Am J Transl Res 2025;17(11):8601-8611
www.ajtr.org /ISSN:1943-8141/AJTR0167041

*Original Article*

# Clinical superiority of artificial intelligence-enabled jaundice monitoring follow-up combined with end-tidal carbon monoxide measurement in neonatal jaundice management

Meng-Meng Kang, Kai Li, Xiao-Ling Zhang, Jia-Wen Zhang

*Department of Neonatology, Guangdong Provincial Maternal and Child Health Hospital, Guangzhou 511442, Guangdong, China*

Received June 25, 2025; Accepted October 10, 2025; Epub November 15, 2025; Published November 30, 2025

**Abstract:** Objective: To evaluate the clinical superiority of artificial intelligence (AI)-enabled jaundice monitoring follow-up combined with end-tidal carbon monoxide (ETCO) measurement in the management of neonatal jaundice. Methods: Sixty jaundiced neonates were studied, with 25 assigned to conventional monitoring and follow-up (control group) and 35 to an AI-enabled jaundice monitoring follow-up plus ETCO assessment (research group). Evaluated endpoints comprised bilirubin concentrations (both serum and transcutaneous), prevalence of hyperbilirubinemia (HB), bilirubin encephalopathy (BE), and ABO hemolytic disease, monitoring/procedure-related adverse events, and time to symptom improvement. The assessment also covered alterations (pre- vs. post-intervention) in the Neonatal Behavioral Neurological Assessment (NBNA), Mental Development Index (MDI), and Psychomotor Development Index (PDI) scores, as well as maternal psychological well-being (Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS)) and parental satisfaction. Results: Post-intervention, the research group exhibited greater reductions in bilirubin, transcutaneous bilirubin, SAS/SDS scores, HB/BE incidence, and overall complications than the control group, coupled with accelerated symptom relief (all $P<0.05$). Post-intervention assessments also confirmed markedly higher NBNA, MDI, and PDI scores, as well as enhanced parental satisfaction in the research group (all $P<0.05$). Conclusion: AI-enabled jaundice monitoring follow-up combined with ETCO measurement offers significant clinical advantages in neonatal jaundice management, supporting its broader clinical adoption.

**Keywords:** Artificial intelligence, jaundice, monitoring and follow-up, end-tidal carbon monoxide, neonate

## Introduction

Jaundice is a preventable and treatable clinical condition in newborns, and it is the leading cause of neonatal readmission during the postnatal period [1, 2]. Statistics indicate that neonatal jaundice affects approximately 60% of full-term infants and 80% of preterm infants, with a mortality rate of up to 10% [3, 4]. Clinically, it is characterized by abnormal yellow discoloration of the sclera and skin [5]. Neonatal jaundice is classified as either physiological or pathological. Physiological jaundice, caused by abnormal bilirubin metabolism, has minimal impact on neonatal health and typically resolves spontaneously without intervention [6]. Pathological jaundice, on the other hand, results from maternal-fetal ABO incompatibility (mother type O, infant type A or B), leading to elevated bilirubin levels. If not addressed promptly, severe hyperbilirubinemia (HB), bilirubin encephalopathy (BE), kernicterus, or other life-threatening complications can arise, posing significant risks to neonatal health and survival [7]. Therefore, timely and effective monitoring of jaundice is crucial for the early detection of high-risk factors and the optimization of neonatal outcomes.

Conventional follow-up for neonatal jaundice typically requires hospital visits, with ABO hemolytic disease of the newborn (ABO-HDN) diagnosis relying primarily on blood sampling and laboratory analysis [8]. In China, with its

https://doi.org/10.62347/JAGX9716

large population, high demographic mobility, and varied educational backgrounds, the post-discharge loss to follow-up is notably high. Delayed identification of high-risk HB in some infants increases the likelihood of severe HB and BE [9-11]. As a result, a new follow-up method - non-invasive, accurate, timely, objective, and convenient - holds considerable clinical value [12]. While remote follow-up systems for neonatal jaundice have been explored, existing methods are often unable to identify high-risk HB populations, leading to inefficient use of medical resources [13]. Additionally, end-expiratory carbon monoxide (ETCO) measurements have shown promise in the early detection of ABO-HDN [14]. Despite potential inaccuracies due to pulmonary conditions and ambient carbon monoxide (CO) interference, ETCO's non-invasive, continuous, bedside nature remains indispensable [15].

This study proposes an innovative approach that combines ETCO testing to accurately identify neonates at high risk of HB with artificial intelligence (AI)-driven remote jaundice monitoring to reduce follow-up attrition. Early identification of hyperbilirubinemic infants, along with targeted treatment guidance, not only reduces the incidence of severe HB and BE but also significantly contributes to improving population health outcomes.

## Materials and methods

### *General data*

In this study, 60 neonates with jaundice were recruited from April 2022 to March 2023. The control group, consisting of 25 neonates, received conventional monitoring and follow-up care. In contrast, the research group, comprising 35 neonates, underwent AI-enabled jaundice monitoring along with ETCO testing. Ethical approval was granted by the Guangdong Provincial Maternal and Child Health Hospital Ethics Committee.

### *Case selection criteria*

Inclusion criteria: (1) All enrolled infants met the diagnostic criteria for neonatal jaundice: Maternal blood type O and neonatal blood type A or B; Postnatal age between 1 and 28 days; Gestational age between 32 and 40 weeks; Serum bilirubin ≥ 220.6 μmol/L [16]. (2) All cases were full-term births. (3) Infants were free of severe congenital disorders. (4) Infants had received regular antenatal care and delivery at the hospital's obstetrics department, with complete medical records.

Exclusion criteria: (1) Infants requiring hospitalization for conditions other than HB. (2) Infants born via in vitro fertilization, as twins, or as part of multiple pregnancies. (3) Infants diagnosed with severe infections and hematological disorders. (4) Infants who failed to complete the experimental procedures as planned.

### *Intervention approaches*

The control group received traditional monitoring and follow-up. Post-birth, neonates were assessed for jaundice at maternal and child health care institutions or community health service centers using traditional methods, including visual inspection, transcutaneous bilirubin (TCB) measurement, and serum bilirubin assays. Specifically, the initial TCB or total serum bilirubin (TSB) was measured within 24 hours of birth. A second measurement was conducted within 72 hours prior to discharge, with results plotted on an hour-specific bilirubin percentile graph (Bhutani Nomogram) for reference.

Post-discharge follow-up: Neonates categorized as low-risk (bilirubin <75th percentile [P75]) were evaluated twice: once between days 3-5 and again between days 7-10. High-risk neonates (with risk factors or bilirubin ≥ P75) underwent daily reassessment until a sustained downward trend in bilirubin was confirmed. A follow-up at 14-21 days was performed to rule out late-onset or breast milk-associated jaundice. During hospitalization, blood sampling or TCB/TSB testing occurred each morning between 8:00 and 10:00 a.m. For home-based follow-up, parents were required to complete TCB testing at community health centers or maternal and child care centers from 8:00 to 9:00 a.m, with supplementary TSB testing if necessary.

Intervention thresholds for abnormal bilirubin values (Bhutani nomogram):

Full-term infants: (1) 24-48 hours after birth: Intervention was initiated if TCB ≥ 257 μmol/L (15 mg/dL) or TSB ≥ P95 for the infant's hour of

age. (2) 48-72 hours after birth: Intervention was initiated when TCB ≥ 290 μmol/L (17 mg/dL) or TSB ≥ P95. (3) Beyond 72 hours: Intervention was activated if TCB ≥ 342 μmol/L (20 mg/dL) or TSB ≥ P95.

Preterm infants or high-risk hemolysis infants: The intervention thresholds were reduced by 1-2 mg/dL. These infants were promptly transferred to a higher-level hospital. Phototherapy was initiated when thresholds were met, and exchange transfusion was considered if TSB ≥ 427 μmol/L (25 mg/dL) or bilirubin levels rose ≥ 8.5 μmol/L per hour. After each intervention, TSB rechecks were conducted every 2-4 hours until the level stabilized below the lower threshold for phototherapy.

The research group received AI-enabled jaundice monitoring and ETCO testing. ETCO screening was performed on neonates within the first 24 hours using the IntelliVue monitor (B1011, Shanghai Jumu Medical Equipment Co., Ltd.). The operational procedure involved measurements taken 1-2 hours post-birth during sleep or quiet states using a nasal sampler at a flow rate of 100 mL/min. Three consecutive 30-second measurements were recorded and averaged. Daily calibration utilized 5 ppm CO standard gas at 30-70% humidity and 22-26°C. An ETCO elevation of ≥ 2.5 ppm [17] indicated neonatal hemolysis and HB risk, triggering entry into the AI tracking system for bilirubin monitoring. Severe bilirubin elevation prompted medical intervention.

*Analysis indexes*

Bilirubin and TCB levels: Fasting venous blood (3 mL) from the elbow was collected before and after intervention from both groups. bilirubin and TCB concentrations were measured using an automatic biochemical analyzer after serum separation.

Incidence rates of HB, BE, and ABO-HDN positivity: HB was diagnosed using the American Academy of Pediatrics neonatal hour-specific bilirubin nomogram [18], with total bilirubin levels exceeding the 95th percentile considered indicative of the condition. BE diagnosis included neurological symptoms (e.g., reduced muscle tone, lethargy, high-pitched crying, poor sucking), hyperintensity in the basal ganglia globus pallidus on MRI T1WI sequences, and prolonged latency in brainstem auditory evoked potential (BAEP). ABO-HDN was defined as maternal-fetal blood group incompatibility, with positive Coombs' and/or antibody release tests.

Complication rates: The occurrence of neonatal complications (e.g., necrotizing enterocolitis, hypoglycemia, infections) was recorded, and the overall complication rate was calculated.

Monitoring/procedure-related adverse events: Both groups were evaluated for adverse events, including device malfunction/data loss, caregiver misinterpretation of alerts, nasal cannula irritation, respiratory depression/oxygen desaturation, skin indentations, subcutaneous bruising, and low-grade fever.

Symptom recovery time: Key time indicators, such as jaundice clearance time, first defecation time, and meconium discoloration time, were compared between groups.

Neonatal neurobehavioral assessment: Neurodevelopment was evaluated using the Neonatal Behavioral Neurological Assessment (NBNA) scale [19], which covers five domains: passive muscle tone, primitive reflexes, behavioral ability, active muscle tone, and general assessment (total 20 items, 0-2 points per item, maximum score 40). A score of 35 or higher indicated better neurodevelopment. Assessments were performed by two independent neonatologists, blinded to group assignments, who were provided only with the infant's ID and postnatal age.

Mental development index (MDI) and psychomotor development index (PDI) [20]: Six months post-discharge, infants underwent evaluations of neonatal cognitive and motor development using the MDI and PDI scales. Both scales were scored out of 130, with scores <69 indicating developmental delays. Higher scores were associated with better developmental outcomes.

Maternal negative emotions: Maternal anxiety and depression were assessed using the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) [21] before and after intervention. Each scale consisted of 20 items (total 80 points), with higher scores reflecting more severe symptoms.

**Table 1.** General data of the research groups

| Indicators | Control group (n=25) | Research group (n=35) | $\chi^2$/ Fisher | P |
|---|---|---|---|---|
| Sex (male/female) | 13/12 | 19/16 | 0.031 | 0.861 |
| Age (years) | 25.87±4.43 | 27.82±6.50 | 1.299 | 0.199 |
| Gestational week | 38.02±2.38 | 37.82±3.03 | 0.275 | 0.785 |
| Birth weight (kg) | 2.85±0.68 | 2.95±0.67 | 0.566 | 0.573 |
| Educational attainment (≥ high school vs. < high school) | 11/14 | 17/18 | 0.122 | 0.726 |
| Family medical history (yes/no) | 5/20 | 4/31 | | 0.469 |
| Mode of delivery (cesarean section/vaginal delivery) | 10/15 | 10/25 | 0.857 | 0.355 |
| Feeding mode (breastfeeding/formula feeding/mixed feeding | 10/9/6 | 12/12/11 | 0.426 | 0.808 |
| Postnatal weight loss percentage | 5.04±1.60 | 4.76±1.82 | 0.617 | 0.540 |

Note: Postnatal weight loss percentage is defined as the highest weight drop recorded in the first 72 hours of life relative to the birth weight. The Fisher's exact test was applied to evaluate the disparity in family medical history across the two groups.

Parental satisfaction: A hospital-developed questionnaire assessed parental satisfaction across several dimensions (e.g., equipment functionality, communication effectiveness, anxiety relief, overall recommendation willingness), with a total score of 100. Scores were categorized as: "very satisfied" (>90), "satisfied" (80-90), "average" (70-79), or "dissatisfied" (<70). The satisfaction rate combined "very satisfied", "satisfied", and "average" responses.

All measurements were conducted by community nurses, who received standardized training and remained unaware of group assignments. The instruments automatically recorded the data, which was later uploaded to the cloud and uniformly exported by the research team. To minimize biases, several measures were implemented:

Assessors recalibrated their scale operation skills quarterly to verify consistency in item understanding, scoring adherence, and individual tendencies.

The order of assessments during same-day follow-ups was randomized by a computer program to prevent time-related biases.

Follow-up sites were equipped with one-way glass, and lighting and noise levels were standardized across all sites to reduce environmental interference.

*Statistical analysis*

Bartlett's variance homogeneity test and the Kolmogorov-Smirnov normality test were used to assess the quantitative data. The data was confirmed to have homogeneous variances and an approximate normal distribution and was thus expressed as mean ± standard deviation ($\bar{x}$ ± sd). The independent samples t-test was used to assess inter-group differences in quantitative data, while the paired t-test was employed to analyze intra-group variations (pre- vs. post-intervention). Intergroup comparisons of categorical data (presented as percentages) were performed using the chi-square test. All data were processed using SPSS 22.0 statistical software, with a significance threshold set at $P<0.05$. The sample size was confirmed to be adequate through a post-hoc power analysis conducted in PASS, which indicated over 80% power at $\alpha=0.05$ for detecting a 20% absolute difference in HB incidence (30% vs. 10%).

## Results

*Comparison of baseline characteristics*

No significant differences were found between groups in baseline characteristics, including sex distribution, age, gestational week, birth weight, educational attainment, family medical history, mode of delivery, feeding mode, and postnatal weight loss percentage (all $P>0.05$). See **Table 1**.

*Comparison of bilirubin and TCB levels*

Before intervention, there were no significant differences in bilirubin or TCB levels between the groups (both $P>0.05$). Post intervention, both indices showed a significant reduction in both groups (both $P<0.05$), with the research

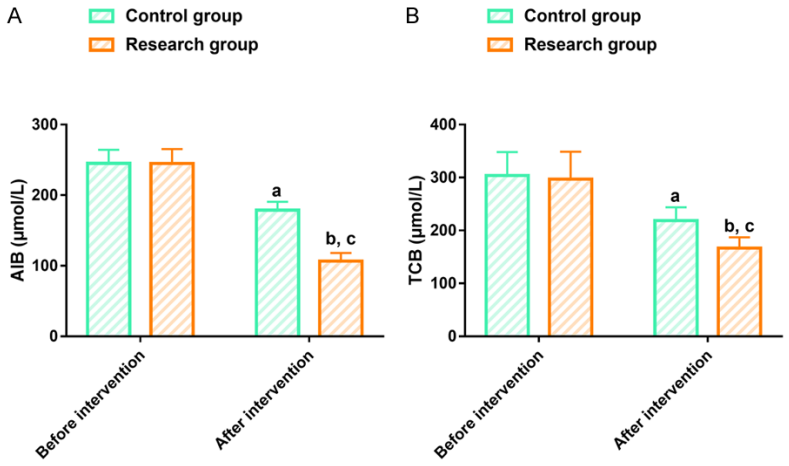


**Figure 1.** Comparative analysis of bilirubin and TCB levels. A. Changes in bilirubin levels pre- and post-intervention. B. Pre- and post-interventional TCB levels in two groups. Note: TCB, transcutaneous bilirubin; [a]P<0.05, [b]P<0.01, versus pre-intervention; [c]P<0.05, versus the control group.

**Table 2.** Incidence rates of hyperbilirubinemia, bilirubin encephalopathy, and ABO hemolytic disease of the newborn

| Indicators | Control group (n=25) | Research group (n=35) | P |
|---|---|---|---|
| Hyperbilirubinemia | 8 (32.00) | 3 (8.57) | 0.039 |
| Bilirubin encephalopathy | 5 (20.00) | 1 (2.86) | 0.073 |
| ABO hemolytic disease of the newborn | 5 (20.00) | 2 (5.71) | 0.117 |

Note: As the sample size in one group was fewer than five (n<5) for all above metrics, Fisher's exact test was used to assess intergroup differences. ABO, ABO blood group system.

**Table 3.** Intergroup comparison of complications rates

| Indicators | Control group (n=25) | Research group (n=35) | P |
|---|---|---|---|
| Necrotizing enterocolitis | 2 (8.00) | 0 (0.00) | 0.170 |
| Hypoglycemia | 2 (8.00) | 1 (2.86) | 0.565 |
| Infections | 5 (20.00) | 2 (5.71) | 0.117 |
| Total | 9 (36.00) | 3 (8.57) | 0.019 |

Note: Intergroup differences for all listed metrics (with n<5 in at least one group) were assessed using Fisher's exact test.

group demonstrating notably lower bilirubin and TCB levels compared to the control group (both P<0.05). See **Figure 1**.

*Comparison of HB, BE incidence, and ABO-HDN positive rate*

The research group had a significantly lower rate of HB (8.57% vs. 32.00%, P=0.021) compared to the control group. The incidences of BE (2.86% vs. 20.00%) and ABO-HDN (5.71% vs. 20.00%) were similar between the groups (both P>0.05). See **Table 2**.

*Comparison of complication rates*

The overall incidence of complications, including necrotizing enterocolitis, hypoglycemia, and infections, was 8.57% in the research group, significantly lower than the 36.00% observed in the control group (P<0.05). See **Table 3**.

*Comparison of monitoring and procedure-related adverse events*

Safety profiles were similar between groups (P>0.05). In the research group, adverse events included two instances of nasal catheter irritation (resolving spontaneously within 30 seconds without epistaxis or mucosal injury) and one instance of transient skin indentation (due to improper probe placement, resolved within 24 hours without ulceration). The control group experienced two cases of skin indentation from TCB transducer pressure, three cases of self-resolving subcutaneous bruising (due to capillary blood sampling, without subsequent infection or hematoma), and one brief episode of low-grade fever from a dislodged temperature sensor during phototherapy, promptly corrected. No serious adverse events were reported in either group (**Table 4**).

*Inter-group comparison of symptom recovery*

The research group demonstrated significant reductions in jaundice clearance time, time to first defecation, and meconium discoloration time compared to the control group (all P<0.05). Data are presented in **Table 5**.

**Table 4.** Comparison of monitoring and procedure-related adverse events between groups

| Indicators | Control group (n=25) | Research group (n=35) | $\chi^2$ | P |
|---|---|---|---|---|
| Device malfunction/data loss | 0 (0.00) | 0 (0.00) | | |
| Caregiver misinterpretation of alerts | 0 (0.00) | 0 (0.00) | | |
| Nasal cannula irritation | 0 (0.00) | 2 (5.71) | | |
| Respiratory depression/oxygen desaturation | 0 (0.00) | 0 (0.00) | | |
| Skin indentations | 2 (8.00) | 1 (2.86) | | |
| Subcutaneous bruising | 3 (12.00) | 0 (0.00) | | |
| Low-grade fever | 1 (4.00) | 0 (0.00) | | |
| Total | 6 (24.00) | 3 (8.57) | 2.723 | 0.099 |

**Table 5.** Intergroup comparison of symptom recovery time

| Indicators | Control group (n=25) | Research group (n=35) | t | P |
|---|---|---|---|---|
| Jaundice clearance duration (d) | 7.56±2.31 | 6.37±2.06 | 2.097 | 0.040 |
| Time to first defecation (h) | 8.72±2.28 | 6.80±1.64 | 3.798 | <0.001 |
| Meconium discoloration time (h) | 50.68±7.87 | 41.09±8.92 | 4.308 | <0.001 |

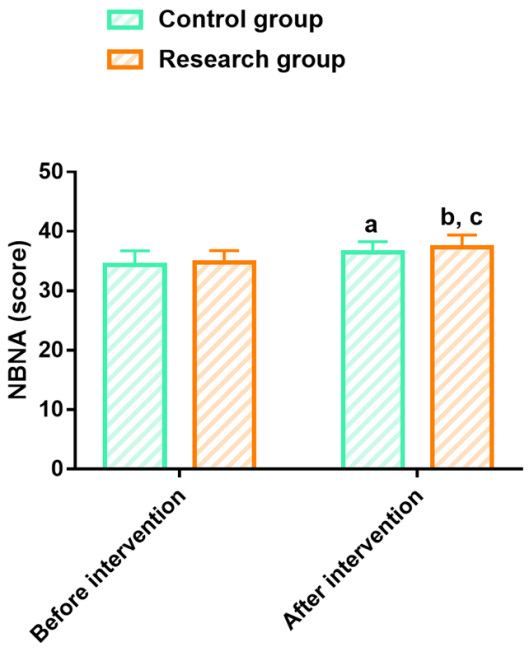


**Figure 2.** Intergroup comparison of NBNA scores before and after intervention. Note: NBNA, Neonatal Behavioral Neurological Assessment; [a]P<0.05, [b]P<0.01 vs. baseline; [c]P<0.05 vs. control.

*Comparison of pre- and post-intervention NBNA scores*

Initial NBNA scores showed no significant difference between groups (P>0.05). Post-intervention, both groups showed significant improvements (P<0.05), with the research group outperforming the control group (P<0.05). See **Figure 2**.

*Inter-group comparison of intellectual and motor development*

The research group scored higher on both the MDI and PDI development scales compared to the control group (both P<0.05). Results are shown in **Figure 3**.

*Comparison of maternal negative emotions*

There were no significant differences in baseline SAS and SDS scores between groups (both P>0.05). Post-intervention, both groups exhibited a significant reduction in scores (both P<0.05), with the research group achieving significantly lower SAS and SDS scores compared to the control group (both P<0.05). See **Figure 4**.

*Comparison of parental satisfaction*

Parental satisfaction in the research group was 94.29%, significantly higher than the 72.00% reported in the control group (P<0.05). See **Table 6**.

## Discussion

Numerous studies have focused on remote neonatal jaundice monitoring, including the use of AI-powered TCB meters and wearable smart devices. These technologies connect to smartphones, enabling at-home monitoring of neonatal bilirubin levels and providing intelligent automatic alerts for abnormal readings [22]. Such innovations facilitate timely detection and

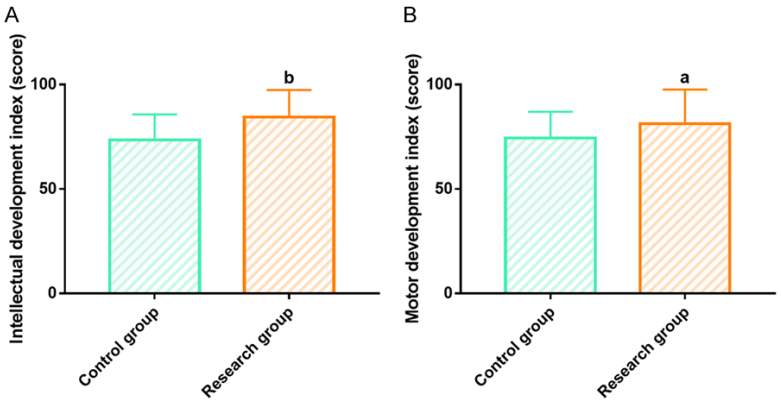


**Figure 3.** Inter-group comparison of intelligence and motor development between two groups of newborns. A. Comparison of neonatal intellectual development (assessed by the Mental Development Index). B. Neonatal motor development (evaluated by the Psychomotor Development Index). Note: [a]P<0.05 and [b]P<0.01 *vs.* before intervention; [c]P<0.05 *vs.* control group.

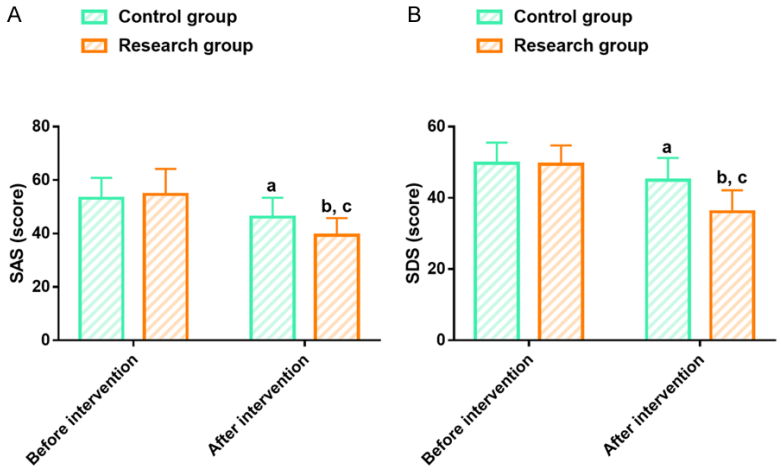


**Figure 4.** Maternal negative emotion scores in both groups. A. Pre- and post-intervention changes in SAS scores. B. Pre- and post-intervention changes in SDS scores. Note: SAS/SDS, Self-Rating Anxiety/Depression Scale; [a]P<0.05 and [b]P<0.01 *vs.* before intervention; [c]P<0.05 *vs.* control group.

**Table 6.** Parental satisfaction rates in both groups

| Indicators | Control group (n=25) | Research group (n=35) | $\chi^2$ | P |
|---|---|---|---|---|
| Very satisfied | 7 (28.00) | 14 (40.00) | | |
| Satisfied | 9 (36.00) | 16 (45.71) | | |
| General | 2 (8.00) | 3 (8.57) | | |
| Dissatisfied | 7 (28.00) | 2 (5.71) | | |
| Overall satisfaction | 18 (72.00) | 33 (94.29) | 5.681 | 0.017 |

intervention to safeguard newborn health while minimizing unnecessary hospital visits [23]. However, current remote jaundice monitoring systems lack the capability to predict high-risk factors, such as ABO-HDN, resulting in the failure to identify key populations (e.g., ABO-HDN) that require monitoring. This limitation can lead to the wastage of medical resources [24]. Consequently, there is an urgent need for a remote jaundice monitoring methodology capable of early detection of high-risk factors and optimization of resource utilization to maximize clinical benefits.

Several studies have evaluated the accuracy of remote jaundice follow-up systems in monitoring bilirubin levels. For instance, Ngeow et al. [25] found that a new smartphone-based machine-learning app correlated well (r=0.84) with laboratory TSB results. Specifically, 82% of data fell within the clinically acceptable range of 3 mg/dL, with 100% sensitivity, 70% specificity, and an AUC (area under the receiver operating characteristic curve) of 0.89 (95% CI, 0.82-0.96). Aune et al. [26] demonstrated that the Picterus smartphone system had strong screening accuracy for neonatal jaundice, particularly in moderate to dark-skinned populations. Their analysis, including a Bland-Altman plot, showed limits of agreement of ±89.2 μmol/L, with a significant positive correlation (r=0.76) between the system's measurements and TSB levels. Shen et al. [27] presented a machine-learning-based smartphone imaging approach as an accessible, non-invasive, and accurate tool for jaundice quantification. The Multilayer Perceptron model achieved high TSB prediction accuracy (r=0.90, root-mean-square error=2.44 mg/dL), identifying 89.4% of neo-

nates with TSB levels exceeding 15 mg/dL, supported by an AUC of 0.96, with 90% sensitivity and 89% specificity.

To improve the clinical practicality of ETCO detection, implementing standardized training for nursing staff, along with daily calibration and environmental CO monitoring, is essential. Additionally, TSB confirmation should be used as a supplement for neonates with pulmonary conditions or those receiving oxygen therapy. Recent studies have highlighted the evolving role of ETCO in managing early-onset hemolysis. For example, Christensen et al. [28] noted its diagnostic potential in perinatal hemolytic disorders, helping to quantify hemolysis severity and supporting efforts to forecast and prevent associated complications. In another study, Christensen et al. [29] emphasized ETCO's utility in monitoring fetal hemolysis, identifying anemia or unexplained neonatal jaundice, and optimizing management by assessing hemolysis duration. Moreover, ETCO corrected for ambient carbon monoxide levels measured upon admission serving as reliable predictors of phototherapy duration in neonates with HB, assisting clinicians in accurately assessing illness severity [30].

This study screened high-risk newborns with ABO-HDN and HB using ETCO detection, followed them up via a remote jaundice monitoring system, and compared various indicators with a traditional neonatal jaundice follow-up control group to explore the clinical superiority of the novel model. Initially, we observed a significant reduction in both bilirubin and TCB levels in the research group compared to the control group, suggesting that ETCO combined with remote AI-enabled jaundice monitoring has a preventive effect on neonatal jaundice cases with elevated bilirubin and TCB. This enables timely and effective interventions to prevent the progressive increase of these biomarkers.

The research group also showed significantly reduced incidences of HB and ABO-HDN compared to the control group, indicating that ETCO plus remote AI-enabled jaundice monitoring helps prevent HB. This could be attributed to the ETCO-based remote AI monitoring system, which serves as an early warning for ABO-HDN or occult hemolysis (ETCO $\geq$ 2.5 ppm) within 1-2 hours of birth, identifying high-risk infants 24-48 hours earlier than conventional methods. This allows for enhanced follow-up and preventive measures before the condition progresses. Previous research has indicated that measuring ETCO within 48 hours of birth is predictive of hemolytic HB [31]. Bhatia et al. [32] reported that an ETCO level exceeding 1.8 ppm indicates hemolysis, with sensitivity and specificity both exceeding 80.0% for diagnosing HB. Herschel et al. [33] demonstrated that ETCO detection is more sensitive for predicting severe jaundice, outperforming the Coombs' test in diagnostic efficiency. This may explain why combining ETCO measurement with remote AI-enabled jaundice monitoring effectively reduces the incidence of severe neonatal jaundice. Additionally, Christensen et al. [28] showed that ETCO monitoring is valuable for early ABO-HDN identification, hemolysis severity assessment, and complication prediction and prevention, thereby contributing to improved clinical outcomes.

The integration of ETCO with remote AI-enabled jaundice monitoring not only mitigated the overall risk of complications such as necrotizing enterocolitis, hypoglycemia, and infections but also significantly shortened the time to jaundice clearance, first defecation, and meconium discoloration, thereby accelerating disease recovery. ETCO, paired with remote AI, enables daily, automated jaundice monitoring. It collects and uploads patient data to the cloud in real-time, integrating this data with the hour-specific Bhutani nomogram to generate preemptive alerts 2-4 hours before bilirubin levels approach critical thresholds. This facilitates timely intervention, preventing treatment delays and improving patient outcomes.

Further evaluation of monitoring procedure-related adverse events revealed a lower overall incidence with the combined ETCO and remote AI jaundice monitoring system. The system mitigates risks through 24/7 cloud backup (preventing data loss), a mandatory app confirmation process with nurse review (preventing user error), and a non-occlusive sensor design (safeguarding against respiratory depression). Post-intervention, the NBNA scores of the research cohort showed significant improvement compared to both baseline values and the control group, demonstrating the positive impact of this combined approach on neurodevelopmental outcomes in jaundiced newborns.

The superiority of the ETCO plus remote AI-enabled jaundice monitoring is further evidenced by the higher MDI and PDI indices in the research group, suggesting its positive effects on intellectual and motor skills. This may be attributed to the model's ability to reduce the incidence of HB, BE, and ABO-HDN, thus protecting neonatal health. Additionally, early intervention facilitated by remote monitoring's preemptive alerts helps reduce peak bilirubin levels. This reduction mitigates the increased permeability of the blood-brain barrier and neuronal oxidative damage in newborns, thereby supporting neurodevelopment [34, 35].

Furthermore, maternal anxiety and depression scores (SAS and SDS) in the research group decreased significantly post-intervention compared to both pre-intervention levels and the control group, highlighting the psychological benefits for caregivers. These findings align with Yan et al.'s [36] research, which reported that remote AI-assisted jaundice monitoring reduces 30-day readmission rates and enhances maternal mental well-being. The decline in neonatal HB incidence and the overall risk of complications may also be linked to the combined ETCO and remote AI-assisted jaundice monitoring, which contributes to improved maternal mood [37]. However, some mothers expressed concerns about the accuracy of the remote monitoring technology and lacked confidence in its use. They suggested incorporating features such as action plans based on readings and clinical symptoms, as well as remote consultation options, to boost both confidence in the system and its adoption rate [22]. Finally, the ETCO-remote AI-enabled monitoring model achieved significantly higher parental satisfaction, indicating strong acceptance of this monitoring approach among families of affected infants.

Several limitations of this study suggest the need for further refinement. First, being a single-center study, its conclusions may be geographically specific, limiting broader applicability. Future research should adopt a multi-center prospective design to improve generalizability. Second, the parental satisfaction assessment relied on a hospital-developed questionnaire, and further evidence is needed to establish its reliability and validity. Third, the study assessed the MDI and PDI of newborns only up to 6 months post-discharge; longer prospective follow-up (≥ 24 months) is necessary to evaluate the long-term effects of both monitoring methods on neurodevelopment. Lastly, no comparison was made between the clinical utility of "AI-based jaundice monitoring + ETCO measurement" and either ETCO-only or AI-only monitoring. Adding such comparative analyses could confirm that the combined approach offers greater synergistic benefits, supporting its wider clinical adoption.

In conclusion, the integration of ETCO measurement and AI-enabled remote jaundice monitoring represents a novel, non-invasive, highly accurate, timely, objective, and safe approach for neonatal jaundice follow-up. This method effectively lowers elevated bilirubin and TCB levels and demonstrates preventive potential against complications such as HB, necrotizing enterocolitis, hypoglycemia, and infections, ultimately facilitating faster recovery in infants. Additionally, this strategy enhances neurodevelopment and motor skills in newborns, alleviates maternal anxiety and depression, and achieves high parental satisfaction.

## Acknowledgements

This study was supported by "A new model for monitoring neonatal jaundice based on artificial intelligence and ETCO", No.: 104287711017.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Jia-Wen Zhang, Department of Neonatology, Guangdong Provincial Maternal and Child Health Hospital, No. 521, Xingnan Avenue, Panyu District, Guangzhou 511442, Guangdong, China. Tel: +86-020-39151760; E-mail: zhangjiawen031@outlook.com

## References

[1] Gidi NW and Siebeck M. Neonatal hyperbilirubinemia treatment by locally made low-cost phototherapy units. Ethiop J Health Sci 2021; 31: 55-62.

[2] Amsalu R, Oltman SP, Baer RJ, Medvedev MM, Rogers EE and Jelliffe-Pawlowski L. Incidence, risk factors, and reasons for 30-day hospital readmission among healthy late preterm infants. Hosp Pediatr 2022; 12: 639-649.

[3] Deng H, Zhou Y, Wang L and Zhang C. Ensemble learning for the early prediction of neonatal jaundice with genetic features. BMC Med Inform Decis Mak 2021; 21: 338.
[4] Birhanu MY, Workineh AA, Molla Y, Abebaw E, Arora A and Bazezew Y. Rate and predictors of neonatal jaundice in northwest Ethiopia: prospective cohort study. J Multidiscip Healthc 2021; 14: 447-457.
[5] Seneadza NAH, Insaidoo G, Boye H, Ani-Amponsah M, Leung T, Meek J and Enweronu-Laryea C. Neonatal jaundice in Ghanaian children: assessing maternal knowledge, attitude, and perceptions. PLoS One 2022; 17: e0264694.
[6] Liu Y, Sun X, Wang Y, Xing C, Li L and Zhou S. Evaluation of associated markers of neonatal pathological jaundice due to bacterial infection. Iran J Public Health 2021; 50: 333-340.
[7] Belay HG, Debebe GA, Ayele AD, Kassa BG, Mihretie GN and Worke MD. Determinants of neonatal jaundice in Ethiopia: a systematic review and meta-analysis. World J Pediatr 2022; 18: 725-733.
[8] Thomas M, Greaves RF, Tingay DG, Loh TP, Ignjatovic V, Newall F, Oeum M, Tran MTC and Rajapaksa AE. Current and emerging technologies for the timely screening and diagnosis of neonatal jaundice. Crit Rev Clin Lab Sci 2022; 59: 332-352.
[9] Duan Y, Yang Z, Bi Y, Wang J, Pang X, Jiang S, Zhang H, Xu L and Lai J. What are the determinants of low exclusive breastfeeding prevalence in China? A cross-sectional study. Matern Child Nutr 2022; 18: e13324.
[10] Li Q, Deng X, Yan J, Sun X, Dong X, Chen X, Han S, Huo J and Yu Z. Neonatal severe hyperbilirubinemia online registry in Jiangsu province: protocol for a multicentre, prospective, open, observational cohort study. BMJ Open 2021; 11: e040797.
[11] Ansong-Assoku B, Adnan M, Daley SF and Ankola PA. Neonatal jaundice. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Mohammad Adnan declares no relevant financial relationships with ineligible companies. Disclosure: Sharon Daley declares no relevant financial relationships with ineligible companies. Disclosure: Pratibha Ankola declares no relevant financial relationships with ineligible companies.: 2025.
[12] Aune A, Vartdal G, Jimenez Diaz G, Gierman LM, Bergseng H and Darj E. Iterative development, validation, and certification of a smartphone system to assess neonatal jaundice: development and usability study. JMIR Pediatr Parent 2023; 6: e40463.
[13] Singh A, Francis HW, Smith PB, Clark RH and Greenberg RG. Association between hyperbilirubinemia and hearing screen failure in the neonatal intensive care unit in infants born preterm. J Pediatr 2021; 231: 68-73.
[14] Osborne J, Sobh M and Trudel G. Carbon monoxide as a clinical marker of hemolysis. Am J Hematol 2023; 98: 1127-1159.
[15] Yang G, Zhang K, Deng L, Liu H, Fu X, Hu Y, Yan X, Zhou X, Luo W, Wang S, Ye X, Zhang T, Li F, Huo Z, Jiang Y, Zeng S, Wu D, Yuan Y and Zhang H. End-tidal carbon monoxide levels as a point-of-care biomarker for the early detection of hemolytic disease in Chinese neonates. Clin Chim Acta 2025; 575: 120368.
[16] Westenberg LEH, van der Geest BAM, Lingsma HF, Nieboer D, Groen H, Vis JY, Ista E, Poley MJ, Dijk PH, Steegers EAP, Reiss IKM, Hulzebos CV and Been JV. Better assessment of neonatal jaundice at home (BEAT Jaundice @home): protocol for a prospective, multicentre diagnostic study. BMJ Open 2022; 12: e061897.
[17] Bhutani VK, Srinivas S, Castillo Cuadrado ME, Aby JL, Wong RJ and Stevenson DK. Identification of neonatal haemolysis: an approach to predischarge management of neonatal hyperbilirubinemia. Acta Paediatr 2016; 105: e189-194.
[18] Zanardo V, Simbi AK, Parotto M, Guerrini P, Severino L, Ferro S and Straface G. Umbilical cord bilirubin level and pre-discharge hyperbilirubinemia risk. J Matern Fetal Neonatal Med 2021; 34: 1120-1126.
[19] Liu C, Messerlian C, Chen YJ, Mustieles V, Huang LL, Sun Y, Deng YL, Cheng YH, Liu J, Liu AM, Lu WQ and Wang YX. Trimester-specific associations of maternal exposure to disinfection by-products, oxidative stress, and neonatal neurobehavioral development. Environ Int 2021; 157: 106838.
[20] Gould JF, Fuss BG, Roberts RM, Collins CT and Makrides M. Consequences of using chronological age versus corrected age when testing cognitive and motor development in infancy and intelligence quotient at school age for children born preterm. PLoS One 2021; 16: e0256824.
[21] Cheng L, Gao W, Xu Y, Yu Z, Wang W, Zhou J and Zang Y. Anxiety and depression in rheumatoid arthritis patients: prevalence, risk factors and consistency between the hospital anxiety and depression scale and Zung's self-rating anxiety scale/depression scale. Rheumatol Adv Pract 2023; 7: rkad100.
[22] Moosa AS, Ngeow AJH, Yang Y, Poon Z, Ng DX, Yi Ling EK and Tan NC. A novel smartphone app for self-monitoring of neonatal jaundice among postpartum mothers: qualitative research study. JMIR Mhealth Uhealth 2023; 11: e53291.

[23] Abiha U, Banerjee DS and Mandal S. Demystifying non-invasive approaches for screening jaundice in low resource settings: a review. Front Pediatr 2023; 11: 1292678.
[24] Du L, Ma X, Shen X, Bao Y, Chen L and Bhutani VK. Neonatal hyperbilirubinemia management: clinical assessment of bilirubin production. Semin Perinatol 2021; 45: 151351.
[25] Ngeow AJH, Moosa AS, Tan MG, Zou L, Goh MMR, Lim GH, Tagamolila V, Ereno I, Durnford JR, Cheung SKH, Hong NWJ, Soh SY, Tay YY, Chang ZY, Ong R, Tsang LPM, Yip BKL, Chia KW, Yap K, Lim MH, Ta AWA, Goh HL, Yeo CL, Chan DKL and Tan NC; BiliSG Study Group. Development and validation of a smartphone application for neonatal jaundice screening. JAMA Netw Open 2024; 7: e2450260.
[26] Aune A, Jimenez-Diaz G, Gierman LM, Vartdal G, Reyes Berlanga M, Tusoy J, Bergseng H, Shakya S and Darj E. Smartphone-based screening of neonatal jaundice in three populations in low and middle-income countries: a cross-sectional study. BMJ Paediatr Open 2025; 9: e002242.
[27] Shen GT, Liu YH, Lin JY, Hsu KC and Chou HH. Development and validation of neonatal jaundice detection using smartphone application. Comput Biol Med 2025; 196: 110845.
[28] Christensen RD, Bahr TM, Pakdeeto S, Supapannachart S and Zhang H. Perinatal hemolytic disorders and identification using end tidal breath carbon monoxide. Curr Pediatr Rev 2023; 19: 376-387.
[29] Christensen RD, Bahr TM, Ohls RK and Moise KJ Jr. Neonatal/perinatal diagnosis of hemolysis using ETCOc. Semin Fetal Neonatal Med 2025; 30: 101547.
[30] Zhan YL, Peng HB, Jin ZC, Su JF, Tan XY, Zhao L and Zhang L. Higher ETCOc predicts longer phototherapy treatment in neonatal hyperbilirubinemia. Front Pediatr 2023; 11: 1154350.
[31] Cheng X, Lin B, Yang Y, Yu Y, Fu Y and Yang C. End-tidal carbon monoxide concentrations measured within 48 hours of birth predict hemolytic hyperbilirubinemia. J Perinatol 2024; 44: 897-901.
[32] Bhatia A, Chua MC, Dela Puerta R and Rajadurai VS. Noninvasive detection of hemolysis with ETCOc measurement in neonates at risk for significant hyperbilirubinemia. Neonatology 2020; 117: 612-618.
[33] Herschel M, Karrison T, Wen M, Caldarelli L and Baron B. Evaluation of the direct antiglobulin (Coombs') test for identifying newborns at risk for hemolysis as determined by end-tidal carbon monoxide concentration (ETCOc); and comparison of the Coombs' test with ETCOc for detecting significant jaundice. J Perinatol 2002; 22: 341-347.
[34] Taylor JA, Stout JW, de Greef L, Goel M, Patel S, Chung EK, Koduri A, McMahon S, Dickerson J, Simpson EA and Larson EC. Use of a smartphone app to assess neonatal jaundice. Pediatrics 2017; 140: e20170312.
[35] Perrone S, Lembo C, Giordano M, Petrolini C, Cannavo L and Gitto E. Molecular mechanisms of oxidative stress-related neonatal jaundice. J Biochem Mol Toxicol 2023; 37: e23349.
[36] Yan Q, Gong Y, Luo Q, Yin X, Yang L, Wang H, Feng J, Xing K, Huang Y, Huang C and Fan L. Effects of a smartphone-based out-of-hospital screening app for neonatal hyperbilirubinemia on neonatal readmission rates and maternal anxiety: randomized controlled trial. J Med Internet Res 2022; 24: e37843.
[37] Joshi SS, Benroy BR, Lawrence IN and Suresh TJ. Telemedicine as progressive treatment approach for neonatal jaundice due to the coronavirus disease 2019 pandemic. Clin Exp Pediatr 2022; 65: 269-271.