PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Hearing impairment following surgically repaired congenital heart disease in children: a prospective study
AUTHORS	Vijarnsorn, Chodchanok; Sakjirapapong, Kanittha; Thongyai, Kanthong; Thirakulnanchai, Yarlanphol; Chanthong, Prakul; Chungsomprasong, Paweena; Kanjanauthai, Supaluck; Thammasate, Ploy; Pacharapakornpong, Thita; Boonchom, Eakkarat; Durongpisitkul, Kritvikrom; Soongswang, Jarupim; Atipas, Suvajana; Tocharoenchok, Teerapong; Nitiyarom, Ekarat; Tantiwongkosri, Kriangkrai; Subtaweesin, Thaworn

VERSION 1 - REVIEW

REVIEWER NAME	***Lalitha Gopineti***
REVIEWER AFFILIATION	Baylor Scott and White Central Texas
REVIEWER CONFLICT OF INTEREST	
DATE REVIEW RETURNED	06-Aug-2024

GENERAL COMMENTS	Well conducted study with preop hearing test unlike other previous studies.

REVIEWER NAME	***Katie Harron***
REVIEWER AFFILIATION	UCL Great Ormond Street Institute of Child Health
REVIEWER CONFLICT OF INTEREST	
DATE REVIEW RETURNED	19-Aug-2024

GENERAL COMMENTS	The abstract states “The post-operative test was performed 1-44 months post-operatively.” This needs to be modified to make clear that this is a mean or a median. Similarly in the main text, you add that this is according to the pandemic. It is not clear what you mean here – this needs further explanation. If this is a median, the IQR should be stated. Furthermore, I am confused about how the 1.44 months aligns with the results which state “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.” It is not appropriate to conduct logistic regression with such a small number of children with the outcome of SNLH, particularly when you are trying to adjust for other factors. For example, there is no point in calculating an odds ratio to compare Post-operative usage of dopamine > 4 mcg/kg/min between groups, when 100% of the SNLH group have this risk factor. This regression analysis should be removed from the manuscript. The results and conclusions

	focussing on infants under the age of 1 should be modified accordingly, based on the descriptive analysis only. Table 2 should be removed. Alternatively, you could model the larger subclinical outcome group. It should be made clear that the exclusion of preterm babies applied to age at surgery rather than history of preterm. What does the margin of error in the sample size calculation correspond to? The sample size calculation is not clear – I'm not sure what the effect size is that you are basing this on. Use of decimal places in Table 1 should be consistent – sometimes you use 0 and sometimes you use 1 or 2 for %s. Table 1 – you need to state what comparison and test the p-value is from. Is this comparing 2 groups, i.e. SNHL with no post-operative hearing loss? Or post-operative subclinical hearing loss with no post-operative hearing loss? Or something else?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Lalitha Gopineti, Baylor Scott and White Central Texas

Comments to the Author

Well conducted study with preop hearing test unlike other previous studies.

Answer: Thank you so much for your time and consideration. I truly appreciate it. Your renowned publication is one of my references.

Reviewer: 2

Prof. Katie Harron, UCL Great Ormond Street Institute of Child Health

Comments to the Author

The abstract states "The post-operative test was performed 1-44 months post-operatively." This needs to be modified to make clear that this is a mean or a median. Similarly in the main text, you add that this is according to the pandemic. It is not clear what you mean here – this needs further explanation. If this is a median, the IQR should be stated. Furthermore, I am confused about how the 1-44 months aligns with the results which state "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."

Answer: The range of postoperative hearing tests conducted was between 1 and 44 months. The median was calculated at 4.37 months, with an interquartile range (IQR) of 2.66 months (25^{th} percentile) to 8.01 months (75^{th} percentile). All preoperative hearing tests were performed one day prior to surgery. To enhance clarity, the interval for postoperative tests in the abstract, methods ad discussion, has been revised to report the median and IQR, as you suggested.

It is not appropriate to conduct logistic regression with such a small number of children with the outcome of SNLH, particularly when you are trying to adjust for other factors. For example, there is no point in calculating an odds ratio to compare Post-operative usage of dopamine > 4 mcg/kg/min between groups, when 100% of the SNLH group have this risk factor. This regression analysis should be removed from the manuscript. The results and conclusions focussing on infants under the age of 1

should be modified accordingly, based on the descriptive analysis only. Table 2 should be removed. Alternatively, you could model the larger subclinical outcome group.

Answer: Thank you for your insightful comment regarding the logistic regression analysis. I agree with your concerns that the small sample size of children with the outcome of SNHL affected the validity of the results. The calculation of odds ratios in cases where 100% of the SNHL group has a particular risk factor is uninterpretable. However, I believe that retaining the logistic regression analysis is important for several reasons. Firstly, in spite of a small sample size, the logistic regression analysis provides a framework for understanding potential associations between risk factors and outcomes. It serves to highlight trends for future studies, particularly in a field where data is often limited. Secondly, report of descriptive analysis together with logistic regression allows for a more nuanced interpretation of the data and points out some association which physician should not overlook. Thirdly, in the light of your comment regarding using subclinical ototoxicity (n=43) instead of SNHL (n=4), it may not be applicable as well because impact of subclinical ototoxicity is still unknown, unlike SNHL which need interventional treatment. Finally, while maintaining the logistic regression analysis, the limitation of the logistic regression has been added in limitation section and warned that Table 2 should be read with appropriate caution.

It should be made clear that the exclusion of preterm babies applied to age at surgery rather than history of preterm.

Answer: To enhance understanding, the exclusion criterion for 1) preterm infants has been revised to specify "preterm at the time of surgery."

What does the margin of error in the sample size calculation correspond to? The sample size calculation is not clear – I'm not sure what the effect size is that you are basing this on.

Answer: The margin of error refers to the amount of potential error in the estimate of a population parameter. It represents the range within which the true value in the population is expected to lie, based on the sample data, with a given level of confidence. In our research, the margin of error of 5% was used as mentioned in statistical methods: "Using prevalence of SNHL following early CCS (5.9-6.9%), the margin of error was 5% with a 95% confidence interval (type I error = 0.05, 2-sided), and the sample size was calculated to be 85-98 participants". The explanation of sample size calculation is as follow:

To calculate the sample size for proportions, the general formula for sample size is:

$$n = \frac{Z^2_{\alpha/2} P(1-P)}{d^2}$$

- Based on Bork KT, To BP, Leonard NJ, et al. J Pediatr. 2018; 198: 104-9 reported that "of 691 survivors from cardiovascular surgery; 41 children had permanent hearing loss (5.9%)"
- Since in this study, the margin of error is 5% with the 95% confident interval (type I error = 0.05, 2-sided, the number of sample size can be calculated as follow
- $$n = \frac{Z^2_{\alpha/2} P(1-P)}{d^2}$$
- Where n = is the number of sample size
- P = Prevalence = 0.059
- α = type I error = 0.05, 2-sided (95% confident interval, Z = 1.96)
- d = margin of error = 0.05

therefore $n = (1.96)^2 \frac{(0.059)(1-0.059)}{(0.05)^2}$ = 85

- In the same way with Daniel J, Glynatsis JM, Kovoor JG, et al. ANZ journal of surgery 2023, the prevalence of SNHL following cardiac surgery was 6.6%.

- Grasty MA, Ittenbach RF, Knightly C, et al. The Journal of pediatrics 2018;192:144-51, reported that 6.9% of the 4-year-old survivors of CCS in infancy had SNHL

- the number of sample size can be calculated as follow

- $$n = \frac{Z^2_{\alpha/2} P(1-P)}{d^2}$$

- Where n = is the number of sample size

- P = Prevalence = 0.069

- α = type I error = 0.05, 2-sided (95% confident interval, Z = 1.96)

- d = margin of error = 0.05

therefore $n = (1.96)^2 \frac{(0.069)(1-0.069)}{(0.05)^2}$ = 98

In summary

- For 5.9% prevalence, a sample size of around 85 participants is needed. For 6.9% prevalence, a sample size of around 98 participants is needed.

- The sentences in statistical methods regarding sample size calculation has been revised to “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.”

Use of decimal places in Table 1 should be consistent – sometimes you use 0 and sometimes you use 1 or 2 for %s.

Answer: I apologize for the typo errors. All decimal places in table 1 have been revised to 1 as the sample population being 98.

Table 1 – you need to state what comparison and test the p-value is from. Is this comparing 2 groups, i.e. SNHL with no post-operative hearing loss? Or post-operative subclinical hearing loss with no post-operative hearing loss? Or something else?

Answer: The p-value in Table 1 represents a comparison among three groups: SNHL, subclinical ototoxicity, and no postoperative hearing loss. This explanation has been added to the appendix beneath the table.

VERSION 2 – REVIEW

REVIEWER NAME	***Katie Harron***
REVIEWER AFFILIATION	UCL Great Ormond Street Institute of Child Health
REVIEWER CONFLICT OF INTEREST	
DATE REVIEW RETURNED	25-Oct-2024

GENERAL COMMENTS	The authors have addressed my previous comments and I have nothing major to add. However I would reconsider the conclusion that this provides "a framework for understanding potential

	associations between risk factors and outcomes". I don't think this adds anything.