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RESEARCH

Neonatal Outcomes of Critical Congenital Heart Defects: A Multicenter Epidemiological Study of Turkish Neonatal Society

Neonatal Outcomes of CCHD

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Abstract
Critical congenital heart disease (CCHD) is one of the leading causes of neonatal and infant mortality. We aimed to elucidate the epidemiology, spectrum, and outcome of neonatal CCHD in Türkiye. This was a multicenter epidemiological study of neonates with CCHD conducted from October 2021 to November 2022 at national tertiary health centers. Data from 488 neonatal CCHD patients from nine centers were entered into the Trials-Network online registry system during the study period. Transposition of great arteria was the most common neonatal CHD, accounting for 19.5% of all cases. Sixty-three (12.9%) patients had extra-cardiac congenital anomalies. A total of 325 patients underwent cardiac surgery. Aortic arch repair (29.5%), arterial switch (25.5%), and modified Blalock–Taussig shunt (13.2%). Overall, in-hospital mortality was 20.1% with postoperative mortality of 19.6%. Multivariate analysis showed that the need of prostaglandin E1 before intervention, higher VIS (> 17.5), the presence of major postoperative complications, and the need for early postoperative extracorporeal membrane oxygenation were the main risk factors for mortality. The mortality rate of CCHD in our country remains high, although it varies by health center. Further research needs to be conducted to determine long-term outcomes for this vulnerable population.

Keywords Newborn · Critical congenital heart defects · Epidemiology · Mortality · Outcome

Introduction

Congenital heart disease (CHD) consists of structural malformations of the heart and/or great vessels and is the most common congenital anomaly with an incidence of 7–8 per 1,000 live births [1]. Approximately one-third of the patients have critical CHD (CCHD) requiring catheterization or surgery within the first year of life [1]. Accurate diagnosis of CCHD in the prenatal or early neonatal period is essential for timely treatment of the disease. While a group of CCHD has obvious clinical signs in the nursery, the physical examination might not detect cyanosis or other clinical signs in some babies before the completion of transitions from fetal to postnatal life [2]. Over the last 30 years, medical and technological advances have improved the outcome of neonatal cardiac surgery [3, 4]. However, CCHD remains an important cause of neonatal mortality [5]. Many studies have been conducted on the course of CHD in children, but rarely focused on neonatal outcomes.

CHD not only contributes to a global health problem with significant morbidity and mortality but also causes tremendous psychological stress and economic burden on the entire family. From this perspective, it would be useful to deepen our knowledge about possible risk factors associated with the poor outcomes of the disease. Although there are some single-center studies on the various aspects of CHD in our

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country, there is no multi-center study designed to investigate the epidemiology of CCHD in Turkey [6–8]. Therefore, in this project, we aimed to present 1-year data on the epidemiology and short-term results of newborns with CHD in our country.

Materials and Methods

Study Design

It was a prospective multicenter epidemiological study performed in tertiary neonatal intensive care units (NICUs) of Türkiye serving as reference centers for newborns with CCHD.

Initially, we announced the project to all the neonatologists serving in our country, via the Turkish Neonatal Society (TNS). Our target audience was neonatologists working in a 3rd-level NICU who followed up newborns with CCHD at both preoperative and postoperative periods in collaboration with pediatric cardiologists and cardiovascular surgeons. Finally, nine neonatal cardiac centers from eight cities were eligible for the study. As per the project's setup, a neonatologist, a pediatric cardiologist, and a cardiovascular surgeon from each center participated in the project.

Neonatologists, as representatives of their centers, were asked to prospectively add the data of their newborn patients with CCHD meeting the inclusion criteria to the online registration system of Trials-Network. (https://www.trialsnetwork.org/project_detail.php?id=68).

From October 2021 to November 2022, pooled records of 488 patients were evaluated and analyzed by the coordinator center (Center 1).

Below is the list of study centers with the number of registered patients:

- Center 1 (coordinator; 73 patients): Health Science University of Türkiye, Dr. Sami Ulus Research and Training Hospital, Ankara, Türkiye
- Center 2 (188 patients): Health Science University of Türkiye, Başakşehir Çam Sakura City Hospital, Istanbul, Türkiye
- Center 3 (114 patients): Health Science University of Türkiye, Gazi Yaşargil Research and Application Center, Diyarbakır, Türkiye
- Center 4 (28 patients): Başkent University, Medical Faculty, Ankara, Türkiye
- Center 5 (23 patients): Çukurova University, Medical Faculty, Adana, Türkiye
- Center 6 (16 patients): Health Science University of Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training And Research Hospital, İzmir, Türkiye
- Center 7 (15 patients): Istanbul Medipol University, International Faculty of Medicine, Istanbul, Türkiye
- Center 8 (14 patients): Uludağ University, Medical Faculty, Bursa, Türkiye
- Center 9 (13 patients): Beykent University Medical Faculty, Istanbul, Türkiye

Study Patients

Inclusion and Exclusion Criteria

Term or near-term (gestational age; GA ≥ 35 weeks) babies diagnosed with CCHD prenatally and/or within the first 30 days of life were eligible for the study. The patients followed up at the same center during both preoperative and postoperative periods with the collaboration of neonatologists, pediatric cardiologists, and cardiovascular surgeons were included. Premature infants (< 35 weeks of GA), non-critical CHD cases (small atrial septal defect; ASD/ventricular septal defect; VSD, hemodynamically insignificant patent ductus arteriosus; PDA, etc.), and patients with CHD but not followed up at the same center during the perioperative period were excluded.

Clinical Variables

Demographic and preoperative data included maternal age, maternal comorbid diseases, antenatal follow-up, delivery mode, delivery center, delivery at the same center (inborn), GA, birth weight, gender, APGAR scores, resuscitation at birth, pulse screening before obstetric discharge, style of presentation, clinical findings on admission, delayed diagnosis (after obstetric discharge), types of CCHD, the presence of major CCHD (Hypoplastic left heart syndrome; HLHS, total anomalous pulmonary venous drainage; TAPVD, transposition of great arteria; TGA, truncus arteriosus, interrupted aortic arch; IAA), and extra-cardiac malformations.

Preoperative clinical data included the need for prostaglandin E1 (PGE1), inotropes and mechanical ventilation (MV), the presence of comorbid conditions such as proven sepsis (positive blood culture), necrotizing enterocolitis ≥ grade 2 (NEC), acute kidney injury (AKI; an increase in serum creatinine of 0.3 mg/dL above the baseline within 48 h or 1.5 to 1.9 times the baseline serum creatinine value), multiorgan dysfunction syndrome (MODS; ≥ 2 organ dysfunctions), and intracranial hemorrhage (ICH; ≥ grade 2). Data on cardiac catheterizations (diagnostic or therapeutic) and associated complications were recorded.

Surgical variables included postnatal age (days) and weight at surgery, type of surgery, and use of cardiopulmonary bypass (CPB). For each patient, the Association of Thoracic Surgeons-European Association

of Cardiothoracic Surgeons (STAT) scores that predict the complexity of cardiac surgery were evaluated to analyze mortality risk [9].

Postoperative data included sepsis, renal failure (requiring dialysis), need for extracorporeal membrane oxygenation (ECMO) support, postoperative complications (diaphragmatic paralysis, chylous effusion, arrhythmia, ICH, low cardiac output syndrome (LCOS; oliguria, tachycardia, poor perfusion, or requiring cardiac arrest high dose inotropic support), and MODS. Major postoperative complications were defined as excessive bleeding (7 mL/kg/h or more for 2 or more consecutive hours in the first 12 postoperative hours), LCOS, MODS, and renal failure requiring dialysis. Data on discharge age and weight, length of stay, and mortality (death before discharge) were also collected.

Management

Echocardiographic (ECHO) comments of consultant pediatric cardiologists were taken into account for the final diagnosis CCHD. After initial evaluations, all cases were followed prospectively by ECHO to assess cardiac functions. Cardiac management were arranged according to the suggestions of the senior cardiologist. Patients received near-standard care according to individual ward protocols. Following surgery, inotropes and vasoactive agents were administered in the operating room at the discretion of the surgeon and cardiologist. Decisions regarding continuous vasoactive/inotropic titration were made by the cardiac team based on each patient's physiological status. In all centers, the patients received milrinone and dopamine/dobutamine as first-line inotropes. Second-line agents were often epinephrine for hypotension with ventricular dysfunction and norepinephrine and/or terlipressin for hypotension without ventricular dysfunction. For each patient, the vasoactive inotropic score (VIS) value for the first 72 h postoperatively was calculated using standard formula: dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × adrenaline dose (μg/kg/min)] + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (units/kg/min) + 100 × norepinephrine dose (μg/kg/min). The maximum score was recorded [6, 8]. CCHD neonatal follow-up intensive care unit locations may vary by study center. Neonates were cared for preoperatively in the NICU of all centers but could be observed postoperatively in the NICU or pediatric cardiac intensive care unit (PCICU) until discharge.

Study Outcomes

The primary endpoint was in-hospital mortality. Secondary outcomes included length of stay in the NICU/PCICU and the presence of major postoperative complications, such as excessive bleeding, LCOS, MODS, and renal failure requiring dialysis.

Statistical Analysis

All data were analyzed using SPSS Statistics for Windows version 23.0 (IBM SPSS Statistics for Windows version 23.0, Armonk, New York, IBM). Nominal variables are expressed as numbers and percentages, and continuous variables are expressed as mean ± standard deviation (SD) or median (min–max), depending on the homogeneity of the distribution assessed using the Kolmogorov–Smirnov test. For continuous variables, the Student's t test was used for the analysis of normally distributed data and the Mann–Whitney U test for non-normally distributed data. Categorical variables were expressed as numbers (n) and frequencies (%) and analyzed using the χ test. A p value of < 0.05 was considered statistically significant. Pearson or Spearman test was used for correlations. To determine the predictive values for mortality, the area under the curve (AUC) of VIS was defined. The best cut-off was chosen to utilize sensitivity and specificity from the Receiver operating characteristics (ROC) curve of the selected data.

Multivariate logistic regression analysis was used to evaluate predictors of mortality. Statistically significant variables in pairwise comparisons or possible risk factors for neonatal CHD mortality including as birth weight, gender, prenatal CHD diagnosis, major CHD diagnosis, early diagnosis (< 3 days of life), need for resuscitation at birth, presence of extra-cardiac anomaly, birth place (outer center), center's case volume (high), preoperative PGE1, MV and need for inotropes, preoperative AKI and MODS, higher STAT category (> 2), higher VIS score (> 17.5), prolonged postoperative MV duration (> 1 week), presence of major postoperative complications, need for postoperative dialysis, and ECMO were entered into the model.

Results

During the study period, 992 newborn patients from 9702 NICU admissions from all nine study centers were diagnosed with CHD. A total of 504 patients were not included in the study because of preterm birth and/or non-severe CHD. Ultimately, 488 neonatal CCHD patients were enrolled in the online registration system. The majority of patients were from the first 3 study centers as seen in the Methods section.

Approximately, 57.4% ($n = 280$) of patients were transferred to the study center from NICUs elsewhere in the country. A pulse oximeter screening test for CHD was performed in only 49 of the 488 study patients. Thirty-three of the 49 (67.3%) had a definitive diagnosis of her CCHD.

Spectrum of Congenital Heart Defects

TGA was the most common neonatal CHD, accounting for 19.5% ($n=95$) of all patients. Other common diagnoses were coarctation of the aorta (CoA) ($n=92$, 18.9%), pulmonary atresia/stenosis ($n=80$, 16.4%), and HLHS ($n=75$, 15.4%) (Fig. 1). A total of 204 patients had one of the five major CHDs. They were diagnosed earlier compared to other CHDs with higher rates of prenatal diagnosis (37.3%, 76/204; $p=0.01$), diagnosis within the first three days of life (80.8%, 165/204; $p<0.001$), and NICU admission at the postnatal first week (86.2%, 176/204; $p<0.001$).

Table 1 displays the demographic and clinical data of all study patients. The mean GA and birth weight were 38.4 ± 1.01 weeks and 3147 ± 473 g, respectively. Male subjects comprised 65% ($n=288$) of the whole study cohort. Most of the mothers (80.3%) belonged to the 21–35 years of age group. A family history of CHD was found to be 5.9%. Of all patients, 46.7% were born in a level three healthcare institution. The income level was less than twice the minimum wage in about half of the families. The educational status of the mothers was generally at the primary level (47.7%), while nearly half of the fathers were high school graduates (43.2%). The rate of immigrants (Syrian) patients was 12.7%.

Among the 488 cases, about one-third ($n=172$, 35.2%) had a prenatal diagnosis of heart defect, 121 (24.8%) were defined before obstetric or NICU discharge, but 92 (18.9%) could be diagnosed on readmission after discharge from the hospital as healthy (late diagnosis). The median (min–max) ages at the diagnosis of CCHD and NICU admission were 1 (0–28) and 2 (0–29) days. The most common presentation findings for CHD were respiratory distress and/or cyanosis ($n=241$, 49.4%), followed by hemodynamic instability ($n=15$, 3.1%) and cardiac murmur ($n=16$, 3.3%). Sixty-three (12.9%) patients had associated congenital anomalies

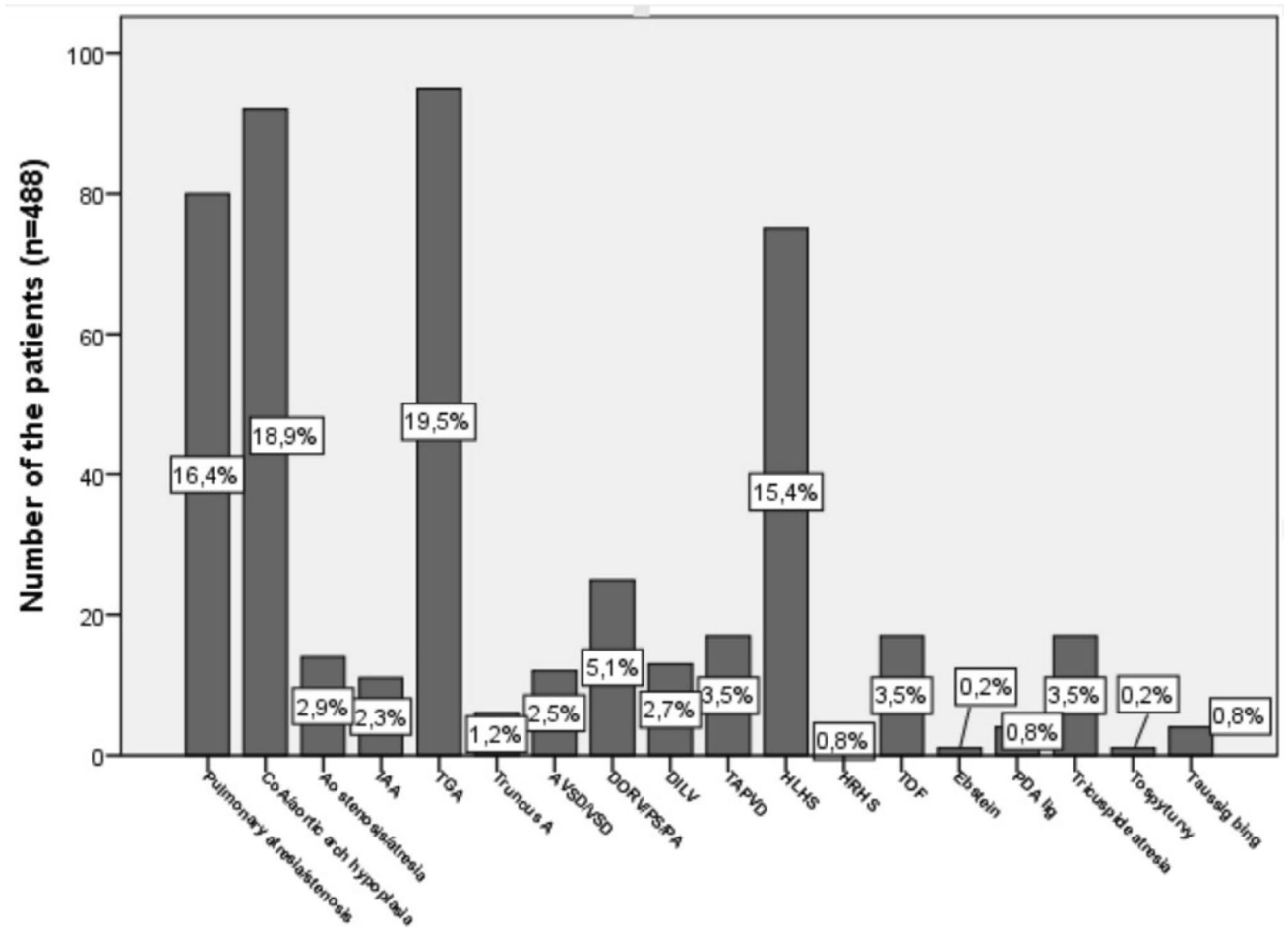

Fig. 1 Spectrum of the critical congenital heart defects (CCHD) in all study patients. TGA (Transposition of great arteria) was the most common disease, representing 19.5% of all cases. The other prevalent CCHDs were CoA (aortic coarctation) (18.9%), pulmonary atresia/stenosis (16.4%), HLHS (Hypoplastic left heart syndrome) (15.4%), and others. *AVSD* Atrioventricular septal defect, *DILV* double inlet left ventricle, *DORV* Double outlet right ventricle, *HRHS* Hypoplastic right heart syndrome, *IAA* Interrupted aortic arch, *PDA* Patent ductus arteriosus (requiring ligation), *TAPVD* Total anomalous pulmonary venous drainage, *TOF* Tetralogy of Fallot

Table 1 The demographic and clinical characteristics of all patients

Variables	All patients ($N=488$)
Maternal age (yr)	28.5 ± 5.5
Maternal disease (*n*, %)	
Gestational diabetes	77 (15.7)
Hypertension	46 (9.4)
Preeclampsia	5 (1.0)
Obesity	3 (0.6)
Smoking	3 (0.6)
Antenatal follow-up (≥ 4) (*n*, %)	287 (58.8)
Prenatal diagnosis (*n*, %)	172 (35.2)
Delivery type (CS/VD)	315/173
Birth center	
3rd-Level Children's Heart Center	228 (46.7)
3rd-Level NICU	163 (33.4)
2nd-Level NICU	91 (18.6)
Home birth	6 (1.2)
Born at the same center (*n*, %)	208 (42.6)
Gestational age (wk)	38.4 ± 1.01
Birth weight (g)	3147 ± 473
Gender (M/F)	288/200 (1.44/1)
Resuscitation at birth (*n*, %)	75 (15.4)
Pulse oximeter screening (n %)	49 (10.1)
Failed	33 (6.8)
Passed	16 (3.3)
Type of presentation (*n*, %)	
Prenatal diagnosis	172 (35.2)
Symptomatic, < 24 h of birth	121 (24.8)
Symptomatic, > 24 h of birth, in NICU	78 (16.0)
Positive pulse oximeter screening	25 (5.1)
Symptomatic after discharge	92 (18.9)
Age at diagnosis of CHD (postnatal day)	3.45 ± 5.9 (1; 0–28)
Age at NICU admission ((postnatal day)	5.02 ± 6.8 (2; 0–29)
Presentation Findings (*n*, %)	
Respiratory distress/cyanosis	241 (49.4)
Hemodynamic instability/shock	15 (3.1)
Heart murmur	16 (3.3)
Extra-cardiac malformations (*n*, %)	63 (12.9)

Numerical data are expressed as number (percentages), mean ± SD, and/or median (min–max)

AKI Acute kidney injury, *CHD* Congenital heart disease, *C/S* Cesarean delivery, *ICH* Intracranial hemorrhage, *MV* Mechanical ventilation, *NEC* Necrotizing enterocolitis, *PGE1* Prostaglandin E1, *VD* Vaginal delivery, *VIS* Vasoactive inotropic score

apart from their CHDs; genitourinary ($n=13$, 20.6%) and gastrointestinal system ($n=6$, 9.5%) anomalies were the commonest.

Preoperative clinical data are seen in Table 2. The 5th-minute APGAR score was < 7 in 41 patients. About 15.4% ($n=75$) of the patients required further resuscitation at birth. MV was needed for 251 (51.4%) patients. PGE1 was used in 325 (66.6%) and inotropic support in 217 cases (44.5%). Sepsis developed in 11.7% of the patients with a MODS rate of 2.0%.

Interventional angiography was performed on 157 (32.2%) patients and diagnostic angiography in 64 (13.1%) patients. Interventional procedures were ductal stent ($n=62$), balloon atrial septostomy ($n=39$), balloon valvuloplasty ($n=30$), aortic balloon angioplasty ($n=19$), and pulmonary stent ($n=7$). The frequency of catheter-related thrombosis was 6.7% ($n=15$).

A total of 325 (66.6%) patients underwent cardiac surgery during the study period (corrective: $n=239$, 74% and palliative: $n=86$, 26%). The mean age and body weight at surgery were 12 ± **9.3** days and 3247 ± 481 g, respectively. The types of the main surgeries were aortic arch repair ($n=96$), arterial switch operations (ASO) ($n=83$), modified Blalock Taussig shunt (MBTS) ($n=43$), pulmonary artery banding (PAB) ($n=27$), Norwood surgery ($n=26$), the hybrid procedure for HLHS ($n=17$), TAPVD correction ($n=12$ cases), and common truncus repair ($n=2$) (Fig. 2). The median postoperative VIS score was 15 (5–320).

Among the 325 neonatal cardiac surgeries, 206 (63.3%) were performed with CPB, and 21 cases (6.4%) needed ECMO. LCOS was defined in 92 patients (28.3%). Five (1.5%) patients had chylous effusion and 6 (1.8%) patients had diaphragmatic paralysis (one needed plication). Excessive hemorrhagic complications were observed in 57 patients (17.5%) (7 of them were on ECMO support). Fifty-eight (17.8%) patients had postoperative bloodstream infections. The commonest organisms were coagulase-negative staphylococci (CONS, 8 cases) followed by acinetobacter (7 cases), klebsiella (5 cases), and pseudomonas (5 cases).

The median postoperative NICU stay was 13 days (0–197). Postnatal age at discharge was 28.0 ± 26.7 days (21; 1–185) with a length of overall hospital stay of 23.8 ± 23.9 days (17; 1–200). Longer hospital stay was related to lower birth weight ($r=-0.04$, $p=0.001$), older age at surgery ($r=0.25$, $p=0.001$), and prolonged MV support (> 1 week) ($r=0.78$, $p<0.001$). Overall, in-hospital mortality was 20.1% (98/488) with a 19.6% (64/325) postoperative mortality rate for all corrective and palliative neonatal cardiac surgeries.

Mortality Groups

The patients were divided into two groups according to mortality status: Group 1 (Non-survivors) ($n=98$) and Group 2 (Survivors) ($n=390$). Maternal age, GA, birth weight, gender, delivery mode, family history of CHD, and prenatal diagnosis were similar in groups. The frequencies of extra-cardiac malformations were higher in Group 1 ($p=0.007$). Only 20 patients weighed < 2500 g at the time of surgery;

Table 2 Perioperative clinical data of all patients

Preoperative	N = 488
PGE1 (*n*, %)	325 (66.6)
Inotrope (*n*, %)	217 (44.5)
Mechanical ventilation (*n*, %)	251 (51.4)
Sepsis (*n*, %)	57 (11.7)
NEC (*n*, %)	5 (1.0)
AKI (*n*, %)	21 (4.3)
MODS (*n*, %)	10 (2.0)
ICH (*n*, %)	3 (0.6)
Operative and postoperative	**N = 325**
Age at surgery (day)	12 ± 9.3
Weight at surgery (g)	3247 ± 481
Type of heart surgery (*n*, %)	325 (66.6)
Open (with CPB)	206 (63.3)
Closed	119 (36.6)
Corrective	239 (73.5)
Palliative	86 (26.4)
STAT category (*n*, %)	
I	27 (8.3)
II	11 (3.4)
III	149 (45.8)
IV	106 (32.6)
V	32 (9.8)
ECMO (*n*, %)	21 (6.4)
Sepsis (*n*, %)	58 (17.8)
Dialysis (*n*, %)	61 (18.8)
Duration of MV (day)	8.68 ± 19.0 (3; 1–197)
VIS score (first 72 h)	28.7 ± 41.1 (15; 5–320)
Postoperative complications	
LCOS	92 (28.3)
Bleeding	57 (17.5)
MODS	14 (4.3)
Diaphragmatic paralysis	6 (1.8)
Chylothorax	5 (1.5)
N. recurrens paralysis	3 (0.9)
Postoperative length of stay	20.0 ± 23.6 (13; 0–197)

Numerical data are expressed as number (percentages), mean ± SD, and/or median (min–max)

AKI Acute kidney injury, *ECMO* Extracorporeal membrane oxygenation, *ICH* Intracranial hemorrhage, *MV* Mechanical ventilation, *NEC* Necrotizing enterocolitis, *PGE1* Prostaglandin E1, *STAT* The Society of Thoracic Surgeons, *VIS* Vasoactive inotropic score

no difference was found in mortality between these patients and those who were heavier ($p = 1.00$). The mortality rate was higher among the patients who needed resuscitation at birth ($p = 0.03$).

As expected, the mortality rate was significantly higher in patients with major CCHD ($p < 0.001$). The rate of post-discharge diagnosis was lower among died patients ($p = 0.006$). The rates of preoperative and postoperative complications were more frequent, STAT categories were higher, postoperative VIS scores were higher, and NICU stay was shorter in non-survivors compared to survivors ($p < 0.05$, for all comparisons) (Table 3).

A greater VIS score was correlated to a longer duration of postoperative MV ($r = 0.14$, $p = 0.01$). AUC was 0.75 ($p < 0.001$, 95% confidence interval; CI 0.67–0.82) for VIS to identify mortality. At a cut-off value of 17.5, as defined by ROC analysis, sensitivity and specificity values of VIS for mortality were 73.6% and 68.5%; VIS was > 17.5 in 130 patients (26.6%).

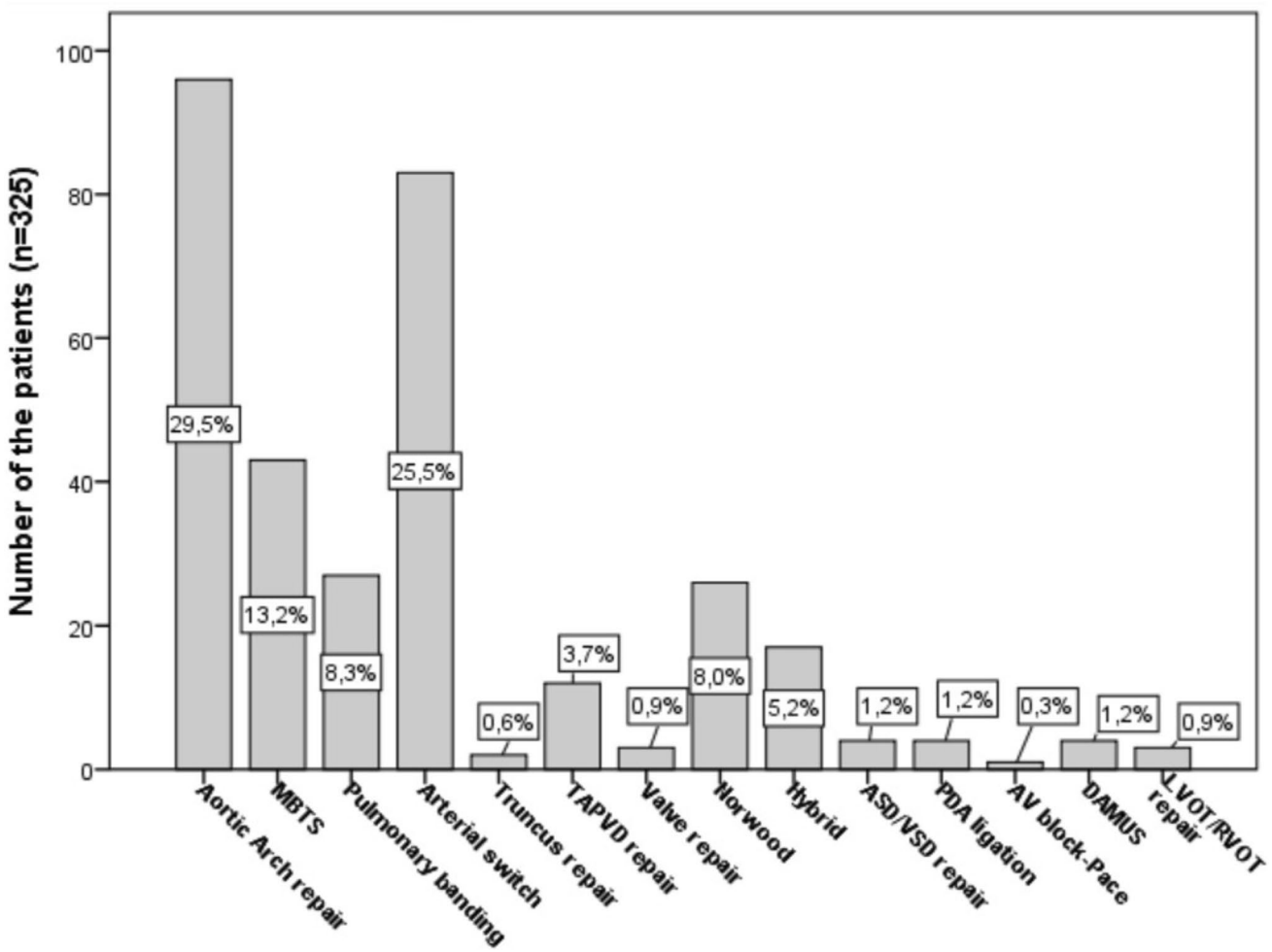

Fig. 2 Spectrum of the cardiac surgeries in all study patients. *TAPVD* Total anomalous venous drainage, *ASD/VSD* Atrial septal defect/ventricular septal defect, *AV block* Atrioventricular block, *LVOT/RVOT* Left ventricular outflow tract/right ventricular outflow tract, *MBTS* Modified Blalock–Taussig shunt, *PDA* Patent ductus arteriosus (requiring surgical ligation)

There were significant differences among STAT categories ($p < 0.001$) and mortality rates ($p < 0.001$) when all centers were compared separately. Figure 3 shows the STAT scores and categories according to mortality in all study centers.

Since the case volume loads were different among the centers, they were grouped as "high volume" (first 3 centers) and "low volume" (other 6 centers) (see Methods section). The groups were compared whether there were differences in terms of clinical features and outcomes. The immigrant rate and postoperative dialysis requirement were higher in the high-volume group, while the rates of prenatal diagnosis, pre- and postoperative sepsis and MODS, as well as VIS scores were higher in low-volume centers. STAT categories and mortality rates were similar between groups (Table 4).

As shown in Table 5, multivariate logistic regression analysis of survival demonstrated that need of PGE1 before intervention, higher VIS, the presence of major postoperative complications, and the need for ECMO during the early postoperative period were the risk factors for mortality.

Discussion

This study showed that neonates with severe CCHD referred for early cardiac intervention/surgery still have high mortality and morbidity. Critical care physicians should therefore be aware of risk factors that may be associated with poor CCHD outcomes. Maternal aging has been suggested to be a risk factor for her CHD in children of various races. In a study by Abkari et al., [10], the odds of CHD were 2.5 for mothers aged 20 to her 30 years and 2.8 for mothers aged 30 years or older. In our study, most mothers were aged between 20 and 35 years. CHD seems to occur in both older and younger mothers. We noted that 5.9% of patients had a family history of CHD, which

Table 3 Pre- and postoperative characteristics of all patients by mortality groups

Preoperative variables ($n=488$)	Group 1 (non-survivors) ($n=98$)	Group 2 (survivors) ($n=390$)	p value
Maternal age (yr)	27.6 ± 5.3	28.7 ± 5.6	0.96
Gestational age (wk)	38.3 ± 1.03	38.5 ± 1.01	0.83
Birth weight (g)	3006 ± 517	3183 ± 455	0.43
Gender (male), *n* (%)	52 (46.9)	236 (60.5)	0.20
Delivery mode (CS), *n* (%)	64 (65.3)	251 (64.4)	0.48
Resuscitation at birth, *n* (%)	22 (22.4)	53 (13.6)	**0.03**
Immigrants, *n* (%)	7 (7.1)	55 (14.1)	0.06
Family history of CHD, *n* (%)	6 (6.1)	23 (5.9)	1.0
Prenatal diagnosis, *n* (%)	41 (41.8)	131 (33.5)	0.15
Extra-cardiac malformations, *n* (%)	21 (21.4)	42 (10.8)	**0.007**
Late diagnosis (after discharge), *n* (%)	14 (14.3)	108 (27.7)	**0.006**
Major CHD, *n* (%)	56 (57.1)	148 (37.9)	**< 0.001**
Mechanical ventilation, *n* (%)	78 (79.6)	173 (44.4)	0.54
Morbidities, *n* (%)			
Sepsis	12 (12.2)	45 (11.5)	0.84
AKI	13 (13.3)	8 (2.1)	**< 0.001**
MODS	6 (6.1)	4 (1.0)	**0.006**
Operative and postoperative variables	Group 1 (non-survivors) ($n=65$)	Group 2 (survivors) ($n=260$)	p value
Age at surgery (d)	11.6 ± 10.7 (9; 2–71)	12.5 ± 8.9 (9; 2–45)	0.45
VIS score	54.4 ± 63.7 (35; 5–320)	22.3 ± 30.1 (15; 5–260)	**< 0.001**
STAT category (> 2), *n* (%)	63 (96.9)	224 (86.2)	**0.01**
Weight at surgery (gr)	3213 ± 529	3256 ± 469	0.18
Postop MV day (day)	11.7 ± 20.6 (3;1–111)	7.9 ± 18.6 (3; 1–192)	0.14
Postoperative morbidities, *n* (%)			
Sepsis	13 (20.0)	45 (17.3)	0.60
AKI	16 (24.6)	23 (8.8)	**< 0.001**
Dialysis	27 (41.5)	34 (13.1)	**< 0.001**
ECMO	16 (24.6)	5 (1.9)	**< 0.001**
Postoperative NICU stay (d)	13.6 ± 23.9 (4; 1–114)	21.2 ± 23.3 (1–197)	**< 0.001**
Overall NICU stay (d)	22.1 ± 26.3 (13.5; 1–150)	24.2 ± 23.3 (17; 1–200)	**0.006**

Numerical data are expressed as number (percentages), mean ± SD, and/or median (min–max)

Bold values denote statistical significance at the $p < 0.05$ level

AKI Acute kidney injury, *CHD* Congenital heart disease, *ECMO* Extracorporeal membrane oxygenation, *MV* Mechanical ventilation, *MODS* Multiorgan dysfunction syndrome, *STAT* The Society of Thoracic Surgeons, *VIS* Vasoactive inotropic score

is not negligible. This may be related to the high rate of consanguineous marriages in our country [11]. Studies in South Asian countries have stated that the CHD is more common in boys in this region due to cultural factors and genetic backgrounds [12–14]. In our project, CHD was also observed to be more common in boys (59%), with a male-to-female ratio of 1.44. Although fetal ultrasound reveals a significant proportion of cardiac defects, 30% of newborns are discharged with her undiagnosed CCHD [15, 16]. After birth, as symptoms and signs are usually subtle or lacking, CCHD may be missed in the routine clinical examination of newborns. In 2011, the American Academy of Pediatrics (AAP) recommended the screening of newborns with pulse oximetry for an early diagnosis of CCHD, and the strategies were updated by an expert panel in 2020 [17]. Today, postnatal CCHD screening has been conducted in many developed countries. In a multicenter study from Türkiye, 4888 babies were screened, and the authors stated that pulse oximetry screening was an effective screening tool for CCHD in newborns at different altitudes [18]. Delayed diagnosis of CCHD has been suggested to be associated with increased risk for permanent injury of vital organs, including the brain and even mortality [19]. Zhang et al. [20] assessed the survival rate of newborns with a delayed diagnosis of CCHD in Beijing between 2010 and 2017. They reported that

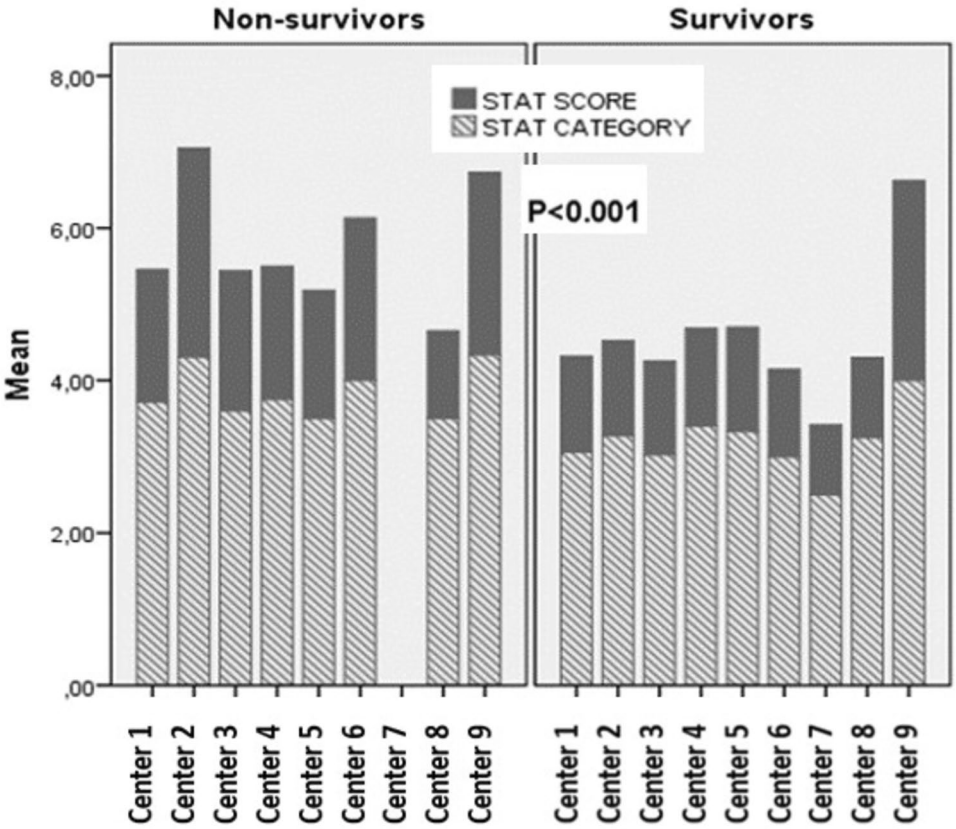

Fig. 3 STAT scores, categories, and mortality rates according to all study centers

the majority (91.4%) of the CCHD cases were identified through prenatal diagnosis, 5.62% were diagnosed before obstetric discharge/transfer, and 2.97% were identified through delayed diagnosis. The authors found that only gestational age at delivery was an important risk factor for death within the first week of life. A study found that 33% of infants with critical CHD were diagnosed post-birth [21]. These infants often have very serious issues, such as TOF, HLHS, pulmonary atresia, TAPVD, TGA, tricuspid atresia, and truncus arteriosus, which can be life-threatening and may need immediate intervention. In our study, the survival rate was higher among patients with delayed diagnosis which might be explained by the higher chance of early diagnosis of complex major CCHDs. In many studies investigating the CHD spectrum, generally, all cardiac defects have been taken into account. A previous study from Atlanta [22] evaluated the data on infants with CHD delivered during 1998 to 2005 identified by the Metropolitan Atlanta Congenital Defects Program. They reported that the prevalence of Tetralogy of Fallot (TOF), the most common cyanotic CHD, was twice that of transposition of the great arteries (4.7 vs 2.3/10 000 births). In 2022, Singh et al. [23] estimated the frequency and pattern of CHD in children in India. They found that TOF was the most common cyanotic CHD, comprising 16% of their cohort. In the current study, the most common CCHD was TGA and accounted for 19.5% of CHD cases. The other frequent diagnoses were CoA (18.9%), pulmonary atresia/stenosis (16.4%), and HLHS (15.4%).

Congenital heart disease is often coexisting with defects affecting structures other than the heart. Chromosomal disorders, central nervous system malformations, abdominal wall defects, gastrointestinal pathologies, and urinary system abnormalities are the most common extra-cardiac malformations, observed in approximately 7–50% of patients with CHD [24]. These defects have a significant impact on the clinical course of CHD and pose a high risk of morbidity and mortality in these patients, in addition to increased risk for surgical correction. In our study, 12.9% of the patients had extra-cardiac anomalies, and genitourinary (20.6%) and gastrointestinal system (9.5%) anomalies were the commonest malformations.

Our results suggest that although recent data indicate a general trend of improving neonatal outcomes, significant differences between centers still exist, similar to previous studies. Mirren et al. [25] used her 5-year data from the military medical system to explore the impact of geographic differences on outcomes for her < 10-year-old patients undergoing CHD surgery. Hospitalization costs are higher for patients admitted from rural or distant locations, but mortality and length of stay are reported to be similar to other patients. Patients were found to be visiting distant hospitals,

Table 4 Preoperative and postoperative characteristics of all patients according to case volume grouping in centers

Preoperative variables ($n=488$)	High volume ($n=375$)	Low volume ($n=113$)	p value
Maternal age (yr)	28.2 ± 5.6	29.5 ± 5.2	0.91
Gestational age (wk)	38.5 ± 1.0	38.5 ± 0.9	0.19
Birth weight (g)	3127 ± 470	3214 ± 477	0.95
Gender (male), *n* (%)	219 (58.4)	69 (61.06)	0.61
Delivery mode (CS), *n* (%)	238 (63.4)	77 (68.1)	0.36
Resuscitation at birth, *n* (%)	63 (16.8)	12 (10.6)	0.11
Immigrants, *n* (%)	58 (15.4)	4 (3.5)	**< 0.001**
Family history of CHD, *n* (%)	24 (6.4)	5 (4.4)	0.43
Prenatal diagnosis, *n* (%)	111 (29.6)	61 (54.0)	**< 0.001**
Extra-cardiac malformations, *n* (%)	45 (12)	18 (15.9)	0.27
Late diagnosis (after discharge), *n* (%)	77 (20.5)	15 (13.2)	0.08
Major CHD, *n* (%)	159 (42.4)	45 (39.2)	0.62
Mechanical ventilation, *n* (%)	187 (49.8)	64 (56.6)	0.20
Morbidities, *n* (%)			
Sepsis	34 (9.06)	23 (20.3)	**< 0.001**
AKI	14 (3.7)	7 (6.1)	0.25
MODS	2 (0.5)	8 (7.08)	**< 0.001**
Operative and postoperative variables ($n=325$)	High volume ($n=238$)	Low volume ($n=87$)	p value
Age at surgery (d)	12.2 ± 9.0 (2–71)	12.6 ± 9.9 (2–45)	0.23
VIS score	21.1 ± 24.6 (12.5; 5–170)	49 ± 64.0 (30; 5–320)	**< 0.001**
STAT category (> 2), *n* (%)	212 (89.1)	75 (86.2)	0.47
Weight at surgery (gr)	3211 ± 469	3348 ± 502	0.27
Postop MV day (day)	7.9 ± 19.2 (3; 1–197)	10.7 ± 18.5 (4; 1–93)	0.10
Postoperative morbidities, *n* (%)			
Sepsis	34 (9.0)	24 (21.2)	**< 0.001**
AKI	30 (12.6)	9 (10.3)	0.57
Dialysis	55 (23.11)	6 (6.9)	**< 0.001**
ECMO	16 (6.7)	5 (5.7)	0.75
Postoperative NICU stay (d)	19.1 ± 22.8 (12; 1–197)	22.3 ± 25.4 (14; 1–148)	0.78
Overall NICU stay (d)	22.1 ± 21.5 (17 (1–200)	29.2 ± 30.1 (19; 1–169)	0.05
Mortality, *n* (%)	71 (18.9)	27 (23.8)	0.24

Numerical data are expressed as number (percentages), mean ± SD, and/or median (min–max)

Bold values denote statistical significance at the $p < 0.05$ level

AKI Acute kidney injury, *CHD* Congenital heart disease, *ECMO* Extracorporeal membrane oxygenation, *MV* Mechanical ventilation, *MODS* Multiorgan dysfunction syndrome, *STAT* The Society of Thoracic Surgeons, *VIS* Vasoactive inotropic score

especially high-volume centers. Our results show variability in morbidity (severe complications) as well as mortality. At the time of this writing, there were approximately 35 pediatric heart centers in our country. The nine centers participating in this study were the busiest hospitals, and patients were referred from regional hospitals to the nearest heart center. In some cases, patients are transferred to more distant centers due to lack of beds at the nearest center or family wishes.

It has been proven that infants with CHD, complex, and/or combined CHD may need extensive resuscitation just after delivery [26]. In the current analysis, the 5th-minute APGAR score was < 7 in 41 patients, and 15.4% of the newborns with critical CHD in required further resuscitation at birth. The mortality rate was higher in those who needed resuscitation. APGAR scores may be reflective of fetal well-being in late gestation, tolerance of labor, adequacy of transitional cardiopulmonary physiology during the first few minutes of life, or quality of initial resuscitation.

The ideal age for cardiac intervention in newborns with CHD is unknown. In newborns, cardiovascular interventions may be performed late because of a wrong/late diagnosis of CHD in another center, delayed transfer of the patients, understaffing of the departments, and clinical condition of the patients. Interestingly, we did not find any relationship between postnatal age at the time of surgery and mortality. In studies of premature infants with CHD, it has been

Table 5 Multivariate regression analysis

Preoperative variables ($n=488$)	Group 1 (non-survivors) ($n=98$)	Group 2 (survivors) ($n=390$)	p value	OR	CI 95% (min–max)
Birth weight	3006 ± 517	3183 ± 455	0.9	1.0	0.9–1.01
Gender (Boy)	52 (53.1)	236 (60.5)	0.32	0.83	0.5–1.1
Prenatal diagnosis (yes)	41 (41.8)	131 (33.5)	0.59	1.1	0.6–1.9
Major CHD (yes)	56 (57.1)	148 (37.9)	0.78	0.9	0.6–1.4
Early diagnosis (< 3 day of life)	84 (85.7)	282 (72.3)	0.9	0.97	0.5–1.6
Resuscitation at birth (yes)	22 (22.4)	53 (13.6)	0.8	0.9	0.5–1.5
Extra-cardiac anomaly	21 (21.4)	42 (10.8)	0.45	1.2	0.7–2.1
Birth place (outer center)	50 (51.0)	230 (59.0)	0.57	1.1	0.7–1.8
Center case volume (high)	71 (72.4)	304 (77.9)	0.51	0.71	0.2–1.9
Preop PGE1 (yes)	87 (88.8)	238 (61.0)	**0.02**	1.8	1.0–3.0
Preop MV (yes)	78 (79.6)	173 (44.3)	0.97	1.0	0.6–1.6
Preop inotrope (yes)	67 (68.4)	150 (38.5)	0.53	1.1	0.7–1.8
Preop AKI (yes)	13 (13.3)	8 (2.1)	0.97	0.97	0.19–4.8
Preop MODS (yes)	6 (6.1)	4 (1.0)	0.47	1.5	0.4–5.0
Operative and postoperative variables ($n=325$)	Group 1 (non-survivors) ($n=65$)	Group 2 (survivors) ($n=260$)	p value	OR	CI 95% (min–max)
STAT category (> 2)	63 (96.9)	224 (86.2)	0.23	1.7	0.6–4.3
VIS score (> 17.5)	47 (72.3)	83 (31.9)	**0.009**	1.7	1.1–2.6
Postop MV (> 1 week)	25 (38.4)	43 (16.5)	0.42	1.1	0.77–1.8
Major postoperative complications (yes)	46 (70.7)	85 (32.6)	**0.01**	2.9	1.2–6.6
Postop dialysis (yes)	27 (41.5)	34 (13.0)	0.56	0.76	0.3–1.9
Postop ECMO (yes)	16 (24.6)	5 (1.9)	**0.001**	3.0	1.5–5.9

Bold values denote statistical significance at the $p < 0.05$ level

AKI Acute kidney injury, *CHD* Congenital heart disease, *CPB* Cardiopulmonary bypass, *ECMO* Extracorporeal membrane oxygenation, *MV* Mechanical ventilation, *PGE1* Prostaglandin E1, *STAT* The Society of Thoracic Surgeons, *VIS* Vasoactive inotropic score

suggested that postponing the surgery for growth and maturation of the patients both delays definitive cardiac intervention and leads to poor outcomes [27, 28].

In this challenging patient population, a weight < 2500 g at the surgery rather than prematurity is reported as a risk factor. In single-center studies, weight during surgery < 2500 g mortality rates range from 10 to 24% [29, 30]. In the current research, small premature babies were not included in the project. Body weight at surgery was < 2500 g in only 20 of the patients. Therefore, weight at surgery was not found to be an important risk factor for surgery-related CHD mortality in the current study.

The repair or palliation of neonatal CCHD often results in a decrease in cardiac output requiring inotropic and vasoactive agents during and after surgery. Gaies et al. [6] developed VIS in 391 children < 6 months of age undergoing cardiac surgery with CPB. They reported high VIS (> 15) in the first 24 h of surgery was significantly associated with 30-day mortality, duration of mechanical ventilation, and ICU stay. In 2019, Dilli et al. [8] studied on newborns with CCHD and stated that a higher VIS within 72 h after cardiac surgery was associated with increased duration of MV and mortality. In the current study, similarly, we found that higher VIS scores were associated with longer MV days, extended NICU stay, and mortality. Increased need for inotropic support in the early postoperative period was a risk factor for mortality in our study. Despite speculative, intensive medical treatment with inotropes and MV may be indicative of instability cardiopulmonary state leading to intervention.

Another score available is STAT Mortality Category for the prediction of morbidity and mortality risk in newborns who underwent CHD surgery. We recorded a 19.6% overall operative mortality rate for all corrective and palliative neonatal cardiac surgeries. It seems higher than the operative mortality reported in the Society of Thoracic Surgeons (STS) database (12.2%) and the European Association for Cardio-Thoracic Surgery (EACT) database (13.3%) [9]. Nevertheless, it is a challenging task to compare outcomes and survival rates due to the complex relationship between cardiac surgical case volumes and mortality rates. This variation was evident across the spectrum of risk and contrary to traditional belief was not confined solely to higher-risk cases. Several previous studies using a variety of different data sources have documented variability in

outcomes across hospitals for patients undergoing congenital heart surgery. In the Pediatric Heart Network's Single-Ventricle Reconstruction Trial, which enrolled patients from 2005 to 2008, the rate of in-hospital death or transplant after the Norwood operation ranged from 7 to 39% across 14 trial sites analyzed [31]. In our study, The STAT category was ≥ 3 in 88.2% of operated patients. The differences in STAT categories and mortality rates among all centers were remarkable.

Many previous studies have shown that center volume is associated with outcome in children undergoing a variety of surgical procedures, including heart surgery [32, 33]. It has been reported that in centers with small pediatric cardiac surgery volumes, mortality was higher when case complexity increased. Pasquali et al. [34] investigated the role of center volume on outcome of CHD in children undergoing heart surgery. A total of 35,776 patients (68 centers) were included. They found that lower center volume was significantly associated with higher in-hospital mortality. The authors commented that the higher mortality observed at lower volume centers might be related to a higher rate of mortality in those with postoperative complications, rather than a higher rate of complications alone. In the current research, we found that STAT categories and mortality rates were similar between groups.

The repair of complex CCHDs frequently requires CBP. However, CPB is associated with inflammation, immune paresis, and disorders in the coagulation system. Therefore, greater surgical mortality is associated with CPB procedure [30]. Recently, Elassal et al. [35] reported that the requirement of postoperative ECMO support, postoperative ICH, and AKI were identified as independent risk factors of mortality following surgery for CHD in newborns. In our study, mortality was similar among patients who were operated on with or without CPB. Multivariate analysis revealed that use of PGE1 before intervention, higher VIS, the presence of major postoperative complications, and the need for dialysis and ECMO during the early postoperative period were the risk factors for mortality.

CHD is a main cause of neonatal mortality due to congenital defects. Despite regional differences, several studies have shown a significant reduction in mortality and morbidity over the past decades thanks to advances in surgery, anesthesia, and NICU/PCICU care [36, 37]. Wu et al. [36] reported that the incidence of CHD was relatively high in developing countries in Africa and Asia, while it was low in most developed countries, remaining stable over the last 30 years (1990–2017). In the Bateson et al. [37] study, 16,040 patients with CHD were evaluated for two years by comparing low- and high-income countries. The average age at cardiac surgery across all centers was 2.2 years, with 36% being < 6 months of age. The overall mortality rate of the cohort was 2.27%, ranging from 2.6% in underdeveloped centers to 0.55 in developed ones. In a recent meta-analysis on 1658 low birth weight infants operated for CHD, Derridj et al. [38] found that mortality before discharge or within one month after surgery was 37%. In our study, the total mortality rate in the neonatal and early post-neonatal period was 20.1%. When compared to the literature, the higher mortality in our study may be due to the smaller postnatal ages and birth weights of the babies, the lower prenatal diagnosis rate (30%), the lack of termination due to social, cultural, and religious beliefs even in cases diagnosed with severe CHD prenatally, and the lack of infrastructure.

Our study has some limitations. First of all, the management of the patients in different centers may have affected the study outcomes. In addition, we did not include premature infants with CHD, which may be a source of selection bias. Finally, available data from nine of 35 pediatric heart centers could not fully represent the CHD profile in Türkiye. However, most of the centers that participated in the project were the ones with the highest patient volume. In addition, as the study centers were from different geographic regions far from each other, we can have some ideas about the country's realities. In this way, we believe that our prospective data reflect multicenter experiences in neonates with CHD in a well-defined study population.

In conclusion, this multicenter study revealed that although there are some differences between pediatric heart centers in our country, mortality in newborns with CHD who was referred for intervention in the first month of life remained high. It is important to consider the implications of our findings in conjunction with other national efforts. More research should be designed to identify differences in long-term outcomes.

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Data Availability The data that support the findings of this study are available on request from the corresponding author (DD).

Declarations

Conflict of interest The authors have no competing interests to disclose.

Ethical Approval This study was approved by the Institutional Review Board of the TNS Multicenter Research Scientific Steering Committee (E-21/04-162, date: April 7, 2021). Verbal and written informed consent were obtained from the parents of the newborns.

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