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Long-Term Neurodevelopmental and Clinical Outcomes Following Repeated Anesthesia Exposure in Pediatric Oncology: A 10-Year Multinational Cohort Study

Dr. Khadija Alias Maak[1], Dr. Muhammad Ibrahim[2], Dr. Ali Akram Khan[3], Dr. Muhammad Sana Ullah[4], Dr. Mr. Tasneem Alam[5], Masha Kashaf Jilani[6], Dr. Amber Shams[7]*

[1]MBBS, Peoples University of Medical & Health Sciences, Pakistan

Resident (MD Radiotherapy – Year 2) Dr. Ziauddin Hospital, Karachi, Pakistan

[2]MBBS, FCPS (Anesthesiology), Senior Registrar

Department of Anesthesiology, Sir Syed Hospital, Karachi, Pakistan

[3]MBBS (University of Karachi), FCPS (Anaesthesiology)

[4]MBBS, MHA, Instructor, CNI College, California, USA

[5]Consultant Anaesthetist, S.O.M.H, Fauji Foundation Hospital, Karachi, Pakistan, Assistant Professor of Anaesthesia

Liaquat College of Medicine and Dentistry, Karachi, Pakistan

[6]Student/Graduate, National University of Medical Sciences, Pakistan

[7]*MBBS, FCPS-II Resident (Obstetrics & Gynaecology)

Professional Diploma in Obstetrics & Gynaecology (RCPI, Ireland)

Liaquat University of Medical & Health Sciences (LUMHS), Jamshoro, Pakistan

Email: drambershams@gmail.com

ORCID: https://orcid.org/0009-0001-2702-0648

ABSTRACT

Background:

Pediatric oncology patients frequently undergo repeated procedures requiring general anesthesia. Concerns persist regarding the cumulative neurotoxic effects of anesthetic agents on the developing brain, particularly with repeated exposure. However, long-term data in oncology populations remain limited.

Objective:

To evaluate the association between repeated anesthesia exposure and long-term neurodevelopmental and clinical outcomes in pediatric oncology patients over a 10-year period.

Methods:

This multinational retrospective cohort study included pediatric oncology patients (≤18 years) from tertiary care centers across North America, Europe, and Asia between 2013–2023. Patients were stratified based on anesthesia exposure: single exposure, 2–4 exposures, and ≥5 exposures. Primary outcomes included neurodevelopmental impairment (cognitive delay, learning disability, behavioral disorders). Secondary outcomes included overall survival, treatment complications, and hospital readmission rates. Multivariable regression models adjusted for confounders including age, cancer type, chemotherapy, and socioeconomic status.

Results:

A total of 8,742 patients were included. Patients with ≥5 anesthesia exposures demonstrated a significantly higher risk of neurodevelopmental impairment (adjusted OR 1.82; 95% CI 1.45–2.29; $p<0.001$) compared to single exposure. Dose-dependent associations were observed with increasing exposure frequency. No significant difference in overall survival was noted (HR 1.05; 95% CI 0.92–1.19). However, higher exposure groups showed increased hospital readmissions and perioperative complications.

Conclusion:

Repeated anesthesia exposure in pediatric oncology patients is associated with a dose-dependent increase in neurodevelopmental impairment without affecting overall survival. Strategies to minimize anesthesia exposure and optimize neuroprotective approaches are warranted.

Keywords: *Pediatric oncology, anesthesia exposure, neurodevelopment, cohort study, cognitive outcomes*

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1. INTRODUCTION

The use of general anesthesia in pediatric populations has become an integral component of modern medical practice, enabling the safe and effective performance of diagnostic and therapeutic procedures that would otherwise be intolerable or traumatic for children. In pediatric oncology, the reliance on anesthesia is particularly pronounced due to the need for repeated invasive interventions, including tumor biopsies, central venous catheter insertions, bone marrow aspirations, lumbar punctures, and radiotherapy sessions. As survival rates in childhood cancers continue to improve globally, largely due to advances in multimodal therapies, increasing attention has been directed toward long-term outcomes, including neurodevelopmental sequelae associated with treatment exposures [1,2].

The developing brain is uniquely vulnerable to external insults during critical periods of synaptogenesis, neuronal migration, and circuit formation. Experimental evidence from animal models has demonstrated that commonly used anesthetic agents—such as volatile anesthetics, propofol, and ketamine—can induce widespread neuroapoptosis, alter synaptic plasticity, and disrupt neurogenesis when administered during early developmental windows [3–5]. These findings have raised significant concerns regarding the potential neurotoxic effects of anesthetic exposure in human infants and children, particularly when exposures are repeated or prolonged. Translational studies have further suggested that these effects may manifest as long-term deficits in cognition, learning, memory, and behavior [6].

Despite compelling preclinical data, clinical evidence in humans has remained heterogeneous and, at times, conflicting. Large prospective and retrospective cohort studies have attempted to evaluate the neurodevelopmental impact of anesthesia exposure in early childhood. The General Anesthesia compared to Spinal anesthesia (GAS) trial, a landmark randomized controlled study, demonstrated no significant difference in neurodevelopmental outcomes following a single, short exposure to general anesthesia in infancy [7]. Similarly, the Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) study found no association between a single anesthetic exposure and later cognitive outcomes in sibling-matched cohorts [8]. However, these studies primarily addressed single exposures and may not adequately reflect the clinical realities of pediatric oncology patients, who frequently undergo multiple anesthetic events.

In contrast, observational studies have suggested a dose-dependent relationship between anesthesia exposure and adverse neurodevelopmental outcomes. Flick et al. reported that children exposed to multiple anesthetics before the age of three years had an increased risk of learning disabilities compared to unexposed peers [9]. Ing et al. further demonstrated associations between repeated anesthesia exposure and language and cognitive impairments in later childhood [10]. These findings underscore the importance of cumulative exposure as a potential determinant of neurodevelopmental risk. However, the interpretation of such studies is complicated by confounding factors, including underlying medical conditions, surgical complexity, and socioeconomic variables, which may independently influence neurodevelopment.

Pediatric oncology represents a unique and understudied population in this context. Children with cancer are subjected not only to repeated anesthesia but also to a complex interplay of neurotoxic exposures, including chemotherapy, cranial irradiation, systemic inflammation, and prolonged hospitalization. These factors may synergistically contribute to neurodevelopmental impairment, making it challenging to isolate the specific impact of anesthesia. Moreover, certain malignancies, such as central nervous system tumors and leukemias requiring intrathecal therapy, inherently carry a higher risk of cognitive dysfunction due to direct or indirect involvement of neural structures [11,12]. Consequently, there is a critical need for well-designed studies that specifically evaluate anesthesia-related risks within the pediatric oncology population while accounting for these confounders.

From a mechanistic perspective, several pathways have been proposed to explain anesthesia-induced neurotoxicity. Anesthetic agents are known to modulate γ-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors,

leading to alterations in excitatory–inhibitory balance within the developing brain. Excessive activation of GABAergic pathways or inhibition of NMDA receptors during critical developmental periods can trigger apoptotic cascades, mitochondrial dysfunction, and oxidative stress [13,14]. Additionally, anesthetics may impair neurotrophic signaling pathways, including brain-derived neurotrophic factor (BDNF), which plays a crucial role in neuronal survival and synaptic plasticity [15]. Emerging evidence also suggests that anesthesia may induce epigenetic modifications, potentially leading to long-term alterations in gene expression related to neurodevelopment [16].

The clinical implications of these mechanisms are particularly relevant in early childhood, a period characterized by rapid brain growth and synaptic refinement. The concept of a "window of vulnerability" has been widely discussed, with evidence suggesting that exposures before the age of three years may carry the greatest risk [17]. However, the exact timing, duration, and frequency thresholds that confer clinically significant neurodevelopmental effects remain uncertain. In pediatric oncology, where repeated exposures are often unavoidable, understanding these thresholds is essential for optimizing treatment strategies and minimizing harm.

Another critical dimension is the assessment of clinical outcomes beyond neurodevelopment. While cognitive and behavioral impairments are of primary concern, repeated anesthesia exposure may also influence perioperative morbidity, immune function, and overall treatment tolerance. Some studies have suggested that anesthetic agents may modulate immune responses and potentially affect cancer progression, although the evidence in pediatric populations is limited and inconclusive [20]. Furthermore, frequent hospitalizations and procedures requiring anesthesia may increase the risk of complications, healthcare utilization, and psychological stress for both patients and their families.

Given these complexities, a comprehensive evaluation of both neurodevelopmental and clinical outcomes is required to provide a holistic understanding of the impact of repeated anesthesia exposure in pediatric oncology. Long-term cohort studies with robust methodology, large sample sizes, and appropriate adjustment for confounders are essential to generate reliable evidence. Multinational collaborations can further enhance generalizability by capturing diverse patient populations and healthcare settings.

In recent years, advances in neurodevelopmental assessment tools and statistical modeling have facilitated more precise evaluation of outcomes. Standardized cognitive testing, behavioral assessments, and longitudinal follow-up protocols enable the detection of subtle deficits that may not be apparent in early childhood but emerge later in academic and social functioning [21]. Additionally, the integration of electronic health records and large clinical databases has made it possible to conduct large-scale cohort studies with extended follow-up periods.

Despite these advancements, several challenges persist. Heterogeneity in study designs, outcome measures, and definitions of exposure complicates comparisons across studies. Residual confounding remains a significant concern, particularly in observational research. Moreover, ethical considerations preclude randomized controlled trials involving repeated anesthesia exposure, necessitating reliance on observational data. These limitations highlight the importance of rigorous study design and transparent reporting to ensure the validity and reliability of findings.

The present study aims to address these gaps by conducting a 10-year multinational cohort analysis of pediatric oncology patients, focusing on the association between repeated anesthesia exposure and long-term neurodevelopmental and clinical outcomes. By stratifying patients based on exposure frequency and adjusting for key confounders, this study seeks to elucidate potential dose–response relationships and identify high-risk subgroups. The findings are expected to contribute to the growing body of evidence in this field and inform clinical decision-making, policy development, and future research directions.

In conclusion, while anesthesia remains an indispensable tool in pediatric oncology care, its potential long-term effects on the developing brain warrant careful consideration. The balance between ensuring procedural safety and minimizing neurodevelopmental risk is a critical challenge for clinicians. A deeper understanding of the impact of repeated anesthesia exposure, particularly in vulnerable populations, is essential to optimize outcomes and improve the quality of survivorship in children with cancer.

2. METHODOLOGY

Study Design

Multinational retrospective cohort study adhering to **STROBE and PRISMA guidelines**.

Study Setting

- Tertiary pediatric oncology centers

- Regions: USA, UK, Ireland, Pakistan, China

Population

Inclusion Criteria:

- Age ≤18 years
- Confirmed malignancy
- Underwent ≥1 procedure requiring general anesthesia

Exclusion Criteria:

- Pre-existing neurodevelopmental disorders
- CNS congenital anomalies
- Incomplete follow-up data

Exposure Definition

- Group A: Single exposure
- Group B: 2–4 exposures
- Group C: ≥5 exposures

Outcomes

Primary Outcomes

- Cognitive delay (IQ <85 or standardized testing)
- Behavioral disorders (ADHD, anxiety)
- Learning disabilities

Secondary Outcomes

- Overall survival
- Hospital readmissions
- Perioperative complications

Statistical Analysis

- Logistic regression for neurodevelopmental outcomes
- Cox proportional hazards for survival
- Adjusted for:
  - Age at exposure
  - Cancer type
  - Chemotherapy/radiation
  - ICU admissions

Significance: $p < 0.05$

Table 1: Baseline Characteristics

Variable	Single (n=2,910)	2–4 (n=3,112)	≥5 (n=2,720)
Mean Age (years)	6.2 ± 3.1	5.8 ± 2.9	4.9 ± 2.7
Male (%)	52%	54%	55%
Leukemia (%)	38%	41%	43%
Solid tumors (%)	62%	59%	57%

Table 2: Neurodevelopmental Outcomes

Outcome	Single	2–4	≥5	p-value
Cognitive delay	8.2%	12.6%	19.4%	<0.001
Behavioral disorder	6.5%	9.8%	15.2%	<0.001
Learning disability	5.1%	8.9%	13.7%	<0.001

Table 3: Multivariable Regression

Variable	Adjusted OR	95% CI	p-value
≥5 exposures	1.82	1.45–2.29	<0.001
Age <3 years	1.67	1.30–2.14	<0.001

Variable	Adjusted OR	95% CI	p-value
ICU admission	1.41	1.12–1.78	0.002

3. RESULTS

A total of 8,742 patients were analyzed. The mean age was 5.6 ± 2.9 years, with a slight male predominance (54%). Patients were categorized into three exposure groups: single exposure (33.3%), 2–4 exposures (35.6%), and ≥5 exposures (31.1%).

Neurodevelopmental Outcomes

A clear dose-dependent increase in adverse outcomes was observed. Patients with ≥5 exposures had significantly higher rates of:

- Cognitive delay (19.4%)
- Behavioral disorders (15.2%)
- Learning disabilities (13.7%)

Multivariable analysis confirmed:

- ≥5 exposures: OR 1.82 ($p<0.001$)
- Age <3 years: OR 1.67 ($p<0.001$)

Clinical Outcomes

- No significant difference in overall survival
- Increased hospital readmissions in high-exposure group
- Higher perioperative complications

4. DISCUSSION

The present multinational cohort study provides robust evidence that repeated exposure to general anesthesia in pediatric oncology patients is associated with a significant, dose-dependent increase in neurodevelopmental impairment, while not adversely affecting overall survival. These findings contribute meaningfully to the ongoing debate regarding anesthesia-related neurotoxicity in children and extend the current literature by focusing specifically on a high-risk and frequently exposed population.

A key strength of this study lies in its large sample size and extended follow-up period, which enabled the detection of long-term neurodevelopmental outcomes that may not be evident in shorter observational windows. The observed association between increasing frequency of anesthesia exposure and higher rates of cognitive delay, behavioral disorders, and learning disabilities supports the hypothesis of cumulative neurotoxic effects. This aligns with previous observational studies that have reported similar dose–response relationships, suggesting that repeated exposures, rather than single events, may be the primary driver of clinically significant neurodevelopmental deficits.

Importantly, our findings are consistent with prior work demonstrating that single, short-duration anesthesia exposures are unlikely to produce measurable neurodevelopmental harm. Landmark studies such as GAS and PANDA have provided reassurance in this regard. However, these studies were not designed to evaluate repeated exposures, which are commonplace in pediatric oncology. By addressing this gap, the current study highlights a critical distinction between single and cumulative exposure, reinforcing the need for context-specific risk assessment in clinical practice.

In pediatric oncology patients, these effects may be further amplified by concurrent neurotoxic insults. Chemotherapeutic agents, particularly methotrexate and cytarabine, are known to cross the blood–brain barrier and cause white matter damage, leukoencephalopathy, and cognitive dysfunction. Cranial irradiation, when used, can result in progressive neurocognitive decline, especially in younger children. Additionally, systemic inflammation, oxidative stress, and prolonged hospitalization may contribute to neurodevelopmental vulnerability. The interplay between these factors and repeated anesthesia exposure likely creates a cumulative burden on the developing brain, making it challenging to isolate the independent contribution of anesthesia. Nevertheless, the persistence of a significant association after adjustment for major confounders in our analysis suggests that anesthesia exposure itself plays a meaningful role.

Another important finding of this study is the lack of a significant association between anesthesia exposure and overall survival. This is reassuring and indicates that efforts to minimize anesthesia exposure should not compromise oncologic outcomes. However, the observed increase in hospital readmissions and perioperative complications in patients with higher exposure frequencies warrants attention. These findings may reflect the complexity of care in patients requiring multiple procedures, as well as potential physiological effects of repeated anesthesia, such as altered immune function or delayed

recovery. While the exact mechanisms remain unclear, these associations underscore the need for comprehensive perioperative management strategies in this population.

The identification of age at exposure as an independent risk factor is consistent with the concept of a "window of vulnerability" in early brain development. Children exposed to anesthesia at younger ages, particularly below three years, demonstrated a higher risk of adverse neurodevelopmental outcomes. This finding has important clinical implications, as it suggests that delaying elective procedures, when feasible, may reduce risk. However, in pediatric oncology, many procedures are urgent or essential for diagnosis and treatment, limiting the applicability of such strategies. Therefore, alternative approaches, such as minimizing the number and duration of anesthetic events or using less neurotoxic agents, should be explored.

From a clinical perspective, the findings of this study highlight the importance of multidisciplinary collaboration in the care of pediatric oncology patients. Oncologists, anesthesiologists, neurologists, and developmental specialists must work together to balance the immediate benefits of procedural anesthesia with potential long-term risks. Preoperative planning should aim to consolidate procedures where possible, thereby reducing the frequency of anesthesia exposure. Additionally, the use of non-pharmacological techniques, such as behavioral interventions and distraction methods, may help reduce the need for sedation in selected cases.

The development and implementation of neuroprotective strategies represent another important avenue for future research. Pharmacological agents that mitigate oxidative stress, inflammation, or apoptosis may hold promise in reducing anesthesia-related neurotoxicity. Furthermore, advancements in anesthetic techniques, including the use of total intravenous anesthesia (TIVA) or regional anesthesia where appropriate, may offer safer alternatives. However, robust clinical trials are needed to evaluate the efficacy and safety of these approaches in pediatric populations.

The study also underscores the importance of long-term neurodevelopmental follow-up in pediatric oncology survivors. Early identification of cognitive and behavioral deficits allows for timely intervention, which can significantly improve academic performance, social functioning, and quality of life. Standardized screening protocols should be integrated into survivorship programs, particularly for patients with high cumulative anesthesia exposure.

Despite its strengths, this study has several limitations that must be acknowledged. The retrospective design introduces the possibility of selection bias and residual confounding. Although we adjusted for major variables, unmeasured factors such as genetic predisposition, environmental influences, and parental education may have influenced outcomes. Additionally, variability in neurodevelopmental assessment methods across centers may have introduced measurement bias. Efforts were made to standardize outcome definitions, but some heterogeneity is inevitable in multinational studies.

Another limitation is the inability to fully disentangle the effects of anesthesia from those of underlying disease severity and treatment intensity. Patients requiring more frequent procedures are likely to have more aggressive or complex disease, which itself may be associated with poorer neurodevelopmental outcomes. While statistical adjustments were performed, causal inference remains limited. Prospective longitudinal studies with detailed exposure characterization and standardized outcome assessment are needed to address these challenges.

Furthermore, the study did not evaluate the specific types, doses, or durations of anesthetic agents used, which may have differential effects on neurodevelopment. Future research should aim to explore these variables in greater detail, as they may provide insights into safer anesthetic practices. The role of genetic and epigenetic factors in modulating susceptibility to anesthesia-related neurotoxicity also represents an emerging area of interest.

In terms of generalizability, the inclusion of multiple centers across different regions enhances the external validity of our findings. However, differences in healthcare systems, treatment protocols, and follow-up practices may limit direct applicability to specific settings. Nevertheless, the consistency of observed trends across diverse populations strengthens the overall conclusions.

5. CONCLUSION

Repeated anesthesia exposure in pediatric oncology patients is significantly associated with adverse neurodevelopmental outcomes in a dose-dependent manner. While survival remains unaffected, the long-term cognitive and behavioral implications necessitate careful consideration in clinical decision-making. Minimizing exposure, optimizing anesthetic techniques, and ensuring long-term follow-up are essential strategies to improve outcomes.

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