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Clinical Research

Predicting 15-Year Mortality in Adults With Congenital Heart Disease Using Disease Severity and Functional Indices

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ABSTRACT

Background: Disease severity and functional indices are widely used for risk stratification of patients with congenital heart disease (CHD). The predictive value of these classification systems for assessing long-term mortality is unknown. We aimed to determine and compare the predictive value of disease severity and functional indices for 15-year mortality in adults with CHD.

Methods: Between 2000 and 2002, we categorized 629 patients with CHD (median age, 24 years; 60% were men) on 5 indices: disease complexity scores based on criteria of Task Force 1 of the 32nd Bethesda Conference; Disease Severity Index; New York Heart Association functional class; Ability Index; and Congenital Heart Disease Functional Index (CHDFI). Harrell's concordance statistics index (C-index) was calculated for each classification system through Cox hazard regression analysis to evaluate their performance on predicting all-cause and cardiac mortality over the subsequent 15 years.

Results: Over the 15-year follow-up period, 40 patients died, resulting in a mortality rate of 4.56 per 1000 person-years. The CHDFI showed

RÉSUMÉ

Contexte : La gravité de la maladie et les indices fonctionnels sont couramment utilisés pour stratifier les risques chez les patients atteints d'une cardiopathie congénitale. Cependant, on ignore dans quelle mesure ces systèmes de classification permettent de prédire la mortalité à long terme chez ces patients. L'objectif de notre étude était de déterminer et de comparer la valeur prédictive de la gravité de la maladie et des indices fonctionnels relativement à la mortalité sur 15 ans chez des adultes atteints d'une cardiopathie congénitale.

Méthodologie : Nous avons réparti en différentes catégories 629 patients atteints d'une cardiopathie congénitale (âge médian : 24 ans; 60 % d'hommes) entre 2000 et 2002 selon 5 indices : les scores de complexité de la maladie selon les critères du groupe de travail n° 1 de la 32e conférence de Bethesda, l'indice de gravité de la maladie, la classe fonctionnelle selon les critères de la New York Heart Association, l'indice de capacité fonctionnelle et l'indice fonctionnel des cardiopathies congénitales (CHDFI, pour *Congenital Heart Disease Functional Index*). L'indice de concordance de Harrell (indice C) de chaque système

Compared with the general population, patients with congenital heart disease (CHD) have a higher mortality risk, shown by a standardized mortality ratio of 2.29.[1] To identify patients with CHD who require the most careful monitoring, clinicians can perform risk stratifications. Mortality risk algorithms or classification schemes have been developed and tested, but currently appear to exist only for pediatric patients[2-4] and specific surgical populations, such as patients with Fontan circulation[5] or patients after heart transplantation,[6] or to require data that are not always readily available.[7] Overall, the use of resource-, time-, and cost-intensive algorithms in clinical practice is often impractical.

To the best of our knowledge, to date no simple algorithm exists that reliably predicts mortality risk in adults with CHD. This may be one reason why risk stratification is often done on the basis of the level of disease complexity, as defined by the Task Force 1 of the 32nd Bethesda conference.[8] This

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the highest discrimination ability for all-cause mortality (C-index = 0.74; $P < 0.001$) and cardiac mortality (C-index = 0.76; $P < 0.001$). The C-index for the other classifications ranged from 0.58 to 0.71 for all-cause mortality and 0.55 to 0.67 for cardiac mortality. The CHDFI showed statistical superiority toward the Disease Severity Index ($P < 0.01$).

Conclusions: These results suggest that the Task Force 1 of the 32nd Bethesda Conference, New York Heart Association functional class, Ability Index, and CHDFI could aid in predicting long-term mortality. The CHDFI demonstrated the highest discrimination ability and emphasizes the importance to integrate both anatomic and physiological variables to predict long-term mortality.

de classification a été calculé au moyen d'une analyse de régression à risques proportionnels de Cox afin d'évaluer la mesure dans laquelle le système permettait de prédire la mortalité toutes causes confondues et la mortalité cardiaque au cours des 15 années suivantes.

Résultats : Au cours de la période de suivi de 15 ans, 40 patients sont décédés; le taux de mortalité était donc de 4,56 pour 1000 années-personnes. Le pouvoir discriminant le plus élevé a été celui du CHDFI, tant pour la mortalité toutes causes confondues (indice C : 0,74; $p < 0,001$) que pour la mortalité cardiaque (indice C : 0,76; $p < 0,001$). L'indice C des autres systèmes de classification variait entre 0,58 et 0,71 pour la mortalité toutes causes confondues et entre 0,55 et 0,67 pour la mortalité cardiaque. Le CHDFI s'est révélé statistiquement supérieur à l'indice de gravité de la maladie ($p < 0,01$).

Conclusions : Ces résultats donnent à penser que le score du groupe de travail n° 1 de la 32e conférence de Bethesda, la classe fonctionnelle de la New York Heart Association, l'indice de capacité fonctionnelle et le CHDFI pourraient aider à prédire la mortalité à long terme. Le CHDFI a affiché le pouvoir discriminant le plus élevé, ce qui souligne l'importance de prendre en compte des variables tant anatomiques que physiologiques pour prédire la mortalité à long terme.

classification system categorizes patients as having simple, moderate, or severely complex heart lesions. This instrument was developed on the basis of expert consensus. However, it does not account for disease evolution and complications, despite high incidence rates of complications in this population.[9] Besides the Bethesda disease complexity classification, there are several other disease severity or functional indices available to categorize patients with CHD, such as the New York Heart Association (NYHA) functional class,[10] Ability Index,[11] Disease Severity Index,[12] and Congenital Heart Disease Functional Index (CHDFI).[13]

Previous studies demonstrated differences in mortality risks among the classes of the Bethesda disease complexity scheme. Patients with a severely complex heart defect have a higher standardized mortality ratio compared with the general population and patients with a simple lesion.[1,14,15] The NYHA functional class also relates to mortality, having a higher hazard ratio (HR) when comparing patients with higher NYHA classes with patients with NYHA Class I.[16] However, the other classification systems have not been scrutinized for their value in identifying patients at risk for premature mortality. Furthermore, a direct comparison of these classification systems has not been done. Therefore, we aimed to determine the predictive value of different disease severity and functional indices for 15-year all-cause and cardiac mortality, and to determine whether one classification is superior to another in detecting adults with CHD at higher risk for mortality.

Material and Methods

Study population and setting

We conducted a cohort study in adults with CHD aged more than 15 years. Between 2000 and 2002, 629 patients were included in a previously conducted cross-sectional study on quality of life and perceived health status.[13,17,18] This study included a consecutive series of patients who visited the adult CHD outpatient clinic of the University Hospitals Leuven, Belgium. Patients were eligible for this initial study if they met the following inclusion criteria: diagnosed with a congenital heart defect, as defined by Mitchell et al,[19] age $\geq$ 18 years, literate, and Dutch speaking. All patients gave oral informed consent. Patients were excluded if it was their first outpatient visit at this clinic, because it is our policy not to approach patients for research projects at their first encounters to build up a trusting relationship first; if they had learning disabilities; or if they were referred for or were in follow-up after closure of an atrial septal defect or patent foramen ovale after cryptogenic stroke.[13]

The treating cardiologist (W.B.) scored each individual patient on 5 different scales for functional status or disease severity at study inclusion.[13] In December 2018, data on mortality were collected retrospectively.

Variables and measurements

Disease severity and functional indices. The 5 classification systems used in this study were as follows: Bethesda disease complexity classification,[8] NYHA functional class,[10] Ability Index,[11] Disease Severity Index,[12] and CHDFI.[13] The Bethesda disease complexity classification categorizes patients into 3 groups: simple, moderate, and severely complex congenital heart defects based on the anatomic complexity.[8] The NYHA has 4 functional classes pertaining to the patient's day-to-day level of functioning and experienced symptoms.[10] The Ability Index scores patients on their capacity to work, capacity to be active, and ability to go through uncomplicated pregnancies (if applicable). It assigns patients to 4 classes.[11] The Disease Severity Index compiles information on the patient's history of surgical or catheter-based interventions and whether they have persistent cyanosis, allocating patients to 1 of 3 categories.[12] Finally, the CHDFI has 5 categories, comprising different elements of the patient's status: surgical history, clinical status, functional capacity, and current frequency of follow-up based on disease complexity or the physician's professional opinion.[13] More details on these scales are presented in Supplementary Table S1.

Mortality. The date and cause of death were obtained from the hospitals' electronic medical records. We classified the cause of death as cardiac or noncardiac. Cardiac death included deaths caused by acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedure (pre- or post-procedure), cardiovascular haemorrhage, or other cardiovascular causes, such as pulmonary embolism. Categories for noncardiac death included deaths caused by pulmonary, renal, gastrointestinal, hepatobiliary, or pancreatic disease; infection; inflammation; neurological issues; noncardiovascular- or non–stroke-related haemorrhage; noncardiovascular procedure or surgery; trauma; cancer; or suicide.[20] For patients presumed alive, we defined the date at which they were last seen alive as the date of the patient's last inpatient or outpatient visit in our hospital or affiliated hospitals or the date of any contact by telephone with a member of the healthcare staff. This resulted in 3 possible end points: (1) patient deceased, date of death is the end point; (2) patient was last seen alive before the end of the 15-year interval, and the patient was right censored; or (3) patient was last seen alive after the end of the 15-year interval and the study end point is 15 years after initial study inclusion. Data at baseline were collected as part of a previous study,[17] as mentioned, for which approval of the ethics committee was previously obtained. Data on mortality were collected retrospectively via the hospital medical records, for which additional approval was acquired by the institutional review board.

Statistical analysis. Categorical data were expressed as absolute numbers and proportions. Age was the only continuous variable, presented as the median with interquartile range because of heteroscedasticity of the data. We calculated Kaplan–Meier survival curves and computed Harrell's concordance statistics index (C-index) through a Cox proportional regression analysis to evaluate prediction models for accuracy.[21] On the basis of the work of Hosmer and Lemeshow,[22] we categorized models using the following cutoffs: a C-index ≥ 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-indices were compared pairwise using a nonparametric approach developed for right-censored survival data.[23] We used IBM SPSS version 25 for Windows (IBM Corp., Armonk, NY) and R version 64 3.4.3.[24] A significance level of $P < 0.05$ was used, and all tests were 2-sided. Bonferroni correction was used to correct for multiple testing when comparing the C-indices of the different classifications, by dividing 0.05 by 20 and obtaining a P value of 0.0025.

Results

Study population

The median age of patients at the time of inclusion was 24 years (interquartile range, 20-29 years), and 60% were men. The median duration of follow-up was 15 years, with 82% reaching the maximum duration of 15 years. The most common primary diagnosis was tetralogy of Fallot, followed by ventricle septal defect and coarctation of the aorta. More than half of the study population had a history of surgical intervention(s), with or without catheter-based intervention(s). Twenty-six patients had a genetic syndrome known to be associated with CHD (Table 1).

Disease severity and functional indices

In our sample of 629 patients, 26% had a simple CHD, 58% had a moderately complex CHD, and 16% had a severely complex heart defect, as determined by the Bethesda disease complexity classification (Fig. 1). The largest group of patients (81%) was categorized as Class I in the NYHA classification scheme (ie, "living without limitation of physical activity"). For the Ability Index, 83% of patients were assigned to Grade 1, which corresponded to having a normal life (eg, full-time work or school). For the Disease Severity Index, 64% of patients were categorized as low disease severity. For the CHDFI, 57% of patients were categorized as Class 3 (Fig. 1).

Mortality

A total of 8764 person-years have been observed in this study. Forty patients died (6%) over the 15 years of follow-up, corresponding to a mortality rate of 4.56 per 1000 person-years. The median age at the time of death was 36 years (interquartile range, 28-43.75 years). The cause of death was available from medical records in 32 patients; 26 (81%) died

Table 1. Demographic and clinical characteristics of 629 adults with CHD at time of inclusion

Variable	n (%)
Median age (y) at inclusion	24 (IQR, 20-29)
Men	378 (60)
Marital status	
Unmarried living with parents	346 (55)
Unmarried living alone	50 (8)
Living together	81 (13)
Married	139 (22)
Divorced	9 (1)
Widow(er)	1 (0.2)
Primary diagnosis for type of heart defect	
Tetralogy of Fallot	112 (18)
Ventricular septal defect	108 (17)
Coarctation of the aorta	89 (14)
Aortic valve stenosis	65 (10)
Pulmonary valve stenosis	48 (8)
Transposition of the great arteries (with atrial switch)	33 (5)
Transposition of the great arteries (with arterial switch)	1 (0.2)
Transposition of the great arteries (Rastelli or Blalock–Hanlon)	2 (0.3)
Mixed aortic valve disease	28 (4)
Atrial septal defect type 2	23 (4)
Mitral valve insufficiency	20 (3)
Univentricular heart	18 (3)
Double outlet right ventricle	12 (2)
Congenitally corrected transposition of the great arteries	11 (1)
Ebstein malformation of the tricuspid valve	9 (1)
Aortic valve insufficiency	8 (1)
Atrial septal defect type 1	8 (1)
Other	35 (6)
History of intervention	
No intervention	202 (32)
Surgery	330 (52)
Catheter intervention	28 (4)
Both surgical and catheter interventions	69 (11)
Genetic syndrome associated with CHD	26 (4)

CHD, congenital heart disease; IQR, interquartile range.

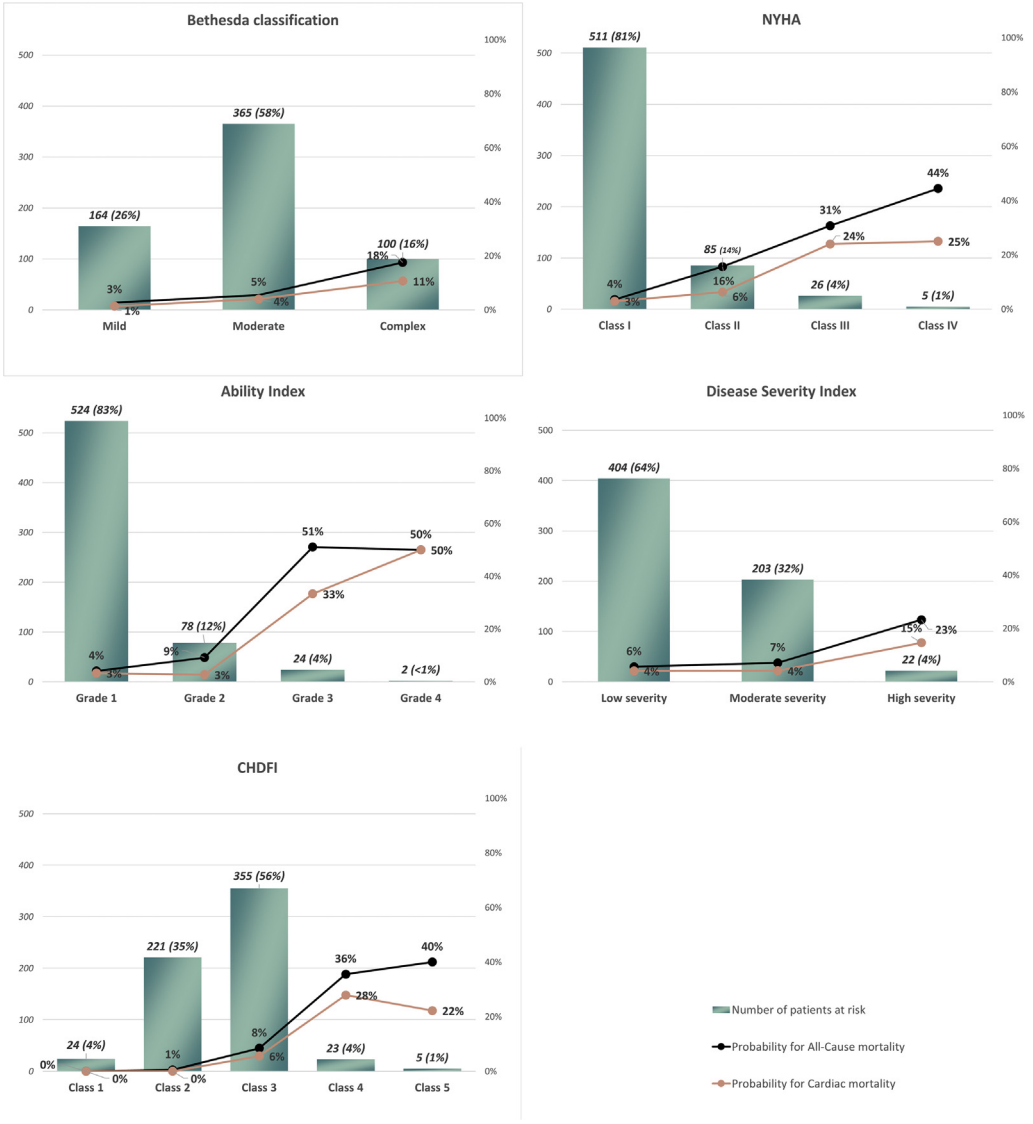

Figure 1. Distribution of included patients' scores on the 5 indices, probability for all-cause, and cardiac mortality at 15 years. CHDFI, Congenital Heart Disease Functional Index; NYHA, New York Heart Association.

of a cardiac cause (Supplementary Table S2). Nine patients (28%) died of sudden cardiac death, 7 patients (22%) died of complications of a cardiovascular surgical procedure, 6 patients (19%) died of heart failure, 1 patient (3%) died of a cardiovascular haemorrhage, 1 patient (3%) died of an acute myocardial infarction, 1 patient (3%) died of Eisenmenger's syndrome, and 1 patient (3%) died of complications related to arrhythmia. Six patients (19%) died of non–cardiac-related causes: 2 suicides, 2 deaths due to malignancy, 1 death after intracranial bleed, and 1 related to fatal injuries associated with a traffic accident. Supplementary Table S2 lists the causes of death, stratified by type of heart defect.

Probability of survival stratified by disease severity and functional indices

The probability of survival over a period of 15 years was 82% for patients with a severely complex heart defect, as operationalized using the Bethesda classification, compared with 95% in patients with a moderately complex defect and 97% in patients with a simple heart defect (Fig. 1). The findings as presented in Figures 1 and 2 show that the proportion of deceased patients increases with increasingly severe categories for all 5 classification systems.

Kaplan–Meier survival curves are plotted in Figure 2. Log-rank tests demonstrated that the mortality curves were significantly different across the diverse categories of the respective classification systems for all-cause and cardiac mortality with an exception for the Disease Severity Index concerning cardiac mortality.

The discriminating performance of each classification system in predicting mortality was assessed using Harrell's C-indices. The CHDFI produced the highest C-index for both all-cause mortality (0.74; $P < 0.001$) and cardiac mortality (0.76; $P < 0.01$) (Table 2). Because these C-indices for the CHDFI exceeded the cutoff of 0.70 as proposed by Hosmer and Lemeshow,[22] the CHDFI represented a good model fit in mortality prediction.

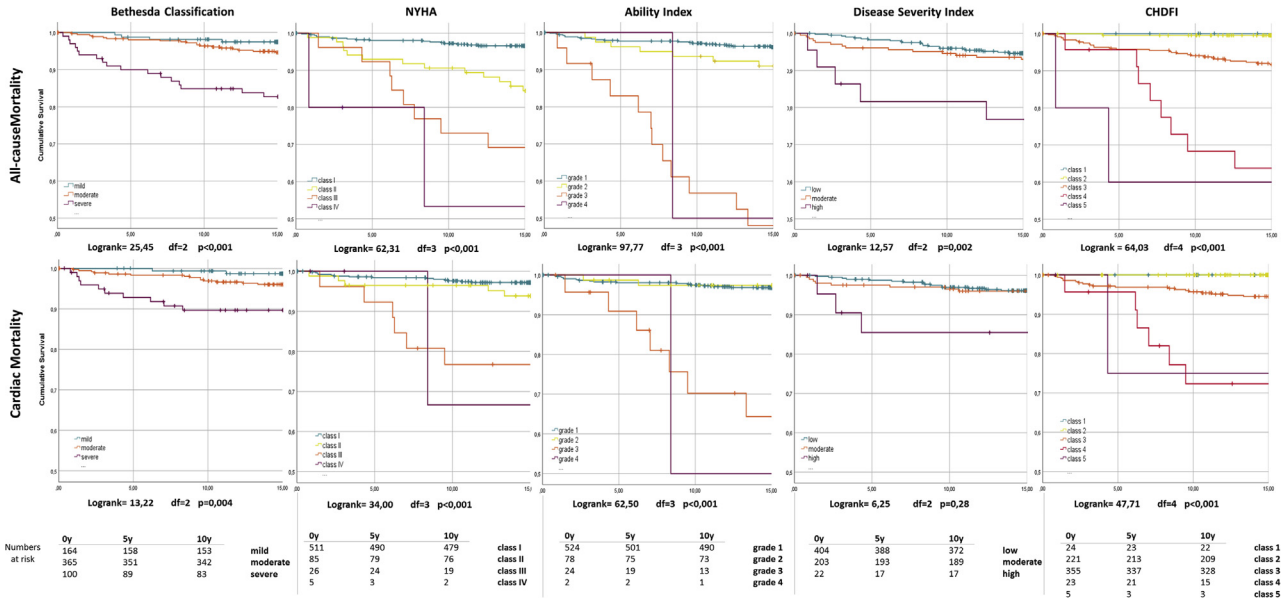

Figure 2. Kaplan–Meier curves for all-cause and cardiac mortality for the 5 functional indices. CHDFI, Congenital Heart Disease Functional Index; NYHA, New York Heart Association.

We statistically compared the C-indices of the different classification systems. The C-index of the CHDFI was significantly higher than the C-index of the Disease Severity Index for all-cause and cardiac mortality. The differences between the other C-indices did not reach statistical significance.

Discussion

To the best of our knowledge, the present study is the first to directly compare 5 disease severity and functional classification systems with the purpose of identifying a quick tool for mortality prediction in adults with CHD. Previous research evaluated only the predictive value of 2 indices: the Bethesda disease complexity classification[1,14,15,25-27] and the NYHA functional class[1,16,26,28] separately. As expected in these studies, patients in higher classes showed higher mortality. Also, compared with mild heart defects, the moderate and complex heart lesions had HRs of 1.3 to 1.7 and 5.3 to 5.9, respectively.[15,27] For the NYHA, the HRs for mortality increased with increasing classes (2.78-2.9).[26,28] Although direct comparisons between our results and the results of these studies are not possible, they do show similar trends.

We found that all scales significantly predicted all-cause and cardiac mortality, with the exception of the Disease Severity Index. The CHDFI had the highest C-index suggesting the best capacity to detect adults with CHD at higher risk for all-cause and cardiac mortality. This index outperformed the other classification systems in accurately predicting mortality. The CHDFI was the only classification system that had areas under the curve > 0.70 for both all-cause and cardiac mortality. Thus, by using the criteria of Hosmer and Lemeshow,[22] the CHDFI served as a good prediction model. Another remarkable characteristic of the CHDFI was that in our study no patient in Class 1 died and only 1 patient in Class 2 died, which in this study resulted in a negative predictive value of 100% when using Class 3 as a cutoff. This suggests that the CHDFI is highly satisfactory for predicting nonevents.

The higher C-index of the CHDFI can be explained by some specific characteristics of this scale. First, the CHDFI captures the current state of the patient's condition, and therefore gives a contemporary view on the status of the patient. Other classification systems, such as the Bethesda classification or the Disease Severity Index, do not change over time, irrespective worsening of the patient's health status. Second, the CHDFI comprises 5 categories, whereas the other classification systems have 3 to 4 classes. This contributes to a higher responsiveness and the ability to capture more subtle differences between patients. Third, the CHDFI integrates scores across different functional domains that can more comprehensively capture the patient's true status. It reflects surgical history, functionality, required frequency of follow-up, sports participation allowed, and presence of cyanosis.[13] Therefore, the CHDFI is likely more fine-tuned to look into the patient's overall condition than, for instance, the Bethesda disease complexity classification, which may only provide a restricted look, missing important aspects besides

Table 2. Harrell's C-index of disease severity and functional indices

	All-cause mortality C-index* (95% CI)	Cardiac mortality C-index* (95% CI)
Bethesda classification	0.67 (0.59-0.75)	0.67 (0.57-0.77)
NYHA	0.71 (0.65-0.77)	0.65 (0.58-0.73)
Ability Index	0.69 (0.63-0.74)	0.64 (0.57-0.71)
Disease Severity Index	0.58 (0.50-0.65)	0.55 (0.46-0.64)
CHDFI	0.74 (0.66-0.82)	0.76 (0.66-0.86)

CHDFI, Congenital Heart Disease Functional Index; CI, confidence interval; C-index, concordance statistics index; NYHA, New York Heart Association.

*C-index < 0.70 is a poor model; C-index 0.70-0.79 is a good model; C-index 0.80-0.89 is an excellent model; C-index ≥ 0.90 is an outstanding model.

anatomic complexity. The refined capacity of the CHDFI likely contributed to its robust predictive value for mortality. The recently proposed Adult Congenital Heart Disease Anatomic and Physiological classification system, presented by the American Heart Association,[29] supports the need for a more fine-tuned tool that captures both anatomic and physiological aspects and encompasses the fluctuations in the patient's health status. Obviously, this Adult Congenital Heart Disease Anatomic and Physiological score needs to undergo validation tests and requires an investigation of its predictive characteristics.

This study can serve as a proof of concept for using functional indices for the purpose of predicting long-term mortality in adults with CHD. The CHDFI might be a useful tool that can be easily implemented in daily clinical practice. It gives a quick overview of the patient's condition, while at the same time providing a good prediction of mortality. Our study suggests that patients in CHDFI Classes 4 or 5 warrant close monitoring of disease progress and identification of specific risk factors for mortality. By implication, patients in Class 3 of the CHDFI may require more in-depth risk assessment, specifically assessing whether genetic syndromes, ventricular dysfunction, ventricular overload, pulmonary arterial hypertension, aneurysms, or ischemic heart disease might be present.[14] Given the absence of mortality in patients in Class 1 and 2 in our study, patients in these classes might not be at higher risk for mortality compared with the general population, and therefore may not need an in-depth risk assessment for mortality. Because the current healthcare system is characterized by a shortage of staff and resources, and CHD is characterized by increasing costs, clinicians and policymakers may also be interested in identifying patients who do not require specialized or frequent follow-up.[30,31] The CHDFI may be an appropriate tool to identify such patients, although more research is required to draw firm conclusions on the specificity of the CHDFI.

Methodological considerations

This study had several strengths. It was the first direct comparison of the predictive value of 5 disease severity and functional indices for long-term mortality. Because mortality in Belgium is comparable to that in other countries, this cohort was representative of patients in follow-up in adult CHD centers in other western countries.[32] A 15-year follow-up made it possible to compare these classification systems for their ability to predict long-term mortality. Furthermore, included patients were classified by a single cardiologist with expertise in adult CHD, avoiding the possibility of inter-rater biases. This also entails the absence of data on inter-rater reliability of these 5 indices.

However, there are also some methodological limitations that warrant caution when generalizing our results to other situations. First, we investigated only the predictive value of the indices and scales with respect to mortality. It would be valuable to evaluate the classification systems in relation to the development of long-term morbidities. For instance, the NYHA functional class and the Ability Index are able to differentiate among patients with and without heart failure.[33] It is not known if they also can predict the development of heart failure. Second, no information on the cause of death was available for 20% of the deceased patients, complicating the distinction between cardiac mortality and noncardiac mortality in our study. However, from a patient's perspective, this distinction is trivial. Third, this study may have been underpowered to find statistically significant differences among the 5 scales because of a low number of deceased patients for some classes of certain indices for which we had only a few patients. For instance, only 2 patients were in Grade 4 of the Ability Index, 5 patients were in Class IV of the NYHA functional class, and 5 patients were in Class 5 of the CHDFI, even though our distributions are in line with those reported in prior research.[16,33]

Future research should determine whether these classifications, and specifically the CHDFI, are reliable when several different healthcare professionals are assessing the patients. The newly developed Adult Congenital Heart Disease Anatomic and Physiological (AP) classification[29] should be added to this list of scales to be further scrutinized in future research, because it shows similar characteristics to the CHDFI and may have a predictive value for long-term mortality despite being designed for other purposes.

Conclusions

Four of the 5 tools showed significant capability to predict 15-year mortality in adult patients with CHD. The predictive value of the CHDFI showed more robustness of the model compared with the other scales. The predictive value of the CHDFI showed more robustness of the model when compared with the other scales and emphasizes the importance to include functional and physiological variables to encompass the fluctuations in a patient's health status. Future research needs to validate the Adult Congenital Heart Disease Anatomic and Physiological classification, as proposed by the 2018 American Heart Association/American College of Cardiology guidelines,[29] and future psychometric evaluations and research in larger samples should determine its usability to detect patients at risk for mortality or morbidity. Additional research should verify its capacity to determine probabilities for no cardiac events occurring in the long term to determine whether this scale is truly superior.

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Disclosures

The authors have no conflicts of interest to disclose.

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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.2019.04.018.