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Development and validation of a risk prediction model in patients with adult congenital heart disease

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ABSTRACT

Aims: To develop and validate a clinically useful risk prediction tool for patients with adult congenital heart disease (ACHD).

Methods and results: A risk model was developed in a prospective cohort of 602 patients with moderate/complex ACHD who routinely visited the outpatient clinic of a tertiary care centre in the Netherlands (2011—2013). This model was externally validated in a retrospective cohort of 402 ACHD patients (Czech Republic, 2004–2013). The primary endpoint was the 4-year risk of death, heart failure, or arrhythmia, which occurred in 135 of 602 patients (22%). Model development was performed using multivariable logistic regression. Model performance was assessed with C-statistics and calibration plots. Of the 14 variables that were selected by an expert panel, the final prediction model included age (OR 1.02, 95%CI 1.00–1.03, $p = 0.031$), congenital diagnosis (OR 1.52, 95% CI 1.03–2.23, $p = 0.034$), NYHA class (OR 1.74, 95%CI 1.07–2.84, $p = 0.026$), cardiac medication (OR 2.27, 95% CI 1.56–3.31, $p < 0.001$), re-intervention (OR 1.41, 95%CI 0.99–2.01, $p = 0.060$), BMI (OR 1.03, 95%CI 0.99–1.07, $p = 0.123$), and NT-proBNP (OR 1.63, 95%CI 1.45–1.84, $p < 0.001$). Calibration-in-the-large was suboptimal, reflected by a lower observed event rate in the validation cohort (17%) than predicted (36%), likely explained by heterogeneity and different treatment strategies. The externally validated C-statistic was 0.78 (95%CI 0.72–0.83), indicating good discriminative ability.

Conclusion: The proposed ACHD risk score combines six readily available clinical characteristics and NT-proBNP. This tool is easy to use and can aid in distinguishing high- and low-risk patients, which could further streamline counselling, location of care, and treatment in ACHD.

1. Introduction

Over the past decades, the treatment and intervention strategies for children with congenital heart disease have enormously improved. This had led to the dawning of a new era, in which nowadays the patient population with adult congenital heart disease (ACHD) outnumbers children with congenital heart disease, and we are confronted with new challenges [1,2]. Today's clinicians face a continuously increasing and aging population of patients with ACHD, who require specialized cardiac care, are at risk of serious adverse events, and in whom monitoring and treatment strategies are largely based on expert opinion [3]. Evidence-based risk stratification would be an important step forward towards individualized management strategies that could lead to better use of health resources, cost savings and improvement of patient care.

To date, many studies have shown that variables such as the complexity of the heart defect [4–6], age [5,7,8], cyanosis [4,5,8], New York Heart Association (NYHA) functional class [5,9], ventricular function [10,11], or biomarkers (N-terminal pro-B-type natriuretic peptide; NT-proBNP) [7,12] are related to adverse outcomes in patients with ACHD. The combination of multiple risk predictors into a tool that provides clinically useful risk predictions is most relevant. For instance,

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in patients with atrial fibrillation [13] or coronary heart disease [14], risk calculators have been developed which are successfully used in daily clinical practice worldwide. In patients with ACHD, few studies have developed risk models [8,15] or validated existing prediction models designed for the general heart failure population in patients with moderate or complex ACHD [16,17]; however, none of these are widely used in daily clinical practice.

The aim of this study was to develop and validate a clinically useful, easy-to-use risk prediction tool that predicts the individualized 4-year risk of death, heart failure or arrhythmia in patients with ACHD. This may aid clinicians in determining the adequate follow-up frequency to monitor patients at the outpatient clinic, to establish the level of care needed for this patient, to provide reliable patient information, and to support clinical judgment when initiating medical therapy.

2. Methods

2.1. Derivation cohort

This study was conducted in accordance with the TRIPOD statement (Appendix 1) [18]. We developed a multivariable prediction model by using the data of a prospective cohort of 602 consecutive patients with moderate or complex congenital heart disease [6]. All patients routinely visited the outpatient clinic of a tertiary referral center in the Netherlands (the Erasmus MC, Rotterdam). Patients with age < 18 years, a mild cardiac lesion (e.g. isolated repaired atrial or ventricular defect, mild pulmonary valve disease), or kidney failure (creatinine >200 μmol/L) were excluded. Patients were prospectively enrolled during a 2-year period (April 2011—April 2013) and underwent clinical assessment, electrocardiography, echocardiography, and venous blood drawing with NT-proBNP measurement at baseline. According to the study protocol, patients were yearly evaluated at our institute during a predefined 4-year period. The primary endpoint was defined as the 4-year risk of all-cause mortality, heart transplant, heart failure (requiring hospital admission or initiation/uptitration of diuretics), or arrhythmia (requiring treatment, or symptomatic and recorded; types are specified in Table 2). Follow-up status at year 4 regarding fatal and non-fatal events was complete in 600 patients (99.7%). The present study complies with the Declaration of Helsinki, the institutional review board of the Erasmus MC approved the study protocol and written informed consent was obtained from all patients included in the cohort. A detailed description of the study protocol, participants and data collection has been previously published [7].

2.2. Model development

The primary endpoint was defined prior to the data analysis as a composite of all-cause mortality, heart failure (requiring hospitalization, or initiation or change in heart failure medication), or arrhythmia (symptomatic and recorded, or requiring treatment). In order to prevent overfitting and preserve external validity, we constructed the multivariable models with the use of ≈10 events per degree of freedom. Therefore, we evaluated a maximum of 14 variables that were selected by an expert panel of adult congenital cardiologists in our centre, based on clinical knowledge and available evidence [4–12]. These variables were specified in advance, were 98.6% complete and were assessed prior to the event adjudication. We used single imputation of covariates based on all covariates considered for the model and based on outcome data to account for missing values; outcome data were not imputed. Continuous variables were analysed continuously, with the exception of oxygen saturation, which was dichotomized at 90% because we considered this as a clinically meaningful threshold value. Highly skewed variables were $\log_2$-transformed (NT-proBNP). With regard to the categorical variables, we collapsed categories with small numbers (NYHA II–III), we analysed ordinal variables as linear terms, and related variables were grouped (cardiac medication use was grouped as no vs. yes, and congenital diagnosis was grouped as moderate vs. complex in accordance with the Bethesda classification [6], further detailed in the legend of Table 3), in order to use only one degree of freedom per categorical variable.

The main effects were first evaluated using univariable binary logistic regression. Nonlinear effects and interaction terms were disregarded. Variables were selected using Akaike's Information Criterion ($p < 0.157$), and were subsequently entered in a multivariable binary logistic regression model. The final prediction model was retrieved using a stepwise backward selection method ($p < 0.157$). Internal validation (in order to obtain the optimism-adjusted C-statistic of the final model) was performed using bootstrap resampling. Shrinkage of model coefficients to adjust for optimism and to improve external calibration was performed using penalized regression [19,20].

2.3. Validation cohort

The model was externally validated by using the data of a cohort of 402 patients that routinely visited the outpatient clinic of the Hospital Na Homolce, Prague, Czech Republic (2004–2013). This centre was chosen because it is routine practice to obtain all clinical parameters and also NT-proBNP levels in this hospital. Patients were selected based on retrospective review of medical records. All patients with a moderate or complex type of diagnosis were included. In all patients, NT-proBNP had been determined in fresh serum samples. Exclusion criteria were: referral for hospitalization with manifest heart failure or arrhythmia, age < 18 years, mild cardiac lesion (isolated repaired atrial or ventricular defect), or kidney failure (creatinine >200 μmol/L). In order to compare the results with the derivation cohort, the occurrence of the primary endpoint as defined above was registered during a period of 4 years from study inclusion.

2.4. External validation

Discrimination of the final prediction model was described using the concordance (C)-statistic, which ranges from 0.5 for non-informative models to 1 for perfectly discriminating models [21]. Calibration was visualized by plotting the predicted risks against the observed risks in a validation plot, and further described with the calibration slope (ideally equal to 1) and intercept (ideally equal to zero) [22]. Finally, the regression coefficients were refitted on a combined dataset including all patients of the derivation cohort and validation cohort ($n = 1004$).

Statistical analyses were performed in IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) and using R statistical software, Version 3.3.4, package rms. Development of the web application was performed in the R Shiny package.

3. Results

3.1. Derivation and validation cohorts

The baseline patient characteristics of the derivation cohort ($n = 602$) and validation cohort ($n = 402$) are detailed in Table 1. The validation cohort additionally included patients with Ebstein

Table 1
Baseline characteristics of the derivation and validation cohort.

Variable	Derivation cohort ($n = 602$)	Validation cohort (n = 402)
Age, years	32.5 [24.7–41.2]	28.3 [22.5–36.2]
Sex, male	348 (58)	206 (51)
Congenital diagnosis		
Congenital aortic stenosis	138 (23)	23 (6)
Aortic coarctation	112 (19)	21 (5)
Arterial switch operation	24 (3)	0 (0)
Tetralogy of Fallot	179 (30)	106 (26)
Ebstein anomaly	0 (0)	37 (9)
Atrioventricular septal defect	0 (0)	20 (5)
Rastelli/REV	11 (2)	7 (2)
Atrial switch operation	65 (11)	87 (22)
Congenitally corrected TGA	21 (4)	22 (5)
Fontan	36 (6)	33 (8)
Functionally univentricular heart	7 (1)	3 (1)
Pulmonary arterial hypertension	9 (1)	43 (11)
NYHA functional class		
I	541 (90)	109 (27)
II	56 (9)	198 (49)
III	5 (1)	94 (24)
IV	0 (0)	1 (0)
Cardiac medication use[a]	212 (35)	233 (58)
≥1 re-interventions after corrective repair	317 (53)	143 (36)
Body mass index, kg/m^2	24.7 ± 4.4	23.8 ± 4.3
Heart rate, beats/min	74 ± 13	72 ± 14
Current smoking	56 (9)	49 (12)
Oxygen saturation < 90%	17 (3)	21 (5)
Loss of sinus rhythm	81 (13)	43 (11)
Systemic ventricular function		
Normal, 0	303 (50)	224 (56)
Mildly impaired, 1	212 (35)	84 (21)
Moderately impaired, 2	69 (12)	57 (14)
Severely impaired, 3	18 (3)	37 (9)
Presence of severe valvular dysfunction[b]	86 (14)	185 (46)
NT-proBNP, pmol/L[c]	15 [7–33]	22 [12–51]

Legend: Values are presented as n (%), mean ± standard deviation or median [interquartile range].
Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; REV, Réparation à l'Etage Ventriculaire (REV procedure); TGA, transposition of the great arteries.
[a] ACE-inhibitor, angiotensin receptor blocker, beta blocker, diuretic, aldosterone antagonist, calcium blocker, or anti-arrhythmic drug.
[b] Defined as maximal aortic or pulmonary valve velocity > 4.0 m/s; grade 3 or 4 out of 4 aortic, pulmonary or mitral valve regurgitation; or grade 4 out of 4 tricuspid valve regurgitation.
[c] $\log_2$-transformed for further analysis.

Table 2
Specification of the primary endpoint in the derivation and validation cohorts.

Variable	Derivation cohort ($n = 602$)	Validation cohort (n = 402)
Primary endpoint	135 (22)	67 (17)
Death	14 (2)	5 (1)
End-stage heart failure	7 (1)	5 (1)
Sudden death/cardiac arrest	6 (1)	0 (0)
Other	1 (0)	0 (0)
Heart transplant	0 (0)	1 (0)
Heart failure	52 (9)	20 (5)[a]
Requiring hospital admission	23 (4)	9 (2)
Requiring initiation or change in diuretics	29 (5)	10 (3)
Arrhythmia	112 (19)	55 (14)
Ventricular fibrillation	7 (1)	1 (0)
Ventricular tachycardia	18 (3)	6 (2)
Atrial flutter/fibrillation	51 (9)	22 (6)
Supraventricular tachycardia (unspecified/other)	26 (4)	17 (4)
Other	10 (2)	9 (2)

[a] Treatment of heart failure was missing in one patient.

anomaly and atrioventricular septal defect, and no patients after arterial switch operation. Moreover, the validation cohort included fewer patients with congenital aortic stenosis or aortic coarctation and more patients with pulmonary arterial hypertension. In the validation cohort 195 patients (49%) with a complex heart defect were included, compared with 149 patients (25%) in the derivation cohort. Furthermore, in the validation cohort the average NYHA class was higher, and more patients used cardiac medication. Age, sex, body mass index, heart rate, smoking, oxygen saturation, rhythm, systemic ventricular function and NT-proBNP levels were comparable between both cohorts.

After 4 years of follow-up, the primary endpoint occurred in 135 patients (22%) in the derivation cohort and in 67 patients (17%) in the validation cohort. All individual components of the primary endpoint occurred less frequently in the validation cohort (Table 2).

3.2. Model development

The majority of the 14 variables that were evaluated were predictors of the primary endpoint in the univariable analysis (Table 3). Only heart rate ($p = 0.833$), smoking ($p = 0.410$) and severe valvular dysfunction ($p = 0.343$) were not related with the primary endpoint, and were therefore excluded from the multivariable model. The final prediction model included all variables that were associated with the primary endpoint in the multivariable analysis: age, congenital diagnosis, NYHA class, cardiac medication use, re-intervention, body mass index (BMI), and NT-proBNP. Of note, the backward selection method resulted in the same final prediction model as a forced entry method of variables with $p < 0.157$ in the multivariable model. The internally validated (optimism-adjusted) C-statistic was 0.85.

3.3. External validation

Similar effects were found for most variables in the validation cohort, except for age and re-intervention. The final prediction model was fitted in the validation dataset to obtain the externally validated C-statistic, which was 0.78 (95%CI 0.72–0.83). Hence, the final model discriminated well between patients with and without a primary endpoint in the validation dataset.

A calibration plot is presented in Fig. 1. The calibration-in-the-large was suboptimal: the prediction model systematically overestimated the risk in the validation dataset. The overall proportion of patients with an event in the validation cohort was lower (17%) than would be expected based on the average predicted risk of our model (36%). However, the calibration slope was acceptable, indicating that the predicted risks were not too extreme or too close to the baseline risk. Therefore, when refitting the final coefficients of the model on the combined dataset, we included a correction factor to adjust for the systematic overestimation in the validation dataset (derivation cohort = 0, validation cohort = 1). After shrinkage of the coefficients, the results of the final prediction model were: age (OR 1.02, 95%CI 1.00–1.03, $p = 0.031$), congenital diagnosis (OR 1.52, 95%CI 1.03–2.23, $p = 0.034$), NYHA class (OR 1.74, 95%CI 1.07–2.84, $p = 0.026$), cardiac medication (OR 2.27, 95%CI 1.56–3.31, $p < 0.001$), re-intervention (OR 1.41, 95%CI 0.99–2.01, $p = 0.060$), BMI (OR 1.03, 95%CI 0.99–1.07, $p = 0.123$), and NT-proBNP (OR 1.63, 95%CI 1.45–1.84, $p < 0.001$). The distribution of the risk calculated using the final model in the derivation and validation cohort is presented in Appendix 2. We implemented the first version of our model in a prototype of a web-based ACHD risk calculator. Based on six clinical variables and the NT-proBNP level, it can provide an estimation of the absolute 4-year risk of death, heart failure, or arrhythmia, as defined in this study. The risk calculator is directly available online at https://achdwebcalculator.shinyapps.io/achdwebcalculator/. The absolute risk estimations of this model can be further improved, and we therefore gladly invite other investigators to share their data in order to further improve the current version of the model. The full R-code of the model development, validation and the R Shiny application is online available in Appendices 3 and 4.

Table 3
Main effects in derivation cohort (n = 602).

Variable	Univariable OR (95% CI)	*p*-Value	Multivariable OR (95% CI)	*p*-Value
Age, years	1.07 (1.05–1.09)	<0.001	1.03 (1.01–1.06)	0.005
Sex, male	0.73 (0.50–1.07)	0.111	1.27 (0.76–2.13)	0.354
Complex congenital diagnosis[a]	3.28 (2.17–4.95)	<0.001	1.73 (0.90–3.34)	0.100
NYHA class II-III	8.90 (5.02–15.79)	<0.001	2.75 (1.33–5.72)	0.007
Cardiac medication use[b]	7.06 (4.62–10.80)	<0.001	2.52 (1.49–4.24)	0.001
≥ 1 re-interventions after corrective repair	2.30 (1.54–3.45)	<0.001	1.67 (0.99–2.80)	0.055
BMI, kg/m^2	1.06 (1.01–1.10)	0.009	1.05 (1.00–1.11)	0.059
Heart rate, beats/min	1.00 (0.98–1.01)	0.833	–	–
Current smoking	0.76 (0.39–1.46)	0.410	–	–
Oxygen saturation < 90%	4.67 (1.71–12.80)	0.003	1.12 (0.29–4.29)	0.874
Loss of sinus rhythm	4.35 (2.67–7.10)	<0.001	1.18 (0.61–2.30)	0.622
Systemic ventricular function, 0–3	2.09 (1.65–2.65)	<0.001	0.95 (0.66–1.37)	0.787
Presence of severe valvular dysfunction	1.29 (0.76–2.17)	0.343	–	–
$\log_2$ NT-proBNP, per two-fold higher value	2.12 (1.82–2.47)	<0.001	1.62 (1.34–1.97)	<0.001

Legend: Effect sizes represent the increased 4-year risk of the primary endpoint (death/transplant, heart failure, and arrhythmia). Abbreviations: OR, odds ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class.

[a] Diagnosis of congenital aortic stenosis, aortic coarctation, arterial switch operation, tetralogy of Fallot, Ebstein anomaly, or atrioventricular septal defect (0) versus Rastelli/REV, systemic RV, univentricular heart, or (un)repaired ASD/VSD with pulmonary arterial hypertension [1].

[b] ACE-inhibitor, angiotensin receptor blocker, beta blocker, diuretic, aldosterone antagonist, calcium blocker, or anti-arrhythmic drug.

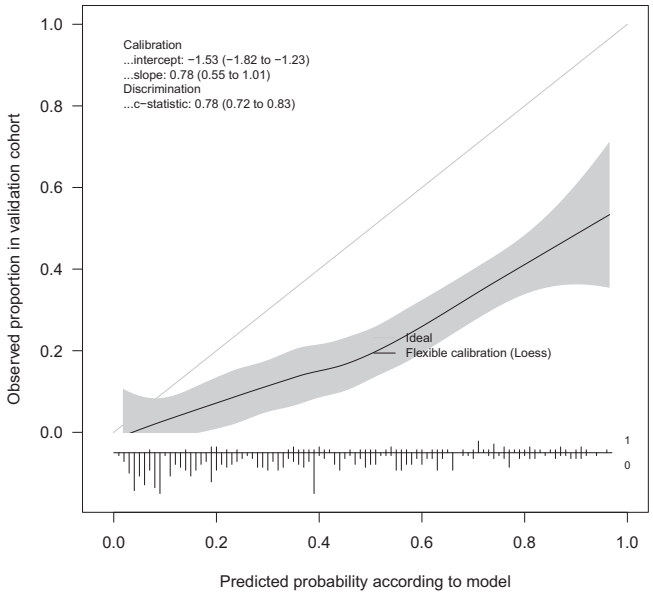

Fig. 1. Calibration plot for the prediction of the primary endpoint in the validation cohort ($n = 402$). Legend: The calibration slope indicates whether the model is overfitted (estimated risks too extreme, value <1) or underfitted (estimated risks too close to baseline risk, value >1). The calibration intercept (calibration-in-the-large) indicates whether predicted probabilities are systematically too low (value >0) or too high (value <0). The linear bar chart shows the distribution of patients with [1] or without (0) a primary endpoint for each predicted probability.

4. Discussion

To our knowledge, this is the first study that aimed to develop and validate a risk prediction model specifically for patients with ACHD. The final model was developed in 602 patients with ACHD and included six readily available clinical variables (age, congenital diagnosis, NYHA class, cardiac medication use, re-interventions, BMI) and NT-proBNP. External validation in a different ACHD population ($n = 402$) with an independent treatment strategy showed that the model could discriminate well between patients with death, heart failure, or arrhythmia within 4 years of follow-up and patients without an event during that period. The results are presented in a web-based ACHD risk calculator that is directly suitable for implication in clinical practice.

4.1. Comparison with other risk scores

Another risk score for congenital patients was previously developed by Yap et al. in 378 patients with ACHD and atrial arrhythmias at baseline [15]. Of the 9 variables that were found to be of importance in univariable analysis, in a multivariable model NYHA class, single ventricle physiology, pulmonary hypertension, and valvular heart disease remained significantly associated with mortality ($n = 40$). These variables were combined in a risk score, which was visualized in a Kaplan-Meier curve; however, no model performance characteristics (discrimination, calibration) were evaluated. The definition of the study population and endpoint was slightly different from our study, but the similarity with our study is that we also included NYHA class and congenital diagnosis (where single ventricle physiology and pulmonary hypertension were both defined as a complex diagnosis) in the final model.

Kempny and colleagues recently presented a multivariable mortality risk stratification model that was developed in a retrospective cohort of 1098 adults with Eisenmenger syndrome [8]. The model included age, pretricuspid shunt, oxygen saturation, presence of sinus rhythm and presence of pericardial effusion. In our cohort of ACHD patients, a pretricuspid shunt or presence of pericardial effusion was uncommon, and oxygen saturation and presence of sinus rhythm were not significantly related to study endpoints in the multivariable analysis. Hence, Eisenmenger patients reflect a distinct disease entity in which other variables may be more important. However, NT-proBNP measurements were not included in this study.

The Seattle Heart Failure Model was developed in a cohort of 1125 patients with heart failure, and allows prediction of survival with the use of easily obtained clinical characteristics, such as age, sex, weight, NYHA class, systemic ejection fraction, systolic blood pressure, cardiac medication use, laboratory values, and presence of a device [23]. In patients with heart failure, the model provides an accurate estimate of mean, 1-, 2-, and 3-year survival. This model was validated in a cohort of 153 patients with ACHD, and was able to identify subjects with adverse outcome; however, the predicted mortality risks by the Seattle Heart Failure Model did not represent actual ACHD survival [16]. Still, the type of variables that are included are largely overlapping with our prediction model (age, weight (BMI), NYHA class, cardiac medication use, and laboratory values such as NT-proBNP).

4.2. Other variables of potential interest

Inuzuka and colleagues comprehensively demonstrated that a combination of peak oxygen uptake and heart rate reserve are strong predictors of midterm mortality in patients with ACHD, in addition to clinical parameters such as age, low oxygen saturation, and use of negative chronotropic agents [24]. It has also been shown by other studies that exercise testing provides prognostic information in patients with ACHD [25–27]. In addition, various cardiac magnetic resonance imaging measurements have been reported to be valuable for risk stratification. It is known that cardiac magnetic resonance imaging provides the most reliable measurements of right ventricular volumes and function, which are also predictors of clinical outcome [28].

Because cardiopulmonary exercise testing and cardiac magnetic resonance imaging are relatively expensive and time-consuming, they were not routinely performed in all patients of our cohort and were therefore not investigated in this study. These variables could perhaps further improve the prediction of our model. However, we believe the current set of variables better reflects clinical practice, is readily available and very easy to use. Therefore, this model may be directly suitable for implementation in day-to-day clinical practice.

4.3. Calibration

Although the validation cohort included more patients with complex congenital diagnoses, a higher NYHA class, and cardiac medication use (Table 1), they had a better outcome compared with patients in the derivation cohort (Table 2). Because these variables were part of the prediction model, the risk in the validation cohort was systematically overestimated. This resulted in a suboptimal calibration-in-the-large (reflected by a calibration intercept <0), which is a common problem when externally validating risk models [21]. This may be explained by a difference in the definition and classification of endpoint events. The definition of heart failure included 'initiation or uptitration of diuretics' and the definition of arrhythmia included 'symptomatic and recorded'. As a result, different clinical strategies among centres with regard to treatment with diuretics or Holter monitoring could result in a different proportion of events. Furthermore, misclassification of (non)events may have occurred, although every attempt was made to avoid this by assuring completeness of follow-up in both cohorts and independent review of the events by two investigators. The definition for NYHA class I in the derivation cohort was 'no limitation in ordinary physical activity', but this is subjective and may have been assessed in a stricter way in the validation cohort. The differences in treatment strategies among centres as described above may also impact cardiac medication

use and the number of re-interventions. Finally, there may be additional important prognostic factors which explain this difference, and that are not part of the current model.

4.4. Clinical implications and future perspectives

In this study, we aimed to combine various risk predictors in order to derive individualized risk predictions. The model provided a good discrimination between high-risk and low-risk patients, and this may serve to optimally inform and, in case of low-risk, reassure patients. High-risk patients should be followed-up in a tertiary care centres, while low-risk patients may be managed in a shared-care model with for instance check-ups every other time in a non-tertiary care centre. Because in this study a composite endpoint is used, specific therapeutic decisions cannot be solely based on predictions of the current model. Nevertheless, it could support clinical judgment in determining the window in which the next outpatient follow-up visit needs to be scheduled, in assessing the need of initiation or change in medical therapy, planning an intervention, or even considering heart transplantation, with the ultimate goal to improve the prognosis of these patients.

Because the absolute predicted risks were not in accordance with the observed risks in the validation cohort, the absolute risks provided by our model in other cohorts of patients with moderate/complex ACHD must be interpreted with caution. Future research is warranted to evaluate whether the implementation of such a risk prediction tool actually can improve a patients' prognosis, and thus leads to clinical benefit. Finally, it should be investigated how much costs can be saved by implementing such a risk prediction tool.

4.5. Study limitations

Although a prospective cohort of 600 patients with ACHD may be considered relatively large in this patient population, it is rather small in comparison with other cohorts in which well-known risk prediction models were developed. Nonlinear terms and interaction terms had to be disregarded in the multivariable prediction model, because we considered it more relevant to analyse the potential additive effects of the highest possible number of different covariates, instead of fully exploring nonlinearity and interactions at the risk of overfitting the model. With larger datasets, it could be worthwhile to explore these potential effects in order to further improve risk prediction.

5. Conclusions

We developed and validated an ACHD risk calculator, which was based on readily available clinical characteristics (age, congenital diagnosis, NYHA class, cardiac medication use, re-interventions, BMI) and NT-proBNP. The final prediction model was able to accurately discriminate between patients at high and low risk of death, heart failure, or arrhythmia within 4 years, and could therefore support clinical judgment in day-to-day practice. Other investigators are invited to share their data in order to further improve the absolute risk estimations of the current model.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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