ORIGINAL RESEARCH

Predicting sudden cardiac death in adults with congenital heart disease

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ABSTRACT

Objectives To develop, calibrate, test and validate a logistic regression model for accurate risk prediction of sudden cardiac death (SCD) and non-fatal sudden cardiac arrest (SCA) in adults with congenital heart disease (ACHD), based on baseline lesion-specific risk stratification and individual's characteristics, to guide primary prevention strategies.

Methods We combined data from a single-centre cohort of 3311 consecutive ACHD patients (50% male) at 25-year follow-up with 71 events (53 SCD and 18 non-fatal SCA) and a multicentre case–control group with 207 cases (110 SCD and 97 non-fatal SCA) and 2287 consecutive controls (50% males). Cumulative incidences of events up to 20 years for specific lesions were determined in the prospective cohort. Risk model and its 5-year risk predictions were derived by logistic regression modelling, using separate development (18 centres: 144 cases and 1501 controls) and validation (two centres: 63 cases and 786 controls) datasets.

Results According to the combined SCD/SCA cumulative 20 years incidence, a lesion-specific stratification into four clusters—very-low (<1%), low (1%–4%), moderate (4%–12%) and high (>12%)—was built. Multivariable predictors were lesion-specific cluster, young age, male sex, unexplained syncope, ischaemic heart disease, non-life threatening ventricular arrhythmias, QRS duration and ventricular systolic dysfunction or hypertrophy. The model very accurately discriminated (C-index 0.91; 95% CI 0.88 to 0.94) and calibrated (p=0.3 for observed vs expected proportions) in the validation dataset. Compared with current guidelines approach, sensitivity increases 29% with less than 1% change in specificity.

Conclusions Predicting the risk of SCD/SCA in ACHD can be significantly improved using a baseline lesion-specific stratification and simple clinical variables.

INTRODUCTION

Although survival beyond the age of 18 years in newborns with congenital heart disease is nearly 90%,[1] life expectancy of adults with congenital heart disease (ACHD) continues to be compromised,[2–5] and sudden cardiac death (SCD) is the leading cause of death of young patients.[6–11] Unfortunately, predicting the risk of SCD in ACHD remains particularly challenging owing to their anatomical and surgical heterogeneity and its relatively low incidence.[3 6 12–18] Disease-specific analyses have been provided for a few conditions such as tetralogy of Fallot (ToF)[19–21] or transposition of the great arteries (TGA).[22–24] These studies have settled the basis for current recommendations,[25 26] although their discriminative ability is known to be poor, and the majority of SCD victims are left unrecognised.[27] Thus, improving primary prevention of SCD in ACHD requires a more precise individualisation of patient's risk.

We hypothesised that predicting the risk of SCD in ACHD should fit for the whole population of ACHD at large and benefit of: (1) merging SCD with episodes of non-fatal sudden cardiac arrest (SCA) into a composite end-point (SCD/SCA); (2) incorporating a baseline lesion-specific risk stratification; and (3) including easily available demographic, clinical, electrophysiological and haemodynamical variables. On these hypotheses, the aim of the present study was to develop, calibrate, test and validate a logistic regression model for accurate risk prediction of SCD/SCA in the individual ACHD patient. We specifically searched for practical risk cut-offs for tailoring clinical decisions. Due to the rarity of the hard endpoint, we combined data from two study groups: an observational single centre prospective cohort—with a wide variety of ACHD patients followed up to 25 years—and a retrospective multicentre case–control group with participation of 20 Spanish ACHD centres.

METHODS

Observational cohort population

A previously reported cohort of 3311 ACHD patients prospectively followed up at La Paz University Hospital in Madrid, Spain,[5] was used with a double purpose: (1) inferring the incidence of the composite end-point (SCD/SCA) and (2) performing an incidence-based lesion-specific stratification in clusters of risk. In brief, we recruited all patients aged ≥18 years old diagnosed with CHD from December 1989 to December 2013 and followed up until death or end of the study (June 2014). The vital status of each patient was confirmed by

Table 1 Distribution of patients by the type of event across the lesion categories in the prospective cohort

	No. cases (%)	SCD (N (%))	Non-fatal SCA N (%)	SCD/SCA (N (%))	Follow-up* (years)	20-year incidence (SE)
1. Left-to-right shunts	1075 (32)	4 (7.5)	1 (5.5)	5 (7.0)	12 063	0.008 (0.004)
Ostium secundum ASD	369	1	0	1		
Ventricular septal defect	355	1	1	2		
Partal/complete AVSD	148	0	0	0		
Ductus arteriosus	90	2	0	2		
Sinus venosus syndrome	70	0	0	0		
Partial/total APVC	33	0	0	0		
Fistula	10	0	0	0		
2. Left heart lesions	747 (23)	7 (13)	1 (5.5)	8 (11)	9262	0.016 (0.006)
Aortic valve lesions	547	6	1	7		
Subvalvular aortic stenosis	115	1	0	1		
Supravalvular aortic stenosis	30	0	0	0		
Mitral valve lesions	36	0	0	0		
Aortic arch anomalies	19	0	0	0		
3. Coarctation of the aorta	353 (11)	4 (7.5)	3 (17)	7 (10)	3909	0.020 (0.01)
4. Non-complex tetralogy of Fallot	327 (10)	4 (7.5)	6 (33)	10 (14)	3731	0.049 (0.017)
5. RVOT lesions (intact septum)	315 (9.5)	0	0	0	3525	0
Pulmonary valve lesions	227	0	0	0		
Pulmonary subvalvar stenosis	50	0	0	0		
Pulmonary supravalvar stenosis	24	0	0	0		
Pulmonary atresia	14	0	0	0		
6. Atrial switch for TGA	104 (3.1)	5 (9.4)	1 (5.5)	6 (8.5)	1213	0.104 (0.043)
7. Ebstein anomaly	76 (2.3)	1 (1.9)	0	1 (1.4)	732	0.077 (0.074)
8. Fontan procedure	69 (2.1)	3 (5.7)	0	3 (4.2)	718	0.107 (0.060)
9. Eisenmenger physiology	67 (2.0)	10 (19)	0	10 (14)	713	0.162 (0.053)
10. Cyanotic non-repaired CHD	57 (1.7)	7 (13)	0	7 (10)	617	0.143 (0.056)
11. Congenitally corrected TGA	42 (1.3)	1 (1.9)	1 (5.5)	2 (2.8)	338	0.091 (0.087)
12. Complex tetralogy of Fallot	33 (1.0)	3 (5.7)	2 (11)	5 (7.0)	323	0.196 (0.093)
Pulmonary atresia with VSD	18	2	2	4		
Double outlet right ventricle	15	1	0	1		
13. Rastelli procedure for TGA	15 (0.5)	2 (3.8)	3 (17)	5 (7.0)	131	0.286 (0.144)
14. Coronary artery anomaly	11 (0.3)	2 (3.8)	0	2 (2.8)	95	0.271 (0.165)
ALCAPA	4	1	0	1		
Large coronary fistula	7	1	0	1		
15. Arterial switch for TGA	6 (0.2)	0	0	0	21	0
16. Miscellanea	14 (0.4)	0	0	0	119	0
Overall	3311	53	18	71	37 510	0.031 (0.004)

Figures between brackets denote partial number of cases.
*Six patients who debuted with non-fatal SCA were excluded from survival analysis.
ALCAPA, anomalous origin of left coronary artery from pulmonary artery; APVC, anomalous pulmonary venous connection; ASD, atrial septal defect; AVSD, atrio-ventricular septal defect; CHD, congenital heart disease; RVOT, right ventricular outflow tract; SCA, sudden cardiac arrest; SCD, sudden cardiac death; TGA, transposition of the great arteries; VSD, ventricular septal defect.

cross-checking with the Spanish National Death Index. Underlying lesions were grouped into 15 lesion categories (table 1).

Multicentre case–control group participants

All cases of SCD/SCA in patients ≥18 years old diagnosed with CHD were collected from 20 affiliated centres of the Spanish ACHD network (online supplementary table 1).[28] Circumstances of death were further investigated on a case-by-case basis by interviewing family members. In addition, hospital records were reviewed to identify non-fatal SCA cases. The control group consisted of a non-selected sample of all patients ≥18 years old diagnosed with CHD consecutively attending the outpatient ACHD clinics at the participating centres from 1 May to 30 June 2017. Underlying lesions were classified into the same lesion categories as in the observational cohort (table 2). Quality of data collected by the participating centres and lesion category were further checked by the adjudication committee at the coordinating centre (Hospital Gregorio Marañon (HGM)). Misclassified cases were excluded from the analysis. Data from 18 centres were chosen for model development, whereas data from the other two (Unitat Integrada de Cardiopaties Congènites Vall d'Hebron-Sant Pau (UIC) and Adult Congenital Heart Disease Unit of Seville (ACS))—with a relatively large volume of cases—were used for model validation.

Outcomes

The primary outcome was the combined endpoint of SCD/SCA. SCD was defined as death within 1 hour of symptom onset or unwitnessed death during sleep and non-fatal SCA included aborted SCD resulting from ventricular tachycardia/fibrillation

Table 2 Distribution of cases and controls in the multicentre study by lesion-specific risk stratification, lesion category and underlying lesions

Lesion category	Underlying lesions	SCD, N (%)	Non-fatal SCA, N (%)	Total SCA, N (%)	Controls, N (%)	SCA/control ratio
High risk						
Rastelli procedure	Complex TGA or DORV after Rastelli procedure.	9 (8.2)	9 (9.3)	18 (8.7)	14 (0.6)	1.3
Coronary anomaly	ALCAPA, ARCAPA, large coronary fistula or other symptomatic severe coronary anomalies.	4 (3.6)	3 (3.1)	7 (3.4)	11 (0.5)	0.64
Cyanotic non-repaired	Non-repaired or only palliated cyanotic CHD.	14 (13)	2 (2.1)	16 (7.7)	47 (2.1)	0.34
Complex Fallot	Tetralogy of Fallot with pulmonary atresia, hypoplastic pulmonary arteries, DORV, truncus or hemitruncus repaired by conduit.	4 (3.6)	10 (10)	14 (6.8)	50 (2.2)	0.28
Eisenmenger physiology	Eisenmenger syndrome or repaired CHD with severe pulmonary vascular disease.	25 (23)	0	25 (12)	109 (4.8)	0.23
Moderate risk						
Non-complex Fallot	Repaired non-complex tetralogy of Fallot.	14 (13)	44 (45)	58 (28)	278 (12)	0.21
ccTGA	Repaired or non-repaired congenitally corrected transposition.	1 (0.9)	6 (6.2)	7 (3.4)	41 (1.8)	0.17
Fontan procedure	Single ventricle physiology after Fontan procedures.	11 (10)	0	11 (5.3)	98 (4.3)	0.11
Atrial switch	Simple TGA after Mustard/Senning repair.	7 (6.4)	4 (4.1)	11 (5.3)	96 (4.2)	0.11
Ebstein anomaly	Repaired or non-repaired Ebstein anomaly.	1 (0.9)	0	1 (0.5)	63 (2.8)	0.02
Low risk						
Coarctation	Repaired or non-repaired coarcatation of the aorta.	4 (3.6)	4 (4.1)	8 (3.9)	258 (11)	0.03
Left heart lesions	Valvar, subvalvar or supravalvar aortic lesions. Bicuspid aortic valve. Mitral valve lesions. Vascular rings.	12 (11)	7 (7.2)	19 (9.2)	296 (13)	0.06
Arterial switch	Simple or complex TGA after arterial switch procedure.	1 (0.9)	2 (2.1)	3 (1.5)	59 (2.6)	0.05
Very low risk						
Left-to-right shunts	Repaired/non-repaired ASD, VSD, sinus venosus syndrome, partial/complete AVSD partial/complete APVC systemic pulmonary or arteriovenous fistula.	2 (1.8)	4 (4.1)	6 (2.9)	638 (28)	0.009
RV outflow tract lesions with intact septum	Repaired or non repaired valvar, subvalvar or supravalvar pulmonary stenosis. Pulmonary atresia. Pulmonary regurgitation. Idiophatic dilation of pulmonary trunk.	1 (0.9)	2 (2.1)	3 (1.5)	225 (10)	0.01
Miscellanea		0	0	0	4 (0.2)	0
Overall		110	97	207	2287	0.09

ALCAPA, anomalous origin of left coronary artery from pulmonary artery; APVC, anomalous pulmonary venous connections; ARCAPA, anomalous origin of right coronary artery from pulmonary artery; ASD, atrial septal defect; AVSD, atrioventricular septal defect; ccTGA, congenitally corrected transposition; CHD, congenital heart disease; DORV, double outlet right ventricle; RV, right ventricle; SCA, sudden cardiac arrest; SCD, sudden cardiac death; TGA, transposition of the great arteries; VSD, ventricular septal defect.

(VT/VF), syncopal VT requiring urgent electrical cardioversion or appropriate implantable cardioverter-defibrillation (ICD) shocks. Event classification was adjudicated by the endpoint committee. Patients with clinically suspected or pathologically confirmed acute myocardial infarction, aortic dissection or rupture, stroke or pulmonary emboli were excluded. Patients with haemodynamically well-tolerated VT were also excluded.The study complied with the Declaration of Helsinki and was approved by local research Ethics Committees that waived the need for patient informed consent, as it required no modification in standard clinical practice.

Statistical analysis

Continuous variables were expressed as mean±SD, or median and IQR (25–75th percentile) if not normally distributed and compared using Student's t-test or Mann-Whitney U test as appropriate. Categorical variables were summarised as frequencies or percentages and compared using the χ^2 test. Figure 1 displays the overall design of statistical analyses.

To stratify the baseline lesion-specific risk for SCD/SCA, we determined their cumulative rates at 20 years in the observational cohort. We took the date of the first episode of SCD/SCA as the event date. Patients in whom the first clinical evaluation was performed after the occurrence of a SCA event were excluded from the actuarial analysis. Miscellanea CHD and lesion categories with ≤10 patients were also excluded. Based on these results, specific lesions were clustered into four risk categories.

We then used these lesion-based clusters and the overall incidence information from the prospective cohort detailed above together with individuals' characteristics to develop, calibrate, test and validate a predictive rare events logistic regression model for SCD/SCA from the development dataset in case–control patient group. A meaningful 'centre' cluster effect was ruled out confirming that adding a random effect in a mixed effects logistic regression design neither improved the conventional logistic regression model predictivity nor relevantly narrowed the confidence intervals of its coefficients.

First, we underwent an univariate analysis of clinically relevant variables as disease complexity, demographic data, previous interventions, symptoms, arrhythmic events, comorbidities and the most recent ECG, chest X-ray, Holter, exercise test, echocardiography (2DE), cardiac magnetic resonance and electrophysiological study in both development and validation datasets. Online supplementary tables 2 and 3 summarise predictors of SCD/SCA and their definitions. To guarantee accurate precision of the regression coefficients only candidate predictors previously reported to be related to SCD in ACHD patients were included in multivariable analysis but variables with missing proportion >5% were excluded (online supplementary table 4).

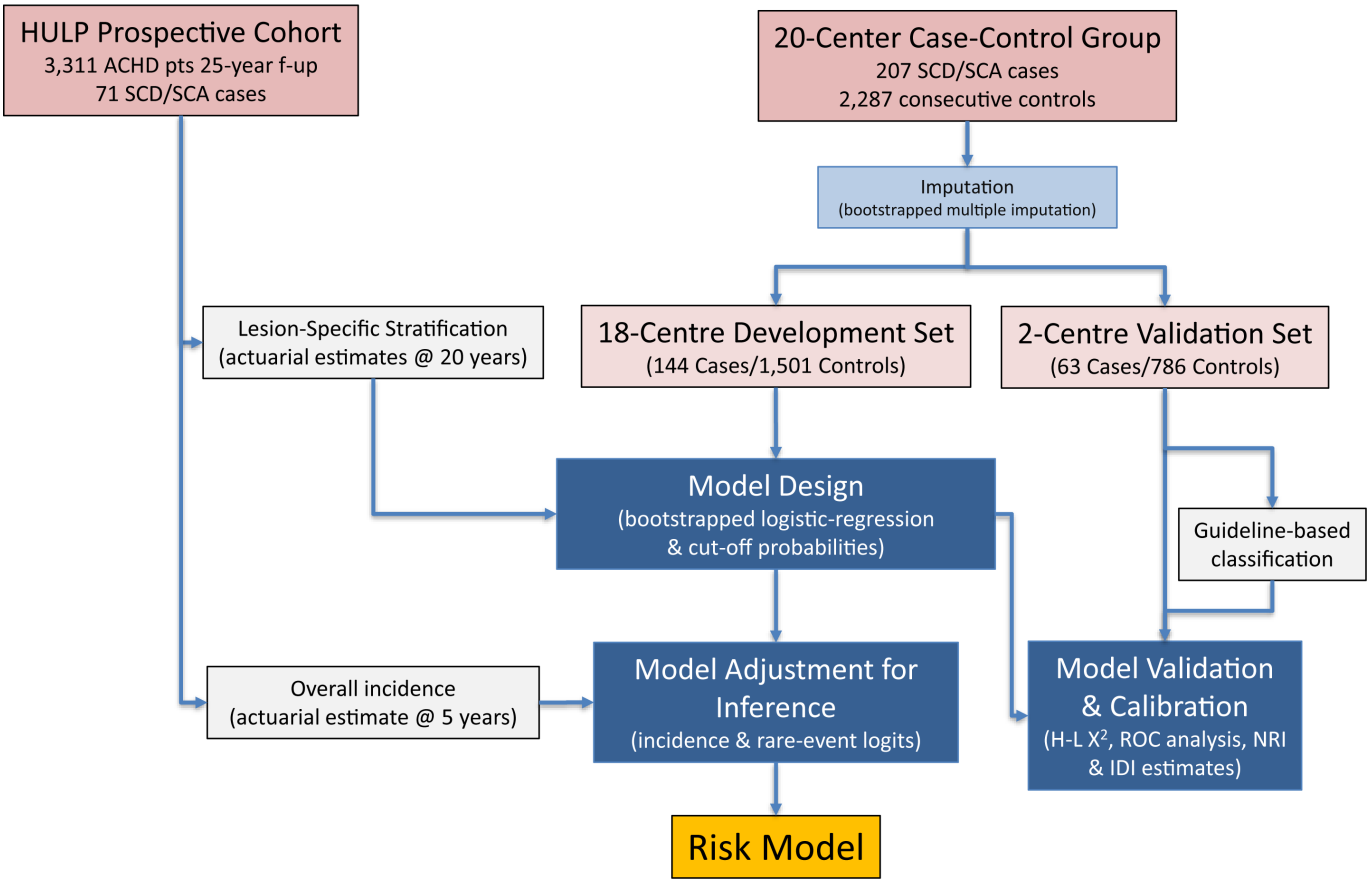

Figure 1 Statistical analysis flow chart. ACHD, adult congenital heart disease; H-L χ^2, Hosmer-Lemeshow χ^2 test; IDI, integrated discrimination improvement; NRI, net reclassification improvement; ROC, receiver operating characteristics; SCA, sudden cardiac arrest; SCD, sudden cardiac death.

Nonetheless, we used multiple imputations based on the predictive mean matching (Harrel's *transcan* algorithm) for the rest of missing data. Variables were selected if they were entered a minimum of 50% of 1000 bootstrap replicates by backward conditional stepwise of candidate predictors based on Alkaike's information criterion. Linearity and significant interactions were tested and treated accordingly. Internal model validation and calibration was then performed by 1000 bootstrap of the fitted model.

We then assessed model calibration, classification and discrimination and cut-off performance for SCD/SCA risk prediction using data from the two validation centres. Model calibration was performed comparing predicted to observed events by the χ^2 test using the Hosmer-Lemeshow method. The discriminative power of the model was tested in 2000 bootstrap replicates to estimate the C-index, with its 95% CIs and SEs. Since syncopal VT or appropriate ICD shocks may be questioned as a surrogate of SCD, we also assessed the risk model performance in the entire dataset of the case–control study with the cases of SCD and non-fatal SCA separately considered (online supplementary table 5). Finally, the model performance was also evaluated in each diagnostic category (online supplementary material).

To infer the risk of SCD/SCA for a given patient, we adjusted the coefficients from the logistic regression for rare event bias as well as for true incidence in the ACHD population, based on the global actuarial 5-year estimate from the prospective observational cohort.[29] We 'a priori' established four risk categories defined on cut-offs of a 5-year risk of SCD/SCA of 5%, 1% and 0.1%. We used non-linear regression to calculate the predicted probabilities in the development dataset corresponding to these risk cut-offs and then calculated their sensitivity, specificity (and empirical 95% CIs), by bootstrapping, on the validation dataset.

Finally, we tested model discrimination in the validation dataset by comparing model's performance with the classification based on the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD.[26] For this purpose, we defined a positive guideline prediction when a patient met a class I or II recommendation. Comparison was performed using C-index analysis and calculating the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) indices.[30] All analyses were performed using R (V.3.6) expanded by appropriate packages. Two-tailed p values <0.05 were considered statistically significant.

RESULTS

Lesion-specific stratification

There were 1673 men and 1638 women in the observational cohort. The median age at first examination was 22.5 (18–39) years old and the median follow-up 10.5 (4.4–18.0) years,

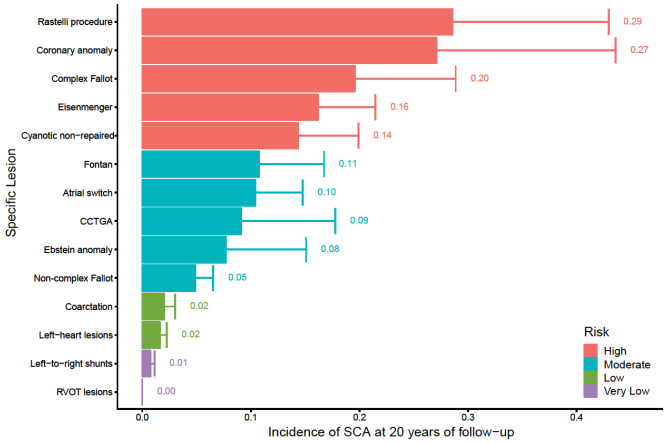

Figure 2 Lesion-specific risk stratification clustering of lesion categories by the actuarial 20-year incidence of SCD/SCA in the prospective cohort. RVOT, right ventricular outflow tract; SCA, sudden cardiac arrest; SCD, sudden cardiac death.

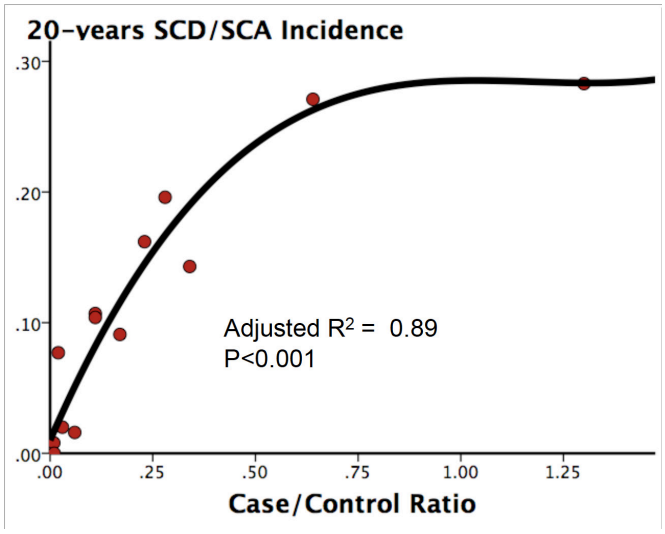

Figure 3 Correlation between case/control ratio and SCD/SCA incidence. Dots show lesion-specific categories as outlined intables 1 and 3. SCD, sudden cardiac death; SCA, non-fatal sudden cardiac arrest.

rendering a cumulative follow-up time of 37 053 person-years. Fifty-three patients suffered SCD and 18 patients survived a non-fatal SCA, including resuscitated SCA (n=8), syncopal VT (n=6) and appropriate ICD shock (n=4), for a total of 71 events (2% of the cohort). Male sex was more frequent in patients with an event (65% vs 50%; p<0.02), and there were no significant differences between the age of patients that reached the combined end-point (40 (28–56) years old) and of those who did not do it (38 (29–50) years old; p=0.86). Six patients who experienced a non-fatal SCA before the first visit as well as 14 patients with miscellaneous CHD, and six with TGA after arterial switch repair were excluded from survival analysis.

The cumulative SCD/SCA incidences at 5, 10 and 20 years were 0.7, 1.8, and 3.1%, respectively, but as expected, there were wide differences across the specific lesion categories (table 1). Lesion categories were classified based on the cumulative 20 years incidence into four risk clusters (figure 2). Patients at highest risk (incidence rate >12%) were those with Rastelli procedure, severe coronary abnormalities, complex ToF and cyanotic patients, either Eisenmenger or non-Eisenmenger; at moderate risk (incidence rate 4%–12%) non-complex ToF, Mustard/Senning repair, Fontan procedures, congenitally corrected TGA and Ebstein anomaly; at low risk (incidence rate 1%–4%) coarctation and left heart lesions; and at very low risk (incidence rate <1%) left-to-right shunts and right ventricular outflow tract lesions (table 1).

Case–control study

Of 212 cases collected from 20 centres, five patients were excluded for inconsistent data, yielding a total of 207 cases (110 SCD, 39 aborted SCD, 41 syncopal VTs and 17 ICD shocks for VT/VF). Median time between last clinical assessment and event date had been 121 (55–244) days. The control group consisted of 2287 consecutive patients. Median age was 34.8 (25–45) years old in cases and 35.3 (24–44) years old in controls (p=0.84). The proportion of men was significantly greater among cases than among controls (75% vs 50%; p<0.001). The correlate between the case/control ratio, and the cumulative incidence of events at 20 years for each lesion category was highly significant (adjusted cubic curve R^2=0.89; p<0.001) (figure 3). Since patients with TGA after arterial switch repair had been excluded from the actuarial analysis in the prospective cohort, those patients were classified as low-risk according to the case/control ratio.

The risk prediction model

The development dataset from 18 centres included 144 cases (73 SCD, 71 non-fatal SCA) and 1501 controls. A positive interaction between systemic and subpulmonary ventricular dysfunction allowed us to merge these variables into a single predictor (dysfunction of either ventricle). Multivariable predictors were lesion-specific cluster, younger age, male sex, unexplained syncope, ischaemic heart disease, non-life threatening ventricular arrhythmias, QRS duration and ventricular systolic dysfunction

Table 3 Final risk prediction model in the development sample after adjustment for overall 5-year incidence of SCA and for rare event bias

	OR	95% CI	Coefficient	P value
Predictors				
Lesion-specific risk stratification (low)	3.39	1.3 to 8.9	1.016	0.025
Lesion-specific risk stratification (moderate)	3.85	1.5 to 9.8	1.036	0.014
Lesion-specific risk stratification (high)	9.77	3.7 to 25	2.000	<0.001
Age (years)	0.98	0.96 to 0.99	−0.025	0.003
Male sex	1.84	1.1 to 3.0	0.671	0.008
Unexplained syncope	4.11	2.0 to 8.4	1.403	<0.001
Symptomatic ischaemic heart disease	7.97	2.8 to 23	1.979	<0.001
Non-life threatening VT	5.28	2.6 to 11	1.562	<0.001
QRS duration	1.02	1.02 to 1.03	0.024	<0.001
Mod-sev. systemic ventricle hypertrophy	3.75	2.2 to 6.5	1.311	<0.001
Mod-sev. subpulmonary ventricular hypertrophy	2.72	1.5 to 5.0	0.963	0.025
Mod-sev. either ventricular dysfunction	3.74	2.3 to 6.2	1.349	<0.001
Intercept β_0			−9.278	<0.001

Mod-sev, moderate to severe; SCA, sudden cardiac arrest; VT, ventricular tachycardia.

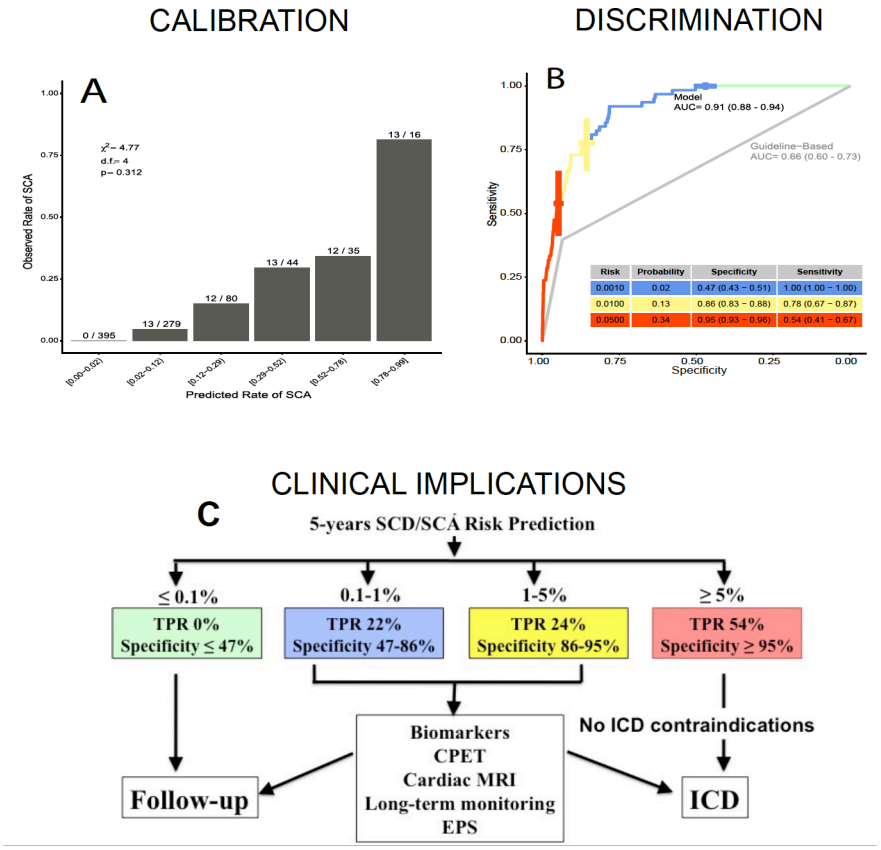

Figure 4 Model performance in the validation dataset and clinical implications. (A) Calibration: Hosmer-Lemeshow χ^2 test matching the predicted (horizontal axis) and the observed rate of events (vertical axis). The predicted rate categories have been divided into quantiles of the predicted rate for cases. The numbers above the bars account for the ratio between the observed number of cases and the number of controls for each risk category. (B) Discrimination: receiver operating characteristic curves of risk model and guidelines-based approach in the validation dataset. The risk model curve is divided into four segments by three prespecified 5-year risk prediction cut-offs of 0.1%, 1% and 5%. (C) Clinical implications: cases and controls from validation centres are clustered in four groups according the prespecified cut-offs of 5-year risk prediction. Suggested recommendations to guide patient management are based on sensitivity and specificity of cut-off values (see text). EPS, electrophysiological study; ICD, implantable cardioverter-defibrillation; SCA, sudden cardiac arrest; SCD, sudden cardiac death; AUC, area under the curve; TPR, true positive rate; CPET, cardiopulmonary exercise test.

or hypertrophy (table 3). The sample from the two validation centres included 63 cases (37 SCD, 26 non-fatal SCA) and 786 controls. Predicted compared with observed event proportions for model calibration was non-significant (χ^2 4.77; p=0.32) (figure 4A) and the C-index of the risk model on validation sample was 0.91 (95% CI 0.88 to 0.94; p<0.001) (figure 4B). This prediction capability remained excellent when cases of SCD and non-fatal SCA as well as each diagnostic category were analysed separately (online supplementary figures 1 and 2). After adjusting the model for the overall 5-year SCD/SCA incidence and for rare events bias, an inferred risk of ≥5% predicted 54% of cases on the validation dataset with a specificity of 95%. On the other side, none of the cases but >50% of controls had an inferred risk at 5 years of <0.1% (figure 4C).

Compared with current guidelines-based recommendations, global NRI and IDI in validation dataset was 1.18 (95% CI 0.99 to 1.37; p<0.001) and 0.28 (95% CI 0.21 to 0.35; p<0.001), respectively. NRI for events was 0.68 (95% CI 0.50 to 0.86; p<0.001), while NRI for non-events was 0.49 (95% CI 0.43 to 0.55; p<0.001). The increase of sensitivity was 0.29 with only −0.006 change in specificity. Reclassification and discrimination improvement were also significant when SCD and non-fatal SCA as well as the main disease conditions were analysed separately (online supplementary table 5).

DISCUSSION

By undergoing an exhaustive identification and characterisation of most cases of SCD/SCA in ACHD patients that occurred in Spain during the last years, we have developed and validated a robust risk model based on simple anatomical, clinical, ECG and echocardiographic data readily collected from routine care. This model can be readily implemented into an electronic calculator (http://cardioim.iisgmsai.org:48080/calc/) and used to drive primary prevention strategies based on individual risk prediction.

Risk stratification on a lesion-by-lesion basis has been recommended by experts.[15 16] Several studies have provided data about the relative SCD incidence in ACHD.[3 6 8 9 11 13 14] However, these studies did not attempt to stratify for the risk of SCD by specific lesions. Our data showed that the 20-year incidence varied widely from 0% to 23% across the diagnostic categories and that lesion-specific stratification based on the cumulative proportion of SCA may be used to improve model performance. Importantly, our model was built using data from a non-selected ACHD population, whereas other studies have focused on selected populations at higher risk such as ToF[19–21] or TGA.[22–24] However, ToF and TGA are also a moving target and modes and timing of repair are in constant flux. Thus, in our prospective cohort, repaired

non-complex ToF patients and TGA patients after atrial switch were at moderate risk, whereas repaired complex ToF patients and patients after Rastelli procedure for complex TGA were at high risk. The multicentre case–control group and its case/control ratio also confirmed these data.

In previous case–control studies, SCD cases were matched to age, sex, underlying lesion and method for repair.[17] Of note, our study shows that these variables play an important role in SCD/SCA risk stratification. However, other variables previously associated with SCD, such as number of cardiac surgeries, ventriculotomy, New York Heart Association (NYHA) functional class, atrial arrhythmias or QT interval[15 16]—although strongly associated with the composite endpoint in the univariate analysis—were not included in the final risk model. Whether the lack of independent association of those variables is due to model design or because they are merely surrogate markers of other risk factors remains to be elucidated.

A key strength of our study was to include in the risk model SCD cases and non-fatal SCA events. Non-fatal SCA events as surrogate of SCD may be questioned since they are not equivalent in terms of risk. Moreover, the arrhythmic mode of death is heterogeneous, and its potential mechanisms may vary according to the underlying lesion and the method and timing of surgical repair. Despite this, patients at risk for SCD and patients with life-threatening ventricular arrhythmias may benefit from preventive strategies and the discriminative power of the model was well adjusted for both SCD and non-fatal SCA events when separately evaluated.

Clinical implications

Recently, Vehmeijer *et al*[27] have shown that discriminative ability of current guidelines is poor (C-index from 0.60 to 0.70), calling for the need of more accurate prediction models. Predicting SCD in this young population is particularly challenging owing to its very low incidence. Fortunately, statistical methods that allow inferring risks from case–control designs have been tailored to deal with rare event data.[29] The evaluation of our model in the validation dataset showed a C-index of 0.91, with 29% increase in sensitivity—without significant reduction in specificity—in comparison with guidelines-based approach. Using these data, we are able to provide SCD/SCA risk estimates and suggest potential clinical consequences (figure 4C). Patients with a predicted risk at 5 years ≥5% should be better managed with an ICD whenever there are no contraindications in current practice guidelines[25] because sensitivity of this cut-off was >50% with an specificity >95%. On the other side, patients with an inferred risk at 5 years <0.1% might be reasonably excluded from any primary prevention strategy because there were none false positive case, and the true negative rate was >50%. Additional markers, such as plasma molecular determinations, exercise testing, myocardial fibrosis on CRM, long-term rhythm monitoring or even programmed ventricular stimulation might be of help when 5-year risk prediction would fall between these cut-offs, particularly when it ranges from 1% to 5%. Furthermore, the high rate of ICD complications and inappropriate discharges in this population[15 16] should also be taken into account for tailored patient decision making.

Limitations

This study has limitations inherent to the retrospective case–control design. The lesion-specific stratification was based on a single tertiary referral centre cohort. However, results are consistent with literature findings and the correlation between lesion-specific incidences and the case/control ratio in the multicentre group was good. The SCD/SCA incidence of lesions with small number of patients—such as severe coronary anomalies—should be taken with caution. Although suspected or confirmed acute myocardial infarction or aortic syndrome, stroke or pulmonary emboli had been excluded; the mechanisms of SCD were unknown in near 50% of cases. The risk model is based only on clinical, electrocardiographic and echocardiographic data. Although this approach simplifies calculations and extends it to the entire ACHD population, it does not include other biomarkers that could improve stratification, particularly in the intermediate risk group. Finally, in our real-world data study quantitative assessment of ventricular dysfunction or hypertrophy was not available for all patients.

CONCLUSIONS

This study provides physicians with a practical algorithm combining data collected for routine care into an easy to use risk model on which to base clinical stratification and guide SCD primary prevention in ACHD patients. By far, the proposed algorithm outperforms current clinical guidelines. Although further external validation is required, the results of this study might be useful to help decision making for primary prevention strategies in many ACHD patients.

Key messages

What is already known about this subject

- Sudden cardiac death (SCD) remains the major cause of death of young adults with congenital heart disease (ACHD) and guidelines recommendations for primary prevention have a poor discriminative ability.

What might this study add?

- We hypothesised that predicting the risk of SCD in ACHD may benefit from merging SCD with episodes of non-fatal sudden cardiac arrest into a composite endpoint and incorporating baseline lesion-specific risk stratification together with individual's characteristics. On this hypothesis, we developed, calibrated, validated and tested a predictive rare events logistic regression model using a large case–control multicentre group. Risk model performance was excellent (C-index 0.91) outperforming current clinical guidelines. An inferred risk at 5-year ≥5% identified >50% of cases with a specificity >95%.

How might this impact on clinical practice?

- Although the risk model may even be improved using new markers and needs to be prospectively tested in an international cohort, it might be readily implemented into an electronic calculator (http://cardioim.iisgmsai.org:48080/calc/) to help decision making for primary prevention strategies in many ACHD patients.

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REFERENCES

1 Moons P, Bovijn L, Budts W, *et al*. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. *Circulation* 2010;122:2264–72.
2 Khairy P, Ionescu-Ittu R, Mackie AS, *et al*. Changing mortality in congenital heart disease. *J Am Coll Cardiol* 2010;56:1149–57.
3 Diller G-P, Kempny A, Alonso-Gonzalez R, *et al*. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. *Circulation* 2015;132:2118–25.
4 van der Bom T, Mulder BJM, Meijboom FJ, *et al*. Contemporary survival of adults with congenital heart disease. *Heart* 2015;101:1989–95.
5 Oliver JM, Gallego P, Gonzalez AE, *et al*. Risk factors for excess mortality in adults with congenital heart diseases. *Eur Heart J* 2017;38:ehw590–41.
6 Silka MJ, Hardy BG, Menashe VD, *et al*. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. *J Am Coll Cardiol* 1998;32:245–51.
7 Oechslin EN, Harrison DA, Connelly MS, *et al*. Mode of death in adults with congenital heart disease. *Am J Cardiol* 2000;86:1111–6.
8 Verheugt CL, Uiterwaal CSPM, van der Velde ET, *et al*. Mortality in adult congenital heart disease. *Eur Heart J* 2010;31:1220–9.
9 Engelings CC, Helm PC, Abdul-Khaliq H, *et al*. Cause of death in adults with congenital heart disease - An analysis of the German National Register for Congenital Heart Defects. *Int J Cardiol* 2016;211:31–6.
10 Yu C, Moore BM, Kotchetkova I, *et al*. Causes of death in a contemporary adult congenital heart disease cohort. *Heart* 2018;104:1678–82.
11 Oliver JM, Gallego P, Gonzalez AE, *et al*. Impact of age and sex on survival and causes of death in adults with congenital heart disease. *Int J Cardiol* 2017;245:119–24.
12 Zomer AC, Vaartjes I, Uiterwaal CSPM, *et al*. Circumstances of death in adult congenital heart disease. *Int J Cardiol* 2012;154:168–72.
13 Moore B, Yu C, Kotchetkova I, *et al*. Incidence and clinical characteristics of sudden cardiac death in adult congenital heart disease. *Int J Cardiol* 2018;254:101–6.
14 Nieminen HP, Jokinen EV, Sairanen HI. Causes of late deaths after pediatric cardiac surgery: a population-based study. *J Am Coll Cardiol* 2007;50:1263–71.
15 Khairy P. Ventricular arrhythmias and sudden cardiac death in adults with congenital heart disease. *Heart* 2016;102:1703–9.
16 Walsh EP. Sudden death in adult congenital heart disease: risk stratification in 2014. *Heart Rhythm* 2014;11:1735–42.
17 Koyak Z, Harris L, de Groot JR, *et al*. Sudden cardiac death in adult congenital heart disease. *Circulation* 2012;126:1944–54.
18 Gallego P, Gonzalez AE, Sanchez-Recalde A, *et al*. Incidence and predictors of sudden cardiac arrest in adults with congenital heart defects repaired before adult life. *Am J Cardiol* 2012;110:109–17.

19 Khairy P, Harris L, Landzberg MJ, *et al*. Implantable cardioverter-defibrillators in tetralogy of Fallot. *Circulation* 2008;117:363–70.
20 Gatzoulis MA, Balaji S, Webber SA, *et al*. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet* 2000;356:975–81.
21 Khairy P, Aboulhosn J, Gurvitz MZ, *et al*. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Circulation* 2010;122:868–75.
22 Kammeraad JAE, van Deurzen CHM, Sreeram N, *et al*. Predictors of sudden cardiac death after mustard or Senning repair for transposition of the great arteries. *J Am Coll Cardiol* 2004;44:1095–102.
23 Khairy P, Harris L, Landzberg MJ, *et al*. Sudden death and defibrillators in transposition of the great arteries with intra-atrial baffles: a multicenter study. *Circ Arrhythm Electrophysiol* 2008;1:250–7.
24 Schwerzmann M, Salehian O, Harris L, *et al*. Ventricular arrhythmias and sudden death in adults after a mustard operation for transposition of the great arteries. *Eur Heart J* 2009;30:1873–9.
25 Khairy P, Van Hare GF, Balaji S, *et al*. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. *Heart Rhythm* 2014;11:e102–65.
26 Priori SG, Blomström-Lundqvist C, Mazzanti A, *et al*. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2015;36:2793–867.
27 Vehmeijer JT, Koyak Z, Budts W, *et al*. Prevention of sudden cardiac death in adults with congenital heart disease: do the guidelines fall short? *Circ Arrhythm Electrophysiol* 2017;10:e005093.
28 Oliver-Ruiz JM, Dos-Subira L, Gonzalez-Garcia A, *et al*. En representacion de la red Española de Cardiopatıas Congenitas del Adulto (RECCA). Cardiopatıas congenitas del Adulto en España: estructura, actividad Y caracterısticas clınicas. *Rev Esp Cardiol* 2020. doi:10.1016/j.recesp.2019.09.007. [Epub ahead of print: 21 Jan 2020].
29 King G, Zeng L. Estimating risk and rate levels, ratios and differences in case-control studies. *Stat Med* 2002;21:1409–27.
30 Pencina MJ, D'Agostino RB, D'Agostino RB, *et al*. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157–72.