# Timing of cardiac surgical interventions and postoperative mortality in children with severe congenital heart defects across Europe: Data from the EUROlinkCAT study

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Short title: cardiac defect surgery in children

Word count: 2658

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**Abstract**

*Background:* To evaluate timing of first cardiac surgery, number of cardiac surgeries performed and 30-days postoperative mortality for children with severe congenital heart defects (sCHD) in their first five years of life.

*Methods and results*: Population-based data linkage cohort study linking information from nine European congenital anomaly registries to vital statistics and hospital databases. Data were extracted for 5,693 children born 1995-2004 with sCHD. Subgroup analysis were performed for specific types of sCHD. Children with sCHD underwent their first surgical intervention at a median age of 3.6 (95% CI: 2.6–4.5) weeks. Timing of first surgery for most sub-types of sCHD was consistent across Europe. In the first five years of life, children with hypoplastic left heart (HLH) underwent the most cardiac surgeries with a median of 4.4 (95% CI: 3.1–5.6). The 30-day postoperative mortality in children under 1 year of age ranged from 1.1% (95% CI: 0.5-2.1) for Tetralogy of Fallot to 23% (95% CI: 12–37%) for Ebstein’s anomaly. The 30-day postoperative mortality was highest for children operated in the first month of life. Overall 5-year survival for sCHD was below 90% for all sCHDs, except Transposition of the Great arteries, Tetralogy of Fallot and Coarctation of the aorta.

*Conclusion*: There were no major differences between the nine regions in the timing, 30-days postoperative mortality and number of operations performed for sCHD. Despite an overall good prognosis for most CHDs, some lesions were still associated with substantial postoperative mortality.

**Keywords**: congenital heart defects, paediatric cardiology, cardiac surgery

**Clinical Perspective**

**What is new?**

* This study offers a comprehensive analysis of surgical interventions in severe congenital heart disease across European regions, revealing consistent timings for conditions like TOF, TGA, and AVSD. Notably, HLH and HRH cases involve early, frequent surgeries. While overall survival is positive, critical conditions like HLH show 5-year survival of approximately 50%.

**What are the clinical implications?**

* The study informs optimal surgical timing for congenital heart disease, aligning with recommendations for TOF and AVSD. Vigilance is crucial for managing high-frequency surgeries and mortality risks in HLH and HRH. Population-based data is vital for accurate mortality assessment, emphasizing the risk of delayed surgical repair, especially for AVSD.

**Nonstandard abbreviations and nonstandard acronyms**

AVSD - atrioventricular septal defect

BGP - Bidirectional Glenn Procedure

CHD - Congenital heart defects

CI - Confidence Interval

CoA - coarctation of the aorta

DORV - Double Outlet Right Ventricle (inferred from context)

EUROlinkCAT – The EUROlinkCAT study relies on EUROCAT infrastructure to support 21 EUROCAT registries in 13 European countries to link their congenital anomaly data to mortality, hospital discharge, prescription and educational databases.

EUROCAT - An established European network of population-based registries for the epidemiologic surveillance of congenital anomalies.

HLH - Hypoplastic Left Heart

HRH - hypoplastic right heart syndrome

ICD-9 - International Classification of Diseases, 9th Revision

ICD-10 - International Classification of Diseases, 10th Revision

ICD-9-CM - International Classification of Diseases, 9th Revision, Clinical Modification

ICU - Intensive Care Unit

IRB - institutional review board

KM - Kaplan Meier

NCSP - NOMESCO Classification of Surgical Procedures

OPCS-4 - Classifications of Interventions and Procedures

PA - Pulmonary Atresia

sCHD - severe CHDs

TAPVR - total anomalous pulmonary venous return

TGA - Transposition of the Great Arteries

TOF - Tetralogy of Fallot

**Introduction**

Congenital heart defects (CHD) are a considerable cause of both morbidity and mortality in infants and children. For instance we showed in an earlier EUROlinkCAT study that, 40% of all surgical interventions in children <1 year of age are performed in those with CHD. The most prevalent severe CHDs (sCHD) include atrioventricular septal defect (AVSD), Tetralogy of Fallot (TOF) and Transposition of the Great Arteries (TGA) 1. Although the surgical strategy differs between lesions (i.e. complete operative correction in one procedure for AVSD versus staged repair in Hypoplastic Left Heart (HLH)), complete surgical correction or stage II palliation is recommended in all children with sCHD within the first year of life 2-6. The optimal timing with regard to age or weight of the child remains to be determined. As pointed out by Holst and co-workers, “*outcomes and practices in CHD continue to be relatively heterogeneous; this is largely because of surgeon-specific practices, institutional preferences, and heterogeneity inherent to CHD*“7. Differences in surgical timing between institutions may further be affected by differences in case-mix and as such it can be difficult to directly compare tertiary sCHD surgical centers. Additionally, not all children with sCHD reach the tertiary surgical centers or they may not be offered surgery. Therefore, population-based studies including all liveborn children with sCHD are important for evaluating their morbidity and mortality.

As part of the EUROlinkCAT project 8 we sought to evaluate timing of the first cardiac surgical intervention, the number of cardiac surgical interventions, postoperative mortality and survival in children born with sCHD across nine European Regions in six countries for the first 5 years of life.

**Methods**

This is a European, population-based linkage cohort study arising from the EUROlinkCAT project 8. This project includes data on morbidity and mortality for children born with congenital anomalies. As described in detail in 9, 21 registers originally agreed to participate. Due to challenges in obtaining local ethics permits or quality of data linkage nine registers were able to participate in the present study; all of which are from Western Europe.

*Study population*: All children reported in the EUROCAT congenital anomaly registries with the below listed ICD-10 diagnoses. Finland and Funen (Denmark) used the equivalent ICD-9 codes for part of the study period, and these were translated and mapped to corresponding ICD-10 codes. For comparison of ICD-9 and ICD-10 codes please refer to Table S1. The following EUROCAT defined cardiac subgroups were included in the study 10:

*Severe CHD (sCHD)*: all diagnoses of common arterial truncus, DORV (double outlet right ventricle), TGA, single ventricle, AVSD, TOF, pulmonary valve atresia (PA), tricuspid atresia or stenosis, Ebstein’s anomaly, hypoplastic right heart syndrome (HRH), aortic valve atresia or stenosis, mitral valve anomalies, HLH, coarctation of the aorta (CoA), interrupted aortic arch, and total anomalous pulmonary venous return (TAPVR).

The main results presented in this study are for children with isolated sCHD only (although a child could have >1 type of cardiac anomaly). Children with associated major anomalies in other organ systems and/or a genetic diagnosis were excluded 11. The consequence of excluding genetic diagnosis is that for instance for AVSD, only non-Down Syndrome children with AVSD were included in the study population. Data on all children with sCHD including those with associated anomalies/genetic syndromes are presented for comparison in Supplementary Table S2.

Data on survival and on surgical procedures performed during in-patient hospital stays for all children up to the child’s tenth birthday or end of 2015, whichever came earlier, were obtained by electronic linkage to mortality statistics or vital statistics databases and hospital databases. Details about the linkage methods have been published elsewhere 8,9.

The hospital databases in Finland, Funen Denmark, Tuscany and England (East Midlands & South Yorkshire, Thames Valley and Wessex) covered hospitalizations in the whole country. For Wales, this included procedures carried out in England. For Valencian Region and Emilia Romagna, the hospital databases covered the same region as the EUROCAT registry.

Surgical procedures were coded according to the coding systems used in the national health systems. Italy and Spain used ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) for the study period, Wales and England used OPCS-4 (Classifications of Interventions and Procedures) and Finland and Denmark used national adaptions of NCSP (NOMESCO Classification of Surgical Procedures). Surgical procedures included catheter procedures, but did not include diagnostic procedures (e.g. right heart catheterization); for an overview of what was included as a surgery please refer to Supplementary Table S3.

*Specific surgical procedures:* For some anomalies it was possible to identify specific codes for surgical correction of a given CHD; this was the case for CoA, AVSD, modified Blalock-Thomas-Taussig-shunt (which included the original subclavian artery to pulmonary artery shunt) and hemi-Fontan (which included all codes for superior cavopulmonary anastomosis and therefore also the Bidirectional Glenn Procedure (BGP)). Fontan codes could only be reliably identified in the OPCS-4/NCSP/ICD9-CM codes from Denmark, Italy and Wales. Data from these registries were also used to compare surgical timing for the specific condition versus having any cardiac surgery. For those lesions without lesion-specific codes we identified both having any cardiac surgery or any surgery in general as a proxy for cardiac surgery.

*Statistical analysis*: The proportions of children having surgery were calculated using Kaplan Meier (KM) survival estimates to allow for the censoring of children occurring on 31st December 2015, date of death or date of emigration from the study region or country, as previously described in detail 12. The numbers of surgical procedures the children had and the age at the time of the first surgery were non-Gaussian with a few extreme outliers, and therefore they were reported as medians and interquartile ranges; meta-analytic methods to combine all results across registries have been previously described elsewhere 13. Briefly, quantile estimation methods were used to obtain pooled estimates of the median age at first operation and the 95% CIs using the “metamedian” package in R, version 4.0.3 14.

 *Release of small numbers*: The release of small numbers (<5) was not allowed for several of the registries; therefore, for most of the rare anomalies survival/mortality rates are pooled estimates from all nine European Regions. Data on survival/mortality could only be reported for individual registries on AVSD, TGA and TOF.

*Postoperative mortality*: For analysis, results were subdivided into five different age categories for each anomaly; 0 to 27 days; 28 days to <1 years; 0 to <1 years: 1 to 4 years and 5 to 9 years. Please note that for postoperative mortality the denominator is only children with a specific diagnosis and a surgical code, this is contrast to the 1 and 5 year mortality and survival rates where the denominator are all children with the specific diagnosis. Due to the smaller numbers of children in the postoperative mortality , the combined mortality was not estimated using a meta-analytic approach, rather all the deaths after surgery from each registry were combined and divided by the total number of children with a specific diagnosis and surgical code.

The 1 and 5 year mortalities, have been obtained from data that were aggregated from 13 registers (both regional and national), as previously described in detail in 15-17. These aggregated mortality data from these two papers are presented separately in supplementary table S4, please note that these values have been published previously in 16,17.

*Ethical clearance*: All registries affiliated with the EUROCAT network possess the essential ethical authorizations and protocols to facilitate standard surveillance, data compilation, and secure transmission of de-identified information to the central EUROCAT database. Adhering to pertinent national directives, the registries provided substantiation of these clearances to the EUROlinkCAT ethical dossier. Ulster University, the central data repository, also secured ethical endorsement (approval reference: FCNUR-21-060). Notably, as per the nature of the study, no institutional review board (IRB) approval was requisite. The implementation of parental consent for the registration of infants with anomalies by local registries aligns with respective national legislations. For comprehensive insights, kindly consult the dedicated protocol paper.

**Results**:

*Population characteristics*: We obtained data from nine EUROCAT registries from six countries for children born from 1995 to 2014. Data were available on 5,693 children born with a sCHD (Table 1).

*Timing of first surgical intervention*: For all children born with sCHD the median age at first surgical intervention was 3.6 (95% CI: 2.6-4.5) weeks (up to 5 years of age) (Table 2). For children with sCHD 78% (95% CI: 70–85%) had a surgery in the first year of life and 36% (95% CI: 31–42 %) between ages 1-4 years. The same pattern was observed for all the subtypes of sCHD with a higher percentage of children undergoing surgery in the first year of life, than at age 1-4 years. The timing of first surgical intervention varied greatly between different sCHDs, ranging from 0.3 (95% CI: 0.0–0.7) week for HRH to 38.6 (95% CI: 33.0-44.1) weeks for AVSD (Table 2). Measures of heterogeneity (I2-values) for all variables can be found in table S2.

*Number of surgical interventions*: Children with sCHD were operated on a median of 3.2 (95% CI: 2.6–3.9) times in their first 5 years of life. This includes both cardiac and non-cardiac operations. Those with the highest median number of cardiac operations in the first five years of life were children with HRH and HLH who underwent 5.0 (95% CI: 3.4–6.5) and 4.4 (95% CI: 3.1–5.6) cardiac surgical procedures, respectively (Table 2). Measures of heterogeneity (I2-values) for all variables can be found in table S2.

*Difference in timing of cardiac surgery between European regions*: The timing of the first cardiac surgical intervention for each of the nine European registries are summarized as the median age and interquartile ranges in Figures 1A and 1B. Timing of first surgery for specific sCHDs was fairly consistent in the first couple of weeks of life for TGA, TAPVR and CoA. Children with AVSD were operated on around 5-6 months of age and TOF at 4-5 months of age (Fig 1A). For both the Blalock shunt and hemi-Fontan procedures we observed consistent timing across Europe (Fig 1B).

*Postoperative mortality*: We evaluated the 30-day postoperative mortality rate (based on the variable “any surgery”) for children with sCHD across all nine European regions divided into five different age categories (Table 3). The highest 30-day postoperative mortality rates occurred when the surgery was performed in the first month of life (0 to 28 days) which for all children with a sCHD was 7.0% (95% CI: 6.1-8.0%). Postoperative mortality was 3.8% (95% CI: 3.2-4.5%) for children aged from 29 days to 1 year, 1.7% (95% CI: 1.2-2.5%), for ages 1 to 4, and 1.9% (95% CI: 1.0-3.5%) for ages 5 to 9. The highest postoperative mortality rates were found in children with Ebstein’s anomaly, HLH, HRH and common arterial truncus.

*Differences in surgical outcomes across Europe*: We examined the 30-day postoperative mortality in the first year of life for all cases of sCHD. Due to problems with small numbers, data on most of the specific sCHD diagnosis had to be excluded from the analysis. It was only possible to compare 30-days postoperative mortality across the nine regions for cases of AVSD, TGA and TOF. With this, restriction data from Funen, Denmark had to be excluded due to small numbers for all three anomalies and data from Valencia Region had to be excluded for AVSD. Generally, 30-days postoperative mortality for TGA and TOF are quite similar across the nine regions. The only notable exception appears to be that Wales has a higher AVSD mortality than the other regions (Fig. 2). Data on all-cause mortality in the first year of life for all nine European regions are included in Supplementary Table 5.

**Discussion**

In this cohort from Western Europe we show that children with sCHD are operated on at a median age of 3.6 weeks of age. For most of the specific sCHDs (TOF, TGA, TAPVR, AVSD and CoA) timing was broadly similar across the included regions. Children born with HLH and HRH underwent the most cardiac surgical procedures, with half of them having at least 5 surgical procedures on average in the first 5 years of life. The 30-day postoperative mortality was highest for children operated in the first month of life. The 30-days postoperative mortality was comparable across the European regions. Although overall survival is good (close to 90%), the 5-year survival for critical conditions such as HLH is still only around 50% (Table S4).

 The suggested optimal timing for surgical correction of TOF in infants with no or mild symptoms is around 3–6 months 18 and for AVSD around 4 months of age 2. This is in line with what we observe across the nine European regions with timing of surgery for TOF at 4-5 months and AVSD at 5-6 months of age (Fig 1A). For critical lesions such as TGA, PA and TAPVR we also observe, as expected, rather consistent surgical timing in the neonatal period across the nine regions. For patients with HLH or HRH the modified Blalock-Taussig-Thomas was performed at a median age of 0.4–0.9 weeks which is in line with other reports 19. Timing of the hemi-Fontan (or BGP) is around 6 months (23.3 weeks in HLH), which is also well in line with other reports 20.

We found the highest 30-day postoperative mortality in the neonates (6.5%), which is consistent with reports from other surgical centers 21. It can be argued that 30-day mortality is not the most optimal parameter to measure if our aim is to assess surgical outcome. Increased capacity to prolong life in the Intensive Care Unit (ICU) can decrease the 30-day mortality without this translating into increased survival to discharge 22. Some authors therefore prefer discharge mortality rate as the primary surgical outcome 23. As such, there is a risk that our results slightly underestimate the postoperative mortality.

There were regional differences in postoperative mortality for children with sCHD, with the highest mortality rate being approximately double that of the lowest. However, it should be cautioned, that when looking at data on all children with sCHD differences in case mix of rare conditions with high mortality such as HRH and HLH might well skew comparisons between regions. For the most prevalent diagnosis (AVSD, TGA and TOF) we had large enough data sets to allow for a more direct comparison between regions. This showed that comparable results with respect to 30-days postoperative mortality was achieved across the European regions. The only notable exception appears to be AVSD cases in Wales. One explanation for this might be, that although in surgical timing was similar, it can be noted that the upper limits of the 95% confidence interval for Wales was 81 weeks with all other regions at around 40 weeks. This shows that some patients were operated in the second year of life. Later surgical repair increases the risk of pulmonary vascular hypertension and may increase mortality 24, which could be a possible explanation for the higher AVSD mortality in Wales.

An important limitation when looking at cardiac surgical intervention is that in most instances we have limited information about the precise repair performed. The primary challenge was differences in coding systems between European regions making it impossible to reliably translate between systems for most procedures. Another important limitation is that we do not have data on when a diagnosis was made and/or the potential referral time to a tertiary surgical center. It is well established that *in utero* diagnosis or early postnatal diagnosis of a duct dependent CHD can decrease mortality 25,26. A significant number of deaths in children with a duct dependent CHD occur in those with late or no referral to a tertiary center 26. Most studies of mortality rates are data from tertiary units reporting their outcome in surgical series 27, and thus to examine the true mortality rate for a specific CHD it is important to have population based data as in the present study.

In conclusion, there were no major differences between the nine Western European regions in timing and number of surgical procedures for children with CHD. Despite an overall good prognosis for most CHDs, some lesions are still associated with substantial postoperative mortality and a 5-year survival of less than 90%. The results of this study can aid medical staff in counselling parents regarding timing of surgery and survival.

**Funding**

This project has received funding from the European Union’s Horizon 2020 research and innovation program under grant agreement No. 733001.

The views presented here are those of the authors only and the European Commission is not responsible for any use that may be made of the information presented here.

**Conflict of interest**

None declared.

**Data Availability Statement**

Aggregated data from the local registries were uploaded to a secure central data repository at Ulster University. A condition for local approval for linking databases was that the linked data cannot be shared.

**Transparency declaration**

The lead author (MD) affirms that the manuscript is an honest, accurate, and transparent account of the study reported; no important aspects of the study have been omitted.

Dissemination to patient and public communities: It is anticipated to disseminate the results of this research to wider community via press release, our webpage and social media platforms.

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**Legends**

**Fig. 1A**: Median age and interquartile range (in weeks) at first cardiac surgery for children with congenital heart defects from the participating European regions. Abbreviations: Transpositions of the great arteries (TGA), tetralogy of Fallot (TOF), atrioventricular septal defect (AVSD), coarctation of the aorta (CoA), total anomalous pulmonary vein return (TAPVR) and pulmonary atresia (PA).

**Fig. 1B**: Median age and interquartile range (in weeks) at first cardiac surgery for children with congenital heart defects from the various participating European regions. Please note that for the Blalock shunt and hemi-Fontan this is not restricted to any specific cardiac diagnosis, only the surgical codes and as such will include any anomaly in which these Surgerical procedures have been undertaken. Abbreviations: hypoplastic left heart syndrome (HLH) and hypoplastic right heart syndrome (HRH).

**Fig. 2**: Plot of 30-day postoperative mortality in first year of life for nine different European regions. Data from Funen, Denmark had to be excluded due to small numbers for all three anomalies and data from Valencia Region had to be excluded for AVSD. Also please note that AVSD includes only non-chromosomal cases. Abbreviations: severe congenital heart defect (sCHD), atrioventricular septal defect (AVSD), transposition of the great arteries (TGA), tetralogy of Fallot (TOF).

**Table 1**: Overview of the participating registries from the nine different European regions. Shown are the births years available from each registry, the number of live births with severe congenital heart hisease (sCHD) and the percentage of children having any surgery for 4 different age categories. Numbers in brackets indicate 95% confidence intervals.

**Table 2**: Median age at first cardiac surgery and median number of cardiac surgical procedures in the first 10 years of life for all participating registries. Numbers in brackets indicate 95% confidence intervals. For those anomalies where it was possible to identify the specific surgical codes for anatomical correction of the anomaly, rather than just the overarching category of cardiac surgery, we have indicated the median age for both. For the anomaly specific surgical procedures, the median number of surgical procedures refers to that specific surgery alone, such that this will only be above one if the surgery is undertaken more than once in the first 5 years of life. The number of children undergoing surgery can be calculated directly from the table. Please note that surgical codes for the Fontan procedure could only be reliably identified in Denmark, Italy and Wales. I2-values are show only for sCHD, all these values can be found in table S2.

**Table 3**: The 30-day postoperative mortality rate for all included severe congenital heart defects, divided into 4 age categories. For each age category, the number of children having surgery, the number that died within 30 days and the calculated post-operative mortality rate is shown. Abbreviations: Severe congenital heart defects (sCHD), atrioventricular septal defect (AVSD), Transpositions of the great arteries (TGA), tetralogy of Fallot (TOF), DORV, pulmonary atresia (PA), hypoplastic left heart syndrome (HLH), hypoplastic right heart syndrome (HRH), coarctation of the aorta (CoA) and total anomalous pulmonary vein return (TAPVR).