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Clinical Research

Short-term Prognostic Value of Heart Failure Diagnosis in a Contemporary Cohort of Patients With Adult Congenital Heart Disease

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ABSTRACT

Background: Heart failure (HF) is the primary cause of premature death in adult congenital heart disease (ACHD). This study aimed to describe the impact of a HF diagnosis on short-term prognosis and to investigate the added prognostic value of an HF diagnosis to the ACHD Anatomic and Physiologic classification (ACHD-AP).

Methods: This study included 3995 patients followed in a tertiary care centre (last follow-up after January 1, 2010). Survival curves were plotted, and predictors of the primary end point (death, heart transplantation, or ventricular assist device [VAD]) were identified with the use of Cox proportional hazard models and compared with the use of Harrell's C-statistic.

Results: Mean age at baseline was 35.7 ± 13.3 years. The prevalence of ACHD-HF was 6.4%. During a median follow-up of 3.1 years (IQR 2.1-3.6 years), 27.3% of ACHD-HF patients reached the primary end point, compared with 1.4% of ACHD patients without HF. Event-free

RÉSUMÉ

Contexte : Chez les patients adultes atteints d'une cardiopathie congénitale (CPC), l'insuffisance cardiaque (IC) est la première cause de décès prématuré. Notre étude visait à décrire les répercussions d'un diagnostic d'IC sur le pronostic à court terme et à examiner la valeur pronostique qu'un tel diagnostic peut ajouter à celle de la classification anatomique et physiologique de la CPC (CAP-CPC).

Méthodologie : L'étude comprenait 3995 patients ayant fait l'objet d'un suivi dans un centre de soins tertiaires (dernier suivi effectué après le 1er janvier 2010). Les courbes de survie ont été tracées et des facteurs de prédiction de la survenue d'un des événements du critère principal (décès, transplantation cardiaque ou pose d'un dispositif d'assistance ventriculaire) ont été établis à l'aide de modèles de Cox à risques proportionnels et comparés au moyen de la statistique C de Harrell.

Résultats : L'âge initial moyen était de 35,7 ± 13,3 ans. La prévalence d'une IC chez les patients adultes atteints d'une CPC

Congenital heart disease (CHD) is the most common type of birth defect,[1] affecting around 1% of newborns.[2,3] Owing to early diagnosis and advances in medical and surgical care for CHD, there has been a significant improvement in long-term survival of newborns with CHD over the past decades, with about 90% surviving into adulthood.[4] Consequently, the number of adult patients with congenital heart disease (ACHD) has increased and now exceeds the number of children with CHD.[5] Despite these advancements, most treatments are still palliative rather than curative. The hearts of ACHD patients remain both anatomically and physiologically abnormal, making them more susceptible to the development of heart failure (HF).[6] Compared with ACHD patients without HF, an HF diagnosis in ACHD patients

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survivals were 78.3%, 61.9%, and 57.5% at 1, 3, and 5 years in ACHD-HF patients, compared with 99.3%, 98.3%, and 98.0% in ACHD patients without HF ($P < 0.001$). An HF diagnosis (HR 6.9, 95% CI 4.3-11.2) and the physiologic classification (HR 2.6, 95% CI 1.9-3.7) were independently associated with the primary end point. The addition of HF to the ACHD-AP classification yielded a Harrell's C-index of 0.8631, providing a significant improvement over the ACHD-AP classification alone ($P = 0.0003$).

Conclusions: The risk of mortality, transplantation, or VAD is increased in ACHD-HF patients. An HF diagnosis appears to be a valuable prognostic marker in addition to the ACHD-AP classification.

(CPC-IC) était de 6,4 %. Sur une période de suivi d'une durée moyenne de 3,1 ans (intervalle interquartile : 2,1 à 3,6 ans), 27,3 % des patients adultes présentant une CPC-IC avaient atteint le critère principal, comparativement à 1,4 % des patients adultes atteints d'une CPC sans IC. Le taux de survie sans événement s'établissait à 78,3 %, 61,9 % et 57,5 % à 1, 3 et 5 ans, respectivement, chez les patients adultes atteints d'une CPC-IC, comparativement à 99,3 %, 98,3 % et 98,0 % chez les patients adultes atteints d'une CPC sans IC ($p < 0,001$). Un diagnostic d'IC (rapport des risques instantanés [RRI] : 6,9; intervalle de confiance [IC] à 95 % : 4,3 à 11,2) et la classification physiologique (RRI : 2,6; IC à 95 % : 1,9 à 3,7) étaient associés, de façon indépendante, au critère principal. L'ajout de l'IC à la CAP-CPC a donné un indice C de Harrell de 0,8631, ce qui constitue une amélioration significative par rapport à la CAP-CPC seule ($p = 0,0003$).

Conclusion : Le risque de mortalité et la nécessité d'une transplantation ou d'un dispositif d'assistance ventriculaire sont accrus chez les patients adultes atteints d'une CPC-IC. Il semble donc qu'un diagnostic d'IC soit un marqueur pronostique important, en plus de la CAP-CPC.

corresponds to a 5-fold increase in mortality risk.[7] As a result, the life expectancy of ACHD patients is still limited compared with the general population, with HF representing the most frequent underlying cause of death.[8]

In 2001, the Bethesda classification, based on anatomic complexity of the underlying heart defect, was proposed to allocate patients to appropriate levels of care.[9] Although the Bethesda classification also predicts outcome,[10-12] its use has been a subject of discussion for years because it does not incorporate functional status (which does not necessarily correlate with anatomic complexity) or account for evolution over time. The 2018 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines proposed a new classification incorporating both anatomical complexity and current physiologic stage of the patient (ACHD-AP),[13] resulting in improved prediction for cardiac mortality.[14] Although some components included in the physiologic stage could be part of the HF syndrome, a true HF diagnosis is not incorporated in the ACHD-AP classification. Because an HF diagnosis has important implications for prognosis, management (strategies), and quality of life, it would be of interest to assess the added weight of a HF diagnosis relative to the anatomic complexity of the underlying heart defect and the physiologic stage of the patient.

Reflecting the increasing importance of HF related to ACHD, there is a well recognised clinical need for population-specific data on ACHD-HF. To better guide physicians in the follow-up and treatment of ACHD patients, this study aimed to 1) describe the impact of a HF diagnosis on the short-term prognosis of ACHD patients, and 2) assess the added prognostic value of an HF diagnosis to the ACHD-AP classification in a contemporary cohort of ACHD patients followed in a tertiary care referral centre.

Methods

Study population

This study includes all ACHD patients (age $\geq$ 16 years) under active follow-up at the University Hospitals Leuven after January 1, 2010. Patients were followed until either the latest follow-up visit or until reaching the primary end point.

Patients were divided into subgroups based on the classification of Task Force 1 of the 32nd Bethesda Conference,[9] and the physiologic severity classification as outlined in the 2018 AHA/ACC guidelines for the management of adults with CHD.[13] The Bethesda disease complexity classification categorises patients into 3 groups (congenital heart defects of simple, moderate, and severe complexity), based solely on the underlying anatomic defect. The physiologic severity classification categorises patients into 4 groups (stages A through D) based on both clinical and physiologic features.[13]

Data on clinical status were recorded from medical records reviewed by one investigator (A.V.D.B.) at the time of their follow-up visit. Data on valvular dysfunction, ventricular dysfunction, and ventricular dilation were obtained from echocardiography reports. Definitions for each recorded patient characteristic, based on the 2018 AHA/ACC guidelines,[13] are provided in Supplemental Table S1. HF associated with ACHD was defined as symptoms and/or signs of HF requiring medical therapy, in addition to at least 1 of the following: 1) impaired ventricular function (systolic, diastolic, or both) with elevated intracardiac pressures; 2) elevated B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP); 3) peak oxygen consumption in the lowest quartile according to published norms for each ACHD subtype; or 4) unique manifestations of Fontan circulatory failure in patients with a Fontan circulation (Fontan pressure $\geq$ 20 mm Hg, plastic bronchitis, protein-losing enteropathy, cardiac index $<$ 2 L/min/m^2)[7,15] Each patient's HF diagnosis was reviewed by 1 investigator (A.V.D.B.) at the moment of inclusion (prevalent cohort). In case of doubt, the case was discussed with colleagues (W.B., E.T., and P.D.M). Data on overall mortality were obtained from the hospital's information system, which is linked to the national statistics office. The composite primary end point was defined as all-cause mortality, heart transplantation, or ventricular assist device (VAD) implantation, whichever occurred first. Patients' records were reviewed after pseudonymising patient data in compliance with the Global Data Protection

Table 1. Patient characteristics for the entire cohort stratified by the composite primary end point, n (%)

Variable	Entire cohort (n = 3995)	End point no (n = 3856)	End point yes (n = 139)	*P* value
Bethesda disease complexity				**< 0.001**
Mild	1338 (33.5)	1308 (33.9)	30 (21.6)	
Moderate	2222 (55.6)	2144 (55.6)	78 (56.1)	
Severe	435 (10.9)	404 (10.5)	31 (22.3)	
Physiologic severity stage				**< 0.001**
A	720 (18.0)	719 (18.6)	1 (0.7)	
B	1421 (35.6)	1408 (36.5)	13 (9.4)	
C	1686 (42.2)	1609 (41.7)	77 (55.4)	
D	168 (4.2)	120 (3.1)	48 (34.5)	
Heart failure diagnosis	257 (6.4)	179 (4.6)	78 (59.1)	**< 0.001**
Age at last FU, y	35.7 ± 13.3	35.3 ± 12.8	48.5 ± 19.0	**< 0.001**
Male sex	2075 (51.9)	2005 (52.0)	70 (50.4)	0.730
Any genetic abnormality	458 (11.5)	433 (11.2)	25 (18.0)	**0.021**
Trisomy 21	146 (3.7)	132 (3.4)	14 (10.1)	**< 0.001**
22q11	82 (2.1)	76 (2.0)	6 (4.3)	0.064
Noonan	61 (1.5)	59 (1.5)	2 (1.4)	1.000
Williams	26 (0.7)	137 (3.6)	2 (1.4)	0.228
Intervention	2700 (67.6)	2593 (41.3)	107 (77.0)	**0.016**
Smoking	500 (12.5)	489 (12.7)	11 (7.9)	0.175
Missing	306 (7.7)	287 (7.4)	19 (13.7)	
Infective endocarditis	110 (2.8)	131 (3.4)	8 (5.8)	0.056
Coronary artery disease	25 (0.6)	24 (0.6)	1 (0.7)	0.589
Atrial arrhythmia	356 (8.9)	305 (7.9)	51 (36.7)	**< 0.001**
AVNRT	9 (0.2)	8 (0.2)	1 (0.7)	0.273
Ventricular arrhythmia	120 (3.0)	127 (3.3)	12 (8.6)	**< 0.001**
RF ablation	162 (4.1)	123 (3.2)	16 (11.5)	**< 0.001**
Pacemaker	215 (5.4)	185 (4.8)	30 (21.6)	**< 0.001**
AICD	72 (1.8)	130 (3.4)	9 (6.5)	**< 0.001**
CRT	25 (0.6)	19 (0.5)	6 (4.3)	**< 0.001**
End-organ dysfunction				**< 0.001**
No	3916 (98.0)	3813 (98.9)	103 (74.1)	
Mild	67 (1.67)	40 (1.0)	27 (19.4)	
Severe	12 (0.3)	3 (0.1)	9 (6.5)	
Clinical characteristics				
NYHA				**< 0.001**
I	3544 (88.7)	3504 (90.9)	40 (28.8)	
II	379 (9.5)	324 (8.4)	55 (39.6)	
III	62 (1.6)	26 (0.7)	36 (25.9)	
IV	10 (0.3)	2 (0.1)	8 (5.8)	
BMI, kg/m^2	25.2 ± 4.9	25.2 ± 4.8	24.5 ± 5.9	0.229
Missing	347 (8.7)	325 (8.4)	22 (15.8)	
SBP, mm Hg	128.2 ± 26.9	128.5 ± 27.0	121.5 ± 23.0	0.005
Missing	228 (5.7)	210 (5.4)	18 (12.9)	
DBP, mm Hg	73.4 ± 11.4	73.5 ± 11.3	69.7 ± 12.5	0.001
Missing	231 (5.7)	213 (5.5)	18 (12.9)	
Heart rate, beats/min	71.9 ± 13.4	71.8 ± 13.3	74.4 ± 15.6	0.067
Missing	270 (6.8)	251 (6.5)	19 (13.7)	
Cyanosis				**< 0.001**
No	3870 (96.9)	3764 (97.6)	106 (76.3)	
Mild	64 (1.6)	59 (4.5)	5 (3.6)	
Severe	61 (1.5)	33 ()0.9	28 (20.1)	
Echocardiography				
Ventricular dilation				**< 0.001**
No	2839 (71.1)	2795 (72.5)	44 (31.7)	
Mild	658 (16.5)	622 (16.1)	36 (25.9)	
Moderate-severe	498 (12.5)	439 (11.4)	59 (42.4)	
Ventricular dysfunction				**< 0.001**
No	3267 (81.8)	3216 (83.4)	51 (36.7)	
Mild	488 (12.2)	449 (11.6)	39 (28.1)	
Moderate-severe	240 (6.0)	191 (5.0)	49 (35.3)	
Valvular dysfunction				**< 0.001**
No	970 (24.3)	965 (25.0)	5 (3.6)	
Mild	1730 (43.3)	1686 (43.7)	44 (31.7)	
Moderate-severe	1295 (32.4)	1205 (31.3)	90 (64.7)	
Aortic dilation				0.131
< 35 mm	3366 (84.3)	3244 (84.1)	122 (87.8)	
35-39 mm	319 (8.0)	315 (8.2)	4 (2.9)	
40-49 mm	274 (6.9)	262 (6.8)	12 (8.6)	
≥ 50 mm	36 (0.9)	35 (0.9)	1 (0.7)	

Continued

Table 1. Continued.

Variable	Entire cohort (n = 3995)	End point no (n = 3856)	End point yes (n = 139)	*P* value
Pulmonary hypertension				**< 0.001**
< 35 mm Hg	3782 (94.7)	3699 (95.9)	83 (59.7)	
35-60 mm Hg	124 (3.0)	98 (2.5)	26 (18.7)	
> 60 mm Hg	89 (2.2)	59 (1.5)	30 (21.6)	
Venous/arterial stenosis	76 (1.9)	69 (1.8)	7 (5.0)	**0.016**
Persistent shunt				**< 0.001**
No shunt	3353 (83.9)	3257 (84.5)	96 (69.1)	
Mild shunt	502 (12.6)	492 (12.8)	10 (7.2)	
Significant shunt	140 (3.5)	107 (2.8)	33 (23.7)	

The composite primary end point is defined as either death, VAD implantation, or transplantation. *P* values in bold are significant.

AICD, automatic internal cardiac defibrillator; AVNRT, atrioventricular nodal re-entry tachycardia; BMI, body mass index; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure. FU, follow-up; NYHA, New York Heart Association functional calss; RF, radiofrequency ablation; SBP, systolic blood pressure.

Regulation. The hospital's Institutional Ethics Committee approved the study protocol and waived the need for individual patient consent. The study was conducted in conformity with the principles of the Declaration of Helsinki.

Statistical analysis

Data were tested for normality by means of the Kolmogorov-Smirnov test. Descriptive data for continuous variables were displayed as mean ± SD or as median (interquartile range [IQR]) as appropriate. Descriptive data for discrete variables were displayed as percentages or frequencies. Duration of follow-up was calculated as the difference between date of first ACHD clinic visit and date of reaching the composite primary end point or censoring (December 1, 2021). For comparison between groups, the chi-square test, Fisher exact test, or independent Student *t* test were used as appropriate. All tests were 2 sided, and the level of statistical significance was set at 0.05.

Kaplan-Meier analyses were used to assess risk of the composite primary outcome over time. The log-rank test was applied to identify differences in survival among different groups. Predictors of the composite primary end point were identified by means of multivariable Cox proportional regression analysis using the composite primary end point as the dependent variable and the following covariates: age (per 10 years), sex, heart rate (per 10 beats/min), mean arterial pressure (per 10 mm Hg), body mass index, underlying genetic abnormality, presence of coronary artery disease, history of infective endocarditis, previous intervention (surgical or percutaneous), Bethesda disease complexity classification, physiologic severity classification, and an HF diagnosis. Intervention was defined as any surgical or percutaneous intervention before inclusion in the study. Covariates already present in the physiologic severity classification (New York Heart Association [NYHA] functional class, pacemaker, arrhythmias, end-organ dysfunction, ventricular dilation, ventricular dysfunction, valvular dysfunction, aortic dilation, pulmonary hypertension, venous/arterial stenosis, persistent shunt) were not included separately in the Cox proportional regression analysis. Results were displayed as hazard ratio (HR) with 95% confidence interval (CI).

Harrell's concordance statistics index (C-index) was calculated with the use of Cox proportional hazard models to assess accuracy of different prediction models.[16] Prediction models were classified based on the following cutoff values: a C-index less than 0.70 was regarded as a poor model; a C-index from 0.70 to 0.79 indicated a good model; a C-index from 0.80 to 0.89 was regarded as an excellent model; and a C-index of 0.90 or more was considered to represent an outstanding model.[14] A nonparametric approach devised for right-censored survival data was used to compare C-indexes in a pairwise fashion.[17] Data analysis was performed with the use of SPSS for Windows (version 24; IBM, Armonk, NY) and R version 64 4.0.3.

Results

Patient characteristics

A total of 3995 ACHD patients (52% male) were included in this study. Mean age at last follow-up was 35.7 ± 13.3 years. An overview of patient characteristics for the entire cohort of ACHD patients is provided in Table 1. Based on the Bethesda disease complexity classification, 33.5% of patients had simple defects, 55.6% moderate defects, and 10.9% severe defects. According to the physiologic severity classification, 18.0% of patients were categorised as physiologic stage A, 35.6% as physiologic stage B, 42.2% as physiologic stage C, and 4.2% as physiologic stage D. Figure 1 depicts the prevalence of HF for each ACHD-AP class. The overall prevalence of ACHD-HF at inclusion was 6.4%.

Average age, Bethesda disease complexity class, physiologic severity stage, and NYHA functional class were significantly higher in patients reaching the primary end point. The presence of HF, any genetic abnormality, trisomy 21, previous intervention or radiofrequency ablation, atrial or ventricular arrhythmia, electrical devices (ie, pacemaker, automatic internal cardiac defibrillator [AICD], cardiac resynchronization therapy [CRT]), venous/arterial stenosis, persistent shunt, ventricular dilation, pulmonary hypertension, and ventricular, valvular, and end-organ dysfunction was significantly higher compared with patients not reaching the primary end point (Table 1).

Primary outcome

During a median follow-up of 3.1 years (IQR 2.1-3.6 years) a total of 139 ACHD patients (3.5%) reached the composite primary end point, consisting of death, transplantation, or VAD implantation. Table 2 summarises the outcome data for the entire cohort. In the HF group, death was due to a noncardiac cause in 11 patients (17%), due to HF in 34 (52%), sudden in 3 (5%), and of unknown cause in

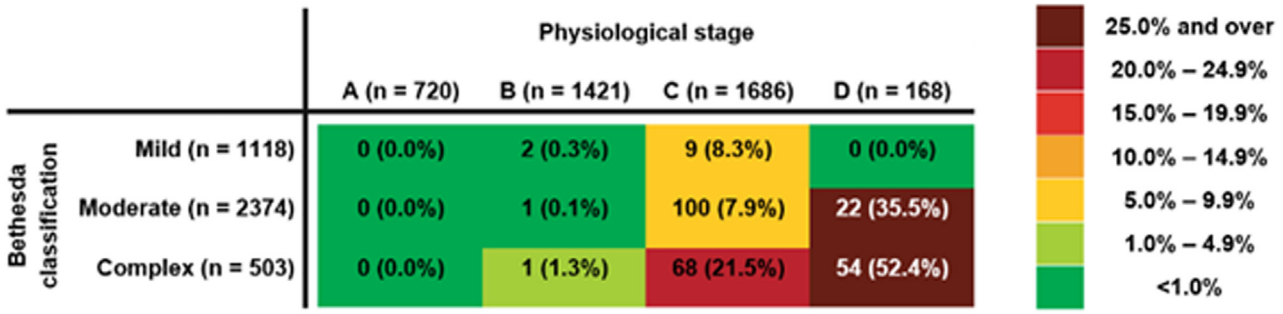


Figure 1. Absolute number and prevalence of heart failure diagnoses for each respective Bethesda disease complexity class and physiologic severity stage.

17 (26%). In the non-HF group, death was due to a noncardiac cause in 27 patients (44%), due to new-onset HF in 2 (3%), sudden in 3 (16%), and of unknown cause in 22 (36%). Seventy-eight ACHD patients (30.4%) with the diagnosis of HF reached the composite primary end point, compared with 61 ACHD patients (1.6%) without HF.

Figure 2 displays the survival plots for ACHD patients with or without HF, as well as each subgroup of the Bethesda disease complexity and physiologic severity classification. In ACHD patients without HF, event-free survivals were 99.3%, 98.3%, and 98.0% at, respectively, 1, 3, and 5 years of follow-up. In ACHD patients with HF, event-free survivals were significantly lower: 78.3%, 61.9%, and 57.5% at 1, 3, and 5 years of follow-up ($P < 0.001$). Event rate rises in the presence of an HF diagnosis ($P < 0.001$), with increasing complexity according to the Bethesda disease complexity classification ($P < 0.001$), and with increasing severity according to the physiologic severity classification ($P < 0.001$). Figure 2, D and E, respectively, depicts the probability of the composite primary end point for physiologic stages C and D stratified by HF diagnosis. Within both physiologic stages C and D, event rate was significantly increased when a HF diagnosis was present ($P < 0.001$). Figure 3 presents event rates for each age group of ACHD patients, stratified by HF diagnosis.

Factors related to the primary outcome and the added value of an HF diagnosis

In multivariable analysis, age at latest follow-up (per 10 years: HR 1.41, 95% CI 1.23-1.62; $P < 0.001$), any genetic abnormality (HR 2.49, 95% CI 1.51-4.11; $P < 0.001$), physiologic stage (HR 2.63, 95% CI 1.86-3.70; $P < 0.001$), and HF diagnosis (HR 6.96, 95% CI 4.33-11.18; $P < 0.001$) were independently associated with the composite primary end point (Fig. 4).

Harrell's concordance statistic indices for Bethesda disease complexity classification, physiologic severity classification, HF, and different combinations in the prediction of the composite primary end point are displayed in Figure 5. Harrell's C-index for the Bethesda disease complexity classification alone was 0.61 (95% CI 0.56-0.65). Combining the physiologic severity classification and the Bethesda disease complexity classification, ie, the ACHD-AP classification, yielded a C-index of 0.81 (95% CI 0.78-0.85), which is significantly better in predicting the primary end point than the Bethesda classification alone ($P < 0.001$). The addition of HF to ACHD-AP classification increased the C-index to 0.86 (95% CI 0.83-0.89), which provides a significant improvement over the ACHD-AP classification alone ($P < 0.001$).

Discussion

This contemporary patient cohort from a large tertiary-care referral centre indicates that an HF diagnosis is strongly related to worse outcome. Moreover, an HF diagnosis adds prognostic value to the ACHD-AP classification.

For patients with CHD, HF represents a significant cause of morbidity, adversely affects patient-reported outcomes,[18] and is the foremost complication impeding normal life expectancy. Recent expert opinions[19] and position statements[6,20,21] therefore highlight the necessity to address ACHD-HF. While they

Table 2. Patient outcome stratified by HF diagnosis, Bethesda disease complexity classification, and physiological severity classification, n (%)

Outcome	End point no (n = 3856)	End point yes (n = 139)	Death (n = 126)	Transplantation (n = 14)	VAD (n = 2)	Total (n = 3995)
Heart failure						
Yes	179 (69.6)	78 (30.4)	65 (25.3)	14 (5.4)	2 (0.8)	257
No	2677 (98.4)	61 (1.6)	61 (1.6)	0 (0.0)	0 (0.0)	3738
Bethesda classification						
Mild	1103 (98.7)	15 (1.3)	15 (1.3)	0 (0.0)	0 (0.0)	1118
Moderate	2301 (96.9)	73 (3.1)	71 (3.0)	3 (0.1)	0 (0.0)	2374
Severe	452 (89.9)	51 (10.1)	40 (8.0)	11 (2.2)	2 (0.4)	503
Physiologic severity						
A	719 (99.9)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	720
B	1408 (99.1)	13 (0.9)	13 (0.9)	0 (0.0)	0 (0.0)	1421
C	1614 (95.7)	77 (4.6)	72 (4.3)	6 (0.4)	1 (0.1)	1686
D	128 (76.2)	48 (28.6)	40 (23.8)	8 (4.8)	1 (0.6)	168

The composite primary end point is defined as either death, VAD implantation, or transplantation.

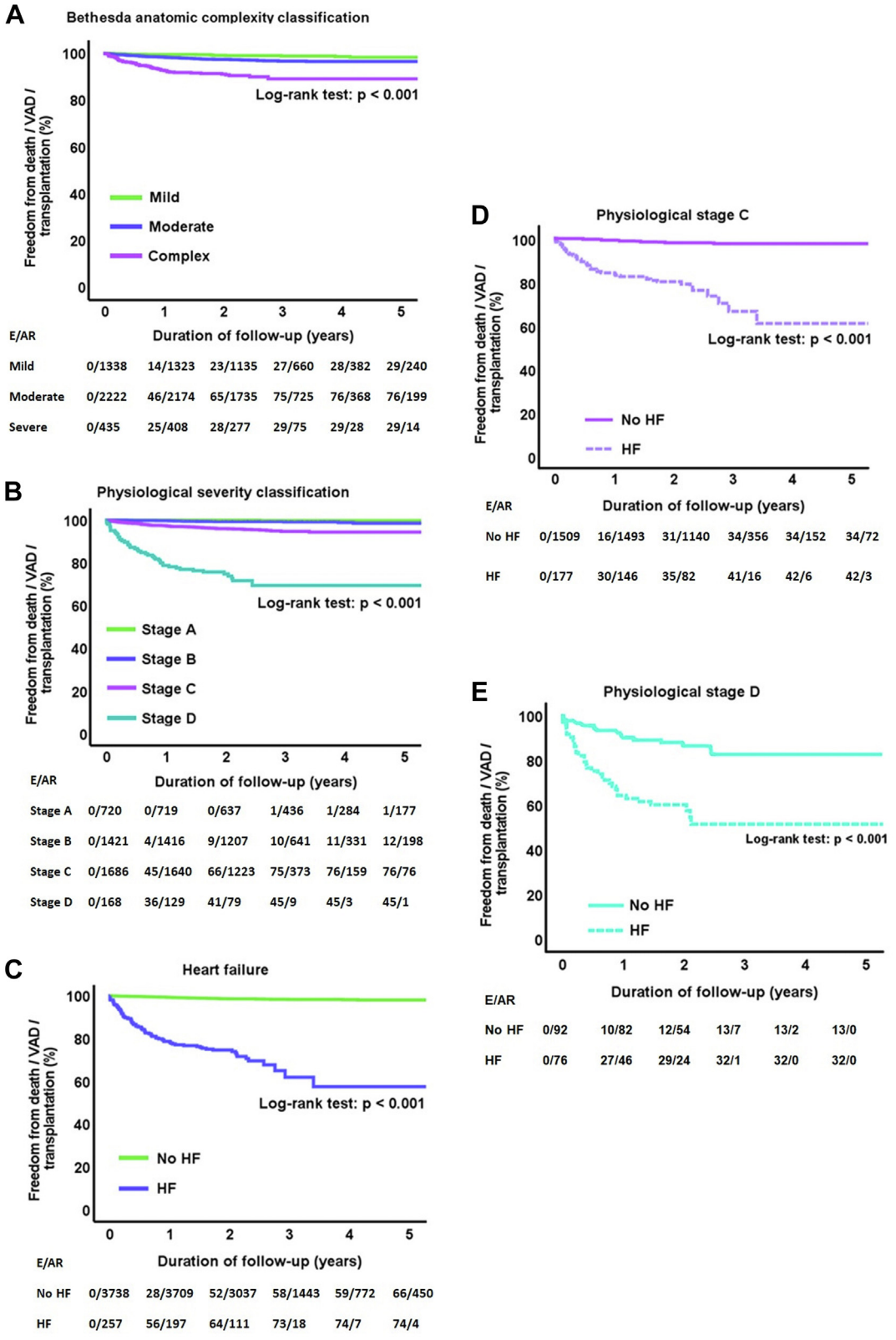
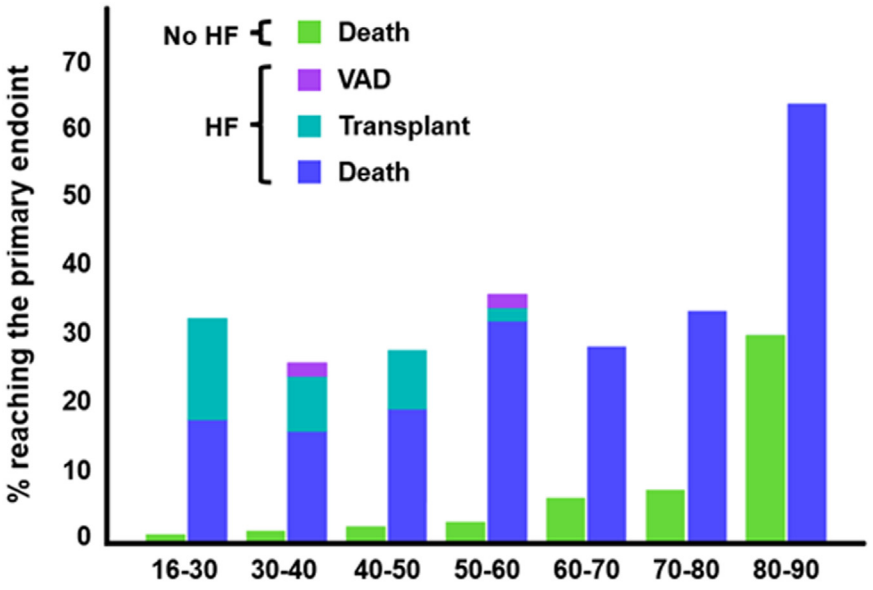


Figure 2. Kaplan-Meier curves for the composite primary outcome (death, ventricular assist device [VAD], or transplantation) stratified by (**A**) Bethesda disease complexity classification, (**B**) physiologic severity classification, (**C**) heart failure (HF) diagnosis, (**D**) HF diagnosis in physiologic stage C, and (**E**) HF diagnosis in physiologic stage D. AR, patients at risk; E, events.



		16-30	30-40	40-50	50-60	60-70	70-80	80-90
No HF:	– Total n	1577	1092	594	261	112	41	10
	– Death n (%)	14 (0.9)	15 (0.9)	12 (2.0)	7 (2.7)	7 (6.3)	3 (7.3)	3 (30.0)
HF:	– Total n	34	50	47	50	39	21	11
	– VAD n (%)	-	1 (2.0)	-	1 (2.0)	-	-	-
	– Transplant n (%)	5 (14.7)	4 (8.0)	4 (8.5)	1 (2.0)	-	-	-
	– Death n (%)	6 (17.6)	8 (16.0)	9 (19.1)	16 (32.0)	11 (28.2)	7 (33.3)	7 (63.3)

Figure 3. Bar chart displaying the percentages of patients reaching each component of the composite primary end point (death, ventricular assist device [VAD], or transplantation) across different age groups. HF, heart failure.

emphasise the need to identify ACHD-specific prognostic markers and appropriate thresholds for referral for advanced HF therapies, they also recognise the challenges in doing so, such as the paucity of population-specific data and marked heterogeneity among ACHD patients. In an effort to meet this demand, our study assessed the (added) prognostic value of an HF diagnosis in ACHD patients.

In our cohort of 3995 ACHD patients with a mean age of 35 years, the prevalence of HF was calculated to be 6.4%, which is slightly higher than in other reports,[8,22] which may be related to the use of administrative labels in the latter rather than a definition for ACHD-HF based on clinical, metabolic, and physiologic features as done in the present analysis.[15] The patient cohort included in this study is similar to the Brompton cohort[11] with slightly less complex defects (11% vs 15%), less simple defects (34% vs 52%), and more moderate defects (56% vs 33%) according to the Bethesda disease complexity classification.

Recognising the limitations of an anatomy-based classification system to capture disease severity of patients with CHD, the most recent ACC/AHA guidelines for the management of adults with CHD introduced the ACHD-AP classification.[13] Based on data suggesting their importance in prognosis, management, and/or quality of life, variables were selected and patients were categorised according to the highest relevant physiologic feature. Our data indicate that variables such as ventricular dilation, ventricular or valvular dysfunction, pulmonary hypertension, end-organ dysfunction, NYHA functional class, the presence of arrhythmias, and the need for electrical therapies (ie, pacemaker, AICD, and radiofrequency ablation) are associated with worse outcome. Because these variables are part of the ACHD-AP classification, our data confirm the validity of its components in predicting (short-term) outcome. The fact that aortic dilation is not related to outcome is likely due to an intervention being performed before occurrence of the overall end point. Some of these variables (such as ventricular dilation, ventricular or valvular dysfunction, pulmonary hypertension, end-organ dysfunction, and NYHA functional class) are often, but not necessarily always, part of an HF syndrome.

Our data indicate that ACHD-HF prevalence rises with increasing anatomic complexity and increasing physiologic severity, with no reports of HF in patients with simple defects in physiologic stage A, and an HF prevalence of 52.4% in patients with severe defects in physiologic stage D (Fig. 1). Still, while an increasing physiologic stage should raise

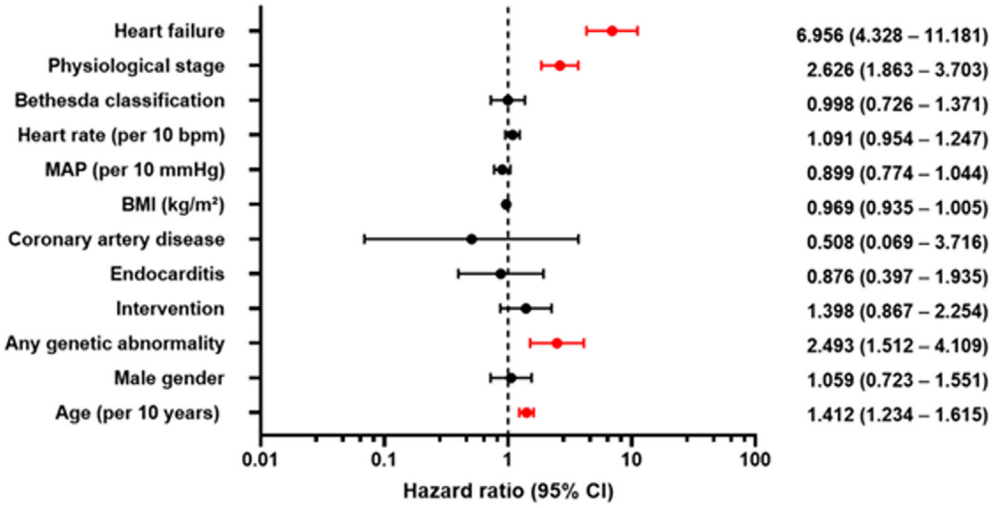


Figure 4. Multivariable regression analysis of variables related with the composite primary outcome (death, ventricular assist device, or transplantation) for the entire cohort, displaying the hazard ratios and 95% CIs. Factors depicted in **red** are independently related to the primary outcome. BMI, body mass index; MAP, mean arterial pressure.

awareness for the possibility of ACHD-HF, our data also indicate that an HF diagnosis is not completely captured by the ACHD-AP classification because it may require additional interpretation of clinical examination, blood work (including natriuretic peptides), and invasive hemodynamics. In other words, there is significant overlap between a more severe physiologic stage and HF, but terminology cannot be used interchangeably. When deciding on appropriate levels of care, an HF diagnosis should always be considered, because it may imply more stringent follow-up or even referral for advanced HF therapies.

Our results highlight the increased short-term risk of mortality or need for transplantation or VAD implantation in ACHD-HF patients. Over a median follow-up of 3.1 years, the event rate was estimated at 30.4% in ACHD-HF patients, which is similar to earlier reports.[23] The event rate was 21.7% in the first year of follow-up. In comparison, the overall event rate in ACHD patients without HF was only 1.6%. These findings are largely similar to the CONCOR registry, where the 1-year mortality rate following the first HF admission was calculated to be 24%.[8] This underscores the importance of early recognition of ACHD-HF to allow for timely referral to centres with combined expertise in ACHD and HF.[19] Unfortunately, we were unable to address how structural interventions, ablation procedures, or implantation of devices changed the course of ACHD-HF.[24,25] Although event rates also rise with increasing anatomic complexity and physiologic severity, an HF diagnosis provides added prognostic information. This is shown in Figure 2, D and E, showing that among ACHD patients in the same physiologic stage, event rate varies significantly depending on the presence of a HF diagnosis. The increased event rate in physiologic stages C and D seems to be largely driven by ACHD-HF patients. This is important because it provides information that will help clinicians to identify patients requiring more intensive follow-up or referral to a quaternary hospital for advanced HF treatment options such as mechanical circulatory support or heart transplantation.[26]

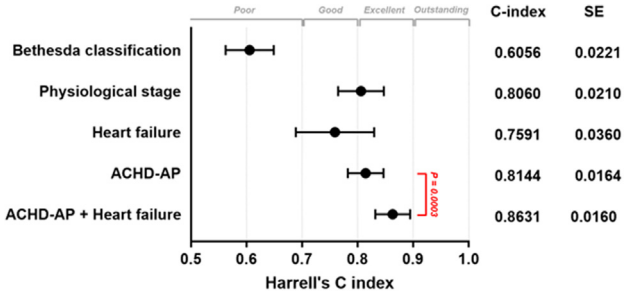


Figure 5. Forest plot of Harrell's concordance statistics index for the Bethesda disease complexity classification, the physiologic classification, heart failure, and combinations to predict the composite primary end point consisting of death, transplantation, or ventricular assist device implantation. ACHD-AP, Adult Congenital Heart Disease Anatomic and Physiologic classification.

The ACHD-AP classification incorporates both anatomic complexity and current physiologic stage of the patient, resulting in an improvement in predicting mortality in ACHD patients,[14] which was confirmed by our findings (Fig. 5). Because HF proves to be an important determinant of mortality in ACHD patients, and is likely not entirely captured by the physiologic stage of the patient, we assessed the added value of a HF diagnosis on top of ACHD-AP classification. As demonstrated in Figure 5, an HF diagnosis indeed represents a valuable addition to the ACHD-AP classification for risk stratification. This was confirmed by a multivariable analysis showing that, next to the physiologic severity classification, the presence of HF was a strong independent predictor associated with mortality, transplantation, or VAD. In addition, old age and any genetic abnormality were independently associated with the primary end point. Expectedly, old age proves to be an important risk factor. Its absence, however, should not subvert appropriate follow-up, because excess mortality compared with the general population is evident also in younger ACHD patients,[8] especially

with the presence of HF (Fig. 3). Although many genetic disorders manifest with considerable comorbidities, our data suggest that mainly trisomy 21 patients are at an increased risk (Table 1), which is likely explained by their predisposition to developing Eisenmenger syndrome.[27,28] Also, 22q11.2 deletion syndrome has previously been associated with premature death, mediated only in part by greater anatomic complexity.[29-31] Although the event rate in patients with 22q11.2 deletion syndrome seemed to be increased in our analyses (Table 1), it did not reach statistical significance.

Strengths and limitations

To the best of our knowledge, this study is the first to describe the added value of an HF diagnosis relative to the ACHD-AP classification on outcome of ACHD patients over time, using a standardised definition of ACHD-HF in a large cohort of ACHD patients. In addition, this study provides more granular data compared with other studies using administrative patient data. Nevertheless, owing to the retrospective nature of the study, our findings remain dependent on the accuracy of the recorded data. Furthermore, this was a single-centre study, resulting in possible measurement of confounders that may vary between different centres. Because all patients were followed in a quaternary referral centre, complex ACHD might be overrepresented in our cohort. However, because distribution of anatomic complexity in this report was similar to previous studies that also include ACHD patients followed in general hospitals,[8] we think that our findings can be extrapolated to ACHD patients who require regular follow-up in general hospitals, most certainly to ACHD patients with HF. We used all-cause mortality instead of cardiovascular death within the composite primary end point, which may overestimate the mortality caused by the underlying heart defect. The survival of prevalent cohorts, as in this study, may be higher when compared with incident cohorts of ACHD-HF.[32] Finally, biomarkers such as BNP or NT-proBNP, although being part of an HF diagnosis for some patients, were not available for all the patients and therefore not used in the predictive model.

Conclusion

Mortality or the need for transplantation or a VAD is substantially increased in ACHD-HF patients. While our findings confirm the validity of the ACHD-AP classification in risk-stratifying ACHD patients, they also indicate that an HF diagnosis affects outcome independently from anatomic complexity and physiologic stage. As such, our data highlight the importance of taking HF into account alongside the ACHD-AP classification. This will help physicians to stratify short-term risk and identify patients requiring referral for advanced HF treatment options, including mechanical circulatory support or heart transplantation.

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Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2022.12.018.