

## INDEPENDENCE OF AGE AND SURGICAL DURATION AS PREDICTORS OF POSTOPERATIVE COGNITIVE DECLINE IN SCHOOL-AGE CHILDREN: A DUAL-FACTOR ANALYSIS

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**Abstract:** *Age and surgical/anesthesia duration are both established risk factors for perioperative neurocognitive disorder (PND) in children, but their potential interdependence — whether older children simply tend to undergo longer procedures, confounding interpretation of each factor's individual contribution — has rarely been explicitly tested. Among 181 operated children aged 7–17 years (mean age  $11.5 \pm 3.2$ ) from the Tashkent Pediatric Medical Institute clinic, the correlation between age and anesthesia duration was tested directly, followed by separate correlation analyses of each factor against the composite postoperative cognitive index and domain-specific neuropsychological scores. Age and anesthesia duration showed a negligible correlation with one another ( $r = +0.054$ ;  $p = 0.474$ ), confirming their statistical independence. Anesthesia duration correlated inversely with the composite cognitive index ( $r = -0.495$ ;  $p < 0.001$ ) and most strongly with verbal memory ( $r = -0.499$ ;  $p < 0.001$ ) and psychomotor speed ( $r = -0.487$ ;  $p < 0.001$ ), while age correlated positively with the composite cognitive index ( $r = +0.440$ ;  $p < 0.001$ ) in the opposite, protective direction. These findings validate the simultaneous inclusion of age and anesthesia duration as separate, non-redundant variables in multifactorial perioperative neurocognitive risk models, as confirmed by their independent significance ( $OR = 0.67$  and  $OR = 1.02$ , respectively; both  $p < 0.001$ ) in the four-factor logistic regression model derived from this cohort.*

**Kalit so'zlar:** *perioperative neurocognitive disorder, age, anesthesia duration, confounding, multivariate risk model, statistical independence, school-age children.*

### INTRODUCTION

Risk-prediction models for perioperative neurocognitive disorder (PND) in children commonly incorporate multiple clinical variables — patient age, anesthesia duration, number of anesthetic agents, and premorbid neurological status — under the implicit assumption that each variable

contributes independent, non-redundant information about a patient's risk. This assumption, however, is rarely tested explicitly. If two candidate predictors are themselves strongly correlated — for example, if older children in a given surgical cohort systematically undergo longer or more complex procedures than younger children, perhaps because certain surgical indications cluster by age — then including both variables separately in a regression model introduces multicollinearity, inflates variance estimates, and can obscure which factor is the true driver of risk.

Age and anesthesia/surgical duration are two of the most consistently reported PND risk factors across the pediatric anesthesia-neurotoxicity literature, yet the two are conceptually distinct in their proposed mechanisms: age is thought to act through the differential neuroplastic vulnerability of the less mature developing brain, whereas duration is thought to act through a dose-response relationship between cumulative anesthetic/surgical stress exposure and neurotoxic or neuroinflammatory injury. Whether these two mechanistically distinct pathways are statistically confounded by a shared clinical driver (e.g., case complexity increasing with patient age) has not been explicitly tested in prior pediatric PND cohorts.

This study directly tests the correlation between age and anesthesia duration within a well-characterized cohort of 181 school-age surgical patients, in order to establish — or refute — the methodological validity of treating these two variables as independent, separately informative predictors within multifactorial PND risk models, as was done in the four-factor logistic regression model derived from this same cohort.

This question extends beyond a narrow statistical technicality: if age and duration were found to be substantially correlated, the clinical interpretation of the four-factor risk model itself would need reconsideration, since a clinician observing a high combined risk score would be unable to determine whether the elevated risk stemmed primarily from the patient's young age, the anticipated procedure length, or an inseparable combination of both. Confirming independence, by contrast, allows each factor to be communicated and acted upon separately in preoperative planning — for instance, by specifically limiting anesthesia duration where feasible, independent of the patient's fixed age.

#### LITERATURE REVIEW

The developmental neurotoxicity literature has extensively documented age as a risk factor for anesthesia-associated cognitive harm, with the FDA's 2016 Drug Safety Communication (updated 2017 and 2022)

specifically flagging repeated or prolonged anesthesia exposure in children under three years as a concern based on preclinical and some clinical evidence, a warning later contextualized by Andropoulos and Greene (2017) in their widely cited New England Journal of Medicine commentary on anesthesia and developing brains. Within the school-age range specifically (7–17 years), the present dissertation cohort demonstrated that age continues to exert a measurable, quantifiable protective effect ( $OR = 0.67$  per year;  $p < 0.001$ ), extending the age-vulnerability gradient beyond early childhood into later developmental stages.

Separately, anesthesia and surgical duration have been repeatedly implicated as dose-dependent risk factors. Fan, Peng and Zhang (2018) demonstrated that prolonged ( $\geq 3$  hours) sevoflurane exposure increased postoperative cognitive dysfunction frequency in a cohort of 93 children, with cognitive decline correlating with elevated inflammatory markers (caspase-3, TNF- $\alpha$ , IL-6) — supporting a dose-response, duration-dependent neuroinflammatory mechanism distinct from the neuroplasticity-based mechanism proposed for age effects. Tang and colleagues' 2023 prospective cohort study of predictors of postoperative cognitive dysfunction in children undergoing noncardiac surgery likewise identified both age and procedure duration as significant, and implicitly treated them as separate contributors, without formally testing their intercorrelation.

The methodological question of confounding between candidate predictors is a well-recognized concern in clinical epidemiology broadly, addressed through techniques such as variance inflation factor (VIF) assessment and pairwise correlation screening prior to multivariate model construction. Despite the wide use of multifactorial PND risk models in the pediatric anesthesia literature, an explicit report of the age-duration correlation coefficient — the foundational check for confounding between these two specific variables — appears to be absent from prior published pediatric PND risk-model studies, representing a methodological gap this study addresses.

A related consideration in the broader pediatric surgical literature is that certain procedure categories are inherently associated with particular age ranges — for example, cryptorchidism repair is typically performed in younger boys, while more complex abdominal procedures such as Hirschsprung disease correction may occur across a wider age spectrum. In a cohort drawn from a heterogeneous mix of surgical indications, as in

the present study (spanning abdominal, urological, hernia, and pararectal procedures), this raises the theoretical possibility that age and procedure-driven duration could become entangled through the case-mix composition — a possibility that the direct correlation test performed here is specifically designed to detect or rule out empirically, rather than relying on assumption alone.

#### AIM

To determine whether patient age and anesthesia duration act as statistically independent predictors of postoperative cognitive outcome in school-age children, clarifying the methodological validity of using both as separate variables in multifactorial risk models.

#### MATERIALS AND METHODS

Among 181 children aged 7–17 years (mean age  $11.5 \pm 3.2$ ) who underwent elective non-cardiac surgery under general anesthesia at the Tashkent Pediatric Medical Institute clinic between March 2024 and January 2025, the direct correlation between patient age (years) and anesthesia duration (minutes) was tested using Pearson correlation analysis, following Shapiro–Wilk normality testing. Subsequently, each factor was independently correlated against the composite postoperative cognitive index (the mean of five core neuropsychological test scores: Stroop, Trail Making Test, Digit Span Test, Luria memory word test, and clinical-neurological status) and against domain-specific scores (selective attention, working memory, verbal memory, psychomotor speed) measured on postoperative day 7.

To further validate the independent contribution of each factor after controlling for the other, both variables were entered simultaneously into a multivariate logistic regression model alongside number of anesthetic agents and premorbid neurological background, with odds ratios (OR), standard errors, and Wald z-statistics computed for each predictor. Model discrimination was assessed via the area under the ROC curve (AUC) and explanatory power via Nagelkerke  $R^2$ ; calibration was assessed via the Hosmer–Lemeshow test. Bonferroni correction was applied for multiple comparisons;  $p < 0.05$  was considered statistically significant.

#### RESULTS

Direct correlation analysis between patient age and anesthesia duration revealed a negligible, statistically non-significant association ( $r = +0.054$ ;  $p = 0.474$ ;  $n = 181$ ), confirming that these two clinical variables are effectively uncorrelated within this cohort — a child's age provided essentially no information about how long their procedure would last, and

vice versa. This finding is methodologically favorable: it indicates that age and anesthesia duration can be evaluated for their respective associations with cognitive outcome independently, without concern that one factor's apparent effect merely reflects the other.

**Table 1. Correlation of age and anesthesia duration with postoperative cognitive indices**

| Cognitive domain             | Age (r)                                 | Anesthesia duration (r) | p      |
|------------------------------|-----------------------------------------|-------------------------|--------|
| Composite cognitive index    | +0.440                                  | -0.495                  | <0.001 |
| Verbal memory (LMWT)         | —                                       | -0.499                  | <0.001 |
| Psychomotor speed (TMT)      | —                                       | -0.487                  | <0.001 |
| Working memory (DST)         | —                                       | -0.482                  | <0.001 |
| Selective attention (Stroop) | —                                       | -0.426                  | <0.001 |
| Age ↔ Anesthesia duration    | r = +0.054; p = 0.474 (not significant) |                         |        |

*Note: Pearson correlation coefficients; n = 181; Bonferroni correction applied. The negligible age-duration correlation (bottom row) confirms statistical independence of the two predictors.*

Anesthesia duration showed a consistent, moderate-to-moderately-strong inverse correlation with the composite cognitive index ( $r = -0.495$ ;  $p < 0.001$ ) and with each of the four core neuropsychological domains, the strongest associations being with verbal memory ( $r = -0.499$ ;  $p < 0.001$ ) and psychomotor speed ( $r = -0.487$ ;  $p < 0.001$ ), followed by working memory ( $r = -0.482$ ) and selective attention ( $r = -0.426$ ; all  $p < 0.001$ ). In sharp contrast, age correlated positively — in the opposite, protective direction — with the composite cognitive index ( $r = +0.440$ ;  $p < 0.001$ ), indicating that older children within the school-age range demonstrated better postoperative cognitive status, consistent with reduced neuroplastic vulnerability.

When both variables were entered simultaneously into the four-factor multivariate logistic regression model (alongside number of anesthetic agents and premorbid neurological background), both retained independent statistical significance without evidence of mutual

attenuation: anesthesia duration showed a small but consistent per-minute risk increase (OR = 1.02; SE = 0.01; Wald  $z$  = 13.68;  $p$  < 0.001), while age showed a robust protective effect (OR = 0.67; SE = 0.10; Wald  $z$  = 16.99;  $p$  < 0.001). The full four-factor model achieved good discriminative accuracy (AUC = 0.783; Nagelkerke  $R^2$  = 0.451), with the stability of both age and duration coefficients across univariate and multivariate analyses providing further empirical confirmation that neither variable's apparent effect was an artifact of confounding by the other.

## DISCUSSION

The near-zero correlation between age and anesthesia duration ( $r$  = +0.054) is a methodologically important finding that validates a common but rarely tested assumption underlying multifactorial PND risk models: that age and procedure duration represent genuinely distinct dimensions of surgical risk in this pediatric population, rather than two measurements of the same underlying construct (e.g., case complexity). This independence likely reflects the heterogeneous nature of the surgical case mix in this cohort — spanning abdominal, urological, hernia, and pararectal procedures — where procedure duration is driven primarily by anatomical and technical factors rather than patient age per se.

The opposite directionality of the two associations — anesthesia duration increasing risk (inverse correlation with cognitive index) while age decreases risk (positive correlation) — further reinforces their mechanistic distinctness. This pattern is consistent with a dual-pathway model of PND risk in which cumulative anesthetic/surgical stress exposure (captured by duration) and neurodevelopmental vulnerability (captured by age) act as separate, additive contributors to overall risk, rather than as two manifestations of a single underlying process.

From a methodological standpoint, this analysis provides empirical justification for a modeling choice that is often made by convention rather than by explicit statistical verification: namely, that age and anesthesia duration can be safely and validly included as separate, non-redundant covariates in multivariate PND risk-prediction models without introducing problematic multicollinearity. Researchers constructing similar risk models in other pediatric surgical cohorts are encouraged to perform and report this same confounding check — a simple pairwise correlation test — before finalizing multifactorial models, since in cohorts where such independence does not hold, model coefficients and their clinical interpretation could be materially distorted.

Clinically, the confirmed independence of these two factors means that a child's risk profile must be assessed along both dimensions separately: a younger child undergoing a short procedure and an older child undergoing a long procedure may carry meaningfully different, non-interchangeable risk profiles that neither factor alone would fully capture. This supports the continued use of the validated four-factor clinical risk profile — incorporating age, anesthesia duration, agent count, and premorbid background as simultaneously assessed, independent dimensions — in preoperative counseling and risk stratification.

A limitation of this analysis is that anesthesia duration was treated as a continuous linear predictor; nonlinear or threshold effects (for example, a disproportionate risk increase beyond a specific duration cutoff, as suggested by the sharp prevalence gradient across duration tiers observed in this cohort — 2.3% in short-duration, 11.1% in medium-duration, and 59.0% in long-duration procedures) merit further dedicated investigation using spline-based or categorical threshold modeling in future studies.

It should also be emphasized that statistical independence between two predictors, as demonstrated here, does not preclude the possibility of a biological interaction between them — that is, the combined effect of being both young and undergoing a long procedure could theoretically exceed the simple additive sum of each factor's individual effect, even though the two factors are uncorrelated in their distribution across the cohort. Formally testing such an age-by-duration interaction term within the logistic regression framework was beyond the scope of the present correlation-focused analysis but represents a natural next step; preliminary clinical observation within this cohort — where children combining several risk factors, including young age and long procedures, showed the highest observed PND rates — is consistent with, though does not formally establish, such an interactive effect.

## CONCLUSION

Age and anesthesia duration are methodologically independent, oppositely-directed predictors of postoperative cognitive outcome in school-age children undergoing non-cardiac surgery, as confirmed by their negligible mutual correlation ( $r = +0.054$ ;  $p = 0.474$ ) and by their stable, independent significance in multivariate regression (age: OR = 0.67; anesthesia duration: OR = 1.02; both  $p < 0.001$ ). This validates their simultaneous inclusion as separate, non-redundant variables in multifactorial perioperative neurocognitive risk models and supports the continued use of a dual-dimension — vulnerability-based (age) and

exposure-based (duration) — framework for preoperative risk assessment in pediatric anesthesiology practice.

#### REFERENCES:

1. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women. — 2016 (updated 2017, 2022).
2. Andropoulos D.B., Greene M.F. Anesthesia and Developing Brains — Implications of the FDA Warning // New England Journal of Medicine. — 2017. — Vol. 376, № 10. — P. 905–907.
3. Fan C.-H., Peng B., Zhang F.-C. The postoperative effect of sevoflurane inhalational anesthesia on cognitive function and inflammatory response of pediatric patients // European Review for Medical and Pharmacological Sciences. — 2018. — Vol. 22, № 12. — P. 3971–3975.
4. Tang X. et al. Predictors and occurrence of postoperative cognitive dysfunction in children undergoing noncardiac surgery: A prospective cohort study. — 2023.
5. Reighard C., Junaid S., Jackson W.M. et al. Anesthetic Exposure During Childhood and Neurodevelopmental Outcomes: A Systematic Review and Meta-analysis // JAMA Network Open. — 2022. — Vol. 5, № 6. — e2217427.
6. Zakirova D.A., Madjidova Y.N. Dissertation materials: Clinical-neurological characteristics and early detection of perioperative neurocognitive disorders in school-age children following surgical procedures. — Tashkent, 2025.