BRIEF COMMUNICATION

Newly Developed Adult Congenital Heart Disease Anatomic and Physiological Classification: First Predictive Validity Evaluation

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***Background*—**Risk stratification for adults with congenital heart disease is usually based on the anatomic complexity of the patients' defect. The 2018 American Heart Association/American College of Cardiology guidelines for the management of adults with congenital heart disease proposed a new classification scheme, combining anatomic complexity and current physiological stage of the patient. We aimed to investigate the capacity of the Adult Congenital Heart Disease Anatomic and Physiological classification to predict 15-year mortality.

***Methods and Results*—**Data on 5 classification systems were collected for 629 patients at the outpatient clinic for a previous study. After 15 years, data on mortality were obtained through medical record review. For this assessment, we additionally collected information on physiological state to determine the Adult Congenital Heart Disease Anatomic and Physiological classification. Harrell's concordance statistics index, obtained through a univariate Cox proportional hazards regression, was 0.71 (95% CI, 0.63−0.78) for the Adult Congenital Heart Disease Anatomic and Physiological classification. Harrell's concordance statistics index of the congenital heart disease anatomic component only was 0.67 (95% CI, 0.60−0.74). The highest Harrell's concordance statistics index was obtained for the anatomic complexity in combination with the Congenital Heart Disease Functional Index (0.79; 95% CI, 0.73–0.84).

***Conclusions*—**This first investigation of the Adult Congenital Heart Disease Anatomic and Physiological classification system provides empirical support for adding the physiological component to the anatomic complexity in the prediction of 15-year cardiac mortality. **(*J Am Heart Assoc*. 2020;9:e014988. DOI: 10.1161/JAHA.119.014988.)**

Key Words: congenital heart disease • classification • mortality

Stratifying patients with congenital heart disease (CHD) for their risk on mortality and morbidity remains a point of discussion among many experts and healthcare professionals in the field. The classification of Task Force 1 of the 32nd Bethesda Conference is the most commonly applied system, categorizing patients into mild, moderate, and complex heart defects, according to the anatomic complexity of their heart defect.[1] Despite its widespread use, the current functional status of the patient and its respective evolution over time cannot be accounted for by the Bethesda classification.

In the 2018 American Heart Association/American College of Cardiology guidelines for the management of adults with CHD, a new classification scheme is proposed, in which both anatomic complexity and current physiological stage of the patient are included.[2] This new classification system, the Adult Congenital Heart Disease Anatomic and Physiological classification (ACHD-AP), comprises 12 categories to which patients can be assigned. This classification scheme has the potential to provide a more comprehensive assessment of patients for their risk of mortality and morbidity. Given that it is a new classification scheme, no data on the validity of the ACHD-AP are available yet.

Recently, we published a study in which we compared 5 scales on their ability to predict 15-year mortality in adults with CHD[3]: the Bethesda classification,[1] the New York Heart Association (NYHA) functional class,[4] the Ability Index,[5] the Disease Severity Index,[6] and the Congenital Heart Disease Functional Index (CHDFI).[7] We found that the CHDFI had the highest discrimination ability for all-cause and cardiac

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mortality.[3] To confirm the added value of the physiological component of the newly developed ACHD-AP score, it is relevant to investigate how this newly developed classification system is performing in relation to the other existing systems. Therefore, we aimed to evaluate the properties of the ACHD-AP to predict 15-year mortality and to compare these predictive properties with the other classification systems.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to KU Leuven at philip.moons@kuleuven.be. Between 2000 and 2002, a total of 629 patients with CHD (median age=24 years; 60% men) who were visiting the outpatient clinic were included in a cross-sectional study on quality of life and perceived health.[7–9] All patients gave oral informed consent. As part of that study, patients were categorized by the treating physician (W.B.) on 5 indexes.[7] The Bethesda disease complexity classification categorizes patients into 3 groups: simple, moderate, and severely complex congenital heart defects, based solely on the anatomic complexity.[1] The NYHA categorizes patients into 4 functional classes based on their day-to-day level of functioning and experienced symptoms.[4] The Ability Index classifies patients into 4 groups based on their capacity to work, capacity to be active, and ability to go through uncomplicated pregnancies (if applicable).[5] The Disease Severity Index compiles information on the patient's history of surgical or catheter-based interventions and whether the patient has persistent cyanosis, allocating patients to 1 of 3 respective categories.[6] The CHDFI comprises 5 classes: class 1, no surgery, good clinical status, medical follow-up not strictly necessary; class 2, with or without surgery, functionally perfect, postoperative normalization of clinical condition, medical checkup every 3 to 5 years, competitive sports permitted; class 3, with or without surgery, functionally good, medical restrictions, medical checkup every 1 to 2 years, recreational sports permitted; class 4, with or without surgery, moderate functional status, functioning at own pace, medical checkup every year; and class 5, with or without palliative surgery, bad functional status, cyanosis present, medical checkup every 6 to 12 months.[7]

Fifteen years later, mortality data were retrieved from the hospital information system. Follow-up time was determined as the time from enrollment until the last contact with the hospital or any affiliated hospital, either in person or through telephone communication.[3] Overall, 40 patients died over the 15-year follow-up period, and the cause of death was available in 32 patients.[3]

For the present analysis, additional information on the physiological stage at study inclusion of these patients was obtained from medical records by one of the researchers (F.O.). The ACHD-AP classification requires 12 different variables that determine the physiological category of a patient (A-D): aortopathy, arrhythmia, concomitant valvular heart disease, end-organ dysfunction, exercise capacity, Eisenmenger syndrome, hypoxemia/cyanosis, NYHA functional classification, pulmonary hypertension, presence of a shunt, venous or arterial stenosis, and ventricular enlargement or dysfunction. Patients are categorized on the basis of the most severe anatomic and physiological features.[2] We acquired information on the following variables: the presence of aortic enlargement (mild, moderate, or severe),[2] ventricular enlargement or dysfunction,[10] arrhythmia (no arrhythmia, arrhythmia not requiring treatment, arrhythmia controlled with therapy, or refractory arrhythmia),[2] end-organ dysfunction (renal, hepatic, or lung),[2] a shunt (trivial/small shunt or hemodynamically significant shunt),[2] valvular heart disease (mild valvular disease or significant valvular disease),[2,11,12] venous or arterial stenosis (present or not),[2] cyanosis (present or not), pulmonary hypertension (less than severe or severe),[2] and Eisenmenger syndrome (present or not).[2] Information on hypoxemia and objective limitations to exercise was not included in our assessment of the ACHD-AP score because these items were not routinely collected at study inclusion. For this additional data collection, a supplementary approval was acquired from the institutional review board of the University Hospitals Leuven.

Statistical Analysis

We computed Kaplan-Meier curves and Harrell's concordance statistics index (C-index) through a Cox proportional regression analysis to evaluate prediction models for accuracy.[13] On the basis of the work of Hosmer and Lemeshow,[14] we categorized models using the following cutoffs: a C-index $\geq$0.90 was considered to be an outstanding model; a C-index between 0.80 and 0.89 represented an excellent model; a C-index between 0.70 and 0.79 indicated a good model; and a C-index $<$0.70 was considered to represent a poor model. C-indexes were compared pairwise using a nonparametric approach developed for right-censored survival data.[15] We used IBM SPSS version 25 for Windows (IBM Corp, Armonk, NY) and R version 64 3.4.3. A significance level of $P<0.05$ was used, and all tests were performed 2 sided. *P* values were adjusted using the Benjamini-Hochberg method to correct for multiple testing when comparing the C-indexes of the different classifications.[16]

Results

Figure 1 depicts the probability for all-cause (Figure 1A) and cardiac mortality (Figure 1B) after 15 years for each

respective ACHD-AP class. The 15-year mortality in patients with mild heart defects was 0%, irrespective of their physiological status. For patients with moderate or complex heart defects, the probability of mortality increased according to the physiological status, both for all-cause and cardiac mortality (Figure 1). One exception is the 10% probability for cardiac mortality in patients with complex heart defects and physiological stage D. The 3 patients who died in this category all had Eisenmenger syndrome. For one of them, a cardiac cause of death was confirmed. For the other 2 patients, the reason of death was unknown and therefore not considered to be cardiac.

Harrell's C-index for the ACHD-AP classification in the prediction of all-cause mortality was 0.71 (95% CI, 0.63–0.78) (Figure 2A). The C-index for cardiac mortality was 0.75 (95% CI, 0.67–0.82) (Figure 2B). For all-cause mortality, this C-index was slightly better compared with the C-index of the CHD anatomic component only (0.67; 95% CI, 0.60–0.74), which did not exceed the cutoff of 0.70 to have a good model fit for mortality prediction. For cardiac mortality, the C-index of the CHD anatomic component was significantly lower (0.64; 95% CI, 0.56–0.73; P=0.02) in comparison with the ACHD-AP. This finding demonstrates an additional benefit in predicting cardiac mortality from adding the physiological component to the CHD anatomic classification. However, the NYHA classification on its own already had a C-index of 0.71 (95% CI, 0.63–0.79). If the physiological stage from the ACHD-AP is replaced by the NYHA classification, the C-index for this CHD anatomic component+NYHA was 0.76 (95% CI, 0.69–0.83). The highest C-index was obtained when combining the CHD anatomic component with the CHDFI (0.78; 95% CI, 0.73–0.84) (Figure 1B), which was significantly better than the ACHD-AP in predicting mortality after 15 years after correction for multiple testing using the false discovery rate.

For cardiac mortality, the ACHD-AP classification is performing significantly better than the CHD anatomic component alone or the NYHA. The C-index for the CHD anatomic component+CHDFI is still higher than the ACHD-AP, but did not reach statistical significance.

Discussion

Using the anatomic complexity to allocate patients to appropriate levels of care has been a point of discussion for many years. With the new 2018 American Heart Association/American College of Cardiology guidelines for the management of adults with CHD,[2] these concerns may have been addressed and have resulted in the development of the ACHD-AP score.

In this brief communication, we aimed to investigate the ACHD-AP classification for predicting mortality after 15 years. Although our findings are preliminary, they indicate the added value of including the physiological stage alongside CHD anatomic component in predicting cardiac mortality. However, given the resource demanding nature of the data collection for obtaining the physiological stage, it can be questioned if simpler methods would be available to assign patients to the appropriate level of care. For instance, the CHDFI is more performant compared with the newly developed ACHD-AP in predicting 15-year all-cause mortality when it is combined with the CHD anatomic classification. However, the CHDFI does require a more in-depth evaluation of the reliability, as no information is currently available on interrater reliability of this instrument.

Evidently, our findings require further scrutiny. The present findings clearly warrant larger and specifically designed replication studies before firm conclusions can be drawn on

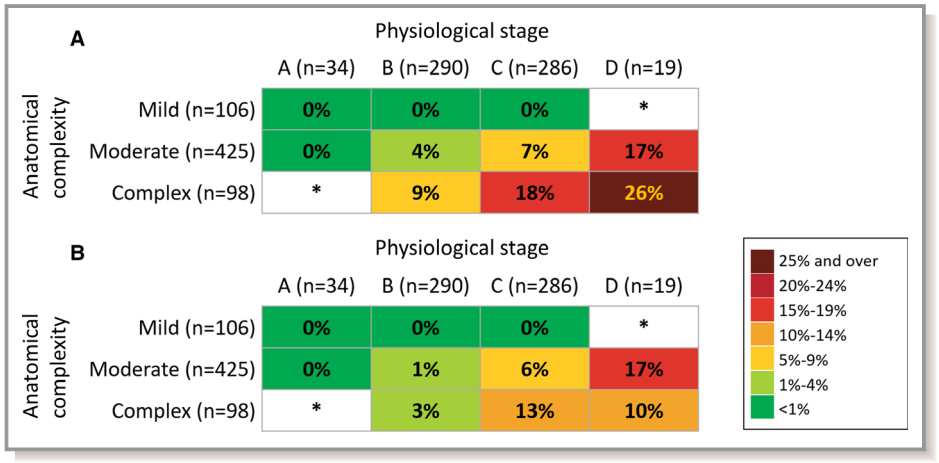

Figure 1. Probability of all-cause mortality (**A**) and cardiac mortality (**B**) for different Adult Congenital Heart Disease Anatomic and Physiological classification classes based on Kaplan-Meier estimates. *Cells comprise only one patient.

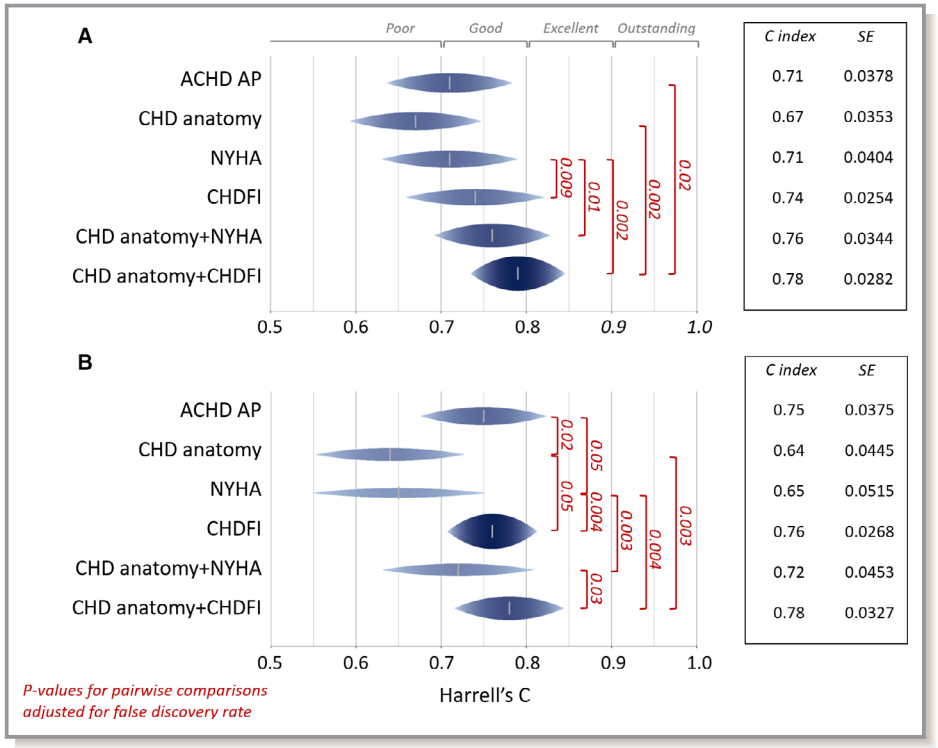

Figure 2. Rainforest plot of Harrell's concordance statistics index of the Adult Congenital Heart Disease Anatomic and Physiological classification (ACHD-AP) and other/combined classifications to predict all-cause mortality (**A**) and cardiac mortality (**B**). CHD indicates congenital heart disease; CHDFI, Congenital Heart Disease Functional Index; NYHA, New York Heart Association.

the ACHD-AP's validity and applicability. Such studies also ought to include other outcomes, such as morbidities, for a comprehensive review of this classification. However, our results show that the physiological status of the patient needs to be taken into account in addition to the anatomic complexity of the defect to predict long-term outcome.

Conclusions

Although the ACHD-AP was not designed to predict mortality or morbidity, adding the current physiological stage to the anatomic complexity showed an improved prediction for cardiac mortality over 15 years. Our findings demonstrated how the anatomic complexity in combination with the CHDFI displayed a significantly better capacity to predict all-cause mortality. Additional research is highly needed, however, to verify its capacity to predict overall outcome, determining the practical value of this tool.

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Disclosures

None.

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