuven (with a last follow-up visit >1 January 2010) were included in the study and followed until the latest follow-up visit or until death. For the purpose of the study, we defined the start of inclusion as age ≥16 years. Patients were divided into subgroups based on their major underlying heart defect, using a modification of the hierarchical classification developed for the Dutch Congenital Cor Vitia Project.[13] Patients were further classified according to the anatomic complexity of their heart defect into mild-, moderate-, or severe-complexity heart defects[14] and based on the physiological severity as outlined in the 2018 American Heart Association (AHA)/American College of Cardiology (ACC) (AHA/ACC) guideline for the management of adults with CHD.[15] Finally, patients were categorized into the following mutually exclusive subgroups: (i) Cyanotic ACHD (including Eisenmenger physiology); (ii) Fontan circulation; (iii) biventricular circulation with a systemic right ventricle (RV); (iv) biventricular circulation with a systemic left ventricle (LV)—shunt lesions; (v) biventricular circulation with a systemic LV—predominant right-sided residual lesions; and (vi) biventricular circulation with a systemic LV—predominant left-sided residual lesions (Table S1).[4]

Data on clinical status were obtained from medical records reviewed by one investigator (A. V. D. B.) at their latest follow-up visit prior to censoring or death. Ventricular dilatation, ventricular dysfunction, and valvular dysfunction (systemic, pulmonic, or both) were recorded from echocardiography reports. Ventricular dysfunction was assessed qualitatively, reported on a scale from 1 (*normal*) to 4 (*severely depressed*). Right and left atrioventricular valve regurgitation was assessed by colour-Doppler and reported on a scale from 1 (*none*) to 4 (*severe*). Data on overall mortality were established from the clinical working station of the hospital, which is linked to the national statistical office. Patients' records were reviewed after pseudonymizing patient data in accordance with the Global Data Protection Regulation. The institutional ethics committee approved the study protocol and the study was conducted in compliance with the principles of the Declaration of Helsinki.

Adult congenital heart disease-heart failure definition

Heart failure related to ACHD was defined as signs and/or symptoms of HF requiring medical therapy[16] plus one of the following: (i) impaired ventricular function (systolic, diastolic or both) with elevated intracardiac pressures; (ii) elevated B-type natriuretic peptide (BNP) or N-terminal BNP; (iii) peak oxygen consumption in the lowest quartile according to published norms for ACHD subtype[17] or 4. Unique HF manifestations in patients with a Fontan circulation (protein loosing enteropathy, plastic bronchitis, Fontan systemic venous pressure ≥20 mmHg, and cardiac index <2 L/min m^2). HF diagnosis was reviewed by one investigator (A. V. D. B.). In case of doubt, the case was discussed with colleagues (W. B., E. T., and P. D. M.).

Statistical analysis

Data were analysed using SPSS® for Windows (version 23, SPSS, Chicago) and tested for normality with the Kolmogorov–Smirnov test. Descriptive data for continuous variables are presented as means ± SD or as medians with interquartile ranges as appropriate. Descriptive data for discrete variables are presented as frequencies or percentages. For between-group comparisons, the independent Student t test, χ^2, or Fisher exact test was used where applicable.

ACHD-HF prevalence in the study cohort is reported for the entire cohort and for the individual subgroups. Patients with ACHD-HF (cases) were matched with patients not developing ACHD-HF (controls) according to sex, date of birth and ACHD subgroup. Baseline in the cases was defined as the date of ACHD-HF diagnosis. Baseline in the controls was defined as the baseline date in the corresponding cases assuring approximately equal age at baseline in cases and controls. Patients with a follow-up of at least 1 year after baseline were included. Mortality rates (deaths per 1000 patient years) were compared between cases and controls, and results are

illustrated using inverse Kaplan–Meier plots and analysed using the log-rank test.

Binary logistic regression analysis was performed with HF diagnosis as a dependent variable. For the entire cohort, a multivariable logistic regression was performed to determine variables related to HF diagnosis using the following covariates: age (per 10 years), sex, underlying genetic abnormality, prior intervention (surgical or percutaneous), smoking, alcohol consumption, history of infective endocarditis, coronary artery disease, a history of atrial, or ventricular arrhythmia, the presence of a pacemaker, end-organ dysfunction (renal, pulmonary, or hepatic), New York Heart Association (NYHA) class, body mass index (BMI), mean arterial pressure (per 10 mmHg), heart rate (per 10 bpm), severity of cyanosis, ventricular dilatation, ventricular dysfunction, valvular dysfunction, aortic dilatation, pulmonary hypertension severity, the presence of venous or arterial stenosis, and shunt severity. For the anatomical/physiological subgroups, because of smaller numbers, only univariable logistic regression with these parameters was performed to assess consistency across subgroups.

Results

Demographics and heart failure prevalence

A total of 3905 [2032 male (52%)] ACHD patients were included in the study with a mean age at last follow up of 35.4 ± 13.2 years. Patient characteristics for the entire cohort are summarized in *Table 1* and for the different subgroups in Supplementary *Tables S2A–S2F*. According to the Bethesda disease complexity classification, 33% of patients had simple defects, 56% moderate, and 11% severe complexity defects. Based on the physiological severity classification, 18% were in physiological Stage A, 36% in physiological Stage B, 42% in physiological Stage C, and 4% in physiological Stage D.

In total, 248 patients (6.4%) had a HF diagnosis at last follow-up. Patients with moderate to severe complexity CHD and those in physiological severity Class C or D were more likely to have ACHD-HF (*Table 1*). HF prevalence was significantly higher in cyanotic patients, patients with a Fontan circulation, and patients with a systemic RV when compared with patients with a biventricular circulation and a systemic LV, although absolute ACHD-HF numbers were lower (*Figure 1*). With increasing age, ACHD-HF prevalence increased from 2.3% in subjects aged 15–35 years to 6.8% in those age 35–50 years and 21.9% in those aged >50 years. This age-related increase was consistent in all groups, but was especially evident in cyanotic patients, patients with a Fontan circulation, and patients with a systemic RV.

Outcome

Of 248 ACHD-HF patients, 186 cases could be matched with one control according to sex, date of birth and ACHD anatomical/physiological subgroup. Mortality rate in the control group was 8.7 (95%CI 3.3–14.4) when compared to 40.6 (95%CI 28.6–52.7) in the ACHD-HF group, resulting in a mortality rate ratio of 4.67 (95%CI 2.36–9.27). *Figure 2* illustrates the inverse Kaplan–Meier plot for ACHD-HF and matched control patients.

Variables related to adult congenital heart disease-heart failure

For the entire cohort, in multivariable logistic regression analysis (complete case analysis, missing cases 8.6%), age at latest follow-up [per 10 years increment; odds ratio (OR) 1.52; 95% confidence interval (CI) 1.31–1.77; $P < 0.0001$], a history of infective endocarditis (OR 4.11; 95% CI 1.80–9.38; $P = 0.001$), a history of atrial arrhythmia (OR 3.52; 95% CI 2.17–5.74; $P < 0.0001$), need for pacemaker implantation (OR 2.66; 95% CI 1.50–4.72; $P = 0.001$), end-organ dysfunction (OR 2.41; 95% CI 1.03–5.63; $P = 0.042$), NYHA class (OR 9.28; 95% CI 6.04–14.25; $P < 0.0001$), heart rate (per 10 bpm increase; OR 1.27; 95% CI 1.08–1.50; $P = 0.003$), ventricular dysfunction (OR 3.62; 95% CI 2.54–5.17; $P < 0.0001$), and pulmonary hypertension severity (OR 1.66; 95% CI 1.21–2.30; $P = 0.002$) were independently related to the presence of ACHD-HF (*Figure 3*).

For the anatomical/physiological subgroups, in univariable regression analysis, age at latest follow-up, atrial arrhythmia, the presence of a pacemaker, NYHA, and ventricular dysfunction were consistently related to ACHD-HF across all subgroups. A history of prior intervention, infective endocarditis, coronary artery disease, end-organ dysfunction, ventricular dilatation, valvular dysfunction and pulmonary hypertension severity appeared important in some but not all subgroups (*Figure 4*). Of note, for patients with a Fontan circulation, there was no difference between different types of Fontan circulation and having a dominant systemic RV was not related to ACHD-HF (*Table S2B*).

Discussion

This study evaluates the prevalence of HF in adult CHD based on a standardized definition for ACHD-HF in a large contemporary ACHD cohort, providing an estimated ACHD-HF prevalence of 6.4% at a median age of 35 years. ACHD-HF prevalence varies across anatomical/physiological subgroups [largest prevalence in cyanotic patients (41%), patients with a Fontan circulation (30%) and patients with a systemic RV (25%)] and increases significantly with older age. An ACHD-HF diagnosis increases all-cause mortality risk almost

Table 1 Patient characteristics

Variable	Entire cohort n = 3905	Heart failure n = 248	No heart failure n = 3657	P value
Bethesda classification				
Mild n (%)	1306 (33.5)	43 (17.3)	1263 (34.5)	
Moderate n (%)	2182 (56.0)	114 (46.0)	2068 (56.5)	
Severe n (%)	417 (10.7)	91 (36.7)	326 (8.9)	<0.0001
Physiological severity				
A n (%)	701 (17.6)	0 (0.0)	701 (19.2)	
B n (%)	1389 (35.6)	4 (1.6)	1385 (37.9)	
C n (%)	1650 (42.2)	171 (69.0)	1479 (40.4)	
D n (%)	165 (4.2)	73 (29.4)	92 (2.5)	<0.0001
Age at last FU (years)	35.4 ± 13.2	49.5 ± 16.7	34.4 ± 12.4	<0.0001
Male gender n (%)	2032 (52.0)	127 (51.2)	1905 (52.1)	0.793
Any genetic abnormality n (%)	441 (11.3)	23 (9.3)	418 (11.4)	0.348
Trisomy 21 n (%)	142 (3.6)	11 (4.4)	131 (3.6)	0.600
22q11 n (%)	77 (2.0)	6 (2.4)	71 (1.9)	0.633
Noonan n (%)	61 (1.6)	1 (0.4)	60 (1.6)	0.182
Williams n (%)	25 (0.6)	1 (0.4)	24 (0.7)	0.731
Intervention n (%)	2639 (67.6)	206 (83.1)	2433 (66.5)	<0.0001
Smoking n (%)	500 (12.8)	25 (10.1)	475 (13.0)	0.200
Missing n (%)	216 (5.5)	13 (5.2)	203 (5.6)	
Alcohol				0.001
Never n (%)	1323 (33.9)	99 (39.9)	1224 (33.5)	
Occasionally n (%)	2023 (51.8)	103 (41.5)	1920 (52.5)	
Frequently n (%)	343 (8.8)	33 (13.3)	310 (8.5)	
Missing n (%)	216 (5.5)	13 (5.2)	203 (5.6)	
Infective endocarditis n (%)	108 (2.8)	23 (9.3)	85 (2.3)	<0.0001
Coronary artery disease n (%)	23 (0.6)	6 (2.4)	17 (0.5)	0.002
Atrial arrhythmia n (%)	346 (8.9)	126 (50.8)	220 (6.0)	<0.0001
Ventricular arrhythmia n (%)	120 (3.1)	36 (14.5)	84 (2.2)	<0.0001
RF ablation n (%)	160 (4.1)	53 (21.4)	107 (2.9)	<0.0001
Pacemaker n (%)	206 (5.3)	82 (33.1)	124 (3.4)	<0.0001
AICD n (%)	71 (1.8)	33 (13.3)	38 (1.0)	<0.0001
CRT n (%)	23 (0.6)	14 (5.6)	9 (0.2)	<0.0001
End-organ dysfunction				<0.0001
No n (%)	3831 (98.1)	193 (77.8)	3638 (99.5)	
Mild n (%)	63 (1.6)	48 (19.4)	15 (0.4)	
Severe n (%)	11 (0.3)	7 (2.8)	4 (0.1)	
Clinical characteristics				
NYHA				
I n (%)	3472 (88.9)	43 (17.3)	3429 (93.8)	
II n (%)	365 (9.3)	145 (58.5)	220 (6.0)	
III n (%)	59 (1.5)	51 (20.6)	8 (0.2)	
IV n (%)	9 (0.2)	9 (3.6)	0 (0.00)	<0.0001
Length (cm)	170.1 ± 11.3	167.8 ± 11.3	170.2 ± 11.3	0.001
Missing n (%)	218 (5.6)	13 (5.2)	205 (5.6)	
Weight (kg)	72.9 ± 16.1	72.1 ± 19.2	73.0 ± 15.9	0.491
Missing n (%)	249 (6.4)	17 (6.9)	232 (6.3)	
BMI (kg/m^2)	25.2 ± 4.9	25.4 ± 5.6	25.1 ± 4.8	0.465
Missing n (%)	257 (6.6)	17 (6.9)	240 (6.6)	
SBP (mmHg)	128.4 ± 27.1	122.1 ± 19.8	128.8 ± 27.5	<0.0001
Missing n (%)	228 (5.8)	14 (5.6)	214 (5.9)	
DBP (mmHg)	73.5 ± 11.3	69.1 ± 13.1	73.8 ± 11.1	<0.0001
Missing n (%)	231 (5.9)	14 (5.6)	217 (5.9)	
Heart rate (bpm)	71.8 ± 13.4	74.2 ± 14.7	71.7 ± 13.3	0.005
Missing n (%)	270 (6.9)	16 (6.5)	254 (6.9)	
Cyanosis				
No n (%)	3784 (96.9)	199 (80.2)	3585 (98.0)	
Mild n (%)	61 (1.6)	17 (6.9)	44 (1.2)	
Severe n (%)	60 (1.5)	32 (12.9)	28 (0.8)	<0.0001
Echocardiography				
Ventricular dilatation				
No n (%)	2766 (70.8)	57 (23.0)	2709 (74.1)	
Mild n (%)	649 (16.6)	55 (22.2)	594 (16.2)	
Moderate–severe n (%)	490 (12.5)	136 (54.8)	354 (9.7)	<0.0001
Ventricular dysfunction				
No n (%)	3193 (81.8)	49 (19.8)	3144 (86.0)	
Mild n (%)	477 (12.2)	74 (29.8)	403 (11.0)	

(Continues)

Table 1 (continued)

Variable	Entire cohort n = 3905	Heart failure n = 248	No heart failure n = 3657	P value
Moderate–severe n (%)	235 (6.0)	125 (50.4)	110 (3.0)	<0.0001
Valvular dysfunction				
No n (%)	940 (24.1)	2 (0.8)	938 (25.6)	
Mild n (%)	1697 (43.4)	80 (32.3)	1617 (44.2)	
Moderate–severe n (%)	1268 (32.5)	166 (66.9)	1102 (30.1)	<0.0001
Aortic dilatation				
<35 mm n (%)	3287 (84.2)	217 (87.5)	3070 (83.9)	
35–39 mm n (%)	313 (8.0)	15 (6.0)	298 (8.1)	
40–49 mm n (%)	269 (6.9)	12 (4.8)	257 (7.0)	
>50 mm n (%)	36 (0.9)	4 (1.6)	32 (0.9)	0.192
Pulmonary hypertension				
<35 mmHg n (%)	3695 (94.6)	146 (58.9)	3549 (97.0)	
35–60 mmHg n (%)	121 (3.1)	57 (23.0)	64 (1.8)	
>60 mmHg n (%)	89 (2.8)	45 (18.1)	44 (1.2)	<0.0001
Venous/arterial stenosis n (%)	76 (1.9)	8 (3.2)	68 (1.9)	0.147
Persistent shunt n (%)				<0.0001
No shunt	3274 (83.8)	170 (68.5)	3104 (84.9)	
Mild/restrictive shunt	493 (12.6)	25 (10.1)	468 (12.8)	
Significant/non-restrictive shunt	138 (3.5)	53 (21.4)	85 (2.3)	
Outcome				
Combined endpoint n (%)	109 (2.8)	64 (25.8)	45 (1.2)	<0.0001
Death n (%)	96 (2.5)	51 (20.6)	45 (1.2)	<0.0001
Transplant n (%)	14 (0.4)	14 (5.6)	0 (0.0)	<0.0001
VAD n (%)	2 (0.1)	2 (0.8)	0 (0.0)	0.004

AICD, automated cardioverter defibrillator; BMI, body mass index; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; FU, follow-up; NYHA, New York Heart Association; SBP, systolic blood pressure; VAD, ventricular assist device.

Figure 1 Adult congenital heart disease (ACHD)-heart failure (HF) (ACHD-HF) prevalence heat map. Heat map indicating the absolute number and proportion of patients with ACHD-HF subdivided per age category and per ACHD subgroup. Although the proportion of patients with ACHD-HF is substantially higher (at younger age) for cyanotic patients, Fontan patients and patients with a systemic right ventricle (RV), the absolute number of patients is higher in the ACHD subgroups with a biventricular circulation and systemic left ventricle (LV).

|	Absolute number	Prevalence (%) All ages	Prevalence (%) 15-35 years	Prevalence (%) 35-50 years	Prevalence (%) >50 years
All patients	248	6,4	2,3	6,8	21,9
Cyanotic/Eisenmenger	43	41	31,9	39,4	62,5
Fontan	29	30,3	20,6	47,8	100
Systemic RV	30	24,8	6,4	32,1	50
Predominant Right-sided	73	7,6	1,5	7,5	31
Shunt lesions	48	3,4	0,6	2,2	18,2
Predominant Left-sided	26	2,3	1	2,1	7,6

fivefold. Age, infective endocarditis, atrial arrhythmia, pacemaker, end-organ dysfunction, NYHA class, heart rate, ventricular dysfunction, and pulmonary hypertension severity were independently related to the presence of ACHD-HF. Some variables (age, atrial arrhythmia, pacemaker, NYHA, and ventricular dysfunction) were related to ACHD-HF in all anatomical/physiological subgroups, whereas others were not.

Adult congenital heart disease-heart failure prevalence

In this cohort of 3905 ACHD patients, estimated prevalence of ACHD-HF was 6.4% at a mean age of 35 years. Those results are comparable, albeit somewhat higher when compared with the prevalence of ACHD-HF-related admissions in the Dutch CONCOR study (4.6% of ACHD patients admitted over a 14 year period),[18] or the Swedish nation-wide cohort study (3.3% of patients over a median follow-up of 27.5 years).[5] Both studies used administrative HF labels to establish ACHD-HF diagnosis, which may explain the higher prevalence in our study. ACHD-HF prevalence is difficult to establish given the challenge to define ACHD-HF.[19] Prior studies have used administrative diagnoses,[7] HF-related hospital admission,[18] signs and symptoms of HF,[20] natriuretic peptides, and/or peak oxygen consumption[21] to define ACHD-HF. In this study, we used a standardized, inclusive definition of ACHD-HF using a combination of the following: signs and symptoms of HF, impaired ventricular function with elevated

Figure 2 Adult congenital heart disease (ACHD)-heart failure (HF) (ACHD-HF) and all-cause mortality. Inverse Kaplan–Meier plots for all-cause mortality in 186 ACHD-HF patients and 186 matched controls. All-cause mortality was 4.67 times higher in ACHD-HF patients as compared with their matched controls. AR, at risk; E, events; HF, heart failure.

E/AR						
Controls	0/186	14/159	21/99	22/74	28/52	31/34
HF patients	0/186	4/182	7/132	8/80	10/55	10/55
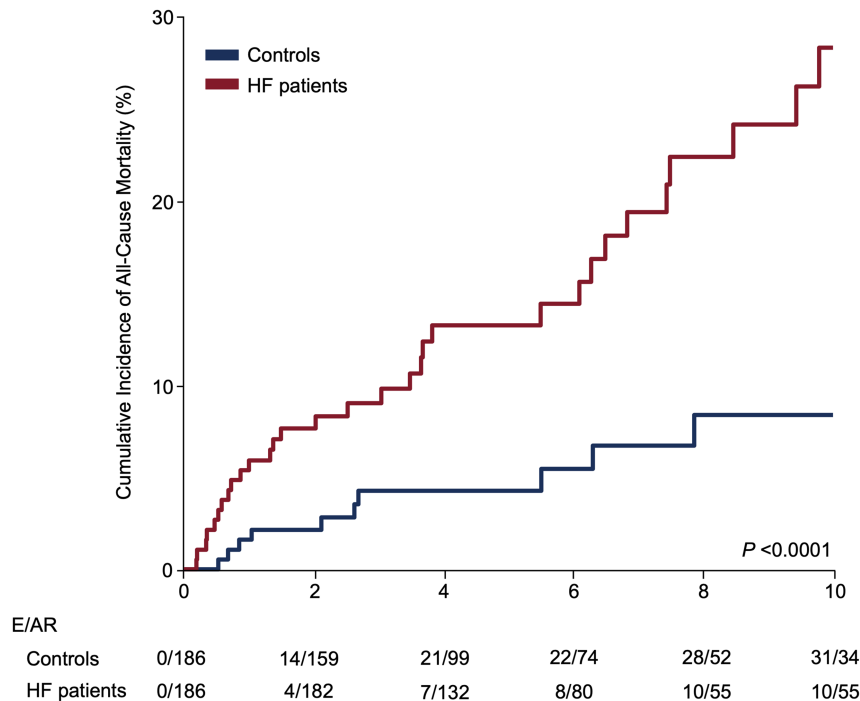
filling pressures, exercise intolerance, elevation of natriuretic peptides and/or unique ACHD-HF manifestations in patients with a Fontan circulation (protein loosing enteropathy or plastic bronchitis).[22] This definition probably reduces the risk of underestimation (because only patients who require hospital admission were included) or overestimation of ACHD-HF prevalence (because patients at risk for HF were also included[23]). This study indicates a substantially earlier increase in HF prevalence in the ACHD population, when compared with the general population. In the general population, HF prevalence increases from 0.9% in subjects aged 55–64 to 17.4% in those aged ≥85 years,[24] which is quite different from our study cohort with ACHD-HF prevalence increasing from 2.3% in subjects aged 15–35 years to 21.9% in subjects aged >50 years. ACHD-HF prevalence was consistently higher in older patients for all anatomical/physiological ACHD subgroups (heat map). This is intuitive and the improved survival of ACHD patients will automatically increase ACHD-HF prevalence over time. Maybe more importantly, ACHD-HF prevalence in cyanotic patients, patients with a Fontan circulation and patients with a systemic RV was >30% from the age of 35 years and even >50% from the age of 50 years, consistent with prior studies.[25,26] Although ACHD-HF prevalence is lower in patients with a biventricular circulation and systemic LV, absolute numbers in these subgroups exceed the combined number of cyanotic patients, patients with a Fontan circulation, and patients with a systemic RV.
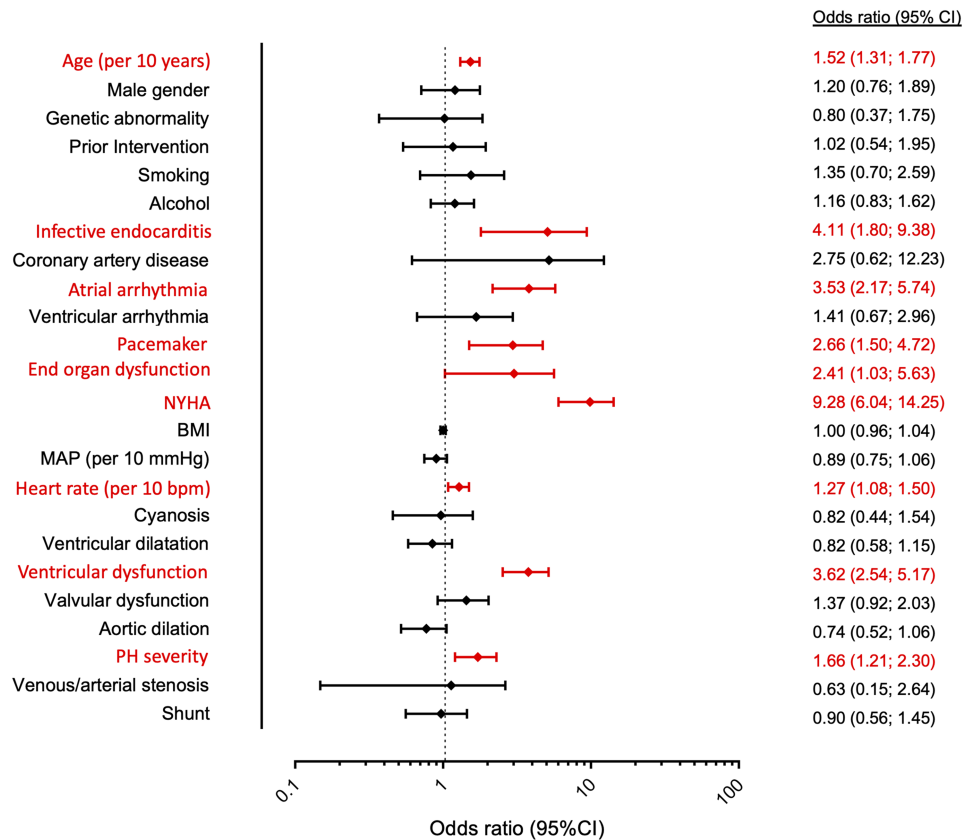
Adult congenital heart disease-heart failure outcome

In this study, patients with ACHD-HF had worse outcome with 25.8% reaching the combined endpoint of death, heart transplant, or VAD implantation, compared with only 1.2% of ACHD patients without HF, which confirms prior reports.[18,27] Our case–control analysis indicates that all-cause mortality was about five times higher in ACHD-HF patients when compared with their matched controls. It also emphasizes the need to better understand factors associated with ACHD-HF so that clinicians can recognize patients at risk for ACHD-HF.[12] These risk factors should trigger a search for modifiable structural or electrical issues[16,28] and heighten ongoing vigilance. Because the ACHD-HF phenotype will differ according to anatomical/physiological subgroups,[4,29] it is equally important to evaluate these risk factors separately for all subgroups.

Factors related to adult congenital heart disease-heart failure

Infective endocarditis is a complication especially frequent in CHD patients with prosthetic valves or valve-containing conduits[30,31] and is associated with increased mortality and morbidity, including HF. The need for high-risk surgery in

Figure 3 Multivariable binary logistic regression analysis. Multivariable analysis for the entire cohort indicating (in red) factors that are independently related with the presence of adult congenital heart disease-heart failure (ACHD-HF) [missing cases: 334 (8.6%)]. BMI, body mass index; NYHA, New York Heart Association.

	Odds ratio (95% CI)
Age (per 10 years)	1.52 (1.31; 1.77)
Male gender	1.20 (0.76; 1.89)
Genetic abnormality	0.80 (0.37; 1.75)
Prior Intervention	1.02 (0.54; 1.95)
Smoking	1.35 (0.70; 2.59)
Alcohol	1.16 (0.83; 1.62)
Infective endocarditis	4.11 (1.80; 9.38)
Coronary artery disease	2.75 (0.62; 12.23)
Atrial arrhythmia	3.53 (2.17; 5.74)
Ventricular arrhythmia	1.41 (0.67; 2.96)
Pacemaker	2.66 (1.50; 4.72)
End organ dysfunction	2.41 (1.03; 5.63)
NYHA	9.28 (6.04; 14.25)
BMI	1.00 (0.96; 1.04)
MAP (per 10 mmHg)	0.89 (0.75; 1.06)
Heart rate (per 10 bpm)	1.27 (1.08; 1.50)
Cyanosis	0.82 (0.44; 1.54)
Ventricular dilatation	0.82 (0.58; 1.15)
Ventricular dysfunction	3.62 (2.54; 5.17)
Valvular dysfunction	1.37 (0.92; 2.03)
Aortic dilation	0.74 (0.52; 1.06)
PH severity	1.66 (1.21; 2.30)
Venous/arterial stenosis	0.63 (0.15; 2.64)
Shunt	0.90 (0.56; 1.45)

Odds ratio (95%CI)

itself, or the sequelae of the infection/intervention may explain the relation with ACHD-HF observed in this study. NYHA class is a strong predictor of outcome in the general ACHD population[32,33] as well as in ACHD-HF patients.[4] Self-reported NYHA class also has a strong association with presence of HF in ACHD patients.[22] Exercise intolerance is one of the cardinal symptoms of HF, so it's reassuring to confirm its value in ACHD patients who may have adapted to a gradually decreasing exercise capacity.

Our study confirms that atrial arrhythmia is closely linked to ACHD-HF. A diagnosis of atrial arrhythmia should raise awareness for ACHD-HF (and vice versa) and should often trigger further investigations. Because atrial arrhythmia in itself could worsen haemodynamics, including worsening ventricular function, restoration, and maintenance of sinus rhythm is a valuable treatment strategy in these patients.[31] Pacemaker implantation has been associated with poor outcome in ACHD subgroups, which may be related to pacing-induced dyssynchrony and subsequent ventricular and/or valvular dysfunction[34] similar to acquired HF. It has also been shown that the degree of structural ACHD complexity is a strong and independent predictor for late device

complications,[35] suggesting that strict follow-up should be planned in complex ACHD patients after pacemaker implantation. Ventricular dysfunction, which mainly relates to systolic systemic and/or pulmonic dysfunction, should always trigger consideration of ACHD-HF. Because ventricular dysfunction alone was insufficient for an ACHD-HF diagnosis, 11% of patients without ACHD-HF had mild, and 3% had moderate/severe ventricular dysfunction. In these patients, who could be considered as having Stage B HF according to the ACC/AHA HF classification system, additional confirmation of an ACHD-HF diagnosis with natriuretic peptides or invasive haemodynamics is of interest and has added prognostic significance,[4,36] especially in patients with moderate/severe complexity CHD.[22,23,25]

Differences between anatomical/physiological subgroups

Coronary artery disease was related to ACHD-HF in patients with a biventricular circulation and a systemic LV. Emergence of a 'geriatric' ACHD population has been described and in

Figure 4 Univariable binary logistic regression analysis. Univariable analysis of factors related with the presence of adult congenital heart disease (ACHD)-heart failure (ACHD-HF) for individual ACHD anatomical/physiological subgroups (numbered 1–6 for cyanotic/Eisenmenger; Fontan; systemic right ventricle; predominant right-sided residual lesions; shunt lesions; and predominant left-sided residual lesions, respectively) for each risk factor assessed in the multivariable analysis of the entire cohort. BMI, body mass index; NYHA, New York Heart Association.
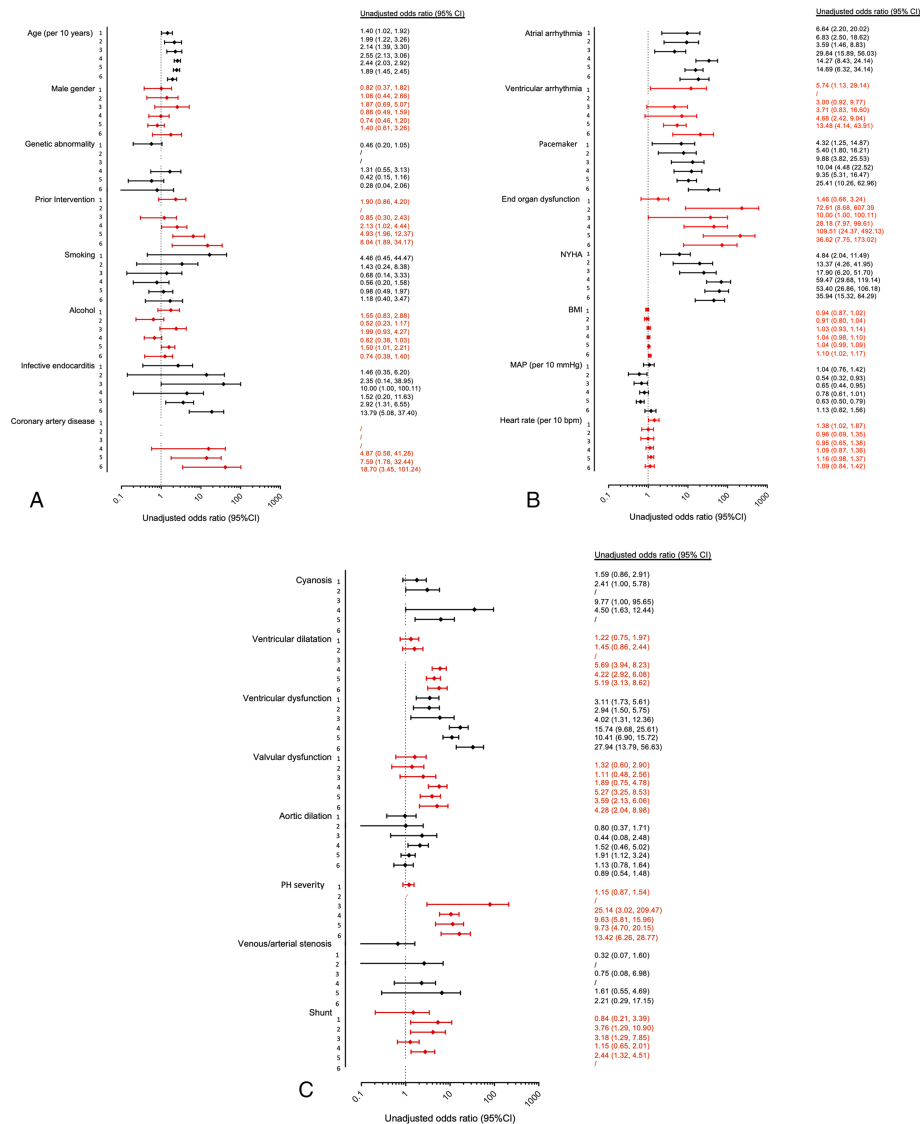
this population acquired morbidities like coronary artery disease likely play a role in HF development and outcome.[3] In (younger) patients with cyanotic heart disease, systemic RV or Fontan circulation, anatomical/physiological complexity still trumps 'classic' cardiovascular risk factors explaining the lack of association with coronary artery disease in these subgroups.

Other parameters will have limited discriminatory value in some anatomically/physiological subgroups if they are uniformly present or absent (for example 'prior intervention' or 'pulmonary hypertension' in patients with a Fontan circulation). Ventricular dilation and valvular dysfunction appear less related to ACHD-HF in patients with cyanotic CHD,

patients with a Fontan circulation and patients with a systemic RV. Although surprising for patients with a Fontan circulation, because the presence of atrioventricular valve regurgitation strongly relates to outcome,[37] dilated ventricles are often observed in the absence of ACHD-HF in these patient groups. Since 2000, transcatheter percutaneous valve implantation (Melody) was described as an alternative to open-heart surgery in patients with predominant right-sided residual lesions (Fallot, pulmonary atresia). Infective endocarditis is significantly more incident in those patients after Melody stents in comparison with homografts.[38] Valve-containing prosthetics is determined as a significant risk for infective endocarditis, whereas other prosthetics,

including valve repair, are not associated with increased risk long term after implantation.[39] In any case, either infective endocarditis itself causing HF or residual lesions after infective endocarditis increase the risk for HF, explaining the stronger association with ACHD-HF in these subgroups of patients.

Strengths and limitations

To the best of our knowledge, the current report represents one of the most detailed studies evaluating the prevalence of ACHD-HF and its associated risk factors in the different subgroups of ACHD, using a uniform definition of ACHD-HF, which provides more granular data when compared with other studies using patient data taken from administrative data.[40] Still, because of the retrospective nature of the study, and although only limited data was missing, our results are dependent on the accuracy of the recorded data. Our study underscores the complex nature of ACHD-HF with involvement of multiple organ systems which require follow-up in a dedicated ACHD-HF clinic with support from interventional cardiologists, congenital cardiac surgeons, electrophysiologists, heart transplant team, and psychologists.[41] We did record data on HF admissions to the hospital, which will be included in future studies. Finally, our study was a single-centre study, resulting in possible measurement of confounders that vary between centres.

Conclusions

Heart failure related to ACHD is prevalent especially in patients with complex CHD and is associated with poor prognosis. Our data provide insight in the factors related to ACHD-HF including differences between specific anatomical/physiological subgroups.

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Conflict of interest

No conflicts of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S2A. Patient characteristics Eisenmenger/Cyanotic CHD patients
Table S2B. Patient characteristics Fontan patients
Table S2C. Patient characteristics systemic RV patients
Table S2D. Patient characteristics shunt lesions patients
Table S2E. Patient characteristics predominant right-sided lesions patients
Table S2F. Patient characteristics predominant left-sided lesions patients

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