ORIGINAL ARTICLE

Predictors of mortality in adult patients with congenital heart disease

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Abstract

Background: *Most patients with congenital heart disease (CHD) reach adulthood thanks to the successful efforts of cardiac surgeons. However, sudden cardiac deaths are significantly more prevalent in this population, and survival is reduced when compared to the general population. The aim of this study is to define the prognostic value of selected clinical parameters to predict mortality in adult CHD patients referred to the specialist outpatient centre. The following parameters were analyzed as potential predictors of long-term survival: complexity of heart defect, past surgical intervention, heart failure (functional class according to NYHA > I), cyanosis, age and gender.*

Methods: *We analyzed data gathered from 1,304 patients (568 male) aged 18 to 72 (mean 29.4 ± 10.6) between 1995 and 2004. Mean duration of follow-up was 3.52 ± 1.83 years.*

Results: *During follow-up, 29 deaths were recorded (2.2%). Higher mortality was found in the group of patients with complex as oppposed to simple CHD (28 [6.7%] vs. 1 [0.1%]; p = 0.00001), in subjects without surgical correction as opposed to those operated on (21 [6.1%] vs. 8 [0.8%], p = 0.00001). General survival was 99.1% at two years and 96.6% at five years. In univariate survival analysis, all single clinical variables except patient gender were associated with increased risk of death (p = 0.00001 for all). All patients who died presented with heart failure. In multivariate analysis, the independent predictor of mortality was cyanosis (heart rate 38.1). Complexity of lesion (heart rate 6.4) represented a relative risk factor.*

Conclusions: *Heart failure and cyanosis are negative predictors of survival in adult patients with CHD. Complexity of the lesion increases the relative risk of mortality. Past cardiac surgery is associated with better survival, but, as with age and gender, it is not a significant prognostic factor.* (Cardiol J 2009; 16, 4: 341–347)

Key words: survival, mortality, adult patients with congenital heart disease

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Introduction

Most adult patients with congenital heart disease (CHD) survive only thanks to the successful efforts of paediatricians and cardiac surgeons.

A couple of decades ago, most such patients died in childhood. Thus there were no adults presenting with CHD and typical problems associated with new a chronic clinical syndrome characterized by the presence of residual defects and post-surgery complications. The natural history of such corrected CHD is also unknown, as survivors vary widely, and surgical techniques evolve with time. Today's mean age of patients with CHD does not exceed 40 [1]. The incidence of sudden death in this population is 25–100 times higher than in the general population, and fatal events are observed even in subjects in their twenties [2]. Survival analysis in patients with CHD is difficult due to methodology issues and the fact that study groups are relatively small. Survival data has been published for certain heart defects, particularly when corrected using specific surgical methods [3–6]. There have however been few reports on survival of heterogeneous populations of patients from single, large reference clinical centres [2, 7]. A broad population-based approach to survival analysis is, in our opinion, highly clinically relevant as it may reveal potential risk factors for mortality. Knowing these would help clinicians to identify subgroups at risk and provide them with special care.

The aim of this study is to define the prognostic value of selected clinical parameters in adult CHD patients referred to the specialist outpatient centre. The following parameters were analyzed as having potential impact on long-term survival: complexity of heart defect, surgical intervention in the past, heart failure (functional class according to New York Heart Association [NYHA] > I), cyanosis, age and gender.

Methods

Our study involved 1,304 adult patients with CHD (718 females), aged 18–72 (mean 29.4 ± 10.6), followed between 1995 and 2004 in the Specialist Outpatient Clinic for Adults with Congenital Heart Disease, I Chair of Cardiology, University of Medical Science in Poznan.

On presentation to the centre, a detailed history was taken focusing on the type of surgical repair done in the past. After physical examination, transthoracic echocardiography and standard 12--lead electrocardiogram were recorded. Based on all the information, a diagnosis was made (or confirmed). Where a patient presented with more than one cardiovascular anomaly, the dominant lesion was used to classify the subject. Using the system proposed by the Working Group of Congenital Heart Disease in Adults of the British Society of Cardiology (Somerville) [8], patients were classified as having simple or complex CHD. Numbers of patients with simple and complex lesions, their demography, types of operations performed, baseline cyanosis and heart failure status are shown in Table 1.

Patients were followed for between one and ten years (mean 3.52 ± 1.83 years). Functional status was assessed according to NYHA classification. Patients at NYHA class > I were classified as presenting with heart failure. Cyanosis was defined as the presence of cyanotic skin and mucosa associated with arterial blood oxygenation ≤ 85% when breathing normal air, when extracardiac causes were excluded.

Statistical analysis

Numerical variables are given as means and standard deviations. Variables following normal distribution were compared using t-Student test, others using the U Mann-Whitney test. Kaplan--Meier survival curves for subsets of patients presenting certain characteristics were compared using log-rank test. Multivariate survival analysis using Cox's regression model was adopted to search for mortality risk factors.

Results

There were 29 deaths (2.2%) during the mean follow-up of 3.52 years. The incidence of deaths in patients with particular types of CHD is shown in Tables 2 and 3. Higher mortality was found in the group of patients with complex *vs.* simple CHD (28 [6.7%] *vs.* 1 [0.1%]; p = 0.00001) and in subjects without surgical correction *vs.* those operated on (21 [6.1%] *vs.* 8 [0.8%], p = 0.00001). Patients who died were significantly older than those who survived (41.9 ± 15.2 years *vs.* 29.1 ± 10.3 years; p = 0.0002). General survival was 99.1% at two years and 96.6% at five years (Fig. 1). In univariate survival analysis, all single clinical variables, except gender, were associated with increased risk of death (p = 0.00001 for all). Because all patients who died presented with heart failure at baseline (NYHA > I), heart failure had to be excluded from multivariate survival analysis using Cox's regression model. In this model the independent predictors of death were

Table 1. Characteristics of study population of adults with coronary heart disease (CHD). Demographic data, past cardiac surgery, presence of cyanosis and heart failure (NYHA > I) at baseline.

	N	Males	Age	No. of operated patients	Age at surgery	No.of cyanotic patients	No. of patients with baseline NYHA > I
Simple CHD							
ASD*	278	102 (36.6%)	32.6 ± 12.9	200 (71.9%)	12.1 ± 9.7	0	3 (1.08%)
VSD*	277	135 (48.7%)	27.6 ± 9.3	226 (81.5%)	8.4 ± 8.0	0	3 (1.08%)
PDA*	120	29 (24.1%)	27.5 ± 9.5	116 (96.6%)	7.2 ± 6.1	0	0
BAV	107	71 (66.3%)	26.9 ± 6.7	36 (33.6%)	15.4 ± 7.1	0	1 (0.93%)
PS	70	30 (42.8%)	27.5 ± 9.1	49 (70%)	9.2 ± 6.6	3(4.3%)	3 (4.3%)
PPVC	10	5 (50%)	31.2 ± 14.5	10 (100%)	14.7 ± 12.6	0	2 (20.0%)
Marfan	9	3 (33.3%)	26.8 ± 9.8	1 (11.1%)	20.0	0	0
IPD	8	2 (25.0%)	32.0 ± 11.8	0	0	0	0
MI	6	1 (16.6%)	24.7 ± 3.8	2 (33.3%)	17.0 ± 1.4	0	0
Williams	1	0	24.0	0	0	0	0
Total	886	378 (42.6%)	29.1 ± 10.6	640 (72.2%)	9.9 ± 8.5	3 (0.34%)	12 (1.35%)
Complex CHD							
CoAo	106	61 (57.5%)	29.9 ± 9.5	103 (97.2%)	10.2 ± 7.0	0	7 (6.6%)
ToF	101	51 (50.5%)	27.8 ± 7.7	96 (95.0%)	7.4 ± 5.2	7 (6.9%)	9 (8.9%)
ASD I	38	17 (44.7%)	28.2 ± 9.9	38 (100%)	11.8 ± 10.8	0	3 (7.9%)
CAVC	32	12 (37.5%)	27.6 ± 8.3	18 (56.2%)	5.7 ± 3.0	8 (25.0%)	8 (25.0%)
Eisenmenger	27	6 (22.2%)	45.5 ± 14.3	0	0	27 (100%)	27 (100%)
SAS	24	14 (58.3%)	30.0 ± 10.3	15 (62.5%)	15.9 ± 13.0	0	0
SV	23	11 (48.7%)	26.7 ± 7.9	16 (69.6%)	8.9 ± 4.2	20 (87.0%)	20 (87.0%)
Ebstein	20	15 (75%)	41.2 ± 11.2	0	0	4 (20.0%)	9 (45.0%)
DTGA	19	9 (47.4%)	24.7 ± 4.8	16 (84.2%)	3.5 ± 3.2	7 (36.8%)	1 (11.1%)
VC	9	5 (55.6%)	26.9 ± 7.1	9 (100%)	18.4 ± 12.0	0	3 (37.5%)
CCTGA	8	6 (75.0%)	31.6 ± 12.6	1 (12.5%)	45.0	2 (25.0%)	0
DORV	5	1 (20.0%)	23.4 ± 3.0	5 (100%)	6.2 ± 4.6	0	0
PA	3	0	22.3 ± 1.2	2 (66.7%)	4.5 ± 0.7	0	0
CCA	2	0	22.0 ± 2.8	2 (100%)	4.5 ± 0.7	0	0
BWG	1	0	28.0	1 (100%)	4.0	0	0
Total	418	208 (49.9%)	30.0 ± 10.5	322 (77.0%)	9.5 ± 8.1	75 (17.9%)	96 (23.0%)

*patients with normal pulmonary pressure; ASD — atrial septal defect type secundum and sinus venosus; ASD I — primum atrial septal defect; BAV — bicuspid aortic valve; BWG — Bland-White'a-Garland syndrome; CCA — congenital coronary anomalies; CAVC — common atrio-ventricular canal; CCTGA — congenitally corrected transposition of the great arteries; CoAo — coarctation of aorta; DORV — double outlet right ventricle; DTGA — transposition of great arteries; Ebstein — Ebstein anomaly; Eisenmenger — Eisenmenger syndrome; IPD — idiopathic pulmonary dilatation; Marfan — Marfan syndrome; MI — mitral insufficiency; PA — pulmonary atresia; PDA — persistent ductus arteriosus; PPVC — partial pulmonary venous connection; PS — pulmonary stenosis; SAS — subvalvular aortic stenosis; SV — single ventricle; ToF — tetralogy of Fallot; VC — valve conduits; VSD — ventricular septal defect; Williams — Williams syndrome

Table 2. Mortality rates in patients with simple congenital heart disease (CHD).
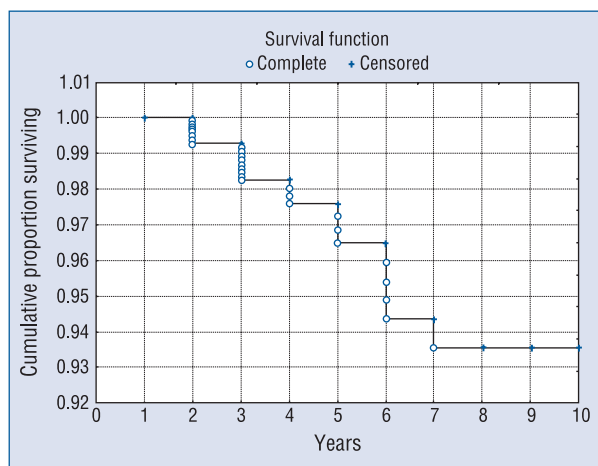
CHD type	Overall	ASD*	VSD*	PDA*	BAV	PS	PPVC	Marfan	IPD	MI	Williams
No. of patients	886	278	277	120	107	70	10	9	8	6	1
Deaths (%)	1 (0.1%)	0	0	0	1 (0.93%)	0	0	0	0	0	0

*patients with normal pulmonary artery pressure; abbreviations — see Table 1

Table 3. Mortality rates in patients with complex congenital heart disease (CHD).

CHD type	No. of patients	Deaths (%)
CoAo	106	0
ToF	101	2 (1.9%)
ASD I	38	0
CAVC	32	0
Eisenmenger	27	14 (51.8%)
SAS	24	0
SV	23	7 (30.4%)
Ebstein	20	1 (5%)
DTGA	19	1 (5.8%)
VC	9	1 (11.1%)
CCTGA	8	2 (25.0%)
DORV	5	1 (20.0%)
PA	3	0
CCA	2	0
BWG	1	0
Overall	418	28 (6.6%)

Abbreviations — see Table 1

Figure 1. Adult patients with coronary heart disease: Kaplan-Meier survival curve based on ten-year follow-up.

cyanosis (heart rate 38.1) and complex lesion (heart rate 6.4) represented a relative risk factor. Age, gender and cardiac surgery in the past were not found to predict mortality risk in long-term follow-up (Table 4).

Discussion

During the follow-up (mean 3.5 years) 2.2% of our patients died. The annual mortality of 1.4% reported from Toronto [7] is thus significantly higher than observed in our series. On the other hand, in a group of 3,589 patients followed for 25 years by Silka et al. [2] only 115 deaths, i.e. slightly over 3%, were observed. Analysis of mortality and causes of deaths in adult patients with CHD represent a major challenge because a substantial number of deaths occur outside the hospital [5, 9–11]. However, high clinical relevance of the problem prompts many authors to search for predictors of mortality in such patients. Cyanosis and age were found to predict the risk of death in patients who survived surgical repair of CHD [12]. Oechslin et al. [13] showed that mortality in such patients was increased by post-operative complications and severe heart failure. In adults with CHD, incidence of sudden death was demonstrated to be higher in subjects presenting with cyanosis and in survivors of procedures involving systemic ventricle outflow tract manipulation [2].

As noted above, we had to exclude heart failure from multivariate survival model. However, it is obvious from our series that in patients who are not functionally compromised, clinical outcome is favourable compared to those with heart failure. Most other authors report similar findings [2, 4, 10, 11, 14, 15]. Thus the ominous prognostic value of heart failure in adults with CHD seems indisputable.

Nollert et al. [11] demonstrated heart failure to be a negative predictor of survival in patients with tetralogy of Fallot (ToF); Gatzoulis et al. [16] and

Table 4. Predictors of mortality in adult patients with congenital heart disease: results of univariate and multivariate survival analysis.

	Univariate analysis	Multivariate analysis		
		p	Hazard ratio	95% confidence interval
Cyanosis	0.00001	0.00001	38.09	9.06–160.1
NYHA > I	0.00001	–	–	–
Lesion complexity	0.00001	0.34	6.42	0.69–59.43
Age (ten-year intervals)	–	0.62	1.22	0.92–1.62
Cardiac surgery in the past	0.00001	0.75	1.00	0.39–2.57
Male gender	0.32	0.78	0.76	0.30–1.41

van den Bosch et al. [17] demonstrated heart failure to be a negative predictor of survival in patients with single ventricle heart physiology. Heart failure has been shown to be the leading cause of death in patients with transposition of the great arteries (DTGA) who survived Mustard/Senning operations [18]. However, Ross-Heselink et al. [19] provided evidence that the only negative predictor of survival in such patients was an operation performed before 1970. In patients presenting with Ebstein anomaly, one cause of death was found to be heart failure resulting from dysfunction of the left ventricle due to extensive fibrosis and inappropriate interaction between left and right ventricle [20].

In our series, 28 deaths (96% of all deaths) occurred in cyanotic patients. Not surprisingly, cyanosis was found to be the independent predictor of mortality, a finding consistent with other reports. In our cohort, the highest mortality (nine deaths) was observed among patients with atrial septal defect (ASD) presenting with pulmonary hypertension. High mortality is a well recognized feature of patients with Eisenmenger syndrome [4, 10, 11, 14]. Using a multivariate model, Cantor et al. [9] demonstrated arterial blood oxygenation lower than 80% to be one of the predictors of mortality in adults with ASD.

Seven patients with ventricular septal defect (VSD) and patent ductus arteriosus who died had pulmonary hypertension. In both these lesions pulmonary hypertension is known to develop earlier in the course of the disease than in the case of ASD [15]. Thus, affected subjects die younger [10].

A similar mechanism leading to cyanosis is one of the main causes of death in patients with congenitally corrected transposition of the great arteries with significant interventricular shunting (two deaths in our series) [3].

The most frequent CHD presenting with cyanosis in adults is ToF. In our cohort there were two deaths of patients with uncorrected defects of this type. One of them was 48 years old, which is quite exceptional bearing in mind that according to published data only 5% of patients without surgical correction reach the age of 40 [21]. The other female patient died soon after attempted complete surgical repair of ToF. Thromboembolic complications typical of secondary polycytemia often lead to fatal post-operative events in patients with such lesions operated on late in the course of the disease [11, 14, 15].

Seven deaths occurred in patients with single ventricle heart physiology. The prognosis for subjects affected with this type of CHD is poor; without a Fontana operation ten-year survival is only about 46%. It is highest in patients with common chamber of left ventricle morphology [22].

In our cohort. only one female patient had undergone a Fontana operation in the past. Although most survivors of such operations present with normal blood oxygenation, some patients develop cyanosis as a consequence of residua and sequels of the lesion, most frequently pulmonary shunts [7]. According to Gatzoulis et al. [16], as many as 38% of patients after Fontana procedure require phlebotomy. Another two patients in our group underwent an unsuccessful Fontana operation; one had VSD dilated, the other was left with pulmonary artery binding intact, and so the exact mechanism of cyanosis could not be elucidated. Finally, two other patients had only Blalock-Taussig systemic-pulmonary shunts constructed, something known to produce only a very limited increase in pulmonary blood supply (205) [23]. No other patients had undergone surgical repair in childhood. Ammash et al. [24] reported the results of long-term follow-up of 13 patients with uncorrected common ventricle heart physiology at the mean age of 42 years. Over the course of ten years, only one death was recorded.

Long-term follow-up of adults with Ebstein anomaly indicates a rather favourable prognosis in this type of CHD [25]. Only one death in a patient with significantly reduced blood oxygenation was recorded. Cyanosis was found to be one of the main causes of mortality in such patients [20].

There is no consensus among experts as to the main causes of mortality in adult patients with CHD. According to Daliento et al. [10], 29% of deaths result from bleeding complications, 23% from heart failure, 3% from cerebral abscesses, 5% are related to pregnancy, 2% are associated with post-operative complications and in 7% the cause is undetermined. Sudden death is believed to be equally frequently caused by acute pulmonary thrombosis and arrhythmic events. According to Niwa et al. [14], sudden death occurred in as many as 68% of cyanotic patients who were relatively stable prior to sudden events (precipitated by strenuous exercise, dehydration). Cantor et al. [9] reported heart failure to be the cause of death in 48% of patients, sudden cardiac death accounted for 20% fatalities, infective endocarditis for 7%, major pulmonary bleeding for 7% and in 8% of cases the cause is undetermined. It may suggest that investigators reporting their findings also failed to gather complete data (out-of--hospital deaths) emphasising the difficulties of drawing general conclusions with respect to the still small population of adults with CHD. Methodology

issues are also raised [2], and so continuous follow-up of such patients and gathering data in co-operation with other investigators seems warranted.

Long-term follow-up data suggests that the median life span of patients with CHD is significantly shorter than in the general population [10, 11, 18]. Our findings confirm better survival in patients with simple CHD. Complexity of the lesion was also found to increase relative risk of death. A higher incidence of clinical complications and the potential for increased mortality led Somerville [8] to distinguish simple from complex lesions, a classification also used in our study of adult patients.

Better survival was observed in all subjects in our group who had undergone past surgical correction of CHD. This obvious finding is confirmed in many other reports. In patients with Marfan syndrome receiving no surgical treatment, average life span does not exceed 40 years, whereas after an operation those patients ususally reach the age of 60 [26].

According to published data, in patients after successful surgery for the coarctation of the aorta, 84% survive at least 20 years and 72% for 30 years [6]. Such patients were quite numerous in our cohort. Of survivors of ToF repair, more than 85% are alive 30 years after the operation [21].

Average survival in subjects operated on for common atrio-ventricular canal depends on the extent of the procedure; in those without VSD closure, 82% reached the age of 32, with VSD repair only 70% lived that long [27].

If patients with DTGA are not operated on early in life, very few reach the age of 20 [3, 7]. The post-Mustard/Senning operation 20-year survival rate has been reported at 76–80% [18].

The Fontana procedure is associated with 77––96% five-year, 60–81% ten-year and 55–76% 15-year survival [16, 22, 24]. However, in this group of patients, operation is not an independent prognostic factor of survival. There are patients with simple CHD who haven't been referred for surgery who are haemodynamically stable and present with normal heart function and blood oxygenation, representing a benign form of the disease. At the same time, there are patients with complex lesions corrected several years earlier, who are in poor condition, presenting with heart failure and cyanosis. These two extreme clinical conditions predict outcomes in the future irrespective of whether they have been operated on.

There is no doubt that, generally speaking, cardiac surgery improves survival for patients with CHD. But in the heterogeneous population of such patients, it is not the fact of being operated on, but other clinical variables reflecting patient status at baseline, that are good predictors of survival.

Our findings do not confirm age as a prognostic factor of survival, as postulated in some reports [28]. It used to be said that ageing is never good for our health. This is true for those born without congenital disease. Individuals making up our cohort were, however, affected from the very first moments of their lives. Thus the natural or modified history of the lesion has a much stronger impact on survival than age per se.

In our cohort, gender was not found to be a risk factor of death. Although gender has often been included in models searching for potential predictors of mortality, in most reports it has turned out to be neutral [5, 9, 11]. Only a few studies have suggested a significant role for gender in this aspect. The unfavourable effect of male gender on survival was reported in patients with Ebstein anomaly [29], also in those who required permanent pacing [30]. Due to the increased risk of thromboembolic complications associated with the use of hormone contaceptives, women with Eisenmenger syndrome are believed to be at higher risk of death than men [5].

Conclusions

Heart failure and cyanosis are negative predictors of survival in adult patients with CHD. Complexity of the lesion increases the relative risk of mortality. Cardiac surgery in the past is associated with better survival, but, like age and gender, is not a significant prognostic factor.

Acknowledgements

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