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Risk Factors in Cardiovascular Surgery in Down Syndrome Patients: Single-center Experience

Down Sendromlu Hastalarda Kardiyovasküler Cerrahide Risk Faktörleri: Tek Merkez Deneyimi

Sinan Yavuz[1], Umut Berk Mercan[1], Selman Kesici[1], Ahmet Aydın[2], Hayrettin Hakan Aykan[1], Mustafa Yılmaz[2], Benan Bayrakçı[1]

[1]*Hacettepe University Faculty of Medicine, Department of Pediatrics, Ankara, Türkiye*
[2]*Hacettepe University Faculty of Medicine, Department of Cardiovascular Surgery, Ankara, Türkiye*

Abstract

Introduction: The aim of this study was to determine the surgical risks in patients with Down syndrome (DS) and cardiac pathology. We aim to share our single-center experience and identify risk factors among patients with DS undergoing cardiac surgery. Patients under the age of 18 who underwent cardiac surgery at Hacettepe University between 1996 and 2019 were included.

Methods: This retrospective cohort study included all pediatric patients with DS who underwent surgery for congenital heart disease (CHD).

Results: A total of 175 patients were included in the study. Seventy-five patients (42.8%) were male and the median age of the patients was 7 months (1-86 months). The most common cardiac pathology was atrial septal defect (19.2%), followed by atrioventricular septal defect (18.7%) and ventricular septal defect (11.3%). According to the risk adjustment for congenital heart surgery classification, most patients were in category 2 (41.7%) and category 3 (42.3%). Sixty-one patients (34.9%) were diagnosed with systemic inflammatory response syndrome (SIRS) in the postoperative period. Seven patients (3.4%) needed extracorporeal membrane oxygenation. Overall mortality was 30.3%.

Conclusion: This single-center study characterized the pattern of CHD in a specific cohort of patients with DS and identified risk factors associated with cardiac surgery. Postoperative SIRS and high-risk surgical procedures were associated with an increased risk of mortality.

Keywords: Cardiac surgery, Down syndrome, risk factors

Öz

Giriş: Down sendromlu (DS) ve kardiyak patolojisi olan hastaların cerrahi risklerinin belirlenmesi amaçlanmıştır. Amacımız, tek bir merkezden deneyimlerimizi paylaşmak ve kardiyak cerrahi geçiren DS'li hastalarda risk faktörlerini belirlemektir. 1996-2019 yılları arasında Hacettepe Üniversitesi'nde kardiyak cerrahi geçiren 18 yaş altı hastalar incelenmiştir.

Yöntemler: Bu geriye dönük kohort çalışması, konjenital kalp hastalığı (KKH) cerrahisi geçiren tüm pediyatrik DS'li hastaları içermektedir.

Bulgular: Çalışmaya 175 hasta dahil edildi. Yetmiş beş hasta (%42,8) erkekti ve hastaların ortanca yaşı 7 aydı (1-86 ay). En sık görülen kardiyak patoloji atriyal septal defekt (%19,2), ardından atriyoventriküler septal defekt (%18,7) ve ventriküler septal defekt (%11,3) idi. Doğuştan kalp cerrahisi için risk ayarlaması kalp cerrahisi sınıflandırmasına göre, hastaların çoğu kategori 2 (%41,7) ve kategori 3 (%42,3) idi. Altmış bir hastaya (%34,9) ameliyat sonrası dönemde sistemik enflamatuvar yanıt sendromu (SIRS) tanısı konuldu. Yedi hastada (%3,4) ekstrakorporeal membran oksijenasyonuna ihtiyaç duyuldu. Genel mortalite oranı %30,3 idi.

Sonuç: Tek bir merkezde yürütülen bu çalışma, DS'li belirli bir hasta grubunda KKH örüntüsünü ve kalp cerrahisiyle ilişkili risk faktörlerini ortaya koydu. Ameliyat sonrası SIRS ve yüksek riskli cerrahi prosedürlerin artan mortalite riskiyle bağlantılı olduğu bulundu.

Anahtar Kelimeler: Kardiyovasküler cerrahi, Down sendromu, risk faktörleri

Address for Correspondence/Yazışma Adresi: Sinan Yavuz, MD, Hacettepe University Faculty of Medicine, Department of Pediatrics, Ankara, Türkiye
E-mail: sinan2438@hotmail.com **ORCID ID:** orcid.org/0000-0001-6159-8710
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Introduction

Down syndrome (DS) is the most common chromosomal abnormality among live-born infants, and DS is characterized by a variety of dysmorphic features, congenital malformations, and medical conditions.[1] Approximately half of individuals with DS have congenital heart disease (CHD).[2] In the largest population-based study, cardiovascular abnormalities were detected in 342 (42%) of 821 babies born with DS between 1985 and 2006 in the northeastern region of England.[3] Twenty-three percent had more than one abnormality, and the secondary lesion was most commonly an atrial septal defect (ASD) or a patent ductus arteriosus (PDA). Primary lesions were ranked by frequency as follows: endocardial cushion defect (37%), ventricular septal defect (VSD) (31%), ASD (15%), tetralogy of fallot (TOF, 5%), and PDA (4%). Given the risk of mortality and morbidity in postoperative patients, follow-up care is as critical as the surgical procedure itself. The first 24 hours are particularly high risk and require intensive monitoring. Pediatric intensive care units and pediatric cardiac intensive care units (PCICU) play an increasingly essential role in managing these critical periods.[4]

In this study, we aimed to report the experiences of patients with DS who underwent congenital heart surgery at a single-center over 23 years and determine associated risk factors.

Materials and Methods

This study was conducted in the PCICU of Hacettepe University Hospital. All pediatric patients (0-18 years) who underwent open CHD surgery between 1996 and 2019 and were admitted to PCICU were evaluated; those with DS were included in the study. Our pediatric intensive care unit comprises 16 beds and is managed by four pediatric intensivists. The PCICU has six beds and is overseen by six cardiovascular surgeons who rotate on a schedule. Approximately 350 pediatric surgical procedures are performed each year. In our unit, standardized protocols are implemented for the perioperative management of pediatric cardiac surgery patients. Each patient is visited by the intensivist both preoperatively and postoperatively. Following surgery, recommendations are provided regarding mechanical ventilation settings and medical treatments are prescribed as indicated. Patients are visited regularly throughout their intensive care stay, except in emergency situations when immediate intervention is required. Upon transfer from the intensive care unit, follow-up visits are conducted in the ward to ensure continuity of care. Patient data were obtained from the hospital archive. Demographic variables, cardiac pathology, type of surgery, pump times, complications, need for transfusion, laboratory parameters, duration of mechanical ventilation, development of systemic inflammatory response syndrome (SIRS), length of PCICU stay and hospital stay, additional disease information, and mortality were recorded. The risk adjustment for congenital heart surgery (RACHS-1) score was used to classify surgeries.[5] Ethical approval for this study was obtained from the Hacettepe University Non-Clinical Research Ethics Committee (approval no: 2019/08-27, date: 19.03.2019). All participants were informed about the study, and written consent was obtained. The study excluded patients with missing data, an uncertain diagnosis of DS, or admission without subsequent surgery.

Statistical Analysis

Descriptive statistics for continuous variables were presented as the mean and standard deviation when the assumption of normality was met, and as the median (minimum-maximum) for non-normal distributions. Moreover, categorical variables were presented with frequencies and percentages. The assumption of normality was assessed using the Kolmogorov-Smirnov test, a histogram, and a boxplot. Two independent groups were compared using an independent-samples t-test or the Mann-Whitney U test, depending on whether the assumptions were met. To assess the association between two categorical variables, Pearson's chi-square test or Fisher's exact test was used. A two-tailed p-value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using IBM SPSS Statistics software, version 23.0.

Results

One hundred and eighty-six DS patients underwent CHD surgery during the study period, of whom 175 with accessible medical data were included in the study. Seventy five patients (42.8%) were male and 100 (57.2%) were female. The median age of the patients was 7 months (range, 1-86 months). Among 175 patients, a total of 276 cardiac diagnoses were recorded. The most common cardiac pathology was ASD (19.2%), followed by endocardial cushion defect (18.7%) and VSD (11.3%) (Table 1). In patients with multiple defects, the most common defects were ASD and VSD (22.8%).

Surgical technical information was available for 175 patients. According to the RACHS-1 score, 27 patients (15.4%) were in category 1, 73 patients (41.7%) were in category 2, 74 patients (42.3%) were in category 3, and one patient (0.6%) was in category 4. Surgical procedure risk groups, mortality, and survival rates by RACHS-1 risk group are presented in Table 2.

SIRS developed in 61 patients (34.9%) during the postoperative period. Mortality was observed in 50.8% of patients with SIRS. These patients accounted for 57% of the total mortality. The relationship between the development of SIRS and mortality was considered statistically significant ($p<0.001$). One hundred and fifty eight patients required blood

transfusion during and after the operation, and 17 patients did not require transfusion. Transfusion was required in 98 of 110 survivors (89.2%) and in 46 of 48 non-survivors (96.3%). There was no statistically significant association between the need for blood transfusion and mortality (p=0.154). A total of seven patients (3.8%) required extracorporeal membrane oxygenation (ECMO) for low cardiac output syndrome; two patients were weaned from ECMO during the postoperative period.

Some patients had more than one accompanying anomaly or disease. A total of 79 additional diagnoses were identified in 70 patients, some of whom had more than one comorbidity. The most common of these was hypothyroidism (29 patients, 36.7%). When the effect of comorbidity on patient mortality was examined, surviving patients had a higher comorbidity burden. Mortality was observed in 34.9% of patients without comorbidity (106 patients), compared with 23.2% of patients with comorbidity (69 patients) (p<0.05).

After the surgical procedure, the median mechanical ventilatory length of stay (MV LOS) for all patients was 2 days. MV LOS was 2 days (min: 0, max: 60 days) in survivors and 4 days (min: 0, max: 52 days) in non-survivors (p<0.05).

The median PCICU LOS for all patients was 6 days. While the median length of stay in the intensive care unit was 6 days (min: 2 days, max: 114 days) for surviving patients, it was 8 days (min: 5 days, max: 108 days) for non-survivors (p=0.06).

Intraoperative cardiac pump times were recorded for 69 patients. Median pump time was 83 minutes (range: 1-256) in survivors and 71.5 minutes (range: 14-213) in non-survivors. There was no statistically significant relationship between intraoperative pump time and mortality (survivors vs. non-survivors; p=0.508). In total, seven patients required ECMO, and two of them could be weaned from ECMO.

Fifty-three (30.3%) of 175 patients died, and 36 (67.2%) of them were female. When we examined the RACHS-1 grouping among the patients who died, we found that patients in category 3 constituted 66% of deaths. Compared with categories 1 and 2, patients undergoing category 3 surgical procedures have a significantly higher risk of death (p<0.001). All identified risk factors are detailed in Table 3.

Table 1. The most common cardiac pathological diagnoses of patients

Cardiac pathology	n	Percent	Percent of cases
Atrial septal defect	80	19.2%	45.7%
Endocardial cushion defect	78	18.7%	44.6%
Ventricular septal defect	47	11.3%	26.9%
Tetralogy of fallot	40	9.6%	22.9%
Patent ductus arteriosus	15	3.6%	8.6%
Double outlet right ventricle	12	2.9%	6.9%
Transposition of great arteries	4	1%	2.3%

Table 2. Surgical procedure risk groups, mortality, and survival rates

		RACHS-1 categories*				
		1	2	3	4	Total (n)
Survivor	Patients	22 (18.0%)	60 (49.2%)	39 (32.0%)	1 (0.8%)	122
Non-survivor	Patients	5 (9.4%)	13 (24.5%)	35 (66%)	0 (0.0%)	53
Total	Patients	27 (15.4%)	73 (41.7%)	74 (42.3%)	1 (0.6%)	175

*: Risk adjusted classification for congenital heart surgery, RACHS-1: The risk adjustment for congenital heart surgery

Table 3. Risk factors of the patients according to preoperative and postoperative features

Risk factors	Survivor	Non-survivor	p-value
SIRS; n, (%)	33 (26.1%)	30 (56.6%)	**<0.001**
Blood transfusion; n, (%)	98 (89.2%)	46 (96.3%)	=0.154
RACHS-1 category 3,4; n, (%)	35 (66%)	40 (32.8%)	**<0.001**
Comorbidity; n, (%)	122 (70%)	53 (30%)	<0.005
MV LOS; mean ± SD (day)	4.5±8.2	8.5±11	<0.005
LOS PCICU; mean ± SD (day)	8.8±10.5	13.6±15.2	=0.06
Pump time; mean ± SD (min)	85.8±45.9	79.5±39.9	=0.508

SIRS: Systemic inflammatory response syndrome, RACHS-1: The risk adjustment for congenital heart surgery, MV LOS: Mechanical ventilatory length of stay, LOS PCICU: Length of stay pediatric cardiac intensive care unit, SD: Standard deviation

Discussion

DS patients frequently have cardiac pathologies, which are the leading cause of mortality and morbidity. In the current study, 57.1% of the patients were female; a total of 58 patients died, of whom 36 (67.9%) were female. The most common cardiac abnormality in DS patients was ASD. Some of the patients had more than one cardiac abnormality. Most surgical procedures were classified in RACHS-1 categories 2 and 3. As expected, the mortality rate was higher in high-risk procedures. The RACHS-1 cardiac surgical procedure group had the highest number of patients in category 3, and an increase in risk category caused increased mortality. Mortality was higher in patients who developed SIRS. When comorbidity was assessed, the most common comorbidity was hypothyroidism, and comorbidities were less common in patients who died. Patients who died had longer stays on MV and in intensive care. In total, 7 patients required ECMO, and two were weaned from ECMO.

CHD is observed in 40-50% of individuals with DS and is an important determinant of survival.[6] The actual rate and relative frequency of certain anomalies vary with the method of detection.[6] The most common cardiac malformation reported in DS was an endocardial cushion defect, followed by ASD, VSD, PDA, aortic coarctation, and TOF.[7] In our study, consistent with previous reports, the most common cardiac pathologies were ASD and endocardial cushion defects. All patients diagnosed with DS during the prenatal and postnatal periods should be examined for these defects.

RACHS-1 is a widely used methodology for risk stratification in pediatric and congenital cardiac surgery.[5] This risk classification enables rare surgical operations to be classified into homogeneous risk categories. Higher categories in the classification indicate that riskier surgeries are performed. In our study, surgical procedures were most frequently classified in risk categories 2 and 3. A statistically significant association was found between increasing risk group level and mortality. Mortality rates increase as the RACHS-1 risk category of operations performed in patients with DS increases.

It is known that DS patients are vulnerable to infections and SIRS, and studies on the immune system of DS have shown multiple, complex lymphoproliferative and myeloproliferative alterations.[8] When investigating why immunodeficiency is seen at such high frequency in children with DS, researchers have expressed differing opinions. Ferrari and Stagi[9] documented a normal proportion of CD4+ T-cells, whereas the percentage of suppressor-cytotoxic CD8+ lymphocytes was significantly increased. In contrast, Corsi et al.[10] showed that peripheral CD4+ T-cells were lower in children with DS, whereas mean values of cytotoxic CD8+ T-cells were close to the normal range. 34.9% of our patients experienced SIRS postoperatively. Faria et al.[11] reported a significant association between severe infections (particularly pneumonia and sepsis) and CHD. In this study, SIRS was present in 85% of DS patients with CHD. DS patients with CHD must be closely monitored for development of infection or SIRS, especially in the postoperative period. Infection control measures must be implemented, and PCICU LOS must be shortened to prevent the development of infections.

Children with DS are at an increased risk for certain health problems, including cardiovascular abnormalities, head and neck abnormalities, extremity problems, behavioral and psychiatric disorders, gastrointestinal tract anomalies, growth deficiency, obesity, ophthalmologic disorders, hearing impairment, endocrine abnormalities, hematologic disorders (e.g., acute lymphoblastic leukemia), pulmonary complications, and immunodeficiency.[12] When additional anomalies were investigated in our patients, hypothyroidism was the most common (36.7%). According to the literature, the prevalence of CHD in DS has been reported to range from 2% to 16.5%. This considerable variation may be attributed to differences in diagnostic methods and criteria, study sample sizes, and the periods during which the investigations were carried out.[13] Although additional anomalies would conventionally be considered unfavorable, we observed an inverse association between their presence and mortality in our patients. We considered mortality in our patients to be associated with the underlying CHD rather than with other comorbidities.

Previous studies have reported that long-term mechanical ventilation is a significant predictor of mortaity after cardiac surgery.[14] Prolonged MV LOS is closely associated with multi-organ failure and mortality. In the current study, we demonstrated that MV LOS was longer in non-survivors.

ECMO provides pivotal perioperative support to pediatric patients undergoing cardiac surgery.[15] Extracorporeal life support organization guidelines regarding the indication for ECMO in patients with a DS diagnosis do not specify any contraindications.[16] Only lethal chromosomal abnormalities (e.g., trisomy 13 or 18) are contraindications to ECMO. In a large cohort study conducted by Cashen et al.[17] 623 of 46.862 ECMO patients were diagnosed with DS. The prevalence of patients diagnosed with DS and undergoing ECMO was 13.5 per 1.000. There were no differences in hospitalization and mortality rates between these patients and non-DS patients. In our study, seven patients required ECMO, of whom two were weaned from ECMO. DS is not a contraindication to ECMO, and ECMO can be beneficial when applied in a timely manner for appropriate indications.

Study Limitations

A limitation of this study is that it was conducted at a single-center, and some patients' information could not be retrieved because of the extended study period.

Conclusion

This single-center study revealed the pattern of CHD in a specific group of patients with DS and the risk factors associated with cardiac surgery. It was found that postoperative SIRS and high-risk surgical procedures are linked to an increased risk of mortality.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Hacettepe University Non-Clinical Research Ethics Committee (approval no: 2019/08-27, date: 19.03.2019).

Informed Consent: All participants were informed about the study, and written consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practises: A.A., H.H.A., M.Y., Concept: S.Y., B.B., Design: S.K., B.B., Data Collection or Processing: U.B.M., Analysis or Interpretation: S.Y., Literature Search: S.Y., U.B.M., Writing: S.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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