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Neonatal Hypoglycemia and Its Associated Long-Term Neurodevelopmental Outcomes in Very- Low-Birth-Weight Infants: A Multicenter Retrospective Cohort Study

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Highlights

What are the main findings?

- Neonatal hypoglycemia in very-low-birth-weight infants is significantly associated with maternal preeclampsia, fetal distress, cesarean delivery, and prenatal magnesium sulfate ($MgSO_4$) exposure, but not with gestational diabetes mellitus.
- Very low birth weight infants with neonatal hypoglycemia were more likely to be small for gestational age, require patent ductus arteriosus ligation, and have a smaller head circumference at discharge.
- Even with prompt treatment, neonatal hypoglycemia was associated with unfavorable long-term neurodevelopmental outcomes in very low birth weight infants, particularly impaired language function.

What are the implications of the main findings?

- Early identification and close glucose monitoring are essential for very-low-birth-weight infants, particularly those exposed to maternal or perinatal risk factors associated with neonatal hypoglycemia.
- Long-term neurodevelopmental follow-up, particularly language assessment, should be considered for VLBW infants who experience neonatal hypoglycemia, even when prompt treatment is provided.

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Abstract

Objectives: To evaluate the perinatal factors, short-term clinical outcomes, and long-term neurodevelopmental outcomes of very low birth weight infants associated with neonatal hypoglycemia. **Methods:** Infants born at ≤29 weeks of gestation or with a birth weight ≤1500 g who fulfilled the inclusion criteria between 2016 and 2020 were enrolled in this retrospective study. Initial blood glucose levels of less than 47 mg/dL were defined as hypoglycemia. Neurodevelopmental assessments were performed at corrected ages of 6, 12, and 24 months using Bayley-III scores and were compared between the neonatal hypoglycemia and non-hypoglycemia groups. **Results:** Of 2132 neonates, significant clinical characteristics associated with neonatal hypoglycemia included maternal preeclampsia,

fetal distress, prenatal magnesium sulfate ($MgSO_4$) exposure, cesarean delivery, and small for gestational age. Additionally, higher rates of patent ductus arteriosus ligation, smaller head circumference at discharge. Furthermore, neonatal hypoglycemia was significantly associated with higher odds of moderate-to-severe language developmental delay, defined as a Bayley-III language composite score below 70, at 6, 12, and 24 months corrected age after adjustment for potential confounders. **Conclusions:** Neonatal hypoglycemia in very low birth weight infants is significantly linked to adverse clinical risks and long-term language delay. Early identification of high-risk characteristics and immediate intervention are critical.

Keywords: neonatal hypoglycemia; very low birth weight infants; premature infants; neurodevelopmental outcomes

1. Introduction

Blood glucose levels were observed to fall after birth in neonates, reaching levels as low as 20–25 mg/dL within the first two hours of life [1]. The severing of the umbilical cord abruptly terminates the exogenous glucose supply. A proportion of neonatal hypoglycemia is transient and resolves spontaneously within 48 h of life [2]. However, cesarean section, preterm birth, gestational diabetes, gestational hypertension, and respiratory distress syndrome were reported as risk factors for significant neonatal hypoglycemia [3], which may lead to subsequent neurological disability, such as poor executive function and visual-motor function [4].

The survival rate for extreme prematurity has shown a better trend than in the previous decade as a result of advanced perinatal care [5]. Improving the adverse neurodevelopmental outcomes of very tiny preterm infants remains a challenge for neonatologists. We need evidence-based practice and standardization of therapeutic trajectory to prevent the occurrence of morbidity of prematurity. Glucose disturbance in the early life of preterm neonates is common and has different presentations at different gestational ages. Hypoglycemia occurs in approximately 27.9% of infants born at ≥34 weeks' gestation and nearly 34% of those born at <33 weeks' gestation, particularly in the setting of limited glycogen stores or increased energy expenditure [6,7]. Hyperglycemia was most common among half of preterm infants <28 weeks, resulting from decreased suppression of hepatic glucose release after receiving glucose-containing fluids [7] or having massive physical stress during birth. Hyperglycemia and hypoglycemia are both related to organ damage. Immature glucose homeostasis makes it difficult for preterm neonates to undergo a normal postnatal adaptation process, especially in the first week of life [8]. The postnatal plasma glucose nadirs occurred earlier in newborns with extremely low gestational age than in late preterm infants, exhibiting an inverse correlation with gestational age [9]. However, there are limited data regarding the normal range of blood sugar in neonates, and the screening or management of neonatal hypoglycemia is also difficult to define [10].

The first report described serious neurodevelopmental impairment in premature infants at a corrected age of 18 months due to hypoglycemia with sugar levels <50.4 mg/dL for five to 30 days [11]. The longer duration of hypoglycemia was strongly related to poorer neurodevelopment [11]. A retrospective population-based study conducted in 2018 analyzed motor and cognitive outcomes at 2–6 years of age in 101,060 healthy neonates and revealed worse neurodevelopmental outcomes in those with hypoglycemia (<40 mg/dL) compared to those with euglycemia [12]. Neuroimaging studies showed that smaller deep grey matter and thinner occipital lobe cortex were observed in neonates with at least one episode of hypoglycemia (<47 mg/dL) [13]. Given concerns about the potential

adverse outcomes of hypoglycemia in very low birth weight (VLBW) neonates (≤1500 g), we conducted a retrospective cohort study from a database to assess both short-term and long-term outcomes following hypoglycemia on the first day of life.

2. Materials and Methods

2.1. Study Participants

This retrospective cohort study analyzed data from the Taiwan Premature Infant Follow-up Network (TPFN) database hosted by the Premature Baby Foundation of Taiwan, including 35 neonatal units, comprising 17 level III and 18 level II units. The TPFN database captures more than 80% of premature infants nationwide. The study population included preterm infants born between 2016 and 2020. The inclusion criteria were as follows: a birth weight of ≤1500 g, or a gestational age of ≤29 weeks. All included infants had a birth weight of ≤1500 g. Infants were excluded if they had a congenital anomaly, died within 48 h of birth, or had missing data. Congenital anomalies included chromosomal, central nervous system, facial, genitourinary tract, gastrointestinal tract, cyanotic heart, respiratory tract, and musculoskeletal anomalies. All enrolled infants had their initial blood glucose measured as soon as possible within one hour of life. Due to hyperglycemia acting as a hyperosmolar stressor that may cause neuronal damage [14], a blood sugar level of more than 180 mg/dL was defined as hyperglycemia of prematurity and was excluded [15]. Queensland Clinical Guidelines (Australia), the Canadian Pediatric Society, and the American Academy of Pediatrics guidelines for screening and management of neonatal hypoglycemia recommended that blood glucose levels less than <47 mg/dL be considered the acceptable threshold [16,17]. Thus, initial Dextrostix or plasma glucose less than 47 mg/dL was defined as hypoglycemia in this study. To ensure comparability, infants without hypoglycemia were matched 1:1 to infants in the hypoglycemia group according to propensity score. Gestational age was included as the sole covariate in the propensity score model.

2.2. Data Collection

Maternal characteristics considered in the study included gestational age, maternal age, paternal age, marital status, maternal education level, maternal occupation, mode of delivery, number of gravidities, parity, and abortion, multiple gestation, preeclampsia, gestational diabetes, fetal distress, preterm premature rupture of membranes (PPROM), chorioamnionitis, prenatal steroid use, and prenatal magnesium sulfate ($MgSO_4$) administration. Neonatal characteristics assessed included birth weight (BW), birth length (BL), head circumference (HC), small for gestational age (SGA), sex, Apgar scores at 1 and 5 min, body temperature, first blood glucose level, arterial blood pH, bicarbonate (HCO_3), base excess (BE) in arterial blood, surfactant administration, and requirement for ventilation at delivery. PPROM was defined as rupture of the fetal membranes before 37 weeks of gestation and lasting greater than 18 h. SGA was defined as infants with birth weights below the 10th percentile for their gestation.

2.3. Outcomes Assessment

Primary outcomes included respiratory distress syndrome (RDS), pulmonary hypertension, air leak syndrome, early-onset sepsis (within the first 72 h of life), late-onset sepsis, duration of respiratory support, patent ductus arteriosus (PDA) ligation, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), grade 4 intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (cPVL), respiratory support until 28 days of life or until postmenstrual age (PMA) of 36 weeks, PMA at discharge, mortality, length of stay in the neonatal intensive care unit (NICU), hearing screen results, and neonatal

anthropometric measures at discharge. IVH and cPVL were based on brain echo reports performed by neurologists. Respiratory support was defined as any form of respiratory assistance, including supplemental oxygen.

Secondary outcomes encompassed the information at the outpatient department (OPD), as well as the primary caregiver, the infant's body weight, body length, head circumference, and Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) for cognitive, motor, and language development at corrected ages of 6, 12, and 24 months. To further evaluate the clinical relevance of our findings, we performed additional categorical analyses using a Bayley-III composite score below 85 and 70 as the threshold for developmental delay. Mild-to-moderate developmental delay was defined with scores <85, whereas moderate-to-severe developmental delay was defined with scores <70. Additionally, visual and hearing impairment and the presence of cerebral palsy were assessed.

Baseline characteristics, primary outcomes, and secondary outcomes were compared between the non-hypoglycemia and hypoglycemia groups using the independent t-test for continuous variables and the chi-square test for categorical variables. Multivariable logistic regression was further used with neonatal hypoglycemia as the dependent variable to analyze neonatal clinical characteristics and subsequent outcomes with adjustment for potential confounding variables. In primary outcomes, these adjusting variables included delivery mode, preeclampsia, PPROM, prenatal $MgSO_4$ administration, fetal distress, BW, BL, birth HC, birth body temperature, respiratory support at delivery, and birth year. The Variance Inflation Factor (VIF) was used to measure collinearity, and values ranged from 1.0 to 2.8. In secondary outcomes, maternal occupation and education, delivery mode, preeclampsia, PPROM, prenatal $MgSO_4$ administration, fetal distress, BW, BL, birth HC, body temperature, respirator at delivery, and birth year were controlled in the regression model. The VIF values ranged from 1.0 to 2.7 among variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to quantify these associations. A p value of <0.05 was considered statistically significant.

3. Results

3.1. Participant Characteristics

A total of 5984 preterm infants were included, and 524 infants were excluded for meeting the exclusion criteria. Of the 5460 infants, 1072 (19.6%) had hypoglycemia at the initial postnatal glucose measurement. After using 1:1 matching by propensity score between the hypoglycemia (<47 mg/dL) and the non-hypoglycemia groups, 1066 infants were included in each group. (Figure 1). Table 1 presents the maternal and neonatal characteristics at birth, and no significant difference was noted between the two groups in gestational age, parents' age, marriage status, gravidity, parity, abortion, multiple birth, gestational diabetes, or prenatal steroid use. However, mothers in the hypoglycemia group had higher educational levels, were more likely to be employed as educators, and were less likely to be unemployed than those in the non-hypoglycemia group (p = 0.021, 0.022, and 0.030, respectively). In addition, the incidence of cesarean delivery was significantly higher in the hypoglycemia group compared with the non-hypoglycemia group (p < 0.001). Mothers in the hypoglycemia group also had significantly higher rates of preeclampsia (p < 0.001), fetal distress (p = 0.001), and prenatal use of $MgSO_4$ (p < 0.001). In contrast, preterm prolonged ruptured membranes and chorioamnionitis were significantly less frequent in the hypoglycemia group (p = 0.031 and 0.020, respectively).

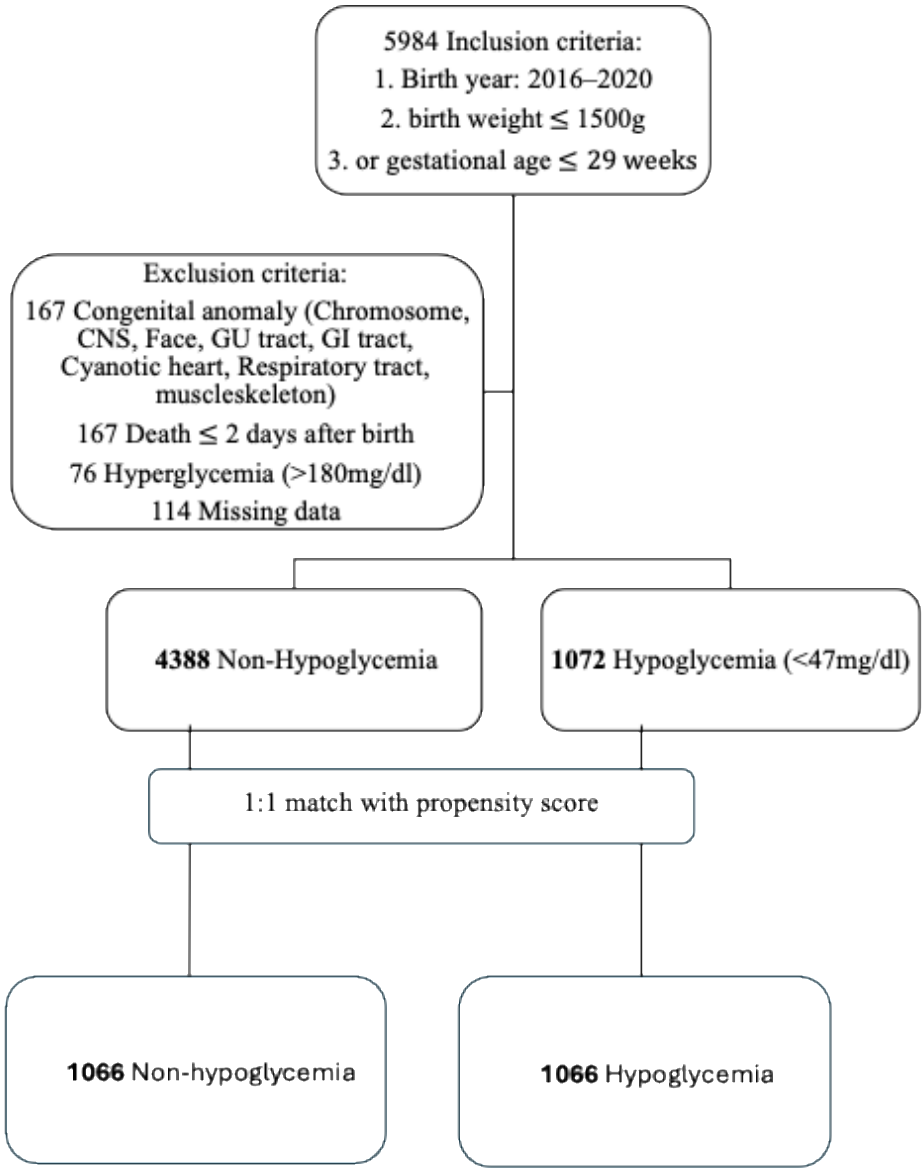

Figure 1. Flowchart of study participant selection.

Table 1. Maternal and Neonatal Characteristics at birth.

Characteristics	Non-Hypoglycemia (*n* = 1066) Mean± SD/*n* (%)	Hypoglycemia (*n* = 1066) Mean ± SD/*n* (%)	*p*
	Maternal		
Gestational age	29.83 ± 2.97	29.86 ± 2.94	0.815
Mothers' age	33.50 ± 5.79	33.59 ± 5.54	0.717
Fathers' age	36.04 ± 6.03	36.06 ± 6.14	0.942
Marriage status Single/Married	63 (5.9)/1003 (94.1)	42 (4.5)/1018 (95.5)	0.262
Maternal Education			
Below senior	48 (4.9)	39 (4.2)	* 0.021
Senior	405 (41.0)	326 (35.4)	
College and above	534 (54.1)	557 (60.4)	
Maternal profession			
Educator	57 (5.8)	80 (8.5)	* 0.022
Medical related	48 (4.9)	46 (4.9)	0.995

Unemployed	439 (44.5)	375 (39.6)	* 0.030
Cesarean Section	813 (76.3)	893 (83.8)	* <0.001
Gravida	2.17 ± 1.45	2.13 ± 1.64	0.529
Para	1.55 ± 0.80	1.50 ± 0.78	0.228
Abortus	0.63 ± 1.05	0.63 ± 1.32	0.985
Multiple birth	355 (33.3)	317 (29.7)	0.076
Preeclampsia	299 (28.0)	418 (39.2)	* <0.001
GDM	93 (8.7)	90 (8.4)	0.817
Fetal distress	151 (14.2)	207 (19.4)	* 0.001
PPROM more than 18 h	266 (25.0)	224 (21.0)	* 0.031
Chorioamnionitis	40 (3.8)	22 (2.1)	* 0.020
Prenatal steroid	777 (72.9)	802 (75.2)	0.217
Prenatal $MgSO_4$	479 (44.9)	593 (55.6)	* <0.001
Neonatal			
Birth weight	1167.22 ± 258.25	1097.09 ± 298.47	* <0.001
Birth length	36.71 ± 5.49	35.97 ± 5.87	* 0.003
Birth head circumference	26.11 ± 3.88	25.50 ± 4.37	* 0.001
Small for gestational age	168 (15.8)	228 (21.4)	* 0.001
Sex (F/M)	511/554	428/428	0.379
Apgar score_1	6.13 ± 2.01	5.99 ± 2.06	0.099
Apgar score_5	8.00 ± 1.59	7.86 ± 1.77	0.052
Body temperature	35.90 ± 0.84	36.07 ± 0.89	* <0.001
The first blood sugar	79.50 ± 26.55	33.77 ± 9.98	* <0.001
Arterial pH (within 4 h of admission	7.30 ± 0.11	7.30 ± 0.10	0.096
Arterial HCO_3	21.92 ± 4.31	22.30 ± 5.25	0.078
Arterial BE	−4.26 ± 4.19	−4.15 ± 4.04	0.521
Intubation at delivery	182 (17.1)	247 (23.2)	* <0.001
Nasal CPAP at delivery	159 (14.9)	119 (11.2)	* 0.010

Abbreviations: BE, base excess; CPAP, continuous positive airway pressure; GDM, gestational diabetes mellitus; HCO_3, bicarbonate; $MgSO_4$, magnesium sulfate; pH, potential of hydrogen; PPROM, preterm premature rupture of membranes; SD, standard deviation. * means $p < 0.05$.

Regarding neonatal characteristics, infants in the hypoglycemia group had a significantly lower BW, shorter BL, and smaller birth HC ($p < 0.001$, $p = 0.003$, and $p = 0.001$, respectively) than those in the non-hypoglycemia group. The proportion of SGA neonates was significantly higher in the hypoglycemia group ($p = 0.001$). Neonates in the two groups had hypothermia at birth, but the non-hypoglycemia group had a significantly lower body temperature ($p < 0.001$). The proportion of neonates requiring invasive ventilator at delivery was significantly higher in the hypoglycemia group ($p < 0.001$), but there were no significant differences in Apgar scores at 1 and 5 min.

3.2. Primary Clinical Outcomes

Table 2 presents the primary clinical outcomes of infants in the non-hypoglycemia and hypoglycemia groups. After controlling for confounding variables, infants in the hypoglycemia group had a lower incidence of RDS, 1.86-fold higher rates of PDA ligation, higher BW at discharge, but smaller HC at discharge than those in the non-hypoglycemia group ($p = 0.014$, 0.007, 0.017, and 0.007, respectively). Neither mortality before PMA 36 weeks nor mortality during the first hospitalization differed significantly between the two groups. We found that the PMA at discharge was higher in the hypoglycemia group, but

there was no significant difference in the regression model. Other outcomes presented in Table 2 showed no significant difference.

Table 2. Primary outcomes.

				Logistic Regression	
Outcomes	**Non-Hypoglycemia (*n* = 1066) Mean ± SD/*n* (%)**	**Hypoglycemia (*n* = 1066) Mean ± SD/*n* (%)**	***p***	**OR (95% CI)**	***p***
Respiratory distress syndrome	858 (80.5)	871 (81.7)	0.472	0.68 (0.49–0.92)	* 0.014
Surfactant administration	309 (28.7)	315 (29.5)	0.948	1.19 (0.87–1.64)	0.278
Pulmonary hypertension	52 (4.9)	64 (6.0)	0.252	0.85 (0.50–1.42)	0.527
Air leak syndrome	46 (4.3)	45 (4.2)	0.915	0.91 (0.52–1.60)	0.752
Early-onset sepsis	14 (1.3)	8 (0.8)	0.198	1.27 (0.42–3.90)	0.674
Late-onset sepsis	63 (5.9)	58 (5.4)	0.640	1.27 (0.77–2.08)	0.349
Days of respiratory support (including oxygen)	41.47 ± 38.34	44.32 ± 45.74	0.119	0.99 (0.99–1.00)	0.482
PDA ligation	106 (9.9)	76 (7.1)	0.020	1.86 (1.18–2.93)	* 0.007
Necrotizing enterocolitis	44 (4.1)	44 (4.1)	1.000	0.85 (0.49–1.45)	0.553
Retinopathy of prematurity	335 (31.4)	402 (37.7)	0.002	1.08 (0.82–1.42)	0.599
Grade 4 Intraventricular Hemorrhage	15 (1.4)	18 (1.7)	0.599	1.02 (0.39–2.69)	0.961
Cystic periventricular leukomalacia	52 (4.9)	36 (3.4)	0.080	1.23 (0.67–2.26)	0.503
Respiratory support till 28 days of life	600 (59.2)	603 (59.9)	0.745	0.94 (0.70–1.27)	0.703
Respiratory support till PMA 36 weeks	419 (41.4)	440 (44.2)	0.195	1.17 (0.88–1.56)	0.268
PMA at discharge	38.37 ± 4.52	39.36 ± 6.23	<0.001	1.02 (0.998–1.04)	0.076
Abnormal hearing screen	51 (5.4)	61 (6.5)	0.324	1.00 (0.59–1.70)	1.000
Body weight on discharge	2431.36 ± 642.80	2571.32 ± 871.76	<0.001	1.00 (1.00–1.00)	* 0.017
Body length on discharge	37.97 ± 16.66	36.28 ± 18.16	0.025	0.99 (0.99–1.00)	0.063
Head circumference on discharge	24.75 ± 13.41	25.38 ± 13.30	0.274	0.98 (0.98–0.99)	* 0.007
Days for NICU	41.88 ± 36.14	48.65 ± 43.5073	<0.001	1.00 (0.99–1.01)	0.205
Mortality before PMA36	33 (3.1)	50 (4.7)	0.057	0.97 (0.53–1.76)	0.916
Mortality at discharge	45 (4.2)	65 (6.1)	0.050	0.96 (0.56–1.65)	0.893

Adjust delivery mode, pre-eclampsia, PPROM. $MgSO_4$, fetal distress, birth weight, birth length, birth head circumference, body temperature, respiratory support at delivery and birth year. Abbreviations: CI, confidence interval; NICU, neonatal intensive care unit; OR, odds ratio; PDA, patent ductus arteriosus; PMA, postmenstrual age; SD, standard deviation. * means $p < 0.05$.

3.3. Secondary Outcomes (Long-Term Follow-Up)

Secondary outcomes were focused on the report of the Bayley-III scale. Table 3 reveals the secondary outcomes at corrected ages of 6, 12, and 24 months. The proportion of mothers serving as the primary caregiver did not differ significantly between groups.

Table 3. Secondary outcomes.

	Non-Hypoglycemia (n = 915)	Hypoglycemia (*n* = 927)		Logistic Regression	
Outcomes	Mean± SD/*n* (%)	Mean± SD/*n* (%)	*p*	OR (95% CI)	*p*
Main caregiver: mother	658 (71.9)	673 (72.6)	0.502	0.89 (0.68–1.17)	0.419
6 months corrected age					
Body weight	7.10 ± 1.24	6.92 ± 1.23	*0.002	1.06 (0.96–1.19)	0.262
Body length	64.81 ± 6.33	63.04 ± 6.98	*0.014	1.00 (0.98–1.02)	0.826
Head circumference	40.58 ± 7.54	40.86 ± 6.35	0.385	1.00 (0.98–1.02)	0.627
12 months corrected age	*n* = 883	*n* = 878			
Body weight	8.58 ± 1.51	8.50 ± 1.32	0.980	1.08 (0.98–1.19)	0.103
Body length	72.20 ± 8.53	72.05 ± 7.45	0.695	1.00 (0.99–1.03)	0.318
Head circumference	43.11 ± 8.36	43.35 ± 7.17	0.523	1.01 (0.99–1.03)	0.152
24 months corrected age	*n* = 834	*n* = 842			
Body weight	10.78 ± 2.18	10.60 ± 2.05	0.089	1.00 (0.94–1.06)	0.898
Body length	82.48 ± 13.97	82.48 ± 11.62	0.999	1.00 (0.99–1.01)	0.663
Head circumference	43.85 ± 11.82	44.32 ± 10.28	0.380	1.00 (0.99–1.01)	0.904
Visual disturbance	11 (1.3)	15 (1.7)	0.430	1.50 (0.45–5.04)	0.509
Hearing impairment	40 (4.8)	39 (4.6)	0.917	0.84 (0.46–1.54)	0.577
Cerebral Palsy	3 (0.3)	20 (2.3)	*<0.001	0.65 (0.09–4.82)	0.670

Adjust maternal job, maternal education, delivery mode, pre-eclampsia, and PPROM. $MgSO_4$, fetal distress, birth weight, BL, HC, Body temperature, respirator at delivery, and birth year. Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.* means $p < 0.05$.

At 6, 12, and 24 months corrected age, the numbers of infants available for follow-up were 915, 883, and 834 in the non-hypoglycemia group and 927, 878, and 842 in the hypoglycemia group, respectively. No significant differences in BW, BL, or HC were observed between the two groups at any of the three follow-up time points. The incidence of cerebral palsy at 24 months corrected age was significantly higher in the hypoglycemia group (1.9% vs. 0.3%, $p < 0.001$), but there was no significant difference after adjusting for confounding factors. In addition, the proportions of visual and hearing impairments did not differ significantly between the hypoglycemia and non-hypoglycemia groups.

Using a composite score <85 as the cutoff, neonatal hypoglycemia was significantly associated with an increased risk of mild-to-moderate language developmental delay at 6 months corrected age. However, this association was not statistically significant at 12 months or 24 months corrected age. No significant associations were observed between neonatal hypoglycemia and cognitive or motor developmental delay at any of the three follow-up time points (Table 4). When a more stringent composite score cutoff of <70 was applied, neonatal hypoglycemia was significantly associated with moderate-to-severe language developmental delay at 6 months, 12 months, and 24 months corrected age. In contrast, no statistically significant associations were identified between neonatal hypoglycemia and moderate cognitive or motor developmental delay at these follow-up time points.

Table 4. Neurodevelopmental outcomes by Bayley-III severity threshold.

Corrected age	Domain	Adjusted OR (95% CI)	*p* value
Mild-to-moderate developmental delay (Bayley-III composite score <85)			
6 months	Cognitive	1.54 (0.97–2.46)	0.068
6 months	Language	2.37 (1.64–3.42)	* <0.001
6 months	Motor	0.99 (0.72–1.36)	0.963
12 months	Cognitive	1.13 (0.68–1.87)	0.641
12 months	Language	1.21 (0.88–1.67)	0.240
12 months	Motor	1.09 (0.75–1.58)	0.641
24 months	Cognitive	1.03 (0.70–1.52)	0.890
24 months	Language	0.97 (0.72–1.32)	0.860
24 months	Motor	0.85 (0.58–1.25)	0.421
Moderate-to-severe developmental delay (Bayley-III composite score <70)			
6 months	Cognitive	2.05 (0.93–4.56)	0.077
6 months	Language	3.16 (1.80–5.55)	* <0.001
6 months	Motor	0.74 (0.40–1.36)	0.333
12 months	Cognitive	1.86 (0.80–4.32)	0.150
12 months	Language	2.18 (1.31–3.62)	* 0.003
12 months	Motor	1.25 (0.66–2.39)	0.494
24 months	Cognitive	0.83 (0.41–1.67)	0.602
24 months	Language	1.76 (1.12–2.77)	* 0.013
24 months	Motor	0.83 (0.41–1.67)	0.602

Adjust maternal job, maternal education, delivery mode, pre-eclampsia, and PPROM. $MgSO_4$, fetal distress, birth weight, BL, HC, Body temperature, respirator at delivery, and birth year. Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.* means $p < 0.05$.

4. Discussion

In this study, our most important finding is that neonatal hypoglycemia (NH), defined as initial glucose < 47 mg/dL, is significantly associated with a higher incidence of PDA ligation, smaller HC at discharge despite a higher BW at discharge, and long-term neurodevelopmental impairment in VLBW infants, especially in language development, particularly language developmental delay, with significant associations observed across multiple follow-up time points when a more stringent Bayley-III composite score threshold (<70) was applied. Our results are consistent with a previous study, which reported that NH is related to lower neurodevelopment at corrected ages of six and twelve months in both symptomatic and asymptomatic NH [18]. However, other previous studies showed that no significant differences in intellectual or academic achievement were found between preterm infants (≤2500 g and ≤37 weeks' gestation) with and without hypoglycemia [19]. In addition, transient hypoglycemia was not associated with adverse neurological outcomes [20], and dextrose gel for hypoglycemia (<47 mg/dL) in neonates with a gestational age ≥35 weeks did not differ from placebo in terms of neurosensory impairment at 2 years' corrected age [21]. There were important methodological differences between these studies and our study. First, our study focused on the VLBW population. VLBW infants have much lower energy stores and more fragile white matter than late preterm or term infants. Lower gestational age is associated with an earlier onset of hypoglycemia [9]. A retrospective cohort study showed that 19% of infants born before 32 weeks of gestation experienced at least one episode of hypoglycemia, with a median time-to-event of 126 min and had sixfold higher odds of hypoglycemia if they did not receive intravenous glucose in the delivery room [22]. Accordingly, early neonatal hypoglycemia (<6 h) may be associated with a twofold increase in the risk of any neurological or

neurodevelopmental outcome and triple the risk of cognitive developmental delay [12]. However, administration of 40% buccal dextrose gel in the delivery room had no evidence of benefit on rates of hypoglycemia at NICU admission [23]. Thus, most VLBW infants receive glucose-containing intravenous fluids after birth as soon as possible to prevent hypoglycemia. Second, the definition of hypoglycemia and assessment tools were different among these studies. A study that defined hypoglycemia as plasma glucose <50 mg/dL—slightly higher than our cutoff (47 mg/dL)—reported findings similar to ours and used a comparable assessment tool for outcomes [18]. However, another study defined hypoglycemia as a glucose level ≤45 mg/dL and conducted standardized cognitive, academic, and behavioral assessments at 3, 8, and 18 years of age [19], all of which differed from our study. Nevertheless, both studies included late preterm or term infants rather than VLBW infants.

An important finding of the present study was that neonatal hypoglycemia was significantly associated with language developmental delay in VLBW infants after adjustment for potential confounders. Using a Bayley-III composite score cutoff of <85, this association was significant only at 6 months corrected age. However, with a more stringent cutoff of <70, significant associations were observed at 6, 12, and 24 months corrected age, suggesting that the association between neonatal hypoglycemia and language impairment may vary according to the severity of developmental delay. One possible explanation is that milder developmental difficulties may become less apparent over time because of developmental variability, maturation, or early intervention, whereas more pronounced language impairment may remain detectable during subsequent follow-up. In contrast to the findings for language development, neonatal hypoglycemia was not significantly associated with cognitive or motor developmental delay at 6, 12, or 24 months corrected age after adjustment for potential confounders, regardless of the Bayley-III cutoff applied. Nevertheless, the precise mechanisms underlying the language-specific associations observed in our cohort remain uncertain.

Infants of diabetic mothers are traditionally considered at high risk for symptomatic hypoglycemia [24]. Physiologically, the cessation of maternal glucose supply after birth, combined with persistent neonatal hyperinsulinism, typically leads to rapid hypoglycemia and impaired metabolic compensation [24]. However, we found that the incidence of maternal gestational diabetes mellitus (GDM) was not significantly higher in the VLBW infants with neonatal hypoglycemia. This may be because the initial blood glucose measurement in very low-birth-weight infants was often obtained immediately after birth, possibly before hypoglycemia developed as a result of hyperinsulinism. In term infants born to mothers with gestational diabetes mellitus (GDM), the nadir of blood glucose levels occurred within the first two hours after birth in 86.11% of cases [25]. Furthermore, VLBW infants routinely receive early intravenous glucose as part of standard NICU care, which may mask subsequent hypoglycemic effects related to maternal GDM in the following hours. As a result, the conventional association between maternal GDM and neonatal hypoglycemia may be less apparent in the VLBW population.

To date, limited data are available regarding the association between hypoglycemia and neurodevelopmental outcomes in preterm neonates with hypoglycemia. The most likely cause is that the analysis of outcomes in preterm infants would be influenced by many confounding factors. Gestational age is the most important factor; thus, this study matched the two groups by gestational age before analysis. Furthermore, higher BW but smaller HC at discharge were found in the hypoglycemia group even after adjusting for confounding factors. HC at birth and slow growth HC were both associated with neurodevelopment in a population-based prospective cohort of preterm infants born under 32 weeks of gestation or 1500 g [26]. The result was comparable with our finding of language delay in the hypoglycemia group.

A critical point of our study is that these adverse outcomes occurred even though the early NH episodes were treated immediately. All Taiwanese citizens have national insurance, and VLBW infants are routinely admitted to the NICU right after birth for premature care regardless of socioeconomic status. Their blood glucose is closely monitored and managed strictly according to protocols. Our results showed that episodes of hypoglycemia before glucose-containing intravenous fluids may trigger brain damage in VLBW infants, who are at high risk for perinatal brain injury. Various brain MRI studies have demonstrated cortical, subcortical, periventricular, and even thalamic injury in newborn infants with hypoglycemia [27]. Severe clinical symptoms were strongly correlated with widespread brain injury affecting the internal capsule, basal ganglia, and thalamus [28]. A systematic review and meta-analysis revealed that hypoglycemia in the neonatal period may be related to visual-motor impairment and executive dysfunction at school age [29]. Long-term follow-up extending to school age may be necessary in these high-risk infants. Our study showed that VLBW infants with a history of cesarean delivery, maternal preeclampsia, prenatal $MgSO_4$ administration, SGA, and hypothermia at birth had a higher risk of hypoglycemia. Early glucose-containing intravenous fluids, frequent blood sugar monitoring, and long-term follow-up are required for these high-risk neonates.

Hypoglycemia-related brain injury in newborns typically affects the parieto-occipital regions of the brain and may lead to visual disturbances, hearing impairment, cognitive abnormalities, and other neurodevelopmental disorders, which depend on the severity and duration of hypoglycemia or comorbidities, most significantly by hypoxic–ischemic encephalopathy. The duration of hypoglycemia was not recorded in our retrospective study because the database only recorded the first blood glucose measurement after birth, whether from Dextrostix or a plasma sample. This was also one of the limitations of our study.

Another limitation of the study was that hospitals differed in the management of hypoglycemia, which depended on hospital protocol and the pediatrician's decision. The timing of enteral feeding initiation, provision of intravenous glucose, parenteral nutrition, and type of milk may influence both the occurrence of hypoglycemia and subsequent growth. However, the Taiwan Society of Neonatology edited a clinical practice handbook named "Recommendation on Nutritional Care of Taiwan Preterm Infants." Most units followed this handbook to provide carbohydrate. The glucose infusion rate should be increased stepwise over one week and adjusted in response to blood glucose levels exceeding 250 mg/dL [30]. Thus, more than 90% of the units supplemented glucose infusion at approximately 4–8 mg/kg/min initially [30]. Notably, after adjustment for potential confounding factors, no significant differences in body weight or body length were observed between infants with and without neonatal hypoglycemia at 6, 12, or 24 months of corrected age. These findings suggest that early neonatal hypoglycemia was not associated with measurable differences in subsequent weight or linear growth during the first two years of corrected age in our cohort. Nevertheless, the potential influence of variations in nutritional management on neonatal glucose concentrations and growth outcomes cannot be completely excluded. Moreover, potential attrition bias during long-term neurodevelopmental follow-up should be acknowledged as an additional limitation of our study. Although follow-up rates were comparable between the hypoglycemia and non-hypoglycemia groups, approximately 21% of infants were not included in the assessment at 24 months of corrected age. Infants who did not complete follow-up may have differed from those who completed follow-up in terms of clinical severity, socioeconomic background, or neurodevelopmental status, potentially introducing selection bias. Furthermore, the retrospective nature of this study limited our ability to determine whether missing follow-up data occurred randomly. Therefore, the associations between neonatal hypoglycemia and long-term neurodevelopmental outcomes should be interpreted with caution.

Strengths of this study include the VLBW population and the large sample size. Many studies have been reported in late-preterm and term babies with neonatal hypoglycemia and their neurodevelopmental outcomes [4,20]. Few manuscripts have discussed the neurodevelopmental outcomes in low-birth-weight newborns with hypoglycemia thus far [15,20]. VLBW newborns should be managed more seriously because they are prone to brain injury. Additionally, almost 80% of the infants were followed for at least two years. The results from this cohort study utilizing large, existing databases provide high statistical power. Therefore, from our results, we recognized that we should screen blood sugar as soon as possible in the delivery room, not in the NICU, for all infants under 1500 g and treat hypoglycemia immediately. Subsequently, close follow-up of these high-risk preterm infants and early intervention for cognitive and language delay would be necessary to improve their long-term quality of life.

5. Conclusions

Our study demonstrates that infants who exhibit hypoglycemia at the initial postnatal blood glucose screening are at increased risk of adverse language developmental outcomes. The development of standardized screening, treatment, and follow-up guidelines for these high-risk infants is warranted.

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Data Availability Statement: The data that support the findings of this study are available on request from Taiwan Premature Infant Follow-up Network (TPFN). The data are not publicly available due to privacy or ethical restrictions.

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Abbreviations

The following abbreviations are used in this manuscript:

BE	base excess
BL	birth length
BW	birth weight
CI	confidence interval
CPAP	continuous positive airway pressure
cPVL	cystic periventricular leukomalacia
GDM	gestational diabetes mellitus
HC	head circumference

HCO_3	bicarbonate
IVH	intraventricular hemorrhage
$MgSO_4$	magnesium sulfate
NEC	necrotizing enterocolitis
NH	neonatal hypoglycemia
NICU	neonatal intensive care unit
OPD	outpatient department
OR	odds ratio
PDA	patent ductus arteriosus
pH	potential of hydrogen
PMA	postmenstrual age
PPROM	preterm premature rupture of membranes
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
SGA	small for gestational age
TPFN	Taiwan Premature Infant Follow-up Network
VIF	variance inflation factor
VLBW	very low birth weight

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