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REVIEW ARTICLE

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Systematic review of guidelines on neonatal hypoglycemia

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Abstract

Objective: In recent years, a series of clinical guidelines on neonatal hypoglycemia have been developed in different countries and regions. This systematic review was aimed at providing evidence for clinical decision-making and providing ideas for future research by comparatively analyzing the contents of various guidelines.

Methods: A multilateral approach was used, including comprehensive literature searches and online research. The retrieved studies were screened by two independent reviewers according to our inclusion criteria. The two reviewers independently extracted the descriptive data. Four appraisers assessed the guidelines using the AGREE-II instrument.

Results: Ten clinical guidelines on neonatal hypoglycemia were included, with a mean score of 45.28%–83.45% in six domains. The guidelines are relatively consistent in their recommendations on clinical symptoms of neonatal hypoglycemia, but different in risk factors, preventive measures, thresholds for clinical management of hypoglycemia, target glucose ranges for its control, and pharmacotherapy.

Conclusion: By summarising the recommendations in the guidelines on neonatal hypoglycemia, we found that blood glucose values were not the only observational indicator, and other indicators (e.g., ketone bodies, lactate) related to glucose metabolism should also be considered for a comprehensive assessment. There is still a lack of consensus on thresholds for the clinical management of hypoglycemia and target glucose ranges for its control, and the recommendations on its pharmacotherapy are rather simple and sketchy. In the future, more high-quality studies are required to further improve the early identification of neonatal hypoglycemia and intervention strategies against it.

KEYWORDS
hypoglycemia, national guideline, neonate, systematic review

1 | INTRODUCTION

Blood glucose is the body's primary source of energy and also an important part of the homeostatic system. Under the interaction of internal and external factors, it either undergoes adaptive fluctuations to maintain normal metabolism, or it fails to regulate and causes dysfunction of vital organs.[1] In the first few hours after birth, the change from the intrauterine environment to the extrauterine environment results in a series of alterations in various physiological characteristics, such as circulation, energy supply, and hormones. Thus, newborns will experience an initial drop in blood glucose followed by a return to normal levels. This transient drop in blood glucose is typically asymptomatic and called transient hypoglycemia, which is a part of adaptive regulation of the body to maintain homeostasis after birth.[2,3] However, screening and intervention strategies have been established to prevent severe, recurrent and persistent neonatal hypoglycemia, which may cause irreversible damage to the nervous system and lead to neurodevelopmental

abnormalities,[4,5] thereby resulting in a huge economic burden on households and society. Thus, early identification of persistent hypoglycemia and timely intervention are crucial. Nonetheless, excessive intervention can also cause problems including mother-infant separation, interruption of breastfeeding, multiple invasive operations, and a waste of medical resources.[6,7]

In recent years, different countries and regions have developed many clinical guidelines on neonatal hypoglycemia, which contain a series of definitions of neonatal hypoglycemia that cover blood glucose levels, the frequency of blood glucose monitoring, and the clinical manifestations of hypoglycemia. Besides stepwise screening, monitoring, prevention, and intervention are also specified based on symptoms and high-risk factors.

These guidelines give different recommendations on screening, monitoring, and intervention for neonatal hypoglycemia. Thus, it is necessary to summarise them to guide individualised treatment. This systematic review was aimed at providing evidence for clinical decision-making and providing ideas for future research by comparatively analyzing the contents of the guidelines.

2 | MATERIALS AND METHODS

With reference to Amy Johnston et al.'s[8] methodological guidance on systematic review of clinical practice guidelines, we developed a "PICAR" statement to search for the eligible guidelines (Figure S1). This systematic review and meta-analysis was conducted in accordance with the PRISMA statement[9] and has been registered on PROSPERO (Registration No. CRD42023442441).[10] Detailed steps are described below.

Inclusion criteria: (1) disease studied: hypoglycemia; (2) target population: neonates; (3) studies that meet the definition of a guideline, including clinical guidelines, expert consensuses, and statements.

Exclusion criteria: (1) guidelines that are not in Chinese or English; (2) old versions of guidelines developed by the same organisation; (3) guidelines that are not developed and published by associations/societies/groups; (4) guideline-related articles including guideline interpretations, translations, and reviews; (5) studies on guideline adherence; (6) reevaluations of guidelines; (7) guidelines whose full texts are not available.

By using the computer, databases were searched, including PubMed, The Cochrane Library, EMbase, CINAHL, JBI, BMJ, UpToDate, SinoMed, KI, WanFan and CQVIP; guideline websites were also searched, including the National Health Service Evidence, the ACP Journal Club, Guidelines International Network (GIN), Scottish Intercollegiate Guidelines Network (SIGN), New Zealand Guidelines Group, Queensland Clinical Guideline and National Institute for Health and Care Excellence (NICE); and also, professional association websites were searched, including Australian National Health and Medical Research Council (NHMRC), Registered Nurses's Association of Ontario (RNAO), China Centre for Evidence-based Medicine and medlive.cn, so as to collect guidelines on neonatal hypoglycemia, all with a search time frame until 10 February 2023. In addition, references of the included studies were retrospectively searched to supplement access to relevant literature. A combination of subject headings and free-text words was adopted for the search. The specific search strategy is shown in Supporting Information S1 (using Pubmed as an example).

Two reviewers (Luo and Tang) independently screened the literature, extracted information, and cross-checked the results. In case of disagreement, a third party (Zhang) was consulted to assist in judgement. The literature was screened by first reading the titles and abstracts, and after the exclusion of apparently irrelevant literature, full texts were further read to assess the eligibility. The two reviewers (Luo and Tang) independently extracted the descriptive data. Extracted data mainly included (1) general information about the included guidelines, including the name of a guideline, publishing organisation, country, region, time of development/update, and population covered; (2) baseline characteristics of the included guidelines, including the purpose of guideline development, health issues covered, target populations, participants, methods and criteria for retrieving evidence, whether the recommendations are clear and explicit, applicability, and editorial independence; (3) recommendations provided by the guidelines regarding identification, prevention, and intervention of neonatal hypoglycemia.

AGREE II instrument was used to assess the quality of guidelines on neonatal hypoglycemia.[11] Quality assessment of the included guidelines was performed independently by 4 appraisers (Luo, Tang, Zhang and He). AGREE II instrument includes the following domains: (1) Scope and Purpose (3 items); (2) Stakeholder Involvement (3 items); (3) Rigour of Development (8 items); (4) Clarity of Presentation (3 items); (5) Applicability (4 items); and (6) Editorial Independence (2 items). Each item was rated on a 7-point scale based on the assessment criteria, from 1 (*strongly disagree*) to 7 (*strongly agree*). Standardised score (%) of the guideline in a domain = (Obtained score − Minimum possible score)/(Maximum possible score − Minimum possible score) × 100%. All the appraisers were trained online using the AGREE training tools. Discrepancies of >3 points were discussed in a consensus meeting.

We used Microsoft Office Excel 2021 to summarise and compare the general characteristics, quality, and hypoglycemia diagnosis and treatment recommendations of each guideline. The intraclass correlation coefficients for the six domains were calculated to assess the reliability of the scores between investigators. The analysis of the reliability was performed using SPSS 26.0 (IBM Corp.)

3 | RESULTS

A total of 1243 studies were initially retrieved, and 10 guidelines on neonatal hypoglycemia,[2,12–20] published between 2011 and 2022, were finally included after hierarchical screening (Table 1 and Figure S2). Some of the retrieved clinically informative reviews, programs and policies on neonatal hypoglycemia are listed in Appendix 1. Strictly, they are not guidelines, so they were not

TABLE 1 General characteristics.

	Guideline name	Publishing organisation	Country	Region	Time of development/ update	Population covered
AAP [12]	Postnatal Glucose Homeostasis in Late-Preterm and Term Infants	American Academy of Pediatrics	United States	North America	2011	Newborns born with a gestational age (GA) of over 34 weeks
ABM [13]	Guidelines for Glucose Monitoring and Treatment of Hypoglycemia in Term and Late Preterm Neonates	The Academy of Breastfeeding Medicine	United States	North America	2021	Newborns born with a gestational age (GA) of over 35 weeks
BAPM [14]	Identification and Management of Neonatal Hypoglycaemia in the Full-Term Infant	British Association of Perinatal Medicine	United Kingdom	Europe	2019	Newborns born with a gestational age (GA) of over 37 weeks
CPS [15]	The screening and management of newborns at risk for low blood glucose	Canadian Paediatric Society	Canada	North America	2019	Newborns
NICE [16]	Diabetes in pregnancy: management from preconception to the postnatal period	National Institute for Health and Care Excellence	United Kingdom	Europe	2020	Newborns whose mothers have diabetes mellitus
PES [2]	Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children	Pediatric Endocrine Society	United States	North America	2015	Newborns
QCG [17]	Hypoglycaemia–newborn	Queensland Health	Australia	Oceania	2022	Newborns
SNG [18]	Prevention and treatment of neonatal hypoglycaemia in newborn infants with gestational age ≥35 weeks	Swedish Neonatal Society	Sweden	Europe	2020	Newborns born with a gestational age (GA) of over 35 weeks
TK [19]	Management of hypoglycemia in newborn	Turkish Neonatal and Pediatric Endocrinology and Diabetes Societies	Turkey	Asia	2018	Newborns born with a gestational age (GA) of over 34 weeks
CN [20]	Expert consensus on standard clinical management of neonatal hypoglycemia in China	The Group of Neonatology, Pediatric Society, Chinese Medical Association	China	Asia	2021	Newborns born with a gestational age (GA) of over 35 weeks

Abbreviations: AAP, American Academy of Pediatrics; ABM, the Academy of Breastfeeding Medicine; BAPM, British Association of Perinatal Medicine Framework for Practice; CN, The Group of Neonatology, Pediatric Society, Chinese Medical Association; CPS, Canadian Paediatric Society; NICE, National Institute for Health and Care Excellence; PES, Pediatric Endocrine Society; QCG, Queensland Clinical Guidelines; SNG, Swedish national guideline; TK, Turkish Neonatal and Pediatric Endocrinology and Diabetes Societies.

included in our systematic review. In the guidelines including AAP,[12] ABM,[13] SNG,[18] TK[19] and CN,[20] the subjects are newborns born at a gestational age (GA) of over 34/35 weeks. The guideline BAPM[14] focuses on full-term newborns only. The guidelines CPS,[15] PES[2] and QCG[17] do not specify the GA range applicable to newborns, and the guideline NICE[16] only covers newborns whose mothers have diabetes mellitus.

We assessed the quality of the included guidelines using Agree II. The intragroup correlation coefficients, 95% confidence intervals, and *p* values in each domain, provided by the four appraisers, are shown in Table S1. The mean scores of the included guidelines ranged from 45.28% to 83.45%; 8 guidelines had a mean score of more than 50%, and the guideline QCG[17] had a maximum score of 83.45% ± 8.06%. Except Domain 5 (Applicability), the mean scores of the remaining 5 domains exceeded 50%, with higher mean scores of 69.86% ± 18.05%, 75.00% ± 14.13% and 70.21% ± 32.02% for Domain 1 (Scope and Purpose), Domain 4 (Clarity of Presentation), and Domain 6 (Editorial Independence), respectively (Table 2).

A total of eight guidelines[2,12,13,15,17–20] describe in detail the signs or symptoms of neonatal hypoglycemia, with no significant differences among them, mainly including sweating, pallor, irritability, tremors, irregular breathing, tachycardia, apnea, feeding difficulties, hypotonia, convulsions, and coma.

The guideline NICE[16] covers the management of mothers with diabetes from preconception to the postnatal period, and therefore only involves diabetes as a high-risk factor. In summary, the most frequently mentioned neonatal risk factors in the guidelines are prematurity, large for gestational age (LGA), small for gestational age (SGA), intrauterine growth retardation, hypothermia, and a history of serious acidosis/hypoxia and ischemia/fetal distress/resuscitation. The most frequently mentioned maternal risk factors are prenatal/gestational diabetes, and a history of β-blocker use (Table 3).

The guideline PES[2] mainly focuses on the evaluation and management of persistently hypoglycemic newborns, so no relevant preventive measures are listed. Among the remaining guidelines, early initiation of breastfeeding, ≤3 h between feedings, and early mother-infant skin-to-skin contact (SSC) are the most common preventive measures. The guidelines AAP,[12] ABM,[13] QCG,[17] SNG,[18] TK[19] and CN[20] suggest that newborns should be breastfed initially within 1 h after birth, while the guideline NICE[16] emphasises the need to initiate breastfeeding within 30 min after birth in newborns of diabetic mothers (Table 4).

Interventions for neonatal hypoglycemia are shown in Table 5. The time for the first glucose monitoring is 30 min after the first feeding in the guidelines AAP,[12] TK[19] and CN,[20] within 2 h after birth in the guideline CPS,[15] before the second feeding and no later than 3 h after birth in the guidelines QCG[17] and SNG,[18] and within 90 min after birth in the guideline ABM[13] specifically for newborns at risk of hyperinsulinemia regardless of feeding or not. For the frequency of subsequent glucose monitoring, the guidelines AAP[12] and TK[19] proposes that blood glucose should be remeasured within 1 h after supplemental feeding; the guidelines CN,[20] CPS[15] and QCG[17] recommend blood glucose remeasurement at 30 min after supplemental feeding/use of glucose gel, intravenous bolus injection of glucose, or change in the rate of intravenous glucose infusion; the guidelines ABM[13] and SNG[18] propose that the frequency of glucose monitoring after intravenous glucose infusion should be 0.5–2 h; the remaining guidelines report no frequency of follow-up glucose monitoring.

For the criteria for admission to the neonatal intensive care unit and the thresholds for intravenous glucose treatment, the guidelines are relatively uniform in terms of glycemic thresholds for newborns with clinical symptoms, 2.5/2.6 mmol/L is recommended, with the exception of the guidelines AAP[12] and TK,[19] both of which recommend 2.2 mmol/L. For newborns without clinical symptoms, the included guidelines divide the blood glucose levels into different ranges and recommend progressive management by glucose gel treatment/supplemental feeding according to the blood glucose ranges. However, cut-off values for the division of blood glucose levels into different ranges vary greatly. The guidelines AAP[12] and

TABLE 2 Domain scores of the 10 guidelines assessed by using the AGREE-II instrument (%).

	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Mean ± *SD*
AAP [12]	88.89%	18.06%	21.35%	66.67%	41.67%	85.42%	53.68% ± 31.22%
ABM [13]	80.56%	44.44%	54.69%	94.44%	56.25%	6.25%	56.11% ± 30.63%
BAPM [14]	31.94%	36.11%	17.19%	50.00%	46.88%	89.58%	45.28% ± 24.65%
CPS [15]	65.28%	25.00%	52.60%	76.39%	40.63%	14.58%	45.75% ± 23.65%
NICE [16]	56.94%	58.33%	39.06%	76.39%	47.92%	89.58%	61.37% ± 18.60%
PES [2]	55.56%	45.83%	72.40%	81.94%	34.38%	81.25%	61.89% ± 19.71%
QCG [17]	79.17%	83.33%	78.13%	94.44%	73.96%	91.67%	83.45% ± 8.06%
SNG [18]	77.78%	70.83%	74.48%	59.72%	53.13%	79.17%	69.19% ± 10.50%
TK [19]	70.83%	54.17%	28.65%	69.44%	34.38%	89.58%	57.84% ± 23.35%
CN [20]	91.67%	76.39%	75.00%	80.56%	46.88%	75.00%	74.25% ± 14.82%
Mean ± *SD*	69.86% ± 18.05%	51.25% ± 21.60%	51.36% ± 23.57%	75.00% ± 14.13%	47.61% ± 11.71%	70.21% ± 32.02%	

TABLE 3 Summary of risk factors for neonatal hypoglycemia.

	AAP [12]	ABM [13]	BAPM [14]	CPS [15]	NICE [16]	PES [2]	QCG [17]	SNG [18]	TK [19]	CN [20]
Neonatal factors										
Premature infant	+	+	NA	+	NA	+	+	+	+	+
Postmature infant	NA	NA	NA	NA	NA	+	+	NA	+	NA
Small for gestational age (SGA)	+	+	NA	+	NA	+	+	+	+	+
Large for gestational age (LGA)	+	+	NA	+	NA	+	+	+	+	+
Macrosomic infant	NA	NA	NA	NA	NA	NA	+	NA	NA	+
Intrauterine growth retardation	NA	+	+	+	NA	+	NA	+	+	+
Low birth weight	NA	+	NA	NA	NA	NA	+	NA	NA	+
Underfeeding/feeding developmental delay	NA	NA	NA	NA	NA	NA	+	+	NA	+
Presence of visible fat and muscle atrophy	NA	+	NA	NA	NA	NA	NA	NA	+	NA
Uneven growth of twins, weight <10% of the larger twin weight	NA	+	NA	NA	NA	NA	NA	NA	NA	NA
Acidosis/hypoxia & ischemia/fetal distress/resuscitation	NA	+	NA	+	NA	+	+	+	+	+
Hypothermia	NA	+	NA	NA	NA	+	+	+	+	+
Erythrocytosis/hyperviscosity syndrome (HVS)	NA	+	NA	NA	NA	+	+	NA	+	+
Fetal erythroblastosis	NA	+	NA	NA	NA	+	NA	NA	NA	NA
Beckwith-Wiedemann syndrome (BWS)	NA	+	NA	NA	NA	+	NA	NA	NA	NA
Micropenis/midline defects	NA	+	NA	NA	NA	+	NA	NA	+	NA
Infection	NA	+	NA	NA	NA	NA	NA	+	+	NA
Respiratory distress	NA	+	NA	NA	NA	+	+	+	+	NA
Congenital heart disease	NA	NA	NA	NA	NA	NA	NA	+	+	NA
Metabolic/endocrine disorder	NA	+	NA	NA	NA	NA	NA	+	+	NA
Hemolytic disease	NA	NA	NA	NA	NA	NA	NA	NA	+	+
A history of use of indomethacin	NA	NA	NA	NA	NA	NA	NA	NA	+	NA
Maternal factors										
Prenatal/gestational diabetes	+	+	+	+	+	NA	+	+	+	+
Preeclampsia/eclampsia/ hypertension	NA	+	NA	NA	NA	+	NA	+	+	NA
Previously giving birth to a macrosomic infant	NA	+	NA	NA	NA	NA	NA	+	NA	NA
Drug abuse	NA	+	NA	NA	NA	NA	NA	+	NA	NA
A history of use of antidepressants	NA	NA	NA	NA	NA	NA	NA	+	NA	+
A history of use of tocolytics	NA	NA	NA	NA	NA	NA	NA	+	NA	NA
A history of use of β-agonists	NA	+	NA	NA	NA	NA	NA	NA	+	NA
A history of use of β-blockers	NA	NA	+	+	NA	NA	+	+	+	+
A history of use of hypoglycemic drugs	NA	+	NA	NA	NA	NA	+	NA	+	+

TABLE 3 (Continued)

	AAP [12]	ABM [13]	BAPM [14]	CPS [15]	NICE [16]	PES [2]	QCG [17]	SNG [18]	TK [19]	CN [20]
Intravenous infusion of glucose before or during delivery	NA	+	NA	NA	NA	NA	NA	NA	+	+
A history of use of glucocorticoids	NA	NA	NA	+	NA	NA	+	NA	NA	+
A family history of metabolic/endocrine diseases	NA	NA	NA	NA	NA	+	+	NA	NA	+

Abbreviation: NA, not available.

TABLE 4 Summary of preventive measures for neonatal hypoglycemia.

	AAP [12]	ABM [13]	BAPM [14]	CPS [15]	NICE [16]	PES [2]	QCG [17]	SNG [18]	TK [19]	CN [20]
Early initiation of breastfeeding	+	+	+	+	+	NA	+	+	+	+
≤3 h between feedings	+	+	NA	NA	+	NA	+	+	NA	+
Early mother-infant skin-to-skin contact (SSC)	NA	+	NA	NA	NA	NA	+	+	NA	+
Preventing mother-infant separation	NA	+	NA	NA	+	NA	+	NA	NA	NA
Warming	NA	+	NA	NA	NA	NA	+	+	NA	NA

Note: AAP, ABM, QCG, SNG, TK and CN: Initiation of breastfeeding within 1 h after birth; BAPM and CPS: No specific early feeding time; NICE: Initiation of breastfeeding within 30 min after birth; NA, not available.

TK[19] set blood glucose thresholds at 1.4 and 1.9 mmol/L, respectively, at 4 h and 4–24 h after birth. The guidelines ABM,[13] BAPM,[14] CPS,[15] QCG,[17] SNG[18] and CN[20] set thresholds at 1 mmol/L, 1.4/1.5 mmol/L, 1.8/1.9/2.0 mmol/L and 2.5/2.6 mmol/L, respectively. The guidelines NICE[16] and PES[2] do not provide blood glucose thresholds.

For the management of hypoglycemia, the guidelines recommend relatively consistent means of management, which is intravenous bolus injection of glucose and maintenance of glucose infusion. Among them, the guidelines AAP,[12] ABM,[13] SNG,[18] TK[19] and CN[20] recommend a glucose infusion rate of 5–8 mg/(kg·min). The guidelines CPS[15] and PES[2] do not specify the rate of glucose infusion. The guideline QCG[17] replaces the glucose infusion rate with a fluid infusion rate that starts at 60 mL/kg/day and increases by 20 mL/kg/day to a maximum of 100 mL/kg/day based on remeasured glucose levels. The guidelines ABM[13] and SNG[18] are in agreement on the frequency of glucose monitoring during treatment, with the cut-off values of 1.4/1.5 mmol/L and 1.9/2.0 mmol/L dividing the time for remeasurement of blood glucose within 0.5 h, 0.5–1 h, and 1–2 h, respectively. The guideline CPS[15] defines target blood glucose as 2.6–5.0 mmol/L (<72 h after birth) and 3.3–5.0 mmol/L (≥72 h after birth). The guidelines PES,[2] QCG,[17] TK[19] and CN[20] define target blood glucose as more than 2.8 mmol/L (the guidelines PES,[2] TK,[19] and CN[20])/2.6 mmol/L (the guideline QCG[17]) within 48 after birth and more than 3.3 mmol/L after 48 h following birth. The AAP[12] guideline defines target blood glucose as 2.2–2.8 mmol/L, and the ABM[13] guideline defines target blood glucose as 2.5–3.0 mmol/L, but neither of them specifies the corresponding day age range.

A total of five guidelines[2,15,17,19,20] provide drug regimens for the treatment of neonatal hypoglycemia, involving five drugs, including glucagon, hydrocortisone, diazoxide, octreotide, and hydrochlorothiazide. The specific indications and usage are shown in Table 6. Glucagon is the most frequently mentioned drug for the treatment of neonatal hypoglycemia, and the indications are hyperinsulinemia, persistent hypoglycemia, and a glucose infusion rate of more than 10 mg/(kg·min). The routes of administration include intravenous bolus injection, intravenous infusion, intramuscular injection, and subcutaneous injection. However, there is a lack of uniformity in the dose among guidelines.

4 | DISCUSSION

The guidelines included in this study were developed and published by relevant professional associations and guideline organisations over a 12-year period (2011–2022). North America issued the largest number of relevant guidelines (4), followed by Europe (3), Asia (2), and Oceania (1). Guidelines related to neonatal hypoglycemia are lacking in the countries in Africa. No studies report the regional characteristics of the incidence of neonatal hypoglycemia worldwide in detail. Therefore, it can only be inferred that there are regional differences in guideline development, which may be related to the economic development, quality of medical care, epidemiological characteristics of the disease, and characteristics of burden in each region.

We evaluated the included guidelines using the AGREE II instrument, and the intragroup correlation coefficients for the four appraisers ranged from 0.844 to 0.954, suggesting a high level of

TABLE 5 Summary of interventions for neonatal hypoglycemia.

	Time for the first glucose monitoring in infants at high risk for hypoglycemia	Criteria for admission to the NICU for intravenous glucose treatment		Hypoglycemia interventions
		Absence of clinical symptoms	Presence of clinical symptoms	
AAP [12]	30 min after the first feeding	(1) 0–4 h after birth, BGL < 25 mg/dL (1.4 mmol/L), after 1 supplemental feeding: BGL 25–40 mg/dL (1.4–2.2 mmol/L) (2) 4–24 h after birth, BGL < 35 mg/dL (1.9 mmol/), after 1 supplemental feeding: BGL 35–45 mg/dL (1.9–2.5 mmol/L)	BGL < 40 mg/dL (2.2 mmol/L)	Intravenous bolus injection of 2 mL/kg of 10% glucose solution, and (or) maintenance solution at a GIR of 5–8 mg/(kg·min), to allow plasma glucose to reach 40–50 mg/dL (2.2–2.8 mmol/L), target BGL > 45 mg/dL (2.5 mmol/L) before regular feeding
ABM [13]	(1) At risk for hyperinsulinemia: within 90 min after birth regardless of feeding or not (2) Population at other risks: before the second feeding, or 2–4 h after birth	(1) BGL < 25 mg/dL (1.4 mmol/L) (2) BGL 25–34 mg/dL (1.4–1.9 mmol/L): BGL < 34 mg/dL (1.9 mmol/L) after 40% glucose gel treatment and/or 1 supplemental feeding (3) BGL 35–45 mg/dL (2.0–2.5 mmol/L): BGL < 45 mg/dL (2.5 mmol/L) after 40% glucose gel treatment and/or 2 supplemental feedings	BGL < 45 mg/dL (2.5 mmol/L)	(1) BGL 35–45 mg/dL (2.0–2.5 mmol/L): remeasured plasma glucose at 1–2 h after treatment (2) BGL 25–34 mg/dL (1.4–1.9 mmol/L): remeasured plasma glucose at 0.5–1 h after treatment (3) BGL < 25 mg/dL (1.4 mmol/L) or BGL < 45 mg/dL (2.5 mmol/L) with hypoglycemia symptoms: remeasured plasma glucose within 0.5 h after treatment If any of the situations (1), (2) and (3) occurs, administer intravenous bolus injection of 1–2 mL/kg of 10% glucose solution and maintenance solution via intravenous infusion at a GIR of 5–8 mg/(kg·min); if remeasured plasma blood glucose is still any of the situations (1), (2) and (3), increase the GIR to reach target BGL: 45–54 mg/dL (2.5–3.0 mmol/L)
BAPM [14]	NA	(1) BGL < 1 mmol/L (2) BGL < 2 mmol/L after 40% glucose gel treatment and/or 2 supplemental feedings	BGL < 2.5 mmol/L	NA
CPS [15]	Within 2 h after birth	BGL < 2.6 mmol/L: (1) BGL is <1.8 mmol/L after 40% glucose gel treatment and/1 supplemental feeding (2) BGL is <2.6 mmol/L after 40% glucose gel treatment and/2 supplemental feedings	BGL < 2.6 mmol/L	Intravenous bolus injection of 10% glucose solution (at a rate of 2 mL/kg for 15 min if hypoglycemia symptoms occurs) Target BGL 2.6–5.0 mmol/L (<72 h after birth)/3.3–5.0 mmol/L (≥72 h after birth) Remeasure blood glucose every 0.5 h and increase the infusion rate at a dose of 1 mL/kg/h for 10% glucose solution at a rate
NICE [16]	Mothers of newborns have diabetes: within 2–4 h after birth	NA	NA	NA
PES [2]	NA	NA	NA	Intravenous bolus injection of 200 mg/kg of glucose solution followed by infusion of 10% glucose solution to maintain the infusion rate (1) Newborns suspected of having congenital hypoglycemia: target plasma glucose >70 mg/dL (3.9 mmol/L)

TABLE 5 (Continued)

	Time for the first glucose monitoring in infants at high risk for hypoglycemia	Criteria for admission to the NICU for intravenous glucose treatment		Hypoglycemia interventions
		Absence of clinical symptoms	Presence of clinical symptoms	
				(2) High-risk newborns without suspected congenital hypoglycemia: target plasma glucose >50 mg/dL (2.8 mmol/L) (<48 h after birth)/60 mg/dL (3.3 mmol/L) (>48 h after birth)
QCG [17]	Before the second feeding, and no later than 3 h after birth	Within 48 h after birth (1) BGL < 1.5 mmol/L (2) BGL 1.5–2.5 mmol/L: BGL is <2 mmol/L after 40% glucose gel treatment and/or 2 supplemental feedings	BGL < 2.6 mmol/L	Intravenous bolus injection of 1–2 mL/kg of 10% glucose solution at a dose of 60 mL/kg/day for maintenance Target BGL ≥ 2.6 mmol/L (≤48 h after birth)/3.3 mmol/L (>48 h after birth) Remeasure blood glucose every 0.5 h and increase the infusion rate at a dose of 20 mL/kg/day (no more than 100 mL/kg/day)
SNG [18]	Before the second feeding, and no later than 3 h after birth	(1) BGL < 1.5 mmol/L (2) BGL 1.5–1.9 mmol/L: BGL is <1.9 mmol/L after 40% glucose gel treatment and/or 1–2 feedings (3) BGL 2.0–2.5 mmol/L: BGL is <2.5 mmol/L after 40% glucose gel treatment and/or 2–3 feedings	BGL < 2.6 mmol/L	(1) BGL 2.0–2.5 mmol/L: remeasured plasma glucose at 1–2 h after treatment (2) BGL 1.5–1.9 mmo/L: remeasured plasma glucose at 0.5–1 h after treatment (3) BGL < 1.5 mmol/L or BGL < 2.6 mmol/L with hypoglycemia symptoms: remeasured plasma glucose within 0.5 h after treatment If any of the situations (1), (2) and (3) occurs, administer intravenous bolus injection of 2 mL/kg of 10% glucose solution and maintenance solution via intravenous infusion at a GIR of 5 mg/(kg·min); if remeasured plasma blood glucose is still any of the situations (1), (2) and (3), increase the GIR gradually at 5/6.7/10/13.3 mg/(kg·min)
TK [19]	30 min after the first feeding	(1) 0–4 h after birth, BGL < 25 mg/dL (1.4 mmol/L), after 1 supplemental feeding: BGL 25–40 mg/dL (1.4–2.2 mmol/L) (2) 4–24 h after birth, BGL < 35 mg/dL (1.9 mmol/), after 1 supplemental feeding: BGL 35–45 mg/dL (1.9–2.5 mmol/L)	BGL < 40 mg/dL (2.2 mmol/L)	Intravenous bolus injection of 2 mL/kg of 10% glucose solution, and (or) maintenance solution at a GIR of 5–8 mg/(kg·min), <24 h after birth: target BGL reaching 40–50 mg/dL (2.2–2.8 mmol/L), BGL > 45 mg/dL (2.5 mmol/L) before regular feeding 24–48 h after birth: BGL > 50 mg/dL (2.8 mmol/L) before regular feeding >48 h after birth: BGL > 60 mg/dL (3.3 mmol/L); persistently hypoglycemic newborns: BGL > 70 mg/dL (3.9 mmol/L)
CN [20]	30 min after the first feeding	(1) BGL < 1 mmol/L (2) BGL < 2.2 mmol/L after 1 supplemental feeding (3) BGL < 2.6 mmol/L after 2 supplemental feedings	BGL < 2.6 mmol/L	(1) BGL 2.2–2.6 mmol/L: Immediately complete a plasma glucose test, and administer maintenance solution at a GIR 5–8 mg/(kg·min) (2) BGL < 2.6 mmol/L with hypoglycemia symptoms (3) BGL < 2.0 mmol/L

(Continues)

TABLE 5 (Continued)

Time for the first glucose monitoring in infants at high risk for hypoglycemia	Criteria for admission to the NICU for intravenous glucose treatment		Hypoglycemia interventions
	Absence of clinical symptoms	Presence of clinical symptoms	
			(4) Presence of pre-existing disorders or BGL < 2.2 mmol/L after clinical treatment If any of the situations (2), (3) and (4) occurs, immediately complete a plasma glucose test, administer intravenous bolus injection of 2 mL/kg of 10% glucose solution and maintenance solution via intravenous infusion at a GIR of 5-8 mg/(kg·min); Remeasured plasma glucose at 0.5 h after treatment Target BGL 2.8–5 mmol/L (<48 h after birth) /3.3–5 mmol/L (>48 h after birth)

Note: The units of measurement of blood glucose provided by the guidelines AAP, ABM and TK are mg/dL, which has been converted into mmol/L and marked in brackets.
Abbreviations: BGL, blood glucose level; GIR, glucose infusion rate; NA, not available; NICU, neonatal intensive care unit.

agreement among the appraisers. However, guidelines cannot be ranked from low to high based on AGREE II scores. They must be used according to clinical conditions. AGREE II scores provide directions for the future improvement of guidelines. As assessed by the AGREE II instrument, most guidelines were scored high in domains including Scope and Purpose, Clarity of Presentation, and Editorial Independence. For participants, although the target populations in the guidelines ABM[13] and BAPM[14] include parents of newborns, the preferences of parents of newborns were ignored in almost all of the guidelines during development. Currently there is no evidence that parents are supposed to accept the burden of choosing glucose levels. The scores for Rigour of Development varied widely between different guidelines. Reasons for the low scores include incomplete descriptions of the methods used to find evidence and the process of forming recommendations, and the lack of external review and update mechanisms. Some of the guidelines can provide tools that promote their application, such as a quick guide and a summary of recommendations, which are conducive to their popularisation and application. However, it is still required to improve analyses of the factors that may hinder their application, such as analysis of whether the requirements for hypoglycemia detection tools, hypoglycemic drugs, and medical professionals may be a hindrance to the application of guidelines.

The definition of neonatal hypoglycemia remains controversial because of a lack of significant correlations among blood glucose levels, clinical symptoms, and long-term sequelae.[21,22] Each guideline defines neonatal hypoglycemia based on clinical manifestations and blood glucose levels, respectively, which is presented in the Results section. Neonatal hypoglycemia is discussed below with additional and further information.

For early identification of neonatal hypoglycemia, clinical signs are easily observable indicators. The clinical symptoms summarised by various guidelines can be summarised into the following two categories: when the blood glucose levels are low, the body will produce a series of neuroendocrine-mediated glycogenolysis, gluconeogenesis, and other glycemic responses, accompanied by increased sympathetic excitability symptoms, like sweating, pallor, irritability, tremors, irregular breathing, and tachycardia; when the blood glucose levels decrease further, the body shows symptoms including apnea, feeding difficulties, hypotonia, convulsions and coma due to a lack of blood glucose in the central nervous system.[23] However, the above symptoms are not characteristic clinical manifestations of neonatal hypoglycemia and do not necessarily correlate with blood glucose levels, with some newborns being asymptomatic at low blood glucose levels and others having symptoms at relatively higher blood glucose levels.[24] Hoermann et al.[25] have recently shown in a prospective cohort study that clinical observation of signs has limited sensitivity and specificity in detecting neonatal hypoglycemia. Thus, guidelines should consider the differentiation between asymptomatic and symptomatic hypoglycemia.

It is also required to consider that some newborns have high-risk factors for hypoglycemia, and the relevant mechanisms are abnormal glucose-related regulatory hormones and/or insufficient self-storage,

TABLE 6 Summary of pharmacotherapies for neonatal hypoglycemia.

	CPS [15]	PES [2]	QCG [17]	TK [19]	CN [20]
Glucagon	**Indication**: GIR >10 mg/(kg·min) **Administration**: (1) 0.1–0.3 mg/kg iv (2) 10–30 μg/(kg·h) iv gtt	**Indication**: Hyperinsulinemia **Administration**: 0.5–1 mg/kg iv, im or sc	**Indication**: Refractory hypoglycemia when hepatic glycogen stores are available **Administration**: 200 mg/kg iv, im or sc; maintenance infusion rate: 10–20 mg/(kg·h) up to 50 mg/(kg·h) depending on response	**Indication**: Persistent hypoglycemia **Administration**: 200 mg/kg, 1 mg/d	**Indications**: (1) Recalcitrant hypoglycemic neonates with glycogen stores; (2) refractory diabetic mothers; (3) neonatal hyperinsulinemic hypoglycemia **Administration**: (1) 0.2 mg/kg iv, maintenance infusion rate: 1–20 μg/(kg·h), maximum dose: 1 mg/d; (2) intravenous glucose should be supplemented at the same time to avoid rebound hypoglycemia
Hydrocortisone	NA	NA	**Indications**: (1) Acute and chronic hypoadrenocorticism; (2) refractory hypoglycemia; (3) adjuvant treatment for persistent hypoglycemia **Administration**: 1–2 mg/kg po or iv q6h-q8h	**Indications**: (1) Hypoadrenocorticism; (2) use for 1–2 days **Administration**: 5–15 mg/kg	**Indications**: (1) GIR > 10 mg/(kg·min); (2) persistent hypoglycemia **Administration**: 1–2 mg/kg iv q6h–q8h
Diazoxide	NA	NA	**Indications**: Persistent hypoglycemia: long-term treatment after withdrawal of glucose infusion **Administration**: 2–5 mg/kg po q8h–q12h	**Indication**: First-line medication for hyperinsulinemia **Administration**: 5–20 mg/kg	**Indications**: (1) Persistent hypoglycemia due to hyperinsulinemia; (2) long-term treatment after withdrawal of glucose infusion **Administration**: 5–20 mg/(kg·d) po tid
Octreotide	NA	NA	**Indications**: Suspected/confirmed hyperinsulinemia: **Administration**: (1) 2–5 mcg/kg up to 7 mcg/kg sc q4h depending on response (2) 1 mcg/kg up to 10 mcg/kg iv q6h depending on response (3) 5–25 mcg/(kg·d) up to 40 mcg/(kg·d) iv gtt depending on response	**Indication**: Hyperinsulinemia **Administration**: 5–10 mcg/kg	**Indications**: (1) Indicated for suspected/confirmed hyperinsulinemia; (2) Not recommended for use in the neonatal period, consultation with a pediatric endocrinologist is required **Administration**: 5–25 μg/(kg·d) sc or iv q6h–q8h
Hydrochlorothiazide	NA	NA	**Indication**: Diuretic, used concomitantly with diazoxide **Administration**: 1–2 mg/kg po q12h	NA	NA

Note: q6h, quaque 6 hora; q8h, quaque 8 hora.

Abbreviations: GIR, glucose infusion rate; NA, not available.

specifically divided into maternal factors, such as gestational diabetes and a history of prenatal high-dose glucose infusion leading to increased insulin secretion in newborns,[15,26,27] and neonatal factors, such as prematurity, LGA, SGA.[15,26] The included guidelines all refer to the above-mentioned high-risk factors. In addition, attention needs to be paid to the screening of endocrine or metabolic diseases.[27] For example, the guidelines ABM,[13] PES[2] and TK[19] emphasise attention to screening for exceptional signs such as micropenis/midline defects, and the guidelines PES,[2] QCG[17] and CN[20] include a family history of metabolic/endocrine diseases as a high-risk factor for neonatal hypoglycemia. In addition, abnormal physiological manifestations or disease states of the newborn such as hypothermia, underfeeding, acidosis, intrapartum hypoxia-ischemia, fetal distress, erythrocytosis and respiratory distress, are also considered high-risk factors by many guidelines.[2,13,15,17–20] It was found that sepsis, respiratory distress syndrome and mechanical ventilation increased the incidence of neonatal hypoglycemia by 7-, 5- and 3-fold, respectively.[28]

Early initiation of breastfeeding, ≤3 h between feedings, and early mother-infant SSC are widely recognised preventive measures against neonatal hypoglycemia. The gastric emptying time in newborns is about 2 h. A feeding interval of no more than 3 h is consistent with the gastric emptying patterns in newborns. Early suckling and SSC can stimulate catecholamine hormone secretion to elevate and stabilise blood glucose,[29] as well as achieve sedation, warmth, and stabilisation of the cardiopulmonary system. The health status of newborns can be assessed by the strength and rhythm of their suckling during breastfeeding.

Blood glucose levels are the most intuitive indicator, and many guidelines recommend a blood glucose threshold of 2.6 mmol/L or close to 2.6 mmol/L for clinical intervention, but the guidelines AAP[12] and TK[19] recommend 2.2 mmol/L, which in the guideline TK[19] is set with reference to that in the guideline AAP.[12] Notably, Adamkin, involved in developing the guideline AAP,[12] emphasised in a subsequent editorial that the guideline AAP[12] applied to newborns within the first 24 h after birth, and the recommended blood glucose threshold for newborns within 24–48 h after birth was 2.5 mmol/L (45 mg/dL).[30] In 1988, a multicenter cohort study performed by Lucas et al.[31] found low Bayley scores in neonates who had experienced blood glucose levels <2.6 mmol/L. Since then, an increasing number of guidelines have used 2.6 mmol/L as a threshold for clinical management of neonatal hypoglycemia. A prospective cohort study that included 614 newborns with a gestational age of over 32 weeks at risk of hypoglycemia[4] found no significant difference in risk of neurosensory impairment at 4.5 years between the hypoglycemic group (less than 2.6 mmol/L) and the non-hypoglycemic group; however, the hypoglycemic group was poorer in executive abilities than the non-hypoglycemic group, suggesting an increased risk of attention deficit hyperactivity disorder, behavioural disorders, and learning problems in the future; the hypoglycemic group also showed poor performance in visual-motor coordination, which may lead to reduced ability of reading, writing, and math. However, the study by Lucas[31] included very premature neonates at a gestational age of 30.5 ± 2.7 weeks, which is not included in any of the guidelines in our systematic review. In addition, Lucas admitted in a follow-up letter that the study method was not optimal and there was "difficulty of proving causation when an observational approach is used".[32] A retrospective cohort study that included 528 neonates at risk of hypoglycemia at a gestational age of 35 weeks or older[33] found no correlation between poor neurodevelopmental outcomes and hypoglycemia at 2 years after birth when 2.6 mmol/L was used as a threshold for clinical intervention. Another 15-year follow-up study that included 543 infants found no differences in physical disability and psychometric assessment between a non-hypoglycemic group and an experimental group experiencing recurrent low blood glucose levels (≤2.5 mmol/L) in the neonatal period.[34] At the same time, some studies have shown that the threshold for clinical management of blood glucose can be further adjusted downward. A meta-analysis in 2006[35] showed that full-term healthy newborns had blood glucose levels (5th percentile) of about 1.6 mmol/L at 1–2 h, about 2.2 mmol/L at 3–48 h, and about 2.7 mmol/L at 48 h after birth. In a multicenter randomised controlled study that included 689 healthy newborns with a gestational age over 35 weeks,[36] 2.0 and 2.6 mmol/L were used as thresholds for hypoglycemia management, respectively, and there was no significant difference in Bayley-III scores between the two groups at 18 months of age, suggesting that 2.0 mmol/L was safe and reliable as a threshold for clinical management of asymptomatic hypoglycemia. In the guidelines AAP[12] and TK,[19] the threshold for management of hypoglycemia infants with clinical symptoms is 2.2 mmol/L, and 1.4 and 1.9 mmol/L are used as thresholds for management of asymptomatic hypoglycemia within 4 h and after 4 h after birth, respectively. It was also believed that the mechanism of blood glucose regulation of insulin secretion in newborns was not mature within 2–3 days after birth; therefore, it was difficult to distinguish transient hypoglycemia from persistent hypoglycemia within 48 h after birth.[2] A prospective observational study on blood glucose levels in healthy newborns found that glucose levels eventually stabilised (4.6 ± 0.7 mmol/L) at 4 days after birth, and 39% of healthy newborns experienced a single glucose level below 2.6 mmol/L within 48 h after birth.[37] Therefore, there is still no unified conclusion on the threshold of clinical management of neonatal hypoglycemia. Currently, 2.6 mmol/L as a threshold for hypoglycemia management is the mainstream view and has been proven safe and reliable by many studies, but whether it is over-medicating to adopt interventions for some newborns with transient hypoglycemia is yet to be verified by more randomised controlled studies.

In addition, a blood glucose level that causes damage to the nervous system cannot be determined because individual differences in the neuroendocrine response result in varying blood glucose thresholds of cognitive impairment, and the boundaries of this range are influenced by alternative fuels such as ketone bodies and acetate at the same time.[38,39] Therefore, it is necessary to introduce indicators related to glucose metabolism (e.g., ketone bodies, bicarbonate, lactate, free fatty acids, insulin, growth hormone, cortisol, carnitine, and acylcarnitine) along with glucose monitoring for a comprehensive assessment.[15] It was found that in healthy

newborns with low blood glucose levels, lactate and β-hydroxybutyrate served as alternative fuels for brain energy supply on Day 1 and Days 2–4 after birth, respectively. Lactate peaked at 12 h after birth and dropped to stable levels within 48 h after birth; β-hydroxybutyrate was low at 12 h after birth, peaked at 48–72 h after birth, and dropped back at 96 h.[40] The guideline AAP[12] suggests that ketone body increases in newborns with low blood glucose levels to serve as an alternative fuel for blood glucose. However, the above study suggests that ketone body production is inhibited in healthy newborns within 24–36 h after birth, and for newborns with persistent hypoglycemia or congenital hypoglycemia, the inhibition lasts for a longer period of time.[40] Therefore, it is important to monitor the lactate and ketone body levels in newborns within 1 day and 2–4 days after birth, respectively, which can help identify the presence of persistent hypoglycemia or congenital hypoglycemia at an early stage.

The rate of glucose utilisation in newborns is 5–8 mg/(kg·min),[41] so many guidelines use it as the rate of glucose infusion. The frequency of glucose monitoring is an essential part of clinical management of neonatal hypoglycemia. An appropriate frequency of glucose monitoring can not only avoid unnecessary painful stimuli but also aid in the early recognition of neonatal hypoglycemia and evaluation of therapeutic efficacy. Not all guidelines propose the frequency of glucose monitoring, and there is a large degree of heterogeneity among them. The time for initial postnatal glucose monitoring is inconsistent, and more clinical trials are needed to provide evidence. Currently, there has been a general consensus in clinical practice that blood glucose should be remeasured at 30 min after supplemental feeding/use of glucose gel. Therefore, only the frequency of glucose monitoring after intravenous glucose infusion is presented in Table 5 to avoid data overload. The guidelines ABM[13] and SNG[18] refine the frequency of glucose monitoring during hypoglycemia management and are worth popularisation in the clinical setting.

The purpose of setting the target blood glucose is to directly evaluate the therapeutic efficacy against neonatal hypoglycemia. The guidelines present two views of setting a threshold at 48 and 72 h after birth. More large-data studies are needed to further define and confirm the physiological range of blood glucose in newborns.

In terms of the pharmacological treatment options for neonatal hypoglycemia, glucagon is most frequently mentioned because it is necessary to be alert to hyperinsulinemia when the need for glucose infusion rate continues to increase or persistent hypoglycemia occurs in hyperglycemic newborns. Besides, glucagon is a simple and quick treatment to manage neonatal hypoglycemia. However, the dosage and administration of glucagon vary widely among various guidelines, and more basic research and clinical practice are needed to provide supporting data. In addition, the clinical application of glucagon still requires caution because insulin is secreted in a biphasic manner and influenced by glucose and nutrients (amino acid, free fatty acid) and an additional signal like metabolic factors, neurotransmitters, and hormones.[42,43] In the diagnosis and treatment of hyperinsulinemia, insulin levels should be measured based on how insulin is secreted. Meanwhile, pH, blood ammonia, lactate, ketone body, fatty acid, C-peptide, glucagon, catecholamines, cortisol, growth hormone and other indicators should also be monitored, and medications should be adjusted in time according to the changes in various metabolites and hormones.[44,45] Although some guidelines propose the use of hydrochlorothiazide and hydrocortisone to treat neonatal hypoglycemia, they will not be used clinically as first-line drugs, because the former carries the risk of causing electrolyte disturbances and pancreatitis,[46] and the latter will cause adverse reactions including water and sodium retention, and blood pressure fluctuation.[47]

We designed a refined guideline search strategy and used the Agree II instrument and four independent appraisers to minimise subjective bias. However, there are still some limitations in this study. Firstly, we only included guidelines on neonatal hypoglycemia that are in English and Chinese, leading to certain selection bias. Secondly, AGREE II, as a quality assessment tool, only provides methodological quality assessment and does not provide criteria for evaluation of the contents of the guidelines, nor does it involve evaluating the reliability of their recommendations. Finally, we evaluated the guidelines only based on their contents and did not use other methods, such as contacting the guideline developers to obtain details of the guideline development process, which may lead to a biased methodological evaluation of the guidelines.

5 | CONCLUSION

A total of 10 clinical guidelines on neonatal hypoglycemia were included in our study, involving 7 countries in 4 continents. Generally, the included guidelines are of moderate quality, with regional differences. By summarising the recommendations on clinical symptoms, risk factors, preventive measures and interventions for neonatal hypoglycemia, we found that blood glucose values were not the only observational indicator, and other indicators (e.g., ketone bodies, lactate) related to glucose metabolism should also be considered for a comprehensive assessment. In addition, based on the latest research, we tried to summarise a variety of observational indicators of hypoglycemia and their key observation points. Future studies are desired to validate and improve these findings to provide more scientific and comprehensive recommendations on the management of neonatal hypoglycemia. In conclusion, there is still a lack of consensus on thresholds for clinical management of hypoglycemia and target glucose ranges for its control, and the recommendations on its pharmacotherapy are rather simple and sketchy. In the future, more high-quality studies are warranted to further improve the early identification of neonatal hypoglycemia and intervention strategies against it.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study were included in this published article and its Supporting Information files.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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