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CLINICAL RESEARCH
Congenital heart disease

Risk factors for excess mortality in adults with congenital heart diseases

Jose Maria Oliver[1,2], Pastora Gallego[3]*, Ana Elvira Gonzalez[1], Diego Garcia-Hamilton[1], Pablo Avila[2,4], Raquel Yotti[2,4], Ignacio Ferreira[5], and Francisco Fernandez-Aviles[2,4]

[1]Adult Congenital Heart Disease Unit, La Paz University Hospital, Madrid, Spain; [2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Facultad de Medicina, Universidad Complutense, Madrid, Spain; [3]Heart Area Clinical Management Unit, Virgen Macarena University Hospital, Sevilla, Spain; [4]Department of Cardiology, Gregorio Marañon University Hospital, Madrid, Spain; and [5]Department of Cardiology, Vall d'Hebron University Hospital, Barcelona, Spain

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Aims To examine factors related to excess mortality in a cohort of adults with congenital heart disease (CHD).

Methods and results We conducted a survival analysis using prospective data of 3311 adults with CHD [50.5% males, median age at entry 22.5 years (IQR 18–39), median follow-up time 10.5 years (IQR: 4.4–18)]. Survival status of each patient was further verified by cross checking with the Spanish National Death Index. During a total follow-up of 37608 person-years, 336 (10%) patients died. Annual death rate was 0.89% and standardized mortality ratio (SMR) 2.64 [95% confidence interval (CI) 2.3–3.0; $P < 0.001$]. Median age at death estimated by left-truncated Kaplan–Meier method was 75.1 years (95% CI 73–77). Survival was reduced compared with the general population whatever their level of complexity, repair status, or underlying CHD. Independent risk factors for excess mortality, including cyanosis, univentricular physiology, genetic disorders, ventricular dysfunction, residual haemodynamic lesions and acquired late complications, among others, were identified by left-truncated Cox regression model. SMR was 5.22 (95% CI 4.5–6.0; $P < 0.001$) and median age at death 55.6 years (95% CI 50–61) for 996 patients (30%) with at least one risk factor. In contrast, SMR was 1.14 (95% CI 0.9–1.5; $P = 0.19$) and median age at death 83.7 years (95% CI 82–87) in 2315 patients (70%) with no risk factors.

Conclusions Clinical parameters, such as anatomical features, haemodynamic sequelae, or acquired complications, were independent predictors of excess mortality in adults with CHD. Survival of individuals with no risk factors did not differ from the reference population.

Keywords Adult congenital heart disease • Heart defects • Congenital • Follow-up studies • Excess mortality • Risk factors for death

Introduction

Over the past few decades long-term outcomes of patients with congenital heart disease (CHD) have dramatically improved,[1,2] the greatest overall survival benefit observed among the most complex defects.[3] As a result, mortality has shifted to adult ages.[4–7] Although survival beyond the age of 18 years in newborns with CHD is now near 90%, normal life expectancy might not be achieved in many patients.[8] Overall mortality and death rate for CHD patients has been assessed in several population-based studies or multicentre registries.[9–15] However, as death rate depends not only on the inclusion criteria but also on the age at entry into the study, estimates of long-term survival using a different method may improve outcome measurement reliability in patients with CHD. As proposed by Lamarca *et al.*,[16] long-term survival may be estimated using standard survival analysis with age as time to event scale and accounting for left-truncation and immortal person-time bias.[17–19] By using this approach, several researches have recently reported that survival of

* Corresponding author. Tel: +34 600162605, Fax: +34 955013045, Email: antoniap.gallego.sspa@juntadeandalucia.es

patients with CHD is worse compared with the expected survival of the general population and that there are substantial differences in lifespan with lesion complexity and specific heart defects.[20–22] However, information on the impact of previous repair strategies on outcomes is still limited and modifiable factors affecting excess mortality have not been identified. We sought to determine risk factors for reduced survival in a large single-centre cohort of adults with CHD prospectively followed up to 25 years.

Methods

Data source and study population

A registry of patients examined, treated, and followed up at the adult CHD (ACHD) unit at La Paz University Hospital (Madrid, Spain) was constructed in December 1989. Since then, data were prospectively entered and updated by the senior investigator (J.M.O.). As of 19 December 2013, the database contained the records of 3764 individuals. Most patients were referred to the ACHD unit from paediatric services on regular basis but a number of them were late referrals, either late presentation of unknown defects or loss to follow up. For this study, CHD was defined according to the criteria of Mitchell *et al.*[23] *Figure 1* summarizes exclusion criteria. In total, 139 out of the 3450 patients that fulfilled criteria of inclusion, whose demographic information (date of birth, hospital medical record number, or National Identification Number) were incomplete, were also excluded. Thus, a total of 3311 adult survivors with CHD comprised the study population. The study was approved by the local research ethics committee.

Outcomes

Death from any cause during the follow-up period constituted the primary endpoint. The vital status of each patient at the end of the study (30 June 2014) was further verified by cross checking the available identifying information on all 3311 patients to the Spain National Death Index. Those patients without an endpoint were treated as censored observations at closing date if they had been examined within the 2 years before (complete follow-up), or at the date of the last visit if they could not have been contacted (incomplete follow-up) (*Figure 1*). Patients entered the study cohort on the date of first visit at the ACHD unit or on 1 January 1990, whether their first visit occurred before database construction. Follow-up time was computed from entry date to censoring or to endpoint date and it was expressed as person-years.

Classifications

To classify patients by the complexity of their heart defects, we used the categories outlined by Task Force 1 of the 32nd Bethesda Conference:[2] simple, moderate, and severe (*Table 1*). Patients diagnosed with sinus venosus type of atrial septal defect or with anomalous pulmonary venous connection were considered together in moderate complexity, and patients with Eisenmenger syndrome and other conditions with pulmonary vascular disease in severe complexity. The individual diagnostic categories that were documented in <20 patients were grouped as others.

To evaluate whether outcomes over time differed among natural or unnatural survival patterns described by Perloff,[24] we stratified the patients into childhood repair and unrepaired survivors to adult life (which also included those patients with only palliative interventions). Unrepaired survivors were then divided into repaired in adulthood, patients with no indication for repair, and patients with inoperable malformations except for organ transplantation (non-repairable) (*Table 2*).

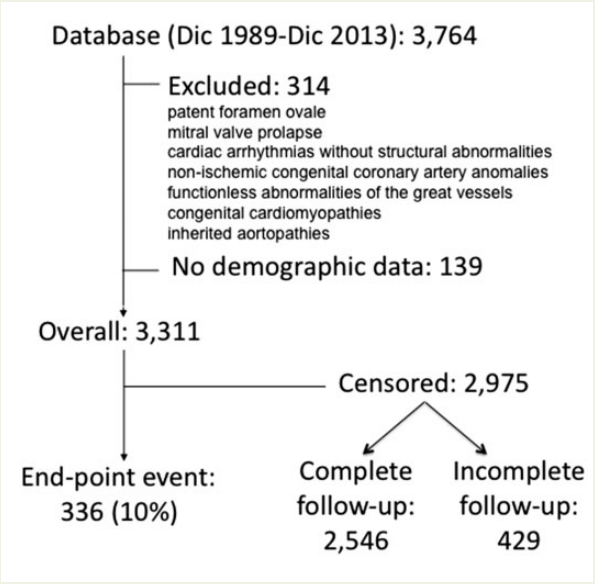


Figure 1 Flowchart of study population.

Predictor variables

Details regarding to demographic characteristics, clinical status, Doppler two-dimensional echocardiography (2DE), cardiac magnetic resonance imaging (MRI), and cardiac catheterization were collected. A number of variables were included in the analysis of predictors related to outcome (*Table 3*). Imaging techniques either qualitatively or quantitatively assessed moderate-to-severe subaortic or subpulmonic ventricular systolic dysfunction. Pulmonary outflow tract stenosis was defined as Doppler or catheter peak pressure gradient >50 mmHg at valvar, subvalvar, or supravalvar level (or above 30 mmHg in the setting of severe subpulmonic ventricular dysfunction) and aortic outflow tract stenosis as Doppler or catheter mean systolic pressure gradient >40 mmHg. Valve regurgitation was considered haemodynamically significant when equal to or more than Grade III, as assessed qualitatively by Doppler echocardiography. Severe pulmonary hypertension was assumed to exist when a maximum velocity of subpulmonary AV valve regurgitation jet >3.5 m/s was measured by Doppler 2DE in the absence of pulmonary stenosis. Left-to-right shunt was defined as any intra- or extracardiac shunt detected by colour Doppler flow, phase-contrast MRI, or catheterization. Cyanosis was defined as arterial oxygen saturation <90% caused by significant right-to-left shunting or clinical cyanosis. Symptomatic arrhythmias included atrial flutter or fibrillation and complete AV block. Aortic aneurysm was defined as ascending or descending aortic dilation of a diameter >50 mm, aortic dissection or aortic rupture. Infective endocarditis included episodes during adult follow-up. Ischaemic heart disease included acute myocardial infarction or angina due to atherosclerotic or congenital coronary lesions.

Statistical analysis

All analyses were performed with statistical package of R Version 3.1.2. Continuous variables were expressed as mean ± SD whether normally distributed or median and inter-quartile range (IQR) whether non-normally distributed. Categorical variables were summarized using numbers and percentages. Annual death rate was measured by relating the number of new events to the person-years at risk during the measurement period. To minimize immortal bias, survival analyses were

Table 1 Long-term survival of 3311 adults with congenital heart disease (CHD)

Complexity	Diagnostic category	*n*	Repair *n* (%)	Age at entry	Follow-up time	Death *n* (%)	Annual death rate	Median age at death	Standardized mortality		
									Rate	95% CI	*P*-value
I. Simple	Overall	1625	816 (50)	26.3 (19–46)	11.3 (6–18)	153 (9.4)	0.79	78.0 (76–82)	1.65	1.4–2.0	<0.001
	Ostium secundum ASD	369	292 (79)	39.4 (23–55)	10.4 (4–18)	51 (14)	1.23	78.0 (77–81)	1.85	1.4–2.5	<0.001
	Ventricular septal defect	356	112 (31)	19.1 (17–23)	10.1 (5–19)	5 (1.4)	0.12	NA (NA–NA)	1.72	0.7–4.5	0.22
	Patent ductus arteriosus	90	60 (67)	28.1 (19–44)	13.3 (7–18)	10 (11)	0.88	76.3 (74.4–NA)	2.16	1.1–4.3	0.013
	Aortic valve disease	547	215 (39)	38.1 (21–55)	12.2 (8–18)	77 (14)	1.12	76.8 (74–82)	1.49	1.2–1.9	<0.001
	Pulmonary valve disease	227	124 (55)	20.2 (18–32)	11.1 (5–19)	9 (4.0)	0.33	81.8 (68–NA)	1.81	0.9–3.8	0.07
	Mitral valve disease	36	13 (36)	19.7 (17–30)	11.0 (6–20)	1 (2.8)	0.22	84.2 (NA–NA)	1.15	0.2–7.9	0.89
II. Moderate	Overall	1278	1063 (83)	21.2* (18–34)	9.9† (4–18)	96 (7.5)	0.68	72.6 (67–78)	3.17	2.5–4.0	<0.001
	Sinus venosus ASD-PVAC	103	82 (80)	31.6 (20–50)	8.6 (4–14)	6 (5.8)	0.61	84.4 (78–NA)	1.43	0.6–3.5	0.37
	AV septal defect	148	133 (90)	20.0 (17–29)	10.5 (5–18)	8 (5.4)	0.48	82.0 (15–NA)	3.66	1.7–7.9	<0.001
	Subvalvar aortic stenosis	115	73 (63)	30.6 (18–51)	13.5 (6–19)	26 (23)	1.79	64.2 (60–82)	2.55	1.7–4.0	<0.001
	Supravalvar aortic stenosis	30	15 (50)	19.2 (18–23)	15.8 (6–21)	0	NA	NA (NA–NA)	NA		
	Coarctation of the aorta	353	337 (95)	20.2 (18–29)	9.4 (4–19)	21 (5.9)	0.54	69.9 (62–NA)	3.80	2.3–6.2	<0.001
	Subvalvar pulmonary stenosis	50	44 (88)	21.7 (18–32)	9.7 (5–18)	1 (2.0)	0.19	NA (NA–NA)	2.11	0.3–15	0.44
	Supravalvar pulmonary stenosis	24	8 (33)	22.1 (20–28)	6.2 (1.5–11)	0	NA	NA (NA–NA)	0	0–33	0.69
	Ebstein anomaly	76	19 (25)	32.4 (20–47)	7.9 (2–16)	9 (12)	1.23	70.8 (56–NA)	3.34	1.6–6.9	<0.001
	Tetralogy of Fallot	327	321 (98)	20.3 (18–27)	10.3 (4–20)	18 (5.5)	0.48	63.2 (60–NA)	5.84	3.5–9.9	<0.001
	Other moderately complex CHD	52	31 (60)	26.4 (18–48)	5.7 (1–13)	7 (13)	1.68	69.0 (39–NA)	4.03	1.8–9.2	<0.001
III. Severe	Overall	408	246 (60)	21.2 * (18–28)	8.4‡ (3–18)	87 (21)	2.04	49.2 (45–53)	21.7	17–28	<0.001
	Transposition of the great arteries	122	120 (98)	19.1 (17–22)	10.6 (5–18)	11 (9.0)	0.80	67.3 (NA–NA)	12.1	6.3–24	<0.001
	AV discordance	42	13 (31)	29.4 (20–48)	5.0 (1–14)	12 (29)	3.55	40.4 (29–NA)	15.1	8.0–29	<0.001
	Double outlet right ventricle	19	19 (100)	21.1 (18–29)	7.9 (3–17)	2 (11)	1.05	NA (35–NA)	15.3	3.6–66	<0.001
	Pulmonary atresia (all forms)	53	32 (60)	21.0 (18–30)	7.6 (3–17)	8 (15)	1.60	53.5 (40–NA)	23.3	11–50	<0.001
	Pulmonary vascular disease	67	9 (13)	27.7 (21–35)	9.3 (4–18)	28 (42)	3.85	30.3 (19–51)	29.5	19–45	<0.001
	Single ventricle physiology	101	53 (53)	22.5 (21–32)	8.5 (3–18)	22 (22)	2.01	48.1 (45–NA)	28.6	18–46	<0.001
	Fontan procedure	53		20.3 (18–24)	6.8 (2–18)	8 (15)	1.56	NA (35–NA)	27.2	13–59	<0.001
	Glenn procedure	14		22.5 (21–32)	10.3 (3–22)	2 (14)	1.14	53.4 (NA–NA)	10.3	2.4–44	<0.001
	Banding/fistula	22		20.8 (19–25)	12.7 (4–18)	8 (36)	3.19	45.2 (34–NA)	44.5	21–96	<0.001
	No intervention	12		23.4 (18–26)	11.7 (7–20)	4 (33)	2.61	49.2 (48–NA)	39.2	13–114	<0.001
	Other severe complexity CHD	4	0	52 (43–60)	4.6 (2–11)	4 (100)	16.7	53.9 (53–NA)	NA		
Total		3311		22.5 (18–39)	10.5 (4–18)	336 (10)	0.89	75.1 (73–77)	2.64	2.3–3.0	<0.001

Continuous variables are presented as median with inter-quartile range.
ASD, atrial septa defect; AV, atrioventricular; CI, confidence interval; NA, non-applicable; PVAC, pulmonary venous anomalous connection.
*$P < 0.001$ compared with Group I; †$P = 0.002$ compared with Group I; ‡$P = 0.001$ compared with Group I.

performed using standard right-censored Kaplan–Meier curves with age as time scale accounting for left truncation. Median ages at death and 95% CI were generated using R programming language with survival library and comparisons between groups were performed by two-sample log-rank test. To ensure that age at entry into the cohort had no impact on outcomes, Kaplan–Meier survival estimates with left truncation of patients with age at first examination below (early referrals) and above the median (late referrals) were compared. Standardized mortality ratios (SMR) from Spanish reference population's age at diagnosis-, sex-, and time of follow-up-adjusted mortality rate were calculated using the

Table 2 Comparison of long-term outcome of adult survivors with congenital heart disease among the different survival patterns

Survival pattern	Patients	No of deaths *n* (%)	Annual death rate	Median age at death (years)	Standardized mortality		
					Ratio	95% CI	*P*-value
Childhood repair	1382	67 (4.9)*	0.44*	75.9	2.66	2.3–3.1	<0.001
Adulthood repair	743	126 (17)*	1.42*	76.2	2.06	1.7–2.5	<0.001
No indication for repair	1024	88 (8.6)	0.75	77.9	1.68	1.3–2.1	<0.001
Non-repairable	162	55 (34)*	3.18*	48.1*	25.0	18–34	<0.001

CI, confidence interval.
*$P < 0.001$ compared with other groups.

Table 3 Factors associated with all-cause death in univariate and multivariate Cox proportional regression analysis accounting for left truncation in 3311 adults with congenital heart disease

Predictor variables	*n* (%)	Univariate analysis			Multivariate analysis		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Female gender	1673 (51)	0.82	0.66–102	0.067	0.88	0.70–1.1	0.316
Genetic syndromes	144 (4.3)	2.19	1.3–3.8	0.004	1.90	1.1–3.4	0.028
Ventricular function							
Subpulmonary ventricular dysfunction	169 (5.1)	3.22	2.5–4.2	<0.001	1.72	1.2–2.5	<0.003
Systemic ventricular dysfunction	236 (7.1)	3.95	3.1–5.0	<0.001	2.18	1.6–3.0	<0.001
Systemic right ventricle	170 (5.1)	3.17	2.1–4.9	<0.001	1.48	0.89–2.5	0.129
Single ventricle physiology	113 (3.4)	6.24	4.2–9.4	<0.001	1.86	1.1–3.3	0.032
Persistent shunt							
Supra-tricuspid left-to-right shunt	474 (14)	0.83	0.63–1.1	0.188	0.93	0.67–1.3	0.658
Ventricular left-to-right shunt	587 (18)	2.83	2.1–3.8	<0.001	1.21	0.83–1.8	0.312
Clinical cyanosis	173 (5.2)	6.68	4.9–9.1	<0.001	2.47	1.5–3.9	<0.001
Right ventricular overload							
Pulmonary outflow tract obstruction	157 (4.7)	3.83	2.6–5.6	<0.001	2.37	1.6–3.6	<0.001
>Moderate pulmonary regurgitation	261 (7.9)	1.49	0.95–2.3	0.078	1.16	0.70–1.9	0.552
>Moderate tricuspid regurgitation	177 (5.3)	1.94	1.4–2.6	<0.001	1.15	0.80–1.7	0.452
Left ventricular overload							
Aortic outflow tract obstruction	188 (5.7)	1.01	0.73–1.4	0.952	1.16	0.82–1.63	0.406
>Moderate aortic regurgitation	212 (6.4)	1.48	1.0–2.1	0.029	1.24	0.82–1.6	0.279
>Moderate subaortic AV valve regurgitation	115 (3.5)	2.48	1.7–3.6	<0.001	1.69	1.1–2.5	0.011
Symptomatic arrhythmias							
Atrial flutter/fibrillation	295 (8.9)	1.90	1.5–2.4	<0.001	0.95	0.70–1.3	0.771
Complete AV block	127 (3.8)	1.90	1.3–2.8	0.002	0.79	0.50–1.2	0.312
Complications							
Pulmonary hypertension	150 (4.5)	3.67	2.8–4.8	<0.001	2.22	1.6–3.1	<0.001
Aortic aneurysm	128 (3.9)	1.61	1.1–2.3	0.008	1.76	1.2–2.6	0.004
Infective endocarditis	91 (2.7)	3.43	2.2–5.2	<0.001	2.90	1.9–4.5	<0.001
Ischaemic heart disease	68 (2.1)	2.30	1.5–3.5	<0.001	1.68	1.0–2.7	0.034
Reintervention at adult age	141 (4.3)	1.45	0.89–2.4	0.133	1.23	0.74–2.0	0.422

AV, atrioventricular; CI, confidence interval; HR, hazard ratio.

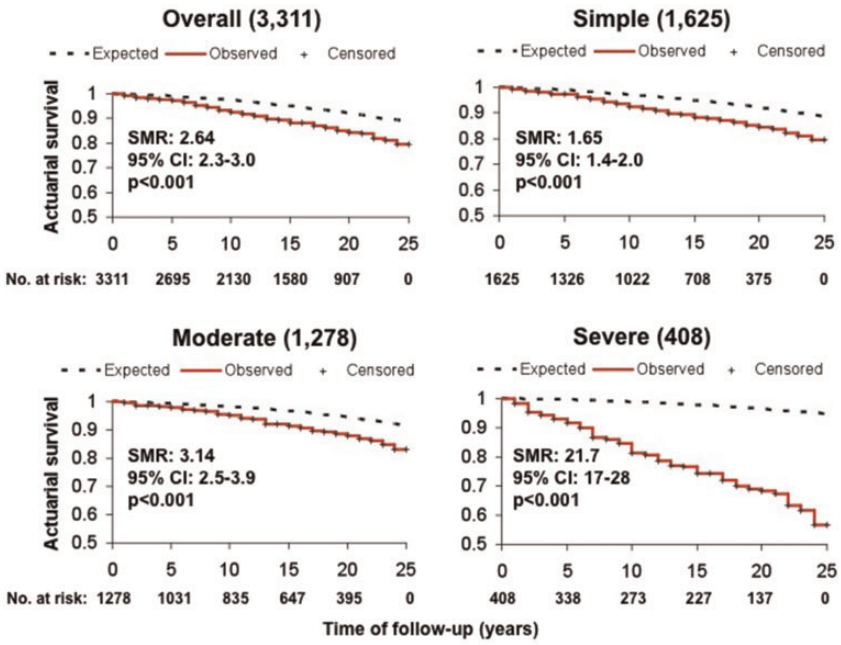


Figure 2 Age at diagnosis-, sex-, and time of follow-up-adjusted standardized mortality ratio (SMR) in adult survivors with congenital heart disease (CHD): upper-left, overall; upper-right, simple CHD; bottom-left, moderately complex CHD; bottom-right, severely complex CHD. CI, confidence interval.

method of Finkelstein *et al.*[25] One-sample log-rank test and 95% CI were determined by online available software: http://hedwig.mgh.harvard.edu/biostatistics/node/30 (12 December 2016). In this software, we substituted the original 2003 USA population mortality rate with 2005–10 Spanish death rate, obtained from the 2015 revision of Unite Nations Word Population Prospect, available in https://esa.un.org/unpd/wpp/Download/Standard/Mortality/ (12 December 2016). For assessing independent risk factors for all-cause death, the potential predictive variables were analysed by univariate and multivariate Cox regression model accounting for left-truncation and hazard ratios (HR) with 95% CI were generated. Excess mortality and median age at death of patients with each independent risk factor and of patients with no risk factors were then calculated using the method above indicated. As cause-specific death information was not completely available, a relative survival model was used to get adjusted effect of the independent risk factors on excess mortality (see Supplementary material online). Two-tailed *P*-values <0.05 were considered statistically significant.

Results

Long-term mortality

Overall, 1625 patients (49%) had a simple CHD; 1278 (39%) had a moderate complexity CHD; and 408 (12%) had a severe complexity CHD. There were 1673 males and 1638 females. The median age at first examination was 22.5 years (IQR 18–39) and median follow-up time was 10.5 years (IQR 4.4–18). During a cumulative follow-up time of 37 608 person-years 336 patients died (10%) with an annual death rate of 0.89%. There were 153 events among simple (9.4%), 96 in moderate (7.5%), and 87 in severe (21%) lesions. The *Table 1* provides an overview over mortality and annual death rate in these subgroups of complexity and of underlying heart defects. As expected, annual death rate was higher in patients with lesions of great complexity ($P < 0.001$); however, mortality rates did not significantly differ between simple and moderate CHDs and overlapped considerably across the different diagnostic categories within the three groups of complexity. For example, death rate was higher than average in patients with atrial septal defect or aortic valve disease, but it was below the average in patients with complete transposition (0.80%), coarctation of the aorta (0.54%), atrioventricular septal defect (0.48%), or tetralogy of Fallot (0.48%). Reasons for this apparent discrepancy may be that the follow-up time and the age at entry ranged widely and patients with simple lesions were older at inclusion and had longer follow-up times.

Excess mortality

Compared with age at diagnosis-, sex-, and time of follow-up-adjusted expected survival for the Spanish general population, the SMR of 2.64 for the entire cohort was significantly higher (95% CI 2.3–3.0; $P < 0.001$) and increased progressively with the level of complexity ($P < 0.001$ for each group) (*Figure 2*). There was also an excess mortality for each underlying heart defect that ranged from 1.49 in patients with aortic valve disease to near 30-fold in patients with single ventricle physiology or pulmonary vascular disease (*Figure 3* and see Supplementary material online, *Figure S1A–C*).

Survival prospects

In the whole cohort, median age at death was 77.2 years for female (95% CI 76–80) and 69.8 years (95% CI 67–75) for male ($P = 0.068$)

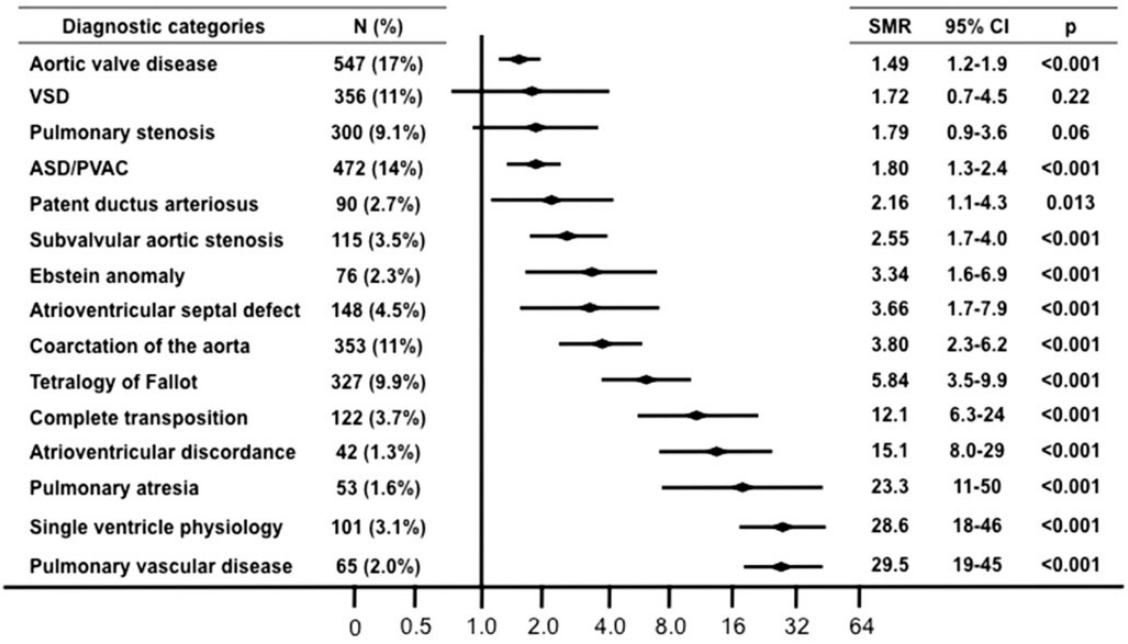


Figure 3 Standardized mortality ratio (SMR) and 95% confidence interval (CI) for the main individual diagnostic categories. Patients with valvar, subvalvar or supravalvar pulmonary stenosis, and patients with ostium secundum or sinus venosus atrial septal defect (ASD) and/or pulmonary venous anomalous connection (PVAC) are considered together. VSD, ventricular septal defect.

(*Figure 4A*). Median age at death was 78.0 years (95% CI 76–82) for patients with simple lesions, 72.6 years (95% CI 67–78) for lesions of moderate complexity, and 49.2 years (95% CI 45–53) for complex defects ($P < 0.001$) (*Figure 4B*). Late referral did not compromise survival significantly (HR 0.94; 95% CI 0.67–1.69; $P = 0.78$). When evaluating the median age at death in different diagnostic categories, it was over 75 years in patients with simple lesions and with non-complicated left to right shunts; between 60 and 75 years in subvalvular aortic stenosis, Ebstein anomaly, coarctation of the aorta, tetralogy of Fallot, and complete transposition; and below 60 years in Eisenmenger patients, atrioventricular discordance, pulmonary atresia, or single ventricle physiology (see Supplementary material online, *Figure S2A–C*).

Repair status

The *Table 2* summarizes mortality indexes in the subgroups of patients according to repair survival patterns. Annual death rate for childhood repair group was significantly lower compared with the three natural survival groups, but there were not significant differences in the median age at death among patients with childhood repair (75.9 years), adult repair (76.2 years), and no indication for repair (77.9 years) (see Supplementary material online, *Figure S3*). As expected, all prognostic indexes were much worse in patients with non-repairable CHD ($P < 0.001$). However, there was also significant excess mortality for patients with childhood repair, adult repair, or no indication for repair compared with the survival matched by age and sex of the reference population (see Supplementary material online, *Figure S4*).

Outcome predictors

In our cohort, 11 variables were found to be predictive of adverse outcome: genetic disorders, single ventricle physiology, clinical cyanosis, severe pulmonary outflow tract stenosis, subaortic and subpulmonic moderate-to-severe ventricular systolic dysfunction, significant subaortic atrioventricular valve regurgitation, severe pulmonary hypertension, infective endocarditis, aortic aneurysm, and ischaemic heart disease (*Table 3*). The SMRs for patients with each of these risk factors are displayed in *Figure 5A* showing significant excess mortality ($P < 0.001$ for each risk factor) ranging from 2.65 for patients with aortic aneurysm to 28.6 for patients with single ventricle physiology. Importantly, the SMR was 1.14 (95% CI 0.9–1.5; $P = 0.19$) and median age at death was 83.7 years (95% CI 82–87) for 2315 patients (70%) with no risk factors (*Figure 5B*). In contrast, the SMR was 5.22 (95% CI 4.5–6.0; $P < 0.001$) and median age at death 55.6 years (95% CI 50–61) for 996 patients (30%) with at least one risk factor (*Figure 5B*). The same variables except for ischaemic heart disease were confirmed as independent risk factors for excess mortality by relative survival model (see Supplementary material online).

Discussion

Survival

In comparison with previous reports on the survival of contemporary cohorts of adults with CHD,[21–22] our data appeared to be worse and we observed a slightly high risk of premature death in the whole group of patients with simple defects and in patients with each

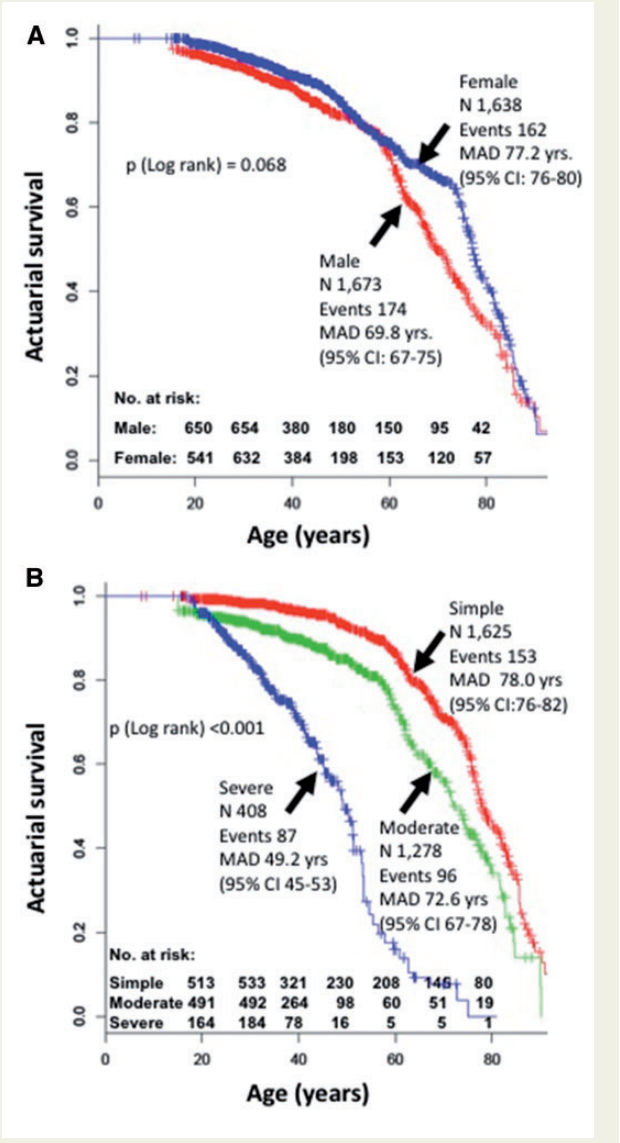


Figure 4 Right-censored Kaplan–Meier survival curves accounting for left-truncation with age as time scale of 3311 adult survivors with congenital heart disease. (*A*) Comparison of median age at death (MAD) by sex. (*B*) Comparison of MAD between patients with simple, moderate, or severe complexity lesions. CI, confidence interval.

individual simple diagnostic category. Some studies[22,26] have shown that survival of older patients with simple CHD may be even better than that of the reference population. Although healthier lifestyle and lifetime follow-up by a cardiologist have been advocated as contributors to explain these findings, there might be some methodological issues leading to an over optimistic estimates of survival prospects of simple lesions. Our study differs from those previous reports in that our study population's age at inclusion was younger (22.5 years) and the follow-up time longer (10.5 years). Additionally, source of data on mortality in these previous studies was administrative data set. As Zomer *et al.*[27] have reported that not all deceased patients could be found in the national registries, leading to less complete data compared with medical records, we obtained mortality data from clinical records and, where needed, telephone follow-up. Moreover, patients without complete clinical follow-up were censored at the last clinical visit in our study. To our knowledge, this represents the first longitudinal clinical registry assessing survival prospects and it might lead to a more realistic approach.

Repair patterns

The population of adults with CHD in our registry is made up with those who survived after surgical repair at paediatric age (42%) and those who reached adult life without previous surgery or with only palliative interventions. The second group includes malformations that did not require intervention (31%), those that were repaired at adult age (22%), and those that were not repairable (5%). These figures are largely consistent with the proportion of patients reported in previous registries[28,29] but our data evaluate for the first time whether outcomes of adults with CHD over time differ between natural and postoperative survival patterns. The annual mortality rate of our patients repaired at paediatric age was significantly lower in comparison with other survival patterns but left-truncated actuarial survival analysis showed that there were no significant differences in median age at death between childhood repair, adult repair, or no indication for repair groups. This could indicate that overoptimistic survival estimates of those repaired in childhood could be—at least in part—attributable to the presence of immortal time bias. In addition, our data also indicate that the life prospects after CHD repair, either in childhood or in adulthood, were as good as that of patients with no indication for repair according to current guidelines, but worse than that of reference population. Finally, it is not surprising that long-term survival indexes of adults with non-repairable CHD were much inferior to that of the general population with an adjusted mortality rate up to 20 times higher. Bearing in mind that these are historical clinical data, it is likely that overall survival will improve with current and future advances and with early intervention in infancy and childhood of patients with complex CHD.

Risk factors for excess mortality

As survival prospects of the cohort of patients with CHD attending at our ACHD clinics were reduced compared with the general population whatever their level of complexity, repair status, or underlying CHD, there is a need for identification of risk factors and protocols for risk reduction. Although clinical variables associated with overall mortality[15,30] in adult survivors with CHD have been previously reported, a systematic analysis of their impact on survival has not been performed yet. We found 11 variables by Cox regression model affecting long-term survival and excess mortality. Patients with unrepaired cyanotic defects, genetic disorders, and anatomical features or haemodynamic sequelae such as univentricular physiology or severe pulmonary outflow tract stenosis had the highest SMRs. Severe pulmonary hypertension, moderate-to-severe subaortic or subpulmonic ventricular systolic dysfunction, and significant subaortic atrioventricular valve regurgitation were also good predictors of adverse outcomes. In addition, infective endocarditis, aortic aneurysm, and ischaemic heart disease were acquired complications associated with excess mortality. Remarkably, long-term survival of patients with at least one risk factor was significantly reduced with >5-fold excess

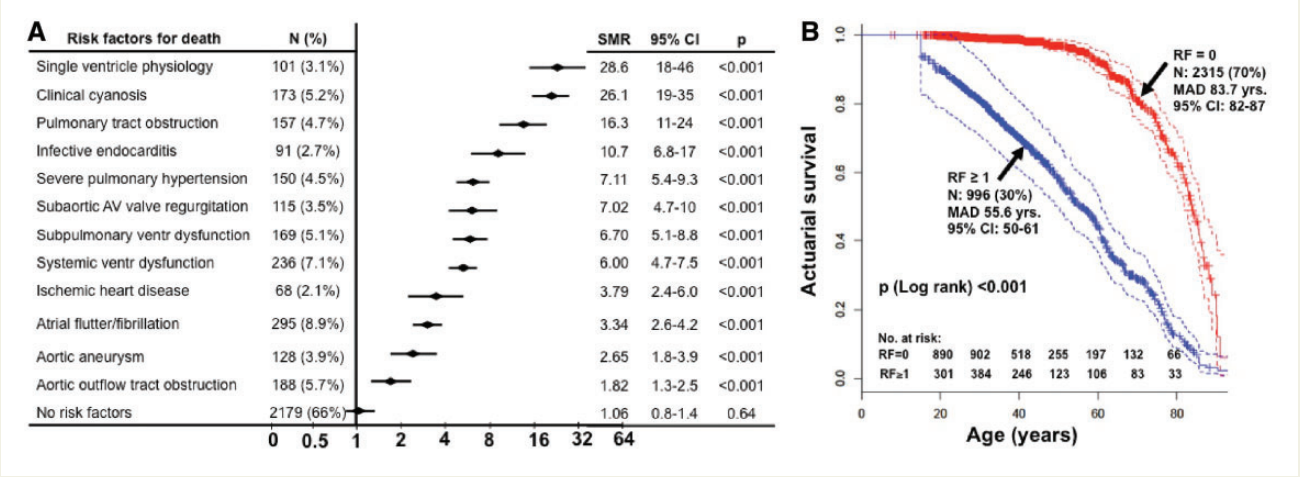


Figure 5 Risk factors for excess mortality and long-term survival. (*A*) Standardized mortality ratio (SMR) with 95% confidence interval (CI) for patients with individual risk factors and patients with no risk factors. (*B*) Comparison of median age at death (MAD) between patients with no risk factors (RF = 0) and patients with at least one risk factor (RF ≥ 1). AV, atrioventricular.

mortality. However, 70% of our patients did not present with any of these risk factors and their survival prospects, whatever their lesion complexity, were close to the general population. The independent effect of these parameters on excess mortality could be also confirmed by relative survival model except for ischaemic heart disease. The low prevalence of coronary heart disease in our cohort may be the reason for this apparent discrepancy. Interestingly, variables such as systemic right ventricle, chronic moderate-to-severe pulmonary, tricuspid or aortic regurgitation, and symptomatic atrial arrhythmias were not *per se* independent predictors for mortality in the absence of ventricular dysfunction or any of the other risk factors. Although these data should be interpreted with caution, they may help to a more comprehensive risk assessment in our contemporary population of adults with CHD.

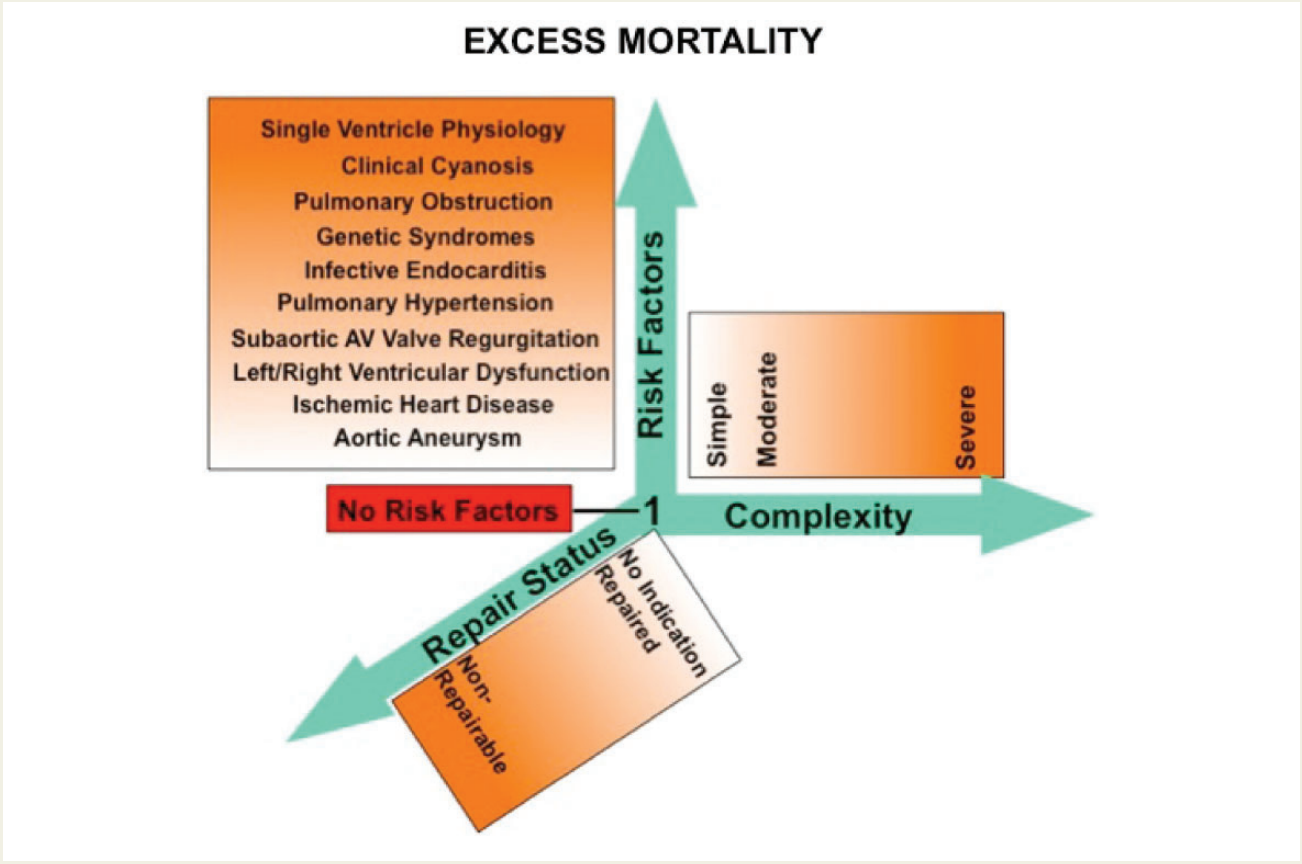
Strengths and limitations

There are a number of noteworthy strengths of our study. First, this is a prospective registry. Baseline information was entered in the database and updated periodically and regularly. Thus patients were longitudinally followed up until the closing or endpoint date. Secondly, mortality data were obtained from clinical records and, where needed, telephone follow-up. For avoiding inaccuracies in administrative data, the Spanish National Death Index was just used to ascertain vital status of all our patients. Finally, patients without complete clinical follow-up were censored as alive at the date of the last clinical examination in our CHD unit.

However, we acknowledge several study limitations: this cohort comes from a single referral ACHD centre, so the study population may not be representative of the community. Nevertheless, the distribution along complexity groups was that expected in the general population.[2] Clinical follow-up was incomplete in 14% of patients although their vital status was further verified with information of the Spanish National Death Index too. Compared with patients with complete follow-up they were younger and had less severe complexity CHD and non-repairable malformations (see Supplementary ma terial online, *Table S1*). Thus, our findings might overestimate the number of adults at risk of death in the global cohort. In a number of cases, there was a late presentation of unknown simple CHD. This adult population with uncorrected defects and late presentation is older at inclusion. The reduced life expectancy of people with additional co-morbidities may explain the higher mortality observed in adults with simple defects. Moreover, given the lack of formal transition programmes from paediatric to adult cardiology centres before the 1990s, those who did not initially transition from paediatric cardiology care will be referred back to our unit late, particularly when complications occur. Although we could have underestimated the magnitude of increase in late mortality risk in these cohorts, we observed that late referral did not compromise survival significantly. Finally, these are historical clinical data. As clinical practice evolves, improvements in care may favourably modify contemporary long-term outcomes in the near future. Nevertheless, our data provide information on the prognosis of the contemporary population of adult patients attending to our ACHD clinics and are based on current clinical practice. Therefore, these limitations should not detract from our results.

Conclusions

Overall, adult survivors with CHD have globally reduced survival compared with the general population with substantial variations with CHD complexity, repair status, and specific CHD. Clinical parameters, such as anatomical features, haemodynamic sequelae, or acquired complications, account for much of long-term survival reduction of contemporary ACHD population. Survival of individuals with no risk factors did not differ from the reference population. Although further studies are warranted to investigate whether prevention and control of modifiable risk factors for excess mortality could favourably modify long-term survival, our data may help to move to a more comprehensive risk assessment in adults with CHD.



Summarizing Figure

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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