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ENHANCING THE CLASSIFICATION OF CONGENITAL HEART DEFECTS FOR OUTCOME ASSOCIATION STUDIES IN BIRTH DEFECTS REGISTRIES

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Abstract

Introduction: Traditional strategies for grouping congenital heart defects (CHDs) using birth defect registry data do not adequately address differences in expected clinical consequences between different combinations of CHDs. We report a lesion-specific classification system for birth defect registry-based outcome studies.

Methods: For Core Cardiac Lesion Outcome Classifications (C-CLOC) groups, common CHDs expected to have reasonable clinical homogeneity were defined. Criteria based on combinations of Centers for Disease and Control-modified British Pediatric Association (BPA) codes were defined for each C-CLOC group. To demonstrate proof of concept and retention of reasonable case counts within C-CLOC groups, Texas Birth Defect Registry data (1999–2017 deliveries) were used to compare case counts and neonatal mortality between traditional versus C-CLOC classification approaches.

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Results: C-CLOC defined 59 CHD groups among 62,262 infants with CHDs. Classifying cases into the single, mutually exclusive C-CLOC group reflecting the highest complexity CHD present reduced case counts among lower complexity lesions (e.g., 86.5% of cases with a common atrium BPA code were reclassified to a higher complexity group for a co-occurring CHD). As expected, C-CLOC groups had retained larger sample sizes (i.e., representing presumably better-powered analytic groups) compared to cases with only one CHD code and no occurring CHDs.

Discussion: This new CHD classification system for investigators using birth defect registry data, C-CLOC, is expected to balance clinical outcome homogeneity in analytic groups while maintaining sufficiently large case counts within categories, thus improving power for CHD-specific outcome association comparisons. Future outcome studies utilizing C-CLOC-based classifications are planned.

Keywords

congenital heart defects; classification; birth defect registry; surveillance programs; congenital anomalies

INTRODUCTION

Affecting 40,000 neonates in the United States (US) annually, congenital heart defects (CHDs) are the largest contributor to birth defect-related mortality.[1] Population-based birth defects registries have been key data sources for describing CHD and other birth defect occurrence by population characteristics and better understanding factors associated with CHD occurrence risk, as they are large and representative of statewide populations.[2–4] Beyond etiologic studies, postnatal outcome studies of individuals with CHDs will be instrumental for understanding the impact of CHDs from birth to adulthood.

Classifying complex combinations of CHDs appropriately for outcome studies is challenging from both clinical and epidemiologic perspectives.[5] Cases evaluated in studies of birth defect registry data are often identified using morphologically-based codes, such as British Pediatric Association (BPA) codes.[6,7] While these codes are helpful to assess the prevalence and etiology of CHDs, they do not capture complex cardiac phenotypes observed among patients with CHDs or the nuances of clinical decision-making. Alternatively, empirically-based classification tools such as the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database (CHSD) offer a diagnosis-based classification system.[8] While tools like the STS CHSD risk models that stratify patients according to procedure type and/or diagnosis are helpful to evaluate outcomes among patients warranting surgical intervention at a tertiary center, they are less helpful for birth defects registry data that do not systematically include these procedure/surgical data. Moreover, registries also include patients without surgical intervention. Further, while databases like the CHSD are helpful to evaluate outcomes within the perioperative and/or postoperative periods specifically, they are not designed for evaluation of outcomes outside this period, which is frequently the focus of birth defect registry studies.

For studies using birth defect registry data, there are currently two common, morphologically-based methods of systematically accounting for multiple CHD codes in

etiologic analyses.[9,10] The first analyzes all cases with the CHD code of interest (a traditional “broad” approach), regardless of co-occurring CHD codes. For example, all cases with the pulmonary stenosis code (746.010) would include both cases with “isolated” pulmonary stenosis (i.e., accompanied by no other major CHD code) and those with ≥1 major co-occurring CHD code in the same analytic group. This approach, however, may be irrelevant to outcomes analyses if coding results in cases with substantially differing mortality/morbidity risk profiles are included in the same group. Additionally, CHD groups may overlap, as this approach only accounts for the presence of a given CHD of interest (e.g., defect A) without accounting for any co-occurring defects (defect B), and therefore individuals possessing both defects A and B would be double counted.

A second method for CHD classification analyzes cases with a single CHD code and no other CHD codes (a traditional “exclusive” approach) and is considered to be more appropriate when the clinical impact is expected to differ between patients with 1 versus >1 CHD codes, such as the pulmonary stenosis subgroups described above. However, the exclusive approach is inadequate for many moderate to high-risk lesions as it ignores common CHD patterns. Thus, it excludes commonly or universally co-occurring CHD combinations, such as cases with interrupted aortic arch type B and a large ventricular septal defect, who comprise most cases with interrupted aortic arch type B, or children with complex lesions and co-occurring CHDs required for survival to birth.[11,12]

Further, there are common multiple CHD patterns with highly differential mortality that would be ignored by either traditional broad or exclusive approaches. In the case of pulmonary atresia (PA; 746.000), a heterogenous lesion with variable mortality estimates depending on its subtypes (with ventricular septal defect, intact ventricular septum, or complex), the broad approach would evaluate PA as a whole group, despite this heterogeneity. Conversely, the exclusive approach would theoretically remove all cases with PA with ventricular septal defect or complex PA that, by definition, include co-occurring CHDs. Therefore, classifying CHDs into core common patterns of lesions may be necessary to optimally parse out heterogeneity, which is not possible using currently available approaches.

Given these aforementioned limitations, a classification system that flexibly balances the benefits of the broad and exclusive approaches is needed. Similar to that of clinical registries like STS, the use of both clinical and epidemiologic expertise to make classification decisions can better ensure that CHD classifications remain clinically relevant while ensuring adequate sample size.[13–15] Here, we report a lesion-specific system for classifying cases with co-occurring CHDs for outcome studies based on consideration of expected clinical impact, surgical/intervention pathway, and the most common combinations of CHDs based on prior work of many experts and investigators. To demonstrate its utility, we applied the proposed outcome-based classification system to data from a large state birth defects registry. Although we developed this approach for investigators studying data from the Texas Birth Defects Registry, we present it here in sufficient detail so researchers may apply it to other datasets.

METHODS

Definition of Isolated and Multiple CHDs

For simplicity, given our focus on CHD combinations, we hereafter broadly refer to "isolated" CHDs as those that conceptually involve a "single" CHD and refer to "multiple" CHDs as those that conceptually involve combinations of distinct CHDs. In both instances, we ignore the presence or absence of non-cardiac defects, though we acknowledge that much prior literature uses similar "isolated" and "multiple" defect terms differently, to describe birth defect co-occurrence across organ systems.

Identification of C-CLOC CHDs of Interest

To develop a standardized lesion classification system designed to evaluate outcomes among individuals with CHDs (entitled the Core Cardiac Lesion Outcome Classifications, or C-CLOC), three pediatric cardiologists and one geneticist identified mutually exclusive CHD categories of primary interest (defined as main CHDs) for outcome studies based on prior literature, genetic observations, clinical care pathways, and prevalence corresponding to common CHD phenotypes (S.A.M, K.N.L, B.A., A.L.). Accounting for anatomic variations in main CHD groups that are expected to modify outcomes, main CHD groups were further divided into subgroups representing more distinct CHD combinations (Supplemental Table 1). For example, the double outlet right ventricle main CHD group was subgrouped as either: 1) double outlet right ventricle with versus 2) without malposition of the great arteries, based on differences in surgical decision-making and mortality between groups.[16] C-CLOC CHDs did not include congenital arrhythmias, cardiomyopathies, or cases with isolated patent ductus arteriosus or patent foramen ovale.

C-CLOC Development

To develop C-CLOC based on main CHD groups and subgroups, keeping in mind the goal to retain reasonably large case counts and homogeneity in terms of risk and complexity within groups, each C-CLOC CHD group was defined based on common combinations of 47 six-digit CHD BPA codes (745.000–747.430), as utilized by the Registry detailed below.[17,18] Specifically, each BPA code was classified as "can have", "cannot have", or "must have" for each C-CLOC CHD, which was then translated to a SAS statistical software program to automate assignment of cases to C-CLOC parent groups, main CHD groups and subgroups (version 9.1 copyright 2002–2008, Cary, NC).

For individual C-CLOC CHDs, each BPA code was audited and hierarchically classified as one of the following: 1) are part of the CHD group's definition (considered "*must* have" defects), 2) would not be expected to substantially change morbidity/mortality risk when co-occurring ("*can* have" defects), or 3) would likely substantially impact morbidity/mortality risk when co-occurring ("*cannot* have" defects). For example, for a child with a code for aortic coarctation to be classified in the complex COA C-CLOC code, they "must have" coarctation, they "can have" mitral stenosis, but they "cannot have" hypoplastic left heart syndrome (HLHS). For CHD code combinations of individual lesions with differing expected clinical severity, the combination was classified into the higher complexity C-CLOC group (e.g. HLHS with coarctation would be classified as C-CLOC HLHS instead

of aortic coarctation). Criteria for inclusion/exclusion for each C-CLOC CHD group is in Supplemental Table 2.

For each CHD of interest, BPA codes were defined as “cannot have” because 1) it would be considered to be physiologically impossible for the defect corresponding to the BPA code to co-occur with the CHD of interest, 2) that the co-occurrence of the BPA-corresponding defect was thought to substantially impact the expected clinical consequence of the CHD of interest. All C-CLOC phenotyping decisions were then verified by two additional pediatric cardiologists (K.N.L., B.A.) and a clinical geneticist (A.L.). All phenotyping decisions were iteratively reviewed by clinicians, whereby differences in individual phenotyping decisions were discussed with investigators and resolved.

Main CHD groups and their respective subgroups were categorized into one of seven parent groups based on fundamental developmental biology (i.e., CHDs that co-occur based on familial clustering, Figure 1): left-sided, right-sided, conotruncal, endocardial cushion, arterial malposition/looping, double outlet right ventricle, and other defects. In the case of double outlet right ventricle, for example, C-CLOC CHDs included 1) parent CHD groups (e.g., conotruncal defects), 2) main CHD groups (e.g., double outlet right ventricle), and 3) CHD subgroups (e.g., double outlet right ventricle with malposition of the great arteries versus without malposition of the great arteries). Defect types that could not be definitively grouped into any of the aforementioned groups were categorized as “other”.

Iterative Refinement of C-CLOC Categories

After the initial C-CLOC classification was applied within the dataset, two rounds of reviews were performed to further curate the classifications. First, cases with no C-CLOC assignment were reviewed from highest to lowest code combination frequency to see if they could be classified by frequency. Adjustments were made, leaving two types of case combinations excluded: 1) *suspected misclassification* due to either impossible combinations (e.g. mitral atresia with tricuspid atresia) or combinations with disparate diagnoses making classification not possible (e.g. truncus arteriosus with pulmonary atresia), and 2) *insufficient information to classify*. For the second exclusion category, cases were included in which the 2 or more BPA codes had similar average severity, but together could have significantly increased mortality, but did not fall easily within a single C-CLOC code with only the information provided (e.g. pulmonary stenosis with VSD or mitral atresia with transposition of the great arteries) and rare high mortality combinations which would be minimally contributory to population-based investigations (e.g. tricuspid atresia with truncus arteriosus or aortic atresia with VSD without HLHS). Second, all cases and classifications were reviewed to ensure that the coding system was mutually exclusive, so cases were classified in 2 C-CLOC codes. This required some creation of hierarchies. For example, double outlet right ventricle (DORV) with malposition of the great arteries (MGA) would most often be classified in the DORV-MGA C-CLOC code. However, if there was also atrioventricular septal defect, the case would instead be classified in the complex endocardial cushion defect C-CLOC code.

After developing the C-CLOC system and iteratively refining it, there were 29 main, mutually-exclusive CHD categories and 24 subgroups within 7 parent CHD categories of

a priori interest, totaling to 59 C-CLOC CHDs (or 60 total analytic groups including CHDs overall; Table 1).

Example of C-CLOC System Refinement

In the case of left-sided lesions, C-CLOC phenotyping identified children with left-sided lesions as a parent group in addition to more granular lesions like simple and complex arch obstruction, congenital aortic stenosis, and HLHS. Given that pulmonary valve and/or pulmonary artery atresia occur with many different heterogeneous lesions, cases with pulmonary atresia that were classified into the pulmonary atresia C-CLOC main CHD group (i.e., cases did not also have a higher complexity code) were further classified into three subgroups: 1) pulmonary atresia with intact ventricular septum (under right-sided lesions), 2) pulmonary atresia with VSD/Tetralogy VSD (under conotruncal lesions), and complex pulmonary atresia (under other CHD type; Supplemental Table 2).

Comparison of Classification Approaches in the Texas Birth Defects Registry

To demonstrate feasibility of C-CLOC in an existing population-based birth defect registry, C-CLOC was applied to the Texas Birth Defects Registry (TBDR). To further compare the C-CLOC approach to the traditional broad and exclusive approaches, cases were also classified using the traditional broad and exclusive approaches and applied to ascertain cases within the TBDR.

To alternatively code for cases using the broad approach, all BPA codes otherwise defined as “cannot have” codes for each C-CLOC CHD were defined as “can have” codes for the purposes of applying the broad approach to ascertain cases in lieu of the C-CLOC approach. Therefore, for the broad approach, all 47 BPA codes were either “must have” (e.g., BPA code corresponding to the CHD of interest) or “can have” codes. Thus, only the BPA code directly corresponding to the CHD of interest was required to define a case, regardless of other co-occurring CHDs. When applying the exclusive approach, all cases that were defined as “can have” codes in the broad approach were considered to be “cannot have” codes. Subsequently, cases identified with a given CHD using the exclusive approach were only considered to have the CHD if they had a BPA code corresponding to the CHD of interest and no other CHDs.

Briefly, the TBDR utilizes active statewide surveillance to collect birth defect data among all live births, stillbirths, pregnancy terminations, and fetal deaths within Texas hospitals, hospital-based clinics, and birthing centers.[19] Maintained by the Birth Defects Epidemiology and Surveillance Branch at the Texas Department of State Health Services (DSHS), diagnoses of structural birth defects and genetic conditions made within the first year of life are identified via abstracted medical records from all delivery centers statewide. To be included, mothers must have resided in Texas at time of delivery. Data are recorded using BPA codes for each documented birth defect, assigned via chart review conducted by trained data abstractors, and reviewed by quality assurance specialists and clinical reviewers. TBDR records are also linked to vital records data available in the DSHS Center for Health Statistics, whereby vital status was determined based on the presence of a linked death

certificate or death as documented in abstracted health records. Children without a death certificate or chart documentation of death were presumed to be alive at last follow-up.

For the present study, TBDR data for all 1999–2017 livebirths, delivered >23 weeks' gestation among Texas residents, with BPA code(s) corresponding to a C-CLOC CHD diagnosed by age 1 year were evaluated. This study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center and the Institutional Review Board of the Texas Department of State Health Services.

Statistical Methods

Audit of Case Retention in C-CLOC CHD Groups—Case counts for each C-CLOC parent group, main group, and subgroup were tabulated. For each BPA code, counts and percentages of cases were tabulated separately for CHD codes: 1) retained in their related C-CLOC group, 2) classified into higher complexity C-CLOC group (e.g., individuals with muscular ventricular septal defect moved into the HLHS group due to having a HLHS BPA code), 3) with suspected misclassification (e.g., impossible CHD combinations), or 4) could not be definitively classified (e.g., insufficiently specific codes). Presence of suspected misclassification/impossible CHD combinations or insufficiently specific codes was determined by a pediatric cardiologist (S.A.M.). Counts and percentages of cases were calculated using the total number of individuals with that respective BPA code as the denominator.

Case Counts and Neonatal Mortality by Approach—To evaluate which C-CLOC CHDs had case counts similar to that of the broad approach (i.e., reflecting our goal to retain reasonably large sample sizes), we compared case counts between C-CLOC CHDs to results of the respective category from the broad and exclusive approaches (e.g., C-CLOC tetralogy of Fallot versus broad and exclusive tetralogy of Fallot).

To then assess which C-CLOC CHDs had a neonatal mortality (death within first 28 days of life) percentage that was similar to the respective percentage under the exclusive approach (i.e., which is expected to result in more CHD homogeneity than the broad approach for many CHDs). Case counts and percent neonatal mortality by coding approach were plotted for visualization. Analyses of neonatal mortality and case counts included only live births with a C-CLOC CHD of interest with a birthweight >400 grams born ≥23 weeks' gestation. Because lesions corresponding to C-CLOC subgroups (e.g., dextro-transposition of the great arteries with ventricular septal defect) could not be ascertained using the broad and exclusive approaches, case count and neonatal mortality estimates for traditional approaches were only reported for C-CLOC parent and main CHD groups.

Diagnostic Metrics of Each Classification Approach Using HLHS as an Example—Lastly, we compared C-CLOC system classification to manual clinical review of HLHS, selected to represent a defect with high potential for misclassification. For all cases with an HLHS BPA code (746.700) born between 1999–2014 (N=1,179), a pediatric cardiologist (S.A.M.) reviewed all available TBDR abstracted clinical records (beyond only BPA codes) to determine if each case met criteria for HLHS and this was considered the

gold standard. For the purposes of manual review, cases were considered to have HLHS if they had any of the following as consistent with prior literature[20]:

1. Severe aortic and mitral hypoplasia, atresia, or obstruction, and a hypoplastic left ventricle
2. Diagnosis of HLHS on cardiac catheterization, echocardiography, cardiac surgical, or pathologic report
3. Left ventricular hypoplasia with an outcome of either Stage 1 palliation, transfer to another hospital, discharge to hospice, discharge home against medical advice, or death

We excluded live births with <400 grams birthweight, born <23 weeks' gestation, or those with documented variants like unbalanced atrioventricular septal defect, double outlet right ventricle with mitral atresia, and Shone complex. Diagnostic metrics including accuracy (% correctly classified), sensitivity, and specificity were generated for the C-CLOC, broad, and exclusive approaches by comparing each to the gold-standard, manual classification. Percent accuracy was calculated as: (sum of true positives plus true negatives)/(number of cases with a HLHS BPA code). All statistical analyses were performed using SAS statistical software (version 9.1 copyright 2002–2008, Cary, NC).

RESULTS

After applying the C-CLOC system to 391,517 cases in the TBDR, 62,262 had an eligible CHD (Table 1). Left-sided lesions were the parent CHD category most frequently observed (13.4% of cases with CHDs), followed by right-sided lesions (9.2%), conotruncal (6.1%), endocardial (4.8%), looping defects (3.3%), and double outlet right ventricle (1.8%). The most frequently observed CHD lesion was ventricular septal defect (59.8%). A small proportion of subjects (4.9%) lacked sufficient information to classify them into any of the 59 C-CLOC groups.

Auditing Case Retention Within C-CLOC CHD Categories

For most CHD BPA codes, including those for high complexity lesions, a large percentage of cases were assigned to the C-CLOC category that corresponded to the original BPA code (e.g., 97% for 745.300, double inlet left ventricle; Table 2). Three-quarters of cases with a BPA code for HLHS (746.700) were classified as having HLHS on C-CLOC, while 21% were coded to another group because they were suspected to be originally misclassified due to additionally harbored coding consistent with complex mitral disease, complex arch obstruction, complex atrioventricular septal defect, double outlet right ventricle or double inlet left ventricle that cannot possibly co-occur together. Based on clinical experts' feedback, pulmonary infundibular/subvalvular stenosis (746.830) and aortic atresia (747.200) were thought to rarely occur in isolation, and therefore all cases with these codes were either moved to a higher complexity group or could not be classified due to limited BPA coding data.

Neonatal Mortality by Approach

For many lesions, applying the C-CLOC approach yielded similar mortality to results from the exclusive approach but with a higher sample size (Figure 2, Table 3). For example, mortality was similar for the C-CLOC and exclusive classification for dextro-transposition of the great arteries (5.2%, n=1,279 and 5.7%, n=837 respectively) but different than for the broad classification (7.8%), which included cases with higher complexity dextro-transposition of the great arteries who would not have been included in the former groups.

Correctly Classified HLHS Cases by Approach

Of 1,179 cases with a BPA code for HLHS (1999–2014) that underwent manual clinical review, 914 were considered to truly have HLHS (77.5%; Table 4). Compared to the manual classification, accuracy of the C-CLOC approach (79.9%) was higher than that of the broad (77.5%) and exclusive (42.3%) approaches.

DISCUSSION

This study proposes a CHD classification system tailored to outcome studies. Within population-based birth defect registries, morphology-based classification systems (broad or exclusive approaches) have been useful for conducting CHD surveillance, association studies, and descriptive epidemiologic investigations. However, the broad approach does not account for major co-occurring CHDs that increase risk for poor outcomes and subsequently may result in heterogenous CHD groups. Conversely, the exclusive approach can improve homogeneity in groups at the expense of statistical power due to low cell counts. Informed by four practicing clinicians and experts in pediatric cardiology, birth defect classification systems, and outcomes research, C-CLOC was developed to balances the benefits of the broad and exclusive approaches. Importantly, C-CLOC classifies CHDs with respect to other commonly co-occurring CHDs that are expected to modify their risk, a feature that is not otherwise available in traditional methods as these subgroups were specified *a priori* by clinical experts' input when devising C-CLOC phenotyping schema. Ideally, C-CLOC groups would be based on validated mortality reports. However, prior population-based CHD mortality reports are primarily one of the following: 1) limited to patients undergoing surgery, 2) insufficiently granular, or 3) are based on the existing BPA codes which have major weakness for mortality reporting as discussed. We hope to use these codes to describe population-based mortality in future work, and may need to refine over time. Our results do suggest that, for many CHDs, C-CLOC groups are more homogeneous than those from the broad approach while retaining case counts that are larger than those from the exclusive approach. C-CLOC also classifies subjects into mutually exclusive CHDs categories, though, as expected, this generally resulted in some cases moving from lower to higher complexity lesion categories due to assignment of cases to the CHD category for the highest complexity lesion present.

Key benefits of C-CLOC include its stratification of CHDs into clinically meaningful groups that can be applied for prognosis-based clinical counseling. In the case of pulmonary atresia, a clinically heterogenous lesion that differs in risk depending on its subtype, stratification of pulmonary atresia into complex, ventricular septal defect, and intact ventricular septum

subtypes allow for better comparisons with published clinical data. Similarly, neonatal mortality estimates for high-risk lesions ascertained via C-CLOC phenotyping were consistent with prior clinical literature.[21–23] Additionally, C-CLOC does not force exclusion of patients with genetic anomalies, enabling its application to study effect modification or stratification by genetic syndromic diagnoses (a notable point given that up to one-third or more of patients with CHDs have a genetic condition).[12,24,25] Importantly, designating a standard classification system created to evaluate CHDs according to their expected clinical consequences rather than morphologic homogeneity, will allow increased utility of coded population-based resources for outcomes-based research (e.g., state birth defects registries) and may be instrumental for risk stratifying individuals with CHDs over the lifespan.

Following replication and validation in other CHD cohorts, C-CLOC may be a useful tool to supplement prior classification systems used in outcome studies. Systems such as the Risk Adjustment in Congenital Heart Surgery (RACHS-1) scores, STS European Association for Thoracic Surgery (STAT) mortality scores, and Aristotle Basic Complexity (ABC) scores have been applied to study mortality risk in children with prior CHD surgery.[26–30] While these systems extrapolate comprehensive information based on available clinical and surgical data, they are limited to those with surgery and cannot characterize patients who did not undergo surgery. Additionally, there has been a call within the surgical community for diagnosis-based classification even among those undergoing surgery, as this would allow comparison of intervention approaches, since not all patients with the same condition undergo the same procedures.[13] With respect to length of outcomes evaluated, prior outcome studies of children with CHDs often focus on perioperative and postoperative outcomes, whereas outcomes evaluating their course following hospital discharge is not well-understood.[26–31] Thus, a comprehensive diagnosis-based approach that can be applied to population-based data sources with outcomes data available like C-CLOC offers many benefits. Investigations comparing utility of C-CLOC to prior systems like RACHS-1, STAT, and ABC scores are needed for further assessment.

There are several other potential classification systems that have been used for outcomes that also do not incorporate surgical history, including those discussed by Reller et al and Glidewell et al.[32,33] Reller's investigation has the strength of cases (n ~ 3,000) being manually reviewed by a team of pediatric cardiologists.[32] This allowed for STS classifications to be assigned which added significant granularity and specificity to the dataset, as 89% of cases had only one primary STS-coded CHD. This manual classification, however, is not feasible many studies, particularly for investigations with tens or hundreds of thousands of cases or who do not have access to electronic medical record. The goal of the C-CLOC classification system is for BPA codes to stand alone and allow for automatic C-CLOC classification without manual review of records or merging with STS databases. Additionally, the Reller classification system as published was not mutually exclusive and did not seem to account for miscoded lesions. For example, a subject with both HLHS and atrioventricular canal defect (AVC) coded (which are mutually exclusive) in the Reller paper would either be counted as both, or perhaps review of the subject record would show that one code was in error. In the C-CLOC system, knowing that unbalanced right-dominant atrioventricular canal defect are often miscoded as HLHS but that the reverse is very rarely true, this would automatically only be coded as complex atrioventricular canal defect.

In the Glidewell et al 2021 study, CHD cases were classified into 4 groups: “severe”, and then three groups of “non-severe”, consisting of “shunt+valve”, “shunt”, and “valve”.[33] While Glidewell et al 2021 assessed a large population using available U.S.-based resources, the classification system was very broad, was not lesion-based, and grouped together very broad risk populations. For example, both simple transposition of the great arteries and hypoplastic left heart syndrome were in the “severe” group, but these have dramatically different mortality rates (for example 5.8% vs. 22% hospital mortality in a multicenter retrospective study.[34] The C-CLOC system aims to be much more granular, especially in regards to more high-risk CHD lesions. Additionally, because C-CLOC groups developmentally similar lesions together, it can be used for genetic association studies as well.

Our initial “validation” in comparison to manual clinical coding for HLHS suggests that applying C-CLOC had a higher classification accuracy than the broad and exclusive approaches, maintaining more of a balance between sensitivity and specificity, whereas the broad and exclusive approaches respectively optimized either sensitivity or specificity but not both. HLHS was well-suited for validation given its frequent misclassification, which may not necessarily be the case for other CHDs. For the present study, “gold standard” HLHS cases were identified by a pediatric cardiologist given there was no standardized tool available to identify a distinct group of HLHS, although given that HLHS gold standard cases were identified by the same team that generated the C-CLOC algorithm, HLHS validation results should be interpreted with caution. While it is likely that manual clinical review of individual records should continue to represent the gold standard for CHD classification, such as that of prior literature, automated approaches such as the C-CLOC system may be increasingly useful for researchers utilizing data from surveillance systems that lack resources to perform manual classification.[32] Further, our approach offers a standardized system for efficiently classifying thousands of cases, with coding criteria that can be easily reapplied as new data emerges or modified and reimplemented as appropriate for specific research questions.

Limitations

As we were unable to differentiate by disease severity between patients in a given CHD group (e.g., larger versus smaller septal defects), or account for surgical characteristics among cases with surgeries, our results should be considered in light of these limitations. Additionally, we did not consider extracardiac defects that may contribute to expected risk of outcomes. It is worth noting that differences in data ascertainment and coding across surveillance systems may result in differential C-CLOC classifications if applied to other datasets. Future studies evaluating outcomes in CHDs using C-CLOC phenotyping may shed more light into outcome trajectories by C-CLOC categories, which may also result in further refinement of the system itself. This current C-CLOC system developed based on BPA codes is not directly correspondent to ICD codes, though future conversion of C-CLOC BPA-based phenotyping to International Classification of Disease (ICD) diagnostic codes is planned, as is applied analyses of mortality and other outcomes using C-CLOC.

Conclusions

Improving on prior phenotyping approaches that focused on peri and post-operative timing, the proposed C-CLOC system groups infants with CHDs in clinically meaningful groups that can be analyzed in outcome studies across the early life course. Such investigations can be instrumental for epidemiologists and clinicians aiming to improve mortality among children with CHDs. Future outcome investigations using C-CLOC phenotyping are planned.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT:

Due to data confidentiality restrictions and existing data agreements, these data cannot be shared.

ABBREVIATIONS

ASD	Atrial septal defect
AV	Atrioventricular
BPA	British Pediatric Association
C-CLOC	Core Cardiac Lesion Outcome Classifications
CDC	Centers of Disease Control and Prevention
CHD	Congenital heart defect
CHSD	Congenital Heart Surgery Database
DORV	Double outlet left ventricle
DSHS	Department of State Health Services
DTGA	Dextro-transposition of the great arteries
GA	Great arteries
HLHS	Hypoplastic left heart syndrome
IAA	Interrupted aortic arch

ICD	International Classification of Disease
IVS	Intact ventricular septum
NOS	Not otherwise specified
PA	Pulmonary atresia
PAPVR	Partial anomalous pulmonary venous return
PV	Pulmonary valve
STS	Society of Thoracic Surgeons
TAPVR	Total anomalous pulmonary venous return
TBDR	Texas Birth Defects Registry
TGA	Transposition of the great arteries
TOF	Tetralogy of Fallot
US	United States
VSD	Ventricular septal defect

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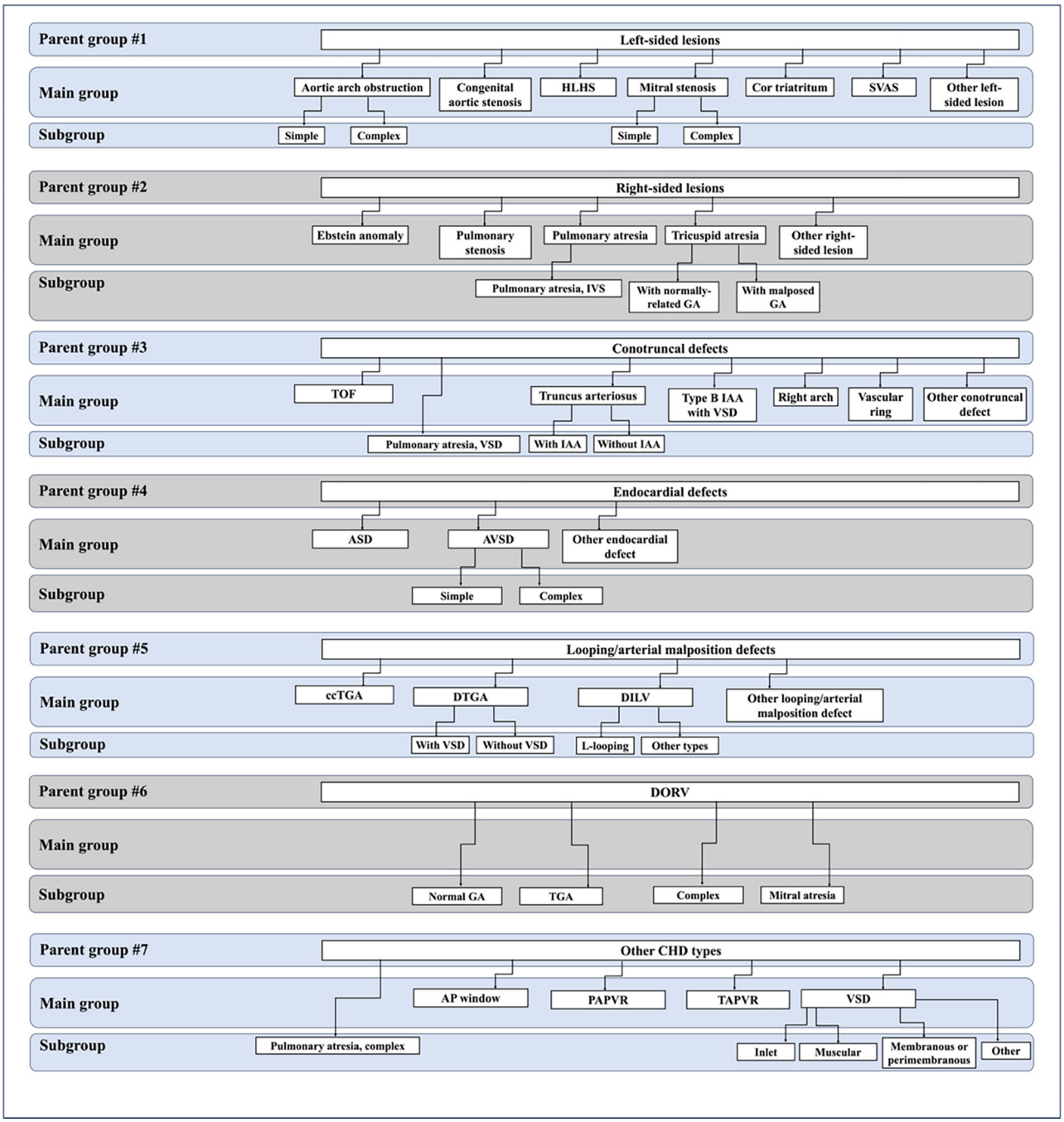

Figure 1. Summarization of 59 Parent Groups, Main Groups, and Subgroups Evaluated Using the C-CLOC Approach

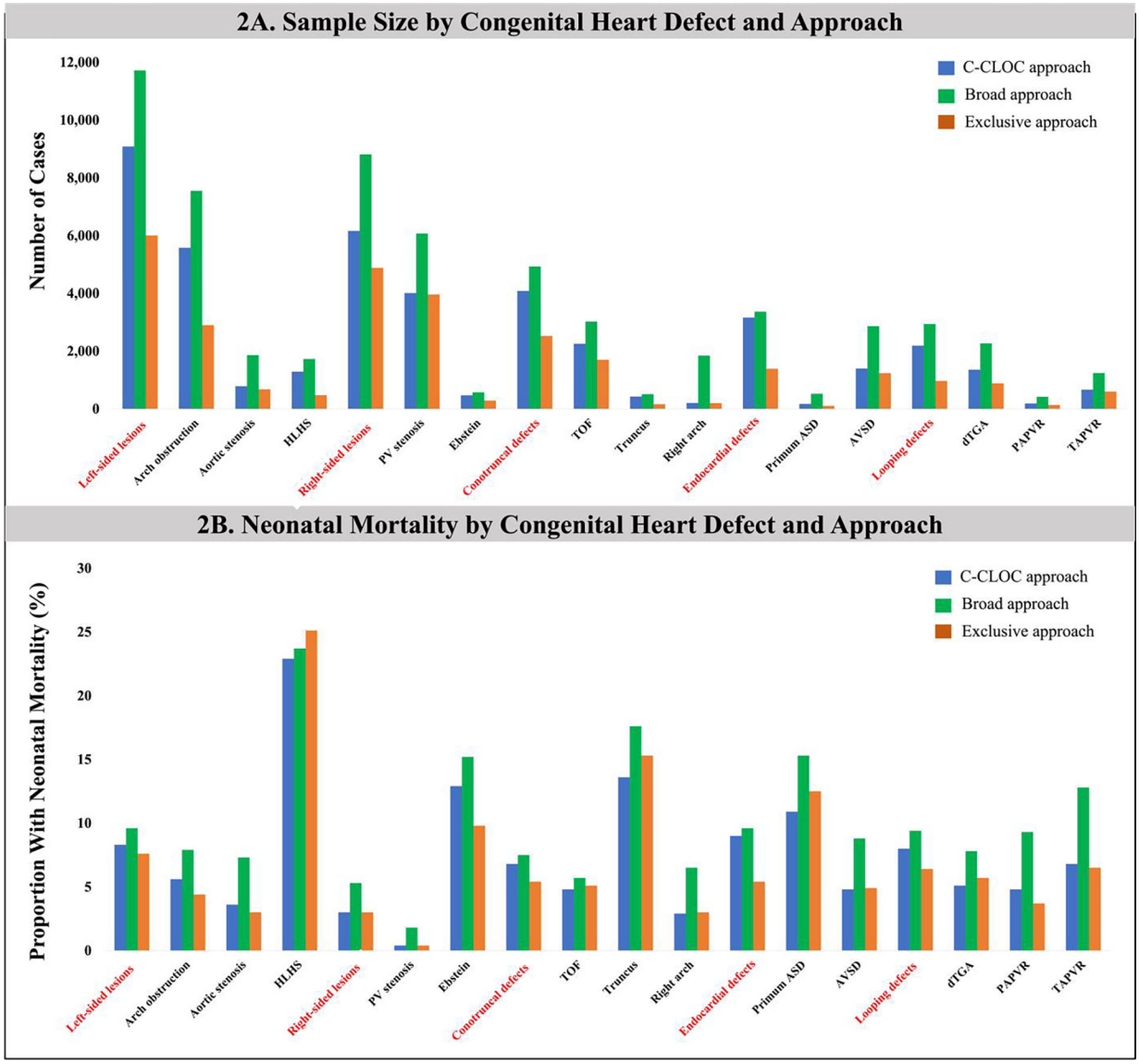

Figure 2. Sample Size and Percent Neonatal Mortality by Congenital Heart Defect and Approach

ASD: Atrial septal defect; CHD: Congenital heart defect; C-CLOC: Core Cardiac Lesion Outcome Classifications; dTGA:Dextro-transposition of the great arteries; HLHS: Hypoplastic left heart syndrome; PAPVR: Partial anomalous pulmonary venous return; PV: Pulmonary valve; TBDR: Texas Birth Defect Registry; TOF: Tetralogy of Fallot. Defects with ≤5 neonatal deaths or defects in which >90% of cases with a given CHD code were excluded on the exclusive approach (resulting in statistically unreliable estimates due to low sample sizes) ascertained in each approach were not included. Parent CHD groups are delineated in red text on the x-axis.

Table 1.

Case Tabulations Among 59 C-CLOC Categories for TBDR Live Births, 1999–2017

n	Defect Name	n cases‡
1	**Left-sided lesions**	**8,359 (13.43%)**
2	Aortic arch obstruction†	5,110 (8.21%)
3	Simple	2,652 (4.26%)
4	Complex	2,469 (3.97%)
5	Congenital aortic stenosis	731 (1.17%)
6	Hypoplastic left heart syndrome	1,206 (1.94%)
7	Mitral stenosis	938 (1.51%)
8	Simple	509 (0.82%)
9	Complex	429 (0.69%)
10	Cor triatriatum	68 (0.11%)
11	Supravalvar aortic stenosis	91 (0.15%)
12	Other left-sided lesion	215 (0.35%)
13	**Right-sided lesions**	**5,744 (9.23%)**
14	Ebstein anomaly	431 (0.69%)
15	Pulmonary valve stenosis	3,730 (5.99%)
16	Pulmonary atresia	1,079 (1.73%)
17	Pulmonary atresia with intact ventricular septum	364 (0.58%)
18	Tricuspid atresia	413 (0.66%)
19	Tricuspid atresia with normally-related great arteries	311 (0.50%)
20	Tricuspid atresia with malposed great arteries	101 (0.16%)
21	Other right-sided lesion	806 (1.29%)
22	**Conotruncal defects**	**3,780 (6.07%)**
23	Tetralogy of Fallot	2,104 (3.38%)
24	Pulmonary atresia with VSD/Tetralogy VSD	574 (0.92%)
25	Truncus arteriosus	394 (0.63%)
26	Truncus arteriosus with interrupted aortic arch	38 (0.06%)
27	Truncus arteriosus without interrupted aortic arch	356 (0.57%)

n	Defect Name	n cases‡
28	Interrupted aortic arch, type B	218 (0.35%)
29	Right aortic arch	175 (0.28%)
30	Vascular ring	255 (0.41%)
31	Other conotruncal defect	235 (0.38%)
32	**Endocardial defects**	**2,959 (4.75%)**
33	ASD only†	157 (0.25%)
34	Atrioventricular canal defect†	
35	Simple	1,315 (2.11%)
36	Complex	1,454 (2.34%)
37	Other endocardial cushion defect	33 (0.05%)
38	**Looping/Arterial malposition defects**	**2,063 (3.31%)**
39	Congenitally corrected transposition of GA	159 (0.26%)
40	Dextro-transposition of the GA (excluding DORV)	1,279 (2.05%)
41	Dextro-transposition of the GA with VSD	512 (0.82%)
42	Dextro-transposition of the GA without VSD	646 (1.06%)
43	Double inlet of the left ventricle	616 (0.99%)
44	Double inlet of the left ventricle with L-looping	99 (0.16%)
45	Double inlet of the left ventricle, other types	517 (0.83%)
46	Other looping/arterial malposition defects	9 (0.01%)
47	**Double outlet right ventricle**	**1,140 (1.83%)**
48	DORV, transposed great arteries (Taussig Bing)	137 (0.22%)
49	DORV, normal great arteries/Tetralogy of Fallot-type	439 (0.71%)
50	DORV, mitral atresia	232 (0.37%)
51	DORV, complex	332 (0.53%)
--	**Other defect types**	--
52	Pulmonary atresia, complex	141 (0.23%)
53	Aortopulmonary window	45 (0.072%)
54	Partial anomalous pulmonary venous return	166 (0.27%)

n	Defect Name	n cases‡
55	Total anomalous pulmonary venous return	630 (1.01%)
56	VSD, any type	37,235 (59.8%)
57	VSD, inlet	5 (<0.01%)
58	VSD, muscular	7,646 (12.28%)
59	VSD, perimembranous or membranous	1,936 (3.11%)
60	VSD, other	27,648 (41.41%)

ASD: Atrial septal defect; AV: Atrioventricular; DORV: Double outlet right ventricle; VSD: Ventricular septal defect. Frequencies were calculated using the number of children with an eligible CHD as the denominator (N=62,262).

†Arch obstruction includes aortic coarctation, aortic hypoplasia, or interrupted aortic arch types A, C, or not otherwise specified. Endocardial cushion defects with ASD only include: ostium primum defects, primum ASD, single common atrium, cor triloculare biventriculare. Endocardial cushion defects with complete AVSD include: Common AV canal with VSD and common AV canal including complete AV canal defect.

‡See Supplemental Table 1 for phenotyping criteria. With each main group, “other” codes were ascertained based on the diagnosis of the parent code without diagnosis of any main CHDs within its group, and thus were not directly dependent on BPA codes. For example, a child was considered to have “other” left-sided lesion if they had a left-sided lesion without simple or complex arch obstruction, congenital aortic stenosis, hypoplastic left heart syndrome, simple or complex mitral stenosis, cor triatriatum, or supravalvar aortic stenosis. The parent group of “Other CHDs” was not computed as a whole group due to heterogeneity of its respective main groups.

Table 2.

Reclassification of CHD-Specific BPA Codes Following Implementation of C-CLOC Approach

n	BPA code(s)	Defect	n with BPA code	n coded to respective C-CLOC category (%)	n moved to higher complexity C-CLOC group (%)	n misclassified (%)	n lacking sufficient information for classification (%)
1	745.000	Persistent truncus arteriosus, absent septum between aorta and pulmonary artery	506	427 (84.3%)	60 (11.9%)	0 (−)	19 (3.4%)
2	745.010	Aortic septal defect, including aortopulmonary window	82¶	47 (57.3%)	--§	0 (−)	35 (42.7%)
3	745.100	Transposition of great vessels, complete (no VSD); D-transposition with no VSD	1,008	781 (77.5%)	199 (19.7%)	0 (−)	28 (2.8%)
4	745.110	Transposition of great vessels, incomplete (with VSD); D-transposition with VSD, Taussig-Bing syndrome, Transposition with inlet VSD, Transposition with perimembranous VSD; excludes: Transposition with muscular VSD	1,146	535 (46.7%)	542 (47.3%)	0 (−)	69 (6.0%)
5	745.120	Corrected transposition of great vessels, L-transposition, ventricular inversion, Ventricular inversion; excludes: Dextrocardia	382	174 (45.6%)	168 (44.0%)	11 (2.9%)	29 (7.6%)
6	745.130	Double outlet right ventricle with normally related great vessels	546	274 (50.2%)	264 (48.4%)	0 (−)	8 (1.5%)
7	745.140	Double outlet right ventricle with transposed/malposed great vessels	730	135 (18.5%)	586 (80.3%)	0 (−)	9 (1.2%)
8	745.150	Double outlet right ventricle, relationship of great vessels not specified	454	189 (41.6%)	260 (57.3%)	0 (−)	5 (1.1%)
9	745.180	Other specified transposition of great vessels, no mention of double outlet right ventricle	24¶	--§	19 (79.2%)	0 (−)	5 (20.8%)
10	745.190	Unspecified transposition of great vessels	93	37 (39.8%)	49 (52.7%)	0 (−)	7 (7.5%)
10	745.200	Tetralogy of Fallot	3,022	2,255 (74.6%)	238 (7.9%)	473 (15.7%)	56 (1.9%)
11	745.300	Double inlet left ventricle	669	650 (97.2%)	0 (−)	0 (−)	19 (2.8%)
12	745.480	Other specified VSD, including crystalline, sub-crystalline, subarterial, conoventricular	28,414	24,541 (86.4%)	3,226 (11.4%)	0 (−)	647 (2.3%)
13	745.485	Perimembranous VSD, including membranous VSD	3,395	2,661 (78.4%)	592 (17.5%)	0 (−)	142 (4.2%)
14	745.486	Muscular VSD, includes mid-muscular and apical VSDs	10,854	9,674 (89.1%)	1,016 (9.3%)	0 (−)	164 (1.5%)
15	745.487	Inlet VSD	37¶	14 (37.8%)	23 (62.2%)	0 (−)	--§
16	745.490	Ventricular septal defect (VSD), NOS, excludes common AV canal type	4,119	3,174 (77.1%)	861 (20.9%)	0 (−)	84 (2.0%)
17	745.600≠	Ostium primum defects, primum ASD	315¶	154 (48.9%)	161 (51.1%)	0 (−)	--§
18	745.610	Single common atrium, cor triloculare biventriculare	214	21 (9.8%)	185 (86.5%)	0 (−)	8 (3.7%)

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n	BPA code(s)	Defect	n with BPA code	n coded to respective C-CLOC category (%)	n moved to higher complexity C-CLOC group (%)	n misclassified (%)	n lacking sufficient information for classification (%)
19	745.630	Common AV canal with ventricular septal defect; Common AV canal, including complete AV canal defect	2,862	2,715 (94.9%)	141 (4.9%)	0 (−)	6 (0.2%)
20	745.680	Other specified cushion defect	52¶	52 (100.0%)	--§	0 (−)	--§
21	745.690	Endocardial cushion defect, NOS	36	36 (100.0%)	0 (−)	0 (−)	0 (−)
22	746.000	Pulmonary valve atresia or hypoplasia, includes absent pulmonary valve‡	1,637	340 (20.2%)	1,255 (76.7%)	0 (−)	42 (2.6%)
23	746.010	Stenosis of pulmonary valve, small pulmonary valve; excludes: Pulmonary infundibular stenosis	6,074	4,008 (66.0%)	1,137 (18.7%)	77 (1.3%)	852 (14.0%)
24	746.100	Tricuspid atresia, right AV atresia; excludes: tricuspid stenosis and hypoplasia	574	432 (75.3%)	62 (10.8%)	36 (6.3%)	44 (7.7%)
25	746.200	Ebstein anomaly, atrialization of right ventricle	574	467 (81.4%)	41 (7.1%)	0 (−)	66 (11.5%)
26	746.300	Congenital stenosis of aortic valve, including: congenital aortic stenosis, subvalvular aortic stenosis, small aortic valve; excludes: supravalvular aortic stenosis	1,858	786 (42.3%)	1,016 (54.7%)	17 (0.9%)	39 (2.1%)
27	746.500	Congenital mitral stenosis, Congenital left AV stenosis, Thickened mitral valve, Thickened left AV valve	776	425 (54.8%)	326 (42.0%)	0 (−)	25 (3.2%)
28	746.505	Absence, atresia, or hypoplasia of mitral valve, abnormal mitral valve, absence, atresia, or hypoplasia of left AV valve, cleft left AV valve, cleft mitral valve, double orifice mitral valve, dysmorphic mitral valve, dysplastic left AV valve, dysplastic mitral valve, left AV valve prolapse, mitral valve anomaly, mitral valve prolapse, parachute left AV valve, parachute mitral valve	2,742	684 (24.9%)	1,940 (70.8%)	0 (−)	118 (4.3%)
29	746.700	Hypoplastic left heart syndrome, atresia, or marked hypoplasia of the ascending aorta and defective development of the left ventricle (with mitral valve involvement)	1,726	1,289 (74.7%)	48 (2.8%)	357 (20.7%)	32 (1.9%)
30	746.820	Cor triatriatum	155	72 (46.5%)	78 (50.4%)	5 (3.2%)	0 (−)
31	746.830†	Pulmonary infundibular (subvalvular) stenosis	720	0 (−)	605 (84.0%)	0 (−)	115 (16.0%)
32	747.100	Preductal (proximal) coarctation of aorta	166	122 (73.5%)	44 (26.5%)	0 (−)	0 (−)
33	747.110	Postductal (distal) coarctation of aorta	195¶	165 (84.6%)	30 (15.4%)	0 (−)	--§
34	747.190	Unspecified coarctation of aorta, juxtaductal coarctation of aorta, long-segment coarctation of aorta, preductal and postductal coarctation of aorta	3,696	2,715 (73.5%)	923 (25.0%)	0 (−)	58 (1.6%)
35	747.200†	Atresia of aorta, Absence of aorta, Atrophy of aorta, Pseudotruncus arteriosus, Stenosis of aorta*	155	0 (−)	148 (95.5%)	0 (−)	7 (4.5%)

n	BPA code(s)	Defect	n with BPA code	n coded to respective C-CLOC category (%)	n moved to higher complexity C-CLOC group (%)	n misclassified (%)	n lacking sufficient information for classification (%)
36	747.210	Hypoplasia of aorta, tubular hypoplasia of aorta, small aorta, narrowing of aorta, proximal distal transverse arch hypoplasia, narrow aortic isthmus, hypoplastic aortic arch	5,222	4,010 (76.8%)	1,056 (20.2%)	76 (1.4%)	80 (1.5%)
37	747.215	Interrupted aortic arch, Type A	75	36 (48.0%)	28 (37.3%)	0 (−)	11 (14.7%)
38	747.216	Interrupted aortic arch, Type B	201	145 (72.1%)	33 (16.4%)	0 (−)	23 (11.4%)
39	747.217	Interrupted aortic arch, Type C	10¶	5 (50.0%)	5 (50.0%)	0 (−)	--§
40	747.220	Supra-aortic stenosis (supravalvular), excludes: aortic valve stenosis, congenital	193	95 (49.2%)	93 (48.2%)	0 (−)	5 (2.6%)
41	747.230	Persistent right aortic arch	1,843	204 (11.1%)	1,414 (76.7%)	139 (7.5%)	86 (4.7%)
42	747.250	Vascular ring (aorta), double aortic arch	469	296 (63.1%)	125 (26.6%)	0 (−)	48 (10.2%)
43	747.285	Interrupted aortic arch, NOS, type not specified	192	22 (11.5%)	160 (83.3%)	0 (−)	10 (5.2%)
44	747.300‡	Pulmonary artery - Atresia, absence or agenesis, main pulmonary artery or NOS	250	145 (58.0%)	95 (38.0%)	0 (−)	10 (4.0%)
45	747.310	Pulmonary artery atresia with septal defect	116¶	77 (66.4%)	39 (33.6%)	0 (−)	--§
46	747.420	Total anomalous pulmonary venous return	1,241	666 (53.7%)	527 (42.5%)	0 (−)	48 (3.9%)
47	747.430	Partial anomalous pulmonary venous return	420	187 (44.5%)	222 (52.9%)	0 (−)	11 (2.6%)

ASD: Atrial septal defect; AV: Atrioventricular; ; NOS: Not otherwise specified; Ventricular septal defect.

†Codes 746.830 and 747.200 were considered to never occur in isolation (i.e., without co-occurring defects). Therefore, none of these variables were considered to have been classified into a C-CLOC group.

‡For code 746.000 and 747.300 the “retained” group referred to is pulmonary atresia with intact ventricular septum.

§Cells with n<5 were repressed.

¶Excludes repressed cells with n<5.

Table 3.

Neonatal Mortality by Approach, 1999–2017

C-CLOC Approach of 59 Lesions			BPA Codes Used to Define CHD	Broad Approach		Exclusive Approach	
Description	**n**	**% neonatal mortality**		**n**	**% neonatal mortality**	**n**	**% neonatal mortality**
All left-sided lesions	8,359	8.6	746300, 746500, 746505, 746700, 746820, 747100, 747110, 747190, 747200, 747210, 747215, 747217, 747220, 747285	10,843	10.0	5,498	7.9
Aortic arch obstruction	5,110	5.9	747100, 747110, 747190, 747200, 747210, 747215, 747217, 747285	6,956	8.2	2,625	4.5
Simple	2,652	4.3					
Complex	2,469	7.6					
Congenital aortic stenosis	731	3.7	746300	1,749	7.4	631	3.0
Hypoplastic left heart syndrome	1,206	23.5	746700	1,619	24.2	440	25.5
Mitral stenosis	938	8.4	746500	711	7.7	182	3.9
Simple	509	4.7					
Complex	429	12.8	746500 or 746505	3,051	13.5	509	4.7
Cor triatriatum	--≠	--†	746820	146	9.6	--≠	--†
Supravalvar aortic stenosis	--≠	--†	747220	179	3.4	--≠	--†
All right-sided lesions	5,744	3.0	746000, 746010, 746100, 746200, 746830, 747300, 747310	8,236	5.3	4,546	3.0
Ebstein anomaly	431	13.0	746200	531	15.3	266	9.8
Pulmonary valve stenosis	3,730	0.3	746010	5,663	1.8	3,680	0.3
Pulmonary atresia	1,079	12.7	746000, 747300, 747310	1,798	14.6	328	18.0
Pulmonary atresia with IVS	364	16.2					
Tricuspid atresia	413	7.5	746100	548	8.6	26	26.9
Tricuspid atresia, normal GA	311	8.0					
Tricuspid atresia, malposed GA	101	5.9					
All conotruncal defects	3,780	6.8	745000, 745200, 747216, 747230, 747310	4,570	7.5	2,336	5.3
Tetralogy of Fallot	2,104	4.7	745200	2,825	5.6	1,593	5.0
Pulmonary atresia with VSD	574	9.8	747310	113	14.2	--≠	--†
Truncus arteriosus	394	13.5	745000	468	18.0	146	15.1
Truncus arteriosus with IAA	38	15.8					
Truncus arteriosus without IAA	356	13.2					
IAA, Type B	218	12.4	747216	184	12.0	--≠	--†

C-CLOC Approach of 59 Lesions			BPA Codes Used to Define CHD	Broad Approach		Exclusive Approach	
Description	**n**	**% neonatal mortality**		**n**	**% neonatal mortality**	**n**	**% neonatal mortality**
Right aortic arch	175	2.9	747230	1,685	6.6	174	2.9
Vascular ring	--≠	--†	747250	410	2.4	--≠	--†
Endocardial cushion defects	2,959	9.0	745600, 745610, 745630, 745680, 745690	3,158	9.7	1,307	5.3
ASD only	157	8.3	745600, 745610	491	14.7	92	9.8
Atrioventricular canal defect			745630, 745680, 74569	2,687	9.0	1,171	5.0
Simple	1,315	4.9					
Complex	1,454	12.9					
Arterial malposition/looping defects	2,063	8.0	745100, 745110, 745120, 745180, 745190, 745300	2,785	9.5	912	6.5
Congenitally corrected TGA	159	6.9	745120	355	8.5	--≠	--†
Dextro-TGA	1,279	5.2	All: 745100,745110, 745180, 745190	2,158	7.8	837	5.7
Dextro-TGA with VSD	512	4.6	With VSD: 745110	1,097	6.9	257	5.8
Dextro-TGA without VSD	646	5.3	Without VSD: 745100	955	8.0	554	5.4
Double inlet left ventricle	616	14.5	745300	635	15.4	17	47.1
Double inlet left ventricle, L-loop	--≠	--†					
Double inlet left ventricle, other	517	16.5					
Double outlet right ventricle	1,140	15.6	All: 745130, 745140, 745150	1,619	15.3	42	19.1
DORV, transposition of GA	137	5.8	DORV + Transposition of GA: 745140	678	11.5	--≠	--†
DORV, normal GA	439	14.8	DORV + Normal GA: 745130	521	14.8	--≠	--†
DORV, mitral atresia	232	22.0	N/A	N/A	N/A	N/A	N/A
DORV, complex	332	16.9	N/A	N/A	N/A	N/A	N/A
Other CHDs	--		N/A	N/A	N/A	N/A	N/A
Pulmonary atresia, complex	141	15.6	N/A	N/A	N/A	N/A	N/A
Aortopulmonary window	45	11.1	745010	82	8.5	29	6.9
PAPVR	166	5.4	747430	381	9.5	120	4.2
TAPVR	630	7.0	747420	1,174	13.1	568	6.7
VSD	37,235	1.7	All: 745480, 745485, 745486, 745487, 745490	43,344	2.7	37,106	1.7
VSD, muscular	7,646	0.7	Muscular: 745486	8,832	1.4	7,606	0.7
VSD, membranous	1,936	2.2	Membranous: 745485	2,798	3.7	1,931	2.2
VSD, inlet	--†	--†	Inlet: 745487	--≠	--†	--≠	--†
VSD, NOS	27,648	1.9	NOS: 745480, 745490	32,122	3.1	27,302	1.9

ASD: Atrial septal defect; AVSD: Atrioventricular septal defect; BPA: British Pediatric Association; CHD: Congenital heart defects; DORV: Double outlet right ventricle; GA: Great arteries; IAA: Interrupted aortic arch; IVS: Intact ventricular septum; NOS: Not otherwise specified; PAPVR: Partial anomalous pulmonary venous return; TAPVR: Total anomalous pulmonary venous return; TGA: Transposition of the great arteries; VSD: Ventricular septal defect.

† Cells with n<5 were repressed.

‡ Excludes repressed cells with n<5.

Table 4.

Diagnostic Metrics by Approach in HLHS Compared to Manual Clinical Review

	C-CLOC Approach	Broad Approach	Exclusive Approach
True Positive	805	914	287
True Negative	137	0	212
False Positive	128	265	53
False Negative	109	0	627
Accuracy[†]	79.9%	77.5%	42.3%
Sensitivity	88.1%	100.0%	31.4%
Specificity	51.7%	0%	80.0%

[†]Accuracy was computed as % correctly classified (true positive + true negative)/total).