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Congenital Heart Defects and Outcome in a Large Cohort of Down Syndrome: A Single-Center Experience from Turkey

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What is already known on this topic?

- *Congenital heart defects are the most common birth defects in individuals with Down syndrome and result in significant morbidity and mortality.*

What this study adds on this topic?

- *We demonstrated that 52.1% of the patients with Down syndrome had congenital heart defect (CHD) and ventricular septal defect was the most common type. Mortality increased significantly in patients with moderate to severe CHD when compared to patients with mild CHD or without CHD.*

ABSTRACT

Objective: Congenital heart defects occur in approximately 50% of children with Down syndrome and they contribute considerably to morbidity and mortality. The aim of this study is to investigate the prevalence, classification, and survival of congenital heart defects in Down syndrome.

Materials and Methods: About 1731 Down syndrome patients who underwent echocardiography between 1986 and 2022 were evaluated. The median follow-up duration was 8.7 years (range 1-35.8 years). Congenital heart defect was grouped as cyanotic and acyanotic.

Results: Among the 1731 patients, 52.1% had congenital heart defects. Congenital heart defect was significantly more common in females than males. The most common cardiac defect was ventricular septal defect (35%), followed by atrial septal defect (31.8%), atrioventricular septal defect (23.4%), tetralogy of Fallot (5%), and patent ductus arteriosus (3.6%). In the follow-up, 43.2% of atrial septal defect, 17.8% of ventricular septal defect, and a total of 20% of congenital heart defects were closed spontaneously. About 34.4% of congenital heart defect was corrected by cardiac surgery/intervention. Five-year survival rate was 97.4% in patients without congenital heart defects, whereas it was 95.6% in mild congenital heart defects and 86.1% in moderate to severe congenital heart defects. There was no relationship between consanguinity, parental age, maternal disease, folic acid supplementation before/during pregnancy, gestational age, birth weight, and congenital heart defects. Neuromotor development was similar in patients with and without congenital heart defects.

Conclusion: We demonstrated that almost half of the patients had congenital heart defects; ventricular septal defect was the most common congenital heart defect type. This study is valuable in terms of the largest single-center study describing the classification, prognostic factors, and survival of Down syndrome patients with congenital heart defect from Turkey.

Keywords: Down syndrome, congenital heart defect, prevalence, classification, prognosis

INTRODUCTION

Down syndrome (DS) (Trisomy 21) is the most common autosomal aneuploidy with an incidence of 1/779 live births.[1] Chromosome 21 is the smallest human chromosome which constitutes 1% of the genome and encodes 225 protein-coding genes.[2] An extra copy of chromosome 21 results in characteristic facial features, variable degrees of intellectual disability, short stature, congenital heart defect (CHD), and other major malformations.[1] The clinical features of the syndrome are not only due to the chromosomal imbalance of the

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protein-coding genes on chromosome 21 but also due to the genome-wide disturbance of methylation patterns.[3]

Among the congenital anomalies, CHD contributes significantly to the morbidity and mortality of children with DS. Before the routine use of an echocardiogram in DS, the prevalence of CHD was 28%, while it reached 45%-58% by routine echocardiographic examinations.[1,4-9] The most common types of CHD in DS are atrioventricular septal defect (AVSD), ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), and tetralogy of Fallot (TOF).[10] However, the prevalence and types of CHD vary in different studies. In recent years, a decrease in severe cardiac defects has been reported. A review in 2021 reported that the frequency of shunt defects was exceeding complex cardiac defects.[11] Similarly, Bergström et al[7] reported that AVSD was more common than VSD from 1992 to 1994, and they were equally common from 2010 to 2012.

Many studies have reported that the CHD prevalence in DS girls is higher than in boys and lack of folic acid supplementation before pregnancy is related to increased risk of CHD.[12-15]

The most significant factor affecting the survival of DS is the presence of CHD. Since 1950s, the median life expectancy for a child with DS has increased from 4 years to 58 years.[16] The overall survival of DS patients at 1 and 5 years of age have been reported 96% and 86%, respectively, which was significantly lower in patients with CHD than without CHD.[17] Health co-morbidities may worsen cognitive abilities; however, it is reported that there is no relation between CHD and poor cognitive outcome.[18]

This study aimed to determine the prevalence and prognosis of CHD in DS, to investigate the common risk factors (sex, consanguinity, parental age, maternal diseases, and folic acid supplementation before/during pregnancy) in relation to the presence of CHD, and to compare neuromotor development and survival in DS patients with and without CHD in a large cohort of patients from a single tertiary center.

MATERIALS AND METHODS

In this study, 1731 DS patients who were followed up by Pediatric Genetic and Pediatric Cardiology Departments between January 1986 and December 2022 were included. Echocardiography was performed by pediatric cardiologist. Written informed consent was obtained from all patients. The study was approved by the Ethics Committee of İstanbul University-Cerrahpaşa with the approval number 626135.

The median age of admission was 4 months (range: 1 day to 25 years). Male-to-female ratio was 1.24. Consanguinity was present in 13.7% of the parents. About 1452 patients were followed up for 1-35.8 years and the median follow-up duration was 8.7 years. Trisomy 21 was confirmed by karyotype analysis in all patients. Regular trisomy was identified in 93.9%, translocation in 4%, and mosaicism in 2.1% of the patients.

The clinical data were retrieved from patient files. Age at admission, gender, consanguinity, parental age, maternal disease, and folic acid consumption before/during pregnancy, anthropometric measurements at birth and during follow-up, types of CHD, cardiac surgery/intervention history, and ages of the neuromotor milestones were recorded. Growth patterns and standard deviation scores (SDS) of anthropometric measurements were evaluated according to national DS-specific growth charts published by Tüysüz et al.[19]

Congential heart defects were grouped as cyanotic and acyanotic. Cyanotic CHD included ToF. Acyanotic CHD was classified mainly as AVSD, VSD, ASD, and PDA. The remaining acyanotic CHD were grouped as "others." The patients who had multiple anomalies were classified into one CHD group. Patent foramen ovale and spontaneously closed PDA were considered normal. Atrioventricular septal defect was classified as complete, partial, or intermediate (transitional) and VSD as perimembranous, muscular, or inlet. The severity of CHD was grouped as mild or moderate to severe. Cyanotic heart defects, AVSD, surgically closed septal defects, and hemodynamically significant PDA were classified as moderate to severe and the remaining defects as mild CHD.

The survival information was obtained from 1331 of the patients and it was noted whether the patient was alive or not in December 2022. Survival rates at 1, 5, 10, and 20 years were calculated according to the presence and severity of CHD.

Statistical analysis was performed in Statistical Package for the Social Sciences 20.0 program (IBM Corp.; Armonk, NY, USA). The descriptive statistics of the data were given as a mean and standard deviation for normally distributed variables and median and range for non-normally distributed variables. We used $\chi 2$ test to compare categorical variables between groups. Continuous variables were compared using the Mann–Whitney *U* test. Wilcoxon signed-rank test was performed for the comparison of values within groups before and after surgery. The survival was calculated by using Kaplan–Meier methods and survival curves were compared using the log-rank test. The significance was accepted as $P < .05$.

RESULTS

A total of 1731 patients underwent echocardiographic examinations, 901 (52.1%) of them had CHD. The most common cardiac defect was VSD which accounted for 35% of CHD, followed by ASD (31.8%), AVSD (23.4%), ToF (5%), and PDA (3.6%) (Table 1). About 73.4% of AVSD was complete, 15.2% was intermediate, and 11.4% was partial. Perimembranous VSD was the most common VSD type (48.2%), followed by muscular (21.3%) and inlet (7.6%) VSD (Table 2).

The cardiac defects were isolated in 67.7% of patients with AVSD, 51.4% of patients with VSD, and 85.7% of patients with ASD. In the follow-up, 43.2% of ASD, 17.8% of VSD, and a total of 20% of CHD were closed spontaneously. Among VSD types, muscular VSD had the highest spontaneous closure rate (32.8%), followed by inlet (16.7%) and perimembranous (14.4%) VSD (Table 2). When we exclude spontaneously closed ASD and VSD, the most common CHD types were as follows: VSD (35.9%), AVSD (29%), and ASD (22.6%). According to DS types (regular, translocation, or mosaic), VSD and ASD were the most common cardiac defects in all DS types (Table 3).

Cardiac surgery/intervention was performed in 34.4% of patients with CHD. The median age of surgery/intervention was 7 months (range 1-204 months). According to the CHD types, 77.8% of ToF, 61.6% of AVSD, and 39% of VSD were closed

Table 1. Distribution of Congenital Heart Defects in Down Syndrome Patients

CHD Type	n	Total	% of CHD
Cyanotic heart disease			
ToF			
Isolated	23	45	5%
+AVSD	17		
+Secundum ASD	3		
+PDA	2		
Acyanotic heart disease			
AVSD			
Complete AVSD (n = 155)		211	23.4%
Isolated	107		
+Secundum ASD	31		
+PDA	15		
+Aortic coarctation	1		
+Pulmonary stenosis	1		
Intermediate AVSD (n = 32)			
Isolated	18		
+secundum ASD	9		
+PDA	4		
+secundum ASD+PDA	1		
Partial AVSD (n = 24)			
Isolated	18		
+secundum ASD	5		
+PDA	1		
VSD			
Isolated	162	315	35%
+secundum ASD	94		
+PDA	27		
+secundum ASD+PDA	29		
+secundum ASD+aortic coarctation	1		
+secundum ASD+PDA+ Ebstein anomaly	1		
+Pulmonary stenosis	1		
Secundum ASD			
Isolated	246	287	31.8%
+PDA	36		
+Bicuspid aortic valve	4		
+MVP+MI	1		
PDA			
Isolated	30	32	3.6%
+Aortic coarctation	2		
Other			
MVP (n = 4), bicuspid aorta (n = 2), pulmonary stenosis (n = 2), right or left pulmonary artery hypoplasia (n = 2), aortic coarctation (n = 1)	11	11	1.2%
Total		**901**	**100%**

ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart defect; MI, mitral insufficiency; MVP, mitral valve prolapse; PDA, patent ductus arteriosus; ToF, tetralogy of Fallot; VSD, ventricular septal defect.

surgically (Table 2). The cardiac surgery/intervention information was obtained from the patients at their last examination; therefore, patients who had a surgery plan but lost to follow-up were not included in the operated group. Among the patients who underwent cardiac surgery/intervention, the weight and height SD were compared. The weight and height SD improved significantly 1 year after surgery (Table 4).

Table 2. The Surgical Correction or Spontaneous Closure of Cardiac Defects Within the CHD Groups

CHD Group	Surgical Correction % (n)	Spontaneous Closure % (n)
AVSD (n = 211)	61.6 (130)	–
Complete (73.4%) (n = 155)	68.4 (106)	–
Intermediate (15.2%) (n = 32)	46.9 (15)	–
Partial (11.4%) (n = 24)	37.5 (9)	–
VSD (n = 315)	39 (123)	17.8 (56)
Perimembranous (48.2%) (n = 152)	43.4 (66)	14.4% (22)
Muscular (21.3%) (n = 67)	19.4 (13)	32.8% (22)
Inlet (7.6%) (n = 24)	54.2 (13)	16.7% (4)
Unspecified (22.9%) (n = 72)	39.7 (31)	11.1% (8)
ASD Secundum (n = 287)	4.5 (13)	43.2% (124)
PDA (n = 32)	28.1 (9)	–
ToF (n = 45)	77.8 (35)	–
Other (n = 11)	–	–
All patients with CHD	**34.4% (310)**	**20.0% (180)**

ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart defect; ToF, tetralogy of Fallot; VSD, ventricular septal defect.

Comparing the patients with and without CHD, the median age at admission was significantly lower in patients with CHD (3 months vs. 5 months; $P < .001$). The female patients had a higher frequency of CHD than males ($P < .001$). Hypothyroidism was present in 47.2% of patients. It was more common in patients with CHD than without CHD (50.9% vs. 43.1%), which was statistically significant ($P = .002$). The frequency of CHD did not differ significantly from each other in regular trisomy, translocation, and mosaic DS groups. There was also no significant difference in the presence of consanguinity, parental age,

Table 3. Distribution of Congential Heart Defect Types According to Down Syndrome Groups

	Regular Trisomy % (n)	Translocation Type % (n)	Mosaic Type % (n)	Total
AVSD	23.9 (205)	17.2 (5)	7.7 (1)	211
VSD	34.9 (300)	37.9 (11)	30.8 (4)	315
ASD	31.8 (273)	34.5 (10)	30.8 (4)	287
PDA	3.4 (29)	3.5 (1)	15.4 (2)	32
ToF	4.9 (42)	6.9 (2)	7.7 (1)	45
Other	1.1 (10)	–	7.7 (1)	11
Total	52.7 (859/1627)	42 (29/69)	37.1 (13/35)	52.1

ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart defect; DS, down syndrome; PDA, patent ductus arteriosus; ToF, tetralogy of Fallot; VSD, ventricular septal defect.

Table 4. The Mean Weight and Height of the Patients Who Underwent Cardiac Surgery

	Preoperative	Postoperative	*P*
Mean weight SDS	−0.60	−0.23	**.001**
Mean height SDS	−0.12	0.23	**.001**

SDS, standard deviation score. Bold *P* values are statistically significant.

folic acid supplementation, and maternal disease. The anthropometric measurements at birth were similar in both groups. There was not any relationship between the presence of CHD and prematurity or intrauterine growth retardation (Table 5).

Neuromotor development was not significantly different between patients with and without CHD. The mean age of head control was 5.9 and 5.6 months in patients with and without CHD, respectively. Sitting without support was achieved at 12 months of age in both groups, and walking was achieved at 27 months in CHD and at 26.5 months in the other group. The patients had their first words at 25.7 and 22.9 months of age in CHD and without CHD groups, respectively.

The mortality was significantly higher in patients with CHD than in patients without CHD ($P < .001$) (Table 5) (Figure 1A).

Table 5. The Presence of Congenital Heart Defects in According to Parental and Patient-Related Factors

	CHD % (n)	No CHD % (n)	*P*
Gender			
Female (44.6%)	56.9% (439)	43.1% (333)	**<.001**
Male (55.4%)	48.3% (463)	51.7% (496)	
Karyotype analysis			
Regular (93.9%)	95.3% (859)	92.5% (768)	.044*
Translocation (4%)	3.2% (29)	4.8% (40)	
Mosaic (2.1%)	1.5% (13)	2.7% (22)	
Age at admission (months) (median and range)	3 (0-193)	5 (0-300)	**<.001**
Parental factors			
Presence of parental consanguinity[a] (13.7%)	14.4% (128)	12.9% (103)	.349
Maternal age at birth[b] (mean ± SD)	32.4 ± 6.9	32.7 ± 6.8	.371
Paternal age at birth[c] (mean ± SD)	35.9 ± 13.6	35.8 ± 6.8	.465
Folic acid before/during pregnancy[d]			
Folic acid used (62.8%)	62.5% (115)	63.6% (103)	.835
None (37.2%)	37.5% (69)	36.4% (59)	
Maternal disease during pregnancy [e](GDM, DM, HT, cardiac, or thyroid disease)			
Present (13.7%)	12.7% (81)	14.8 % (85)	.297
No (86.3%)	87.3% (557)	85.2% (491)	
Patient-related factors			
Gestational week (mean ± SD)[f]	37.8 ± 2.3	38.2 ± 13.2	.961
Prematurity[g]			
Yes (22.9%)	21.8% (175)	24% (170)	.304
No (77.1%)	78.2% (627)	76% (537)	
Intrauterine growth retardation[h]			
Yes (7.8%)	8.1% (67)	7.5% (55)	.673
No (92.2%)	91.9% (758)	92.5% (674)	
Birth weight (g) (mean ± SD)[i]	2910 ± 561	2930 ± 581	.268
Birth length (cm) (mean ± SD)[j]	49.2 ± 17	49.1 ± 17	.483
Hypothyroidism (congenital and acquired)[k]			
Yes (47.2%)	50.9% (419)	43.1% (326)	**.002**
No (52.8%)	49.1% (403)	56.9% (431)	
Neuromotor development[l]			
Head control (months) (mean ± SD)	5.9 ± 7.1	5.6 ± 0.2	.390
Sitting without support (months) (mean ± SD)	12.8 ± 7.6	12.3 ± 6.2	.854
Walking (months) (mean ± SD)	27 ± 11.5	26.5 ± 11.9	.394
First words (months) (mean ± SE)	25.7 ± 18.5	22.9 ± 16	.093
Mortality[m]			
Deceased patients	10.5% (72/689)	3.3% (21/642)	**<.001**
Cardiovascular complications	47.2% (34)	—	
In postoperative period	47.1% (16)	—	
Infectious diseases, sepsis	20.8% (15)	52.4% (11)	
Hematological malignancies	13.9% (10)	33.3% (7)	
Other or unknown	18% (13)	14.3% (3)	

CHD, congenital heart defect; DM, diabetes mellitus; GDM, gestational diabetes mellitus; HT, hypertension; SD, standard deviation. Bold P values are statistically significant.
Number of patients who had available data: [a]1686; [b]1693; [c]1603; [d]346; [e]1214; [f]1507; [g]1509; [h]1554; [i]1610; [j]1250; [k]1579; [l]1537; [m]1331.
*Bonferroni post hoc test showed karyotype groups do not differ significantly from each other at 0.05 level.

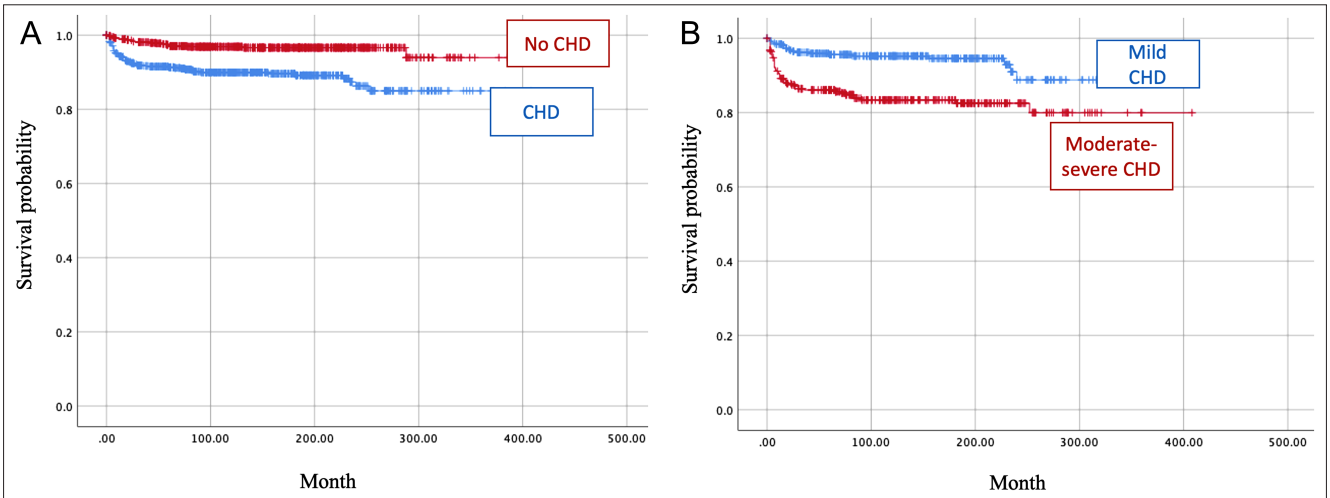

Figure 1. The survival curve of patients with (A) CHD (blue) and without CHD (red), the survival curve of patients with (B) mild CHD (blue) and moderate to severe CHD (red).

Cardiovascular complications were the leading cause of death in patients with CHD (47.2%), followed by infectious diseases (20.8%), whereas infectious diseases (52.4%) and hematological malignancies (33.3%) were the most common causes of death in patients without CHD. Among the patients who died due to cardiovascular complications, 47.1% of them died in the postoperative period (Table 5). Since hypothyroidism was more common in patients with CHD, its effect on postoperative mortality was investigated. We found that 25% of patients who died in the postoperative period had hypothyroidism, whereas it was 53.7% in patients who survived after the operation. The survival rates at 1, 5, 10, and 20 years were 94.9%, 91.4%, 90.0%, and 86.4%, respectively, in patients with CHD and 98.9%, 97.4%, 96.9%, and 96.6%, respectively, in patients without CHD (P < .001). When we compared the survival according to CHD severity, 1-, 5-, 10-, and 20-year survival was 98.4%, 95.6%, 95.2%, and 94.6% in mild CHD and 90.5%, 86.1%, 83.4%, and 82.6% in moderate to severe CHD (Figure 1B) (P < .001).

DISCUSSION

This study evaluates the frequency and distribution of CHD types and the prognosis in a single center over 36 years. Congenital heart defect was present in 52.1% of our patients. Congenital heart defect was reported in 40%-60% of DS patients in several studies.[6-9] In 3 large cohort studies which included 1079, 2588, and 1251 DS patients, CHD was found in 45%, 54%, and 58% of patients, respectively.[5,7,8]

The prevalence of CHD in DS was increased within years due to the routine echocardiographic investigation. A study conducted in 1996 reported that CHD prevalence in DS was 32% in Sweden, 23% in France, and 21% in Italy.[20] Similarly, the prevalence was found 22% in 1980s in Turkey and was increased to 39.5% by routine screening in 2008.[21-22] Two recent studies from Turkey reported that CHD prevalence was 58.8% and 65.5% in DS patients.[23,24] Congenital heart defect was reported more frequently in the latter since it included the patients who were followed up neonatal intensive care unit.

Atrioventricular septal defect was reported as the most common CHD type in DS in several studies worldwide.[7,25,26] In 1998, Freeman et al[27] reported that 44% of DS patients had CHD including AVSD in 45%, VSD in 35%, secundum ASD in 8%, PDA in 7%, and TOF in 4%. In our cohort, we found that VSD was the most common CHD type followed by ASD and AVSD (Table 1). Similar to our study, there are several studies reporting VSD as the most common cardiac anomaly.[9,28-30] In studies from Turkey, Nisli et al[22] reported AVSD, Erol et al[23] reported VSD, and Aldudak et al[24] reported AVSD, and VSD were the most common CHD types. In our cohort, during the follow-up, 43.2% of ASD and 17.8% of VSD were closed spontaneously. When we exclude spontaneously closed ASD and VSD, the most common CHD was still VSD (35.9%), while AVSD (29%) became the second most common. The increase in the detection of minor heart defects that will close spontaneously in routine echocardiography may cause an increased prevalence of these defects. Besides, due to the selective abortions of DS fetuses with severe cardiac defects, a decrease in CHD prevalence has also been reported.[7] Fetal diagnoses were not included in this study; however, the frequency of termination of pregnancies due to DS was quite low in our center, therefore this was not expected to affect the frequency of CHD types in our cohort.

Cardiac surgery/intervention was performed in 34.4% of CHD in our group. The median age of cardiac surgery was 7 months (range 1-204 months). Similarly, Zahari et al[9] reported that 35% of DS patients with CHD underwent cardiac surgery.

Congenital heart defect affects growth adversely in patients with CHD. It is reported that weight decreased significantly in patients with severe CHD in the first months of life and continued until 4 years of age.[19] The gain of growth was observed in children who underwent cardiac surgery/intervention.[31] Concomitant with this data, we found that weight and height SD were improved significantly 1 year after surgery (Table 4).

When we compared patients with CHD and without CHD, the median age at admission in patients with CHD and without CHD was 3 and 5 months, respectively (P < .001). The female predominance in CHD is well described previously.[13,14] Likewise, the females had significantly more frequent CHD than males in our group. In addition to sex, many other factors affect the development of CHD. Corona-Rivere et al[15] evaluated

the relationship between the potential risk factors including parental age, consanguinity, family history of CHD, maternal history of chronic disease, folic acid supplementation before pregnancy, gestational age, low birth weight, and CHD in DS patients. They reported that except for the lack of folic acid supplementation, none of the other risk factors were related to CHD. Similarly, we did not find any relation between consanguinity, parental age, maternal chronic disease, gestational age, low birth weight, and CHD; however, different from the study of Corona-Rivere et al[15] lack of folic acid supplementation was not related to CHD in our cohort.

Variable degree of intellectual disability is a characteristic feature of DS. Higher rates of comorbidities in DS might worsen neuromotor development. In 2020, Startin et al[18] evaluated the correlation between comorbidities and the course of neuromotor outcome. They found that the presence of CHD was not related to poor cognitive abilities; however, autism and epilepsy were correlated with worse neurological outcomes. In our cohort, we compared the neuromotor milestones between patients with and without CHD, and we did not find any difference between these groups.

Thyroid disorders are commonly seen in DS patients. In a previous study from our center, the prevalence of hypothyroidism in DS patients was reported as 25.3%.[32] The congenital hypothyroidism was reported in 6 patients (1.8%) and 5 of them had CHD. In our cohort, we detected hypothyroidism in 47.2% of the patients which was significantly common in patients with CHD (50.9% vs. 43.1%). We also found that 25% of patients who died in postoperative period had hypothyroidism, whereas it was 53.7% in patients who survived after the operation. The lower frequency of hypothyroidism in patients who died in the postoperative period suggested that there was no association between postoperative mortality and hypothyroidism. The lower frequency was attributed to the fact that some surviving patients developed hypothyroidism in later follow-ups.

The prognosis of DS is strongly associated with the presence and type of CHD. The 5 years survival in DS increased from 91.8% to 95.8% after the year 2000; however, mortality rates were 4-7 times higher in patients with severe CHD.[8] In our group, CHD was related to higher mortality rates (P <. 001). About 10.5% of patients with CHD and 3.3% of patients without CHD died during follow-up (Table 5).

Five-year survival rate was 91.4% in patients with CHD and 97.4% in patients without CHD (P < .001). It was also significantly lower in patients with moderate to severe CHD than in mild CHD (86.1% vs. 95.6%). Cardiovascular complications were the major cause of death in patients with CHD and almost half of them died due to cardiovascular complications.

In conclusion, we demonstrated the frequency and distribution of CHD types in a large cohort of Turkish patients from a single tertiary center. We found that CHD frequency was significantly higher in females than males. The most common CHD type was VSD, followed by ASD and AVSD. In the follow-up, 43.2% of ASD, 17.8% of VSD, and a total of 20% of CHD were closed spontaneously. About 34.4% of CHD were corrected by cardiac surgery/intervention. The growth of patients with CHD improved significantly after cardiac surgery/intervention. Hypothyroidism was significantly higher in patients with CHD (50.9% vs. 43.1%), however, there was no relation between hypothyroidism and postoperative mortality. Neuromotor development was similar in patients with and without CHD. We did not find any relation between parental risk factors, types of DS, low birth weight, prematurity, and CHD. Five-year survival rate was 91.4% in patients with CHD (86.1% in moderate to severe and 95.6% in mild CHD), whereas it was 97.4% in patients without CHD. This study presents a large cohort of DS followed up over a 36-year period and provides valuable information about CHD spectrum, prognosis, and mortality in DS patients.

Ethics Committee Approval: This study was approved by Ethics Committee of İstanbul University-Cerrahpaşa (Approval No: 626135, Date: 22.02.2023).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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