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Neonatology

Mortality and associated risk factors in neonates with critical congenital heart disease: A retrospective single-center study

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ABSTRACT

Objective: Congenital heart diseases (CHDs) include congenital structural and functional abnormalities of the cardiovascular system and are associated with a high risk of mortality and morbidity. To evaluate early outcomes in infants with congenital heart disease (CHD), with a particular focus on critical CHD (CCHD), and to identify factors associated with mortality in patients with CCHD.

Material and Methods: Patients were grouped into five categories according to echocardiographic findings and clinical presentations: normal, non-significant, important, serious, and critical. In addition, all patients who underwent surgery for CHD were evaluated according to the RACHS-1 classification.

Results: CCHD (serious/critical) constituted 11.6% (71/608) of CHD cases. Mortality occurred in 32 of 71 neonates with CCHD (45.1%). Antenatal diagnosis (OR: 3.1), inoperability (OR: 4.6), ventilation requirement (OR: 8.1), and postoperative arrhythmia (OR: 8.4) were identified as risk factors for mortality in patients with CCHD. In multiple logistic regression analysis, genetic syndrome (OR: 17.3, 95% CI [1.04–28.7], p=0.010) and postoperative arrhythmia (OR: 42.6, 95% CI [4.1–44.09], p=0.002) were the strongest risk factors for mortality.

Conclusion: Integration of echocardiographic and risk-based classifications may guide better clinical decision-making in patients with CCHD. Early identification, antenatal diagnosis, and preoperative stabilization are key to improving outcomes. The risk of mortality was higher in patients who required mechanical ventilation, had genetic anomalies, or developed postoperative arrhythmias.

Keywords: Cardiac surgery; congenital heart diseases; mortality; neonatal intensive care unit.

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Kritik konjenital kalp hastalığı olan yenidoğanlarda mortalite ve ilişkili risk faktörleri: Retrospektif tek merkezli bir çalışma

ÖZET

Amaç: Konjenital kalp hastalıkları (KKH), kardiyovasküler sistemdeki konjenital yapısal ve işlevsel anormallikleri içerir ve yüksek mortalite ve morbidite riski taşır. Bu çalışmanın amacı, konjenital kalp hastalığı (KKH) olan bebeklerde erken dönem sonuçlarını, özellikle kritik KKH'ye (KKKH) odaklanarak değerlendirmek ve KKKH olan hastalarda mortalite ile ilişkili faktörleri belirlemektir.

Gereç ve Yöntemler: Hastalar, ekokardiyografi sonuçları ve klinik bulgularına göre normal, önemsiz, önemli, ciddi ve kritik olmak üzere beş kategoriye ayrılmıştır. Ayrıca, KKH nedeniyle ameliyat geçiren tüm hastalar RACHS-1 sınıflandırmasına göre değerlendirilmiştir.

Bulgular: KKKH (ciddi/kritik) vakaları, KKH vakalarının %11,6'sını (71/608) oluşturdu. KKKH olan 71 yenidoğanın 32'sinde mortalite görüldü (%45,1). Doğum öncesi tanı (OR: 3,1), ameliyat edilemezlik (OR: 4,6), ventilasyon ihtiyacı (OR: 8,1) ve ameliyat sonrası aritmi (OR: 8,4), KKKH'de mortalite için risk faktörleri olarak belirlendi. Çoklu lojistik regresyon analizinde, genetik sendrom (OR: 17,3; %95 CI [1,04–28,7]; p=0,010) ve ameliyat sonrası aritmi (OR: 42,6; %95 CI [4,1–44,09]; p=0,002) mortalite açısından en önemli risk faktörleri olarak saptandı.

Tartışma: Ekokardiyografik ve risk temelli sınıflandırmaların birleştirilmesi, KKKH olan hastalarda daha iyi klinik karar verme sürecine yol gösterebilir. Erken teşhis, doğum öncesi tanı ve ameliyat öncesi stabilizasyon, sonuçların iyileştirilmesinde kilit öneme sahiptir. Mekanik ventilasyona ihtiyaç duyan, genetik anomalileri olan veya ameliyat sonrası aritmi gelişen hastalarda mortalite riski daha yüksekti.

Anahtar Kelimeler: Kardiyak cerrahi girişim; konjenital kalp hastalıkları; mortalite; siyanotik kalp hastalığı; yenidoğan.

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INTRODUCTION

Congenital heart diseases (CHDs) include congenital structural and functional abnormalities of the cardiovascular system (1, 2). The prevalence of CHD among live births is approximately 0.8–1% (3–5). Despite modern diagnostic and treatment methods, CHD is associated with a high risk of mortality and morbidity.

There are many studies on the neonatal mortality rate during the first year of life. Although the mortality rate has gradually decreased over the last 40 years, an analysis conducted in the USA in 2012 reported a neonatal mortality rate of 0.32% (6–8). In Türkiye, this rate was 1.07% according to 2015 data from the Turkish Statistical Institute (9–11). Mortality in the neonatal period is associated with many causes, such as prematurity-related diseases, congenital malformations, sepsis, and congenital heart diseases (12–17).

In the United States, between 1999 and 2006, 0.21% of all reported deaths were associated with congenital heart disease (CHD), and the CHD-related mortality rate during the first year of life was reported as 41.48 per 100,000 live births (18). Similarly, a 20-year study conducted in the United Kingdom reported that 10.3% of deaths occurring within the first year of life were attributed to CHD (7). Other studies conducted in Türkiye have reported that the incidence of CHD in NICUs ranges from 1.6% to 15% (19–21).

CHDs that require surgical and/or catheter intervention in the first year of life and can cause death in the neonatal period are called critical CHDs (CCHDs) and account for approximately 25% of all CHDs (22). In a recent study conducted in the USA, the overall prevalence of CCHD was 19.6 per 10,000 live births (23).

Neonatal intensive care units (NICUs) with experienced staff, sufficient equipment, and adequate supplies are critical for these patients. Data on the epidemiology, mortality, and morbidity of newborns with CHD followed up in NICUs are quite limited in Türkiye. Currently, neonatal cardiac surgery is a developing field and can be performed in only a few centers in Türkiye.

A recent study covering the years 2018–2021 found that, among 41,490 infant deaths nationwide, 4,083 were due to CCHD, accounting for approximately 9.8% of infant deaths (24). The study reported that CCHD accounts for approximately 8% of neonatal deaths, with a neonatal mortality rate due to CCHD of 4.6 per 10,000 live births. The report also identified regional differences within Türkiye; for example, the mortality rate due to CCHD per 10,000 births was 8.4 in the Western region and approximately 9.0 in the Central, Southern, and Eastern regions (24).

Prematurity, low birth weight, sepsis, and pulmonary hypertension, along with poor preoperative clinical condition and low Apgar scores, are major factors that increase mortality in

Table 1. Grouping study population according to echocardiographic and clinical findings (40)

Group number	Group name	Description
Group 1	Normal	Normal echocardiography findings
Group 2	Insignificant	Lesions that do not cause clinical symptoms and resolve spontaneously within six months. For example, small PDA, PFO, small ASD, muscular VSD.
Group 3	Important	Lesions not classified as serious or critical but require medication or follow-up longer than six months
Group 4	Serious	Lesions that require intervention within the first year of age are not classified as critical
Group 5	Critical	All lesions that died within the first 28 days or that require intervention.

ASD: Atrial septal defect; PDA: Patenat ductus arteriosus; PFO: Patent foramen ovale; VSD: Venticular septal defect.

neonates with CHD (25–32). Additionally, high RACHS-1 scores, prolonged bypass time, preoperative mechanical ventilation, and postoperative complications, such as low cardiac output syndrome and infections, significantly increase the risk of death (33). Genetic syndromes, congenital airway anomalies, and the presence of perinatal stroke are also additional risk factors that negatively affect survival (26, 34–36).

The Risk Adjustment in Congenital Heart Surgery (RACHS-1) score is a widely used system for predicting surgical mortality in pediatric cardiac procedures and classifies surgeries into six categories based on their complexity (37). RACHS-1 scores can predict CCHD-related mortality by category as follows: category 1, 0.4%; category 2, 3.8%; category 3, 8.5%; category 4, 19.4%; category 5, insufficient number; and category 6, 47.7% (37).

Determining the factors affecting prognosis will play a role in developing approaches to reduce mortality and morbidity in patients with CHD. In this cross-sectional retrospective study, we aimed to evaluate both the prevalence and mortality rate of CCHDs and to identify the risk factors affecting mortality.

MATERIALS AND METHODS

Newborns with CHD were identified by reviewing the electronic records of all patients hospitalized in the NICU of Ege University Pediatric Hospital between January 2014 and December 2015. Approval was obtained from the Ege University Faculty of Medicine Clinical Research Ethics Committee for this study (Decision Number: 16-11.1/14; Date: 01.12.2016). The study was conducted in accordance with the Declaration of Helsinki.

The present retrospective study included 750 patients from 2014 and 902 from 2015, for a total of 1,652 patients hospitalized in the Ege University NICU. Demographic characteristics, the presence of antenatal diagnosis, clinical features at the time of diagnosis, disease-related or independent risk factors affecting morbidity and mortality, such as renal failure, heart failure, other organ failures, immunological and genetic conditions, medical treatments, angiographic catheter interventions, surgical procedures, time of surgical decision, and time of death were examined from the patient files.

Patients were categorized into five CHD groups (normal, non-significant, important, serious, and critical) based on echocardiographic findings and clinical severity using the classification terms of Ewer et al. (38). Group 1 (Normal) included patients with no structural abnormalities. Group 2 (Insignificant) comprised minor defects such as small PDAs or patent foramen ovales (PFOs) that were asymptomatic and typically resolved spontaneously within six months. Group 3 (Important) involved conditions requiring prolonged follow-up or medication but not meeting the criteria for more severe classifications. Group 4 (Serious) included lesions requiring intervention within the first year of life, excluding those considered critical. Finally, Group 5 (Critical) encompassed defects necessitating urgent intervention or resulting in death within the neonatal period (the first 28 days). These groups are presented in Table 1 (38). Premature infants with PDA were excluded from the study.

CCHDs were defined as serious (Group 4) and critical (Group 5) according to this classification after screening with pulse oximetry before postnatal discharge.

In addition, the same treatment group was scored using the RACHS-1 classification system. The RACHS-1 classification is a scoring system used to predict the short-term mortality of congenital heart surgery in patients under 18 years of age (39). The risk categorization system for surgical procedures is divided into six different risk categories (39). Appendix 1 shows the RACHS-1 risk categories and related operations in the supplementary data.

Mortality rates in the study were calculated separately for CHD groups according to diagnoses and RACHS-1 classification categories. The risk factors that might affect mortality were determined by comparing the demographic, clinical, and interventional characteristics of patients with CCHD (serious [Group 4] and critical [Group 5]).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, version 19.0 (IBM Corporation, Armonk, NY, USA). Numerical variables with a normal distribution were analyzed using the t-test and ANOVA, whereas those that were not normally distributed were evaluated using the Mann–Whitney U test and Kruskal–Wallis test. Mean±standard deviation and median (minimum–maximum) values were calculated as appropriate. The chi-square test and Fisher's exact test were used for comparisons between categorical variables. After determining the risk

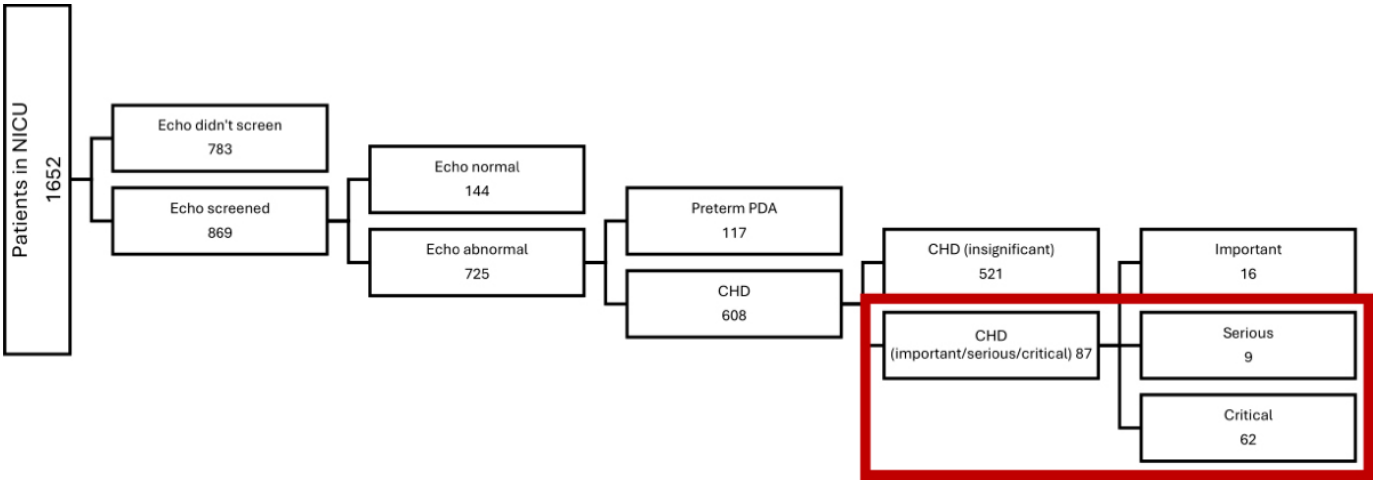

Figure 1. Echocardiographic evaluations of patients followed in the NICU between 2014 and 2015 and distribution of CHD.

CHD: Congenital heart disease; Echo: Echocardiography; NICU: Neonatal intensive care unit; PDA: Patients ductus arteriosus.

factors, univariate logistic regression analysis was performed, and parameters found to be significant were analyzed using multivariate regression analysis (full model, stepwise forward selection, and backward selection). Values of $p<0.05$ were considered statistically significant. Data analyses were carried out at the Department of Biostatistics, Ege University Faculty of Medicine.

RESULTS

This study included a cohort of 869 patients who underwent echocardiographic screening. Echocardiographic examinations were normal in 144 patients, while abnormalities were detected in the remaining 725 patients (83.4%). Among patients with abnormal echocardiographic findings, 117 (16.1%) had isolated PDA detected in preterm infants, while the remaining 608 patients (83.9%) had CHDs (Fig. 1). After excluding isolated PDA cases in preterm infants, a total of 608 patients remained, corresponding to 36.8% of all NICU patients. Echocardiographic abnormalities were classified as "insignificant" in 521 patients (31.6% of NICU patients), while the remaining patients were classified as "important" (n=16, 0.96% of NICU patients, 16/1652), "serious" (n=9, 0.54% of NICU patients, 9/1652), and "critical" (n=62, 3.75% of NICU patients, 62/1652) CHDs.

During the screening period, 6,440 live births were recorded at our center. In other words, 87 of 6,440 (1.3%) live births had CHD (important/serious/critical). The most common lesions in the "important," "serious," and "critical" CHD groups were TGA in 14 patients (2.3%, 14/608) and CoA in 14 patients (2.3%, 14/608). CHDs (important/serious/critical) were classified as cyanotic and acyanotic diseases in 54 (62%) and 33 (38%) patients, respectively. The numbers of cyanotic and acyanotic patients are shown in Appendix 2 in the supplementary data. In the acyanotic group, the most common diagnosis was aortic coarctation, observed in 16% of patients (14/87), as shown in Appendix 2. Similarly, in the cyanotic group, the most frequent diagnosis was transposition of the great arteries (TGA), also comprising 16% of the cohort (14/87), as detailed in Appendix 2.

In our study population, the mean gestational age was 37.1±2.4 (29–41) weeks, and the mean birth weight was 2,887±643 (1,010–4,230) g among the 87 patients with important/serious/critical CHD. Twenty-six patients (29%) were preterm (<37 weeks), and the median chronological age on the day of hospitalization was 1 day (IQR, 2; min, 1; max, 41). These demographic data are shown in Appendices 3, 4.

Serious/Critical Congenital Heart Diseases (CCHD): Demographic Data

Seventy-one of the 87 patients had serious/critical CHD. Demographic data, clinical features, and interventional characteristics of patients with CCHD are provided in the supplementary data (Appendices 3–5).

Among patients with CCHD, 43 had an antenatal fetal echocardiographic diagnosis of critical congenital heart disease, while 28 had no previous diagnosis during the fetal period. Among the patients who died, 24 had an antenatal diagnosis, while 8 had no antenatal diagnosis. This difference was statistically significant (p=0.024).

Seven patients with CCHD had genetic syndromes, including DiGeorge syndrome in one patient, LACTH syndrome in one patient, Turner syndrome in one patient, trisomy 18 in one patient, situs inversus totalis in one patient, and Johanson–Blizzard syndrome in one patient (Appendices 6, 7).

Mortality in Congenital Heart Diseases

The total number of neonatal deaths in the NICU was 132 during the two-year period (2014–2015), and patients who died with a diagnosis of CHD accounted for 24.2% (32/132) of all deaths. Other deaths were due to complications of prematurity, sepsis, and genetic and metabolic diseases. Of the 71 neonates with CCHD, 32 died, yielding an overall mortality rate of 45.1%.

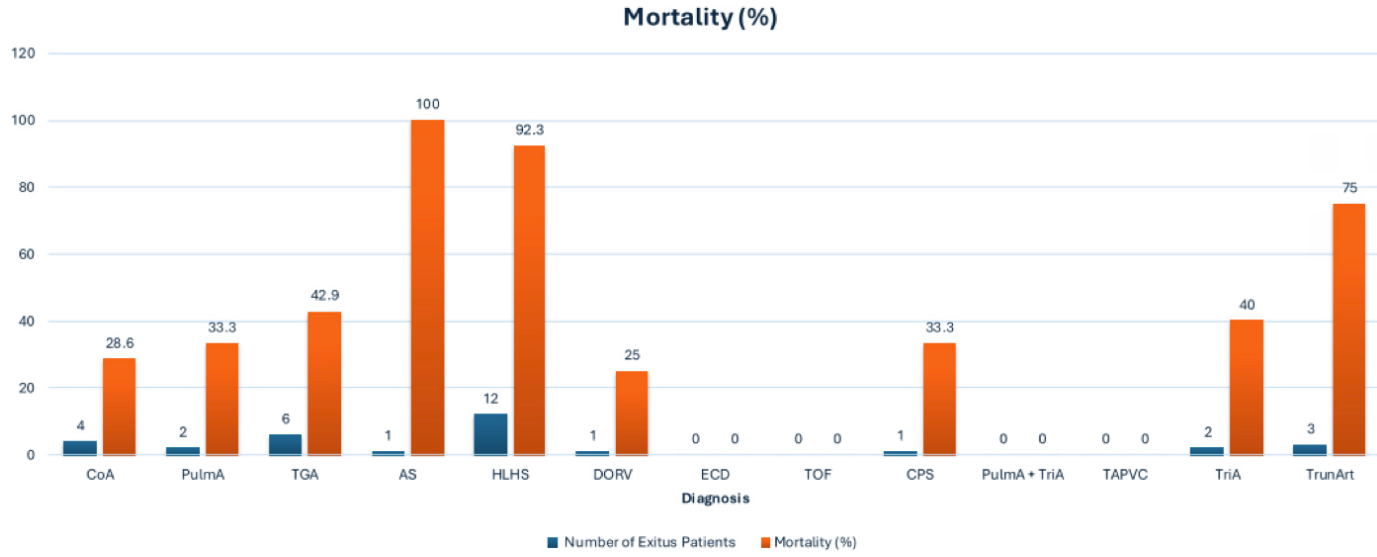

Figure 2. Mortality rates according to the diagnosises of CCHD.

AS: Aortic stenosis; CoA: Aortic coarctation; CPS: Critical pulmonary stenosis; DORV: Double output right ventricule; ECD: Endocardial cushion defect; HLHS: Left hypoplastic heart syndrome; PulmA: Pulmonary atresia; PTA: Truncus arteriosus; VSD: Ventricular septal defect; TAPVS: Total anomalous pulmonary venous connection; TOF: Tetralogy of fallot; TriA: Tricuspid atresia; CPS: Critical pulmonary stenosis.

Mortality was evaluated across the CHD groups. As expected, no patient in Group 4 (serious) died, whereas the mortality rate in Group 5 (critical) was 51.6% (32/62), which was statistically significant (p=0.003).

Fifty-three (74%) of the 71 patients with CCHD who underwent surgery were evaluated based on the RACHS-1 score. Eleven patients were classified as category 2, 26 as category 3, 7 as category 4, and 9 as category 6.

Among the 32 neonates who died, 10 (31%) died before surgery, while 6 (19%) and 16 (50%) died within 72 hours and after 72 hours following surgery, respectively. Four of the six early postoperative deaths occurred intraoperatively. The mean time to late postoperative death was 32.6±6.8 days (min–max, 4–90). The distribution of deceased patients according to diagnosis is summarized in Figure 2. The mortality of the 53 operated patients was evaluated using the RACHS-1 scoring system. Based on the RACHS-1 score, no patient died in category 2; the mortality rate was 34.6% in category 3, 42.9% in category 4, and 88.9% in category 6 (Appendix 8). A statistically significant difference was observed among the three groups (p=0.022).

Mortality rates were relatively high in patients diagnosed with aortic valve stenosis, HLHS, and truncus arteriosus. Early 3-month mortality in patients with CCHD according to surgical status was demonstrated by Kaplan–Meier analysis in Figure 3.

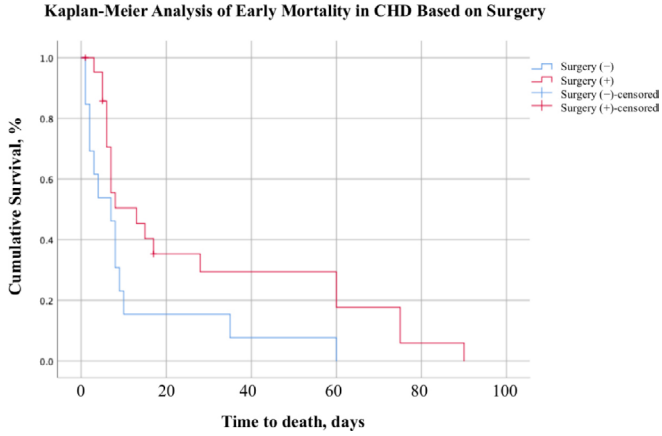

Figure 3. Kaplan-Meier curves demonstrating cumulative survival in CHD patients with and without surgical intervention. The x-axis indicates time to death (days), and the y-axis shows cumulative survival (%). Patients undergoing surgery exhibited higher early survival rates, particularly within the first 20 days. Censored observations are indicated on the curves.

Characteristics of Patients Who Died and Possible Risk Factors Associated with Mortality

Risk factors associated with mortality were investigated by comparing the demographic, clinical, and interventional characteristics of surviving and deceased neonates (Table 2).

When risk factors for mortality were compared between the groups, the need for mechanical ventilation during the preoperative period was significantly higher among patients who died (87% vs. 46%, p=0.004). Among the 71 patients with CCHD, 19 (26.7%) developed multiple organ failure (MOF) during the postoperative period. All patients who developed MOF died (p<0.001). Liver failure developed in 9 patients (12%), with a mortality rate of 66.6% (6/9). All 10 patients who developed renal failure died (p<0.001). Dialysis was performed in 5 patients, all of whom died. The mortality rate was 100% and was statistically significant (p<0.001). Among patients with CCHD, 17 of the 28 patients with sepsis survived, while 11 died. There was no statistically significant association between mortality in CHD and sepsis (p=0.156).

Table 2. Mortality-demographic data in CCHD

Demographics	Survived (n=39)	Died (n=32)	p
Gestational week, week, mean (±SD), min–max	37 (±1.9), 32–41	36 (±2.2), 31–40	0.143
Birth weight	3.021 (±547), 1590–4230	2.771 (±722), 1010–4000	0.186
Gender, n (%)			0.619
Male	27 (70)	20 (62.5)	
Female	12 (30)	12 (37.5)	
Antenatal diagnosis, n (%)	19 (48%)	24 (75%)	**0.024**
Age at diagnosis, days, mean (± SD), min–max	0 (IQR 5), 0–28	0 (IQR 0), 0–22	0.091
Those born in the outer center, n (%)	12 (30)	5 (15)	0.141
Gestational week <37, n (%)	7 (17.9)	11(34)	0.303
Birth Weight <2500, n (%)	7 (17.9)	10 (31)	0.369
Genetic Syndrome, n (%)	3 (7.6)	4 (12.5)	0.449
Clinical Findings			
Cyanosis, n (%)	26 (66)	28 (87)	0.166
Mechanical Ventilation, n (%)	18(46)	28 (87)	**0.004**
Mechanical Ventilation Time, median (IQR) min–max	7 (IQR 12), 1–31	9(IQR 15), 1–90	0.319
Ventilator-Associated Pneumonia, n (%)	4 (10)	4(12.5)	0.770
Sepsis, n (%)	17 (43.5)	11 (34)	0.156
MOF, n (%)	0	19 (59)	**<0.001**
Renal Insufficiency, n (%)	0	10 (31)	**<0.001**
Liver Failure, n (%)	3 (7.6)	6 (18.7)	0.285
Hematological Insufficiency, n (%)	2 (5.1)	2 (6.2)	0.839
Genetic abnormality, n (%)	3 (7.6)	4 (12.5)	0.502
Length of stay, median, n (%)	16 (IQR 24), 1–90	7.5 (IQR), 1–90	0.407
Interventional characteristics			
Prostaglandin Infusion, n (%)	23 (44)	30 (56%)	**0.003**
Atrial septostomy, n (%)	4	3	0.166
Atrial septostomy age, median (IQR) min–max	3 (IQR 15), 1–20	1 (IQR 0), 1–2	0.358
Surgical operation, n (%)	34 (87)	19 (60)	**0.007**
RACHS-1-2	11	0	**0.020**
RACHS-1-3	17	9	
RACHS-1-4	4	3	
RACHS-1-6	1	8	
Postoperative takeover time, median day (IQR) min–max	1(IQR 3), 0–14	2.5 (IQR 7.5), 1–12	0.232
Multiple inotrop requirements, n (%)	25 (52)	23 (48)	0.802
Preoperative arrhythmia, n (%)	1 (2.9)	5 (26)	0.830
Postoperative arrhythmia, n (%)	2 (5.8)	9 (47)	**0.009**

C/S: Cesarean section; IQR: Interquartile range; MOF: Multiple organ failure; RACHS-1: Risk adjustment for congenital heart surgery-1.

Initially, mortality risk in our study population was assessed, and then factors frequently reported in the literature were analyzed using univariate logistic regression for each variable, followed by multivariate logistic regression analysis to evaluate their combined effects. This approach allowed us to clearly distinguish the individual and collective impacts of these factors on mortality risk. The presence of an antenatal diagnosis, PGE1 infusion, inoperability, the need for invasive mechanical ventilation before surgery, and postoperative arrhythmia were identified as factors associated with an increased risk of mortality (Appendix 5).

Table 3. Risk and mortality relationship in CCHD

Features*	OR	95% CI	p (<0.05)
Prematurity (<37 weeks of gestational age)	2.898	0.315- 26.635	0.347
Birth Weight <2500 gr	5.271	0.668- 41.574	0.057
Genetic Syndrome	**17.310**	**1.043-28.716**	**0.010**
Having Antenatal Diagnosis	4.358	0.819- 23.185	0.084
PGE1 treatment requirement	3.720	0.468- 29.598	0.214
Ventilation before surgery	2.606	0.418- 16.250	0.305
Pre-operative arrhythmias	5.834	0.348-97.699	0.220
Post-operative arrhythmias	**42.664**	**4.128-44.968**	**0.002**

OR: Odds ratio; CI: Confidence interval; PGE1: Prostaglandin E1; *: Variables performed in Full Model Multiple Logistic Regression Analysis.

Table 4. Cox regression analysis of risk factors associated with mortality

Variables	B	SE	Wald	df	p	Exp(B) HR	95% CI for Exp(B)
Post-operative arrhythmias	0.807	0.800	1.018	1	0.313	2.242	0.467–10.756
Inoperability	0.938	0.433	4.684	1	0.030*	2.554	1.093–5.969
Genetic syndrome	0.317	0.627	0.256	1	0.613	1.374	0.402–4.699
Mechanical ventilation before surgery	0.609	0.617	0.973	1	0.324	1.839	0.548–6.166

B: Regression coefficient; SE: Standard error; Wald: Wald chi-square statistic; df: Degrees of freedom; Exp(B): Exponentiated B; HR: Hazard ratio; CI: Confidence interval; *: Among the variables analyzed, inoperability was significantly associated with an increased risk of mortality (p=0.030). Other factors did not reach statistical significance.

Forty-six of the 71 patients (64%) with CCHD received preoperative invasive mechanical ventilation. Among the patients who died, a higher proportion required preoperative mechanical ventilation than among survivors (87% vs. 46%, p=0.004). The median duration of mechanical ventilation was 7 days (IQR 12 [min–max: 1–31]) for survivors and 9 days (IQR 15 [min–max: 1–90]) for nonsurvivors, with no statistically significant difference between the two groups (p=0.319).

In the multivariate logistic regression analysis conducted for patients with CCHD (Table 3), postoperative arrhythmias were found to be the strongest predictor of mortality (OR: 42.6, 95% CI: 4.1–44.09, p=0.002). The presence of a genetic syndrome was also significantly associated with an increased risk of mortality (OR: 17.3, 95% CI: 1.04–28.7, p=0.010). Although other variables, such as low birth weight, antenatal diagnosis, RACHS-1 score, and preoperative mechanical ventilation, showed elevated odds ratios, they did not reach statistical significance.

Among the variables analyzed in the Cox regression model, inoperability was the only factor significantly associated with an increased risk of mortality (p=0.030; HR=2.55; 95% CI: 1.09–5.97). Postoperative arrhythmias, genetic syndromes, and preoperative mechanical ventilation did not reach statistical significance (Table 4).

DISCUSSION

In this retrospective single-center cohort, we evaluated the clinical characteristics, mortality outcomes, and factors associated with mortality among neonates with congenital heart disease admitted to a tertiary neonatal intensive care unit (NICU), with a particular focus on critical congenital heart disease (CCHD). Among 608 neonates with CHD identified after exclusion of isolated patent ductus arteriosus in preterm infants, 71 (11.7%) were classified as having critical CHD. The proportion of CCHD among neonates with CHD was 11.7%, rather than representing the population-based incidence of CCHD. Thirty-two of the 71 patients with CCHD died, corresponding to an overall mortality rate of 45.1% within the CCHD group. Importantly, CCHD accounted for 24.2% of all neonatal deaths occurring in our NICU during the study period, emphasizing the substantial contribution of severe cardiac disease to neonatal mortality in a tertiary-care setting.

Previous studies have emphasized that undiagnosed or late-diagnosed CCHD remains a significant cause of neonatal death, underlining the need for early detection and intervention (40). In particular, neonates with CCHD account for a disproportionately high proportion of ICU mortality compared with other patient groups, reflecting the severity and complexity of their condition (41). Furthermore, the American Heart Association and the American Academy of Pediatrics have jointly stated that accurate estimation of the burden of CCHD-related mortality is critical for shaping effective screening policies and guiding healthcare resource allocation (42). Therefore, presenting the proportion of CCHD-related deaths among all NICU deaths in our study provides clinically

relevant insight into the disease burden and supports the importance of early diagnosis and specialized care pathways.

In this study, almost all patients (n=32) who died were in the CCHD group. Only one patient with a diagnosis of ASD in the non-CCHD group died due to intracranial hemorrhage associated with a vein of Galen aneurysm. Forty percent of the patients who died had complex cardiac pathologies, such as hypoplastic left heart syndrome (HLHS), while others had TGA and CoA.

It has been reported that 24% of patients with important/severe/critical CHD had acyanotic heart disease, while the remaining 76% had cyanotic heart disease, and 73% of these patients had duct-dependent circulation. Prostaglandin infusion was initiated preoperatively in patients requiring urgent surgery. In our study, 28 (87%) of the patients who died had cyanotic CHDs. Cyanotic CHDs account for approximately one-third of fatal cases among all CHDs (43).

Considering our study cohort, antenatal diagnosis, PGE1 infusion, inoperability, the need for preoperative mechanical ventilation support, and postoperative arrhythmia were associated with an increased risk of mortality. Üstün et al. (44) identified significant independent variables associated with mortality, including gestational age, the presence of associated disease, preoperative mechanical ventilation requirement, pulmonary hypertension, sepsis, RACHS-1 score, postoperative low cardiac output, and heart failure. Cheng et al. (30) identified independent risk factors associated with mortality in 174 patients undergoing cardiac intervention, including 5-minute Apgar scores <7, preoperative mechanical ventilation requirement, and RACHS-1 scores >4. In our study, only two infants had Apgar scores <7. The mean 5-minute Apgar score was 8.9±0.93 (min–max, 6–10). The results did not support a strong association between the Apgar score and mortality in our cohort (p=0.072).

Several risk-scoring systems are used in the field of CHD surgery, and RACHS-1 has been accepted as one of the most reliable scoring systems. The degree of surgical complexity has been recognized as one of the factors associated with increased mortality both in Türkiye and worldwide. In the current study, the majority of patients (49%, 26/53) were classified as category 3. The highest mortality rate was observed in RACHS-1 risk category 6, at 88.9%. There was a significant association between mortality and RACHS-1 score (p=0.020). In addition, contemporary studies increasingly use alternative risk-adjustment systems, including the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) mortality categories (45). Therefore, direct comparisons of surgical mortality across studies should take into account differences in risk-adjustment methodology.

Previous studies from different parts of the world have reported 1-year mortality rates of approximately 24.1%–25.5% among neonates with CCHD (11, 46).

In a nationwide study covering 2018–2021, Çaylan et al. (24) reported that CCHD-related deaths accounted for 9.8% of all infant deaths and 8.0% of all neonatal deaths, with a CCHD-specific infant mortality rate of 8.8 per 10,000 live births. Although these population-based mortality estimates cannot be directly compared with the 45% mortality observed within the first three months of life among neonates with CCHD admitted to our tertiary NICU, this rate was higher than the 35.2% reported by Üstün et al. (44) in another Turkish cohort, highlighting the substantial mortality burden associated with CCHD in this population. However, more recent Turkish data suggest a substantial improvement in outcomes over time. Dilli et al. (45) recently reported the results of a multicenter study involving 488 neonates with CCHD treated at nine tertiary centers in Türkiye between October 2021 and November 2022. In that cohort, in-hospital mortality was 20.1% and postoperative mortality was 19.6%, considerably lower than the mortality observed in our 2014–2015 cohort. This difference may reflect advances in prenatal diagnosis, neonatal stabilization, cardiac surgical techniques, perioperative management, intensive care practices, and access to advanced postoperative support over the intervening years. It may also reflect differences in case mix and referral patterns between a single-center historical cohort and a multicenter registry. Therefore, the difference in mortality should not be interpreted as a direct comparison of center performance but rather as evidence of the evolving outcomes of neonatal CCHD care in Türkiye. Despite the difference in overall mortality, the two Turkish cohorts demonstrated important similarities in the factors associated with adverse outcomes. In our study, preoperative PGE1 use was associated with increased mortality, and PGE1 requirement was also identified as an independent risk factor in the multicenter study by Dilli et al (45). PGE1 requirement is likely to represent the underlying physiological severity of the cardiac lesion, particularly ductal-dependent systemic or pulmonary circulation, rather than a direct harmful effect of the treatment itself. This concordance between two cohorts from different periods supports the importance of underlying disease severity and ductal dependency as persistent determinants of neonatal outcomes. A comparison of the two cohorts is presented in Table 5.

The specific postoperative predictors differed between the two studies. In our cohort, postoperative arrhythmia was the strongest independent predictor of mortality in multivariable logistic regression, while the presence of a genetic syndrome was also independently associated with increased mortality. In contrast, Dilli et al. (45) identified higher vasoactive-inotropic support (VIS>17.5), major postoperative complications, and early postoperative extracorporeal membrane oxygenation as independent predictors of mortality. These apparently different predictors may represent different manifestations of a common underlying pathway: greater disease severity, hemodynamic instability, and postoperative organ dysfunction.

Thanks to advances in NICU technology and healthcare, as well as the development of mechanical ventilators, the survival rate and prognosis of children with chronic conditions such as congenital heart disease have improved over time (43). Previous studies, such as that by Üstün et al. (44), have also reported an association between preoperative mechanical ventilation and

Table 5. Comparison of mortality outcomes and associated risk factors in two Turkish CCHD cohorts

Characteristic	Present study	Dilli et al. (45)
Study period	2014–2015 (two years)	2021–2022 (one year)
Study design	Retrospective, single-center	Multicenter
Number of centers	1	9
CCHD cohort	71	488
Cardiac surgery	53/71 (74.6%)	325/488 (66.6%)
Mortality outcome	32/71 (45.1%)	20.1% in-hospital
CCHD-related deaths among all NICU deaths	32/132 (24.2%)	—
Surgical risk scores	RACHS-1	STAT
Preoperative PGE1 infusion	Associated with mortality	Independent mortality risk factor
Preoperative mechanical ventilation	Associated with mortality	Not reported as an independent major predictor
Postoperative arrhythmia	Strongest multivariable predictor	—
Genetic syndrome	Independent predictor	Extracardiac anomalies reported in 12.9%
High vasoactive support	—	VIS >17.5 associated with mortality
Major postoperative complications	—	Independent mortality risk factor
Early postoperative ECMO	—	Independent mortality risk factor
Cox regression	Inoperability	Not the principal analysis
Main contribution	Detailed mortality-risk assessment in a tertiary NICU cohort	Contemporary multicenter Turkish epidemiology and outcomes

CCHD: Critical congenital heart disease; ECMO: Extracorporeal membrane oxygenation; NICU: Neonatal intensive care unit; PGE1: Prostaglandin E1; RACHS-1: Risk adjustment for congenital heart surgery-1; STAT: Society of thoracic surgeons–european association for cardio-thoracic surgery congenital heart surgery mortality categories; VIS: Vasoactive-inotropic score.

increased mortality in patients with CCHD undergoing cardiac intervention. However, it is important to consider that this association likely reflects the severity of the patients' underlying cardiac conditions rather than complications directly related to mechanical ventilation. Factors such as poor cardiac function, resistance to medical therapy, and the need for high-dose inotropes contribute significantly to this outcome. Although patients requiring mechanical ventilation had higher mortality, the focus should not solely be on limiting its use. Instead, the goal should be to avoid unnecessary mechanical ventilation while recognizing that invasive mechanical support can be life-saving in critically ill patients when appropriately indicated. Reducing the duration of mechanical ventilation remains an important treatment goal, but clinical judgment must prioritize patient stability and survival.

Limitations

This study has several limitations. First, its retrospective and single-center design limits generalizability and introduces the possibility of selection and information bias. Second, the relatively small number of patients with CCHD limits statistical power and results in wide confidence intervals for some multivariable estimates, particularly for postoperative arrhythmia and genetic syndromes. Third, the study period predates major advances in neonatal cardiac surgery, intensive care, and extracorporeal support; therefore, the mortality estimates should not be considered representative of current national outcomes. Fourth, RACHS-1 was used for surgical risk adjustment, whereas contemporary multicenter studies may use alternative systems such as STAT, limiting direct comparisons between studies. Finally, our definition of CCHD was operationalized according to the serious/critical classification used in this study and should therefore be interpreted in the context of that classification rather than assumed to be directly equivalent to all contemporary definitions of CCHD.

CONCLUSION

In conclusion, CCHD was associated with substantial mortality in this tertiary NICU cohort, accounting for nearly one-quarter of all neonatal deaths. Higher surgical complexity, poor preoperative clinical condition, PGE1 requirement, postoperative arrhythmia, genetic syndromes, and postoperative organ dysfunction were associated with adverse outcomes. Importantly, comparison with multicenter Turkish data suggests a marked improvement in CCHD survival over time. Nevertheless, the persistence of disease severity and postoperative physiological instability as major determinants of outcome underscores the importance of early diagnosis, timely referral, appropriate preoperative stabilization, and high-quality perioperative cardiac intensive care. These findings provide a benchmark and may help contextualize the evolution of neonatal CCHD outcomes in Türkiye.

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Appendix 1. RACHS-1 risk categories*

RACHS-1 risk category	Category operation
Risk category -1	- Atrial septal defect surgery (secundum, sinus venosus, PFO closure) - Aortopexy - Patent ductus arteriosus surgery (>30 days) - Coarctation repair (>30 days) - Partially anomalous pulmonary venous connection surgery
Risk category -2	- Aortic valvotomy or valvuloplasty (>30 days) - Subaortic stenosis resection - Pulmonary valvotomy or valvuloplasty - Pulmonary valve replacement - Right ventricular infundibulectomy - Pulmonary outflow tract augmentation - Repair of coronary artery fistula - Atrial and ventricular septal defect repair - Atrial septal defect primum repair - Ventricular septal defect repair - VSD closure + pulmonary valvotomy/infundibular resection - VSD closure + pulmonary artery band removal - Repair of unspecified septal defect - Total repair of tetralogy of Fallot - Repair of total anomalous pulmonary veins (>30 days) - Glenn shunt - Vascular ring surgery - Repair of aorta-pulmonary window - Coarctation repair (≤30 days) - Repair of pulmonary artery stenosis - Transection of pulmonary artery - Common atrium closure - Left ventricular to right atrial shunt repair
Risk category -3	- Aortic valve replacement - Ross procedure - Left ventricular outflow tract patch - Ventriculomyotomy - Aortoplasty - Mitral valvotomy or valvuloplasty - Mitral valve replacement - Valvectomy of tricuspid valve - Tricuspid valvotomy or valvuloplasty - Tricuspid valve replacement - Tricuspid valve repositioning for Ebstein anomaly (>30 days) - Repair of anomalous coronary artery (without intrapulmonary tunnel) - Repair of anomalous coronary artery (with Takeuchi intrapulmonary tunnel) - Closure of semilunar valve (aortic or pulmonary) - Right ventricular to pulmonary artery conduit - Left ventricular to pulmonary artery conduit - Repair of double-outlet right ventricle (+/- RV obstruction repair) - Fontan procedure - Repair of transitional/complete AV canal (+/- valve replacement) - Pulmonary artery banding - Repair of tetralogy of Fallot with pulmonary atresia - Repair of cor triatriatum - Systemic-to-pulmonary artery shunt - Atrial switch operation - Arterial switch operation - Reimplantation of anomalous pulmonary artery - Annuloplasty - Repair of coarctation + VSD closure - Excision of intracardiac tumor

Appendix 1 (cont). RACHS-1 risk categories*

RACHS-1 risk category	Category operation
Risk category -4	- Aortic valvotomy or valvuloplasty (≤30 days) - Konno procedure - Repair of complex anomaly (single ventricle) with VSD enlargement - Repair of total anomalous pulmonary veins (≤30 days) - Atrial septectomy - Rastelli repair (transposition, VSD, subpulmonary stenosis) - Atrial switch + VSD closure - Atrial switch + repair of subpulmonary stenosis - Arterial switch + pulmonary artery band removal - Arterial switch + VSD closure - Arterial switch + repair of subpulmonary stenosis - Repair of truncus arteriosus - Repair of hypoplastic/interrupted arch without VSD closure - Repair of hypoplastic/interrupted arch with VSD closure - Transverse arch graft - Unifocalization for tetralogy of Fallot + pulmonary atresia - Double switch
Risk category -5	- Tricuspid valve repositioning for neonatal Ebstein anomaly (≤30 days) - Repair of truncus arteriosus + interrupted arch
Risk category -6	- Stage 1 repair of hypoplastic left heart syndrome (Norwood) - Stage 1 repair of nonhypoplastic left heart conditions - Damus-Kaye-Stansel procedure

*: Adapted from article written by Jenkins et al. (39)

Appendix 2. Types of congenital heart diseases within the study group

Acyanotic heart diseases (N=33)	N	% (n/87)	Cyanotic heart diseases (N=54)	N	% (n/87)
Coarctation of aortica	14	16	D-Great Artery Transposition	14	16
Severe pulmonary stenosis	3	3.4	HLHS	13	14.9
AVSD	6	6.8	Pulmonary valve atresia	5	5.7
ASD	4	4.4	Tricuspid valve atresia	6	6.8
VSD	3	3.4	Pulmonary valve atresia + Tricuspid valve atresia	3	3.4
Tricuspid insufficiency	2	2.2	DORV	5	5.7
Aortic stenosis	1	1.1	Persistant truncus arteriosus	4	4.5
			TAPVC	2	2.2
			TOF	2	2.2

ASD: Atrial septal defect; AVSD: Atrioventricular septal defect; DORV: Double output right ventricule; HLHS: Left hypoplastic heart syndrome; VSD: Ventricular septal defect; TAPVC: Total anomalous pulmonary venous connection; TOF: Tetralogy of Fallot.

Appendix 3. Demographics, clinical findings, and interventional characteristics of the patients with CCHD

Demographics	n=71
Gestational age, week, mean (±SD), min–max	37.2 (±1.9), 32–41
Birth weight, gr	2.900 (±640), 1010–4230
Gender, n (%)	
Female	24 (33)
Male	47 (66)
Hospitalization day, day, mean (±SD), min–max	55 (77)
Antenatal diagnosis, n (%)	0 (IQR 1), 0–34
Those born in the outer center, n (%)	43 (60)
Maternal age	17 (23)
Hospitalization day, day, mean (±SD), min–max	28.5 (±6.3), 17–52
Age at diagnosis	
Ege University birth	2.3 (±1.9), 1–7
Eccentric birth	8.2 (±7.4), 1–22
Age at diagnosis, days, mean (±SD), min–max	4.4 (±3.6), 1–22
Clinical findings	
Cyanosis N, %	54 (76)
Mechanical ventilation, n (%)	46 (64%)
Mechanical ventilation time, median	8 (IQR 25), 1–90
Ventilator-associated pneumonia, n (%)	8 (17)
Sepsis	28 (39)
Early sepsis	12 (17)
Late sepsis	16 (22)
Proven sepsis	8 (11)
MOY	19 (26)
Renal insufficiency	10 (14)
Liver failure	9 (12)
Hematological Insufficiency	4 (5.6)
Immunodeficiency	2 (2)
Genetic abnormality	7 (9.8)
Length of stay	13 (IQR 19), 1–90
Interventional characteristics	
Prostaglandin infusion, n (%)	52 (73)
Atrial septostomy, n (%)	7 (9.8)
Atrial septostomy age, days, median (IQR)	1 (IQR 19)
The surgical operation, n (%)	53 (74)
RACHS-1-2	11 (21)
RACHS-1-3	25 (48)
RACHS-1-4	7 (13.4)
RACHS-1-6	9 (17)
Operation Day, mean±(min–max)	13.9±4.5 (0–90)
Postoperative takeover time, days, mean±(min–max)	3.48±3.6 (0–14)
Need of multiple inotrope drugs, n (%)	47 (90)
Preoperative arrhythmia, n (%)	6 (8.4)
Postoperative arrhythmia, n (%)	11 (21)
Mortality, n (%)	32 (45)

CCHD: Critical congenital heart disease; IQR: Interquartile range; MOY: Multiple organ failure; RACHS-1: Risk adjustment in congenital heart surgery-1; SD: Standard deviation.

Appendix 4. Demographic data in patients with congenital heart disease

Characteristics	Patients with (important/severe/critical) CHD (n= 87)	Patients with CCHD (severe/critical) (n=71)
Gestational age, weeks, mean±SD (min–max)	37.1±2.4 (29–41)	37.2 (±1.9), 32–41
Birth weight, g, mean±SD (min–max)	2.887±643 (1010–4230)	2.900±640 (1010–4230)
Gender, n (%)		
Female	32 (36)	24 (33)
Male	55 (63)	47 (66)
Cesarean delivery, n (%)	69 (79)	55 (77)
Preterm birth (<37 weeks), n (%)	28 (32.1)	26 (36.6)
Multiple pregnancy (twins, triplets), n (%)	8 (9.1)	7 (9.8)
Assisted reproductive technology (ART), n (%)	6 (6.8)	6 (8.4)
Maternal age, years, mean±SD (min–max)	28.7±6.2 (17-–52)	28.5±6.3 (17–52)

ART: Assisted reproductive technology; CCHD: Critical congenital heart disease; CHD: Congenital heart disease; SD: Standard deviation.

Appendix 5. Risk and mortality relationship in CCHD as a result of univariate model in logistic regression analysis

Features	OR	95% CI	p
Prematurity (<37 weeks of gestational age)	1.926	0.55–6.69	0.303
Birth weight ≤ 2500 gr	2.300	0.95–7.16	0.118
Type of Delivery, C / S	1.500	0.74–1.10	0.461
Gender, male	1.300	0.53–3.60	0.551
Antenatal diagnosis	**3.100**	**1.14–8.73**	**0.024**
Length of hospital stay (days)	1.000	0.87–1.10	0.930
Age at diagnosis of CHD	1.100	0.97–1.22	0.116
Assisted reproductive techniques (ARTs)	1.900	0.39–12.2	0.493
Apgar 5, <7	1.400	0.96–2.20	0.251
Genetic syndrome	1.871	0.37–9.46	0.449
Acyanotic heart defects	2.400	0.74–7.70	0.143
Prostaglandin infusion before surgery	**6.700**	**1.70–25.90**	**0.006**
Inoperability	**4.600**	**1.40–15.00**	**0.010**
After surgery admission time to NICU	1.000	0.77–1.80	0.311
Need of mechanical ventilation	**8.100**	**2.40–27.70**	**0.001**
Ventilation time	0.970	0.93–1.00	0.278
Ventilator-associated pneumonia	1.200	0.94–1.10	0.541
Clinical Sepsis	1.800	0.75–5.00	0.203
Proven Sepsis	2.200	0.36–13.70	0.382
Need of inotropic drugs	1.200	0.40–3.30	0.681
Preop. Arrhythmias	7.037	0.77–63.69	0.830
Postop. Arrhythmias	**8.409**	**1.60–41.00**	**0.009**

ART: Assisted reproductive technology; C/S: Cesarean section; CCHD: Critical congenital heart disease; CHD: Congenital heart disease; CI: Confidence interval; NICU: Neonatal intensive care unit; OR: Odds ratio; Postop: Postoperative; Preop: Preoperative.

Appendix 6. Neurological findings in CCHD

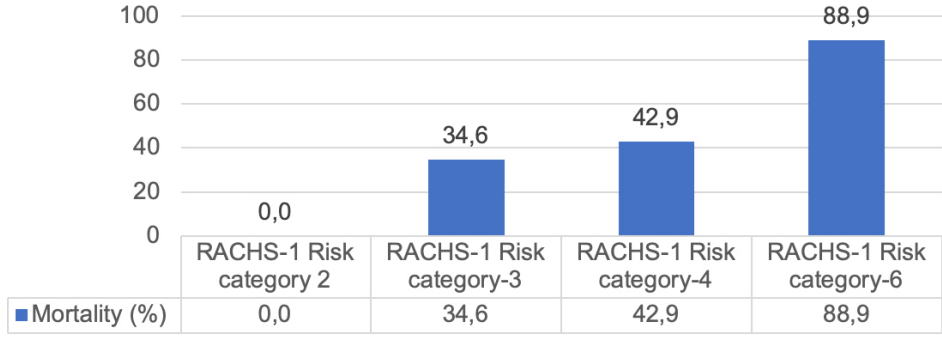
Features	N=71, %
Seizures	16 (22)
Intracranial hemorrhage	3 (4.2)
Ischemia	2 (2.8)
Cerebral Infarct	2 (2.8)
Diffuse Cerebral Atrophy	2 (2.8)
Abnormal USG	17 (23)
Abnormal CT	4 (5.6)
Abnormal MRI	9 (12.6)

CCHD: Critical congenital heart disease; CT: Computed tomography; MRI: Magnetic resonance imaging; USG: Ultrasonography.

Appendix 7. Patients diagnosed with genetic syndromes in CHD

Genetic syndrome	Diagnosis	Prognosis
Turner syndrome	Aortic coarctation	Discharged
Situs inversus totalis	DORV + TGA	Discharged
LACHT syndrome	Endocardial cushion defect	Discharged
Trisomy 18	Hypoplastic left heart syndrome	Deceased
Johanson-Blizzard syndrome	TGA	Deceased
Noonan syndrome	Pulmonary atresia	Deceased
DiGeorge syndrome	Hypoplastic left heart syndrome	Deceased

DORV: Double outlet right ventricle; HLHS: Hypoplastic left heart syndrome; TGA: Transposition of the great arteries.



Appendix 8. Mortality in CCHD patients according to RACHS-1 risk categories.