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Therapeutic drug monitoring-guided individualized caffeine dosing for apnea of prematurity: Clinical efficacy and association with early neurobehavioral outcomes in preterm infants

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Abstract: **Background**: Given the high incidence of apnea of prematurity (AOP) and the repeated hypoxia-induced nerve damage, treatment optimization from the dosing perspective is critical. Caffeine is the current first-line therapeutic drug for AOP. However, the conventional dose results in low blood concentration compliance, with significant variation among individuals. **Objectives**: To explore the clinical efficacy and safety of a therapeutic drug monitoring (TDM)-guided individualized caffeine dosage regimen and its association with early neurobehavioral development and weight gain in preterm infants (PTIs). **Methods**: In this retrospective propensity score-matched cohort study, 130 PTIs with AOP were included after 1:1 matching, with 65 infants in the TDM-guided individualized dosing group and 65 in the conventional fixed-dose group. Inter-group comparative assessments were conducted from the perspectives of blood drug concentration compliance rates, apnea control, adverse reactions, neurobehavioral development scores, clinical outcomes and weight gain rates. **Results**: Compared with the conventional fixed-dose group, the TDM-guided individualized dosing group had a significantly higher target attainment rate of blood caffeine concentration (92.31% vs 70.77%; OR=5.22, 95% CI 1.68-12.74, P=0.002), lower apnea episode frequency at 4 weeks (MD -1.40 times/day, 95% CI -2.13 to -0.67, P<0.001), lower overall incidence of adverse reactions (6.15% vs 20.00%; OR=0.26, 95% CI 0.09-0.87, P=0.035), higher NBNA score at 40 weeks of corrected gestational age (MD 1.74, 95% CI 1.23-2.25, P<0.001), shorter hospital stay (MD -4.11 days, 95% CI -6.51 to -1.71, P=0.001) and faster weight gain rate (MD 7.88 g/day, 95% CI 3.21-12.55, P=0.001). **Conclusion**: The TDM-guided individualized caffeine dosing regimen was associated with improved precision of AOP treatment, better short-term therapeutic efficacy and safety, and higher early neurobehavioral assessment scores and weight gain in preterm infants within 6 months of corrected gestational age. Multicenter studies with longer follow-up are needed to further verify its long-term clinical benefits.

Keywords: Apnea of prematurity; Caffeine; Neurobehavioral development; Preterm infants; Therapeutic drug monitoring

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INTRODUCTION

Apnea of prematurity (AOP) is one of the most common emergencies in the neonatal intensive care unit (NICU) (Pergolizzi *et al.*, 2022; Canning *et al.*, 2025), with an incidence negatively correlated with gestational age: reaching 85% in preterm infants (PTIs) ≤34 weeks' gestation, over 90% in very-low-birth-weight infants and nearly 100% in extremely preterm infants (gestational age <28 weeks) (Erickson *et al.*, 2021). Defined as respiratory pauses lasting ≥20s (or <20s with concurrent bradycardia and hypoxemia), AOP is caused by immature respiratory center function (Martin *et al.*, 2022; Thompson *et al.*, 2024). Caffeine is the first-line pharmacotherapy for AOP, as it stimulates the respiratory center, enhances diaphragmatic contractility, and is recommended for routine use in multiple clinical guidelines (Bruschettini *et al.*, 2023). However, PTIs have marked interindividual variability in caffeine pharmacokinetics due to immature hepatic and renal function. Under conventional fixed-dose regimens, only 40%-60% of PTIs maintain blood caffeine concentrations within the 5-20 μg/mL therapeutic window: 20%-30% have subtherapeutic concentrations with persistent AOP and 10%-15% develop dose-related adverse effects such as tachycardia and irritability (Dai *et al.*, 2022; Saini & Kumar, 2021). Thus, the safety and efficacy of conventional fixed-dose caffeine regimens remain suboptimal.

Therapeutic drug monitoring (TDM) enables individualized dose adjustment by precisely quantifying blood drug concentrations and is widely used to optimize pharmacotherapy in both adult and pediatric populations (B *et al.*, 2023; Coggins *et al.*, 2026). While TDM has been applied to caffeine therapy for AOP, existing studies have notable limitations: most focus solely on short-term apnea control efficacy, have small sample sizes, lack systematic long-term follow-up, and pay insufficient attention to the impact of TDM-guided dosing on neurobehavioral development in PTIs (Long *et al.*, 2022; Long *et al.*, 2021). Given that repeated intermittent hypoxia from AOP is a major driver of neurodevelopmental impairment in this population (El-Saie & Shivanna, 2024), there remains a lack of individualized caffeine regimens that simultaneously balance treatment efficacy, safety and neurodevelopmental outcomes.

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Consequently, this study developed a TDM-guided individualized caffeine dosing regimen with standardized dynamic dose adjustment. It systematically evaluated its efficacy, safety and association with early neurobehavioral outcomes in PTIs with AOP via multi-time-point follow-up up to 6 months of corrected gestational age. Specifically, this study addressed three key gaps in existing research: (1) Most studies focus solely on short-term apnea control, with limited data on comprehensive clinical benefits including safety, neurobehavioral outcomes and weight gain; (2) Previous relevant studies have small sample sizes and lack standardized, clinically feasible TDM dose adjustment protocols; (3) Few studies have performed continuous multi-time-point neurodevelopmental assessments to clarify the association between TDM-guided caffeine therapy and early neurobehavioral development in PTIs. This study aims to provide evidence-based support for optimizing AOP treatment strategies and advancing precision neonatal clinical pharmacy practice.

MATERIALS AND METHODS

Research design

This retrospective propensity score-matched cohort study was conducted in the NICU of Yongkang First People's Hospital from January 2024 to October 2025. The medical records of preterm infants diagnosed with apnea of prematurity and treated with caffeine were retrospectively reviewed. Infants were divided into the TDM-guided individualized dosing group and the conventional fixed-dose group according to the caffeine dosing strategy actually used during hospitalization. Ethical clearance has been obtained from the Ethics Committee of Yongkang First People's Hospital (No. Y2024152), together with signed written informed consent provided by the guardians of all enrolled research participants. The research process strictly adhered to the Helsinki Declaration and related principles of medical ethics.

Study size and propensity score matching

Propensity score matching was performed to reduce baseline imbalance between the TDM-guided individualized dosing group and the conventional fixed-dose group. The propensity score was estimated using a logistic regression model including gestational age, birth weight, sex, time of first AOP onset, multiple birth status, antenatal steroid exposure, grade I-II intraventricular hemorrhage within 72 h after birth, early enteral nutrition and maternal educational level. A 1:1 nearest-neighbor matching strategy was applied. After matching, 130 infants were included in the final analysis, with 65 infants in each group (the screening process is shown in table S1).

Case selection criteria

Fulfillment of all the following criteria means eligibility: (1) a gestational age of 28-34 weeks and a birth weight of 1000-2500 g; (2) an AOP diagnosis by referring to relevant diagnostic criteria (apnea duration ≥20s, or apnea duration <20s with heart rate <100 beats/min and transcutaneous oxygen saturation <85%); (3) the development of the initial AOP attack within 24-72h after birth; (4) no contraindications for caffeine use; (5) voluntary participation with signed informed consent obtained from the guardians. Exclusion is indicated if any of the following criteria is met: (1) congenital respiratory malformations, congenital heart disease, or neurological disorders (cerebral palsy, hydrocephalus, etc.); (2) severe infections (e.g., septicemia, purulent meningitis) or hepatorenal insufficiency (serum creatinine >88 μmol/L, alanine aminotransferase >80 U/L); (3) allergies to caffeine or research-related reagents; (4) post-birth mechanical ventilation treatment duration >72 hours; (5) incomplete clinical data or the guardian's inability to cooperate to complete the long-term follow-up.

Baseline data collection

The following baseline characteristics and potential confounding factors were collected for all enrolled infants: gestational age, birth weight, gender, time of first AOP onset, multiple birth status, antenatal steroid exposure, severity of respiratory distress (assessed by Silverman-Andersen score within 2h after admission), incidence of grade I-II intraventricular hemorrhage (IVH) within 72h after birth, early enteral nutrition implementation and maternal socioeconomic status (assessed by maternal educational level). All the above indicators are core clinical factors related to neurodevelopmental outcomes in preterm infants. All enrolled infants received a standardized early enteral nutrition protocol (initiation within 24-48h after admission with consistent feeding advancement criteria) to minimize nutritional confounding. To reduce variability in post-discharge management, all infants were discharged according to the same unit criteria and caregivers received standardized instructions on feeding, medication use and scheduled follow-up. However, post-discharge home environment, caregiver practices and community healthcare exposure could not be fully standardized and were therefore considered potential sources of residual confounding.

Grouping

Treatment grouping was determined retrospectively according to the caffeine dosing strategy recorded in the medical records. Infants who received caffeine therapy with dose adjustment guided by serum caffeine concentration monitoring were assigned to the TDM-guided individualized dosing group. Infants who received conventional fixed-dose caffeine therapy without TDM-guided dose adjustment were assigned to the conventional fixed-dose group. No prospective randomization or allocation concealment was performed.

Intervention measures

Both groups were given basic treatments, including keeping warm in the incubator, providing nutritional support, maintaining electrolyte balance and preventing infections. On this basis, caffeine treatment was administered. Control group (conventional dose group): Patients received routine fixed-dose caffeine treatment: a loading dose of 20 mg/kg was given, which was mixed with 5 mL of 5% glucose injection for intravenous drip for ≥30 minutes; 24 hours following loading dose administration, a maintenance dose of 5 mg/kg was given, administered intravenously once daily for a duration of ≥30 minutes. The treatment lasted for 4 weeks.

Experimental group (TDM-guided individualized dosing group): With the effective blood concentration range of caffeine (5-20 μg/mL) as the target, an individualized dosing plan was formulated based on the TDM results. (1) The same initial dose as in the control group (loading dose 20 mg/kg) was administered; (2) Blood concentration detection: 2 mL of venous blood was collected 12 hours after loading dose administration, 30 minutes before the first administration of maintenance dose and once a week following maintenance dose administration. The serum, obtained by centrifugation, was analyzed for blood caffeine concentration by high-performance liquid chromatography (HPLC). The instrument used was a high-performance liquid chromatograph (Agilent 1260), with paternoster setting as follows: chromatographic column: C18 column (4.6 mm×250 mm, 5 μm), mobile phase: methanol-water mixture (40:60, V/V), flow rate: 1.0 mL/min, detection wavelength: 273 nm, column temperature: 30℃ and injection volume: 20 μL. This detection method has been methodologically verified, with a linearity range of 5-50 μg/mL (r=0.9996), a recovery rate of 95.2%-102.3% and an RSD of <5%, meeting the requirements for TDM detection. (3) Dose adjustment strategy: If the blood concentration was below 5 μg/mL, the maintenance dose was increased by 1 mg/kg with the maximum not exceeding 8 mg/kg; in case of a blood concentration over 20 μg/mL, the maintenance dose was reduced by 1 mg/kg (not lower than 3 mg/kg); no dosage adjustment was performed when the blood concentration was in the range of 5-20 μg/mL. The treatment was continued for 4 weeks, during which the dose was dynamically adjusted according to the blood concentration test results.

Endpoints

Apnea episodes: The frequency (times/day) and average duration (min/time) of apnea episodes in both groups were recorded at 1, 2, and 4 weeks post-intervention, with data collected by a specially assigned person using monitoring devices and bedside observations. Additionally, the adverse reactions that occurred during the treatment were monitored. Neurobehavioral development: At 40 weeks, 3 months and 6 months of corrected gestational age, neurobehavioral development was evaluated by the Neonatal Behavioral Neurological Assessment (NBNA) Scale (Zhou *et al.*, 2021) (full score 40, score <35 indicating abnormal development) and the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). The Bayley-III assessment covers five core domains: Receptive language, Expressive language, Fine motor, Gross motor development, with higher scores in each domain indicating better developmental function. All neurobehavioral assessments were performed by two trained neonatologists blinded to group allocation and the final score was the average of the two evaluations to minimize observer bias. Follow-up was conducted up to 6 months of corrected gestational age because this time point is commonly used to assess early neurobehavioral status in preterm infants and was feasible for standardized follow-up in our single-center cohort. In the present study, the 6-month assessment was intended to describe short-term developmental status rather than to serve as a surrogate for definitive long-term neurodevelopmental outcomes.

Statistical analysis

Data processing was performed with SPSS 26.0. This study used the mean±standard deviation to statistically describe the measurement data, and comparisons employed independent-samples t tests (between groups) and paired-samples t tests (within groups across time points); data from repeated measurements were analyzed using repeated-measures analysis of variance. The counting data were presented as counts (percentages), with comparisons between groups performed using $\chi 2$ tests or Fisher's exact test. Multivariable linear regression analysis was used to adjust for the measured baseline covariates collected in this study, including gestational age, birth weight, sex, time of first AOP onset, multiple birth status, antenatal steroid exposure, Silverman-Andersen score on admission, grade I-II intraventricular hemorrhage within 72 h after birth, early enteral nutrition and maternal educational level, when comparing neurobehavioral development scores and weight gain rates between the two groups. These analyses were performed to assess whether the observed between-group differences remained after adjustment for measured baseline factors; unmeasured NICU practice-related and post-discharge environmental influences could not be fully excluded. $P<0.05$ is the significance threshold.

RESULTS

Baseline data of the study subjects

After propensity score matching, 130 preterm infants were included in the final analysis, including 65 infants in the TDM-guided individualized dosing group and 65 infants in the conventional fixed-dose group. Baseline characteristics of the matched cohort are shown in table 1. Baseline characteristics were generally comparable between the two groups after propensity score matching.

Table 1: Comparison of apnea episodes between the two groups.

Groups (65 per group)	Control	Experimental	95%CI	Statistics (t/χ^2)	P	SMD
Gestational age	31.06±2.11	30.65±2.18	-1.16 ~ 0.33	1.104	0.272	0.191
Birth weight (g)	1783.05±323.43	1800.49±310.50	-92.59 ~ 127.51	0.314	0.754	0.055
Male/female	35/30	32/33	0.61 ~ 2.39	0.277	0.599	0.092
Time of first AOP onset (h)	49.26±9.71	46.60±12.56	6.56 ~ 1.24	1.351	0.179	0.237
Single/multiple births	61/4	63/2	0.09 ~ 2.15	Fisher's exact test	0.680	0.147
Antenatal steroid exposure	58 (89.23)	54 (83.08)	0.59 ~ 4.356	0.367	0.545	0.179
Grade I-II IVH within 72h	7 (10.77)	5 (7.69)	0.47 ~ 4.28	0.367	0.546	0.106
Early enteral nutrition within 48h	65 (100.0)	65 (100.0)	1.00 ~ 1.00	1.000	>0.999	0.000
Maternal high school education or above	48 (73.85)	41 (63.08)	0.81 ~ 3.55	1.746	0.186	0.233

Table 2: Comparison of adverse drug reactions between the two groups.

Groups (65 per group)	Rate of reaching the target at 12h after loading dose	The average rate of reaching the target	Abnormal blood drug concentration
Control	37 (56.92)	46 (70.77)	18 (27.69)
Experimental	50 (76.92)	60 (92.31)	5 (7.69)
95%CI	1.15 ~ 5.14	1.68 ~ 12.74	0.08 ~ 0.59
Statistics (χ^2)	5.873	10.021	8.927
P	0.015	0.002	0.003

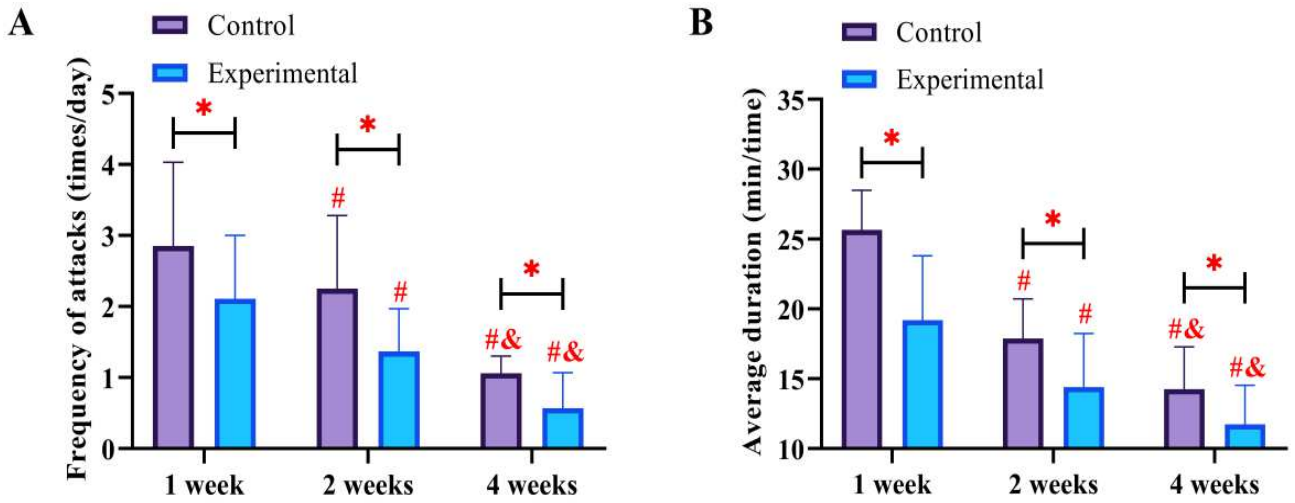

Fig. 1: Changes in (A) apnea episode frequency and (B) average duration in the two groups at 1 week, 2 weeks and 4 weeks post-intervention. # indicates P<0.05 compared with 1 week, & indicates P<0.05 compared with 2 weeks and * indicates P<0.05 compared with control group.

Comparison of the rate of caffeine blood concentration reaching the target

During the treatment period, the proportion of patients achieving target caffeine blood concentrations (maintained at 5–20 μg/mL) was significantly higher in the experimental group than in the control group (P<0.05). At 12 hours after the loading dose, the rate of target attainment was 76.92% (50/65) in the experimental group and 56.92% (37/65) in the control group. During the maintenance phase (administered once weekly), the average target achievement rate was 92.31% in the experimental group compared to 70.77% in the control group. In the control group, 18 cases exhibited abnormal caffeine concentrations: 12 cases were below 5 μg/mL (indicating subtherapeutic levels) and 6 cases exceeded 20 μg/mL (associated with an increased risk of adverse

effects). In contrast, only 5 patients in the experimental group had out-of-range concentrations, all of which were below 5 μg/mL; these were successfully adjusted back into the therapeutic range following dose optimization (Table 2).

The incidence of apnea was compared between the two groups

After intervention, the frequency of apnea attacks in the two groups showed a downward trend, but the decline in the experimental group was significantly greater than that in the control group and there were statistically significant differences between the two groups at each time point ($P<0.05$). The trend in the average apnea duration was consistent with the attack frequency, and the shortening range in the experimental group was significantly better than that in the control group ($P<0.05$) (Fig. 1).

The incidence of adverse drug reactions was compared

During the treatment, the incidence of adverse drug reactions in the experimental group was lower than that in the control group ($P<0.05$). There were 4 cases of adverse reactions in the experimental group, with an incidence rate of 6.15%, including 2 cases of restlessness and 2 cases of vomiting, all mild and not affecting treatment. In the control group, 13 cases had adverse reactions, of which 3 were relieved after a brief adjustment of the dosing interval due to tachycardia (Table 3).

Neurobehavioral development scores were compared between the two groups

At the corrected gestational age of 40 weeks, the NBNA score in the experimental group was 37.69 ± 1.30, significantly higher than that in the control group (35.95±1.40; $P<0.05$). No infants in the experimental group had abnormal NBNA scores (<35 points), whereas 4 infants (6.15%) in the control group did. At the corrected gestational age of 3 months, the experimental group demonstrated significantly higher Bayley-III scores in all assessed domains, including receptive language (93.32±4.84 *vs* 87.45±6.74, $P<0.05$), expressive language (92.22±4.88 *vs* 85.85±6.69, $P<0.05$), fine motor (88.69±5.23 *vs* 83.72±6.55, $P<0.05$) and gross motor (96.86±1.98 *vs* 87.52±4.65, $P<0.05$), compared with the control group. This significant between-group difference in all Bayley-III domains was maintained at the corrected gestational age of 6 months ($P<0.05$) (Fig. 2).

Other clinical indexes were compared

The hospitalization time and oxygen therapy time in the experimental group were significantly shorter than those in the control group, and the mechanical ventilation utilization rate was significantly lower than that in the control group ($P<0.05$) (Table 4).

Comparison of weight gain

After 4 weeks of intervention, there was no stagnation or decline in weight growth in both groups and the weight growth rate of the experimental group was significantly higher than that of the control group ($P<0.05$) (Table 5).

DISCUSSION

In this study, an individualized caffeine dosing regimen was constructed based on TDM and applied to the treatment of AOP in PTIs. The experimental group showed superior performance than the controls, with a higher blood caffeine concentration compliance rate, better apnea symptom control, a lower adverse reaction rate, higher neurobehavioral development scores, more favorable clinical outcomes, and greater weight gain. These findings support the clinical utility of TDM-guided individualized caffeine administration in this setting.

Blood drug concentration is the core determinant of caffeine's therapeutic efficacy and safety in PTIs, given their immature hepatic and renal function and marked interindividual pharmacokinetic variability (Roblin *et al.*, 2024). In this study, our TDM-guided dynamic dose adjustment strategy achieved a significantly higher target attainment rate (92.31%) in the experimental group, consistent with previous reports that TDM improves caffeine concentration compliance to over 85% (Correa *et al.*, 2022). Our relatively large sample size further strengthens the credibility of this finding.

The significantly reduced frequency and duration of apnea episodes, as well as the lower adverse reaction rate in the experimental group, further validate the efficacy and safety of the TDM-guided regimen. The high target attainment rate in the experimental group ensured consistent therapeutic drug exposure within the 5-20 μg/mL window, leading to rapid and stable improvement in apnea symptoms, while subtherapeutic or supratherapeutic concentrations in the control group accounted for poorer symptom control and higher adverse event risk (Petrova *et al.*, 2026).

Caffeine exerts its therapeutic effect by competitively antagonizing adenosine A1 and A2A receptors to stimulate the respiratory center and enhance diaphragmatic contractility, with effects positively correlated with blood concentration within the 5-20 μg/mL therapeutic window (Elmowafi *et al.*, 2022). The high target attainment rate in the experimental group ensured consistent therapeutic drug exposure, leading to rapid and stable improvement in apnea symptoms, whereas subtherapeutic concentrations in nearly 30% of the control group were associated with poorer symptom control (Guo *et al.*, 2021). The lower adverse reaction rate in the experimental group can be attributed to the effective avoidance of supratherapeutic caffeine concentrations via TDM, given the dose-dependent nature of caffeine-related adverse events.

Table 3: Comparison of neurobehavioral development scores between the two groups.

Groups (65 per group)	Fidgety	Tachycardia	Feeding difficulties	Vomiting	Overall incidence
Control	5 (7.69)	3 (4.62)	3 (4.62)	2 (3.08)	13 (20.00)
Experimental	2 (3.08)	0 (0.00)	0 (0.00)	2 (3.08)	4 (6.15)
95%CI					0.09 ~ 0.87
Statistics					Fisher's exact test
P					0.035

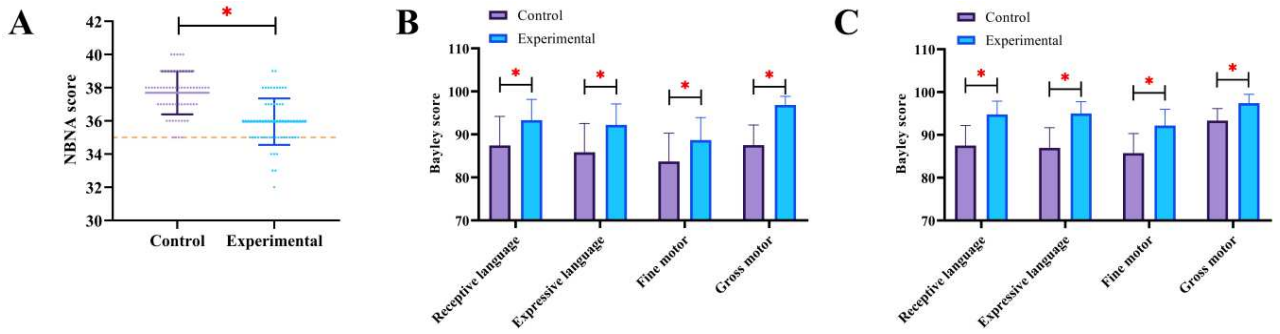

Fig. 2: (A) The NBNA scores of the two groups of children at 40 weeks of corrected gestational age and (B-C) Bayley Scales of Infant Development scores (Receptive language, Expressive language, Fine motor, Gross motor) in the two groups at (B) 3 months and (C) 6 months of corrected gestational age. * indicates P<0.05 compared with the control group.

Table 4: Comparison of other clinical outcomes between the two groups

Groups (65 per group)	Length of stay (d)	Duration of oxygen therapy (d)	Mechanical ventilation
Control	33.08±7.62	17.49±4.80	15 (23.08)
Experimental	28.97±6.15	12.58±3.23	6 (9.23)
95%CI	1.71 ~ 6.51	6.33 ~ 3.49	0.13 ~ 0.89
Statistics (t/χ^2)	3.383	6.839	4.600
P	0.001	<0.001	0.032

Table 5: Comparison of weight-related outcomes between the two groups.

Groups (65 per group)	Weight before treatment (g)	Weight (g) after 4 weeks of intervention	Rate of weight gain (g/day)
Control	1920.15±305.90	2437.86±296.21	18.49±13.25
Experimental	1891.34±320.85	2629.71±322.21	26.37±13.67
95%CI	79.98 ~ 137.61	84.43 ~ 299.31	3.21 ~ 12.55
Statistics (t)	0.524	3.534	3.337
P	0.601	<0.001	0.001

The experimental group had higher neurobehavioral assessment scores during follow-up and this association remained after adjustment for measured baseline covariates. These findings should be interpreted cautiously. A more conservative explanation is that improved apnea control and more stable caffeine exposure may have reduced short-term physiological stress during a vulnerable developmental period, rather than demonstrating a definite long-term neuroprotective effect of individualized caffeine dosing. Recent literature continues to discuss a possible relationship between caffeine exposure and later developmental performance, but the optimal exposure strategy and the underlying causal mechanisms remain uncertain (Tang *et al.*, 2021). The higher weight gain rate observed in the experimental group may likewise reflect better feeding tolerance and fewer treatment-related disturbances.

However, this study has several limitations that should be clearly acknowledged. First, although propensity score matching was used to reduce baseline imbalance between the two groups, the retrospective single-center design may still introduce selection bias and limit the generalizability of the findings. Second, PSM can only adjust for measured covariates; therefore, residual confounding from unmeasured factors, including subtle variations in NICU routine care, clinician decision-making, post-discharge home environment, caregiver practices and

community healthcare exposure, could not be fully excluded. Third, some information was obtained retrospectively from medical records, and potential information bias may exist. Fourth, follow-up was limited to 6 months of corrected gestational age, which reflects only early neurobehavioral outcomes and is insufficient to draw definitive conclusions about the long-term neurodevelopmental effects of the TDM-guided regimen. Finally, pharmacogenomic analysis was not performed in this study. Given that caffeine metabolism may be influenced by genetic variability, the lack of pharmacogenomic data limits further optimization of individualized dosing strategies, which should be addressed in future studies.

CONCLUSION

The TDM-guided individualized caffeine dosing regimen was associated with significantly improved target attainment of serum caffeine concentrations, better short-term efficacy, safety, early neurobehavioral assessment scores and weight gain in PTIs with AOP during follow-up to 6 months of corrected gestational age. These findings support the clinical feasibility of TDM-guided dose adjustment in the NICU, but they should not be interpreted as evidence of definite long-term neurodevelopmental benefit. Multicenter studies with longer follow-up are needed to confirm long-term outcomes and generalizability.

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Author's contributions
All the work for this study was performed by Jiajia Ying.

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Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
Ethical clearance has been obtained from the Ethics Committee of Yongkang First People's Hospital (No. Y2024152). This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest
The authors report no conflict of interest.

Consent to participate
All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Supplementary data
https://pjps.pk/uploads/2026/09/SUP1788606627.pdf

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