Research Square

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Association Between Postoperative Delirium and Salivary Cortisol Levels in Children: A Pilot Study

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Abstract

Objective

This study explored salivary cortisol as an objective biomarker for pediatric postoperative delirium (POD) and analyzed its correlation with PAED scale ratings.

Methods

Pediatric patients under general anesthesia were enrolled. Postoperatively, they were divided into delirium and control groups via PAED assessment. Saliva samples were collected within 30 minutes postoperatively, and cortisol levels were measured by UPLC-MS/MS. Multivariate logistic regression identified independent risk factors for POD.

Results

Salivary cortisol levels were significantly higher in the delirium group ($P < 0.05$). Cortisol independently predicted POD (OR = 39.111, 95% CI: 1.528–1001.154). The combined model of PAED scores and cortisol showed excellent diagnostic efficacy (AUC = 0.904).

Conclusion

Salivary cortisol is a valid objective biomarker for pediatric POD. Combining cortisol testing with PAED assessment enables accurate POD detection and supports targeted clinical interventions.

1. Introduction

Postoperative delirium (POD) is an acute neuropsychiatric condition triggered by perioperative stress. It affects both older adults and children, with young patients—especially those emerging from general anesthesia—being particularly vulnerable. Reported POD rates in children range widely from 2% to 80%. Much of this variability stems from inconsistent diagnostic criteria and the lack of objective testing methods. Clinically, POD presents as hyperactive, hypoactive, or mixed subtypes, making quick, reliable diagnosis challenging. POD also raises risks for adverse events, longer hospital stays, and higher mortality in pediatric populations.

The PAED scale is currently the clinical standard for assessing emergence delirium in children. Still, it relies on subjective behavioral observations, which can vary between observers and depend on how well a child cooperates. This limitation creates a real need for objective tools to complement clinical assessment. POD arises from two key factors: inherent vulnerabilities in the child, such as immature physiology, and perioperative stressors, including anesthesia exposure and surgical trauma. Growing

evidence points to hypothalamic-pituitary-adrenal (HPA) axis dysregulation as a critical link between surgical stress and neurocognitive problems. Few studies have translated this theoretical connection into practical, clinically applicable biomarker tests. Our work combines the validated PAED scale with salivary cortisol—a non-invasive biomarker sensitive to stress.

Our main goal was to build a dual-method evaluation framework. By measuring how cortisol changes relate to PAED scores, we aimed to validate a biochemical basis for objective POD diagnosis in children.

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2. Materials and Methods

2.1 Study Population

We recruited pediatric patients aged 1 to 18 years undergoing surgery with propofol-fentanyl anesthesia at a tertiary hospital in Zhejiang Province. Enrollment ran from January 2024 to March 2025. Written informed consent was obtained from all pediatric patients' legal guardians, and verbal assent was acquired from cognitively competent children. We excluded those with pre-existing delirium, unstable hemodynamics, or participation in other trials that could confound results.

2.2 PAED Assessment and Stratification

The PAED scale was used for assessing POD right after surgery. The scale includes five items—such as eye contact and purposeful behavior—each scored from 0 to 4. We reverse-scored items 1 through 3. A total score of 10 or higher defined delirium.

2.3 Saliva Collection and Assay

The unstimulated whole saliva was collected by passive drool into sterile tubes (about 1 mL/min) between 8:00 and 10:00 a.m., exactly 10 minutes after admission to the post-anesthesia care unit (PACU). Children fasted for at least 30 minutes before sampling to reduce variability. Samples were stored at −80°C until analysis.

For measurement, we extracted 200 μL saliva with 1 mL ethyl acetate, dried it under nitrogen gas, and reconstituted it in 100 μL methanol. Chromatography used an Acquity BEH C18 column (1.8 μm, 2.1 × 50 mm) with a mobile phase of acetonitrile–0.1% formic acid (35:65) at 0.4 mL/min. Mass spectrometry used positive electrospray ionization with multiple reaction monitoring (ESI-MRM). Source settings included a nebulizer pressure of 45 psi and a desolvation temperature of 350°C.

2.4 Statistical Analysis

We presented continuous data as mean ± standard deviation (SD) for normally distributed variables or median with interquartile range (IQR) for non-normal data. Group comparisons used the t-test or Mann-Whitney U test. Categorical variables were analyzed with the chi-square test or Fisher's exact test. Variables with a univariate P-value less than 0.1 entered multivariate logistic regression. We used receiver

operating characteristic (ROC) curves to evaluate diagnostic performance and determined optimal cutoffs via the Youden index. All analyses were done in SPSS 26.0 (IBM Corp.).

3. Results

3.1 Baseline Characteristics

A total of 24 children were enrolled in this study. Nine (37.5%) met the PAED criteria for delirium. The two groups were comparable in terms of age, sex, weight, and surgical site (all P > 0.05; Table 1).

Table 1
Comparison of general baseline data between the two groups of children

Indicators		**Delirium group (n = 9)**	**Non-delirium group (n = 15)**	**T/Z/X^2**	**P**
Age (years) M (P25, P75)		7 (4,8)	7 (6,8)	-0.816	0.446
Body weight (kg), M (P25, P75)		24.5 (16.25,28.25)	23.5 (20,26)	-0.448	0.682
Operation duration (min) $\bar{x}\pm s$		18.78 ± 4.94	24.87 ± 8.37	1.976	0.061
Surgical site, n (%)	Tonsil combined with adenoid	5 (55.56)	11 (73.33)	0.412	
	Others	4 (44.44)	4 (26.67)		

3.2 Univariate and Multivariate Analysis

Univariate screening revealed significantly elevated salivary cortisol in the delirium cohort ($P < 0.05$; Table 2). Multivariate regression identified cortisol as an independent predictor (β = 3.666, OR = 39.111, 95% CI: 1.528–1001.154; $P < 0.05$), while operation duration lost significance (Table 3).

Table 2
Univariate analysis of influencing factors for postoperative delirium in children

Indicators		Delirium group (n = 9)	Non-delirium group (n = 15)	$T/Z/X^2$	P
Operation duration (min)		18.78 ± 4.94	24.87 ± 8.37	1.976	0.061
Anesthesia regimen	Predominantly sevoflurane combined with propofol (%)	7(77.78%)	15(100%)	0.130	
	Predominantly sevoflurane (%)	2(22.22%)	0(0%)		
Anesthesia duration (min)		37.56 ± 5.00	42.20 ± 11.86	1.332	0.198
Postoperative salivary cortisol concentration (μg/mL)		1.393(0.46955,2.30325)	0.0621(0.0448,0.4491)	-3.250	0.001

Table 3
Multivariate Logistic regression analysis of influencing factors for postoperative delirium in children

Independent variable	Regression coefficient	Standard Error (SE)	Wald	P-value	Odds Ratio (OR)	95% CI
Salivary cortisol levels after surgery	3.666	1.654	4.912	0.027	39.111	1.528-1001.154

3.3 Diagnostic Performance

We used ROC analysis to test how well salivary cortisol diagnoses pediatric POD, plotting sensitivity versus 1 − specificity. The AUC was 0.904 (95% CI: 0.786–1.000), which by usual cutoffs (≥ 0.9 excellent, 0.8–0.9 good, 0.7–0.8 moderate, < 0.7 poor) counts as excellent (Table 4, Fig. 1). The Youden index gave an optimal cutoff of 0.733 μg/mL, at which sensitivity reached 1.000 and specificity 0.733.

Table 4
Efficacy indicators of different diagnostic models for evaluating postoperative delirium in children

Diagnostic Model	AUC	95%CI	Sensitivity	Specificity	Optimal Diagnostic Threshold
Salivary cortisol	0.904	0.786-1.000	1	0.733	0.733

4. Discussion

4.1 Pathophysiology and Biomarker Rationale

Our POD rate of 37.5% aligns with typical clinical ranges of 2% to 80% reported elsewhere. Salivary cortisol emerged as an independent predictor of POD (OR ≈ 39), highlighting its key role in delirium development.

This nearly 40-fold increase in risk underscores how strongly acute stress affects the pediatric brain. Children's neuroendocrine systems are immature, so even routine surgical stress can trigger sharp cortisol spikes.

High cortisol levels may disrupt neurotransmitter balance (including acetylcholine and dopamine) and alter cerebral blood flow, contributing to delirium. Choosing saliva over blood avoids repeated needle sticks.

Saliva also reflects free, biologically active hormone levels better. Strict timing of sampling further reduces measurement error, supporting reliable results.

4.2 Integration with PAED Scale

The PAED scale offers standardized behavioral assessment for POD, but it depends heavily on observer judgment. Salivary cortisol addresses this gap with a measurable physiological marker. Notably, cortisol in our cohort had perfect sensitivity (1.000), meaning it could signal risk even before obvious behavioral changes appear on the PAED scale. We did not formally build a combined diagnostic model, but cortisol's strong standalone performance (AUC = 0.904) suggests real clinical potential. Pairing PAED scores with salivary cortisol testing improves risk stratification. This combined clinical and biological approach makes POD diagnosis more accurate.

4.3 Comparison with Existing Literature

Our findings support and extend prior work. Earlier studies linked serum cortisol to delirium in adults, but few explored salivary testing in children. We identified a clear cortisol cutoff of 0.733 μg/mL, giving clinicians a concrete reference value—something missing from many earlier reports. Some studies report lower cortisol in delirious patients, but these differences likely reflect chronic illness or steroid use in those cohorts, which we excluded by focusing on relatively healthy surgical children. This distinction matters when selecting biomarkers for specific patient groups.

4.4 Limitations

This study has several important limitations. First, it was single-center with a small sample (n = 24), due to ethical and practical challenges in pediatric research. Second, we measured cortisol only once, within 30 minutes postoperatively, so we cannot capture full stress response dynamics over time. We also did not account for factors like pain scores or sleep quality, which may influence POD risk. We lacked an intervention arm to test whether lowering cortisol could prevent delirium.

4.5 Clinical Implications

Translating these findings into practice requires a two-step approach: use the PAED scale for behavioral checks in the PACU, and add salivary cortisol testing—especially useful for young or uncooperative children who cannot communicate symptoms clearly. Beyond diagnosis, this method helps spot high-risk patients early.

Our data also suggest that optimizing anesthesia depth and pain control to limit excessive cortisol release might help prevent POD. Children with elevated cortisol need closer monitoring to reduce complications.

5. Conclusion

Salivary cortisol is a reliable biomarker for pediatric POD and a key mediator linking surgical stress to delirium. Combining it with the PAED scale creates a more accurate diagnostic strategy, bridging subjective behavioral symptoms and objective physiological changes.

Future work should include large, multicenter trials to validate this biomarker, track cortisol levels over longer periods, and test interventions that improve perioperative care for children.

Declarations

Ethics approval and consent to participate

This pilot study was performed in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Taizhou Maternal and Child Health Hospital (Ethics Approval Number: 2025-KY009-01).Written informed consent was obtained from all pediatric patients' legal guardians, and verbal assent was acquired from cognitively competent children. All participant data were fully anonymized to protect privacy, and participants could withdraw voluntarily at any time.

Consent for publication

Not applicable. All data in this study are anonymized aggregated results without identifiable individual information, so participant publication consent is not required.

Availability of data and materials

De-identified datasets are available from the corresponding author upon reasonable request. Raw data are not publicly available due to pediatric privacy and institutional data regulations.

Competing Interests

The authors declare no competing financial or non-financial interests in this study.

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Author contribution

Chengbao HUANG and Yi WANG conceived the study. Lan LUO and Fangyi WANG collected and collated patients' data.Chengbao HUANG carried out data verification, cleaning and statistical analysis.Yi WANG Shihui BAO and XU Youwen drafted the manuscript and delivered a critical revision of it with improvements to the important intellectual content. All authors read and approved the final manuscrip.

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Figures

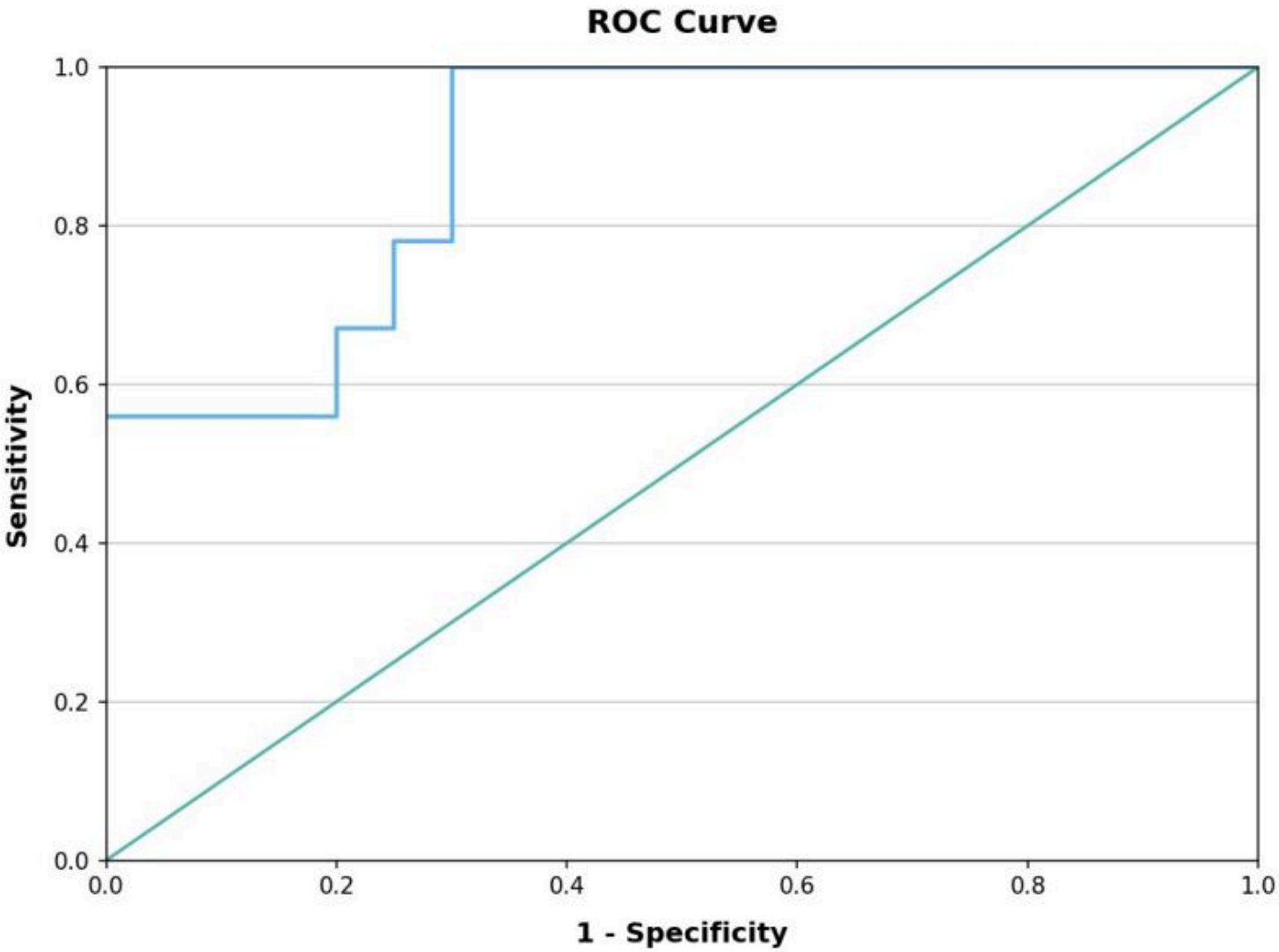


Figure 1

ROC curve of salivary cortisol for diagnosing postoperative delirium in childrenNote: The horizontal axis represents 1-specificity, and the vertical axis represents sensitivity; the AUC of the ROC curve is 0.904, indicating excellent diagnostic efficiency.