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ORIGINAL RESEARCH

Associations Between Clinical Outcomes and a Recently Proposed Adult Congenital Heart Disease Anatomic and Physiological Classification System

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BACKGROUND: American Heart Association and American College of Cardiology consensus guidelines introduce an adult congenital heart disease anatomic and physiological (AP) classification system. We assessed the association between AP classification and clinical outcomes.

METHODS AND RESULTS: Data were collected for 1000 outpatients with ACHD prospectively enrolled between 2012 and 2019. AP classification was assigned based on consensus definitions. Primary outcomes were (1) all-cause mortality and (2) a composite of all-cause mortality or nonelective cardiovascular hospitalization. Cox regression models were developed for AP classification, each component variable, and additional clinical models. Discrimination was assessed using the Harrell C statistic. Over a median follow-up of 2.5 years (1.4–3.9 years), the composite outcome occurred in 185 participants, including 49 deaths. Moderately or severely complex anatomic class (class II/III) and severe physiological stage (stage D) had increased risk of the composite outcome (AP class IID and IIID hazard ratio, 4.46 and 3.73, respectively, versus IIC). AP classification discriminated moderately between patients who did and did not suffer the composite outcome (C statistic, 0.69 [95% CI, 0.67–0.71]), similar to New York Heart Association functional class and NT-proBNP (N-terminal pro-B-type natriuretic peptide); it was more strongly associated with mortality (C statistic, 0.81 [95% CI, 0.78–0.84]), as were NT-proBNP and functional class. A model with AP class and NT-proBNP provided the strongest discrimination for the composite outcome (C statistic, 0.73 [95% CI, 0.71–0.75]) and mortality (C statistic, 0.85 [95% CI, 0.82–0.88]).

CONCLUSIONS: The addition of physiological stage modestly improves the discriminative ability of a purely anatomic classification, but simpler approaches offer equivalent prognostic information. The AP system may be improved by addition of key variables, such as circulating biomarkers, and by avoiding categorization of continuous variables.

Key Words: adult congenital heart disease ■ classification ■ cohort study ■ congenital heart disease ■ guidelines ■ mortality ■ outcomes

Patients with adult congenital heart disease (ACHD) are a growing population with high healthcare resource use.[1–4] ACHD describes a broad spectrum of diagnoses associated with distinct clinical courses and many potential complications.[2,3,5] Consequently, it has been challenging to identify a broadly applicable classification schema for clinical management and risk stratification.

The most commonly used ACHD classification system, initially proposed at the 32nd Bethesda

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CLINICAL PERSPECTIVE

What Is New?

- In 2018, American Heart Association and American College of Cardiology guidelines proposed an anatomic and physiological adult congenital heart disease classification, integrating traditional concepts of anatomic complexity with markers of pathophysiological severity.
- The current analysis of 1000 adults with congenital heart disease reports that physiological stage does add discriminative power to anatomic classification alone.
- However, the anatomic and physiological classification did not outperform simpler approaches to predicting outcome, such as measurement of circulating natriuretic peptides.

What Are the Clinical Implications?

- The proposed American Heart Association and American College of Cardiology adult congenital heart disease anatomic and physiological classification scheme provides a conceptual framework for personalizing adult congenital heart disease care, but further tuning and validation is required before large-scale clinical implementation.

Nonstandard Abbreviations and Acronyms

ACHD	adult congenital heart disease
AnatC	anatomic class
AP	anatomic and physiological
NYHA FC	New York Heart Association functional class
PhyS	physiological stage

Conference, are based mainly on congenital heart disease (CHD) anatomy.[6] There is little consideration of other variables with implications for management and prognosis, including prior interventions, complications, comorbidities, and current functional status.[6,7]

The anatomic and physiological (AP) classification system, introduced in the 2018 American Heart Association/American College of Cardiology ACHD guidelines, attempts to address the shortcomings of the anatomic classification. The AP system includes 2 components: anatomic class (AnatC) and physiological stage (PhyS). AnatC is a largely anatomic classification similar to the 32nd Bethesda Conference scheme. Conversely, PhyS reflects a distinct dimension of the status of patient with ACHD, combining aspects of physiology, complications, and functional status.[6,8] Patients are assigned an AnatC of I to III and a PhyS of A to D; therefore, patients fall into one of 12 possible categories (IA–IIID).[8]

To assign PhyS for a given patient, a clinician considers a broad array of variables.[8] This dimension and some of its component variables, such as New York Heart Association functional class (NYHA FC), would be expected to be associated with clinical outcomes, including early postoperative and longterm mortality.[9,10] However, it is not yet clear how well the AP system compares with other approaches, particularly in terms of outpatient follow-up. A recent study from our group highlighted obstacles to implementing PhyS in practice, including ambiguities in definitions resulting in interobserver variability.[11]

The present study of an outpatient ACHD referral cohort has 4 aims: (1) to assess the distribution of the AP system classifications and component variables; (2) to assess the ability of the AP system, especially PhyS, to predict outcomes important to the care of patients with ACHD; (3) to compare the AP system to other prognostic models and variables currently used in clinical practice; and (4) to identify areas of potential improvement for future iterations of the AP system.

METHODS

Data Disclosure Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Description of the Cohort

Patients enrolled in the BACH (Boston ACHD Biobank) were included in the current study. The BACH is a prospective cohort study that enrolled outpatients ≥18 years old with congenital heart disease at Boston Children's or Brigham and Women's Hospitals between March 2012 and January 2019. We obtained written informed consent from each participant or their legally authorized representative. Details of the design and methodology of this cohort study have been published.[12] Additional data were collected to assign AP classification by chart review accurately. This study was approved by Boston Children's Hospital's Institutional Review Board with a formal reliance agreement between the Partners HealthCare/Brigham and Women's Hospital and Boston Children's Hospital institutional review boards.

Data Collection and AP Assignment

Baseline data, including CHD diagnosis, clinical characteristics, and clinically indicated testing were collected from the electronic health record at the time of enrollment and reflect the index visit.[12] Information about any

outcomes, interventions, and hospitalizations that are reported to the patient's BACH physician is collected at regular intervals for each patient. For this study, we collected additional information about diagnostic tests, anatomy, and physiologic data as needed to assign AnatC and PhyS. When not explicitly described in the guideline document, AP category definitions were developed based on existing literature and expert opinion (Tables S1 and S2).[8,11,13–17] These were discussed by an expert panel (M.G., M.J.L., A.R.O., and A.M.V.) and approved by consensus. Each patient was assigned an AP category according to the most severe clinical features at the time of their index visit. These classifications were not changed for follow-up analysis.

Outcomes of Interest

The primary outcomes of interest were: (1) all-cause mortality and (2) a composite outcome of all-cause mortality or nonelective cardiovascular hospitalization. We defined nonelective cardiovascular hospitalization as overnight hospital admission for heart failure, arrhythmia, thromboembolism, bleeding event, or any other complications related to their CHD (eg, endocarditis). This end point was satisfied at the first hospitalization or death. Secondary outcomes, assessed separately, included: (1) new or worsening heart failure, defined as requiring hospitalization or an increase/initiation of diuretic therapy; (2) arrhythmia event resulting in hospitalization; pacemaker or defibrillator placement; electrical cardioversion; or initiation/change of antiarrhythmic medications; (3) thromboembolic event requiring hospitalization or new therapy; (4) bleeding event resulting in hospitalization or therapy/intervention; and (5) cardiac catheter-based or surgical intervention.

Statistical Analysis

Variables were compared across AnatC and PhyS. Continuous variables are presented as mean (standard deviation) for normally distributed variables and as median (25th, 75th percentile) for nonnormally distributed variables and analyzed using Welch's ANOVA. Categorical variables are presented as number (percent) and compared between categories using the Fisher exact test.

We modeled the relationship between AP class and each primary and secondary outcome using Cox proportional hazards methods and calculated Harrell C statistic to assess the discriminative power of the AP model and each other model (listed below). AP classification was assessed as an unordered variable. Complete case analysis was used for Cox regression. Additionally, receiver operating characteristic curves were plotted, with an event defined as sustaining the outcome of interest within 1 year of follow-up; these analyses included only participants who had at least 1 year of event-free survival or had sustained the event of interest within 1 year. In addition to AP classification, other models assessed include AnatC alone, PhyS alone, Bethesda classification, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and NYHA FC. We also assessed the predictive value of PhyS component variables, including maximal aortic diameter, exercise limitation (percent predicted, Wasserman equations[18]), and resting arterial oxygen saturation. Cardiopulmonary exercise testing data were available for only 68.3% of patients from the 5 years before enrollment, so cardiopulmonary exercise testing variables were not included in the analysis. NT-proBNP was measured as part of a separate research study in 2018; patients enrolled after 2018 did not have NT-proBNP measured. For the subset of participants without data on NT-proBNP (17.2%), we used multiple imputation by chained equations (n=20 imputations, Table S3) to impute $\log_2$ NT-proBNP.[19] Analyses used R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Description of the Cohort

There were 1153 patients enrolled and had sufficient data to assign AP classification. One hundred fifty-three patients were excluded from analysis because of incomplete follow-up data. Of the 1000 subjects analyzed, the median age at enrollment was 35.25 years (25th, 75th percentiles: 27.2, 47.9 years); 48.5% were women. The most common CHD diagnoses were left-sided outflow tract lesions (n=212, 21.2%), tetralogy of Fallot (n=176, 17.6%), and single ventricle heart disease with Fontan physiology (n=133, 13.3%). Many patients, 52.3%, were classified as moderate complexity (AnatC II), and only 95 (9.5%) as simple (AnatC=I). Most patients, 57.4%, were classified as PhyS C, whereas only 5.7% were PhyS A.

More complex AnatC tended to be associated with more severe PhyS, though exceptions were common (eg, 48.4% of AnatC I patients were PhyS C or D) (Table 1). Although there was no apparent relationship between AnatC and NYHA FC, worse PhyS was strongly associated with higher NYHA FC (Table 2). PhyS was also associated with various complications and comorbidities such as heart failure, pulmonary hypertension, type 2 diabetes, liver cirrhosis, and chronic kidney disease. Worse PhyS was also associated with higher NT-proBNP (Table 2).

Comparison of AnatC and Bethesda classifications revealed 64 patients with isolated bicuspid aortic valve who were classified as simple CHD per Bethesda and moderate CHD per the AP classification, and 6 patients

Table 1. Descriptive and Clinical Characteristics of the Cohort by Anatomic Class

	I	II	III	*P* value	Missing (%)
No.	95	523	382		
Age, y	37.9 [29.0, 54.2]	38.4 [29.0, 51.7]	31.5 [24.8, 40.4]	<0.001	0.0
Sex, % women	55 (57.9)	258 (49.3)	172 (45.0)	0.069	0.0
Race (%)				0.560	2.0
Non-White*	6 (6.5)	25 (4.9)	24 (6.3)		
Unknown	8 (8.7)	54 (10.6)	49 (12.9)		
White	78 (84.8)	430 (84.5)	306 (80.7)		
BMI, kg/m^2	26.6 [23.5, 29.1]	26.9 [23.3, 31.1]	24.8 [22.3, 28.6]	<0.001	0.8
Systolic blood pressure, mm Hg	121.0 [112.0, 130.0]	122.0 [112.0, 130.0]	118.0 [109.0, 125.0]	<0.001	0.5
Diastolic blood pressure, mm Hg	69.0 [61.5, 77.5]	69.0 [61.0, 75.8]	67.0 [59.0, 73.0]	<0.001	0.5
NYHA FC (%)				0.290	0.0
I	73 (76.8)	410 (78.4)	276 (72.3)		
II	19 (20.0)	96 (18.4)	93 (24.3)		
III/IV	3 (3.2)	17 (3.3)	13 (3.4)		
CHD diagnosis (%)				<0.001	0.0
Tetralogy of Fallot	0 (0.0)	136 (26.0)	40 (10.5)		
Left-sided valve/outflow tract disease (excluding coarctation)	0 (0.0)	117 (22.4)	6 (1.6)		
Fontan	0 (0.0)	0 (0.0)	133 (34.8)		
Atrial septal defect	27 (28.4)	59 (11.3)	0 (0.0)		
Coarctation	0 (0.0)	89 (17.0)	0 (0.0)		
Atrial switch for TGA	0 (0.0)	0 (0.0)	57 (14.9)		
Ventricular septal defect	33 (34.7)	11 (2.1)	0 (0.0)		
DORV	0 (0.0)	0 (0.0)	42 (11.0)		
Valvar pulmonary stenosis	16 (16.8)	12 (2.3)	0 (0.0)		
Arterial switch for TGA	0 (0.0)	0 (0.0)	30 (7.9)		
Ebstein anomaly	0 (0.0)	27 (5.2)	0 (0.0)		
Physiologically corrected TGA	0 (0.0)	0 (0.0)	26 (6.8)		
Atrioventricular septal defect	0 (0.0)	23 (4.4)	0 (0.0)		
Pulmonary atresia with intact ventricular septum	0 (0.0)	0 (0.0)	17 (4.5)		
Eisenmenger physiology	8 (8.4)	1 (0.2)	2 (0.5)		
Complex cyanotic, eg, unrepaired double-inlet ventricle	0 (0.0)	0 (0.0)	8 (2.1)		
Rastelli procedure for TGA	0 (0.0)	0 (0.0)	9 (2.4)		
Other	11 (11.6)	48 (9.2)	12 (3.1)		
Physiological stage (%)				<0.001	0.0
A	17 (17.9)	26 (5.0)	14 (3.7)		
B	32 (33.7)	135 (25.8)	66 (17.3)		
C	31 (32.6)	309 (59.1)	234 (61.3)		
D	15 (15.8)	53 (10.1)	68 (17.8)		
Genetic syndrome (%)	10 (10.5)	37 (7.1)	22 (5.8)	0.254	0.0
Heart failure (%)	0 (0.0)	19 (3.6)	21 (5.5)	0.041	0.0
CAD (%)	0 (0.0)	7 (1.3)	0 (0.0)	0.040	0.0

(*Continued*)

Table 1. (Continued)

	I	II	III	*P* value	Missing (%)
Hypertension (%)	13 (13.7)	111 (21.2)	15 (3.9)	<0.001	0.0
Mechanical valve (%)	1 (1.1)	45 (8.6)	9 (2.4)	<0.001	0.0
Pulmonary hypertension (%)	10 (10.5)	23 (4.4)	10 (2.6)	0.003	0.0
Type 2 diabetes (%)	2 (2.1)	25 (4.8)	13 (3.4)	0.355	0.0
Liver cirrhosis (%)	0 (0.0)	4 (0.8)	20 (5.2)	<0.001	0.0
Chronic kidney disease (%)	2 (2.1)	4 (0.8)	6 (1.6)	0.380	0.0
Obstructive sleep apnea (%)	9 (9.5)	41 (7.8)	29 (7.6)	0.829	0.0
Cyanosis, O_2 saturation <92% (%)	6 (6.8)	9 (1.9)	67 (18.7)	<0.001	8.1
NT-proBNP, pg/mL	78.9 [40.6, 182.2]	113.9 [46.1, 272.3]	173.0 [70.5, 384.8]	0.030	17.2
Systemic ventricular function (%) (%)				<0.001	5.5
Normal	79 (87.8)	380 (75.0)	164 (47.1)		
Borderline/mildly decreased	9 (10.0)	106 (20.9)	125 (35.9)		
Moderately/severely decreased	2 (2.2)	21 (4.1)	59 (17.0)		

Descriptive and clinical data for the 1000 patients with anatomic and physiological classification by anatomic class. Categorical variables are presented as number (percent) and compared using Fisher exact test. Continuous variables are presented as mean (standard deviation) for normally distributed variables and as median [25th, 75th percentiles] for nonnormally distributed variables. Continuous variables are analyzed using Welch's ANOVA. BMI indicates body mass index; CAD, coronary artery disease; CHD, congenital heart disease; DORV, double outlet right ventricle; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA FC, New York Heart Association functional class; and TGA, transposition of the great arteries.

*The category "non-White" refers to individuals with documented race other than White. This includes Black, Asian, Native American, and any other race.

with simple shunts and Eisenmenger syndrome were classified as great complexity per Bethesda, but simple per the AP classification.

Association With Clinical Outcomes

Over a median follow-up of 2.5 years (25th, 75th percentiles: 1.4–3.9 years), the primary composite outcome of all-cause mortality or nonelective cardiovascular hospitalization occurred in 185 patients, including 49 deaths. Those with and without measurement of NT-proBNP were clinically similar, and the incidence of clinical events per person-year was similar between those who did and did not have NT-proBNP data; however, because of shorter follow-up time for those without NT-proBNP data, a smaller proportion of these participants experienced the primary outcome (Table S4). Kaplan-Meier analysis for the primary composite outcome demonstrated a difference between AnatC III compared to AnatC I and II (Figure 1A); only 8.4% of patients classified as AnatC I suffered an event compared to 26.4% for AnatC III. Similarly, PhyS C and D were both associated with a higher risk for the primary composite outcome compared to PhyS A or B (Figure 1B). The proportion of participants suffering the composite outcome in PhyS A, B, C, and D were 3.5%, 6.9%, 17.9%, and 47.1%, respectively. Of note, there was no statistically significant difference in risk for the primary composite outcome for PhyS A compared with PhyS B (*P*=0.41) (Figure S1).

AnatC in isolation was a poor predictor of adverse outcomes; for the primary composite outcome, the C statistic was 0.57 (95% CI, 0.55–0.59). When comparing C statistic point estimates, AnatC was less strongly associated with this composite outcome than was the original Bethesda classification (C statistic, 0.61 [95% CI, 0.59–0.63]). PhyS was more strongly associated with the composite outcome, with a C statistic of 0.66 (95% CI, 0.64–0.68). The combination of AnatC and PhyS (AP classification) was only modestly better than PhyS alone (C statistic, 0.69 (95% CI, 0.67–0.71) (Figures 2 and 3A). For all-cause mortality alone, the C statistics for AnatC, PhyS, and AP were 0.62 (95% CI, 0.58–0.66), 0.78 (95% CI, 0.75–0.81), and 0.81 (95% CI, 0.78–0.84), respectively (Figure 3B).

Using AP IIC as the reference group (too few patients were classified as IA to serve as a reliable reference), Cox proportional hazards analysis demonstrated a significantly higher hazard for the primary composite outcome for those categorized as IID (hazard ratio [HR], 3.73; 95% CI, 2.25–6.18; *P*<0.0001) and IIID (HR, 4.46; 95% CI: 2.88–6.90; *P*<0.0001) (Table 3). Equivalent analysis with a dependent variable of all-cause mortality or the secondary outcomes followed a similar pattern, with a higher risk for groups IID and IIID for all-cause mortality, heart failure, arrhythmia, thromboembolic event, and bleeding event (Table 3, Table S5).

We then assessed discriminative power of other available predictors for the primary composite outcome; a univariable model with only NT-proBNP had

Table 2. Descriptive and Clinical Characteristics of the Cohort by Physiological Stage

	A	B	C	D	*P* value	Missing (%)
No.	57	233	574	136		
Age, y	31.0 [24.7, 38.0]	31.2 [24.7, 41.3]	35.6 [27.6, 48.4]	45.3 [33.5, 53.7]	<0.001	0.0
Sex (% women)	37 (64.9)	123 (52.8)	255 (44.4)	70 (51.5)	0.007	0.0
Race (%)					0.905	2.0
Non-White*	3 (6.0)	11 (4.9)	36 (6.3)	5 (3.7)		
Unknown	7 (14.0)	25 (11.1)	63 (11.1)	16 (11.9)		
White	40 (80.0)	190 (84.1)	470 (82.6)	114 (84.4)		
BMI, kg/m^2	25.4 [22.6, 29.2]	25.4 [22.6, 29.4]	26.2 [23.0, 30.5]	25.4 [22.7, 29.3]	0.767	0.8
Systolic blood pressure, mm Hg	119.0 [113.8, 125.2]	120.0 [112.0, 129.2]	121.0 [111.0, 129.0]	117.0 [107.5, 128.0]	0.055	0.5
Diastolic blood pressure, mm Hg	69.5 [64.0, 73.0]	68.0 [61.0, 75.0]	68.0 [60.0, 75.0]	67.0 [56.5, 76.5]	0.054	0.5
NYHA FC (%)					<0.001	0.0
I	57 (100.0)	202 (86.7)	447 (77.9)	53 (39.0)		
II	0 (0.0)	31 (13.3)	111 (19.3)	66 (48.5)		
III/IV	0 (0.0)	0 (0.0)	16 (2.8)	17 (12.5)		
CHD diagnosis (%)					<0.001	0.0
Tetralogy of Fallot	3 (5.3)	34 (14.6)	117 (20.4)	22 (16.2)		
Left-sided valve/ outflow tract disease (excluding coarctation)	6 (10.5)	37 (15.9)	75 (13.1)	5 (3.7)		
Fontan	2 (3.5)	19 (8.2)	85 (14.8)	27 (19.9)		
Atrial septal defect	9 (15.8)	23 (9.9)	35 (6.1)	19 (14.0)		
Coarctation	6 (10.5)	32 (13.7)	47 (8.2)	4 (2.9)		
Atrial switch for TGA	2 (3.5)	13 (5.6)	37 (6.4)	5 (3.7)		
Ventricular septal defect	7 (12.3)	14 (6.0)	19 (3.3)	4 (2.9)		
DORV	2 (3.5)	5 (2.1)	25 (4.4)	10 (7.4)		
Valvar pulmonary stenosis	1 (1.8)	7 (3.0)	17 (3.0)	3 (2.2)		
Arterial switch for TGA	1 (1.8)	7 (3.0)	20 (3.5)	2 (1.5)		
Ebstein anomaly	1 (1.8)	4 (1.7)	22 (3.8)	0 (0.0)		
Physiologically corrected TGA	3 (5.3)	4 (1.7)	15 (2.6)	4 (2.9)		
Atrioventricular septal defect	0 (0.0)	4 (1.7)	14 (2.4)	5 (3.7)		
Pulmonary atresia with intact ventricular septum	1 (1.8)	4 (1.7)	12 (2.1)	0 (0.0)		
Eisenmenger physiology	0 (0.0)	0 (0.0)	0 (0.0)	11 (8.1)		
Complex cyanotic, eg, unrepaired double-inlet ventricle	1 (1.8)	0 (0.0)	1 (0.2)	6 (4.4)		
Rastelli procedure for TGA	0 (0.0)	2 (0.9)	5 (0.9)	2 (1.5)		
Other	12 (21.1)	24 (10.3)	28 (4.9)	7 (5.1)		
Anatomic class (%)					<0.001	0.0
I	17 (29.8)	32 (13.7)	31 (5.4)	15 (11.0)		
II	26 (45.6)	135 (57.9)	309 (53.8)	53 (39.0)		
III	14 (24.6)	66 (28.3)	234 (40.8)	68 (50.0)		
Genetic syndrome (%)	2 (3.5)	17 (7.3)	39 (6.8)	11 (8.1)	0.709	0.0

(*Continued*)

Table 2. (Continued)

	A	B	C	D	*P* value	Missing (%)
Heart failure (%)	0 (0.0)	1 (0.4)	22 (3.8)	17 (12.5)	<0.001	0.0
CAD (%)	0 (0.0)	0 (0.0)	5 (0.9)	2 (1.5)	0.328	0.0
Hypertension (%)	4 (7.0)	32 (13.7)	83 (14.5)	20 (14.7)	0.478	0.0
Mechanical valve (%)	4 (7.0)	13 (5.6)	29 (5.1)	9 (6.6)	0.849	0.0
Pulmonary hypertension (%)	0 (0.0)	0 (0.0)	10 (1.7)	33 (24.3)	<0.001	0.0
Type 2 diabetes(%)	0 (0.0)	2 (0.9)	24 (4.2)	14 (10.3)	<0.001	0.0
Liver cirrhosis (%)	0 (0.0)	0 (0.0)	18 (3.1)	6 (4.4)	0.013	0.0
Chronic kidney disease (%)	0 (0.0)	0 (0.0)	5 (0.9)	7 (5.1)	<0.001	0.0
Obstructive sleep apnea (%)	1 (1.8)	13 (5.6)	47 (8.2)	18 (13.2)	0.018	0.0
Cyanosis, O_2 saturation <92% (%)	0 (0.0)	2 (0.9)	44 (8.3)	36 (29.8)	<0.001	8.1
NT-proBNP, pg/mL	48.5 [31.9, 103.2]	90.5 [37.7, 180.3]	135.8 [57.8, 314.6]	372.7 [150.0, 955.5]	<0.001	17.2
Systemic ventricular function (%)					<0.001	5.5
Normal	51 (92.7)	166 (73.8)	337 (61.8)	69 (57.5)		
Borderline/mildly decreased	4 (7.3)	53 (23.6)	146 (26.8)	37 (30.8)		
Moderately/severely decreased	0 (0.0)	6 (2.7)	62 (11.4)	14 (11.7)		

Descriptive and clinical data for the 1000 patients with anatomic and physiological classification by physiological stage. Categorical variables are presented as number (percent) and compared using Fisher exact test. Continuous variables are presented as mean (standard deviation) for normally distributed variables and as median [25th, 75th percentiles] for nonnormally distributed variables. Continuous variables are analyzed using Welch's ANOVA. BMI indicates body mass index; CAD, coronary artery disease; CHD, congenital heart disease;; DORV, double outlet right ventricle; NT-proBNP, N-terminal proB-type natriuretic peptide; NYHA FC, New York Heart Association functional class; and TGA, transposition of the great arteries.*The category "non-White" refers to individuals with documented race other than White. This includes Black, Asian, Native American, and any other race.

a C statistic of 0.69 (95% CI, 0.67–0.71), whereas 2-variable models were slightly superior; AnatC+NT-proBNP, PhyS+NT-proBNP, and NYHA+NT-proBNP had C statistics of 0.70 (95% CI, 0.68–0.72), 0.72 (95% CI, 0.70–0.74), and 0.72 (95% CI, 0.70–0.74), respectively. The combination of AP+NT-proBNP had the highest C statistic, 0.73 (95% CI, 0.71–0.75) (Figure 3A). For all-cause mortality, the pattern was similar, though the absolute value of C statistics was consistently higher. Once again, AP+NT-proBNP had the highest C statistic, 0.85 (95% CI, 0.82–0.88). AnatC had the lowest C statistic, 0.62 (95% CI, 0.58–0.66), and was less strongly associated with mortality than was the original Bethesda classification, 0.67 (95% CI, 0.64–0.7) (Figure 3B).

Some PhyS component variables were only modestly associated with the primary outcomes, including categorical aortic dimension, with C statistics of 0.57 (95% CI, 0.55–0.59) and 0.57 (95% CI, 0.51–0.63), and valve disease with C statistics of 0.55 (95% CI, 0.53–0.57) and 0.57 (95% CI, 0.52–0.62) for the composite outcome and all-cause mortality, respectively (Figure 3C and 3D). Other continuous variables that were reasonably strongly associated with the outcomes, such as oxygen saturation, are included as dichotomous/categorical variables in the AP classification system; the derived categorical variables were consistently less able to discriminate between those who went on to suffer the composite outcome from those who did not (eg, the C statistic for continuous oxygen saturation [%] was 0.67; for the 3-level categorical variable hypoxemia [oxygen saturation <85%, 85%–90%, >90%] the C statistic was 0.57) (Figure 3C).

Interestingly, several PhyS component variables were more strongly associated with outcomes than PhyS itself (or than the overall AP classification). Arrhythmia status was the strongest predictor of the primary composite outcome (C statistic: 0.71 [95% CI, 0.69–0.73]) (Figure 3C) among the components of PhyS. History of arrhythmia and continuous resting oxygen saturation were the strongest predictors of mortality (C statistics of 0.75 [95% CI, 0.72–0.78], 0.76 [95% CI, 0.70–0.82], and 0.77 [95% CI, 0.73–0.81], respectively) (Figure 3D).

Distribution of AP Variables

On further analysis of the reasons patients were assigned a specific PhyS, we identified the component variable most often associated with classification to a

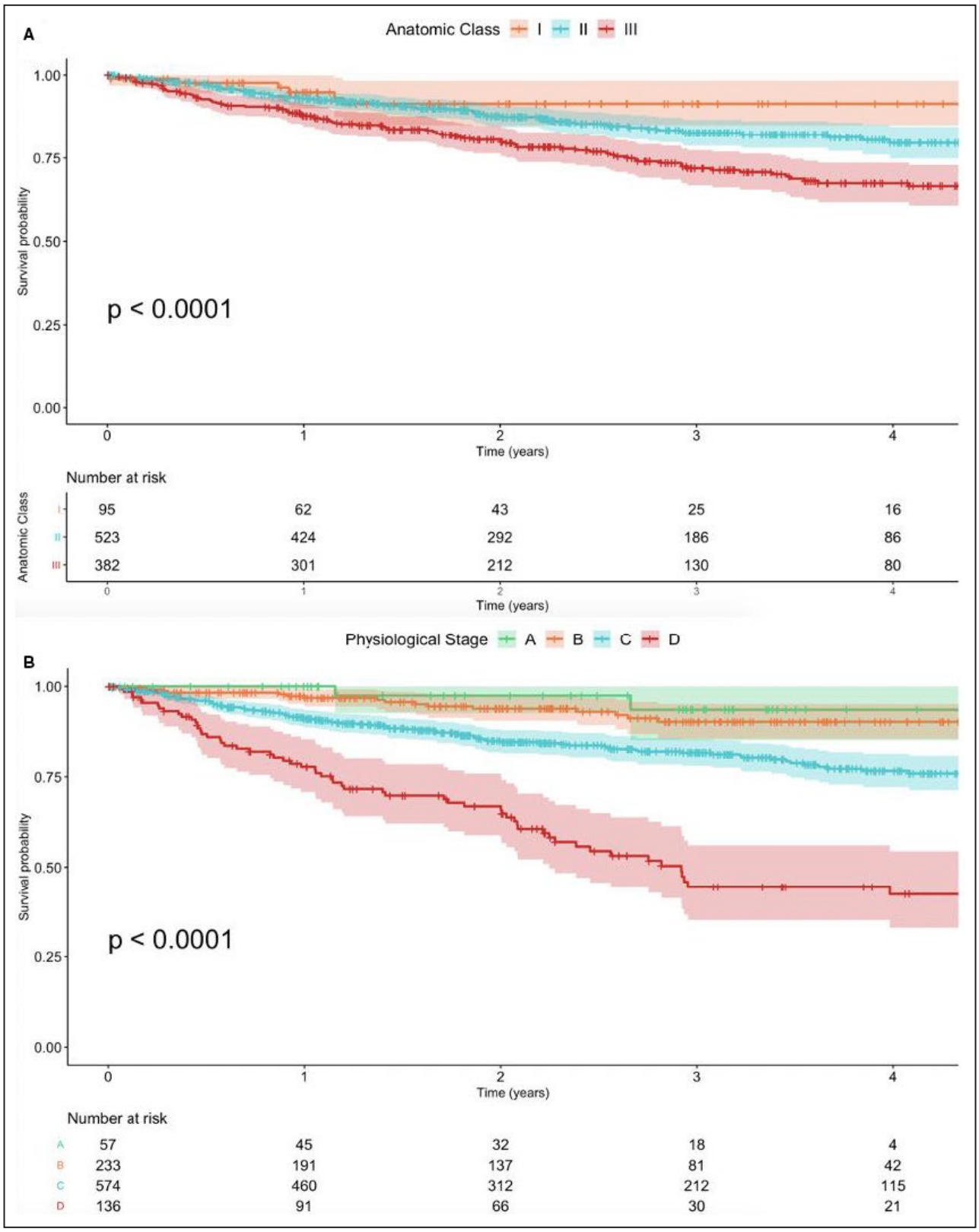

Figure 1. Kaplan-Meier curves depicting survival free from a composite clinical outcome of death or nonelective cardiovascular hospitalization according to anatomic class and physiological stage.
Kaplan-Meier curves of survival free of the composite outcome by (**A**) anatomic class and (**B**) physiological stage. Curves are compared using the log-rank test. Shaded regions indicate 95% CIs.

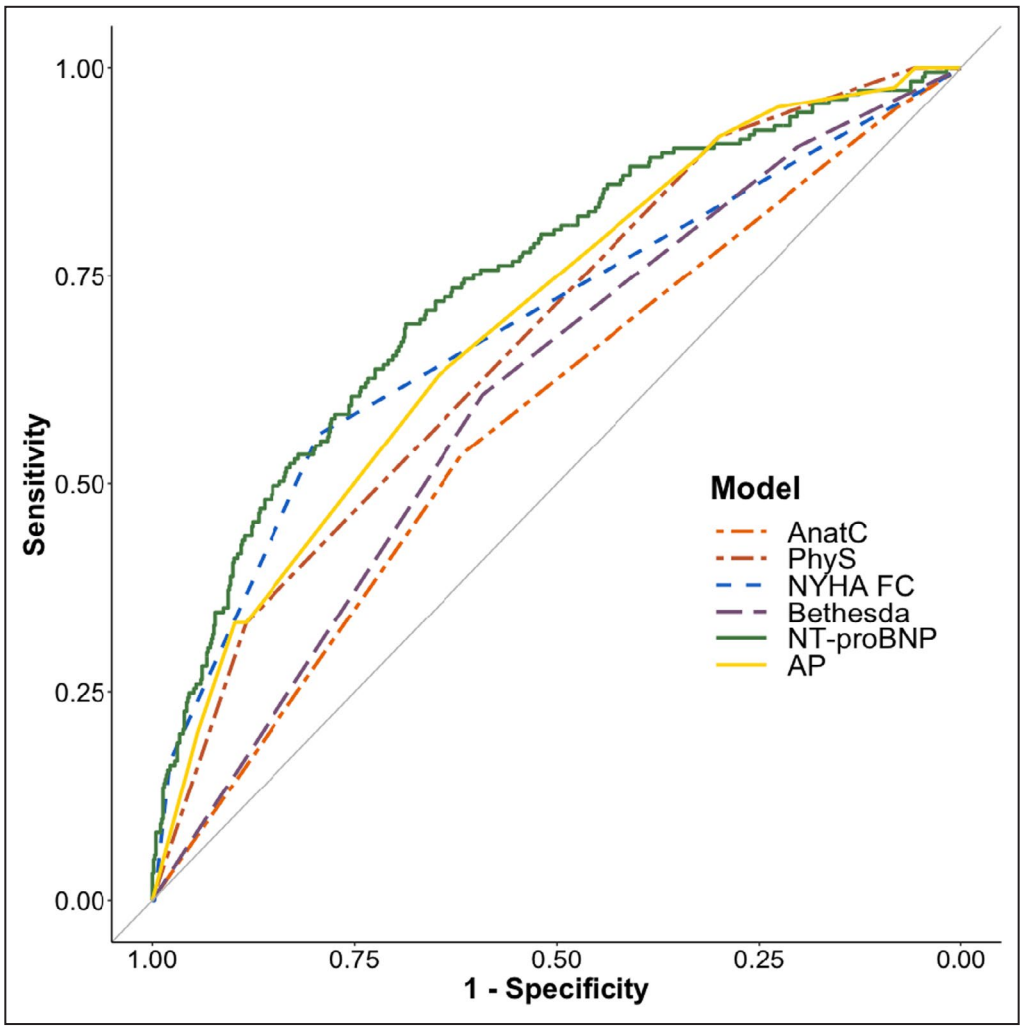

Figure 2. Receiver operating characteristic (ROC) curves comparing the anatomic and physiological classification and other clinical models for the composite outcome of death or nonelective cardiovascular hospitalization within 1 year after enrollment.
ROC curves for anatomic and physiological classification, physiological stage, anatomic class, New York Heart Association functional class (NYHA FC), the Bethesda classification, and imputed NT-proBNP (N-terminal proB-type natriuretic peptide). The grey line indicates area under the curve=0.5. There were 872 participants with follow-up time ≥1 year or an event within the first year, with a total of 84 events by 1 year. The ROC curve plotted for NT-proBNP is based on the 10th complete imputed data set; however, the area under the curve presented was calculated using all 20 imputed data sets. Area under the curve for each model is as follows in ascending order: AnatC=0.58, Bethesda classification=0.61, PhyS=0.67, NYHA FC=0.69, AP=0.69, and NT-proBNP=0.75 (averaged across 20 imputed data sets). AnatC indicates anatomic class; AP, anatomic and physiological; and PhyS, physiological stage.

worse PhyS (ie, if all other variables indicated a less severe PhyS) (Figure 4). For example, 96 patients were classified as PhyS C rather than PhyS B only because of qualifying valve disease, and 68 were classified as PhyS C only because of a maximal aortic dimension of 4.0 to 4.9 cm (Figure 4).

DISCUSSION

In this analysis of the AP classification system proposed in the 2018 American Heart Association and American College of Cardiology ACHD guidelines, we report that: (1) PhyS adds discriminative prognostic value to anatomic diagnosis-focused classification systems, but its overall prognostic value is limited by including variables relevant to clinical care but not associated with prognosis. (2) AP classification is associated with future mortality, and to a lesser degree, nonelective hospitalization of patients with ACHD. (3) The AP system is similarly associated with clinical outcomes as other individual variables and simple multivariable approaches.

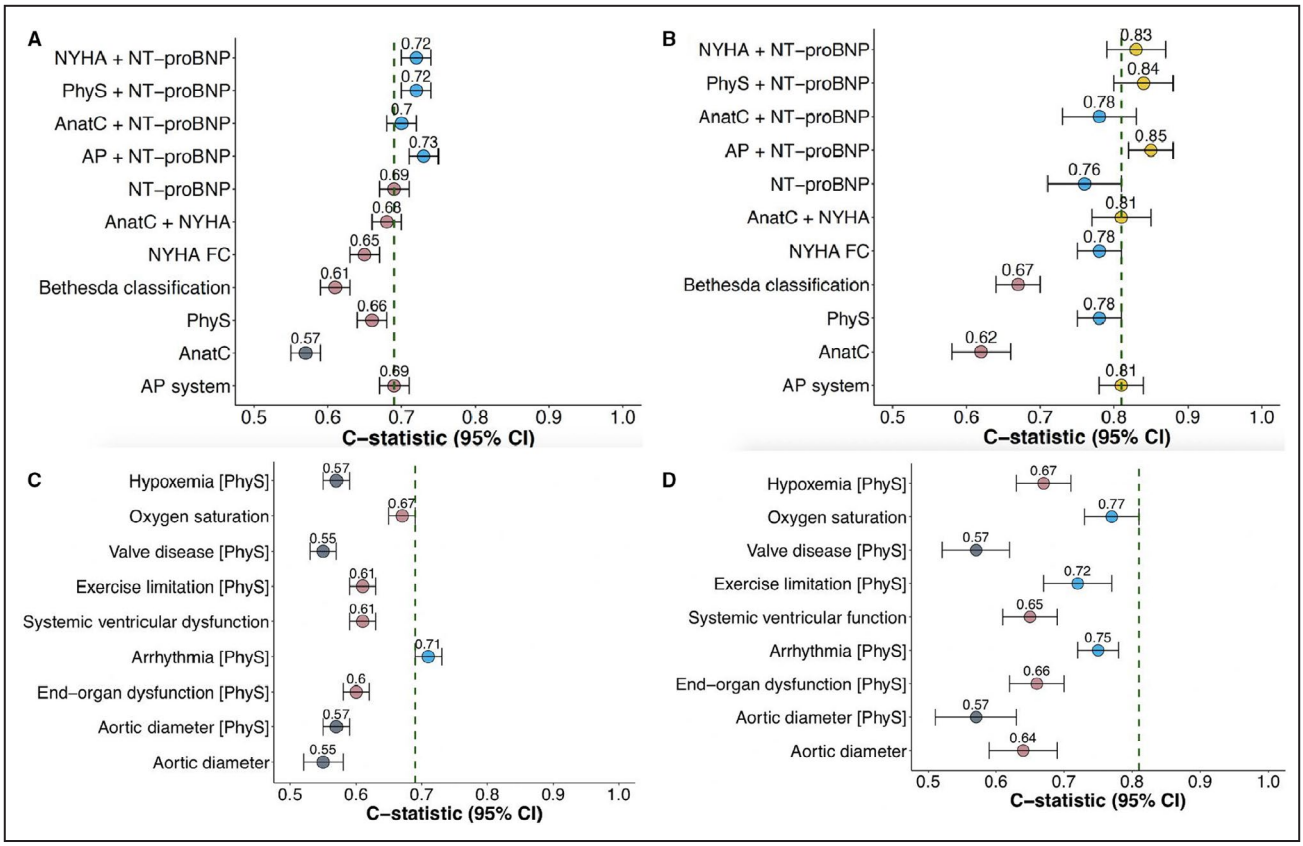

Figure 3. Concordance statistics for AP classification and other clinical predictors for (A) the composite outcome of all-cause death or nonelective cardiovascular hospitalization and (B) all-cause mortality.
C, The C statistics for individual variables used to define physiological stage, for the primary composite outcome of all-cause mortality or nonelective cardiovascular hospitalization, either the categorical variables used to assign physiological stage (PhyS) (designated by [PhyS]) or, when applicable, the equivalent continuous variables. **D**, The equivalent data for all-cause mortality. Error bars represent 95% CI. The green dashed line indicates the C statistic for overall AP class, 0.69 for the composite outcome (**A** and **C**), and 0.81 for mortality (**B** and **D**). NT-proBNP (N-terminal pro-B-type natriuretic peptide) estimates are based on the multiply imputed data. Multivariable modeling was not performed with peak oxygen consumption as a covariate given >30% missing data. AnatC indicates anatomic class; AP, anatomic and physiological classification system; NYHA, New York Heart Association; and NYHA FC, New York Heart Association functional class.

ACHD poses a challenge to straightforward classification.[20,21] There are numerous distinct diseases, interventions, and comorbidities.[22,23] Each of these may impact the probability of suffering an adverse outcome, with variability between diagnoses.[20] Although ACHD classification has traditionally focused on underlying CHD anatomic diagnosis, this approach is not well-suited to identifying the change in risk over time.[20,21] Past studies of risk-stratification in the ACHD population are limited to short-term or surgical outcomes or focus on specific disease subsets.[24–26] Other studies have focused on identifying risk factors across the ACHD population, but this is difficult to apply to a heterogeneous population, with generalizability undermined by the local referral patterns and the variable approach to management between different countries and between centers within the same country.[20,21,27] The AP system is the first effort to use both anatomic and physiologic variables to offer individualized risk stratification for all patients with ACHD.

The current study design parallels other work evaluating similar, multidimensional classification systems, such as cancer grading/staging.[28–30] Two recent studies have assessed the prognostic and discriminative value of the ACHD AP classification system.[9,10] One retrospectively assessed the association between the AP system and 15-year all-cause and cardiovascular mortality; as with the current study, the C statistics indicated good discrimination, but other clinical models were superior.[9] The second study found the AP system to be strongly associated with early mortality after cardiovascular surgery.[10] The current study is the first to assess not only mortality but also more common clinically relevant outcomes (nonelective cardiovascular hospitalization) and to assess this model in a

Table 3. Hazard Ratios for the Primary and Secondary Outcomes According to the Anatomic and Physiological Classification

		All-cause mortality or nonelective cardiovascular hospitalization			All-cause mortality			New/worsening heart failure			Arrhythmia	
		185 (18.5%)			49 (4.9%)			149 (14.9%)			138 (13.8%)	
No. events	n/N (%)	HR	*P* value	n/N (%)	HR	*P* value	n/N (%)	HR	*P* value	n/N (%)	HR	*P* value
IA	1/17 (5.9)	0.78	0.802	0/17 (0.0)	…	…	0/17 (0.0)	…	…	1/17 (5.9)	0.72	0.748
IB	2/32 (6.3)	0.56	0.419	0/32 (0.0)	…	…	1/32 (3.1)	0.27	0.197	2/32 (6.3)	0.63	0.519
IC	2/31 (6.5)	0.62	0.514	1/31 (3.2)	1.92	0.542	4/31 (12.9)	1.23	0.695	3/31 (9.7)	1.18	0.783
ID	3/15 (20.0)	1.42	0.560	1/15 (6.7)	3.23	0.274	4/15 (26.7)	2.41	0.094	3/15 (20.0)	1.97	0.259
IIA	1/26 (3.9)	0.28	0.211	0/26 (0.0)	…	…	0/26 (0.0)	…	…	0/26 (0.0)	…	…
IIB	8/135 (5.9)	0.42	0.02*	0/135 (0.0)	…	…	4/135 (3.1)	0.22	0.004*	5/135 (3.7)	0.32	0.016*
IIC	44/309 (14.2)	Reference		7/309 (2.3)	Reference		39/309 (12.6)	Reference		35/309 (11.3)	Reference	
IID	23/53 (43.4)	3.73	<0.0001*	10/53 (18.9)	7.02	<0.0001*	17/53 (32.1)	3.04	0.0001*	15/53 (28.3)	2.96	<0.0001*
IIIA	0/14 (0.0)	0.00	0.992	0/14 (0.0)	…	…	0/14 (0.0)	…	…	0/14 (0.0)	…	…
IIIB	6/66 (9.1)	0.58	0.206	0/66 (0.0)	…	…	4/66 (6.1)	0.42	0.099	8/66 (12.1)	0.99	0.981
IIIC	57/234 (24.4)	1.58	0.02*	12/234 (5.1)	1.81	0.215	47/234 (20.1)	1.49	0.068	41/234 (17.5)	1.44	0.111
IIID	38/68 (55.9)	4.46	<0.0001*	18/68 (26.5)	10.11	<0.0001*	29/68 (42.6)	3.69	<0.0001*	25/68 (36.8)	4.16	<0.0001*
C statistic (95% CI)		0.69 (0.67–0.71)			0.81 (0.78–0.84)			0.70 (0.68–0.72)			0.69 (0.67–0.71)	

Harrell C statistic was calculated for Cox regression models. Ellipses represent cells with no events. HR indicates hazard ratio; and n/N, number of events and number of patients at risk in that category.
*$P<0.05$.

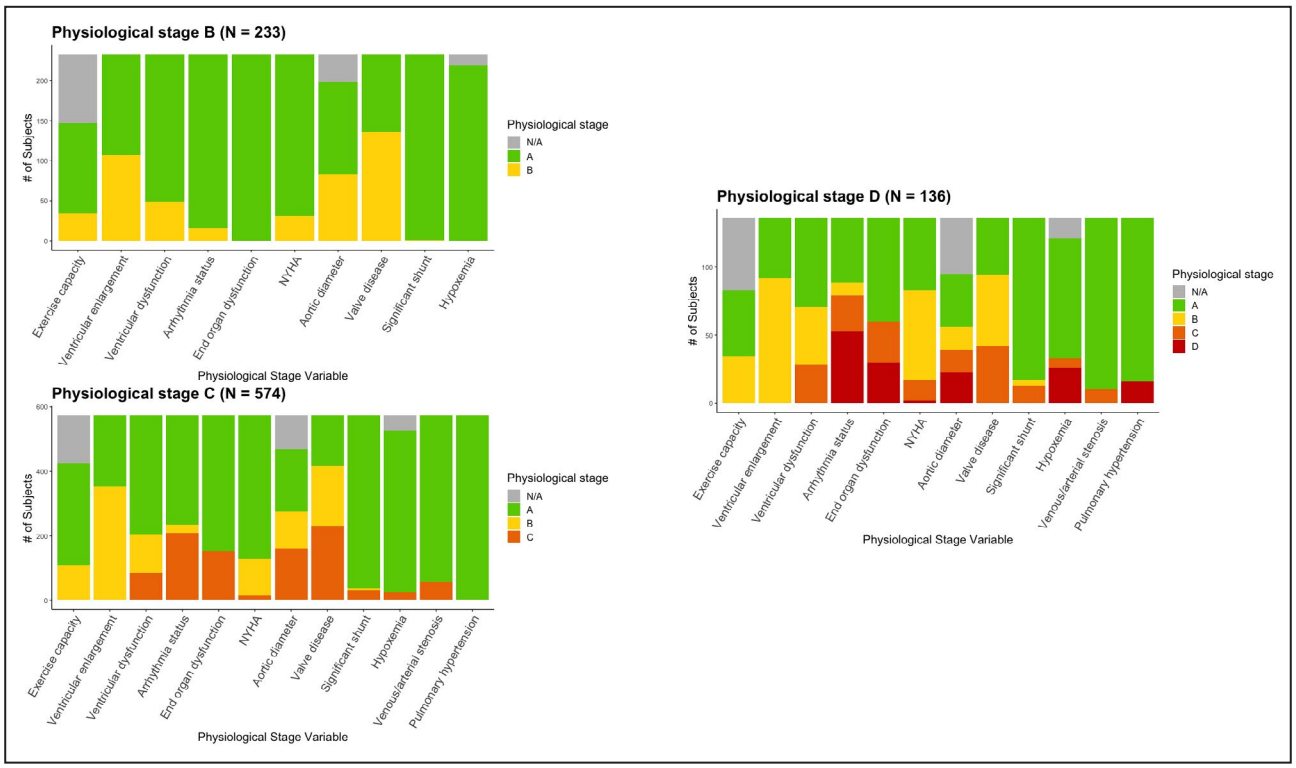

Figure 4. Distribution of the individual component variables of physiological stage for subjects classified as overall physiological stage B, C, or D.

Individual physiological variables were assessed for each participant according the anatomic and physiological consensus definitions. Subjects were assigned physiological stage according to their single worst variable. Component variable assignment is presented for subjects classified as physiological stages B, C, or D. For example, of the 574 physiological stage C patients, only 16 met physiological stage C criteria by NYHA functional class (ie, functional class III), whereas the other 558 met A or B criteria (ie, NYHA functional class I or II). Patients classified as physiologic stage B cannot have either venous/arterial stenosis or pulmonary hypertension; these variables are omitted from the top panel. NYHA indicates New York Heart Association. N/A indicates not applicable, in instances where there are missing data.

prospectively enrolled cohort. Additionally, the current cohort includes patients with more complex CHD and worse functional status than those used in these other studies; over 13% (n=136) of patients in the current cohort were categorized as PhyS D, compared with 3% (n=19/629) and 6% (n=22/353) in prior studies; only 17 patients in the prior studies combined were classified as IIID, compared with 69 in the current report.[9,10] This, along with the larger overall sample size, allowed us to explore in more detail how individual component variables contributed to AP classification and prognostic value.

Predicting prognosis was not the goal of the 2018 AHA/ACC ACHD guidelines or the proposed AP classification scheme; these guidelines are primarily designed to guide cardiovascular care and timing of follow-up for patients with ACHD with a broad array of diagnoses and subsequent interventions.[8] Decisions in that context usually focus on predicted probability of adverse events ≈3 months to ≈3 years in the future. Therefore, this near-term and medium-term prediction of clinical risk are most relevant when considering the value of the AP system. The PhyS system is more reflective of a patient's functional status and overall health than AnatC in isolation, which could classify a patient with ASD and Eisenmenger syndrome as simple. Although it is clear that PhyS adds predictive value beyond anatomic classification, it also intermingles variables that have broad prognostic implications (eg, functional class) with others that have follow-up relevance for only a subset of patients (eg, aortic dimension). Prognosis is an important consideration when determining appropriate follow-up, but so are other variables, independent of their impact on prognosis. It may be reasonable to separate those roles in future iterations of this classification scheme. That is, the decision about frequency of evaluations may change if either there was an indication of a high risk of deterioration in the near to medium term, or if there were particular clinical characteristics that may compel intervention. With this in mind, we identified other individual variables that were more strongly associated with prognosis across the range of outcomes compared with the AP classification. These included

circulating biomarkers (NT-proBNP), clinical history (prior atrial arrhythmia), and simple assessments of functional class (NYHA FC).

Another notable finding was the exceptionally uneven distribution of AP class, for example, with few patients in this cohort classified as PhyS A. Our results suggest little difference in terms of prognosis between PhyS A and B, and perhaps combining these stages would both simplify and strengthen the AP system. Furthermore, patients with a broad range of disease phenotypes can be categorized in the same PhyS. For example, a patient who is NYHA FC III is assigned the same PhyS as a patient with moderate pulmonary regurgitation.[8] Revisiting the dichotomization/categorization of continuous variables and their relationship to cardiovascular care, as well as reducing the heterogeneity within each PhyS, could help improve the prognostic power of the AP system.

It may seem surprising that the Bethesda classification of CHD was more strongly associated with outcomes than the more recently developed AnatC. One possible explanation is the divergent classification of congenital aortic valve disease. The Bethesda classification assigned bicuspid aortic valve to simple complexity CHD, whereas these patients are AnatC II (moderate complexity) in the AP system. AnatC also focuses more on underlying anatomy rather than physiology. For example, Eisenmenger syndrome is considered severely complex by the Bethesda criteria, whereas a patient with Eisenmenger syndrome could be classified as AnatC I or II (eg, small atrial septal defect with Qp:Qs<1.5:1 and without chamber enlargement). The presence of pulmonary vascular disease does not directly influence AnatC, emphasizing the importance of interpreting AnatC in concert with PhyS.

This study identified several aspects of the AP classification that might benefit from reconsideration. For example, including continuous variables rather than categorical variables with arbitrary cut points would improve the association with clinical outcomes. Likewise, it could be helpful to integrate quantitative biomarkers, such as NT-proBNP or C-reactive protein, which are easily measured and associated with clinical outcomes across the spectrum of ACHD.[31,32] Inclusion of such biomarkers could be accomplished through the use of risk scores,[33] such as have been developed for atherosclerotic cardiovascular disease.[34]

Limitations

This study must be interpreted in the context of its study design. AP classification was assigned based on information available in the electronic health record. Prospective assessment of AP class may be more accurate and reproducible particularly for PhyS, though there is currently no empirical evidence to suggest that. Additionally, classifying patients required defining more detailed criteria than provided in the AP guidelines; there may be alternative interpretations that could be more strongly associated with outcomes, though our definitions were based on a consensus of an expert panel, including several authors of the existing guidelines. It is important to note that the BACH enrolls patients at a referral center, and enrollment at the time of clinical visit may be more likely to include sicker patients, because those patients are likely to be seen more frequently. This may limit our ability to assess the AP system's performance in subjects with simpler, less severe CHD (eg, IA). From a statistical standpoint, the methods for comparing C statistics are limited, unsettled, and controversial. This limited our ability to compare the different models quantitatively.[35] Finally, we did not aim to derive the most robust predictive model but rather to understand better the predictive value of the AP classification relative to its component variables and other straightforward 1- and 2-variable models. We do not propose any of the models described in this analysis as the preferred approach to predicting future events in ACHD.

CONCLUSIONS

This study has fundamental implications for the application of the ACHD AP system to clinical practice. Future versions of the AP system could include risk scores or nomograms, which would better capture the heterogeneity of this population. Our results suggest that incorporating multiple individual continuous variables, rather than a summary category, retains important prognostic information; the AP system might be improved by reconsidering categorizations and incorporating additional variables. Although this is a first step toward personalizing ACHD care, the prognostic performance of the AP system may not offer an advantage beyond existing, simpler approaches.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S5
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Criteria used to assign anatomic class: simple, moderate complexity, or great complexity.

I: Simple	Consensus Criteria Used	ACC/AHA Guidelines
Native disease		
Isolated small ASD	Isolated secundum ASD, excluding primum ASD and sinus venosus. Qp:Qs < 1.5:1 and no chamber enlargement distal to the shunt defined as subjectively enlarged or Z score > +2 for quantitative measurement (e.g., cMR)	An intracardiac shunt not meeting these criteria (Qp:Qs ≥1.5:1, chamber enlargement distal to the shunt) would be described as small or trivial
Isolated small VSD	Isolated VSD for which Qp:Qs is < 1.5:1 and there is no chamber enlargement distal to the shunt defined as mild subjectively or Z score > +2 for quantitative measurement (e.g., cMR)	An intracardiac shunt not meeting these criteria (Qp:Qs ≥1.5:1, chamber enlargement distal to the shunt) would be described as small or trivial
Mild isolated pulmonic stenosis	TTE peak gradient < 36mmHg (velocity < 3m/s) if reported; otherwise "mild" by subjective imaging report; mild to moderate in TTE report without reported gradient = mild pulmonary stenosis	Peak gradient < 36 mm Hg (peak velocity < 3 m/s)
Repaired conditions		
Previously ligated or occluded ductus arteriosus		No Comment
Repaired secundum ASD or sinus venosus defect without significant residual shunt or chamber enlargement	Significant shunt defined as ≥1.5:1; chamber enlargement defined as mild+ subjectively, Z score > +2 for quantitative measurement (e.g., cMR)	Significant shunt is Qp:Qs≥1.5:1
Repaired VSD without significant residual shunt or chamber enlargement	Significant shunt defined as ≥1.5:1; chamber enlargement defined as mild+ subjectively, Z score > +2 for quantitative measurement (e.g., cMR)	Significant shunt is Qp:Qs≥1.5:1
Vascular ring		Not mentioned

II: Moderate Complexity	Consensus Criteria Used	ACC/AHA Guidelines

Aorto-left ventricular fistula		No Comment
Anomalous pulmonary venous connection, partial or total		No Comment
Anomalous coronary artery arising from the pulmonary artery		No Comment
Anomalous aortic origin of a coronary artery from the opposite sinus		No Comment
AVSD (partial or complete, including primum ASD)		No Comment
Congenital aortic valve disease		No Comment
Congenital mitral valve disease	Excluding mitral valve prolapse	No Comment
Coarctation of the aorta		No Comment
Ebstein anomaly (mild, moderate, and severe)		No Comment
Infundibular right ventricular outflow obstruction		No Comment
Ostium primum ASD		No Comment
Moderate and large unrepaired secundum ASD		No Comment
Moderate and large persistently patent ductus arteriosus		No Comment
Pulmonary valve regurgitation (moderate or greater)	Regurgitant fraction ≥20% (cMR) and/or ≥moderate (TTE)	No Comment
Pulmonary valve stenosis (moderate or greater)	Peak gradient ≥ 36mmHg (velocity ≥3 m/s) or subjectively ≥ moderate	≥Moderate RVOT obstruction (≥36 mmHg (peak velocity ≥3 m/s))
Peripheral pulmonary stenosis		
Sinus of Valsalva fistula/aneurysm		No Comment
Sinus venosus defect		No Comment
Subvalvar aortic stenosis (excluding HCM)		No Comment
Supravalvar aortic stenosis		No Comment
Straddling AV valve		No Comment
Repaired tetralogy of Fallot (toF)	Repaired toF, without pulmonary atresia	No Comment
VSD with associated abnormality and/or moderate or greater shunt	VSD & ≥ moderate shunt (Qp:Qs≥1.5:1) or chamber enlargement (≥mild subjectively or Z score >+2)	An intracardiac shunt is hemodynamically significant if: there is chamber enlargement distal to the shunt or Qp:Qs≥1.5:1.
Double-chambered Right Ventricle		
Cor triatriatum		Not mentioned

III: Great Complexity (or Complex)	**Consensus Criteria Used**	**ACC/AHA Guidelines**
Cyanotic congenital heart defect (unrepaired or palliated, all forms)		No Comment

Double-outlet ventricle		No Comment
Fontan procedure		No Comment
Interrupted aortic arch		No Comment
Mitral atresia		No Comment
Single ventricle (including double inlet left ventricle, tricuspid atresia, hypoplastic left heart, any other anatomic abnormality with a functionally single ventricle)		No Comment
Pulmonary atresia (all forms)	Includes repaired or unrepaired PA/IVS or toF/PA	No Comment
TGA (classic or d-TGA; CCTGA or l-TGA)		No Comment
Truncus arteriosus		No Comment
Other abnormalities of atrioventricular and ventriculoarterial connection (i.e., crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)		No Comment

Categorization and wording of the diagnoses listed are taken from the ACC/AHA guidelines. In cases where there might be ambiguity (e.g., does mitral valve prolapse qualify as "congenital mitral valve disease"), further clarification of the definitions used in classification is listed. Diagnoses omitted from the guidelines were classified according to expert opinion. Unless otherwise specified, a diagnosis recorded consistently in clinical notes and testing was used to define specific diagnoses.

ASD = atrial septal defect, AV = atrio-ventricular, AVSD = atrio-ventricular septal defect, CHD = congenital heart disease, cMR = cardiac magnetic resonance, HCM = hypertrophic cardiomyopathy, IVS = intact ventricular septum, PA = pulmonary atresia, PS = pulmonary stenosis, RVOT = right ventricular outflow tract, toF = tetralogy of Fallot, TGA = transposition of the great arteries (cc = congenitally/physiologically corrected), TTE = trans-thoracic echocardiograph, VSD = ventricular septal defect

Table S2. Consensus criteria use to assign ACC/AHA physiological stage: A, B, C, or D[1].

Stage A	Consensus Criteria Used	ACC/AHA Guidelines
NYHA FC I symptoms	Cardiac disease with no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.	No Comment
No hemodynamic or anatomic sequelae	This may vary by diagnosis and includes the absence of: ventricular dilation/dysfunction, heart failure, aortic enlargement, systemic hypertension in aortic coarctation (resting blood pressure ≥ 130/80), and pulmonary hypertension.	No Comment
No arrhythmias	No clinically relevant arrhythmia other than asymptomatic isolated PACs/PVCs. This excludes any arrhythmia leading to therapy including medication, ablation, cardioversion, emergency room visit, or hospitalization in prior 24 months. Isolated PACs/PVCs (e.g., causing palpitations or lightheadedness) would not be considered a clinically relevant arrhythmia.	No documented clinically relevant atrial or ventricular tachyarrhythmias
Normal exercise capacity	Peak VO_2 ≥85% of the mean value for their diagnostic group[17]	Abnormal: exercise maximum ventilatory equivalent of oxygen* below the range expected for the specific CHD anatomic diagnosis.
Normal renal, hepatic, and pulmonary function	No restrictive or obstructive lung disease (i.e., FVC>80% predicted); no liver abnormality on imaging or exam, no splenomegaly, MELD-XI score ≤ 12[14,15], normal albumin; eGFR >60[16]	No Comment

Stage B	Consensus Criteria Used	ACC/AHA Guidelines
NYHA FC II symptoms	Cardiac disease resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain	No Comment
Mild hemodynamic sequelae (aortic enlargement, ventricular enlargement, ventricular dysfunction)	Mild sub-pulmonary/sub-systemic ventricular dysfunction (LVEF 40-50% and/or RVEF 35-45%, per Boston Children's Hospital protocol), mild aortic enlargement (maximum diameter 3.5-3.9 cm), mild sub-systemic/sub-pulmonary ventricular enlargement (per imaging report) on imaging or testing from the prior 5 years.	Mild aortic enlargement (maximum diameter 3.5-3.9 cm)
Mild valvular disease	Mild AS/AR/MS/MR/TS (per imaging report). This will not include mild PR or TR as these can be found in healthy patients.	No Comment
Trivial or small shunt (not hemodynamically significant)	No evidence of chamber enlargement distal to the shunt (TTE report of Z score > +2 per cMR), Qp:Qs<1.5:1	No evidence of chamber enlargement distal to the shunt, Qp:Qs<1.5:1
Arrhythmia not requiring treatment	Clinically relevant arrhythmia (including atrial or ventricular tachyarrhythmia, bradyarrhythmia with HR <50) in prior 24 months not treated with medication currently (including antiarrhythmic medication or digoxin for the purpose of suppressing arrhythmia) or ablation or cardioversion > 24 months prior without further clinically apparent arrhythmia. Clinically relevant will exclude PACs/PVCs.	Bradyarrhythmia, atrial or ventricular tachyarrhythmia not requiring antiarrhythmic therapy, cardioversion, or ablation
Abnormal objective cardiac limitation to exercise	Peak VO_2<85% of the mean value for that diagnostic group[17]	Exercise maximum ventilatory equivalent of oxygen below the range expected for specific CHD anatomic diagnosis

Stage C	Consensus Criteria Used	ACC/AHA Guidelines
NYHA FC III symptoms	Cardiac disease resulting in marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain	No Comment
Significant (≥ moderate) valvular disease; ≥moderate ventricular dysfunction (systemic and/or sub-pulmonic)	≥Moderate grade of any valve dysfunction (imaging report); ≥moderate reduction in sub-systemic or sub-pulmonary ventricular function (LVEF < 40% and/or RVEF <35%, per Boston Children's Hospital protocol) on imaging/testing. From the prior 5 years.	No Comment
Moderate aortic enlargement	Per guidelines	Moderate aortic enlargement defined as maximum diameter 4.0-4.9cm
Venous or arterial stenosis	Per guidelines	Re-coarctation after CoA repair, supravalvular aortic obstruction, venous baffle obstruction, supravalvular pulmonary, branch PA stenosis, stenosis of cavo-pulmonary connection, pulmonary vein stenosis
Mild or moderate hypoxemia/cyanosis	Per guidelines, with O_2 saturation ≤90% and >85%	Hypoxemia is defined as oxygen saturation measured by pulse oximetry ≤ 90%
Hemodynamically significant shunt	Evidence of chamber enlargement distal to shunt (imaging report or Z score > +2 on cMR) and/ or evidence of sustained Qp:Qs ≥1.5:1	Evidence of chamber enlargement distal to shunt and/or evidence of sustained Qp:Qs ≥1.5:1
Arrhythmias controlled with treatment	Clinically relevant arrhythmia in prior 24 months treated with medication currently (including anti-arrhythmic medication, digoxin for the purpose of suppressing arrhythmia), ablation in prior 24 months without further clinical arrhythmia, cardioversion in prior 24 months, ICD, pacemaker dependent	Bradyarrhythmia requiring PPM; atrial or ventricular tachyarrhythmia requiring antiarrhythmic therapy, cardioversion, or ablation; AF and controlled ventricular response; patients with ICD

	for high grade conduction disease or to maintain HR > 50 bpm. Rate control target for tachyarrhythmias 90-115 w/ exercise/anaerobic threshold, 60-80 at rest[17]	
Pulmonary hypertension (less than severe)	PA pressure by right heart catheterization ≥ 25mm Hg and not currently requiring treatment	Mean PA pressure by right heart catheterization ≥25 mmHg.
End-organ dysfunction responsive to therapy	Organ dysfunction responsive to therapy that directly stems from their cardiac disease or treatment, or which may otherwise impact cardiovascular care, including: eGFR 30-60[16], moderate restrictive lung disease (FVC 50-70% predicted), cirrhosis with albumin concentration ≥ 3 g/dL or MELD-XI score ≤ 12[14,15] with therapy to improve cardiac output/reduce fluid overload, protein losing enteropathy w/ albumin ≥3	No Comment

Stage D	Consensus Criteria Used	ACC/AHA Guidelines
NYHA FC IV symptoms	Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present at rest. Physical activity increases discomfort.	No Comment
Severe aortic enlargement	Per guidelines, relating to dilation at any level of aorta	Severe aortic enlargement is defined as maximum diameter ≥ 5.0cm
Arrhythmia refractory to treatment	Clinically relevant arrhythmia including symptomatic bradyarrhythmia and atrial or ventricular tachyarrhythmias, in the prior 24 months with continued arrhythmia despite medical therapy (including anti arrhythmic medication or digoxin for the purpose of suppressing arrhythmia), ablation, or cardioversion. Rate control goals for tachyarrhythmia are 60-80 at rest and 90-115 with exercise and at maximal exertion	Atrial or ventricular tachyarrhythmia currently unresponsive to or refractory to antiarrhythmic therapy or ablation
Severe hypoxemia (almost always associated with cyanosis)	Per guidelines	Severe hypoxemia is defined as oxygen saturation at rest <85%
Severe pulmonary hypertension	Mean pulmonary arterial pressure ≥35 mm Hg diagnosis confirmed by right heart catheterization (limited primary sources define PH by severity); or treatment for PH/PAH	No Comment
Eisenmenger syndrome	Presence of right-to-left shunt (Qp:Qs <1) and elevated pulmonary pressures	No Comment
Refractory end-organ dysfunction	On dialysis, eGFR<30,[5] severe restrictive lung disease (FVC <50% predicted), cirrhosis with albumin <3 and/or MELD-XI score >12 despite therapy to improve cardiac output/reduce fluid overload,[14,15] protein losing enteropathy with albumin <3, or other severe end organ dysfunction directly or indirectly related to congenital heart disease (i.e., caused by or exacerbating the clinical course of CHD)	No Comment

Consensus definitions used in assignment of physiological stage, as defined by the ACC/AHA guidelines and with additional information from expert opinion and the literature when additional definition was needed. AR = aortic regurgitation, AS = aortic stenosis, CHD = congenital heart disease, cMR = cardiac magnetic resonance, eGFR = estimated glomerular filtration rate, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, HR = heart rate, MR = mitral regurgitation, MS = mitral

stenosis, NYHA FC = New York Heart Association functional class, PA = pulmonary artery, PAC = premature atrial complexes, PAH = pulmonary arterial hypertension, PH = pulmonary hypertension, PR = pulmonary regurgitation, PS = pulmonary stenosis, PVC = premature ventricular complexes, Qp:Qs = pulmonary flow:systemic flow, TR = tricuspid regurgitation, TS = tricuspid stenosis, TTE = trans-thoracic echocardiography, VO_2 = oxygen uptake

*The 2018 ACC/AHA guideline refers to “ventilatory equivalent for oxygen”, a term indicating the relationship between minute ventilation and oxygen consumption ($VE:VO_2$). Based on context and confirmed in discussion with several authors of those guidelines, this was a typo and was intended to refer to peak oxygen consumption or uptake (VO_2).

Table S3. Variables used for imputation of NT-proBNP, using multiple imputation by chained equations.

Variable	Missing (%)		Variable	Missing (%)
Sex	0.0		Log_2 area deprivation index, national rank	3.4
Anatomic complexity	0.0		Log_2 area deprivation index, state rank	3.4
Physiological stage	0.0		Race	1.7
Anatomic and physiological class	0.0		Heart failure	0.0
Death or non-elective cardiovascular hospitalization	0.0		Any cardiopulmonary medications	0.0
Time, death or nonelective hospitalization	0.0		Number cardiopulmonary medications	0.0
Vital status at last follow-up	0.0		BMI, kg/m^2	0.8
Time until last follow-up or death	0.0		Log_2 peak VO_2, % predicted	31.7
Composite primary outcome at one year	0.0		Arrhythmia event	0.0
Log_2 NT-proBNP	17.2		Bleeding event	0.0
Log_2 CRP	5.5		Heart failure event	0.0
Log_2 glucose	5.1		Catheter/surgical intervention	0.0
Log_2 triglycerides	5.2		Thromboembolic event	0.0
NYHA FC	0.0		Age	0.0
Bethesda classification, CHD severity	1.7		Any psychiatric diagnosis	0.0
Education, grade completed	15.7		Number of procedures	2.0
Fulltime employment	6.2		CAD	0.0
Systemic ventricular function, %	0.2		Type 2 DM	0.0

NT-proBNP was imputed with multiple imputation by chained equations, with 20 imputed data sets.

BMI = body mass index, CAD = coronary artery disease, CHD = congenital heart disease, CRP = C-reactive protein, DM = diabetes mellitus, NYHA FC = New York Heart Association functional class

Table S4. Comparison of those with and without NT-proBNP, among the 1,000 enrollees in the cohort with follow-up data.

	Yes	No	P value	Missing (%)
N	828	172		
Age, years	35.5 [27.3, 48.5]	34.2 [26.8, 42.1]	0.409	0.0
Sex (% female)	401 (48.4)	84 (48.8)	0.989	0.0
Race (%)			0.861	2.0
Non-white	45 (5.5)	10 (5.9)		
Unknown/other	90 (11.1)	21 (12.4)		
White	676 (83.4)	138 (81.7)		
BMI, kg/m^2	26.0 [22.8, 30.0]	26.2 [23.3, 29.6]	0.461	0.8
Systolic blood pressure, mmHg	120.0 [111.0, 129.0]	120.0 [110.5, 128.0]	0.947	0.5
Diastolic blood pressure, mmHg	68.0 [60.0, 75.0]	68.0 [59.5, 75.0]	0.701	0.5
NYHA FC (%)			0.614	0.0
I	624 (75.4)	135 (78.5)		
II	177 (21.4)	31 (18.0)		
III/IV	27 (3.3)	6 (3.5)		
Physiological stage (%)			0.312	0.0
A	43 (5.2)	14 (8.1)		
B	193 (23.3)	40 (23.3)		
C	483 (58.3)	91 (52.9)		
D	109 (13.2)	27 (15.7)		
Anatomic complexity (%)			0.399	0.0
Great complexity	313 (37.8)	69 (40.1)		
Moderate complexity	440 (53.1)	83 (48.3)		
Simple	75 (9.1)	20 (11.6)		
Heart failure (%)	35 (4.2)	5 (2.9)	0.555	0.0
CAD (%)	7 (0.8)	0 (0.0)	0.479	0.0
Hypertension (%)	118 (14.3)	21 (12.2)	0.560	0.0
Pulmonary hypertension (%)	34 (4.1)	9 (5.2)	0.648	0.0
Type 2 DM (%)	35 (4.2)	5 (2.9)	0.555	0.0
Liver cirrhosis (%)	20 (2.4)	4 (2.3)	1.000	0.0
Chronic kidney disease (%)	9 (1.1)	3 (1.7)	0.737	0.0
Obstructive sleep apnea (%)	69 (8.3)	10 (5.8)	0.337	0.0
Cyanosis (O_2 saturation < 92%) (%)	64 (8.4)	18 (11.6)	0.257	8.1
Peak VO_2, % predicted	70.0 [59.0, 83.0]	73.0 [62.0, 84.0]	0.113	31.7
Systemic ventricular function (%)			0.227	0.2
Normal	639 (77.3)	142 (83.0)		
Borderline/mildly decreased	121 (14.6)	20 (11.7)		
Moderately/severely decreased	67 (8.1)	9 (5.3)		
Death or nonelective cardiovascular hospitalization (%)	165 (19.9)	20 (11.6)	0.015	0.0
Follow-up time, days	1043.0 [658.8, 1506.2]	435.0 [293.8, 747.5]	<0.001	0.0

Event rate per person-years, composite outcome	0.0766	0.0747	1.00	0.0

Categorical variables are presented as number (percent) and compared using Fisher's exact test. Continuous variables are presented as mean (standard deviation) for normally distributed variables and as median [inter-quartile range] for non-normally distributed variables. Continuous variables are analyzed using the independent t-test (if normal distribution) or the Wilcoxon rank sums test (if non-normal distribution). Rate of death or non-elective cardiovascular hospitalization per year was compared with the Poisson test.

BMI = body mass index, NYHA FC = New York Heart Association Functional Class, CAD = coronary artery disease

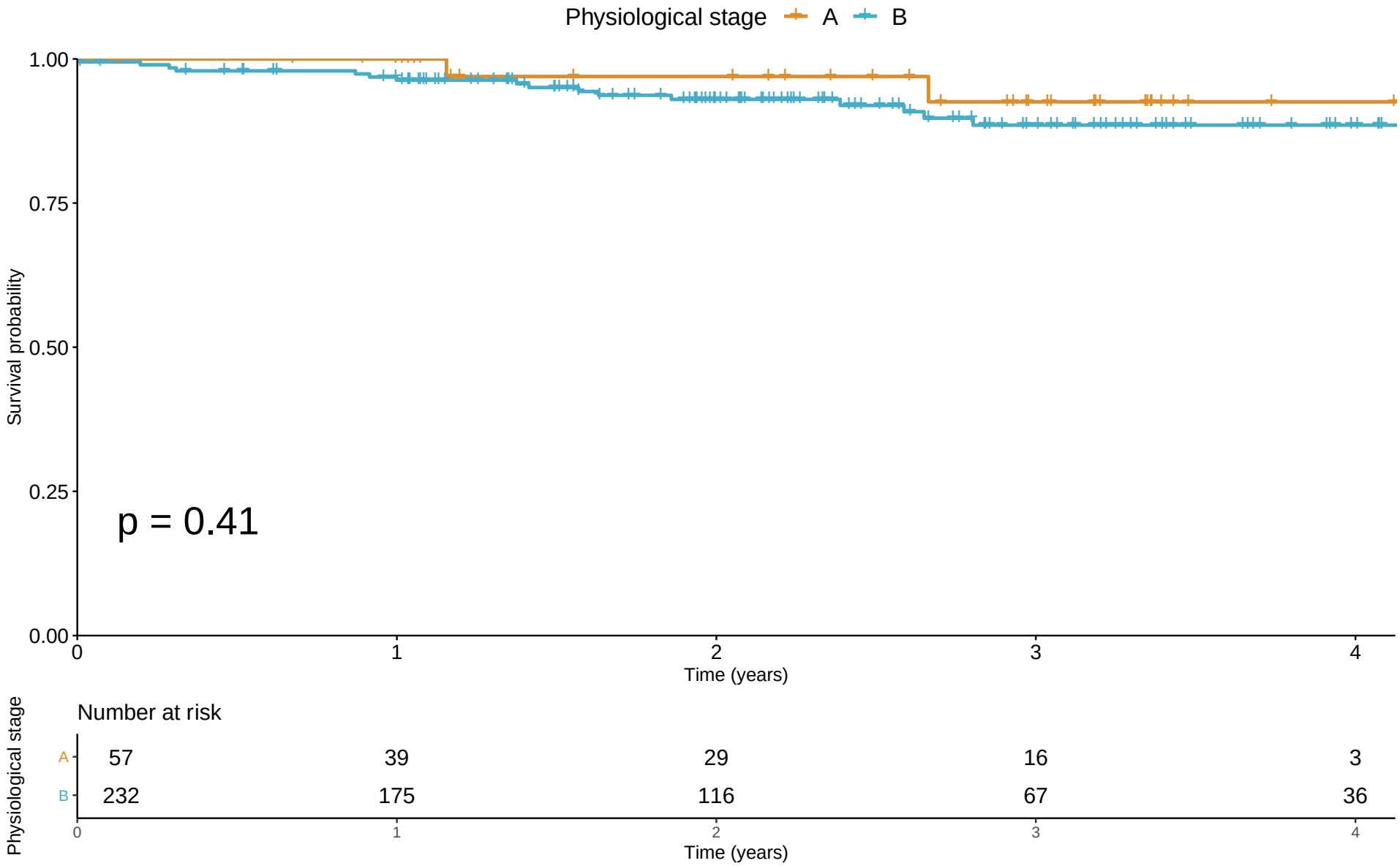
Table S5. Hazard ratio and event rate for thromboembolic events, bleeding events, and catheter- or surgical-based intervention.

		Thromboembolic event			**Bleeding event**			**Catheter or surgical intervention**	
# events		41 (4.1%)			32 (3.2%)			196 (19.6%)	
	n/N (%)	*HR*	*P value*	*n/N (%)*	*HR*	*P value*	*n/N (%)*	*HR*	*P value*
IA	0/17 (0.0)	--	--	0/17 (0.0)	--	--	0/17 (0.0)	--	--
IB	1/32 (3.1)	1.94	0.541	0/32 (0.0)	--	--	3/32 (9.4)	0.37	0.093
IC	0/31 (0.0)	--	--	0/31 (0.0)	--	--	3/31 (9.7)	0.42	0.146
ID	0/15 (0.0)	--	--	0/15 (0.0)	--	--	3/15 (20.0)	0.80	0.699
IIA	0/26 (0.0)	--	--	0/26 (0.0)	--	--	0/26 (0.0)	--	--
IIB	4/135 (3.0)	1.54	0.506	1/135 (0.7)	0.39	0.379	11/135 (8.1)	0.30	0.000*
IIC	6/309 (1.9)	REFERENCE		6/309 (1.9)	REFERENCE		78/309 (25.2)	REFERENCE	
IID	8/53 (15.1)	7.89	0.000*	6/53 (11.3)	6.07	0.002*	17/53 (32.1)	1.09	0.761
IIIA	0/14 (0.0)	--	--	0/14 (0.0)	--	--	0/14 (0.0)	--	--
IIIB	4/66 (6.1)	2.74	0.119	0/66 (0.0)	--	--	5/66 (7.6)	0.25	0.003*
IIIC	11/234 (4.7)	1.93	0.198	13/234 (5.6)	2.09	0.147	49/234 (20.1)	0.64	0.015*
IIID	7/68 (10.3)	4.46	0.007*	6/66 (8.8)	4.33	0.011*	27/68 (39.7)	1.39	0.142
C-statistic (95% CI)		0.72 (0.68, 0.76)			0.76 (0.72, 0.80)			0.65 (0.63, 0.67)	

Values are presented by anatomic and physiological classification, with IIC as the reference group. Double dashes represent cells with no events. * indicates p-values <0.05.

HR = hazard ratio

Figure S1. Kaplan-Meier curve for survival free of the combined outcome of death or non-elective cardiovascular hospitalization for patients classified as either physiological stage A or B.



There were 290 patients classified as A or B. Curves are compared with the log-rank test