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Original Article

A population-based study of extra-cardiac anomalies in children with congenital cardiac malformations

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Abstract We describe the prevalence of extra-cardiac anomalies in children with congenital cardiac malformations, and their impact on survival, compared to the outcome in children with the congenital cardiac lesions as the only recognised anomaly.

Our population comprises the 3527 children born with congenital cardiac anomalies between 1990 and 1999, and registered at the largest tertiary centre for Paediatric Cardiology in Norway. Extra-cardiac anomalies were found in one-fifth of the population, with Down's syndrome accounting for nearly one-third. Survival improved for children born between 1995 and 1999 compared with those born in the period from 1990 to 1994 for all groups, except for children with additional extra-cardiac anomalies in the absence of Down's syndrome. The results were the same for children undergoing surgical treatment of their cardiac malformation. The survival in children with Down's syndrome improved in comparable fashion to those without extra-cardiac anomalies. Children with extra-cardiac anomalies in the absence of Down's syndrome represent a heterogeneous group, with varying patterns of survival. Survival did not improve in these latter patients during the period of our study.

Keywords: Survival; mortality; cardiac surgery; Down's syndrome; epidemiology

THE IMPACT OF NON-CARDIAC ANOMALIES ON survival for those patients with congenital cardiac disease is incompletely defined. Outcome is often based on data from selected groups,[1] and few studies have been based on data derived by studying defined populations. With this is mind, we have investigated the prevalence of extra-cardiac anomalies, and their impact on survival, in children with such additional extra-cardiac anomalies when compared to those having a cardiac malformation as the only recognised congenital anomaly. Because Down's syndrome is such a common extra-cardiac anomaly in the setting of children with congenitally malformed hearts, we have investigated this group of patients separately.

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Material and methods

Population studied

We obtained our data from the register of congenital cardiac malformations collated at the Department of Paediatric Cardiology at Rikshospitalet University Hospital, Oslo, Norway. The population studied includes all 3527 live-born children registered with congenital cardiac malformations from January 1st 1990 to December 31st 1999. Of these, 1415 underwent cardiac surgery during the same period of time. Cardiac surgery during this period was performed in two Norwegian centres. The centre in Oslo serves 75% of the population, corresponding to 450,000 births during the period of study. Patients who died

prior to referral were not entered into the register. The register was designed to serve essential functions in the Department of Paediatric Cardiology, with data from every examination, procedure, and all contacts with patients, entered into the database on a daily basis. To ensure the quality of the register, only senior paediatric cardiologists enter data. Patients are identified according to the unique personal identification number assigned by the National Population Registry, which also provides data on date of death and date of emigration. The cause of death was not registered in the database. Follow-up data in terms of survival was 99% complete.

Variables

Cardiac defects. We classified the cardiac defects on the basis of results from echocardiograph examinations, cardiac catheterisations, and in some instances, findings during surgery or autopsy. Children coded as having acquired heart disease, anomalies of rate or rhythm, cardiomyopathies, and positional anomalies were excluded from the study if they were not also coded as exhibiting structural congenital cardiac malformations. The conditions were assigned to groups according to the system of classification formulated by Van Mierop,[2,3] and the 10th revision of the International Classification.

We registered all patients with structural congenital cardiac defects, but also assigned to subgroups those with, first, a functionally univentricular arrangement. In this subgroup we included all patients registered with hypoplastia of the left heart, those with functionally univentricular physiology, and those with tricuspid atresia in whom Fontan palliation was considered the ultimate surgical option. As a second group, we registered those with severe cardiac defects, including patients with atrioventricular septal defects, discordant ventriculo-arterial connections (transposition), double outlet right ventricle, tetralogy of Fallot, totally anomalous pulmonary venous connection, pulmonary atresia with intact ventricular septum, interruption of the aortic arch, common arterial trunk and Ebstein's malformation. Excluding those with the functionally univentricular arrangement, and those with the severe defects listed above, established a third subgroup of those with less severe anomalies.

In terms of extra-cardiac anomalies, we first registered all those with significant extra-cardiac congenital malformations and syndromes. Down's syndrome was registered only if the patient was verified as having trisomy of chromosome 21. Minor anomalies, such as syndactyly of the fingers or toes, isolated vascular skin anomalies, congenital pigmented naevuses, and congenital dislocation of the hip, are examples of anomalies that we did not deem to be significant. The registered children were assigned into 3 groups. The first group was comprised of all those children in whom extra-cardiac anomalies were not present. The second group was made up of those with a congenital cardiac malformation in the setting of verified Down's syndrome, albeit that Down's syndrome was the only extra-cardiac anomaly. The third group included all those with an extra-cardiac anomaly other than Down's syndrome. In this group, we also included those children with Down's syndrome, but also with an additional extra-cardiac anomaly.

Period of survival

In those children undergoing surgical procedures, the time of survival was defined as the period from the initial cardiac surgical procedure to the date of death. When analysing all patients, we used the period of survival from birth to death. The data on death or emigration were complete for the population studied until September 1st 2002. For those children not registered as dead, we censored the data for survival at this date, or at the date of emigration.

Periods for analysis of surgical procedures

When analysing the results of surgical intervention, we divided our cohort in two groups, those born and initially undergoing attempted surgical treatment in the period from 1990 until 1994, and those born and having their initial surgical procedure from 1995 until 1999. The 173 patients born between 1990 and 1994, but having their first surgical procedure between 1995 and 1999, were excluded from the analysis of surviving surgical patients to equate for age at first cardiac surgery. We also excluded 19 patients who had their surgical procedure elsewhere.

Ethical considerations

The study was approved by the Regional Committee for Medical Research Ethics, South Norway, the Data inspectorate, and the Norwegian Directorate of Health and Social Services.

Statistical analyses

Prevalence was computed with associated 95% confidence intervals. Data concerning survival data was presented as Kaplan-Meier curves. Comparison of survival was performed with log-rank tests, considering p-values of less than 5% as statistically significant.

Results

Approximately one-fifth of all the children born with congenital cardiac anomalies also had additional

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Table 1. Children with congenital heart defects. Distribution of extra-cardiac anomalies and surgical treatment.

	Born 90–94		Born 95–99	
Cardiac defects	All n/(%)	Operated n/(%)	All n/(%)	Operated n/(%)
All cardiac defects	1742	573	1784	668
Extra-cardiac anomalies not present	(80.2)	(75.9)	(79.3)	(76.3)
Congenital heart defect and Down's syndrome	(7.2)	(12.0)	(8.0)	(11.8)
Extra-cardiac anomaly present other than Down's syndrome	(12.6)	(12.0)	(12.7)	(11.8)
Functionally univentricular arrangement	111	42	124	72
Extra-cardiac anomalies not present	(88.3)	(85.7)	(89.5)	(90.3)
Congenital heart defect and Down's syndrome	(0)	(0)	(3.2)	(2.8)
Extra-cardiac anomaly present other than Down's syndrome	(11.7)	(14.3)	(7.3)	(6.9)
Severe cardiac defects	293	204	314	256
Extra-cardiac anomalies not present	(66.2)	(69.1)	(66.6)	(67.6)
Congenital heart defect and Down's syndrome	(20.5)	(19.1)	(18.2)	(19.1)
Extra-cardiac anomaly present other than Down's syndrome	(13.3)	(11.8)	(15.3)	(13.3)
Less severe cardiac defects	1339	327	1346	340
Extra-cardiac anomalies not present	(82.5)	(69.1)	(81.3)	(80.0)
Congenital heart defect and Down's syndrome	(4.9)	(19.1)	(6.1)	(8.2)
Extra-cardiac anomaly present other than Down's syndrome	(12.5)	(11.8)	(12.6)	(11.8)

extra-cardiac anomalies (Table 1). Down's syndrome accounted for nearly one-third of these conditions. Of the 286 children registered with Down's syndrome, 17 (6%) had additional extra-cardiac anomalies. Down's syndrome was prevalent in the group deemed to have severe cardiac defects. Only 12% of the children undergoing surgery for palliation of a functionally univentricular arrangement had additional non-cardiac anomalies. When comparing the data for the periods from 1990 to 1994, and 1995 to 1999, we found no major changes in the prevalence of extra-cardiac anomalies in the total population, nor in the children undergoing cardiac surgery. A greater proportion of children with either severe cardiac defects or a functionally univentricular arrangement, however, underwent surgical treatment during the second period, albeit that the proportion of children with additional extra-cardiac anomalies did not change.

In Table 2, we have listed the various extra-cardiac anomalies other than Down's syndrome identified in the two cohorts. The most common anomalies were intestinal malformations and oesophageal atresia, and these increased from 47 to 72 patients. The prevalence was unchanged in the second largest group, namely malformation of the urinary tract. The numbers were small for all other diagnostic groups, making it difficult for us to detect any trends. Only 1/3 of the children with extra-cardiac anomalies other than Down's syndrome were submitted to surgical correction of their congenital cardiac malformations.

In Table 3, we have included data on the children with extra-cardiac anomalies other than Down's syndrome who underwent attempted surgical correction of their congenital cardiac defects but subsequently died. Death within 30 days of the initial surgical procedure accounted for two-fifths of all mortality. It should be noted that, of the 29 children who died, five had complex cardiac conditions and asplenia.

The Kaplan-Meier curves shown in Figure 1 present survival in both cohorts for all our included children, and for those who were submitted to cardiac surgery. The total population studied is divided into the three main groups of those without any extra-cardiac anomaly, those with a congenital cardiac lesion in the setting of Down's syndrome, and those with an extra-cardiac anomaly other than Down's syndrome.

As shown by the Figure, survival improved significantly in those born from 1995 through 1999 when the congenital cardiac anomaly was the only malformation, as it did for those with a congenital cardiac defect in the setting of Down's syndrome. In contrast, survival did not improve in the children with a congenital cardiac lesion associated with an extra-cardiac anomaly other than Down's syndrome.

Of the 17 children with a congenital cardiac malformation in the setting of Down's syndrome, but with an additional extra-cardiac anomalies, 7 underwent attempted surgical treatment and survived. Of 10 similar children not submitted to cardiac surgery, two born in the period from 1990 to 1994 died.

The representiveness of the population studied can be calculated from the birth rate in the geographic area served by the Rikshospitalet during the same period. The total number of births were 450,000, giving a prevalence of congenital cardiac anomalies of 7.8 per 1000 births, with 95% confidence intervals from 7.6 to 8.1. The prevalence of the 12

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Table 2. All children with congenital heart defects and non-Down extra-cardiac anomalies.

		Born 90–94			Born 95–99		
Major variables	**Subgroups of major variables**	**All n**	**Operated n**	**(%)**	**All n**	**Operated n**	**(%)**
Cardiac defects		219	69	(31.5% of All)	227	79	(34.8% of All)
	Functionally univentricular arrangement	13	6	(8.7)	9	5	(6.3)
	Severe cardiac defects	39	24	(34.8)	48	34	(43.0)
	TOF	11	7		10	7	
	AVSD	10	4		9	5	
	Interrupted Ao arch	7	5		6	4	
	TGA	4	3		6	4	
	DORV	3	2		7	5	
	TAPVC	2	1		4	4	
	Com. arterial trunk	2	2		2	2	
	PA with IVS	0	0		4	3	
	Less severe cardiac defects	168	39	(56.5)	170	40	(50.1)
Non-Down extra-cardiac anomalies							
	Intestinal malformation	27	5		42	15	
	Oesophagus atresia	20	7		30	7	
	Urinary tract malformation	21	8		24	8	
	Facial cleft	19	5		15	8	
	Limb malformation	17	9		17	9	
	Cerebral malformation	7	5		9	2	
	Diaphragmatic hernia	5	0		15	1	
	Situs inversus	5	4		7	5	
	Asplenia/polysplenia	4	2		9	7	
	Unclassified/other syndromes	33	13		28	7	
	Williams syndrome	12	2		9	1	
	Noonan syndrome	11	2		6	3	
	Di George's syndrome	7	5		9	7	
	Turner syndrome	7	4		1	1	
	Marfan syndrome	6	0		2	0	
	CHARGE syndrome	4	2		2	2	
	Alagilles syndrome	4	0		1	0	
	Holt Oram syndrome	3	1		0	0	
	VACTERL syndrome	2	0		3	3	
	Tuberous sclerosis	2	0		0	0	
	Trisomy 18	2	0		5	1	
	Trisomy 13	0	0		3	2	
	Inborn errors of metabolism	4	0		2	1	

Abbreviations: TOF: tetralogy of Fallot; AVSD: atrioventricular septal defect; interrupted Ao arch: interrupted aortic arch; TGA: transposition; DORV: double outlet right ventricle; TAPVC: totally anomalous pulmonary venous connection; Com. arterial trunk: common arterial trunk; PA with IVS: pulmonary atresia with intact ventricular septum

most severe cardiac defects, specifically those registered as having a functionally univentricular arrangement or the defects we deemed to be severe, was 1.87 per 1000 births, with 95% confidence intervals from 1.7 to 2.0.

Discussion

In agreement with previous studies,[4–9] we discovered extra-cardiac anomalies in one-fifth of all our children registered with congenital cardiac malformations. Down's syndrome was the most frequent anomaly; present in almost one-tenth of all children with congenital cardiac anomalies. Gastrointestinal malformations were the second most frequent extra-cardiac anomaly, discovered in 3.4% of the population with congenital cardiac disease. We found no specific change in diagnostic or referral policies regarding gastrointestinal disease that could explain the increased prevalence noted in the cohort of patients born from 1995 to 1999. In the later years of the study, identification of deletions of chromosome 22 improved, and chromosomal analysis is now offered more frequently to children with cardiac defects involving the ventricular outflow tract. In our study, however, the diagnosis was limited to children with

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Table 3. Children with additional extra-cardiac anomalies other than Down's syndrome operated for congenital heart defect, and registered as dead.

Cardiac group	Cardiac defect	Extra-cardiac anomalies	Age at initial cardiac operation (days)	Number of cardiac operations	Age at death (days)
U	LV-hypolasia, AV-defect, PAPVC, ASD sec.	Asplenia	2	3	697
U	Single RV, RVOT-obstruction, AVSD, TAPVC	Asplenia, situs inversus, duodenal atresia	315	2	895
U	LV-hypoplasia, TGA, PS, AV-defect, ASD	Asplenia	95	1	348
U	RV-hypoplasia, VSD, ASD, PAD	Oesphagus atresia	2	3	458
U	RV-hypoplasia, DORV, Coa, AVSD, TAPVC	Visceral heterotaxy	16	3	653
S	DORV, AVSD, TAPVC, ASDsec.	Asplenia, situs inversus	1	1	2
S	TGA, AVSD, TAPVC, PS, ASDsec., PAD	Situs inversus	38	1	68
S	AV-defect, single atrium, VSD, PAD	Autosomal Chromosomal anomali, blindness, deafness, limb malformations	166	2	256
S	IAA, LVOT-obstruction, VSD, PAD	Pulmonary malformation	7	1	7
S	AVSD	Noonan syndrome	75	1	259
S	AVSD, TAPVC, aortic valve atresia, PA-anomaly	Asplenia	25	1	25
S	PA-atresia, VSD, PDA	Unclassified syndrome, oesophagus atresia	28	2	30
S	TOF, ICV to coronary sinus	VACTERL syndrome	117	3	233
S	TOF, PA-hypoplasia	Cleft lip/palate	4	2	939
S	Common arterial trunk, VSD, PS	Di George's syndrome	34	1	235
S	TOF	Multiple malformations; hydrocephalus, cleft palate, intestinal atresia, urinary tract malformations	32	1	159
S	TAPVC, ventricle septum anomaly, ASD	Unclassified syndrome	23	1	27
S	TGA, LVOT-obstruction	Cerebral malformation	43	1	162
S	TAPVC, SCV to coronary sinus	Urinary tract malformation	65	1	74
S	TOF, SCV to coronary sinus, pulmonary collaterals	Rubinstein-Taby syndrome	478	1	893
S	IAA, multiple VSDs, PAD, dextrocardia	Unclassified syndrome, cleft lip/palate	30	1	46
LS	Coa, PAPVC	Oesophagus atresia	175	1	175
LS	Coa, VSD, PAD	Di George's syndrome	4	2	19
LS	VSD	VACTERL syndrome, oesophagus atresia, intestinal atresia	25	1	34
LS	Multiple VSDs	Trisomy 13	134	1	298
LS	PA-valve atresia, single PA-branch, VSD	Urinary tract malformation	0	1	1
LS	VSD, ASDsec.	Werding Hoffmann syndrome	16	1	52
LS	Coa, VSD, PAD	Apert's syndrome	13	1	343
LS	Coa, tricuspid valve hypoplasia, VSD, ASD, PAD	Oesophagus atresia	8	1	10

Abbreviations: U: functionally univentricular arrangement; S: severe cardiac defects; LS: less severe cardiac defects; LV: left ventricle; LVOT: left ventricular outflow tract; RV: right ventricle; RVOT: right ventricular outflow tract; AV: atrioventricular valve; PAPVC: partially anomalous pulmonary venous connection; TAPVC: totally anomalous pulmonary venous connection; ASD: atrial septal defect; AVSD: atrioventricular septal defect; VSD: ventricular septal defect; PAD: patent arterial duct; TGA: transposition; DORV: double outlet right ventricle; Coa: coarctation of the aortae; TOF: tetralogy of Fallot; IAA: interrupted aortic arch; PS: pulmonary valve stenosis; PA: pulmonary artery; ICV: inferior caval vein; SCV: superior caval vein

classical clinical features of Di George's syndrome.[5] We observed a particularly high prevalence of additional anomalies in the children with cardiac defects we had deemed to be severe. Children with a functional univentricular arrangement are severely compromised haemodynamically, and one might expect that anomalies would occur in several systems of organs in a large proportion of these children. Our data, however, reveal that extra-cardiac anomalies were less frequent in this group. This finding is in agreement with a previous study on risk factors for mortality after the Norwood procedure.[10] It could reflect a bias in selection, since the referring hospitals may withhold centralised hospitalisation for children with disease of multiple systems of organs, since the prognosis may seem extremely poor. Alternatively, a large fraction of this group of children may die in the immediate postnatal phase. Data

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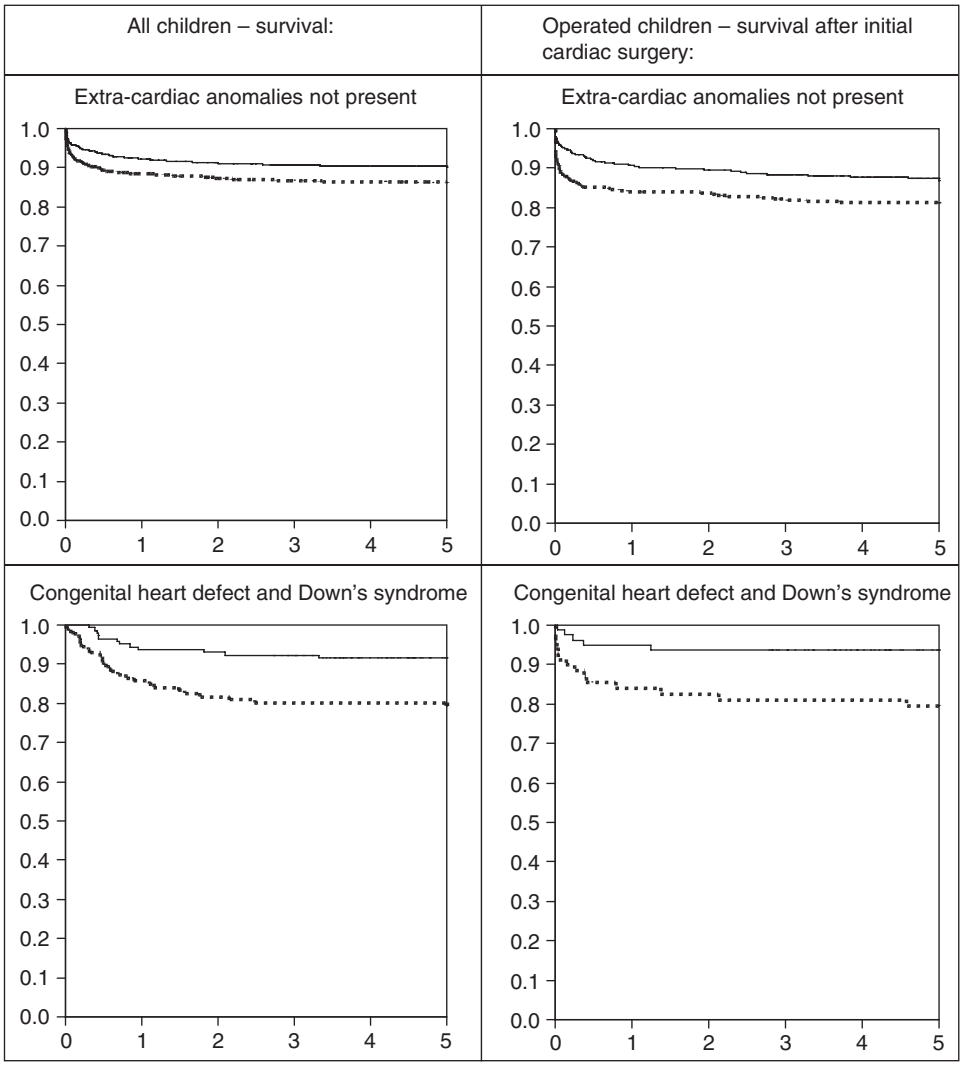

Figure 1.

Both survival curves have the y-axis set for cumulative survival. For all children (left panels), the x-axis shows years from birth. For children undergoing surgery (right panels), the x-axis shows the number of years after the initial cardiac surgery. In all curves, the solid line represents children born from 1995 to 1999, while the dotted line represents children born from 1990 to 1994. Upper panels: In all the children in whom extra-cardiac anomalies were not present, 1397 were born from 1990 to 1994, 192 died. After 5 years, 10 were censored and 1195 were left for observation. In the period from 1995 to 1999, 1414 were born, and 136 died. After 5 years, 549 were censored and 729 left for observation. Survival improved significantly for those born in the last cohort ($p < 0.001$). In all children undergoing cardiac surgery in whom extra-cardiac anomalies were not present, 435 were born and underwent their surgical procedure from 1990 through 1994, and 82 died. After 5 years, 3 were censored, and 351 were left for observation. Over the period from 1995 to 1999, 510 children were born and underwent a cardiac surgical procedure, and 64 died. After 5 years, 265 were censored, leaving 181 for observation. Survival improved significantly for those born and undergoing surgery from 1995 through 1999 ($p = 0.014$). Middle panels: In all 126 children born with a congenital heart defect and Down's syndrome over the period 1990 through 1994, 25 died. After 5 years, 1 was censored, leaving 100 for observation. Over the period 1995 to 1999, 143 children were born with this combination, and 12 died. After 5 years, 64 were censored, leaving 67 for observation. Survival improved significantly for those born in the last cohort ($p = 0.004$). In the 69 children born with a congenital heart defect and Down's syndrome and undergoing surgery between 1990 and 1994, 14 died. After 5 years, 1 was censored and 54 were left for observation. In the period from 1995 to 1999, 79 children were born and operated, and 5 died. After 5 years, 43 were censored, leaving 31 for observation. Survival improved significantly for those born and undergoing surgery from 1995 through 1999 ($p = 0.014$). Lower panels: In all the 219 children born between 1990 and 1994 with an extra-cardiac anomaly other than Down's syndrome, 50 died. After 5 years, 169 were left for observation. Over the period from 1995 to 1999, 227 children were born, and 55 died. After 5 years, 91 were censored, leaving 81 left for observation. There was no significant difference in survival between the cohorts. In the 69 children born with an extra-cardiac anomaly other than Down's syndrome, and undergoing surgery, 12 died, leaving 57 for observation. Over the period 1995 to 1999, 79 children had surgical procedures, and 17 died. After 5 years, 35 were censored, leaving 27 for observation. There was no significant difference in survival between the cohorts.

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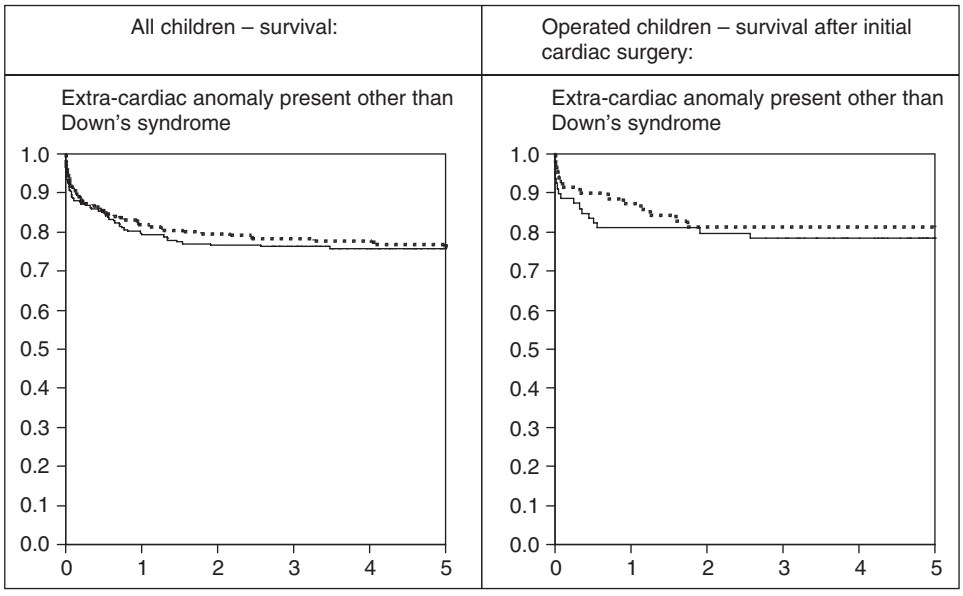

Figure 1. (*Continued*)

from one Norwegian county supports this latter explanation (Meberg A, personal communication). These children may be so compromised in terms of their reserves that transportation and stabilisation are difficult. Accordingly, one study found that many children that died in infancy had unrecognised congenital cardiac lesions, along with an increased prevalence of non-cardiac anomalies.[11]

Another explanation could be that a proportion of such children is aborted spontaneously, or that recognition during screening procedures leads to termination of pregnancies.[12,13] During the period of our study, the routine ultrasonic screening programme in Norway consisted of only one investigation, performed at 17 to 18 weeks of gestation. Most cardiac defects are detected at a later stage in pregnancy,[13] and a recent Norwegian study showed that the number of pregnancies terminated on the basis of prenatally detected cardiac defects is negligible.[14] Our present data, furthermore, demonstrate that there was no active selection towards not offering surgery to children with a functionally univentricular heart associated with additional anomalies. It is noteworthy that Down's syndrome seems to be less prevalent among the children with a functionally univentricular arrangement than in the other subgroups of children with congenital cardiac malformations.

Our study has confirmed the complexity of combined cardiac and extra-cardiac anomalies. For this reason, we did not attempt creating sub-groups based on combinations of cardiac and extra-cardiac anomalies. Previous studies have focused on the combination of asplenia and congenital cardiac malformations.[15–17] Our data suggest that such children, with isomerism of the right atrial appendages, are at particularly high risk.

Less than half of the children with congenital cardiac anomalies referred to our centre were offered surgical intervention. The selection of children for surgical treatment will certainly influence not only the surgical outcome, but also the overall survival for all children referred. Our data demonstrate that death occurring more than 30 days after the initial cardiac surgical procedure is significant. This fact is supported by a recent publication from the United Kingdom.[18]

Children born from 1995 through 1999 with their congenital cardiac lesion as the only recognised malformation showed a significantly improved survival compared with their peers born from 1990 to 1994. This improvement was evident both for children selected for surgery, and for all children included. Children with Down's syndrome as the only additional extra-cardiac anomaly had the same improved survival. Even when the few children with Down's syndrome and additional non-Down extra-cardiac anomalies were included, the results were the same. Several studies have focused on Down's syndrome as a risk factor for poor outcome after repair of congenital cardiac malformations.[1,19] Our study revealed that outcome for children with Down's syndrome born and undergoing surgery between 1995 and 1999 was not unfavourable. Early mortality after initial surgery has clearly declined, reflecting the same change in the pattern of mortality seen among the children born with a cardiac defect as their only congenital malformation.

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In children with extra-cardiac anomalies other than Down's syndrome, however, there was no significant difference in survival between the children born and undergoing surgery in the two different periods of time. In both cohorts, nonetheless, only one third of those born were submitted to a surgical cardiac procedure, and a possible difference in selection for surgery must be considered. As can be calculated from our tables, there was a trend towards greater severity of the cardiac defects in the children undergoing surgery from 1995 to 1999. When comparing survival for all children included in this group, the results were the same. There was no significant change in survival between the two cohorts.

Several authors have identified non-cardiac anomalies to be a risk factor for congenital cardiac surgery.[10,20,21] Our study has shown the data for survival over 5 years. For some children born between 1995 and 1999, the period of observation was limited to 30 months. The impact of various syndromes, genetic abnormalities, and extra-cardiac structural anomalies may be stronger when viewed over a longer perspective. It is important to provide data on how the various extra-cardiac anomalies influence therapeutic strategies for children born with congenital cardiac anomalies. International co-operation would be beneficial in providing sufficient long-term follow-up for the range of conditions involved. The complexity of medical and ethical challenges related to the handling of these children has been discussed recently.[22,23]

Survival has improved for most children with congenital cardiac malformations over recent years, but not for those with additional extra-cardiac anomalies other than Down's syndrome. Such children made up one-eighth of all children undergoing surgery for congenital cardiac anomalies in the population we studied. If survival is also to be improved for those in this group, we will need increased knowledge of the interactions between the various extra-cardiac anomalies and the cardiac malformations.

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