

NEUROLOGICAL COMPLICATIONS FOLLOWING PEDIATRIC CONGENITAL CARDIAC SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS

MADHU A YADAV^{1*}, REKHA A ASSADI², NEHA K KUDUMULA³

¹Department of Cardiac Anaesthesia, Sri Padmavathi Children's Heart Centre, Tirupathi, Andhra Pradesh, India. ²Balaji Clinic, Chennai, Tamil Nadu, India. ³Clinical Trials Unit, University Hospital Limerick, Ireland.

*Corresponding author: Dr. Madhu A Yadav; Email: assad.icewaves1228@gmail.com

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ABSTRACT

Objectives: The study was designed to ascertain the incidence of neurological complications in children following cardiac surgery for congenital heart defects (CHD).

Methods: An extensive search was conducted using Medical Subject Headings in the Cochrane Controlled Trials databases, PubMed, and Embase in July 2023. Data extraction was done using a customized data extraction sheet, adhering to Cochrane's standard methodological procedures. As the heterogeneity was high among the included studies, random-effect models were employed during the meta-analysis.

Results: Seventeen articles were included in our analysis, encompassing a total sample size of 23,930 pediatric patients who underwent congenital cardiac surgeries. The calculated incidence of neurological complications following these procedures was found to be 0.21 (95% confidence interval: 0.14–0.28). A random-effects model employing the DerSimonian-Laird estimator was utilized for the meta-analysis. The assessment of heterogeneity revealed Tau of 0.134, an I² value of 99.63%, and an H² value of 267.078, indicating heterogeneity (p<0.001).

Conclusion: The study highlights the substantial incidence of neurological complications following congenital cardiac surgery, with infants <1 year old being at a higher risk.

Keywords: Congenital heart defects, Surgery, Pediatric age, Neurological complications, Mortality.

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INTRODUCTION

Congenital heart defects (CHDs) encompass a diverse array of structural abnormalities affecting the heart and great vessels that are present at birth. Over time, advancements in diagnostic methods and medical interventions have significantly improved the prognosis for newborns with CHDs. Surgical interventions have become the gold standard for treating complicated cases, ranging from palliative measures to full repair. These transformative procedures have revolutionized pediatric cardiology and led to numerous lives being saved. However, concern has arisen among physicians and researchers due to the emergence of post-operative neurological problems [1]. The complexity of congenital cardiac surgery exposes patients to a wide range of risk factors, stemming from intricate anatomical linkages and physiological processes. This increases the likelihood of neurological consequences, such as hemodynamic instability, embolic events, cerebral hypoperfusion, and inflammatory reactions [2]. Thus, to enhance patient outcomes and refine surgical procedures, a comprehensive investigation of the incidence, types, and associated risk factors of these complications is imperative [3]. Recent studies have shown that neonates undergoing open-heart surgery displayed poorer motor functions compared to the general population, despite having normal cognitive function. This suggests that even children without apparent brain injury may experience neurodevelopmental abnormalities later in infancy [4,5]. The most common symptom observed was seizures. Although these post-operative seizures are often considered benign and attributed to post-perfusion syndrome, they have been linked to the subsequent development of severe cognitive sequelae [2]. However, previous research on the possibility of neurological problems after congenital heart surgery has yielded inconsistent findings and suffered from limited sample sizes. Therefore, drawing definitive conclusions from individual studies remain challenging. Similarly, the mortality associated with pediatric congenital cardiac surgery has been

a critical concern for both clinicians and researchers. Despite significant advancements in surgical techniques, perioperative care, and post-operative management, adverse outcomes, including mortality, continue to pose challenges in this field. While numerous studies have investigated the mortality rates following congenital cardiac surgery, the findings have shown considerable variability, and limited sample sizes have hindered the ability to draw definitive conclusions.

To address this issue, a meta-analysis serves as a robust method to amalgamate data from various studies, allowing for a more accurate and reliable evaluation of the prevalence and consequences of neurological problems. By combining data from multiple patient cohorts, a meta-analysis can discern patterns and trends that might be overlooked in smaller studies, offering a more comprehensive understanding of this critical subject.

The objective of this meta-analysis is to furnish a thorough synthesis of available data on neurological side effects following congenital heart surgery. The secondary objective is to determine the mortality rate in these cases. By identifying the incidence, types, and potential risk factors associated with these complications, we aim to facilitate informed decision-making, enhance patient care, and lay the groundwork for future research in this crucial domain. Ultimately, the findings of this research are anticipated to provide valuable inputs in the improvement of long-term neurodevelopmental outcomes and the overall quality of life in children undergoing surgeries for CHD.

METHODS

Literature search

The search strategy employed in this study involved the use of Medical Subject Headings terms, specifically "Heart Defects, Congenital,"

“Surgical Procedures, Operative,” and “Neurological complications,” to comprehensively explore relevant literature in the Cochrane Controlled Trials databases, PubMed, and Embase in July 2023. Data extraction was done using a customized data extraction sheet, adhering to Cochrane’s standard methodological, preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [6] were adhered to during the search process. There were no restrictions for the publication years, and this allowed maximum studies to be included thereby maximizing the scope of data collection for this meta-analysis. By meticulously implementing these search parameters, we sought to obtain a comprehensive and representative collection of studies pertaining to neurological problems following congenital heart surgery for a robust analysis and synthesis of relevant findings.

Selection of studies

To ensure the reliability and credibility of the literature selection process, a pre-screening, or pilot literature review, was meticulously conducted. This pre-screening was performed by two independent researchers, and discrepancies were settled by a third reviewer. Each study’s title and abstract were thoroughly examined to ascertain its relevance to the research objectives. From the identified papers, full text was obtained and scrutinized to extract the relevant outcome estimates reported in each study. By adopting this rigorous approach, we aimed to maintain a high standard of methodological integrity and accuracy throughout the data collection process, thus establishing a solid foundation for the subsequent analysis and synthesis of findings.

Data extraction

Data collection was performed by two independent researchers to ensure the rigor and accuracy of information retrieval. In addition to data on neurological problems following congenital cardiac surgery, we also extracted pertinent details such as the publication year, first author, country of origin, sample size; mean age at the time of surgery employed in each study.

Assessment of risk of bias

We employed “The Cochrane Collaboration’s tool for assessing risk of bias.” Utilizing “risk of bias” tables, we systematically evaluated potential sources of bias in each study, including concerns related to participant selection, incomplete data, selective reporting of outcomes [7]. By employing this standardized approach, we aimed to comprehensively evaluate the methodological quality and potential biases of each included study, thus ensuring the reliability and validity of the synthesized findings in our meta-analysis.

Statistical analysis

For the present investigation, data analyses were conducted by Review Manager Version 5.4 and Jamovi Version 2.4.2. A $p < 0.05$ was considered statistically significant. To assess the heterogeneity among the studies’ effect estimates, we employed I^2 statistics. As the heterogeneity was high among the included studies, random-effect models were employed during the meta-analysis.

Subgroup analysis was conducted separately for infants and children older than 1 year of age. Funnel plots were utilized to investigate the possibility of bias in publication. In addition, we meticulously assessed the bias risk in each study, adhering to the Cochrane Collaboration’s guidelines [8]. By applying these rigorous analytical and assessment methodologies, we sought to uphold the scientific integrity and robustness of our meta-analysis, ensuring reliable and meaningful conclusions from the findings.

RESULTS

Study and patient characteristics

We began by identifying 648 studies. Following an assessment of the titles and abstracts, 36 papers were chosen for further consideration. Following that, 19 studies were eliminated, including 9 cases with unreported data, 7 cases failed to meet the laid down inclusion criteria,

and 1 case in a language other than English. Finally, we considered seventeen studies [4,9-24]. A thorough search of the references of the included studies yielded no new articles. The process of study selection is illustrated in the PRISMA study selection diagram (Fig. 1).

Salient features of the included studies

Our investigation comprised a total of seventeen articles (Table 1). The publishing year spanned from 1995 to 2023, a pretty long period of time. Six of the 17 investigations were prospective, while the other eleven were retrospective. The research featured spanned a large geographical range ranging from North America to Asia, including Africa. The average age of children at the time of operation was present in 16 studies out of 17 studies taken for meta-analysis.

Primary outcome-neurological complications

The total sample size in all the 17 included studies was 23930. The incidence (95% confidence interval [CI]) of neurological complications following pediatric congenital cardiac surgeries was found to be 0.21 (0.14–0.28). Random-effects model using DerSimonian-Liard estimator was used. The heterogeneity tests showed Tau 0.134, I^2 at 99.63%, and H^2 at 267.078 with a significant $p < 0.001$ as illustrated in the forest plot in Fig. 2.

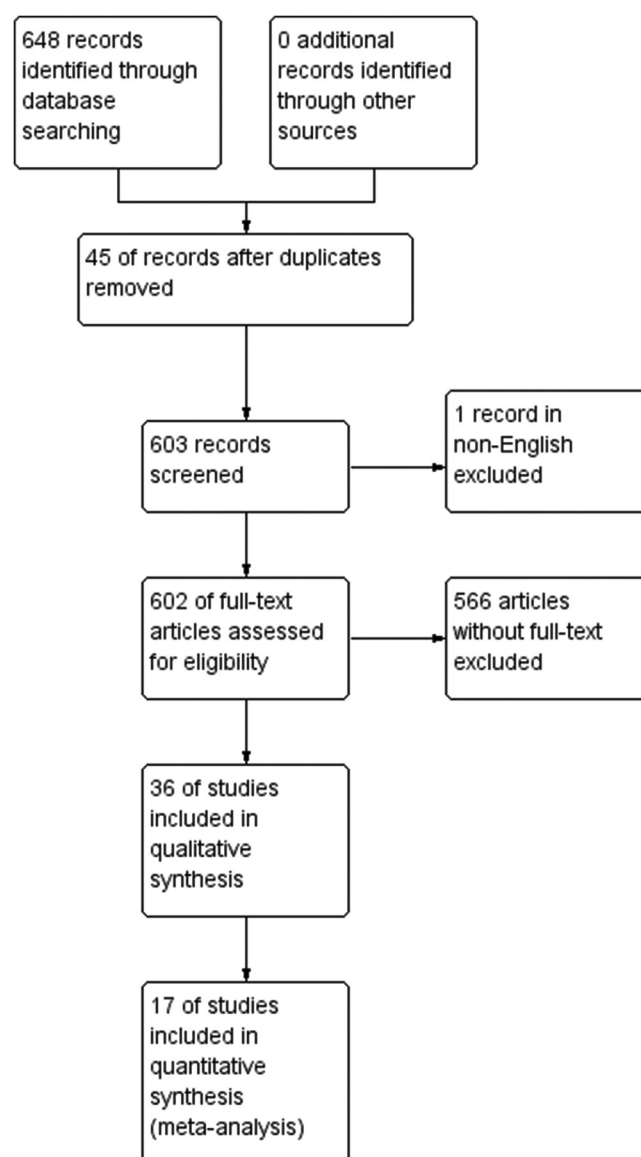


Fig. 1: Preferred reporting items for systematic reviews and meta-analysis study selection diagram

Table 1: Salient features of the included studies

Author, year	City, Country	Design of the study	Sample size	Mean age at operation	Mortality	Incidence of neurological complications
Fallon <i>et al.</i> , 1995 [9]	London, UK	Retrospective	523	35 months	7.1	5.93
Limperopoulos <i>et al.</i> , 2002 [10]	Calgary, Canada	Prospective	131	19 months	NA	41
Trittenwein <i>et al.</i> , 2003 [11]	Vienna, Austria	Retrospective	534	16 months	NA	6.26
Galli <i>et al.</i> , 2004 [12]	Philadelphia, USA	Prospective	105	6 days	NA	54
Majnemer <i>et al.</i> , 2004 [13]	Toronto, Canada	Retrospective	94	64 months	NA	28.4
Kansy <i>et al.</i> , 2010 [14]	Warsaw, Poland	Retrospective	14843	11.8 days	10.7	29.2
Meyer <i>et al.</i> , 2012 [15]	Saarland, Germany	Prospective	313	54.2 months	NA	2.5
Agarwal <i>et al.</i> , 2014 [16]	Nashville, USA	Retrospective	3253	6 months	7.5	37
Jordan <i>et al.</i> , 2015 [7]	North America	Prospective	204	18.6 months	25	29
Jafri <i>et al.</i> , 2017 [4]	Karachi, Pakistan	Retrospective	2000	19.5 months	0.004	1.75
Bar-Yosef <i>et al.</i> , 2018 [18]	Tel Aviv, Israel	Retrospective	75	3 months	NA	26.67
Chung <i>et al.</i> , 2019 [19]	Ohio, USA	Prospective	672	NA	7	26
Arslanoglu <i>et al.</i> , 2021 [20]	Istanbul, Turkey	Retrospective	3849	60.59 months	33.33	4.2
Agha <i>et al.</i> , 2022 [21]	San Donato, Italy	Retrospective	63	12 months	19.05	31.7
Abdshah <i>et al.</i> , 2022 [22]	Tehran, Iran	Prospective	267	32 months	NA	5.22
Rohde <i>et al.</i> , 2022 [23]	Europe	Retrospective	230	24 months	24.5	20
Walaa <i>et al.</i> , 2023 [24]	Cairo, Egypt	Prospective	105	9 months	14	15.2

NA: Not available

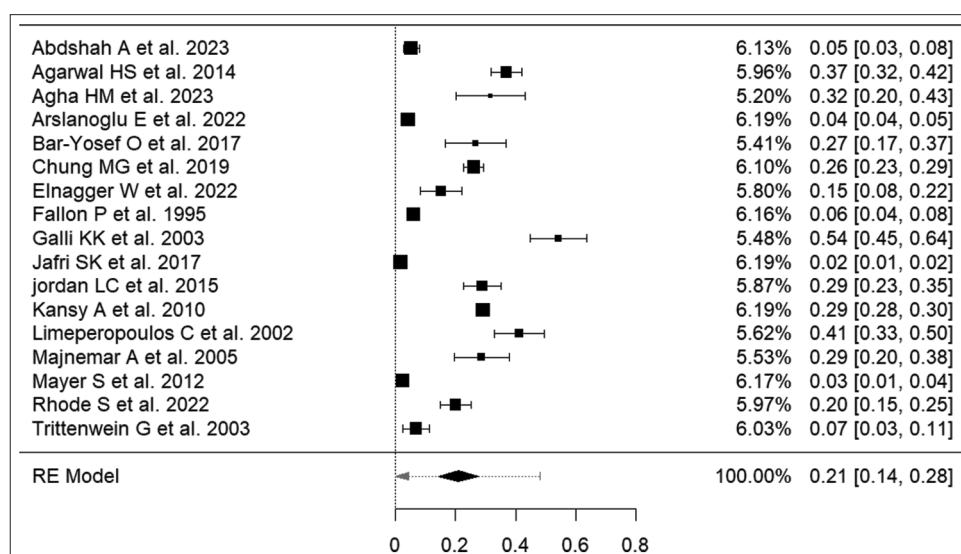


Fig. 2: Forest plot showing the incidence of neurological complications following pediatric congenital cardiac surgery

Subgroup analysis of primary outcome

The incidence or occurrence of neurological complications was analyzed for two separate age groups: Below 1 year and above 1 year; the incidence (95% CI) of neurological complications following pediatric congenital cardiac surgeries in the <1 year age group was found to be 0.32 (0.25–0.39). Random-effects model using DerSimonian-Liard estimator was used. The heterogeneity tests showed Tau at 0.085, I^2 at 90.22%, and H^2 at 10.221 with a significant $p < 0.001$ as illustrated in Fig. 3.

The incidence (95% CI) of neurological complications following pediatric congenital cardiac surgeries at the more than 1-year age group was found to be 0.11 (0.08–0.14). Random-effects model using DerSimonian-Liard estimator was used. The heterogeneity tests showed Tau at 0.041, I^2 at 96.54%, and H^2 at 28.902 with a significant $p < 0.001$ as illustrated in Fig. 4.

The incidence of neurological complications was found to be higher in infants when compared to children above 1 year of age following corrective surgeries for congenital cardiac disease. Therefore, age was found to be a significant factor in the development of neurological complications following pediatric congenital cardiac surgeries.

Secondary outcome

The mortality data were reported in 10 studies (Table 1). The mortality rate (95% CI) following pediatric congenital cardiac surgeries was found to be 0.13 (0.08–0.19). Random-effects model using DerSimonian-Liard estimator was used. The heterogeneity tests showed Tau at 0.085, I^2 at 99.70%, and H^2 at 333.482 with a significant $p < 0.001$ as illustrated in Fig. 5.

Sensitivity analysis

Meta-analysis was conducted separately after including and excluding each individual study. This was done to determine if there are any changes in the incidence of neurological complications following heart surgery. The results did not change after performing this sensitivity analysis.

Publication bias

The tests for publication bias were done using Egger's test and Funnel plots. There was no evidence of publication bias as the plots were symmetrical. The data are illustrated in Fig. 6.

Risk of bias

Almost all the studies taken up for this meta-analysis were considered to have a moderate to low risk of bias which is illustrated in Fig. 7.

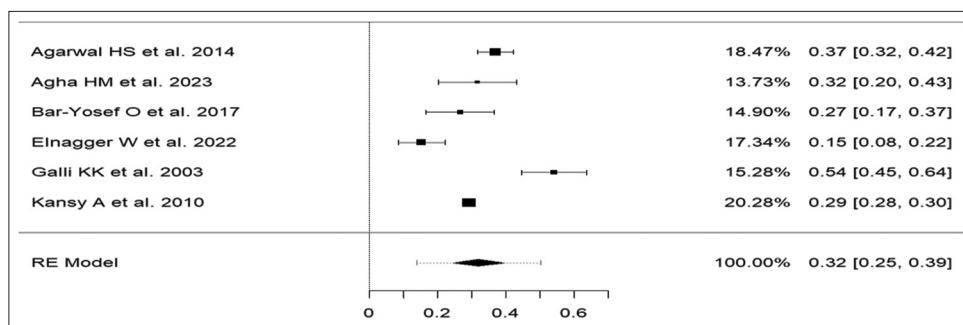


Fig. 3: Forest plots showing the incidence of neurological complications following pediatric congenital cardiac surgery <1 year of age

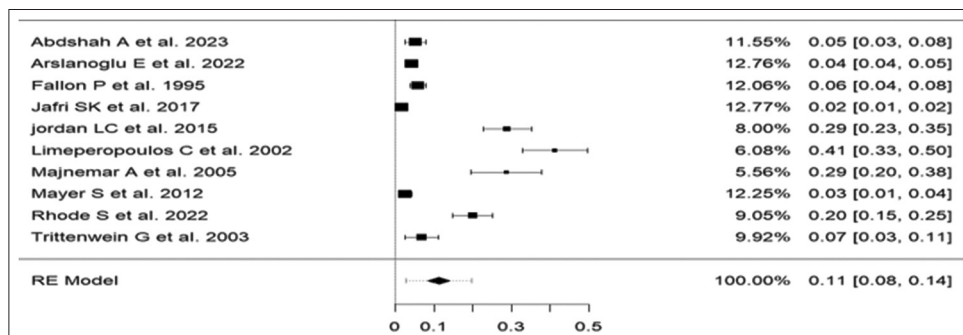


Fig. 4: Forest plots showing the incidence of neurological complications following pediatric congenital cardiac surgery - More than 1 year of age

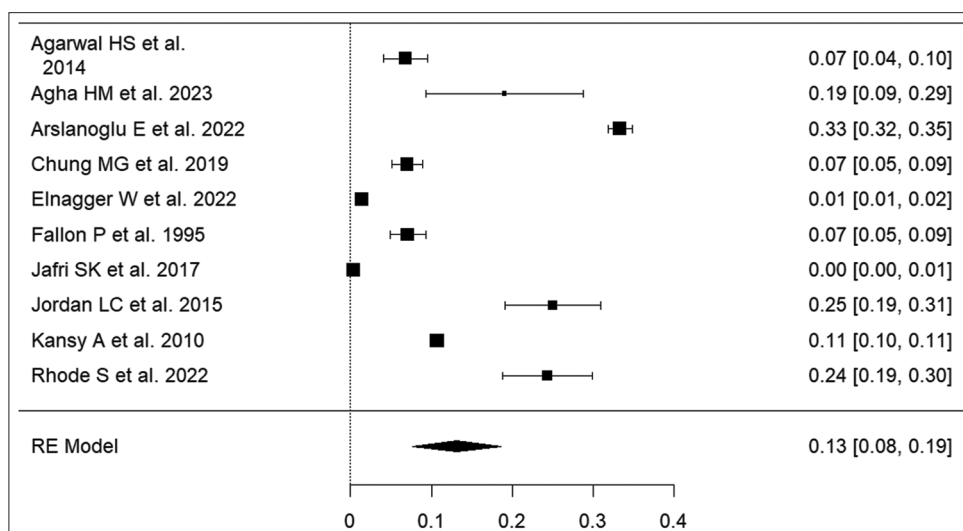


Fig. 5: Forest plot showing the mortality rate following pediatric congenital cardiac surgery

DISCUSSION

In the past few decades, significant progress made in pediatric cardiac surgery has led to enhanced survival rates for children born with congenital heart abnormalities. Despite these notable achievements, post-operative neurological complications continue to be a major concern. This meta-analysis was designed to conduct a comprehensive investigation into the prevalence of neurological problems following congenital heart surgery and to explore potential age-related differences in this occurrence.

Through the meticulous analysis of data from 17 studies encompassing a substantial number of individuals, valuable insights were obtained regarding the overall prevalence of neurological problems. The results revealed an alarming, pooled incidence of 21.41% of infants developing neurological issues after undergoing congenital heart surgery. This high

rate underscores the critical importance of continuous monitoring and proactive management of neurological consequences in this vulnerable patient population. As we endeavor to further enhance patient care and improve long-term outcomes, these findings serve as a compelling call to address and mitigate this gap.

A noteworthy finding from our comprehensive meta-analysis is the presence of age-related variations. Infants exhibited a significantly higher incidence of 32.29% compared to those above 1 year, who showed an incidence of 14.42%. These findings give rise to serious considerations regarding the potential impact of age-related factors on neurological susceptibility and recovery in this context [25].

Numerous variables could contribute to the increased frequency of neurological problems observed in infants under 1 year old [26]. First,

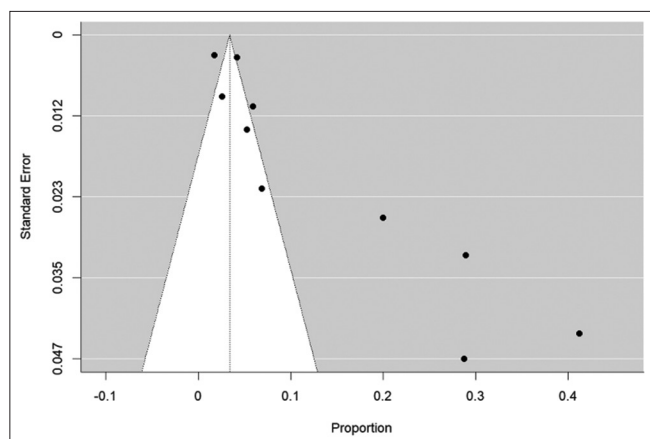


Fig. 6: Funnel plot for publication bias

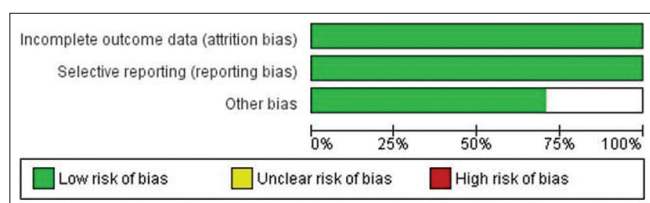


Fig. 7: Risk of bias graph of included studies

the developing brains of infants are more vulnerable to the physiological stress imposed by cardiac surgery and cardiopulmonary bypass, leading to an elevated risk of cerebral hypoperfusion and ischemia [27]. Second, younger children often present with more complex and severe congenital cardiac abnormalities, necessitating lengthier and more invasive surgical procedures that may heighten the risk of neurological complications [28]. Finally, the immature blood-brain barrier in infants may render the brain more susceptible to the inflammatory and oxidative stress induced by the surgical process [29]. These factors collectively underscore the importance of age-specific considerations in the assessment and management of neurological outcomes. Further research and tailored interventions are essential to mitigate the impact of age-related variables and improve the overall neurodevelopmental outcomes in this vulnerable population.

The observed lower frequency of neurological problems in children over 1 year of age can likely be due to their more developed and resilient neurological systems, which may better withstand the challenges posed by heart surgery. In addition, older children may present with less complex cardiac defects, leading to less invasive surgical interventions and subsequently reducing the risk of neurological sequelae [28,29].

Nevertheless, it is essential to underscore that despite the apparent age-related disparities in the prevalence of neurological problems, the influence of other confounding variables should not be underestimated. Factors such as the type and complexity of congenital cardiac abnormalities, the expertise and skill of the surgical team, and the overall health status of the patients may all play significant roles in shaping the occurrence of neurological complications [30].

While age-related variations provide valuable insights into the neurological outcomes following pediatric congenital cardiac surgery, it is evident that a multifactorial approach is necessary to fully comprehend the intricate interplay of factors affecting the occurrence of these complications. Future studies with larger and more diverse cohorts, as well as meticulous data collection and analysis, are warranted to gain a deeper understanding of the complex relationships between age, other confounding variables, and the neurological outcomes in this patient population. Such investigations are essential

for refining clinical practices, optimizing patient care, and advancing long-term outcomes.

In this meta-analysis, we carefully synthesized data from 10 extracted studies to evaluate the pooled incidence of mortality resulting from pediatric congenital cardiac surgery. The analysis revealed a pooled incidence rate of 0.13, indicating that approximately 13 out of 100 children undergoing surgeries experienced mortality. While the advancements in pediatric cardiac surgery have undeniably improved outcomes and survival rates, this finding emphasizes the ongoing significance of mortality as a crucial concern in this patient population. Understanding these factors contributing to this mortality rate will ultimately improve patient safety and long-term prognosis. Furthermore, these findings underscore the need for continuous efforts in research and quality improvement initiatives to optimize the overall success and safety of pediatric congenital cardiac surgeries.

To elucidate the underlying mechanisms of neurological problems in this specific patient population, forthcoming research endeavors should prioritize large-scale, prospective, and multi-center studies employing standardized methodologies. The evaluation of long-term neurodevelopmental outcomes will be instrumental in discerning the enduring effects of these issues on the cognitive and functional capacities of affected children. To advance our understanding and optimize patient care, collaborative efforts involving multidisciplinary teams comprising cardiac surgeons, neurologists, and pediatricians are essential. By synergizing expertise from diverse fields, we can collectively strive to enhance the overall quality of treatment and outcomes for children undergoing congenital heart surgery. Rigorous scientific inquiry, in conjunction with comprehensive and integrated approaches, will pave the way for substantial advancements in managing neurological complications and improving the long-term well-being of these young patients.

Limitations

This study, like many meta-analyses of observational studies, inherently possesses certain limitations, primarily stemming from potential methodological heterogeneity among the included studies. Variability in the number of patients across studies, with a concentration of participants in two specific studies, further adds to the complexities. In addition, patient management strategies in the included studies were dictated by individual center protocols, leading to diverse approaches and indications.

Despite these limitations, our meta-analysis contributes valuable data to aid physicians, academics, and policymakers in gaining deeper insights into the landscape of neurological problems following congenital heart surgery. The notably high overall frequency of neurological problems underscores the importance of augmenting post-operative neurological surveillance and developing targeted preventive interventions. By leveraging these findings and addressing these areas of concern, we can work toward enhancing patient care and ultimately improving neurodevelopmental outcomes in children.

CONCLUSION

The study highlights the significant occurrence of neurological problems following pediatric congenital heart surgery, with children under the age of 1 year being at a greater risk. This highlights the importance of extensive pre-operative screening, diligent neurological monitoring, and tailored therapies to reduce the impact of these problems on these susceptible individuals' long-term neurodevelopmental outcomes.

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AUTHORS CONTRIBUTIONS

Dr. Madhu A Yadav involved in collection of articles, discussion, manuscript writing, and final editing of manuscript. Dr. Rekha A Assadi involved in the collection of articles, manuscript writing, and statistical

analysis. Dr. Neha K Kudumula involved in final screening of articles editing and proofreading.

CONFLICT OF INTEREST

Nil.

FUNDING

Nil.

KEY POINTS

- Question: What is the incidence of neurological complications in pediatric congenital cardiac surgery for CHD?
- Findings: Neurological complications occurred in 0.21 (95% CI: 0.14–0.28) of pediatric patients after congenital cardiac surgery.
- Meaning: Highlighting the imperative, advanced neuromonitoring, timely interventions, and vigilant post-operative surveillance stand as crucial measures for averting the occurrence of neurological complications.

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