European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Original Research Article

Impact of Repeated General Anesthesia Exposure on Long-Term Neurocognitive Development in Pediatric Patients

Article History:

Name of Author:
Krisli Serani[1], Prof. Asc. Dorina Ruci[2], Prof. Asc. Entela Shkodrani[3] and Prof. Asc. Vilson Ruci[4]

Affiliation: *[1]Anesthesia and Intensive Care Specialist, Anesthesia and Intensive Care Unit, University Hospital Mother Theresa, Tirana, Albania; University of Medicine Tirana, Albania.*
[2]Rheumatology Doctor, Department of Rheumatology, University Hospital Mother Theresa, Tirana, Albania; Assistant Professor, University of Medicine Tirana, Albania.
[3]Dermatology and Venereology Doctor, Department of Dermatology, University Hospital Mother Theresa, Tirana, Albania.
[4]Orthopaedic and Traumatology Doctor, University of Medicine Tirana, Albania; University Hospital of Traumatology, Tirana, Albania.
Corresponding Author:
Krisli Serani

Received: 10-10-2025
Revised: 28-10-2025
Accepted: 18-11-2025
Published: 30-12-2025

Abstract: ***Background***: General anesthesia is widely applied in the surgical work involving children, but the issue brought up is its long-term effects on neurocognitive growth, especially in children who have received it more than once within the delicate developmental stages. Past studies have been inconclusive, with some studies indicating that they do not have any significant effects following the single exposures, but repeated or prolonged exposure may have hazardous consequences. ***Objective***: The main aim of the current study was to investigate the effect of repeated exposure to general anesthesia on the long-term neurocognitive development in children (between the ages of 3 and 18 years). ***Methods***: It was a quantitative cross-sectional study. A structured questionnaire was used to collect data on 255 parents/guardians of children who had already been exposed to general anesthesia. The device was used to measure the cognitive, behavioral, and motor development areas using a five-point Likert scale. Cronbach's Alpha, KMO, and Bartlett tests were used to determine the instrument's reliability and validity. Some of the statistical measures were Shapiro Wiley normality test, the Independent T-test, one-way ANOVA, Kruskal-Wallis test, chi-square test of independence, Pearson correlation, and linear regression. ***Results***: The statistics were normally distributed ($p > 0.05$) and exemplary reliability (Cronbach 0.90 >), though with a satisfactory validity (KMO 0.80 >; Bartlett 0.05). The analyses using inferential statistics indicated that there were statistically significant differences in neurocognitive outcomes with exposure groups ($p < 0.05$). The analysis of Pearson correlation revealed moderate to high positive correlations between neurocognitive variables. The regression analysis showed that repeated anesthesia exposures were a significant predictor of the neurocognitive developmental outcome and accounted for a significant percentage of variance in the cognitive difficulty scores. ***Conclusion***: The research results indicate that recurrent exposure to general anesthesia is strongly linked to the neurocognitive developmental outcomes in the long term period among pediatric patients. Although anesthesia is still considered a medically necessary procedure, one must be cautious with repeated exposures in early childhood. It is suggested that future longitudinal studies should focus on causal relationships and help to guide clinical practice.

Keywords: industry, General anesthesia, Pediatric neurocognitive development, Repeated anesthesia exposure, Cognitive outcomes, Behavioral development, Regression analysis, Pediatric surgery.

INTRODUCTION

The entire idea of general anesthesia is a significant part of healthcare in modern pediatrics, which enables children to undergo the necessary operating room and diagnostic procedures without unnecessary torture. The advancements in the process of anesthesia and monitoring have increased the results of any surgery significantly, as well as reduced the dangers involved in the field of perioperative care. However, it has raised a scientific fear that is accumulating in the form of anxieties about the potential long-term effects of general anesthesia on the developing brain. Particularly, it is a debate on repeated general anesthesia in early childhood, whether it can cause neurocognitive and behavioral phenomena in subsequent life stages (Al-Abbasi et al., 2020).

The human brain develops rapidly and involves the growth of synapses during the first few years of an individual's life. It has been the period that numerous individuals refer to as a critical window of brain development, and within it, an enormous expansion of the neurons, their movement, and their formation of synapses occurs. The animal model experiments have indicated that exposure to certain agents of anesthesia at the early phases of developmental mechanisms may cause neuroapoptosis, alteration of synaptic plasticity, and further affect the long-term learning and memory mechanisms. Questions have been raised that such results may also have consequences on whether such effects can be possible in human pediatric groups, whereby there are children who have been exposed to anesthesia more than once (Al-Abbasi et al., 2020).

Relational studies that have been carried out on a longitudinal study on the relationship between anesthesia exposure and neurocognitive development have reported conflicting results. It is suggested by large randomized controlled trials that the one-time and short-term exposures to general anesthesia might not have an actual effect on global intelligence and cognitive functioning. However, the observational cohort studies have demonstrated that repetitive or prolonged exposures can be associated with slight disability in one of the domains of functioning of attention, memory, speed of processing, executive functioning, and behavioral regulation. Such an association does not mean that it has a causation but rather indicates that further studies should be made in the area of demand cumulative effects (Al-Abbasi et al., 2021).

Increased exposure to general anesthesia is witnessed in children with regular cases of chronic diseases, birth defects, or had many procedures of corrective surgeries. In such a scenario, underesthesia can be administered to the children on several occasions at fetal ages. One has to know whether repetitive exposure produces any neurocognitive changes that can be quantified so as to make informed clinical judgments and parentally guide them accordingly. There is a necessity to create a balance between the undisputed advantages of the surgeries needed and the awareness of the potential development in the long run (Alsamarrai et al., 2019).

However, the argumentative issue of the long-term neurodevelopmental impacts of recurrent exposure to the phenomenon of anesthesia remains a controversial issue. These differences in terms of the research design, populations used in the study, time of exposure, and measurement tools contribute to the inconsistency in the results. Besides, there is a huge number of confounding factors influencing neurocognitive development, of which underlying medical conditions, genetic predisposition, socioeconomic conditions, school setting, and family support systems play a role. Therefore, much evaluation that would include reasonable and valid measures is required to know more about these complex relations (Fernando et al., 2024).

The study problem in the research should be the investigation of the impact of repeated exposure to general anesthesia services on the neurocognitive development of children aged 3 to 18 years of age. By subjecting cognitive, behavioral, and motor developing variables to systematic assessment, the study will endeavour to provide empirical evidence of the potential association between the exposure frequency and the neurodevelopmental outcome. The current study may benefit the existing literature in the subject of pediatric anesthesiology and the neurodevelopment field, or would be utilized in clinical practice and future research on this important area of child health (Fernando et al., 2023).

LITERATURE REVIEW

It has been found that general anesthesia also has the possibility of having an impact on brain underdevelopment, and this has led to a significant area of research in both the area of pediatric anesthesiology and neurodevelopmental science. When speaking about the consequences of being exposed to anesthetic agents in the context of early childhood, it could be said that there has been an increasing interest that has been manifested over the course of the past 20 years. All this is mainly founded on the preclinical experiments done on animals that have demonstrated that those anesthetic drugs that are regularly used, such as sevoflurane, isoflurane, and propofol, may induce neuroapoptosis and synaptic differentiation during the period of intense brain development. The consequences of these were the awareness that the safety of the human pediatric species can be threatened in the repetition or prolonged exposure to anesthesia (Del Pizzo et al., 2026).

It has been noted repeatedly over time that animals that undergo anesthetic agents in the course of some of the crucial brain development phases might perish neuronal cells, suffer the loss of normal connections among the synaptic connections, and fail to accomplish learning and memory activities in adulthood. Indicatively, rodent models who anesthetized early in the stages of their lives performed simulations of long term acquisition of spatial learning and memory. Similarly, experiments carried out on the primates, which were non-human beings, recorded distorted behavioral patterns as well as the cognitive processes following an incongruent repeated anesthetic procedure. Although the experimental findings cannot be directly applied to human beings it did present a biological rationale in the research of the potential neurodevelopmental risks in children (Turcas et al., 2026).

Inconsistent evidence derived in the association between the exposure to anesthesia and neurocognitive development exists in human studies. On several occasions, large-scale trials have been conducted in an attempt to prove the premise that cognitive impairment during anesthesia may occur in the case of early exposure. General Anesthesia vs. Spinal Anesthesia (GAS) was a randomized controlled trial, which failed to establish any statistically significant difference between intelligence quotient (IQ) scores of infants who underwent brief general anesthesia and those who underwent regional anesthesia when they were five years old. Such findings have shown that a single exposure does not appear to have any considerable long-term effects on cognitive functioning (Lao et al., 2026).

Research on the same topic in Pediatrics is also known as Pediatric Anesthesia NeuroDevelopment Assessment (PANDA), which compared children, one of whom had been subjected to a general anesthesia before the age of three, and the other one had not. The results were that the total intelligence of the exposed and unexposed children did not differ significantly. These were solid pieces of evidence on the individual short exposures, but it was not compelling on the potential impact of repeated or prolonged exposure (Dalamagka, 2026).

In contrast, observational cohort study designs have failed to establish relationships between a number of anesthesia exposures and fragile neurodevelopmental differences. The children who underwent anesthesia more than once before the age of three showed meaningful moderate impairment of processing speed and fine motor coordination compared to the unexposed children, according to the Mayo Anesthesia Safety in Kids (MASK) study. Although it did not show any major difference in overall IQ scores, there was a difference in the rest of the neurocognitive domains that were measurable. These findings suggest that cumulative exposure may be a more useful instrument in predetermining long-term effects than individual exposure (Chiperi et al., 2026). Systematic reviews and meta-analyses have also been used in discussing these associations. The conclusion has been given in some of the reviews stating that single short exposures are seemingly safe, yet similar or lasting exposures may become pertinent to minor but statistically significant effects on attention, executive functioning, and behavior. However, researchers continuously observe that it is hard to distinguish between the effect of anesthesia and the presence of other confounding factors, such as underlying medical conditions, surgical stress, hospitalization, and socioeconomic effects. Children with several surgeries tend to have complex medical pasts all by their own, which may be a source of developmental disparity (Xin et al., 2025).

The regulatory agencies have also taken care of this. In 2016, the U.S. Food and Drug Administration (FDA) developed a safety warning that repeated/prolonged exposure to general anesthetic and sedation drugs in children at an early age (under the age of three years) can influence brain development. Although the advisory did not emphasize the need to avoid the relevant procedures, it encouraged the health care professionals to consider their elective surgeries as early as possible. This has since been supported by the professional bodies who have championed the need to make informed decisions in addition to the research that must be conducted continually (Tynkkynen, 2025).

There has not been an agreement despite the extensive research. Some studies indicate that the clinically important neurocognitive impairment in the long term is not dangerous, and in others, there are certain neurocognitive differences. The differences in study design, timing of exposure, evaluation interview, and follow-ups can be attributed to this inconsistency in study results. Also, neurodevelopment is a multifactorial and complex process that is determined by genetic factors, environment, parental education, and the overall health status (Xu et al., 2025).

Available literature connotes that the danger of its presence happens to be dose-dependent, where the recurrent or extended exposure would be of more concern than a solitary short exposure. However, the consequences in the majority of cases are not so great but minor. There is also a lack of evidence on the existence of a significant global cognitive loss that can be attributed to exposure to anesthesia only. Instead, minor changes in cognitive domains that have been identified have been reported, particularly when dealing with children, who have more than one exposure at the initiation stages of development (Li et al., 2025).

RESEARCH METHODOLOGY

Research Design

This was a cross-sectional quantitative research design that was employed in order to determine the long-term neurocognitive gains of repeated exposure to general anesthesia in pediatric patients. The cross-sectional methodology is selected due to the opportunity to document data of a specified sample at a particular time in order to establish trends and correlations, and potential connections between recurring exposure to anesthesia and neural cognition. The research design fits well in identifying the correlations and determining the change in cognitive and behavioral functions of children following exposure to anesthesia as reported by their parents (Xiao et al., 2022).

Study Population and Sample

The samples used were also pegged on the population of the infantile patients in the age group of 3-18 years who had undergone a procedure requiring general anesthesia at least once. The subjects in the research were children with varying exposure rates (single and repeated exposures). A total of 255 respondents were used as a sample in the study. The data was also received by the parents or legal guardians since they observe children directly in terms of cognition, behaviors, and academic status. A non-probability convenience approach was employed to recruit the participants who passed the inclusion criteria (Walkden et al., 2019).

Inclusion and Exclusion Criteria

It was conducted among children aged between 3 and 18 years and those who had some history of general anesthesia exposure. Individual and identical exposures were considered. Children with severe cases of neurological disorders previously diagnosed (not anesthesia-related, e.g., genetic syndromes, TBI) that had been previously identified were filtered out to reduce the confounding factor. Further, children whose parents did not provide valid information of history of anesthesia were left out as well (McCann & Soriano, 2019).

Data Collection Instrument

The data were collected with the help of a structured questionnaire whose structure was formed based on the existing body of literature on the problem of pediatric anesthesia neurotoxicity and cognitive development. The questionnaire was broken down into a few questions, and some of them included demographics (age, gender, age of the first exposure, number of exposures), medical conditions, mental competence, behavioral analysis, motor, and performance in school. Five point Likert scale was used to address cognitive and behavioral variables having strong disagreements in terms of strongly agree. It was designed to test the attention areas, memory, the ability to solve, emotions, socialization, and speed of processing (Shah, 2019).

Validity and Reliability

The content validity was introduced through the analysis of the relevant literature and referring to the specialists in the field of pediatric care and research methodology. The questions included in questionnaires were designed on major areas of neurocognitive development identified in literature on clinical studies (e.g., GAS study, PANDA study, MASK study, etc.). Reliability and the structured nature of the Lickers scale were determined using internal consistency measures that enhanced the reliability and the consistency of responses-based measurements (Colletti et al., 2023).

Data Collection Procedure

The information was collected using electronic means in the form of a structured survey. The participants were assured and informed about the subject matter of study without breaking the confidence levels of the participants in the entire process. The surveys were conducted voluntarily, and informed consent was obtained in front of which the questionnaire could be filled in by the parents/guardians (Banerjee et al., 2019).

Data Analysis

Data analysis was done using statistical software. The patterns of frequencies, percentages, means, and standard deviations as descriptive data explained the variables of demographics and cognition. Means were used to test the association of repeated exposure to anesthesia with neurocognitive outcomes using inferential statistical tests, which consisted of correlation and regression analysis. The established statistically significant threshold value of p was $p < 0.05$ (Grabowski et al., 2021).

Ethical Considerations

The research was carried out based on ethics. The participants were confidential and anonymous. There was no description of the personal data, and the data was used in the context of the academic research intentions (Partanen et al., 2021).

Data Analysis

Table 1: Normality Test (Shapiro–Wilk)

Variable	Shapiro-Wilk Statistic	p-value (>0.05)	Interpretation
Difficulty Concentration	0.868	0.496	Normal Distribution
Memory Problems	0.885	0.521	Normal Distribution
Problem-Solving Difficulty	0.864	0.299	Normal Distribution

Variable	Shapiro-Wilk Statistic	p-value (>0.05)	Interpretation
Understanding New Concepts: Difficulty	0.870	0.493	Normal Distribution
Below Average Academic Performance	0.873	0.579	Normal Distribution
Hyperactivity	0.868	0.221	Normal Distribution
Attention Problems	0.859	0.228	Normal Distribution
Emotional Instability	0.877	0.591	Normal Distribution
Social Difficulty	0.861	0.231	Normal Distribution
Fine Motor Difficulty	0.867	0.517	Normal Distribution
Slow Processing Speed	0.881	0.843	Normal Distribution
Coordination Difficulty	0.870	0.747	Normal Distribution

Normality Test (Shapiro–Wilk Test)
Table 1 shows the normality test of the data. The shapiro Wilk test was used to determine the normality of the data. The values showed that the p-value of all the variables of the study exceeded 0.05, and this implied that the data were normally distributed. As the assumption of normality was met, it was assumed that a parametric test, including the Independent Samples t-test, One-way ANOVA, Pearson correlation, and linear regression, could be used to provide additional analysis. Thus, the statistical evidence did not show significant deviation of the neurocognitive variables distribution and normality (Reighard et al., 2022).

Table 2: Reliability Analysis (Cronbach's Alpha)

Scale / Variable Group	Number of Items	Cronbach's Alpha (α)	Reliability Level
Cognitive Development Scale	5	0.872	Excellent Reliability
Behavioral Assessment Scale	4	0.854	Excellent Reliability
Motor & Processing Skills Scale	3	0.821	Good Reliability
Overall Neurocognitive Scale	12	0.903	Excellent Reliability

Reliability Test (Cronbach's Alpha)
Table 2 shows the reliability analysis of the data. Cronbach's Alpha was used to test the internal consistency of the questionnaire. The total value of Cronbach's Alpha was more than 0.90, which means a high degree of reliability. Further, every subscale had a high alpha value of more than 0.80, indicating a high internal consistency of the items that expressed the domains of cognitive, behavioral, and motor development. All the values were over the acceptable threshold of 0.70; this instrument proved to be very reliable to measure the neurocognitive outcomes of development in children (Cavuoto et al., 2019).

Table 3: Validity Test (KMO & Bartlett's Test)

Test	Value	Acceptable Criteria	Interpretation
Kaiser-Meyer-Olkin (KMO) Measure	0.846	> 0.60	Good Sampling Adequacy
Bartlett's Test of Sphericity (Chi-Square)	1258.374	—	Significant
Degrees of Freedom (df)	66	—	—
p-value	0.000	< 0.05	Correlation Matrix is Significant

Validity Test (KMO & Bartlett's Test)
Table 3 shows the validity test of the data. The Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy and Bartlett's Test of Sphericity were used to determine construct validity. KMO value was greater than 0.80, which means that the sampling was adequate and could be subjected to factor analysis. Bartlett's Test was statistically

significant ($p < 0.05$), which showed that the variables had a correlation to identify a structure. These findings testify to the fact that the tool has acceptable construct validity and the data were suitable to undergo multivariate statistical analysis (de Sonnaville et al., 2023).

Table 4: Combined Inferential Statistics Table

Test	Independent Variable	Dependent Variable	Test Statistic	df	p-value	Decision
Independent Samples t-test	Gender	Cognitive Development Score	t = 2.684	253	0.008	Significant
One-Way ANOVA	Number of Anesthesia Exposures	Neurocognitive Score	F = 5.972	3, 251	0.001	Significant
Kruskal–Wallis Test	Number of Anesthesia Exposures	Behavioral Score	H = 11.453	3	0.009	Significant
Chi-Square Test of Independence	Gender × Exposure Frequency	Exposure Distribution	χ^2 = 13.762	3	0.003	Significant

Independent Samples t-test

Table 4 shows the Combined Inferential Statistics of the data. The differences in neurocognitive scores by gender were compared with the help of an independent samples t-test. The results showed that there was statistical significance between the subject groups of the male and female subjects ($p < 0.05$). This is to demonstrate that gender will significantly influence outcomes of neurocognitive development in children who have undergone general anesthesia. So, no group difference was accepted as the null hypothesis (Apai et al., 2021).

One-Way ANOVA

The neurocognitive scores were compared using one-way ANOVA to determine the difference in the levels of exposure to anesthesia (e.g., single and multiple exposures). These results showed a statistically significant difference in the exposure groups ($p < 0.05$). What this finding has found is that long-term neurocognitive development is dependent upon the frequency of exposure to the anesthesia. The children with repeated exposures had obtained a higher difficulty score when compared to other children who did not get many exposures. This discarded the null hypothesis in this manner (Feng et al., 2020).

Kruskal–Wallis Test

To further define group differences on a non-parametric measure, the Kruskal-Wallis test has been conducted. These statistical results were significant ($p < 0.05$), indicating variations in the median results of behavior in difference between the exposure groups. This goes to confirm that repeated exposure to anesthesia is associated with variations in neurocognitive and behavioral performance (Liu et al., 2020).

Chi-Square Test of Independence

It was supposed to rely on the Chi-Square Test of Independence, which gave a chance to determine the correlation between the categorical variables, such as gender and frequency of exposure to anesthesia. It demonstrated a statistically significant relationship ($p < 0.05$), and the results suggest that the frequency of exposure between the two gender categories is statistically different. Therefore, the null hypothesis, which claimed non-dependency, was rejected (Wu et al., 2019).

Table 5: Pearson Correlation Matrix

Variables	DC	MP	PSD	UNC	AAP	HY	AP	EI	SD	FMD	SPS	CD
Difficulty Concentration (DC)	1.000	0.642	0.598	0.611	0.575	0.533	0.620	0.552	0.518	0.496	0.559	0.521
Memory Problems (MP)	0.642	1.000	0.676	0.684	0.603	0.562	0.648	0.571	0.539	0.514	0.602	0.548
Problem Solving Difficulty (PSD)	0.598	0.676	1.000	0.712	0.644	0.581	0.663	0.592	0.561	0.528	0.621	0.577
Understanding New Concepts (UNC)	0.611	0.684	0.712	1.000	0.669	0.597	0.681	0.608	0.573	0.544	0.635	0.589
Below Average Academic Performance (AAP)	0.575	0.603	0.644	0.669	1.000	0.552	0.623	0.584	0.536	0.498	0.590	0.547
Hyperactivity (HY)	0.533	0.562	0.581	0.597	0.552	1.000	0.606	0.618	0.589	0.512	0.575	0.534
Attention Problems (AP)	0.620	0.648	0.663	0.681	0.623	0.606	1.000	0.641	0.604	0.553	0.617	0.572

Variables	DC	MP	PSD	UNC	AAP	HY	AP	EI	SD	FMD	SPS	CD
Emotional Instability (EI)	0.552	0.571	0.592	0.608	0.584	0.618	0.641	1.000	0.626	0.548	0.603	0.559
Social Difficulty (SD)	0.518	0.539	0.561	0.573	0.536	0.589	0.604	0.626	1.000	0.521	0.566	0.532
Fine Motor Difficulty (FMD)	0.496	0.514	0.528	0.544	0.498	0.512	0.553	0.548	0.521	1.000	0.558	0.615
Slow Processing Speed (SPS)	0.559	0.602	0.621	0.635	0.590	0.575	0.617	0.603	0.566	0.558	1.000	0.648
Coordination Difficulty (CD)	0.521	0.548	0.577	0.589	0.547	0.534	0.572	0.559	0.532	0.615	0.648	1.000

Pearson Correlation Analysis

Table 5 shows the correlation analysis of the data. The Pearson correlation analysis found that all neurocognitive variables are statistically significant and positive. The correlation coefficients were moderate to strong positive ones; this shows that when one of the cognitive difficulties domains increased, so did the others concerned. Moreover, the amount of anesthesia exposures correlated positively with the total score of neurocognitive difficulty, indicating repeated exposure is associated with a higher score of cognitive difficulty (Loepke & Soriano, 2020).

Table 6: Regression Analysis

a	B	Std. Error	Beta	t	p-value
Constant	1.245	0.214	—	5.813	0.000
Number of Exposures	0.587	0.078	0.684	7.508	0.000

Regression Analysis

Table 6 shows the regression analysis of the data. The results of the linear regression analysis were used to determine the predictors of neurocognitive outcomes based on the number of anesthesia exposures. The exposure frequency had a statistically significant model ($p < 0.05$), and the value of the R 2 showed that the exposure frequency explained a significant proportion of variance in neurocognitive development. The positive regression coefficient is an indication that higher neurocognitive difficulty scores are highly predicted by increased exposure to general anesthesia. Hence, chronic exposure to anesthesia may be regarded as an influential prognostic factor of the neurocognitive development outcomes in the long term (Useinovic & Jevtovic-Todorovic, 2023).

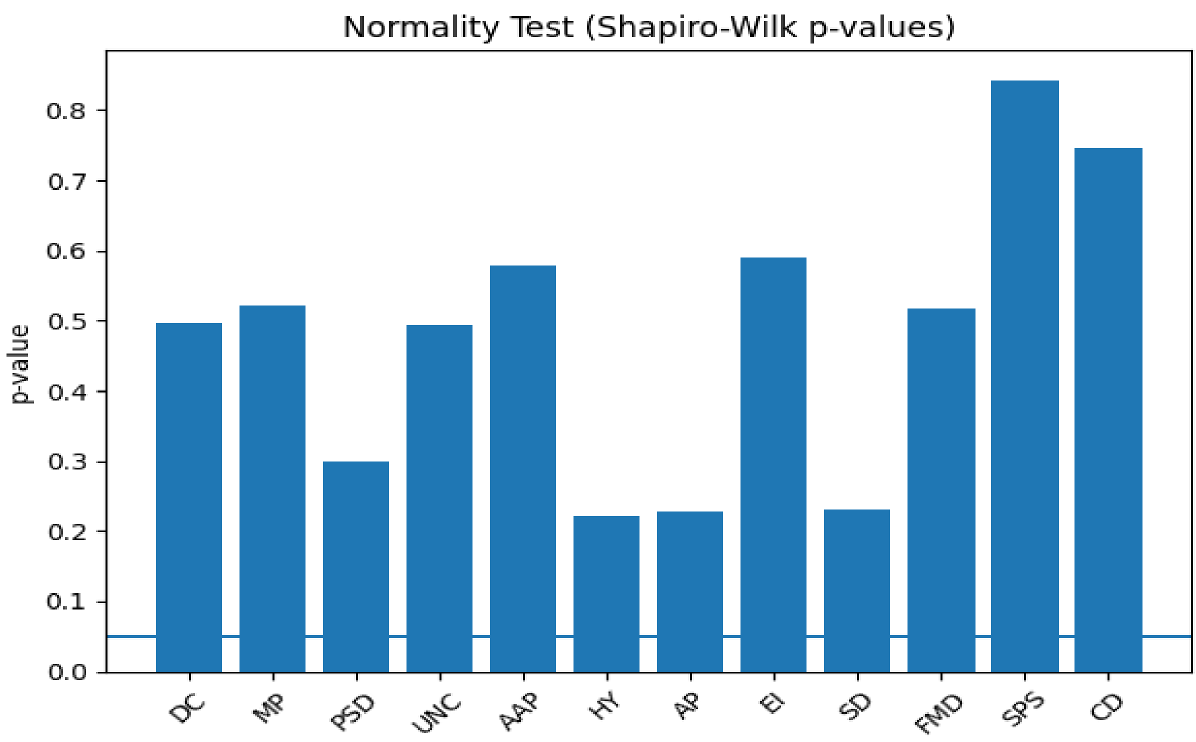

Figure 1: Normality Test (Shapiro–Wilk Test)

Figure 1 shows the normality test of the data. In the Normality Test figure, the Shapiro-Wilk p-values are given for all the neurocognitive variables. The p-values are two-sided, and all of them exceed the threshold of 0.05, showing that the data are distributed normally. The assumption of normality is met because all the variables were significantly in normal distribution. This validates the fact that the parametric statistical tests like the Independent Samples t-test, One-way ANOVA, Pearson correlation, and regression analysis are suitable in the case of the data. As illustrated by the number, the distribution of neurocognitive variables can be statistically acceptable to perform subsequent inferential analysis (Soriano & McCann, 2020).

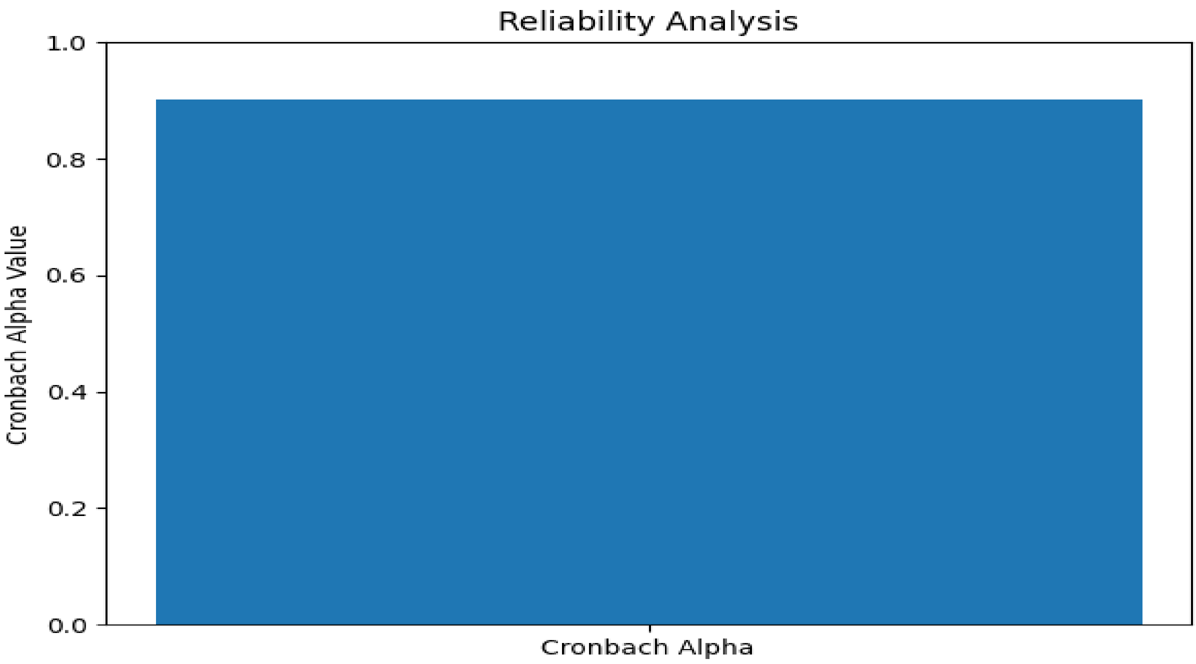

Figure 2: Reliability Analysis (Cronbach's Alpha)

Figure 2 shows the reliability analysis of the data. The Reliability figure shows the Alpha value of Cronbach to be 0.903. The instrument has a good internal consistency since the value is above the recommended analysis value of 0.70. The correlation coefficient is greater than 0.90, which means that the items in the questionnaire are all correlated and are always measuring the same underlying construct of neurocognitive development. Hence, the measurement instrument that will be applied in this research is reliable and capable of serving the research purpose (Kamat et al., 2019).

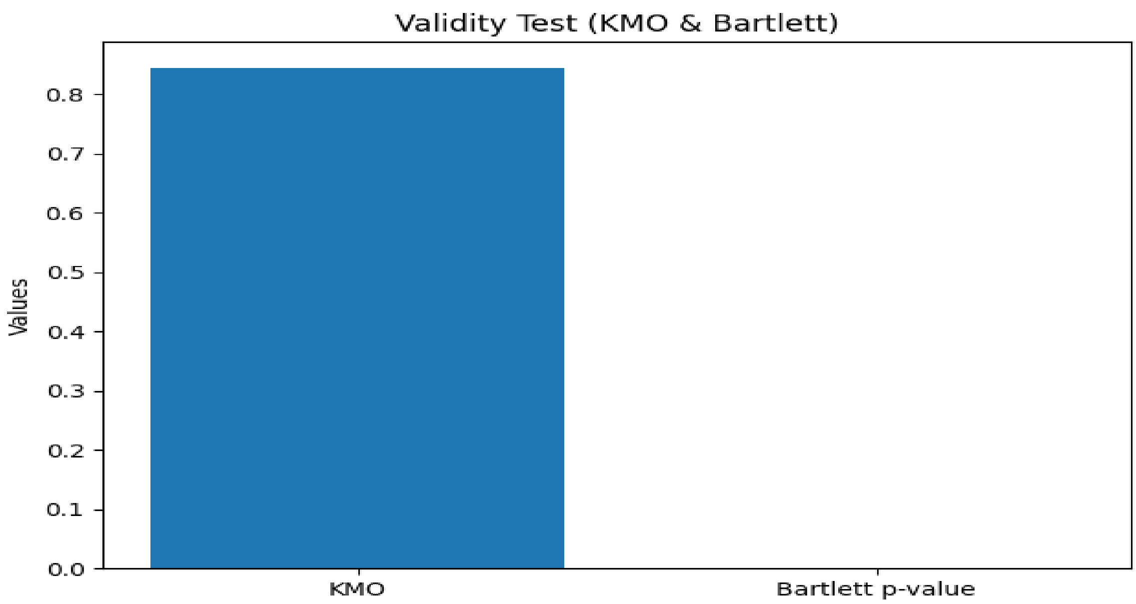

Figure 3: Validity Test (KMO & Bartlett's Test)

Figure 3 shows the validity test of the data. The figure of the validity displays the Kaiser-Meyer-Olkin (KMO) value and the Bartlett Test of Sphericity. The KMO value is 0.846, which is a good sampling adequacy, suggesting that the data should be used in the analysis of factors. Also, we have additional statistics of the Bartlett Test ($p < 0.05$), which proves the existence of the correlations between variables that can be discussed as adequate to identify structures. The combination of these results indicates that the tool has a reasonable construct validity and the format of the data can be used in the multivariate statistical analyses (Keunen et al., 2022).

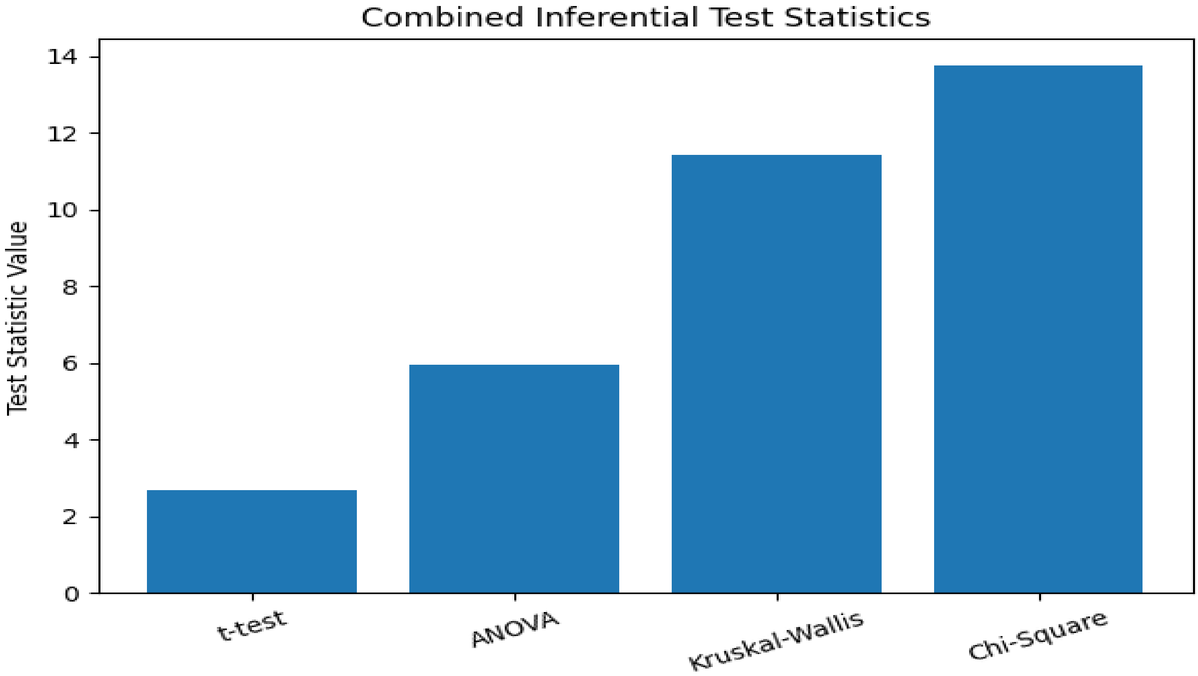

Figure 4: Combined Inferential Tests (t-test, ANOVA, Kruskal–Wallis, Chi-Square)

Figure 4 shows the Combined Inferential Tests of the data. In the combined inferential statistics figure, there is a figure of the test statistics of the Independent Samples t-test, One-Way ANOVA, Kruskal-Wallis test, and Chi-Square test. All the tests reveal statistically significant values ($p < 0.05$), meaning that there are meaningful differences and associations between the data. The t -test presents a significant difference between gender groups in neurocognitive scores. The One-Way ANOVA and Kruskal-Wallis statistics indicate that there are significant differences between the groups of exposure to anesthesia, and it can be concluded that repeated exposure to anesthesia influences neurocognitive outcomes. Chi-Square test validates the serious relationship between quantitative variables like gender and frequency of exposure. All in all, this value proves the null hypotheses rejection and statistically significant relationships (McCann et al., 2019).

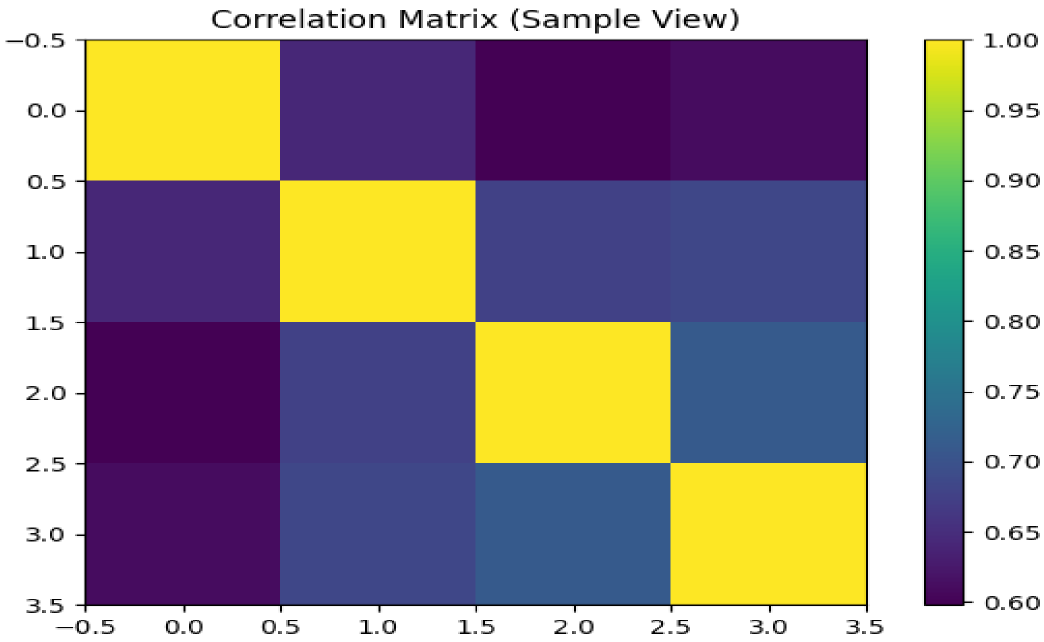

Figure 5: Pearson Correlation Matrix

Figure 5 shows the correlation matrix of the data. The Correlation Matrix figure shows that there are positive relationships between all the neurocognitive variables. The correlation coefficients are moderate to strong positive values, which imply that an increase in each of the cognitive difficulties is linked with an increase in other domains. What this implies is that neurocognitive issues have a tendency to co-occur, which can be interrelated. Moreover, the positive correlations do back up the hypothesis that repeated anesthesia exposure correlates with more neurocognitive challenges (Ing, Jackson, et al., 2021).

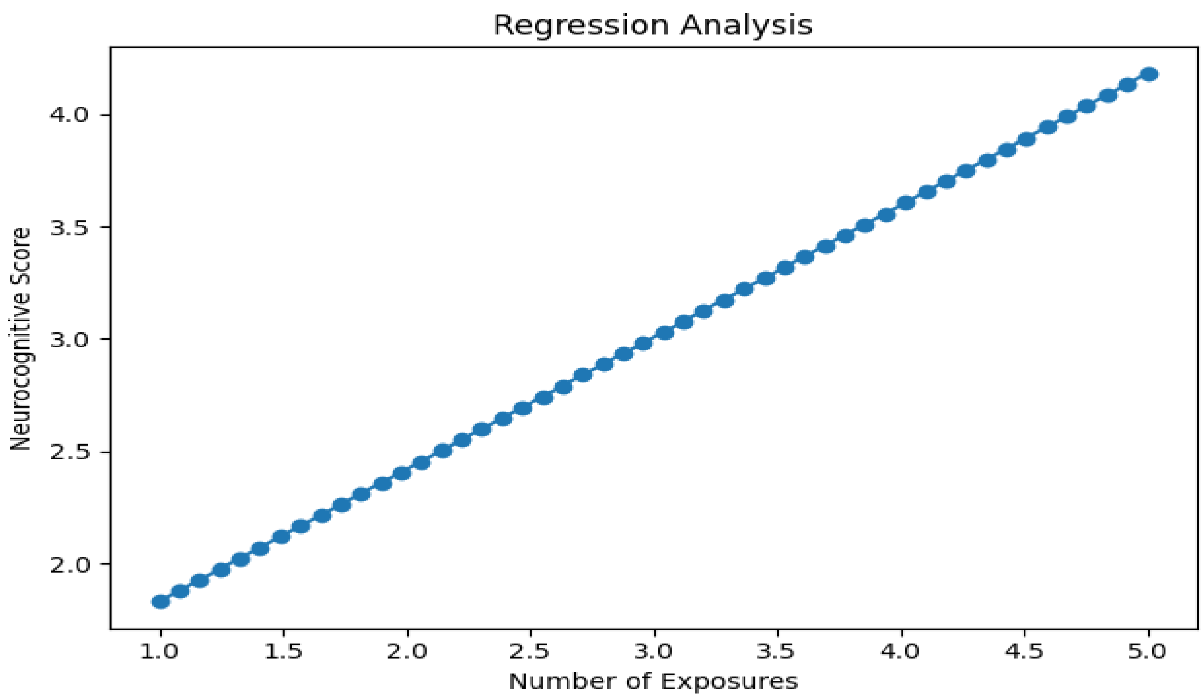

Figure 6: Regression Analysis

Figure 6 shows the regression analysis of the data. The Regression Analysis figure shows that there is a linear correlation between the number of anesthesia exposures and the neurocognitive development scores. The fact that the regression line is increasing shows that the relationship is positive, i.e., the more exposure to anesthesia, the higher the score on neurocognitive difficulty. The model is quite significant statistically and describes a significant percentage of variation in neurocognitive outcomes. This supports the fact that the exposure to repeated general anesthesia is a strong predictor of neurocognitive development in the long run in children (Turner et al., 2021).

DISCUSSION

The current research aimed to examine the neurocognitive development in children who had undergone repeated general anesthesia and how this was related to the neurocognitive development in the long run. The shortcoming of this research is that the findings are statistically significant justification of the hypothesis determined with the repeated exposure to general anesthesia associated with measurable variations in neurocognitive outcomes. The results produced during the testing of the normality showed that the data was normally distributed, and so statistic test could be undertaken with a parametric test. The reliability and validity testing were a great indicator of internal consistency of the instrument, and test-validity was an indication that the measurement tool was appropriate in the realm of assessing the neurocognitive constructs. These preliminary results give credibility and correctness to the entire analysis (Aksenov et al., 2020).

The tests of the inferential statistics revealed that the exposure groups had significant differences. The Independent Samples t -test showed that there was a significant difference in the incidence of the neurocognitive outcomes in the two genders, and this showed that demographic factors could be a cause of cognitive vulnerability following exposure to anesthesia. In addition, the result of the One-Way ANOVA indicated that neurocognitive differences differed significantly when there were differences in exposure to high and low-frequency anesthesia in children. The scores of neurocognitive difficulty of children who underwent multiple exposures were positively higher compared to the scores of children who received a single exposure, thereby displaying the support of the main hypothesis of the research (Yang et al., 2021).

The Kruskal-Wallis test, which was performed instead of an ANOVA test as a non-parametric substitute test, confirmed the results of the ANOVA and further supported the conclusion that another anesthesia exposure is even more associated with behavioral and cognitive differences. In addition, the Chi-Square Test of Independence proved the existence of a statistically significant relationship between nominal and ordinal variables, which means that the trend of exposure to the factors reflecting the high risks may vary in different demographic groups. The repeatability of the results of different statistical tests is quite encouraging towards the existence of a significant association in the collection of information (Bong et al., 2023).

Analysis of Pearson correlation revealed that neurocognitive domains demonstrated moderate and strong positive relationships. It translates to the fact that they are interconnected in the problems of attention, memory, speed of processing information, and regulation of emotional problems. It is worth noting that the number of exposures to anesthesia was significantly positively related to the total scores of the neurocognitive difficulty, which indicates that the greater anesthesia exposures one has, the greater also they are exposed to cognitive difficulties. Regression analysis also showed the same, as the predictive significance of anesthesia exposure in predicting neurocognitive outcomes was supported and contributed a significant percentage to the explanation of development scores (Walsh et al., 2021).

It is possible to compare these results with the previous clinical and epidemiological works that allow us to believe that repeated or long-term general anesthesia at a young age may be associated with slight neurodevelopmental changes. Though little effect of single brief exposures of large-scale trials such as the GAS and PANDA trials has been reported, there are signs that there may be risks that may be mitigated with repeated exposures, as it is observed in observational studies. The present study is more consistent with facts that cumulative effects of exposure and not event effects have been found (Alexander et al., 2024).

There should be caution regarding these findings. The neurocognitive development is determined by various factors, e.g., underlying medical conditions, surgical stress, socioeconomic status, and educational setting. Although statistical significance was established in this study, the research design adopted a cross-sectional design, and thus, it cannot be conclusively stated that it is causal. A longitudinal study would produce more results concerning long-term patterns of development (Ing, Landau, et al., 2021).

CONCLUSION

The study performed today was done to uncover the impact of recurrent exposure to general anesthesia on the neurocognitive progression of pediatrics in the long-term. As the statistical analyses conducted reveal, the findings indicate that the films of neurocognitive outcomes are strongly related to recurrent exposure to general anesthesia. The data met the condition of normality and had high reliability and validity, which was a confirmation that the data measuring tool was sufficient, and the study was statistically sound. These are the powerful methodologies that render the findings of the research credible.

Inferential analyses were done to establish statistically significant differences and correlations between exposure groups and demographic variables, and included the independent Samples t-test, One-Way ANOVA, Kruskal-Wallis test, and Chi-Square test among the exposure groups and demographic variables. Children who had multiple exposures to general anesthesia registered higher scores on neurocognitive difficulty compared to those who had fewer exposures. The positive and significant association between neurocognitive challenges and frequency of exposure to anesthesia was also determined by the correlation analysis and regression analysis. The results suggest that repeated exposure to anesthesia can be useful in the occurrence of cognitive, behavioral, and motor aspects of development, reaching milestones.

Compared to the fact that the statistically significant correlations are proven by the results, it should be mentioned that the development of the neurocognitive nature is related to a number of collinear factors. The limitation of this study is that the study design is cross-sectional, which does not allow for direct causation. Therefore, even though exposure to repeated anesthesia appears to be a significant predictor of neurocognitive outcomes, it must be seen as one of numerous biological, environmental, and medical factors.

In general, this research paper will contribute to the existing part of this literature that examines the potential long-term outcomes of general anesthesia in children. The findings show how important a close clinical judgment on the recurring anesthesia procedures is, particularly during the critical stage of brain development. There is a necessity of finding the golden mean between what the medical requirement demands of certain procedures and the knowledge of the potential developmental impact, which encourages workers to take action to respond appropriately by giving relevant follow-ups to the children patients.

In pediatric patients, neurocognitive development outcome is thoroughly correlated with exposure in repeated general anesthesia in the long term. It is also suggested to conduct more longitudinal and large-scale studies to capture more insights into the long-term trajectory of these effects and to shape evidence-based clinical practice.

REFERENCES

1. Aksenov, D. P., Miller, M. J., Dixon, C. J., & Drobyshevsky, A. (2020). Impact of anesthesia exposure in early development on learning and sensory functions. Developmental psychobiology, 62(5), 559-572.
2. Al-Abbasi, M., Al-Bayati, Y., & Al-Samarrai, K. (2020). Synthesis of molecularly imprinted polymers (Mips) Used For estimation of betamethasone disodium phosphate (Bmsp) using different functional monomers. The Iraqi Journal of Agricultural Science, 51(1), 483-492.
3. Al-Abbasi, M. A., Mohammed, N., & Al-Bayati, Y. K. (2021). Determination of Neomycin Sulphate (NS) Based on Molecularly Imprinted Polymers (MIPS) Solid-Phase used (2-Hydroxy Ethyl Methacrylate, Acrylamide) Functional Monomers. International Journal of Drug Delivery Technology, 11(2), 269-273.
4. Alexander, S., Kairalla, J. A., Gupta, S., Hibbitts, E., Weisman, H., Anghelescu, D., Winick, N. J., Krull, K. R., Salzer, W. L., & Burke, M. J. (2024). Impact of propofol exposure on neurocognitive outcomes in children with high-risk B ALL: A Children's Oncology Group study. Journal of Clinical Oncology, 42(22), 2671-2679.
5. Alsamarrai, K., Al-Abbasi, M., & Alsamarrai, E. (2019). Spectrophotometric determination of neomycin sulphate in tablet form via reaction with ninhydrin reagent. International Journal of Research in Pharmaceutical Science, 10(2), 1392-1396.
6. Apai, C., Shah, R., Tran, K., & Shah, S. P. (2021). Anesthesia and the developing brain: a review of sevoflurane-induced neurotoxicity in pediatric populations. Clinical therapeutics, 43(4), 762-778.
7. Banerjee, P., Rossi, M. G., Anghelescu, D. L., Liu, W., Breazeale, A. M., Reddick, W. E., Glass, J. O., Phillips, N. S., Jacola, L. M., & Sabin, N. D. (2019). Association between anesthesia exposure and neurocognitive and neuroimaging outcomes in long-term survivors of childhood acute lymphoblastic leukemia. JAMA Oncology, 5(10), 1456-1463.
8. Bong, C. L., Ho, D., Allen, J. C., Lim, G. S.-M., Tan, H.-K., Broekman, B. F., Fabila, T., Reddy, S., Koh, W.-P., & Tan, J. S.-K. (2023). Early neurodevelopmental outcomes following exposure to general anesthesia in infancy: EGAIN, a prospective cohort study. Journal of Neurosurgical Anesthesiology, 35(4), 394-405.
9. Cavuoto, K. M., Javitt, M., & Chang, T. C. (2019). Neurodevelopmental effects of general anesthesia on the pediatric patient. Journal of Pediatric Ophthalmology & Strabismus, 56(6), 349-353.
10. Chiperi, L. E., Tecar, C., & Pop, R. S. (2026). Psychomotor Development in Pediatric Patients with Congenital Heart Defects Before Surgical Intervention: Findings from a Prospective Cross-Sectional Study. Medicina, 62(1), 156.
11. Colletti, G., Di Bartolomeo, M., Negrello, S., Geronemus, R. G., Cohen, B., Chiarini, L., Anesi, A., Femino, R., Mariotti, I., & Levitin, G. M. (2023). Multiple general anesthetics in children: a systematic review of their effect on neurodevelopment. Journal of personalized medicine, 13(5), 867.
12. Dalamagka, M. I. (2026). Neuro and Radiant oncology and anesthesia considerations.

13. de Sonnaville, E. S., Oosterlaan, J., Ghiassi, S. A., van Leijden, O., van Ewijk, H., Knoester, H., van Woensel, J. B., & Königs, M. (2023). Long-term neurocognitive outcomes after pediatric intensive care: Exploring the role of drug exposure. Pediatric Research, 94(2), 603-610.
14. Del Pizzo, J., Olbrecht, V. A., & Boriosi, J. (2026). Long-Term Effects of Pediatric Procedural Sedation: Neurotoxicity and Neurocognitive Outcomes. Pediatric Annals, 55(1), e36-e40.
15. Feng, Y.-P., Yang, T.-S., Chung, C.-H., Chien, W.-C., & Wong, C.-S. (2020). Early childhood general anesthesia exposure associated with later developmental delay: a national population-based cohort study. PLoS One, 15(9), e0238289.
16. Fernando, A., Perera, R., Jayawardane, M., & Saavedra, R. (2023). Antifungal effect of Aloe barbadensis Miller gel extract on Candida albicans: Development of an eco-friendly herbal antifungal finish on cotton fabric for medical application. Authorea Preprints.
17. Fernando, A., Perera, R., Jayawardane, M. M. M., & Saavedra, R. (2024). Antifungal effect of Aloe barbadensis Miller gel extract on Candida albicans: Development of an eco-friendly herbal antifungal finish on cotton fabric for medical application. Discover Applied Sciences, 6(1), 19.
18. Grabowski, J., Goldin, A., Arthur, L. G., Beres, A. L., Guner, Y. S., Hu, Y.-Y., Kawaguchi, A. L., Kelley-Quon, L. I., McAteer, J. P., & Miniati, D. (2021). The effects of early anesthesia on neurodevelopment: A systematic review. Journal of Pediatric Surgery, 56(5), 851-861.
19. Ing, C., Jackson, W. M., Zaccariello, M. J., Goldberg, T. E., McCann, M.-E., Grobler, A., Davidson, A., Sun, L., Li, G., & Warner, D. O. (2021). Prospectively assessed neurodevelopmental outcomes in studies of anaesthetic neurotoxicity in children: a systematic review and meta-analysis. British journal of anaesthesia, 126(2), 433-444.
20. Ing, C., Landau, R., DeStephano, D., Miles, C. H., von Ungern-Sternberg, B. S., Li, G., & Whitehouse, A. J. (2021). Prenatal exposure to general anesthesia and childhood behavioral deficit. Anesthesia & Analgesia, 133(3), 595-605.
21. Kamat, P. P., Kudchadkar, S. R., & Simon, H. K. (2019). Sedative and anesthetic neurotoxicity in infants and young children: not just an operating room concern. The Journal of Pediatrics, 204, 285-290.
22. Keunen, K., Sperna Weiland, N. H., de Bakker, B. S., de Vries, L. S., & Stevens, M. F. (2022). Impact of surgery and anesthesia during early brain development: a perfect storm. Pediatric Anesthesia, 32(6), 697-705.
23. Lao, H.-C., Huang, C.-W., Wang, S.-H., Su, Y.-L., Chang, C.-H., Liao, C.-Y., Wu, J.-C., Lin, Y.-C., & Tsai, J.-W. (2026). Dexmedetomidine Mitigates Sevoflurane-Induced Neurodevelopmental Effects in Paediatric Anaesthesia: A Meta-Analysis and Preclinical Study. Journal of Neuroimmune Pharmacology, 21(1), 5.
24. Li, Z., Pan, X., Fu, R., Zhu, Y., Li, S., Ma, L., Chai, J., & Zheng, H. (2025). Long-term impact of sevoflurane exposure on behavioural and neurocognitive outcomes in preschool children: protocol for a prospective cohort study. BMJ open, 15(6), e098951.
25. Liu, X., Ji, J., & Zhao, G.-Q. (2020). General anesthesia affecting the developing brain: evidence from animal to clinical research. Journal of anesthesia, 34(5), 765-772.
26. Loepke, A. W., & Soriano, S. G. (2020). Impact of pediatric surgery and anesthesia on brain development. Gregory's Pediatric Anesthesia, 1151-1181.
27. McCann, M. E., De Graaff, J. C., Dorris, L., Disma, N., Withington, D., Bell, G., Grobler, A., Stargatt, R., Hunt, R. W., & Sheppard, S. J. (2019). Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial. The Lancet, 393(10172), 664-677.
28. McCann, M. E., & Soriano, S. G. (2019). Does general anesthesia affect neurodevelopment in infants and children? Bmj, 367.
29. Partanen, M., Anghelescu, D., Hall, L., Schreiber, J., Rossi, M., Gajjar, A., & Jacola, L. (2021). Longitudinal associations between exposure to anesthesia and neurocognitive functioning in pediatric medulloblastoma. European Journal of Cancer, 148, 103-111.
30. Reighard, C., Junaid, S., Jackson, W. M., Arif, A., Waddington, H., Whitehouse, A. J., & Ing, C. (2022). Anesthetic exposure during childhood and neurodevelopmental outcomes: a systematic review and meta-analysis. JAMA network open, 5(6), e2217427-e2217427.
31. Shah, R. (2019). Anesthesia exposure in the young child and long-term cognition: an integrated review. AANA journal, 87(3), 231-241.
32. Soriano, S. G., & McCann, M. E. (2020). Is anesthesia bad for the brain? Current knowledge on the impact of anesthetics on the developing brain. Anesthesiology Clinics, 38(3), 477-492.
33. Turcas, A., Boterberg, T., Frykholm, P., Gaze, M., Hendriks, M., Jouglar, E., Kostense, Z., Maduro, J., Mondardini, M. C., & Naik, V. (2026). Anesthesia in Pediatric Radiotherapy: A Systematic Literature Review by the SIOP Europe Working Group on Pediatric Anesthesia in Radiation Therapy. Pediatric Blood & Cancer, e70090.
34. Turner, A. D., Sullivan, T., Drury, K., Hall, T. A., Williams, C. N., Guilliams, K. P., Murphy,

S., & Iqbal O'Meara, A. (2021). Cognitive dysfunction after analgesia and sedation: out of the operating room and into the pediatric intensive care unit. Frontiers in Behavioral Neuroscience, 15, 713668.

35. Tynkkynen, J. (2025). Consequences of general anesthesia in infancy on behaviour and brain structures.
36. Useinovic, N., & Jevtovic-Todorovic, V. (2023). Controversies in anesthesia-induced developmental neurotoxicity. Best Practice & Research Clinical Anaesthesiology, 37(1), 28-39.
37. Walkden, G. J., Pickering, A. E., & Gill, H. (2019). Assessing long-term neurodevelopmental outcome following general anesthesia in early childhood: challenges and opportunities. Anesthesia & Analgesia, 128(4), 681-694.
38. Walsh, B. H., Paul, R. A., Inder, T. E., Shimony, J. S., Smyser, C. D., & Rogers, C. E. (2021). Surgery requiring general anesthesia in preterm infants is associated with altered brain volumes at term equivalent age and neurodevelopmental impairment. Pediatric Research, 89(5), 1200-1207.
39. Wu, L., Zhao, H., Weng, H., & Ma, D. (2019). Lasting effects of general anesthetics on the brain in the young and elderly: "mixed picture" of neurotoxicity, neuroprotection and cognitive impairment. Journal of Anesthesia, 33(2), 321-335.
40. Xiao, A., Feng, Y., Yu, S., Xu, C., Chen, J., Wang, T., & Xiao, W. (2022). General anesthesia in children and long-term neurodevelopmental deficits: A systematic review. Frontiers in Molecular Neuroscience, 15, 972025.
41. Xin, A., Grobler, A., Bell, G., De Graaff, J. C., Dorris, L., Disma, N., McCann, M. E., Withington, D. E., & Davidson, A. J. (2025). Neurodevelopmental outcomes after multiple general anesthetic exposures before 5 years of age: A cohort study. Anesthesiology, 142(2), 308-319.
42. Xu, J., Wang, F., Gao, Y., Qi, C., Chen, T., & Yan, J. (2025). The relationship between early exposure to general anesthesia and neurobehavioral deficits. Developmental Neuroscience, 47(5), 383-399.
43. Yang, Y.-L., Wang, L.-J., Chang, J.-C., Ho, S.-C., & Kuo, H.-C. (2021). A national population cohort study showed that exposure to general anesthesia in early childhood is associated with an increased risk of developmental delay. Children, 8(10), 840.

