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CLINICAL TRIAL REPORT

Associations of Preoperative HMGB-1 and Systemic Immune-Inflammation Index with Short-Term Behavioral Improvement After Adenotonsillectomy in Children with OSAHS

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Objective: To explore the association of High-Mobility Group Box-1 (HMGB-1) with behavioral improvement after obstructive sleep apnea-hypopnea syndrome (OSAHS) surgery in children during short-term follow-up.

Methods: In this prospective observational cohort study, 138 children with OSAHS who underwent bilateral tonsillectomy and adenoidectomy were enrolled between December 2024 and June 2025. Preoperative levels of HMGB-1 and the Systemic Immune-Inflammation Index (SII) were measured. The Rutter Behavior Scale was assessed 1 day before surgery and 30 days after surgery. Patients were classified into three groups: markedly effective, effective, and ineffective. Associations between HMGB-1, SII, and behavioral improvement were assessed using Spearman rank correlation. Mediation analysis evaluated whether SII is associated with behavioral change. ROC curves assessed the discrimination of HMGB-1 and SII for postoperative behavioral improvement.

Results: Of the 138 children initially enrolled, 112 completed follow-up and were classified by therapeutic efficacy: markedly effective (n = 37), effective (n = 40), and ineffective (n = 35). Postoperative Rutter scores significantly decreased in the markedly effective and effective groups (both $P < 0.05$) but not in the ineffective group ($P = 0.066$). Preoperative HMGB-1 and SII levels were highest in the ineffective group, intermediate in the effective group, and lowest in the markedly effective group ($P < 0.05$). Ordered logistic regression identified preoperative HMGB-1 (OR 2.91, 95% CI 1.89~4.48, $P < 0.05$), SII (OR 1.01, 95% CI 1.00~1.01, $P < 0.05$), and baseline Rutter score (OR 0.67, 95% CI 0.54~0.81, $P < 0.05$) as significant independent predictors of behavioral improvement. The degree of postoperative behavior improvement was negatively correlated with serum HMGB-1 and SII levels. Mediation analysis showed that SII mediated 13.1% of HMGB-1's total effect (indirect effect −0.129, 95% CI −0.247 to −0.035). ROC curves indicated strong predictive performance for HMGB-1 (AUC 0.890) and SII (AUC 0.794).

Conclusion: Elevated preoperative serum HMGB-1 levels were independently associated with reduced postoperative behavioral improvement in children with OSAHS, and this relationship showed a pattern consistent with partial mediation by SII levels, compatible with the hypothesis of systemic inflammatory pathway involvement. These findings provide preliminary evidence that preoperative inflammatory biomarkers may help identify high-risk children for closer monitoring during short-term recovery, though causal mechanisms require further validation in interventional studies.

Keywords: high-mobility group box-1, systemic immune-inflammation index, pediatric obstructive sleep apnea-hypopnea syndrome, mediation effect, behavioral improvement

Introduction

Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS) in children is a prevalent sleep-related breathing disorder characterized by recurrent upper airway collapse during sleep, leading to disrupted ventilation and sleep architecture.[1]

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With an estimated incidence ranging from 1.2% to 13%,[2] adenotonsillar hypertrophy is the primary etiology.[3] Beyond hallmark nocturnal symptoms such as snoring, gasping, and mouth breathing, pediatric OSAHS is frequently associated with significant neuropsychological sequelae,[4] including cognitive impairment, inattention, learning difficulties, and emotional dysregulation. These behavioral problems, highly prevalent in this population, can severely impact social functioning and quality of life, and potentially lead to long-term adverse cognitive and psychological outcomes.

Adenotonsillectomy (ATE) remains the first-line treatment for pediatric OSAHS,[5] effectively alleviating respiratory symptoms and improving sleep quality. However, postoperative behavioral improvement is highly variable, influenced by baseline OSA severity, age, and obesity. This heterogeneity highlights a critical gap: Currently, no validated method exists to preoperatively identify which specific children will experience meaningful short-term behavioral benefit from surgery. This predictive gap represents a critical unmet clinical need, as it hinders targeted counseling and early identification of high-risk patients. A recent umbrella review of OSA interventions underscores the urgent need for predictive biomarkers to stratify patients by their likelihood of treatment response, given the multifactorial nature of OSA pathophysiology.[6]

The pathophysiological mechanisms underpinning OSAHS and its complications involve chronic intermittent hypoxia, sleep fragmentation, oxidative stress, and systemic inflammation, which are also implicated in associated cardiovascular, metabolic, and neurological sequelae. Consequently, there is growing interest in identifying serum biomarkers that can assess disease severity and predict outcomes,[7] including postoperative recovery. Various inflammatory biomarkers have been studied in pediatric OSAHS, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), which are elevated in affected children and correlate with disease severity. However, these markers lack specificity for tissue injury and direct cellular stress mechanisms.[8,9] High-Mobility Group Box-1 (HMGB-1), a ubiquitous nuclear protein acting as a key damage-associated molecular pattern (DAMP),[10] may offer advantages over conventional inflammatory markers. Unlike CRP or IL-6, which represent generalized inflammatory responses, HMGB-1 is passively released specifically upon cellular damage or actively secreted under inflammatory stress, making it a more specific indicator of tissue injury. Extracellular HMGB-1 initiates potent immune responses by triggering the production of various inflammatory mediators (eg., ICAM-1, VCAM-1, IL-1β, IL-6, IL-8) and amplifying inflammatory cascades.[11] Critically, HMGB-1 can induce neuroinflammation within the central nervous system (CNS), potentially modulating behavioral manifestations and interfering with neurobehavioral recovery post-surgery. Preclinical evidence suggests that targeting HMGB-1 can ameliorate anxiety and cognitive dysfunction,[12] supporting its relevance to neurobehavioral outcomes. While we cannot directly measure neuroinflammation in this clinical setting, peripheral HMGB-1 may serve as a surrogate marker of the systemic inflammatory burden that potentially affects CNS function. Yet its specific role in the postoperative behavioral recovery of children with OSAHS remains unexplored.

Complementarily, the Systemic Immune-Inflammation Index (SII), a composite biomarker derived from routine blood counts (neutrophils, lymphocytes, platelets), provides an integrated measure of systemic immune activation. We selected SII not merely as another correlate of inflammation, but specifically as a potential mediator in the pathway between HMGB-1 release and behavioral outcomes. The rationale is that HMGB-1, once released from damaged or stressed cells, triggers innate immune activation characterized by neutrophil recruitment, lymphocyte modulation, and platelet activation—precisely the cellular components captured by SII.[13] Elevated SII levels have also been associated with an increased risk of postoperative neurobehavioral complications in surgical populations,[14] suggesting its clinical relevance as an intermediate endpoint. Unlike complex cytokine panels requiring specialized assays, SII is computable from standard complete blood counts, offering practical clinical utility. We hypothesize that HMGB-1 may be associated with postoperative behavioral recovery through pathways involving systemic immune activation as reflected by elevated SII.

Significant differences exist between children and adults regarding sleep-respiratory physiology, OSAHS presentation, and treatment approaches. Early identification and intervention for pediatric OSAHS are crucial for preventing detrimental long-term consequences.[15] While some studies have evaluated short-term respiratory outcomes after ATE, systematic analyses of postoperative behavioral changes and their predictors are lacking. Therefore, this study aims to: (1) Evaluate the predictive value of preoperative serum HMGB-1 and SII levels for postoperative behavioral improvement in children undergoing ATE for OSAHS; (2) Explore whether SII mediates the relationship between HMGB-1 and neurobehavioral outcomes; (3) Comprehensively analyze factors associated with postoperative behavioral changes. We

hypothesize that elevated preoperative HMGB-1 and SII levels predict poorer behavioral improvement, potentially mediated through inflammatory pathways. The findings aim to provide a foundation for targeted perioperative interventions and precise management strategies to optimize neurobehavioral recovery in these children.

Materials and Methods

Research Design

This single-center prospective cohort study investigated the associations between preoperative serum HMGB-1 and SII levels and postoperative behavioral improvement in pediatric OSAHS patients, with a focus on potential mediating mechanisms. We prospectively collected standardized perioperative data from children undergoing bilateral tonsillectomy and adenoidectomy and conducted systematic follow-up behavioral assessments. Correlation and mediation analyses were performed to evaluate the relationships between HMGB-1/SII levels and postoperative behavioral changes.

The study protocol was approved by the Medical Ethics Committee of Changzhi People's Hospital (Approval No.: 2,024,060). The study was registered with the Chinese Clinical Trial Registry (ChiCTR2500103471) on 2025–05-29. Written informed consent was obtained from all participants' legal guardians. Retrospectively registered.

Sample Size Calculation

This study was powered for the primary outcome of behavioral improvement (an ordinal 3-level variable: markedly effective, effective, and ineffective). Based on our pilot data showing an HMGB-1 effect size f = 0.32 for predicting behavioral categories, we performed an a priori power analysis using G*Power 3.1. For one-way ANOVA with three groups ($\alpha = 0.05$, power = 0.80, effect size f = 0.32), the minimum required sample size was 99 subjects. Accounting for an anticipated 10% loss to follow-up, we planned to enroll 110 patients.

Patients

The study cohort comprised children with OSAHS who underwent bilateral tonsillectomy and adenoidectomy at the Department of Otorhinolaryngology Head and Neck Surgery between December 2024 and June 2025. Patients were consecutively enrolled. All children presenting for surgical evaluation during this period were screened for eligibility, and those meeting the inclusion criteria were invited to participate. Inclusion criteria: Age 3~10 years; ASA grade I~II; Be able to complete postoperative follow-up and assessment as required; Parental or guardian informed consent. Exclusion criteria: Previous history of neurological diseases, mental disorders, or concurrent other serious neurological, psychological or developmental disorders; Anticipated anatomically difficult airway; Combined respiratory system diseases; Premature birth history (<37 weeks' gestation); Head/neck or respiratory function-affecting surgery within 3 months; Concurrent participation in other clinical trials.

Anesthesia Management

All children underwent standard bilateral tonsillectomy and adenoidectomy. Intraoperative anesthesia was managed by experienced anesthesiologists using combined intravenous-inhalation general anesthesia. During induction, midazolam (0.05 $mg \cdot kg^{-1}$ IV) and propofol (2~3 $mg \cdot kg^{-1}$ IV) were administered intravenously. Sufentanil (0.1~0.2 $\mu g \cdot kg^{-1}$ IV) and cisatracurium (0.1~0.2 $mg \cdot kg^{-1}$ IV) were used to achieve adequate sedation, analgesia, and muscle relaxation. During maintenance, propofol (4~6 $mg \cdot kg^{-1} \cdot h^{-1}$) and remifentanil (0.05~0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were continuously infused, supplemented with sevoflurane (1.5%~2.0%) inhalation. The oxygen flow rate was maintained at 2 $L \cdot min^{-1}$ to ensure appropriate anesthetic depth and hemodynamic stability.

During the procedure, standardized vital sign monitoring was performed, including electrocardiography, non-invasive arterial blood pressure, pulse oximetry, and end-tidal carbon dioxide ($EtCO_2$) monitoring. Mechanical ventilation was used with a mixture of 50% oxygen and air, maintaining $SpO_2 \geq 95\%$ and $EtCO_2$ between 25 and 30 mmHg; adjustments were made according to each patient's specific condition. Body temperature was maintained above 36°C using a liquid warming system to prevent hypothermia.

Hemodynamic parameters were recorded at the following time points: pre-induction (T1), 5 minutes post-intubation (T2), surgical incision (T3), procedure completion (T4), and 10 minutes after awakening (T5). Mean arterial pressure (MAP) and heart rate (HR) were documented to evaluate circulatory changes during anesthesia. Anesthetic infusions were discontinued at the end of surgery. Patients were transferred to the post-anesthesia care unit (PACU) for monitored recovery. Tracheal extubation was performed once spontaneous breathing resumed, circulation stabilized, normothermia (>36°C) was achieved, and appropriate neurological recovery was confirmed.

Observation Indicators

General Observation Indicators

Upon admission, baseline demographics—including age, sex, body mass index (BMI), ASA physical status, and past medical history—were documented. On the morning following admission, fasting venous blood was collected. Absolute platelet, neutrophil, and lymphocyte counts were determined using an automated hematology analyzer, and the systemic immune-inflammation index (SII) was calculated as follows: SII = (platelet count × neutrophil count) / lymphocyte count. For HMGB-1 measurement, preoperative fasting venous blood samples (5 mL) were collected into vacuum tubes and allowed to clot at room temperature (20~25°C) for 30 minutes. Samples were then centrifuged at 2500 × g for 20 minutes, and serum aliquots (2 mL) were stored at −80°C until analysis. Serum HMGB-1 concentrations were measured using a commercially available ELISA kit (Human HMGB-1 ELISA Kit, Cat No. SEA399Hu, Cloud-Clone Corp., Wuhan, China) according to the manufacturer's instructions. The assay sensitivity was 0.012 μg/L, with an intra-assay CV < 8% and inter-assay CV < 10%. The standard curve ranged from 0.312 to 20 μg/L. All samples were assayed in duplicate by technicians blinded to clinical outcomes. Absorbance was read at 450 nm within 15 minutes of adding the stop solution. Intra-operatively, the following variables were recorded: operative time, anesthesia duration, time to extubation, length of stay in the post-anesthesia care unit (PACU), total hospital length of stay (LOS), estimated blood loss, and intraoperative doses of sufentanil, propofol and dexmedetomidine.

Neuropsychological Indicators

Behavioral assessments were performed using the Rutter Child Behavior Scale—Parent Version[16] one day prior to surgery and again on postoperative day 30. This 31-item questionnaire yields a total score ranging from 0 to 62, with higher scores indicating more severe behavioral disturbance. The scale has reported sensitivity of 83%, specificity of 92%, and overall efficiency of 75%.[17] Improvement was defined as the reduction in total score from baseline to follow-up : Marked effect: The total score drops to normal or decreases by more than 5 points; Effective: The total score drops by 2 to 5 points. Invalid: The total score drops by less than 2 points or increases.[18] For analytical purposes, improvement comprised both "marked effect" and "effective" outcomes, whereas no improvement comprised "invalid" outcomes and clinical deterioration. The scale evaluates four domains: emotion, attention, social interaction, and neurological symptoms, with the sum of item scores reflecting global functional impairment. Postoperative pain was assessed by trained nurses immediately upon the child's emergence from anesthesia using the FLACC scale (range 0~10; higher scores indicate greater pain), which evaluates five behavioral categories: facial expression, leg movement, activity, cry, and consolability.[19]

Statistical Analysis

All statistical analyses were performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data were presented as mean ± standard deviation (SD); between-group comparisons were conducted using one-way analysis of variance (ANOVA), and within-group comparisons over time were analyzed using repeated-measures ANOVA. Non-normally distributed variables were expressed as median (M) with interquartile range (IQR); between-group comparisons were performed using the Kruskal–Wallis *H*-test, and inter-group paired comparisons were conducted with the Wilcoxon signed-rank test. Significant findings from ANOVA or Kruskal–Wallis tests were followed by appropriate post-hoc tests to identify specific group differences. Categorical variables were reported as frequencies and percentages (n, %), and comparisons were performed using the chi-square test (χ^2) or Fisher's exact test, as applicable. The association between preoperative

serum levels of HMGB-1 or the Systemic Immune-Inflammation Index (SII) and the change in Rutter Behavior Score was evaluated using Spearman's rank correlation coefficient. To investigate whether SII mediates the relationship between HMGB-1 and postoperative behavioral improvement, a mediation analysis was conducted using the PROCESS v4.2 macro for SPSS (Model 4) with 5,000 bootstrap samples to generate bias-corrected confidence intervals. Receiver operating characteristic (ROC) curve analysis was employed to evaluate the predictive accuracy of preoperative HMGB-1 and SII levels for postoperative behavioral improvement in children with obstructive sleep apnea hypopnea syndrome (OSAHS). To address potential overfitting, bootstrap resampling with 1000 iterations was performed to calculate optimism-corrected AUCs. Statistical significance was defined as a two-tailed P value < 0.05.

Result

General Situation

A total of 138 OSAHS patients who underwent surgical treatment from December 2024 to June 2025 were included and excluded Of the 26 patients, 18 did not meet the inclusion criteria, 3 underwent reoperation, and 5 were lost to follow-up. Finally, 112 patients were included Patients. According to the behavior improvement, 112 patients were divided into three groups: markedly effective group (H group, n=37), effective group (L Group, n=40) and ineffective group (group N, n=35) (Figure 1). The overall behavior improvement rate (marked effect + effective) was 69% (77/112).

No significant differences were observed among groups in baseline demographic and clinical characteristics (age, sex, ASA physical status, BMI, and baseline Rutter scores; all $P > 0.05$). As expected given the outcome-based grouping, preoperative HMGB-1 and SII levels differed significantly across the markedly effective, effective, and ineffective groups ($P < 0.001$) and represent the primary predictor variables of interest (Table 1). No significant differences were observed among groups in perioperative variables, including hemodynamics (T1~T5), operative and anesthesia duration, extubation time, PACU stay, hospital length of stay, blood loss, sufentanil/propofol/dexmedetomidine dosage, postoperative complications, or nausea/vomiting (Table 2; all $P > 0.05$).

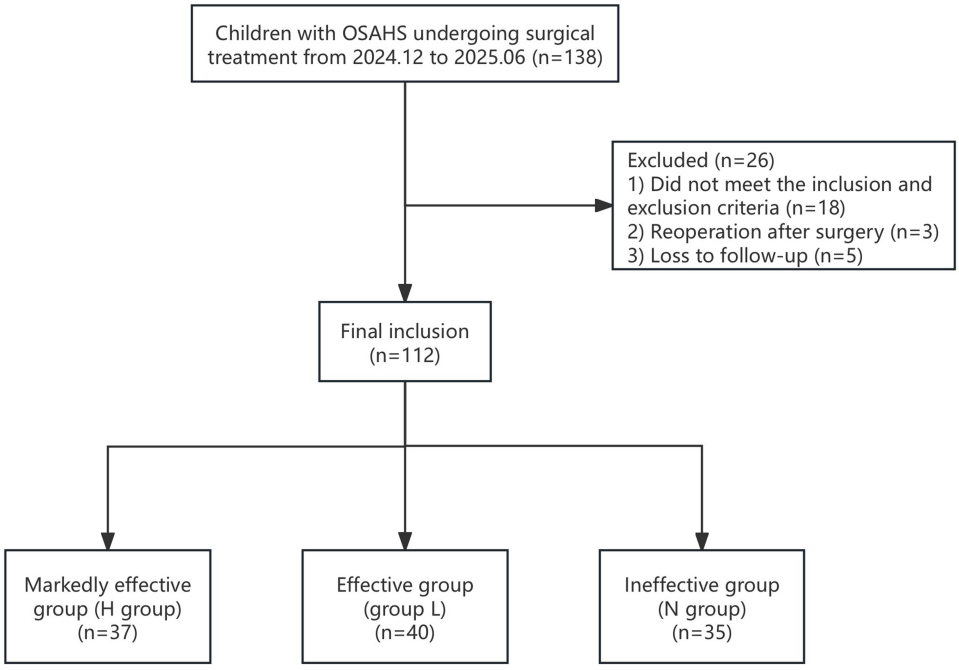

Figure 1 Study flow diagram showing patient selection and grouping. Of the 138 screened patients, 112 were finally included and divided into three groups: H (markedly effective, n=37), L (effective, n=40), and N (ineffective, n=35).

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Table 1 Baseline Characteristics

Basic Information		All Patients (n=112)	Group H (n=37)	Group L (n=40)	Group N (n=35)	F/X^2	*P*
Age		6.79±1.83	7.08±1.74	6.70±1.76	6.57±2.00	0.764	0.468
Sex	Male	60	20	21	19	0.029	0.986
	Female	52	17	19	16		
ASA	I	102	34	36	32	0.093	0.955
	II	10	3	4	3		
BMI		18.61±2.88	18.76±2.86	18.60±3.20	18.45±2.59	0.105	0.900
HMGB-1		5.33±1.74	3.76±1.15	5.40±1.25	6.91±1.21	61.633	< 0.001
SII		602.62±279.15	408.66±83.34	589.30±207.10	822.89±326.74	30.401	< 0.001

Note: Data are presented as mean ± SD for continuous variables and n (%) for categorical variables. Group H: markedly effective; Group L: effective; Group N: ineffective. BMI: body mass index; HMGB-1: high-mobility group box-1; SII: systemic immune-inflammation index; ASA: American Society Of Anesthesiology. Differences among the three groups were assessed by one-way ANOVA (continuous variables) or χ^2-test (categorical variables). $P < 0.05$ was considered statistically significant.

Table 2 Intraoperative Data

Intraoperative Data		All Patients (n=112)	Group H (n=37)	Group L (n=40)	Group N (n=35)	F/H/X^2	*P*
T1	MAP	77.35±9.22	78.06±9.65	79.21±9.54	74.46±7.83	2.728	0.070
	HR	97.55±15.98	95.51±16.34	97.54±14.61	99.71±17.23	0.617	0.541
T2	MAP	71.02±10.67	69.35±9.52	73.94±12.90	69.47±8.31	2.381	0.097
	HR	92.58±16.76	88.19±18.40	92.35±15.38	97.49±15.56	2.865	0.061
T3	MAP	74.40±9.26	74.03±10.72	73.78±7.80	75.51±9.30	0.370	0.692
	HR	96.40±18.28	92.68±21.32	94.93±14.28	102.03±18.04	2.633	0.076
T4	MAP	75.27±7.63	75.44±7.77	76.16±7.21	74.07±8.00	0.709	0.494
	HR	92.88±15.69	92.00±18.44	91.85±14.46	95.00±14.04	0.459	0.663
T5	MAP	82.07±10.22	82.29±9.49	84.12±9.51	79.51±11.39	1.947	0.148
	HR	113.42±15.21	109.41±17.62	114.58±14.89	116.34±12.00	2.091	0.128
Operation time		35.40±13.55	34.46±13.94	37.18±12.10	34.37±14.82	0.529	0.591
Anesthesia time		54.29±13.13	52.49±11.84	56.28±13.55	53.91±13.98	0.818	0.444
Extubation time		28.05±10.65	25.22±11.51	28.25±10.82	30.83±8.90	2.579	0.080
PACU stay time		56.09±14.99	56.24±18.55	53.53±13.99	58.86±11.34	1.188	0.309
LOS		5.00 (5.00–5.00)	5.00 (5.00–5.00)	5.00 (5.00–5.00)	5.00 (5.00–5.50)	0.066	0.967
Intraoperative blood loss		5.00(3.00–7.00)	5.00 (3.00–6.00)	5.00 (5.00–7.50)	5.00 (4.00–8.00)	2.741	0.254
Dosage of sufentanil		12.50(7.50–17.00)	12.00 (8.00–17.00)	12.50 (6.50–16.50)	14.00 (7.50–17.50)	0.083	0.959
The dosage of propofol		138.87±34.26	147.38±36.19	139.05±35.55	129.66±28.81	2.471	0.089
Dosage of dexmedetomidine		3.44±1.54	3.53±1.47	3.30±1.59	3.50±1.58	0.248	0.781
Postoperative complications							
Nausea and vomiting		15 (13%)	5 (14%)	3 (8%)	7 (20%)	2.515	0.284
FLACC score		5.00(4.00–7.00)	5.00 (4.00–6.00)	5.00 (4.00–6.00)	7.00 (6.00–7.50)	26.609	< 0.001

Note: Data are presented as mean ± SD, median (IQR), or n (%). T1: Pre-induction; T2: 5 min post-intubation; T3: Surgical incision; T4: Procedure completion; T5: 10 minutes after awakening.

Abbreviations: MAP, mean arterial pressure (mmHg); HR, heart rate (beats/min); LOS, length of hospital stay (days); PACU, post-anaesthesia care unit. Extubation time and PACU stay are expressed in minutes. Between-group comparisons were performed with one-way ANOVA (F), Kruskal–Wallis test (H), or χ^2-test as appropriate. $P < 0.05$ was considered statistically significant.

The Rutter Behavior Scale Scores of the Three Groups Were Compared

Between-Group Comparison of Rutter Behavior Scale Score Improvement

Between-group comparisons of Rutter Behavior Scale scores were performed using the Kruskal–Wallis test. Preoperative scores (measured one day prior to surgery) did not differ significantly among the three groups (H = 5.673, $P = 0.059$). In contrast, postoperative scores (at 1 month) showed significant intergroup differences (H = 23.225, $P < 0.05$). Pairwise

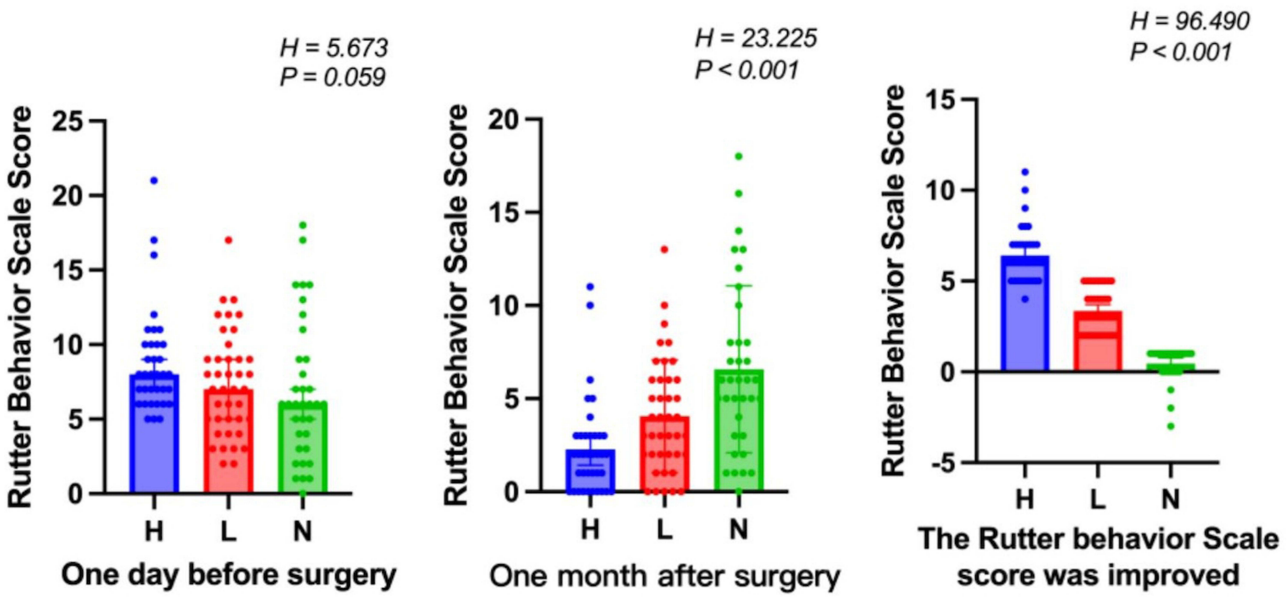

Figure 2 Inter-group differences in Rutter Behavior Scale Scores. Group H (markedly effective, n=37), Group L (effective, n=40), and Group N (ineffective, n=35). H represents the Kruskal–Wallis statistic.

comparisons revealed that Group H (markedly effective) had the lowest postoperative scores, followed by Group L (effective), and Group N (ineffective) had the highest ($P < 0.05$ for all pairwise comparisons).

The magnitude of improvement (reduction in scores from baseline to postoperative day 30) also differed significantly among groups (H = 96.490, $P < 0.05$). Post-hoc pairwise comparisons indicated that improvement was greatest in Group H, intermediate in Group L, and least pronounced in Group N (all $P < 0.05$) (Figure 2 and Table 3).

Inter-Group Comparison of Rutter Behavior Scale Scores

Within-group comparisons of Rutter Behavior Scale scores were performed using the Wilcoxon signed-rank test. Rutter scores decreased significantly from preoperative baseline to postoperative day 30 in Group H (markedly effective; Z = –5.358, $P < 0.05$) and Group L (effective; Z = –5.563, $P < 0.05$). In contrast, Group N (ineffective) showed no significant change between the two time points (Z = –1.836, $P = 0.066$) (Figure 3 and Table 4).

Comparison of Preoperative HMGB-1 and SII Levels Among the Three Groups

One-way ANOVA revealed that both preoperative serum HMGB-1 levels (F = 61.633, $P < 0.05$) and SII levels (F = 30.401, $P < 0.05$) differed significantly among the three groups. Post-hoc pairwise comparisons demonstrated parallel hierarchical gradients for both biomarkers: For HMGB-1, Group H (markedly effective) exhibited the lowest levels (3.76 ± 1.15 μg/L), followed by Group L (effective; 5.40 ± 1.25 μg/L), and Group N (ineffective) showed the highest levels (6.91 ± 1.21 μg/L). Similarly, for SII, levels were lowest in Group H (408.66 ± 83.34), intermediate in Group L (589.30 ± 207.10), and highest in

Table 3 Inter-Group Comparison of Rutter Behavior Scale Score

Rutter Behavior Scale score	All Patients (n=112)	Group H (n=37)	Group L (n=40)	Group N (n=35)	H	P
One day before the operation	7.00 (5.00–9.75)	8.00 (6.00–10.00)	7.00 (5.00–9.00)	6.00 (3.00–9.00)	5.673	0.059
One month after the operation	3.00 (1.00–6.00)	2.00 (0.00–3.00)	3.50 (2.00–6.00)	6.00 (3.00–8.00)	23.225	< 0.001
The score of the Rutter scale has improved	3.00 (1.00–5.00)	6.00 (5.00–7.00)	3.00 (2.00–4.00)	1.00 (0.00–1.00)	96.490	< 0.001

Note: Data are presented as median (interquartile range, IQR: 25th–75th percentile). The "improvement" is calculated as (pre-operative score Subtract post-operative score). Between-group comparisons were performed with the Kruskal–Wallis test (H). $P < 0.05$ was considered statistically significant.

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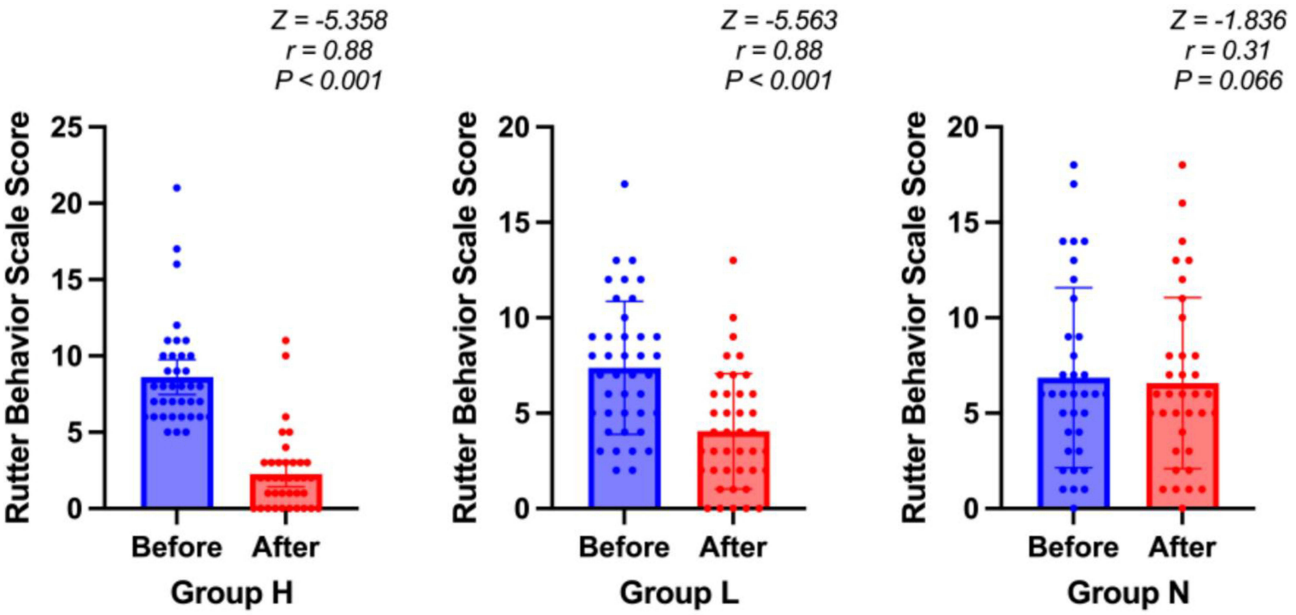

Figure 3 Within-group differences in Rutter Behavior Scale Scores. Blue bars represent preoperative scores and red bars represent postoperative scores. Z represents the Wilcoxon signed-rank test statistic; r represents the effect size.

Group N (822.89 ± 326.74). All pairwise comparisons for both biomarkers were statistically significant (all $P < 0.05$), with the intergroup trend following the pattern H < L < N for each index (Figure 4 and Table 1).

These findings suggest that lower preoperative serum HMGB-1 levels and reduced systemic inflammation (as reflected by SII) are both associated with better postoperative behavioral improvement, whereas higher levels of either biomarker predict poorer outcomes.

Ordered Logistic Regression Analysis

To examine the independent effects of preoperative HMGB-1 and SII on behavioral improvement, ordered logistic regression analysis was conducted with behavioral improvement grade (markedly effective, effective, ineffective) as the ordinal outcome. The primary predictors were preoperative HMGB-1 and SII, while postoperative FLACC score, baseline Rutter score, age, sex, BMI, and ASA physical status were included as covariates.

After adjustment, preoperative HMGB-1 (OR 2.91, 95% CI 1.89~4.48, $P < 0.001$), SII (OR 1.01, 95% CI 1.00~1.01, $P < 0.001$), and baseline Rutter score (OR 0.67, 95% CI 0.54~0.81, $P < 0.001$) remained significant independent predictors. Higher HMGB-1 and SII levels were associated with poorer improvement categories (ORs > 1 indicate increased likelihood of being classified as ineffective versus markedly effective). Age, sex, BMI, ASA status, and postoperative FLACC score were not significantly associated with outcome (all $P > 0.05$) (Table 5). The Brant test confirmed that the proportional odds assumption was not violated ($\chi^2 = 2.34$, $P = 0.67$), supporting model validity.

Table 4 Within-Group Comparison of Rutter Behavior Scale Score

Rutter Behavior Scale	One day Before The Operation	One Month After The Operation	Z	r	*P*
Group H (n=37)	8.00 (6.00–10.00)	2.00 (0.00–3.00)	−5.358	0.88	< 0.001
Group L (n=40)	7.00 (5.00–9.00)	3.50 (2.00–6.00)	−5.563	0.88	< 0.001
Group N (n=35)	6.00 (3.00–9.00)	6.00 (3.00–8.00)	−1.836	0.31	0.066

Data are presented as median (interquartile range) [Mdn (P25–P75)]. Within-group comparisons were performed using the Wilcoxon signed-rank test. Effect size r was calculated as $|Z|/\sqrt{N}$, where N denotes the number of paired observations. A *P* value < 0.05 was considered statistically significant.

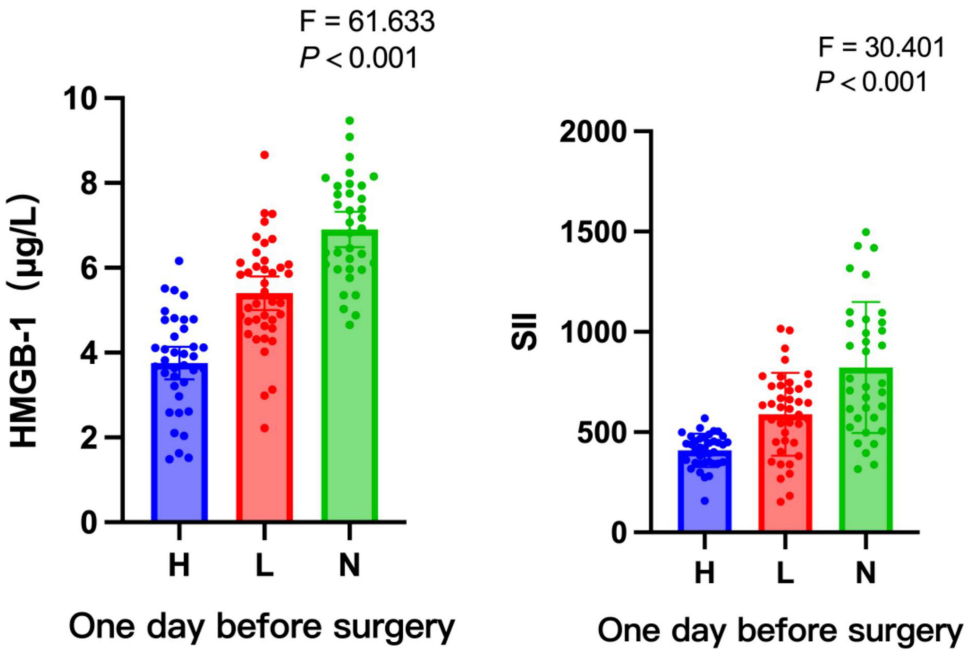

Figure 4 Comparison of HMGB-1 and SII among the three groups before the operation. H, markedly effective group; L, effective group; N, ineffective group. One-way ANOVA: HMGB-1, F(2, n) = 61.633, $P < 0.001$; SII, F(2, n) = 30.401, $P < 0.001$.

Correlation Analysis of Preoperative HMGB-1 and SII Levels and the Improvement of Postoperative Rutter Score

Spearman correlation analysis revealed that both preoperative HMGB-1 (r = –0.678, $P < 0.05$) and SII (r = –0.480, $P < 0.05$) levels were negatively correlated with the magnitude of postoperative Rutter score improvement (Figure 5). These findings indicate that higher preoperative inflammatory markers are associated with less pronounced behavioral improvement.

Mediating Effect

Mediation analysis indicated that pre-operative HMGB-1 was associated with the change in Rutter Behavior Scale scores in a pattern consistent with both direct and indirect (via SII) pathways. The indirect (mediated) pathway accounted for approximately 13.1% of the total effect (indirect effect = −0.129, 95% CI −0.247 to −0.035), while the direct effect remained significant (direct effect = −0.849, $P < 0.05$). Overall, higher pre-operative HMGB-1 predicted poorer behavioral improvement (total effect = −0.978, $P < 0.05$), indicating that the inflammatory protein partly exerts its effect by modulating systemic immune-inflammatory status.

Table 5 Ordered Logistic Regression Analysis of Behavioral Improvement

Factor	OR (95% CI)	B	Standard Error	Wald	*P*
HMGB-1	2.91 (1.89~4.48)	1.068	0.221	4.841	< 0.001
SII	1.01 (1.00~1.01)	0.008	0.002	4.715	< 0.001
Baseline Rutter score	0.67 (0.54~0.81)	−0.407	0.103	−3.968	< 0.001
Sex	0.88 (0.31~2.51)	−0.130	0.536	−0.243	0.808
Age	0.82 (0.56~1.18)	−0.203	0.189	−1.072	0.284
BMI	0.96 (0.76~1.22)	−0.039	0.120	−0.322	0.748
ASA	5.04 (0.85~30.00)	1.618	0.910	1.778	0.075
FLACC	1.49 (0.99~2.22)	0.396	0.205	1.935	0.053

Note: OR, odds ratio; 95% CI in parentheses. B = regression coefficient. The outcome variable "behavioral improvement" was treated as an ordered 3-level variable (markedly effective, effective, ineffective). HMGB-1, SII, and baseline Rutter score were significant independent predictors (all $P<0.001$). Higher HMGB-1 and SII predicted poorer improvement, while higher baseline Rutter score predicted better improvement.

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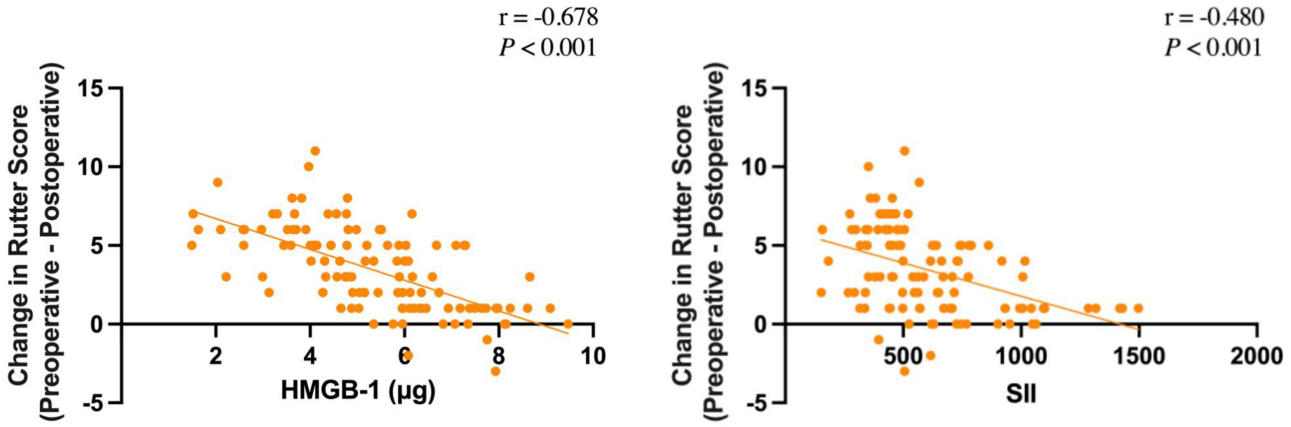

Figure 5 Correlation between preoperative HMGB-1/SII and postoperative Rutter score improvement. Left panel: Spearman correlation between preoperative serum HMGB-1 levels and postoperative Rutter score improvement. Right panel: Spearman correlation between preoperative SII and postoperative Rutter score improvement. r represents the Spearman correlation coefficient.

Receiver Operating Characteristic (ROC) Curve

To evaluate predictive performance, the outcome was dichotomized into improved (Groups H and L combined) versus not improved (Group N). ROC curve analysis demonstrated that preoperative serum HMGB-1 exhibited strong predictive accuracy for postoperative behavioral improvement, with an area under the curve (AUC) of 0.890 (95% CI 0.831~0.950, $P < 0.05$). The optimal cutoff value was 5.92 μg/L, yielding a sensitivity of 0.805, specificity of 0.829, and Youden's index of 0.634. Preoperative SII showed acceptable but inferior predictive performance: AUC 0.794 (95% CI 0.699~0.888, $P < 0.05$), optimal cutoff 568.90, sensitivity 0.714, specificity 0.771, and Youden's index 0.485. Direct comparison revealed that HMGB-1 significantly outperformed SII, with superior AUC (0.890 vs. 0.794), sensitivity (0.805 vs. 0.714), specificity (0.829 vs. 0.771), and Youden's index (0.634 vs. 0.485; all $P < 0.05$). Internal validation using bootstrap resampling (1000 iterations) yielded optimism-corrected AUCs of 0.872 (95% CI 0.814~0.930) for HMGB-1 and 0.761 (95% CI 0.682~0.840) for SII, indicating robust predictive performance despite the modest sample size. These findings suggest that preoperative HMGB-1 possesses superior diagnostic efficacy for predicting post-operative behavioral improvement in pediatric OSAHS (Figure 6).

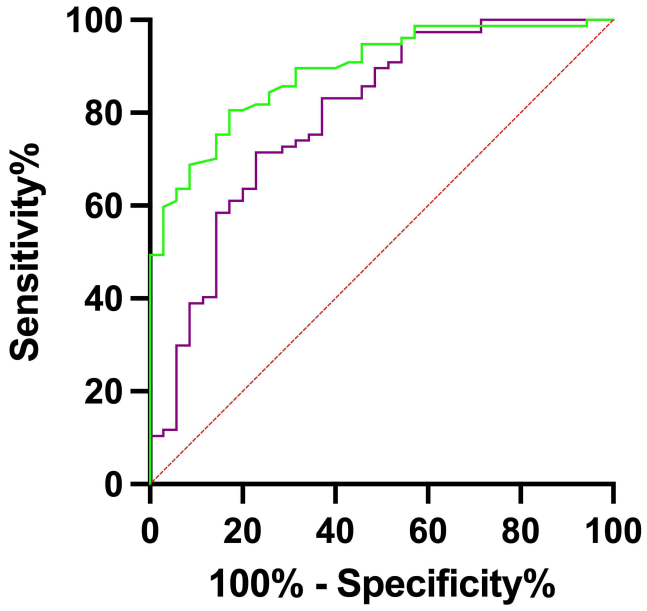

Figure 6 ROC curve analysis of the predictive value of preoperative HMGB-1 and SII. The green line represents HMGB-1 (AUC=0.890) and the purple line represents SII (AUC=0.794). The ROC curves plot the true positive rate against the false positive rate at various threshold settings, with the AUC value indicating the overall performance of the biomarkers.

Discussion

This study demonstrates that elevated preoperative serum levels of HMGB-1 and the systemic immune inflammation index (SII) are associated with less pronounced short-term behavioral improvement following surgical intervention for obstructive sleep apnea-hypopnea syndrome (OSAHS) in children. Importantly, our findings reveal that HMGB-1 levels are correlated with behavioral outcomes and this relationship is partially accounted for by SII. This is consistent with the hypothesis that inflammatory responses, potentially associated with HMGB-1, may represent a contributing factor to postoperative behavioral alterations, suggesting a potential role of inflammation in the behavioral recovery of pediatric OSAHS patients post-surgery. The observed gradient decrease in postoperative behavioral scores across groups, most significant in the markedly effective group, further underscores the close relationship between therapeutic efficacy and behavioral improvement. Preoperatively, both HMGB-1 and SII levels exhibited a graded increase from the markedly effective to the ineffective group, supporting the notion that higher levels of HMGB-1 and systemic inflammation may contribute to the severity of behavioral disturbances. This reinforces the proposed mechanism whereby HMGB-1 impacts neurological function and behavioral recovery through the promotion of inflammatory cascades.

With the increasing emphasis on sleep health in society, sleep medicine has developed rapidly and become a hot research field.[20] Childhood OSAHS, a prevalent condition with significant morbidity,[21] arises primarily from anatomical upper airway obstruction often associated with adenotonsillar hypertrophy, obesity, craniofacial anomalies, or allergic rhinitis. These factors, alone or in combination, lead to intermittent hypoxia and sleep fragmentation.[22] During critical neurodevelopmental periods, the resulting chronic hypoxemia poses a substantial risk for potential neurological damage and associated behavioral deficits.[23] Given the serious consequences of untreated OSAHS and the focus on predicting surgical outcomes for optimized long-term management, identifying biomarkers like HMGB-1 and SII is clinically relevant.

Recent evidence indicates that sleep-related motor activities, particularly sleep bruxism, frequently coexist with sleep-disordered breathing and may share underlying neurophysiological pathways with OSAHS.[24] Complementary research on portable physiological monitoring devices further illustrates the potential for objective characterization of complex sleep-related conditions in apnea populations.[25] Additionally, insights from pulmonary rehabilitation regarding respiratory gas exchange adaptation may offer relevant perspectives for interpreting postoperative functional recovery in sleep-disordered breathing.[26]

HMGB-1, a prototypical damage-associated molecular pattern (DAMP) molecule, is released during cellular stress, injury, or hypoxia.[27,28] It activates inflammatory pathways (eg., via TLRs and RAGE) and plays a pivotal role in various pathological states, ranging from acute infections to chronic inflammatory and neurological diseases.[29] While involved in tissue homeostasis under physiological conditions, its dysregulated release in pathology drives excessive inflammation.[30] SII, integrating neutrophil, lymphocyte, and platelet counts, provides a robust composite measure of systemic inflammatory status, with higher values indicating increased inflammation. Based on the established role of HMGB-1 in inflammation, the comprehensive nature of SII, and the mediation effect observed in this study, we propose that HMGB-1 adversely affects postoperative behavioral recovery partly by upregulating systemic inflammation. Specifically, pathological HMGB-1 release activates inflammatory signaling, elevates systemic inflammatory burden (reflected by increased SII), which in turn may negatively impact the central nervous system, hindering neural repair and functional recovery, thus impeding behavioral improvement. Conversely, reducing HMGB-1 or mitigating its triggered inflammation could lower SII, alleviate systemic inflammation, and foster a more favorable environment for neurological recovery and behavioral gains. Clinically, the observed behavioral improvements post-adenotonsillectomy are crucial, potentially influencing not only perioperative recovery but also long-term neuropsychological development.[31]

Our analysis within this pediatric OSAHS surgical cohort revealed a preoperative gradient: higher serum HMGB-1 and SII levels predicted smaller reductions in postoperative behavioral scores (ie., poorer improvement). Mediation analysis confirmed that HMGB-1 indirectly impedes behavioral improvement by increasing SII, suggesting that the "HMGB-1 → SII (Systemic Inflammation) → Neuroinflammation → Behavioral Outcome" axis may be a key regulatory pathway for postoperative recovery in these children. Consequently, preoperative combined assessment of HMGB-1 and SII may offer utility for exploratory risk stratification, identifying children at risk for suboptimal short-term behavioral recovery who may

warrant closer perioperative monitoring. However, these findings require validation in independent cohorts before consideration for clinical implementation, and any therapeutic implications remain speculative at this stage.

We emphasize that this study is exploratory in nature, designed to identify associations between preoperative inflammatory biomarkers and short-term behavioral trajectories rather than to establish causal mechanisms or clinical practice changes. The observed relationships between peripheral HMGB-1/SII and parent-reported behavioral outcomes suggest potential inflammatory pathways but cannot confirm direct neurobiological mechanisms or long-term neurobehavioral trajectories. Several limitations should be acknowledged. First, while ROC curves indicated strong predictive performance for HMGB-1 (AUC 0.890), such high predictive performance derived from a relatively small single-center cohort should be interpreted cautiously. External validation in larger, multi-center studies is necessary before these biomarkers could be considered clinically applicable predictive tools. Second, this single-center, prospective observational design and relatively modest sample size may limit the generalizability and stability of the findings. Third, behavioral assessment relied solely on the parent-reported Rutter Behavior Scale, which, while validated, is subjective and could be complemented by objective neuropsychological tests in future work. Fourth, we measured HMGB-1 and SII only preoperatively; serial postoperative measurements and correlations with neuroimaging or neurotransmitter profiles would provide deeper mechanistic insights. Fifth, behavioral outcomes were assessed only at one month post-surgery, leaving longer-term trajectories unexplored. Sixth, we lacked objective overnight sleep study data for all patients; baseline disease severity was approximated using clinical indicators and preoperative behavioral scores. Finally, the observational nature precludes definitive causal inference, despite the mediation analysis suggesting pathways. Causality requires confirmation through interventional studies or animal models.

Future research should focus on: (1) Expanding sample sizes and conducting multi-center validation; (2) Extending follow-up to evaluate long-term behavioral outcomes; (3) Investigating whether perioperative anti-inflammatory interventions can improve behavioral recovery, offering novel targets for managing pediatric OSAHS.

Conclusion

In conclusion, this study identifies elevated preoperative HMGB-1 levels as associated with reduced short-term behavioral improvement after OSAHS surgery in children, with a pattern consistent with partial mediation through systemic inflammation as reflected by SII. These findings illuminate potential inflammatory pathways underlying postoperative behavioral abnormalities and provide a rationale for preoperative risk stratification and the exploration of targeted perioperative interventions in high-risk children. Furthermore, this exploratory work is compatible with the hypothesis that systemic inflammatory markers are associated with behavioral outcomes following OSAHS surgery, supporting future research into inflammatory pathways and their potential relevance to postoperative recovery. Causal mechanisms and clinical utility require confirmation in larger, validated cohorts with longer follow-up periods.

Trial Registration

The study was registered with the Chinese Clinical Trial Registry (Registration No.: ChiCTR2500103471).

Abbreviations

HMGB-1, High-Mobility Group Box-1; SII, Systemic Immune-Inflammation Index; OSAHS, Obstructive Sleep Apnea-Hypopnea Syndrome; ASA, American Society of Anesthesiologists; BMI, Body Mass Index; MAP, Mean Arterial Pressure; HR, Heart Rate; PACU, Post-Anaesthesia Care Unit; LOS, Length of Hospital Stay; FLACC, Face, Legs, Activity, Cry, Consolability; OR, Odds Ratio; CI, Confidence Interval; IQR, Interquartile Range; SD, Standard Deviation; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve.

Data Sharing Statement

All data and protocols used and analyzed in this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study protocol was approved by the Medical Ethics Committee of Changzhi People's Hospital (Approval No.: 2024060). Written informed consent was obtained from all participants or their legal guardians prior to study enrollment. This study adhered to the principles of the Declaration of Helsinki.

Author Contributions

Jiarun Qin: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review and editing.

Xiaoyan Ma: Conceptualization, Resources, Writing – review and editing.

Jiangbo Qin: Conceptualization, Resources, Writing – review and editing.

Jialei Zhang: Data curation, Writing – review and editing.

Mengyuan Ge: Data curation, Writing – review and editing.

Kai Shen: Data curation, Writing – review and editing.

Dacheng Gu: Formal analysis, Writing – review and editing.

Yifan Liu: Formal analysis, Writing – review and editing.

Jianing Bo: Formal analysis, Writing – review and editing.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this study.

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