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Hearing impairment following surgically repaired congenital heart disease in children: a prospective study

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Hearing impairment following surgically repaired congenital heart disease in children: a prospective study

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Abstract

Objectives: To determine the prevalence of sensorineural hearing loss (SNHL) in children who underwent congenital cardiac surgery (CCS) by using a pre- and post-operative hearing test; a conventional audiometry, an extended high-frequency audiometry (HFA) or auditory steady-state response (ASSR), and distortion-product otoacoustic emissions (DPOAE).

Study design: This prospective study enrolled children with CCS in Siriraj Hospital, Thailand between 2019 and 2023. Conventional audiometry including HFA or ASSR and DPOAE were performed pre- and post-operatively. The patients with bilateral abnormal hearing loss or an incomplete examination were excluded. Collected data included: demographics, cardiac surgery, and ototoxic medication. Prevalence of SNHL by conventional audiometry and subclinical hearing impairment by HFA or DPOAE were ascertained and risks were analysed.

Results: Ninety-eight patients were eligible for the study. The median age (IQR) was 5.3 (1.5-9.6) years. Fifteen patients (15.3%) had univentricular hearts. The pre-operative audiologic test was performed one day prior to the CCS. The post-operative test was performed 1-44 months post-operatively. Pre-operative unilateral hearing impairments were reported in 17 patients (17.3%). Post-operatively, 4 patients (4.1%) showed significantly abnormal audiogram (> 25 dB) or 15 dB shift at 250-8000 Hz consistent to a new SNHL. Subclinical hearing impairment by HFA were affected in 10 patients (10.2%). Thirty-three patients (33.6%) had abnormal DPOAE

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exclusively. Therefore, new SNHL, including subclinical hearing loss revealed a prevalence of ototoxicity up to 47.9%. Age < 1 year at surgery was the independent risk of post-operative SNHL (adjusted odds ratio 18.5, 95% CI 1.2-293.8, p=0.04).

Conclusion: Routine post-CCS audiological surveillance especially CCS in infancy is recommended for early recognition and timely management based on the 43.8% subclinical and the 4.1% SNHL that was found in this study.

Trial registration: TCTR20200421001

Keywords: pediatric, cardiac surgery, hearing loss, sensorineural hearing loss (SNHL)

Abbreviations: ASSR (auditory steady-state responses), CCS (congenital cardiac surgery), CHD (congenital heart disease), CPB (cardiopulmonary bypass), DPOAE (distortion-product otoacoustic emissions), ECMO (extracorporeal membrane oxygenation), HFA (extended high-frequency audiometry), OR (odds ratio), PHL (permanent hearing loss), SNHL (sensorineural hearing loss), STAT (The Society of Thoracic Surgeons Congenital Heart Surgery)

Key messages

- **What is already known on this topic**

The incidence of sensorineural hearing loss (SNHL) increased in adults following bypass surgery. Data of SNHL in children following congenital cardiac surgery (CCS) is limited. Based on a few of studies, the incidence of hearing loss was 65.6 per 1000 operations.

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However, no pre-operative audiologic assessments were conducted, and co-occurring SNHL and CHD prior to CCS could have been confounded in the data.

- **What this study adds**
  - A prevalence of post-operative SNHL of 4.1% by using conventional audiometry and subclinical SNHL detected by HFA and DPOAE of 43.8%. High-frequency hearing impairment is mostly affected.
  - Multivariable analysis showed that age < 1 year at surgery was the significant risk of post-operative SNHL (adjusted odds ratio 18.5, 95% CI 1.2-293.8, p=0.04).
  - No associations with post-operative SNHL were found for single ventricle repair, syndromic disorders, moderate hypothermic cardiopulmonary bypass, furosemide > 4 mg/kg/day or route of administration or duration of intravenous bolus, use of vancomycin, high vasoactive inotropic score, or duration of mechanical ventilation.
- **How this study might affect research, practice or policy**

The findings from the study suggest that children undergoing CCS may be at risk for SNHL, potentially increasing risk of neurodevelopmental difficulties. Post-CCS audiological surveillance is recommended for early recognition and timely management particularly in infants under 1 year old.

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Introduction

Congenital heart disease (CHD) is a common birth defect worldwide affecting millions of live births per year.[1] Dramatic improvements in surgical correction and medical treatment have led to an increase in the survival of children with CHD into adulthood, though a considerable percentage of the survivors continue to have a neurodevelopmental disability. Hearing loss is one of potential problems that can limit CHD patients from developing speech capabilities and social skills.[2] The sensorineural hearing loss (SNHL) in CHD has been recognized, with a plausible mechanism for their co-occurrence involving developmental dysregulation of the inner ear and heart and genetic etiologies.[3] There were some risk indicators for pediatric hearing loss possibly associated with the CHD care and surgery, such as the prolonged intensive care, use of an extracorporeal membrane oxygenator, using assisted ventilation, exposure to ototoxic medications (aminoglycosides) or loop diuretics (furosemide).[4] Furosemide, which are commonly used to treat CHD patients after cardiac surgery, may induce pathological ischemic damage or edema to the stria vascularis and cochlear lateral wall that occurs with the hearing impairment.[5] The ototoxic effects of high dosage intravenous furosemide and kidney injury have been reported from prior studies.[6 7]

The greater incidence of SNHL in adult patients after coronary bypass surgery, compared to the incidence in the normal population has been reported. Possible attributing factors include: thromboembolic phenomena; perfusion failure; hypothermia; ototoxic drug use; and central nervous system injury. Nevertheless, no proven etiologies have been established.[8 9] Data for pediatric patients following congenital cardiac surgery (CCS) and SNHL are limited and unique.[10] Robertson reported the prevalence of permanent hearing loss

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(PHL) after Norwood right ventricular-pulmonary artery shunt for hypoplastic left heart syndrome (HLHS) to be 28.6% at the 4-year-old audiologic examination.[11] Grasty et al. reported that 6.9% of the 4-year-old survivors of CCS in infancy had SNHL, and 2.3% had indeterminate hearing loss [12], which is in accordance with Bork and colleagues reported prevalence of PHL (5.9%) after complex cardiac surgery at less than 6 weeks of age at the 4-year-old audiologic examination.[13] Gopineti et al. estimated the prevalence of hearing loss to be 11.6% for 172 palliated/repaired CHD patients.[14] The incidence of hearing loss across these studies was 97 out of 1,342 (65.6 per 1000 operations).[10] However, no pre-operative audiologic assessments were conducted for the pediatric patients in these studies, and co-occurring SNHL and CHD prior to CCS could have been confounded in the data.

Therefore, we conducted this prospective study to: 1) investigate the changes between pre- and post-operative hearing thresholds, measured by conventional audiometry with extended high frequency audiometry (HFA) or auditory steady-state response (ASSR) in uncooperative children and distortion-product otoacoustic emissions (DPOAE), in pediatric patients undergoing CCS to ascertain the prevalence of SNHL in this population, and 2) identify the risk factors for SNHL. Importantly, the audiology screening was scheduled pre- and post- operation to ascertain whether the patients had abnormal hearing or not prior CCS. We hypothesized that pediatric patients who underwent CCS may have a reduced hearing threshold, compared to their pre-operation threshold, especially in patients who received high dosage of furosemide, moderate hypothermic cardiopulmonary bypass, or underwent a high complexity operation or had single ventricle repair.

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Materials and Methods

Study population and study design

This prospective observational study was approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University [Study number 075/2562(EC2), COA: Si 382/2019]. The study period was June 2019 to June 2023, when 1,357 pediatric patients (age < 18 years) underwent CCS in Siriraj Hospital, Thailand. A total of 137 children were enrolled in the study and had pre-operative hearing assessments. Informed consents were obtained from the parents or legal guardians. The exclusion criteria were: 1) pre-term baby, 2) underlying chronic renal insufficiency, 3) inability to complete the audiologic examination, 4) presence of bilateral conductive hearing loss such as otitis media with effusion (OME), or 5) presence of bilateral SNHL. Finally, 98 children were eligible for the analysis (Figure 1).

Figure 1. Flow diagram of the study (n=98). (CCS=congenital cardiac surgery; SNHL= sensorineural hearing loss; OME=otitis media with effusion; HFA=extended high frequency audiometry; DPOAE=distortion product otoacoustic emission)

Demographic data, including age, gender, weight, height, CHD diagnosis, presence of syndromic disorders, previous cardiac surgery, pre-operative furosemide usage, pre-operative unilateral abnormal hearing on HFA/ASSR; intraoperative data including type of operation, single ventricular repair, and complexity of the surgical procedure using Aristotle Basic Complexity (ABC) score, The Society of Thoracic Surgeons-European Association for Cardio-

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Thoracic Surgery (STAT) mortality score, operative time, cardiopulmonary bypass (CPB) time, aortic cross clamp (AoX) time, minimal temperature during CPB, extracorporeal membrane oxygenator (ECMO) usage was collected. The post-operative parameters included duration of ventilator usage, maximal vasoactive inotropic score, cumulative furosemide usage in 72 hours (mg), maximal furosemide dosage (mg/kg/day), route of maximal dose furosemide, duration of intravenous furosemide, maximal creatinine level (mg/dL) and hospital length of stay (LOS) were explored.

Audiological assessment and outcome measure

The 1st and 2nd audiologic examinations were scheduled pre- and post-operatively, respectively. The pre-operative test was performed one day prior to the CCS. The post-operative test was performed 1-44 months post-operatively, according to the COVID-19 pandemic. Each audiologic assessment was performed in the Otorhinolaryngology department using age appropriate and standard techniques. For hearing thresholds, young children and developmentally delayed children were tested by ASSRs, while cooperative older children underwent behavioral audiological assessment using pure tone audiometry. Beyond the conventional audiometry (0.25-8 kHz), we tested in the HFA (9-20 kHz) or extra-high frequency audiometry (EFA) to cover HF-SNHL, which we postulated to occur post-CCS. The SNHL from conventional audiometry in the study was defined according to the 1991 World Health Organization's (WHO's) grading of hearing impairment and current Common Terminology Criteria for Adverse Events (CTCAE) [2 15-17]. Hearing loss at any particular frequency (0.25-8 kHz) was defined as a dropped response of more than a 25-decibel hearing level (dB HL) in either ear. The degree of hearing loss was classified as mild (grade 1), 26-40;

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moderate (grade 2), 41-60; severe (grade 3), 61-80; profound/deafness (grade 4), ≥ 81 dB HL. In addition, a change of 15 dB or more, in either ear, at any test frequency from 500 through 6000 Hz determined by pre- and post-operative audiometry was also defined as SNHL according to National Institute of Occupational Safety and Health recommended definition of a standard threshold shift in SNHL[18 19]. Another audiologic examination was the DPOAE. Two primary frequencies, f1 and f2, were presented simultaneously with f2/f1 equaling 1.22. Twelve points per octave were measured and plotted as a function of f2 ranging about 1.5 to 10 kHz. DPOAE was interpreted to be present if: Signal-to-noise ratio (SNR) of DPgrams ≥ 6 dB at each frequency. In addition, it was normal if the absolute DP amplitude is in the range of the normative values or above 95th percentile of hearing impaired that based on the Boys Town 65-55 reference set[20]. The deficit of hearing in each frequency is considered if the SNR is less than 6 dB (absent DP response) or the absolute DP amplitude of each frequency is out of the range of the normative values. All participants were tested with hearing assessment tests as described. Subclinical ototoxicity included abnormal hearing response (> 25 dB) or threshold shift of 15 dB or more in HFA (> 8 kHz) or/and abnormal/absent DPOAE. The primary outcome was the presence of a new SNHL, based on conventional audiometry. The secondary outcome was abnormal hearing threshold on HFA, or abnormal/absent DPOAE which is called subclinical ototoxicity.

Statistical methods

Statistical analyses were performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Sample size was calculated based on prior literature in 2018 and 2023.[10 12 13] Using prevalence of SNHL following early CCS (5.9-6.9%), the margin of error was 5% with

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a 95% confidence interval (type I error = 0.05, 2-sided), and the sample size was calculated to be 85-98 participants. Demographics, pre-operative, perioperative, and post-operative data were presented as frequencies with percentages for the categorical variables and mean ± SD or median with interquartile range for the continuous variables. Comparisons of the hearing thresholds in the pre- and post-operative HFA and DPOAE were analyzed and the prevalence of progressive SNHL and ototoxicity following CCS were calculated. The data for patients with progressive SNHL following CCS detected by the conventional audiometry and patients without progressive SNHL were analyzed and compared using chi-square or the Fisher exact test. Factors associated with SNHL following CCS were analyzed using univariate analysis and logistic regression. The factors which represented p-value < 0.25 in univariate analysis were chosen for binary logistic regression. A p-value < 0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 98 pediatric patients who had CHD and underwent CCS in the medical center were eligible for the analysis (Figure 1). The median age was 5.29 years, and 55 (56%) of the included patients were boys. Pre- and post-operative hearing assessments were performed a day prior to surgery, and 4.37 (IQR 2.66-8.01) months post operatively, respectively. Demographic characteristics including clinical features, and pre- and post-operative data are shown in Table 1. Nine patients (9.2%) had syndromic disorders (4 trisomy 21, 1 velocardiofacial syndrome, 1 Marfan syndrome, 1 Scimitar syndrome, 1 multiple anomalies, 1 fetal alcohol syndrome). Pre-operative unilateral hearing impairments were reported in 17

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patients (17.3%); 9 unilateral SNHL on conventional audiometry, 5 unilateral abnormal hearing thresholds on HFA, and 3 unilateral conductive hearing loss. These 17 patients were noted to have unilateral HL and the outcomes were measured from the contralateral ear. The types of lesions are illustrated in Figure 2. Most surgical procedures for the patients in the study were in STAT categories 1-3 (88.2%) since most of the procedures were elective and the patients were eligible for the pre-operative hearing test (Figure 3). Most of the patients (82.7%) used mild hypothermia during CPB. No patients in the study required post-operative ECMO or renal replacement therapy (Table 1).

Table 1. Baseline characteristics (n=98)

Figure 2. Types of congenital heart disease (n=98)

(ASD=atrial septal defect; TOF=tetralogy of Fallot; VSD=ventricular septal defect)

Figure 3. Number of patients in STAT categories 1-5 (n=98) (STAT=The Society of Thoracic Surgeons Congenital Heart Surgery)

In comparison to their pre-operative hearing assessments, 58 patients underwent conventional audiometry plus HFA with DPOAE and 40 patients underwent ASSR with DPOAE. Notably, 4 patients (4.1%) showed significantly new abnormal hearing threshold (> 25 dB) or 15 dB shift or more, defined as SNHL on conventional audiometry; 3 ASSR and 1 audiometry (250-8000 Hz). Abnormal DPOAE responses were also noted in all patients. These 4 patients were classified as SNHL grade 1 WHO classification for hearing loss. Using extended HFA range > 8000 Hz, 10 patients (10.2%) were detected newly abnormal hearing

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response (> 25 dB) or 15 dB shift. Of 10 patients, 4 patients were additionally shown abnormal DPOAE. There were 33 patients (33.7%) had post-operative DPOAE abnormalities exclusively (Figure 4). Overall, the prevalence of SNHL after CCS in this study was 4.1%. Subclinical hearing impairment which was detected early by extended HFA and DPOAE was 10.2% and 33.6%, respectively, raises the prevalence of subclinical ototoxicity to 43.8%. During the median time of follow-up (20 months), 18 patients with subclinical ototoxicity continued their follow-up at the otology clinic. Among them, two patients exhibited delayed speech, and one patient had an articulation disorder. Notably, one patient with multiple anomalies, including microcephaly, which may lead to global developmental delay, was identified among these cases. No patients in the study required hearing aids or cochlear implants.

Risks of SNHL following CCS

The risk analysis of SNHL following pediatric CCS is illustrated in Table 2. The univariate analysis revealed a significant association between age at surgery younger than 1 year (odds ratio 15.8, 95% CI 1.53-162.31, p=0.02) and post-operative SNHL. In the binary logistic regression model, age at surgery younger than 1 year remained independently associated with post-operative SNHL (adjusted odds ratio 18.5, 95% CI 1.2-293.8, p=0.04).

Table 2. Risk factors for SNHL following CCS (n=98)

Discussion

Herein, we reported a prevalence of postoperative SNHL of 4.1% by using conventional audiometry and subclinical SNHL detected by HFA and DPOAE of 43.8%. High-

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frequency hearing impairment is mostly affected. The age at surgery younger than 1 year was independently associated with post-operative SNHL (adjusted odds ratio 18.5, 95% CI 1.2-293.8, p=0.04). To our knowledge, this is the first study assessed prevalence of SNHL following CCS in children with pre- and post-operative hearing test using conventional audiometry in addition to HFA and DPOAE to cover subclinical hearing abnormality. An update systematic review[10] also indicated that the incidence of pediatric hearing loss was 65.6 per 1000 operations which was consistent to our finding. Gopineti et al.[14] reported that a prevalence of SNHL in children post repaired or palliated CCS was 11.6% which was higher than our study. It was possibly owing to the pre-operative hearing test screening which reduced the confounded cases in our study protocol. Overall, the prevalence of post-operative SNHL is substantially greater than that in the general pediatric population, which has been reported to be 0.2% at birth and 0.35% in adolescence.[21]

Subsequent SNHL following cardiac surgery is related to several possible mechanisms. A few pediatric studies have summarized the risks of SNHL following CCS. El Ganzoury et al.[22], for example, found an association between subtle cochlear dysfunction and moderate hypothermic CPB in pediatric patients having CCS (n=40). In a Quebec, 1-5 year surveillance study of 85 children, post-CCS in infancy, low birth weight and Apgar score at 5 min and older age at surgery was found to be associated with SNHL.[23] In Gopineti et al.'s study14, independent risks were not found from the multivariable analysis. Our findings with the logistic regression analysis showed that age at surgery younger than 1 year (adjusted odds ratio 18.5, 95% CI 1.2-293.8, p=0.04) was a significant risk for post-operative SNHL. The plausible explanation may relate with cochlear hypoperfusion after CCS especially in infancy.

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No associations were found for single ventricle repair, syndromic disorders, moderate hypothermic CBP, furosemide > 4 mg/kg/day or route of administration or duration of intravenous bolus, use of vancomycin, high vasoactive inotropic score, or duration of mechanical ventilation.

While the progression of subclinical ototoxicity and new-onset sensorineural hearing loss (SNHL) after CCS and their impact on neurodevelopmental outcomes are intriguing, they lie beyond the scope of our current research protocol. Initially, our protocol did not include long-term outcome data collection for participants. However, we established follow-up schedules for participants diagnosed with SNHL or subclinical ototoxicity. Over a median follow-up period of 20 months, 18 patients with subclinical ototoxicity continued their follow-up at the otology clinic. Among these cases, two patients exhibited delayed speech, and one had an articulation disorder. Notably, one patient with multiple anomalies, including microcephaly, was identified. This case may involve confounding factors related to developmental delay. Unfortunately, none of the participants diagnosed with SNHL attended their scheduled otology appointments. Future research with more comprehensive data aggregation is necessary to assess the progression and impact of SNHL and subclinical ototoxicity in children following CCS.

Study Limitations

Our prospective study has some limitations since it was conducted during the COVID-19 pandemic. As noted previously, not all survivors following CCS in the medical center between 2019 and 2023 could be enrolled in the study. Nevertheless, the 98 eligible

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participants was a sufficiently large group for the analysis based on the prevalence of SNHL in a previous study in 2018 and a systematic review in 2023 that was mentioned in the Methods section.[10 12 13] The eligible participants were selected from all consecutive CCS patients who were clinically stable enough for pre-operative hearing assessments. Nonetheless, single ventricle repair and high complexity cases were included in 10-15% of all patients. Regarding hearing method, the ASSR assesses a hearing threshold with maximal frequency of 4000 Hz, not equal to conventional audiometry which is up to 8000 Hz, not extends to 20,000 Hz as HFA. This may indeterminate subclinical ototoxicity in some patients. The variable time interval for post-operative hearing assessments due to COVID-19 pandemic was noted (median 4.37 months, IQR 2.66-8.01 months). This variability allows for the healing process to potentially ameliorate hearing loss or for additional hearing loss from ongoing hemodynamically significant cardiac lesions and cyanosis. Nevertheless, comparing the median time intervals among three groups; post-operative SNHL (n=4), post-operative subclinical hearing loss (n=43), and no post-operative hearing loss (n=51), revealed no statistically significant differences.

Conclusion

In this study, the prevalence of new SNHL in the children following CCS is 4.1%. An abnormal hearing threshold from the baseline (based on DPOAE and HFA) is reported for up to 43.8%. High-frequency hearing impairment is mostly affected. Surgery at an age younger than 1 year is associated with a higher incidence of post-operative SNHL. These findings suggest that children undergoing CCS may be at risk for SNHL, potentially increasing risk of

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neurodevelopmental difficulties. Post-CCS audiological surveillance is recommended for early recognition and timely management particularly in infants under 1 year old.

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Contributors

CV, YT and KT designed the study. CV, KT, KS and EK enrolled participants, conducted the study and collected the data. CV and KS led the data analysis and drafted the manuscript. All authors made critical comments, and contributed to and approved the final manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

Patient consent for publication

Informed consents were obtained from all parents who participated in the study.

Ethics approval

This prospective observational study was approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University [Study number 075/2562(EC2), COA: Si 382/2019].

Data availability statement

Data is available upon request. Portions of this study were submitted to be a poster presentation at the 57th Annual Meeting of the Association for European Pediatric and Congenital Cardiology to be held in Porto, Portugal, May 8-11, 2024.

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Table 1. Baseline characteristics (n=98)

	Total (n=98)	**Post-operative SNHL (n=4)**	**Post-operative subclinical hearing loss (n=43)**	**No post-operative hearing loss (n=51)**	***p*-value**
Age at surgery (years)	5.29 (1.50-9.56)	0.77 (0.58-5.19)	6.92 (2.00-9.94)	4.82 (1.49-8.81)	0.415
Age < 1 year at surgery	18 (18.4%)	3 (75%)	4 (9.3%)	11 (21.5%)	0.004*
Male gender	55 (56%)	2 (50%)	26 (60.5%)	27 (52.9%)	0.593
Weight (kg)	19.89 ± 14.38	11.00 ± 9.81	22.12 ±15.28	18.73 ± 13.68	0.237
Height (cm)	106.66 ± 29.62	81.75 ± 35.76	112.70 ± 28.72	103.52 ± 29.00	0.073
Diagnosis					
Cyanotic heart disease	36 (36.7%)	0	18 (41.9%)	18 (35.3%)	0.240
Presence of syndromic disorder	9 (9.18%)	1 (25%)	4 (9.3%)	4 (7.8%)	0.519
Down syndrome	4 (44.4%)	1 (100%)	0 (0%)	3 (75%)	
DiGeorge syndrome	1 (11.1%)	0 (0%)	1 (25%)	0 (0%)	
Others	4 (44.4%)	0 (0%)	3 (75%)	1 (25%)	
History of pre-term	8 (8.2%)	1 (25%)	2 (4.7%)	5 (9.8%)	0.301
Previous cardiovascular surgery	24 (24.5%)	0 (0%)	14 (32.6%)	10 (19.6%)	0.177
Pre-operative usage of furosemide	37 (37.8%)	3 (75%)	18 (41.9%)	16 (31.4%)	0.169
Pre-operative unilateral abnormal hearing on HFA/ ASSR	17 (17.3%)	1 (25%)	8 (18.6%)	8 (15.7%)	0.857
Pre-operative unilateral SNHL	9 (9.2%)	1 (25%)	3 (7.0%)	5 (9.8%)	0.478
Operative factors					
Single ventricular repair	15 (15.3%)	0 (0%)	10 (23.3%)	5 (9.8%)	0.135
Procedure STAT mortality score	0.35 (0.20-0.60)	0.60 (0.35-0.75)	0.50 (0.20-0.60)	0.30 (0.20-0.60)	0.155
Procedure STAT category 4-5	11 (11.2%)	0 (0%)	5 (11.6%)	6 (11.8%)	0.768
Procedure Aristotle Basic Complexity score	7.01 ± 2.01	6.65 ± 0.85	7.13 ± 1.97	6.93 ± 2.13	0.841
CPB time (min)	100.05 ± 63.47	55.5 ±53.68	100.12 ± 61.79	103.49 ± 65.30	0.350
Aortic cross clamp time (min)	56.39 ± 51.29	45.25 ± 39.85	47.09 ±46.74	65.10 ± 54.89	0.217
Operative time (min)	170.48 ± 77.06	123.75 ± 58.51	171.79 ± 83.59	173.04 ± 72.53	0.468
Minimal temperature in CPB (°C)	31.36 ± 2.82	32.25 ± 3.69	31.27 ±2.89	31.36 ± 2.74	0.804
Moderate hypothermic CPB	17 (17.3%)	1 (25%)	7 (16.3%)	9 (17.6%)	0.710
Post-operative factors					
Post-operative vancomycin	4 (4.1%)	0 (0%)	1 (2.3%)	3 (5.9%)	0.628

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Post-operative maximal vasoactive inotropic score	7.80 (23.50)	17.00 ± 18.78	15.89 ± 21.88	18.35 ±24.12	0.874
Post-operative usage of dopamine > 4 mcg/kg/min	25 (25.5%)	4 (100%)	7 (16.3%)	14 (27.5%)	0.001*
Post-operative cumulative furosemide in 72 h (mg)	67.37 ± 36.17	42.88 ± 18.66	75.24 ±42.82	62.66 ± 29.23	0.093
Post-operative maximal furosemide dosage (mg/kg/day)	3.38 ± 2.54	3.13 ± 1.64	2.93 ± 1.68	3.78 ±3.11	0.270
Post-operative maximal furosemide dosage > 4 mg/kg/day	27 (27.6%)	1 (25%)	10 (23.3%)	16 (32%)	0.639
Route of maximal dose furosemide					0.847
- IV drip	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
- IV bolus	44 (44.9%)	3 (75%)	19 (44.2%)	22 (44%)	
- Oral and IV bolus	28 (28.6%)	1 (25%)	12 (27.9%)	15 (30%)	
- Oral	19 (19.4)	0 (0%)	10 (23.3%)	8 (18%)	
- IV bolus and IV drip	6 (6.1)	0 (0%)	2 (4.7%)	4 (8%)	
Duration of intravenous furosemide (days)	3.89 ± 2.11	3.25 ± 0.96	3.74 ± 2.29	4.06 ± 2.01	0.641
Post-operative maximal creatinine level (mg/dL)	0.43 ± 0.15	0.29 ± 0.13	0.46 ± 0.16	0.42 ± 0.14	0.082
Oxygen saturation before discharge home (%)	96.81 ± 4.58	98.25 ± 1.26	95.91 ± 5.44	97.45 ± 3.82	0.219
Hospital length of stay (days)	8.05 ± 4.91	9.50 ± 7.68	7.51 ± 3.76	8.39 ± 5.54	0.577
Time interval from surgery to 2nd audiologic examination (months)	4.37 (2.66-8.01)	4.32 (3.15-6.86)	3.61 (1.77-6.60)	5.35 (2.95-9.03)	0.176

Data presented as n (%), mean ± SD, and median (interquartile range p25-p75)

* Statistically significant at p-value < 0.05

SNHL=sensorineural hearing loss; HFA=extended high frequency audiogram; ASSR=auditory steady-state responses; STAT= The Society of Thoracic Surgeons Congenital Heart Surgery; CPB=cardiopulmonary bypass; ECMO=extracorporeal membrane oxygenator

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Table 2. Risk factors for SNHL following CCS (n=98)

Variables	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Male gender	0.7 (0.1, 5.7)	0.801	[redacted]	[redacted]
Age <1 year at surgery	15.8 (1.5, 162.3)	0.019*	18.5 (1.2, 293.8)	0.038*
Presence of genetic syndromes	3.6 (0.3, 38.6)	0.263	[redacted]	[redacted]
Single ventricle	0.9 (0.9, 1.0)	0.385	[redacted]	[redacted]
Cyanotic heart disease	0.9 (0.9, 1.0)	0.293	[redacted]	[redacted]
Previous cardiovascular surgery	0.9 (0.9, 1.0)	0.569	[redacted]	[redacted]
Pre-operative furosemide	5.3 (0.5, 52.9)	0.149	1.5 (0.1, 24.1)	0.754
Pre-operative unilateral SNHL	3.6 (0.3, 38.6)	0.263	[redacted]	[redacted]
Procedure STAT mortality score > 0.6	1.4 (0.2, 10.4)	0.735	[redacted]	[redacted]
Procedure STAT category 4-5	0.9 (0.9, 1.0)	0.468	[redacted]	[redacted]
CPB time > 90 min	0.4 (0, 3.6)	0.620	[redacted]	[redacted]
Moderate hypothermic CPB	1.6 (0.1, 16.6)	0.539	[redacted]	[redacted]
Post-operative maximal vasoactive inotropic score > 20	0.8 (0.1, 8.3)	0.872	[redacted]	[redacted]
Post-operative usage of dopamine > 4 mcg/kg/min	307709498.0 (0, -)	0.997	[redacted]	[redacted]
Post-operative vancomycin usage	0.9 (0.9, 1.0)	0.674	[redacted]	[redacted]
Post-operative cumulative furosemide in 72 h > 85 mg	0.9 (0.9, 1.0)	0.220	0 (0, -)	0.998
Post-operative maximal furosemide dosage > 4 mg/kg/day	0.8 (0.1, 8.6)	0.897	[redacted]	[redacted]
Route-intravenous bolus of maximal furosemide	3.9 (0.4, 38.7)	0.217	8.9 (0.7, 118.8)	0.096
Post-operative maximal creatinine level > 0.45 (mg/dL)	0.5 (0, 4.7)	0.643	[redacted]	[redacted]

Adjusted Odds ratio by binary logistic regression
* Statistically significant at p-value < 0.05
OR=Odds ratio; SNHL=sensorineural hearing loss; STAT= The Society of Thoracic Surgeons Congenital Heart Surgery; CPB=cardiopulmonary bypass

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Figure 1. Flow diagram of the study (n=98)

(CCS=congenital cardiac surgery; SNHL= sensorineural hearing loss; OME=otitis media with effusion; HFA=extended high frequency audiometry; DPOAE=distortion product otoacoustic emission)

Figure 2. Types of congenital heart disease (n=98)

(ASD=atrial septal defect; TOF=tetralogy of Fallot; VSD=ventricular septal defect)

Figure 3. Number of patients in STAT categories 1-5 (n=98)

(STAT=The Society of Thoracic Surgeons Congenital Heart Surgery)

Figure 4. Hearing impairment (n=4) detected by ASSR or conventional audiometry (*) plus DPOAE and subclinical ototoxicity (n=43) detected by DPOAE + HFA or HFA or DPOAE

(ASSR=auditory steady-state responses; DPOAE=distortion-product otoacoustic emissions; Audiogram 250-8=conventional audiometry; HFA=extended high frequency audiometry)

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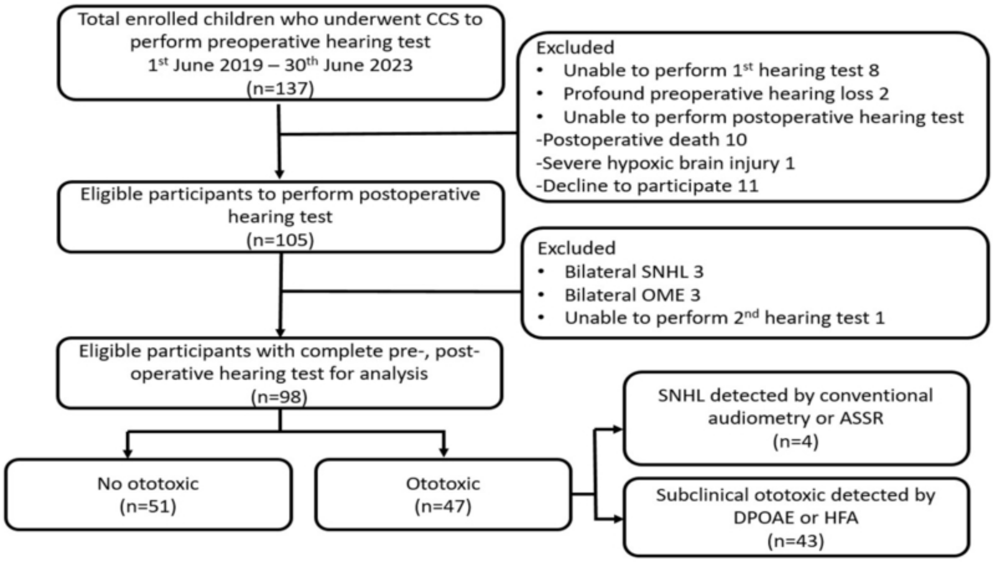

Figure 1. Flow diagram of the study (n=98)

34x19mm (600 x 600 DPI)

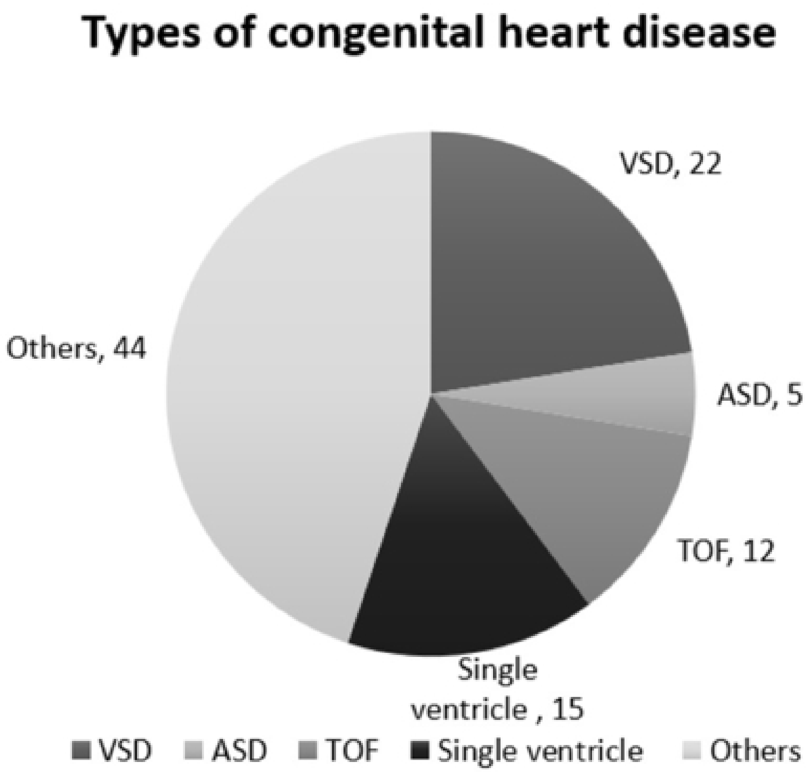

Figure 2. Types of congenital heart disease (n=98)

22x19mm (600 x 600 DPI)

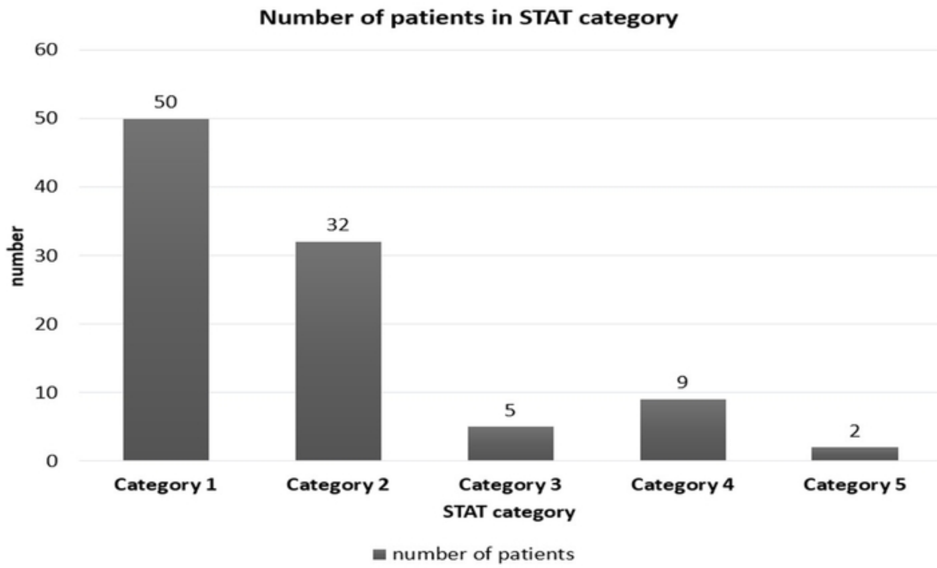

Figure 3. Number of patients in STAT categories 1-5 (n=98)

31x19mm (600 x 600 DPI)

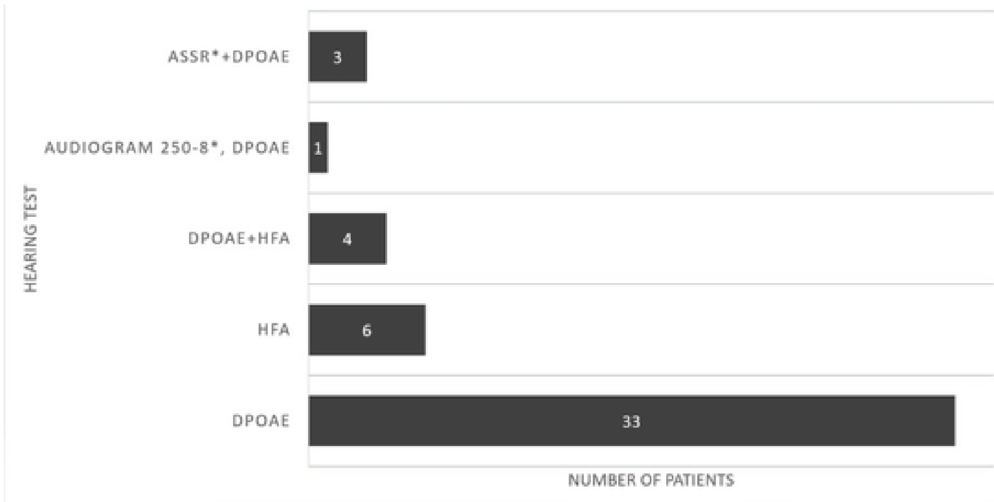

Figure 4. Hearing impairment (n=4) detected by ASSR or conventional audiometry (*) plus DPOAE and subclinical ototoxicity (n=43) detected by DPOAE + HFA or HFA or DPOAE

23x11mm (600 x 600 DPI)

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Hearing impairment following surgically repaired congenital heart disease in children: a prospective study

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Keywords:	Cardiac Surgery, Audiology, Cardiology

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Hearing impairment following surgically repaired congenital heart disease in children: a prospective study

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Abstract

Objectives: To determine the prevalence of sensorineural hearing loss (SNHL) in children who underwent congenital cardiac surgery (CCS) by using a pre- and post-operative hearing test; a conventional audiometry, an extended high-frequency audiometry (HFA) or auditory steady-state response (ASSR), and distortion-product otoacoustic emissions (DPOAE).

Study design: This prospective study enrolled children with CCS in Siriraj Hospital, Thailand between 2019 and 2023. Conventional audiometry including HFA or ASSR and DPOAE were performed pre- and post-operatively. The patients with bilateral abnormal hearing loss or an incomplete examination were excluded. Collected data included: demographics, cardiac surgery, and ototoxic medication. Prevalence of SNHL by conventional audiometry and subclinical hearing impairment by HFA or DPOAE were ascertained and risks were analysed.

Results: Ninety-eight patients were eligible for the study. The median age (IQR) was 5.3 (1.5-9.6) years. Fifteen patients (15.3%) had univentricular hearts. The pre-operative audiologic test was performed one day prior to the CCS. The post-operative test was performed at a median of 4.4 (IQR: 2.7-8.0) months post-operatively. Pre-operative unilateral hearing impairments were reported in 17 patients (17.3%). Post-operatively, 4 patients (4.1%) showed significantly abnormal audiogram (> 25 dB) or 15 dB shift at 250-8000 Hz consistent to a new SNHL. Subclinical hearing impairment by HFA were affected in 10 patients (10.2%). Thirty-three

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patients (33.6%) had abnormal DPOAE exclusively. Therefore, new SNHL, including subclinical hearing loss revealed a prevalence of ototoxicity up to 47.9%. Age < 1 year at surgery was the independent risk of post-operative SNHL (adjusted odds ratio 18.5, 95% CI 1.2-293.8, p=0.04).

Conclusion: Routine post-CCS audiological surveillance especially CCS in infancy is recommended for early recognition and timely management based on the 43.8% subclinical and the 4.1% SNHL that was found in this study.

Trial registration: TCTR20200421001

Keywords: pediatric, cardiac surgery, hearing loss, sensorineural hearing loss (SNHL)

Abbreviations: ASSR (auditory steady-state responses), CCS (congenital cardiac surgery), CHD (congenital heart disease), CPB (cardiopulmonary bypass), DPOAE (distortion-product otoacoustic emissions), ECMO (extracorporeal membrane oxygenation), HFA (extended high-frequency audiometry), OR (odds ratio), PHL (permanent hearing loss), SNHL (sensorineural hearing loss), STAT (The Society of Thoracic Surgeons Congenital Heart Surgery)

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Key messages

- **What is already known on this topic**

The incidence of sensorineural hearing loss (SNHL) increased in adults following bypass surgery. Data of SNHL in children following congenital cardiac surgery (CCS) is limited. Based on a few of studies, the incidence of hearing loss was 65.6 per 1000 operations. However, no pre-operative audiologic assessments were conducted, and co-occurring SNHL and CHD prior to CCS could have been confounded in the data.

- **What this study adds**

A prevalence of post-operative SNHL of 4.1% by using conventional audiometry and subclinical SNHL detected by HFA and DPOAE of 43.8%. High-frequency hearing impairment is mostly affected. The age < 1 year at surgery was the significant risk of post-operative SNHL (adjusted odds ratio 18.5, 95% CI 1.2-293.8, p=0.04).

- **How this study might affect research, practice or policy**

The findings from the study suggest that children undergoing CCS may be at risk for SNHL, potentially increasing risk of neurodevelopmental difficulties. Post-CCS audiological surveillance is recommended for early recognition and timely management particularly in infants under 1 year old.

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Introduction

Congenital heart disease (CHD) is a common birth defect worldwide affecting millions of live births per year.[1] Dramatic improvements in surgical correction and medical treatment have led to an increase in the survival of children with CHD into adulthood, though a considerable percentage of the survivors continue to have a neurodevelopmental disability. Hearing loss is one of potential problems that can limit CHD patients from developing speech capabilities and social skills.[2] The sensorineural hearing loss (SNHL) in CHD has been recognized, with a plausible mechanism for their co-occurrence involving developmental dysregulation of the inner ear and heart and genetic etiologies.[3] There were some risk indicators for pediatric hearing loss possibly associated with the CHD care and surgery, such as the prolonged intensive care, use of an extracorporeal membrane oxygenator, using assisted ventilation, exposure to ototoxic medications (aminoglycosides) or loop diuretics (furosemide).[4] Furosemide, which are commonly used to treat CHD patients after cardiac surgery, may induce pathological ischemic damage or edema to the stria vascularis and cochlear lateral wall that occurs with the hearing impairment.[5] The ototoxic effects of high dosage intravenous furosemide and kidney injury have been reported from prior studies.[6 7]

The greater incidence of SNHL in adult patients after coronary bypass surgery, compared to the incidence in the normal population has been reported. Possible attributing factors include: thromboembolic phenomena; perfusion failure; hypothermia; ototoxic drug use; and central nervous system injury. Nevertheless, no proven etiologies have been established.[8 9] Data for pediatric patients following congenital cardiac surgery (CCS) and SNHL are limited and unique.[10] Robertson reported the prevalence of permanent hearing loss

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(PHL) after Norwood right ventricular-pulmonary artery shunt for hypoplastic left heart syndrome (HLHS) to be 28.6% at the 4-year-old audiologic examination.[11] Grasty et al. reported that 6.9% of the 4-year-old survivors of CCS in infancy had SNHL, and 2.3% had indeterminate hearing loss [12], which is in accordance with Bork and colleagues reported prevalence of PHL (5.9%) after complex cardiac surgery at less than 6 weeks of age at the 4-year-old audiologic examination.[13] Gopineti et al. estimated the prevalence of hearing loss to be 11.6% for 172 palliated/repaired CHD patients.[14] The incidence of hearing loss across these studies was 97 out of 1,342 (65.6 per 1000 operations).[10] However, no pre-operative audiologic assessments were conducted for the pediatric patients in these studies, and co-occurring SNHL and CHD prior to CCS could have been confounded in the data.

Therefore, we conducted this prospective study to: 1) investigate the changes between pre- and post-operative hearing thresholds, measured by conventional audiometry with extended high frequency audiometry (HFA) or auditory steady-state response (ASSR) in uncooperative children and distortion-product otoacoustic emissions (DPOAE), in pediatric patients undergoing CCS to ascertain the prevalence of SNHL in this population, and 2) identify the risk factors for SNHL. Importantly, the audiology screening was scheduled pre- and post- operation to ascertain whether the patients had abnormal hearing or not prior CCS. We hypothesized that pediatric patients who underwent CCS may have a reduced hearing threshold, compared to their pre-operation threshold, especially in patients who received high dosage of furosemide, moderate hypothermic cardiopulmonary bypass, or underwent a high complexity operation or had single ventricle repair.

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Materials and Methods

Study population and study design

This prospective observational study was approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University [Study number 075/2562(EC2), COA: Si 382/2019]. The study period was June 2019 to June 2023, when 1,357 pediatric patients (age < 18 years) underwent CCS in Siriraj Hospital, Thailand. A total of 137 children were enrolled in the study and had pre-operative hearing assessments. Informed consents were obtained from the parents or legal guardians. The exclusion criteria were: 1) preterm at the time of surgery, 2) underlying chronic renal insufficiency, 3) inability to complete the audiologic examination, 4) presence of bilateral conductive hearing loss such as otitis media with effusion (OME), or 5) presence of bilateral SNHL. Finally, 98 children were eligible for the analysis (Figure 1).

Figure 1. Flow diagram of the study (n=98). (CCS=congenital cardiac surgery; SNHL= sensorineural hearing loss; OME=otitis media with effusion; HFA=extended high frequency audiometry; DPOAE=distortion product otoacoustic emission)

Demographic data, including age, gender, weight, height, CHD diagnosis, presence of syndromic disorders, previous cardiac surgery, pre-operative furosemide usage, pre-operative unilateral abnormal hearing on HFA/ASSR; intraoperative data including type of operation, single ventricular repair, and complexity of the surgical procedure using Aristotle Basic Complexity (ABC) score, The Society of Thoracic Surgeons-European Association for Cardio-

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Thoracic Surgery (STAT) mortality score, operative time, cardiopulmonary bypass (CPB) time, aortic cross clamp (AoX) time, minimal temperature during CPB, extracorporeal membrane oxygenator (ECMO) usage was collected. The post-operative parameters included duration of ventilator usage, maximal vasoactive inotropic score, cumulative furosemide usage in 72 hours (mg), maximal furosemide dosage (mg/kg/day), route of maximal dose furosemide, duration of intravenous furosemide, maximal creatinine level (mg/dL) and hospital length of stay (LOS) were explored.

Audiological assessment and outcome measure

The 1st and 2nd audiologic examinations were scheduled pre- and post-operatively, respectively. The pre-operative test was performed one day prior to the CCS. The post-operative test was performed at a median of 4.4 (IQR: 2.7-8.0) months post-operatively, according to the COVID-19 pandemic. Each audiologic assessment was performed in the Otorhinolaryngology department using age appropriate and standard techniques. For hearing thresholds, young children and developmentally delayed children were tested by ASSRs, while cooperative older children underwent behavioral audiological assessment using pure tone audiometry. Beyond the conventional audiometry (0.25-8 kHz), we tested in the HFA (9-20 kHz) or extra-high frequency audiometry (EFA) to cover HF-SNHL, which we postulated to occur post-CCS. The SNHL from conventional audiometry in the study was defined according to the 1991 World Health Organization's (WHO's) grading of hearing impairment and current Common Terminology Criteria for Adverse Events (CTCAE) [2,15-17]. Hearing loss at any particular frequency (0.25-8 kHz) was defined as a dropped response of more than a 25-decibel hearing level (dB HL) in either ear. The degree of hearing loss was classified as mild (grade 1),

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26-40; moderate (grade 2), 41-60; severe (grade 3), 61-80; profound/deafness (grade 4), ≥ 81 dB HL. In addition, a change of 15 dB or more, in either ear, at any test frequency from 500 through 6000 Hz determined by pre- and post-operative audiometry was also defined as SNHL according to National Institute of Occupational Safety and Health recommended definition of a standard threshold shift in SNHL[18 19]. Another audiologic examination was the DPOAE. Two primary frequencies, f1 and f2, were presented simultaneously with f2/f1 equaling 1.22. Twelve points per octave were measured and plotted as a function of f2 ranging about 1.5 to 10 kHz. DPOAE was interpreted to be present if: Signal-to-noise ratio (SNR) of DPgrams ≥ 6 dB at each frequency. In addition, it was normal if the absolute DP amplitude is in the range of the normative values or above 95th percentile of hearing impaired that based on the Boys Town 65-55 reference set[20]. The deficit of hearing in each frequency is considered if the SNR is less than 6 dB (absent DP response) or the absolute DP amplitude of each frequency is out of the range of the normative values. All participants were tested with hearing assessment tests as described. Subclinical ototoxicity included abnormal hearing response (> 25 dB) or threshold shift of 15 dB or more in HFA (> 8 kHz) or/and abnormal/absent DPOAE. The primary outcome was the presence of a new SNHL, based on conventional audiometry. The secondary outcome was abnormal hearing threshold on HFA, or abnormal/absent DPOAE which is called subclinical ototoxicity

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Statistical methods

Statistical analyses were performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Sample size was calculated based on prior literature in 2018 and 2023.[10 12 13] Based on the prevalence of SNHL following early CCS (5.9-6.9%), we used a margin of error of 5% (d = 0.05) with a 95% confidence interval (type I error = 0.05, two-sided). As a result, the calculated sample size needed was between 85 and 98 participants. Demographics, pre-operative, perioperative, and post-operative data were presented as frequencies with percentages for the categorical variables and mean ± SD or median with interquartile range for the continuous variables. Comparisons of the hearing thresholds in the pre- and post-operative HFA and DPOAE were analyzed and the prevalence of progressive SNHL and ototoxicity following CCS were calculated. The data for patients with progressive SNHL following CCS detected by the conventional audiometry and patients without progressive SNHL were analyzed and compared using chi-square or the Fisher exact test. Factors associated with SNHL following CCS were analyzed using univariate analysis and logistic regression. The factors which represented p-value < 0.25 in univariate analysis were chosen for binary logistic regression. A p-value < 0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 98 pediatric patients who had CHD and underwent CCS in the medical center were eligible for the analysis (Figure 1). The median age was 5.29 years, and 55 (56%) of the included patients were boys. Pre- and post-operative hearing assessments were performed a day prior to surgery, and 4.4 (IQR 2.7-8.0) months post operatively, respectively. Demographic

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characteristics including clinical features, and pre- and post-operative data are shown in Table 1. Nine patients (9.2%) had syndromic disorders (4 trisomy 21, 1 velocardiofacial syndrome, 1 Marfan syndrome, 1 Scimitar syndrome, 1 multiple anomalies, 1 fetal alcohol syndrome). Pre-operative unilateral hearing impairments were reported in 17 patients (17.3%); 9 unilateral SNHL on conventional audiometry, 5 unilateral abnormal hearing thresholds on HFA, and 3 unilateral conductive hearing loss. These 17 patients were noted to have unilateral HL and the outcomes were measured from the contralateral ear. The types of lesions are illustrated in Figure 2. Most surgical procedures for the patients in the study were in STAT categories 1-3 (88.2%) since most of the procedures were elective and the patients were eligible for the pre-operative hearing test (Figure 3). Most of the patients (82.7%) used mild hypothermia during CPB. No patients in the study required post-operative ECMO or renal replacement therapy (Table 1).

Table 1. Baseline characteristics (n=98)

Figure 2. Types of congenital heart disease (n=98)

(ASD=atrial septal defect; TOF=tetralogy of Fallot; VSD=ventricular septal defect)

Figure 3. Number of patients in STAT categories 1-5 (n=98) (STAT=The Society of Thoracic Surgeons Congenital Heart Surgery)

In comparison to their pre-operative hearing assessments, 58 patients underwent conventional audiometry plus HFA with DPOAE and 40 patients underwent ASSR with DPOAE. Notably, 4 patients (4.1%) showed significantly new abnormal hearing threshold (>

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25 dB) or 15 dB shift or more, defined as SNHL on conventional audiometry; 3 ASSR and 1 audiometry (250-8000 Hz). Abnormal DPOAE responses were also noted in all patients. These 4 patients were classified as SNHL grade 1 WHO classification for hearing loss. Using extended HFA range > 8000 Hz, 10 patients (10.2%) were detected newly abnormal hearing response (> 25 dB) or 15 dB shift. Of 10 patients, 4 patients were additionally shown abnormal DPOAE. There were 33 patients (33.7%) had post-operative DPOAE abnormalities exclusively (Figure 4). Overall, the prevalence of SNHL after CCS in this study was 4.1%. Subclinical hearing impairment which was detected early by extended HFA and DPOAE was 10.2% and 33.6%, respectively, raises the prevalence of subclinical ototoxicity to 43.8%. During the median time of follow-up (20 months), 18 patients with subclinical ototoxicity continued their follow-up at the otology clinic. Among them, two patients exhibited delayed speech, and one patient had an articulation disorder. Notably, one patient with multiple anomalies, including microcephaly, which may lead to global developmental delay, was identified among these cases. No patients in the study required hearing aids or cochlear implants.

Risks of SNHL following CCS

The risk analysis of SNHL following pediatric CCS is illustrated in Table 2. The univariate analysis revealed a significant association between age at surgery younger than 1 year (odds ratio 15.8, 95% CI 1.53-162.31, p=0.02) and post-operative SNHL. In the binary logistic regression model, age at surgery younger than 1 year remained independently associated with post-operative SNHL (adjusted odds ratio 18.5, 95% CI 1.2-293.8, p=0.04).

Table 2. Risk factors for SNHL following CCS (n=98)

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Discussion

Herein, we reported a prevalence of postoperative SNHL of 4.1% by using conventional audiometry and subclinical SNHL detected by HFA and DPOAE of 43.8%. High-frequency hearing impairment is mostly affected. The age at surgery younger than 1 year was independently associated with post-operative SNHL (adjusted odds ratio 18.5, 95% CI 1.2-293.8, p=0.04). To our knowledge, this is the first study assessed prevalence of SNHL following CCS in children with pre- and post-operative hearing test using conventional audiometry in addition to HFA and DPOAE to cover subclinical hearing abnormality. An update systematic review[10] also indicated that the incidence of pediatric hearing loss was 65.6 per 1000 operations which was consistent to our finding. Gopineti et al.[14] reported that a prevalence of SNHL in children post repaired or palliated CCS was 11.6% which was higher than our study. It was possibly owing to the pre-operative hearing test screening which reduced the confounded cases in our study protocol. Overall, the prevalence of post-operative SNHL is substantially greater than that in the general pediatric population, which has been reported to be 0.2% at birth and 0.35% in adolescence.[21]

Subsequent SNHL following cardiac surgery is related to several possible mechanisms. A few pediatric studies have summarized the risks of SNHL following CCS. El Ganzoury et al.[22], for example, found an association between subtle cochlear dysfunction and moderate hypothermic CPB in pediatric patients having CCS (n=40). In a Quebec, 1-5 year surveillance study of 85 children, post-CCS in infancy, low birth weight and Apgar score at 5 min and older age at surgery was found to be associated with SNHL.[23] In Gopineti et al.'s study14, independent risks were not found from the multivariable analysis. Our findings with

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the logistic regression analysis showed that age at surgery younger than 1 year (adjusted odds ratio 18.5, 95% CI 1.2-293.8, p=0.04) was a significant risk for post-operative SNHL. The plausible explanation may relate with cochlear hypoperfusion after CCS especially in infancy. No associations were found for single ventricle repair, syndromic disorders, moderate hypothermic CBP, furosemide > 4 mg/kg/day or route of administration or duration of intravenous bolus, use of vancomycin, high vasoactive inotropic score, or duration of mechanical ventilation.

While the progression of subclinical ototoxicity and new-onset sensorineural hearing loss (SNHL) after CCS and their impact on neurodevelopmental outcomes are intriguing, they lie beyond the scope of our current research protocol. Initially, our protocol did not include long-term outcome data collection for participants. However, we established follow-up schedules for participants diagnosed with SNHL or subclinical ototoxicity. Over a median follow-up period of 20 months, 18 patients with subclinical ototoxicity continued their follow-up at the otology clinic. Among these cases, two patients exhibited delayed speech, and one had an articulation disorder. Notably, one patient with multiple anomalies, including microcephaly, was identified. This case may involve confounding factors related to developmental delay. Unfortunately, none of the participants diagnosed with SNHL attended their scheduled otology appointments. Future research with more comprehensive data aggregation is necessary to assess the progression and impact of SNHL and subclinical ototoxicity in children following CCS.

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Study Limitations

Our prospective study has some limitations since it was conducted during the COVID-19 pandemic. As noted previously, not all survivors following CCS in the medical center between 2019 and 2023 could be enrolled in the study. Nevertheless, the 98 eligible participants was a sufficiently large group for the analysis based on the prevalence of SNHL in a previous study in 2018 and a systematic review in 2023 that was mentioned in the Methods section.[10 12 13] The eligible participants were selected from all consecutive CCS patients who were clinically stable enough for pre-operative hearing assessments. Nonetheless, single ventricle repair and high complexity cases were included in 10-15% of all patients. Regarding hearing method, the ASSR assesses a hearing threshold with maximal frequency of 4000 Hz, not equal to conventional audiometry which is up to 8000 Hz, not extends to 20,000 Hz as HFA. This may indeterminate subclinical ototoxicity in some patients. The variable time interval for post-operative hearing assessments due to COVID-19 pandemic was noted (median 4.4 months, IQR 2.7-8.0 months). This variability allows for the healing process to potentially ameliorate hearing loss or for additional hearing loss from ongoing hemodynamically significant cardiac lesions and cyanosis. Nevertheless, comparing the median time intervals among three groups; post-operative SNHL (n=4), post-operative subclinical hearing loss (n=43), and no post-operative hearing loss (n=51), revealed no statistically significant differences. Lastly, the small sample size of children with SNHL limited the validity of the logistic regression. However, the risk analysis offers a framework for understanding potential associations between risk factors and outcomes, highlighting

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trends for future studies in this often data-limited field. Thus, Table 2 should be interpreted with caution.

Conclusion

In this study, the prevalence of new SNHL in the children following CCS is 4.1%. An abnormal hearing threshold from the baseline (based on DPOAE and HFA) is reported for up to 43.8%. High-frequency hearing impairment is mostly affected. Surgery at an age younger than 1 year is associated with a higher incidence of post-operative SNHL. These findings suggest that children undergoing CCS may be at risk for SNHL, potentially increasing risk of neurodevelopmental difficulties. Post-CCS audiological surveillance is recommended for early recognition and timely management particularly in infants under 1 year old.

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Conceptualisation/design and methodology: CV, YT, KT. Data collection and acquisition: CV, KT, KS, EK. Data analysis and interpretation: CV, KT, KS. Provide and care for study patients: CV, KT, PC, PWC, SK, PT, TP, KD, JS, SA, TT, EN, KKT, TS. Manuscript writing (1st draft): CV, KS. Manuscript preparation and final approval: all authors (KS, CV, KT, YK, PC, PWC, SK, PT, TP, EB, KD, JS, SA, TT, EN, KKT, TS). Study accountability: CV. Guarantor: CV

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Conflicts of interest

The authors declare no conflicts of interest.

Patient consent for publication

Not applicable

Ethics approval

This prospective observational study was approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University [Study number 075/2562(EC2), COA: Si 382/2019].

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data availability statement

Data is available upon request.

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Table 1. Baseline characteristics (n=98)

	Total (n=98)	**Post-operative SNHL (n=4)**	**Post-operative subclinical hearing loss (n=43)**	**No post-operative hearing loss (n=51)**	***p*-value among 3 groups**
Age at surgery (years)	5.3 (1.5-9.6)	0.8 (0.6-5.2)	6.9 (2.0-9.9)	4.8 (1.5-8.8)	0.415
Age < 1 year at surgery	18 (18.4%)	3 (75.0%)	4 (9.3%)	11 (21.5%)	0.004*
Male gender	55 (56.0%)	2 (50.0%)	26 (60.5%)	27 (52.9%)	0.593
Weight (kg)	19.9 ± 14.4	11.0 ± 9.8	22.1 ±15.3	18.7 ± 13.7	0.237
Height (cm)	106.7 ± 29.6	81.7 ± 35.7	112.7 ± 28.7	103.5 ± 29.0	0.073
Diagnosis					
Cyanotic heart disease	36 (36.7%)	0	18 (41.9%)	18 (35.3%)	0.240
Presence of syndromic disorder	9 (9.2%)	1 (25.0%)	4 (9.3%)	4 (7.8%)	0.519
Down syndrome	4 (44.4%)	1 (100%)	0 (0%)	3 (75%)	
DiGeorge syndrome	1 (11.1%)	0 (0%)	1 (25%)	0 (0%)	
Others	4 (44.4%)	0 (0%)	3 (75%)	1 (25%)	
History of pre-term	8 (8.2%)	1 (25.0%)	2 (4.7%)	5 (9.8%)	0.301
Previous cardiovascular surgery	24 (24.5%)	0 (0%)	14 (32.6%)	10 (19.6%)	0.177
Pre-operative usage of furosemide	37 (37.8%)	3 (75%)	18 (41.9%)	16 (31.4%)	0.169
Pre-operative unilateral abnormal hearing on HFA/ ASSR	17 (17.3%)	1 (25%)	8 (18.6%)	8 (15.7%)	0.857
Pre-operative unilateral SNHL	9 (9.2%)	1 (25%)	3 (7.0%)	5 (9.8%)	0.478
Operative factors					
Single ventricular repair	15 (15.3%)	0 (0%)	10 (23.3%)	5 (9.8%)	0.135
Procedure STAT mortality score	0.4 (0.2-0.6)	0.6 (0.3-0.7)	0.5 (0.2-0.6)	0.3 (0.2-0.6)	0.155
Procedure STAT category 4-5	11 (11.2%)	0 (0%)	5 (11.6%)	6 (11.8%)	0.768
Procedure Aristotle Basic Complexity score	7.0 ± 2.0	6.6 ± 0.8	7.1 ± 1.9	6.9 ± 2.1	0.841
CPB time (min)	100.0 ± 63.5	55.5 ±53.7	100.1 ± 61.8	103.5 ± 65.3	0.350
Aortic cross clamp time (min)	56.4 ± 51.3	45.2 ± 39.8	47.1 ± 46.7	65.1 ± 54.9	0.217
Operative time (min)	170.5 ± 77.1	123.7 ± 58.5	171.8 ± 83.6	173.0 ± 72.5	0.468
Minimal temperature in CPB (°C)	31.4 ± 2.8	32.2 ± 3.7	31.3 ± 2.9	31.4 ± 2.7	0.804
Moderate hypothermic CPB	17 (17.3%)	1 (25.0%)	7 (16.3%)	9 (17.6%)	0.710
Post-operative factors					
Post-operative vancomycin	4 (4.1%)	0 (0%)	1 (2.3%)	3 (5.9%)	0.628

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Post-operative maximal vasoactive inotropic score	7.8 (23.5)	17.0 ± 18.8	15.9 ± 21.9	18.3 ±24.1	0.874
Post-operative usage of dopamine > 4 mcg/kg/min	25 (25.5%)	4 (100%)	7 (16.3%)	14 (27.5%)	0.001*
Post-operative cumulative furosemide in 72 h (mg)	67.4 ± 36.2	42.9 ± 18.7	75.2 ± 42.8	62.7 ± 29.2	0.093
Post-operative maximal furosemide dosage (mg/kg/day)	3.4 ± 2.5	3.1 ± 1.6	2.9 ± 1.7	3.8 ±3.1	0.270
Post-operative maximal furosemide dosage > 4 mg/kg/day	27 (27.6%)	1 (25.0%)	10 (23.3%)	16 (32.0%)	0.639
Route of maximal dose furosemide					0.847
- IV drip	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
- IV bolus	44 (44.9%)	3 (75%)	19 (44.2%)	22 (44%)	
- Oral and IV bolus	28 (28.6%)	1 (25%)	12 (27.9%)	15 (30%)	
- Oral	19 (19.4)	0 (0%)	10 (23.3%)	8 (18%)	
- IV bolus and IV drip	6 (6.1)	0 (0%)	2 (4.7%)	4 (8%)	
Duration of intravenous furosemide (days)	3.9 ± 2.1	3.2 ± 0.9	3.7 ± 2.3	4.1 ± 2.0	0.641
Post-operative maximal creatinine level (mg/dL)	0.4 ± 0.1	0.3 ± 0.1	0.5 ± 0.2	0.4 ± 0.1	0.082
Oxygen saturation before discharge home (%)	96.8 ± 4.6	98.2 ± 1.3	95.9 ± 5.4	97.4 ± 3.8	0.219
Hospital length of stay (days)	8.0 ± 4.9	9.5 ± 7.7	7.5 ± 3.7	8.4 ± 5.5	0.577
Time interval from surgery to 2nd audiologic examination (months)	4.4 (2.7-8.0)	4.3 (3.1-6.9)	3.6 (1.8-6.6)	5.3 (2.9-9.0)	0.176

Data presented as n (%), mean ± SD, and median (interquartile range p25-p75)

* Statistically significant at p-value among three groups < 0.05

SNHL=sensorineural hearing loss; HFA=extended high frequency audiogram; ASSR=auditory steady-state responses; STAT= The Society of Thoracic Surgeons Congenital Heart Surgery; CPB=cardiopulmonary bypass; ECMO=extracorporeal membrane oxygenator

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Table 2. Risk factors for SNHL following CCS (n=98)

Variables	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Male gender	0.7 (0.1, 5.7)	0.801		
Age <1 year at surgery	15.8 (1.5, 162.3)	0.019*	18.5 (1.2, 293.8)	0.038*
Presence of genetic syndromes	3.6 (0.3, 38.6)	0.263		
Single ventricle	0.9 (0.9, 1.0)	0.385		
Cyanotic heart disease	0.9 (0.9, 1.0)	0.293		
Previous cardiovascular surgery	0.9 (0.9, 1.0)	0.569		
Pre-operative furosemide	5.3 (0.5, 52.9)	0.149	1.5 (0.1, 24.1)	0.754
Pre-operative unilateral SNHL	3.6 (0.3, 38.6)	0.263		
Procedure STAT mortality score > 0.6	1.4 (0.2, 10.4)	0.735		
Procedure STAT category 4-5	0.9 (0.9, 1.0)	0.468		
CPB time > 90 min	0.4 (0, 3.6)	0.620		
Moderate hypothermic CPB	1.6 (0.1, 16.6)	0.539		
Post-operative maximal vasoactive inotropic score > 20	0.8 (0.1, 8.3)	0.872		
Post-operative usage of dopamine > 4 mcg/kg/min	307709498.0 (0, -)	0.997		
Post-operative vancomycin usage	0.9 (0.9, 1.0)	0.674		
Post-operative cumulative furosemide in 72 h > 85 mg	0.9 (0.9, 1.0)	0.220	0 (0, -)	0.998
Post-operative maximal furosemide dosage > 4 mg/kg/day	0.8 (0.1, 8.6)	0.897		
Route-intravenous bolus of maximal furosemide	3.9 (0.4, 38.7)	0.217	8.9 (0.7, 118.8)	0.096
Post-operative maximal creatinine level > 0.45 (mg/dL)	0.5 (0, 4.7)	0.643		

Adjusted Odds ratio by binary logistic regression
* Statistically significant at p-value < 0.05
OR=Odds ratio; SNHL=sensorineural hearing loss; STAT= The Society of Thoracic Surgeons Congenital Heart Surgery; CPB=cardiopulmonary bypass

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Figure 1. Flow diagram of the study (n=98)

(CCS=congenital cardiac surgery; SNHL= sensorineural hearing loss; OME=otitis media with effusion; HFA=extended high frequency audiometry; DPOAE=distortion product otoacoustic emission)

Figure 2. Types of congenital heart disease (n=98)

(ASD=atrial septal defect; TOF=tetralogy of Fallot; VSD=ventricular septal defect)

Figure 3. Number of patients in STAT categories 1-5 (n=98)

(STAT=The Society of Thoracic Surgeons Congenital Heart Surgery)

Figure 4. Hearing impairment (n=4) detected by ASSR or conventional audiometry (*) plus DPOAE and subclinical ototoxicity (n=43) detected by DPOAE + HFA or HFA or DPOAE

(ASSR=auditory steady-state responses; DPOAE=distortion-product otoacoustic emissions; Audiogram 250-8=conventional audiometry; HFA=extended high frequency audiometry)

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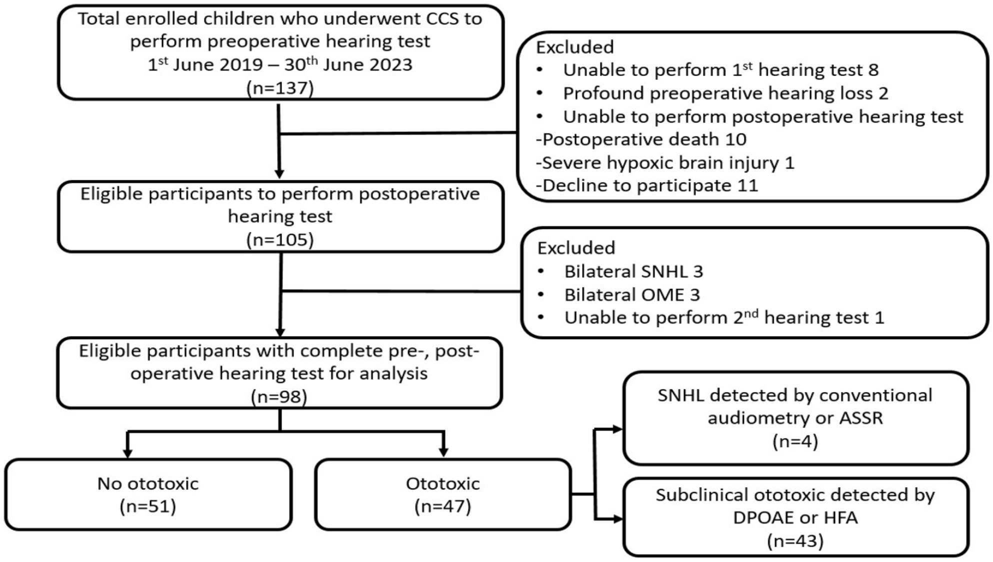

Figure 1. Flow diagram of the study (n=98)

34x19mm (1000 x 1000 DPI)

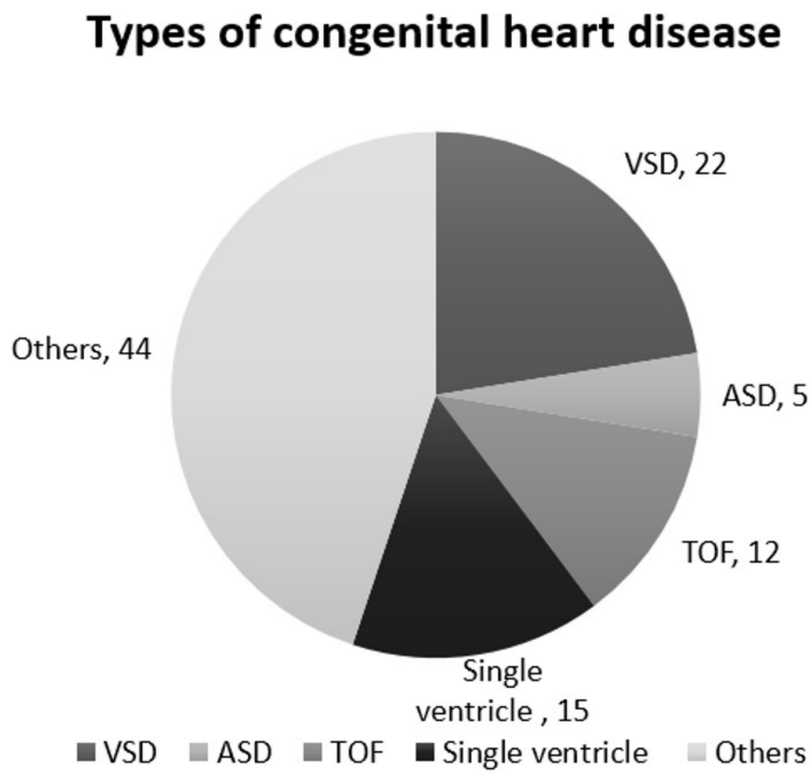

Figure 2. Types of congenital heart disease (n=98)

22x19mm (1000 x 1000 DPI)

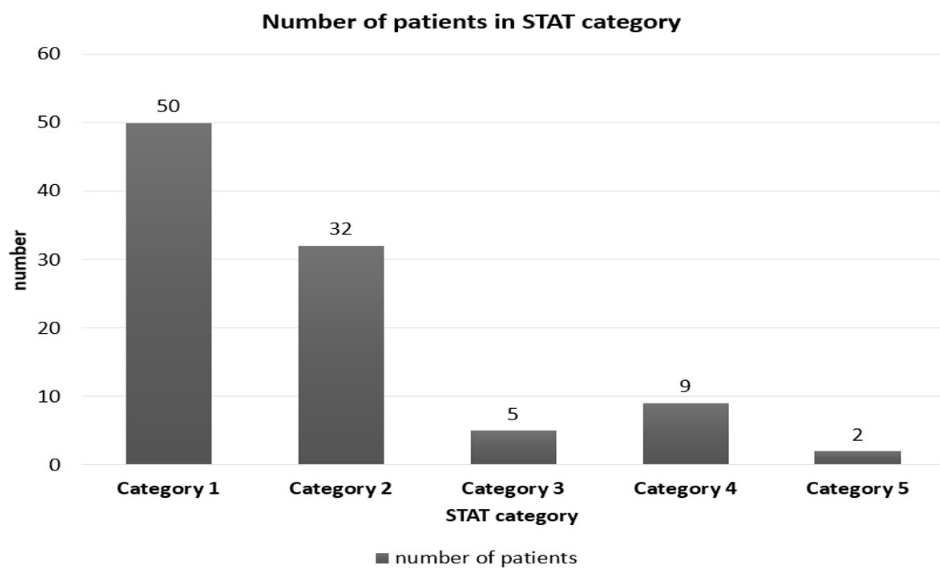

Figure 3. Number of patients in STAT categories 1-5 (n=98)

31x19mm (1000 x 1000 DPI)

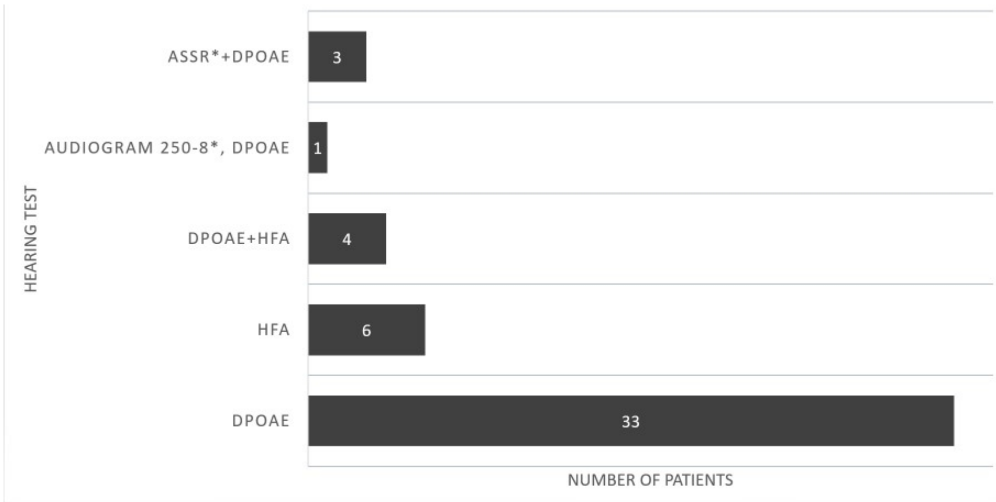

Figure 4. Hearing impairment (n=4) detected by ASSR or conventional audiometry (*) plus DPOAE and subclinical ototoxicity (n=43) detected by DPOAE + HFA or HFA or DPOAE

23x11mm (1000 x 1000 DPI)