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Posted Date: 5 January 2026

doi: 10.20944/preprints202601.0177.v1

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Article

Early Neonatal Hyperglycemia, Risk Factors, and Adverse Outcomes in Extremely Preterm Infants: A Propensity-Matched Cohort Study

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Highlights

- Early neonatal hyperglycemia (NH) in extremely preterm (EP) infants was linked to higher rates of ventilator-associated pneumonia, prolonged mechanical ventilation, severe ROP, and a trend toward increased moderate-to-severe bronchopulmonary dysplasia (BPD), even after propensity score matching.
- These associations suggest that early NH may be an independent contributor to adverse short-term outcomes in this high-risk population.
- Early recognition and targeted management of NH may help reduce respiratory and ophthalmologic morbidities.
- Findings support the need for standardized glucose-monitoring protocols and future interventional studies to determine whether better glycemic control improves outcomes.

Abstract

Background: Neonatal hyperglycemia (NH) is a common metabolic complication among (NH) infants. However, early risk factors and clinical outcomes of NH remain unclear. **Objective:** To evaluate the association of NH with clinical outcomes and neurodevelopmental(NDD) risk in EP infants. **Methods:** This retrospective propensity score matching (PSM) study, included EP, born between 2018-2019 at women's wellness and research Center who met the NH criteria (blood glucose >8.3 mmol/L). Hyperglycemia severity, maternal factors, delivery room interventions, early physiological markers, neonatal morbidities, and follow-up outcomes were compared. Propensity score matching (1:1) was used to adjust for significant baseline demographics and clinical characteristics. **Results:** Out of 225 EP infants, 131 (58.2%) developed NH in the first week of life of infants, with mild hyperglycemia in 31.0%, moderate in 14.6%, and severe in 11.1% of cases. Before matching, infants with NH were more preterm and had lower birth weight and head circumference. Their mothers had lower rates of premature rupture of membranes (PPROM). Affected infants required more surfactant in the delivery room and had higher oxygen and mechanical ventilation needs during the first week. After matching, NH was associated with significantly higher rates of ventilator-associated pneumonia (VAP), with 23.6% vs 3.7%, OR 8.04 CI: 1.72–37.66, p=0.003, longer duration of mechanical ventilation (19.8±25.3 vs 8.9±24.8 days, MD -10.942, CI -21.470–0.420, p=0.042), higher postnatal steroid use (18.2% vs 5.5%, OR 4.64, CI 1.56–14.37, p=0.040) After matching, NH was associated with significantly higher rates of severe retinopathy of prematurity (ROP), (21.6% vs 6.4%, OR 4.03 CI: 1.04–15.50, p= 0.032).and trend towards moderate to severe bronchopulmonary dysplasia (BPD) (33.3% vs 15.9%, OR 2.64, CI 0.96–7.23, p=0.054). No significant differences in mortality were observed between the groups; however, infants with NH who died were older. **Conclusion:** Early NH in EP infants is associated with an increased risk of ventilator-associated

pneumonia, prolonged mechanical ventilation, severe ROP, and moderate to severe BPD. These findings suggest that NH may contribute to poorer short-term outcomes in this vulnerable population.

Keywords: extremely preterm; infants; neonatal hyperglycemia; ROP; ventilator-associated pneumonia; propensity score matching

1. Introduction

Neonatal hyperglycemia (NH) is among the most common metabolic disorders in extremely preterm (EP) infants [1]. It results from multiple factors, including insulin resistance, stress-related catecholamine release, immature pancreatic beta-cell function, and exogenous glucose administration [2–4]. Incidence rates vary widely, from 20% to 80%, depending on gestational age, illness severity, and nutritional management [5,6]. NH has been associated with adverse outcomes such as necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), sepsis, and increased mortality [6–10]. However, these associations are confounded by the biological vulnerability of this population, making it unclear whether NH is an independent risk factor or merely a marker of disease severity [6,10,11].

Recent studies confirm that hyperglycemia is common in EP infants and linked to significant short- and long-term morbidities. It is associated with increased mortality, intraventricular hemorrhage (IVH), and ROP, particularly when blood glucose exceeds 10 mmol/L or when hyperglycemia is prolonged. Observational data also suggest associations with chronic lung disease and neurodevelopmental impairment, though causality remains uncertain. Pathophysiologically, NH reflects a combination of insulin resistance and impaired insulin secretion, both strongly influenced by prematurity. Hyperglycemic neonates exhibit reduced endogenous insulin production, and exogenous insulin therapy does not suppress pancreatic secretion, underscoring the complexity of metabolic immaturity [12–14].

NH may also contribute to oxidative stress, inflammation, and endothelial dysfunction, mechanisms implicated in ROP, BPD, and heightened infection risk [2,10,15–17]. Furthermore, prolonged hyperglycemia may disrupt retinal vascular development, increasing the likelihood of severe ROP or the need for intervention. Long-term follow-up studies show that each day of hyperglycemia >8 mmol/L is associated with lower intelligence scores and worse motor outcomes at 6.5 years of age, while insulin treatment does not appear to improve neurodevelopmental outcomes. Despite these associations, optimal thresholds for intervention and management strategies remain controversial, as lowering glucose infusion risks calorie deficits and growth impairment, while insulin therapy increases hypoglycemia risk [18–20].

Given these uncertainties, we aimed to determine whether NH is independently associated with major neonatal morbidities after adjusting for confounders using propensity score matching (PSM). To address this question, we conducted a matched-cohort study to evaluate the impact of early NH on clinical outcomes in this high-risk population.

2. Materials and Methods

2.1. Study Design, Setting, and Population

We conducted a retrospective propensity-matched cohort study in the level III Neonatal Intensive Care Unit (NICU) of the Women's Wellness and Research Center, Hamad Medical Corporation, Doha, Qatar.

All live-born infants with a gestational age (GA) <28 weeks, who were admitted to the NICU within 24 h of birth between January 2018 and December 2019, were eligible. Infants who died in the first 12 hours of age, as well as infants with major congenital anomalies, chromosomal syndromes, or metabolic disorders that affect glucose homeostasis, were excluded.

2.1.2. Variables and Outcomes

Maternal variables—including age, hypertensive or diabetic disorders, chorioamnionitis, prolonged rupture of membranes, antenatal steroid exposure, body mass index, and glycated hemoglobin—and neonatal variables such as birth weight, head circumference, gestational age, sex, birthweight z-score, and delivery room interventions were extracted from electronic records. Clinical parameters included modes and duration of respiratory support, metabolic markers (FiO₂, lactate, and base excess), insulin therapy, and postnatal steroid use. Major outcomes assessed were intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), patent ductus arteriosus, ventilator-associated pneumonia (VAP), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and NDD outcome at 18 month corrected gestational age.

2.1.4. Definitions

BPD severity was classified according to Jensen's 2019 criteria [21], based on respiratory support at 36 weeks PMA (mild: nasal cannula \leq 2 L/min; moderate: non-invasive support or cannula $>$ 2 L/min; severe: invasive ventilation). Severe IVH was defined as Papile grade III–IV [22], and severe ROP as stage \geq 3 or requiring treatment [9]. Neonatal hyperglycemia (NH) was defined as blood glucose $>$ 150 mg/dL ($>$ 8.3 mmol/L) within the first week of life; the daily peak value was used when multiple measurements were available and categorized as mild 150–180 mg/dL (8.3–10.0 mmol/L), moderate 180–200 mg/dL (10.0–11.1 mmol/L), or severe $>$ 200 mg/dL ($>$ 11.1 mmol/L) [2]. Neurodevelopmental impairment (NDI) was evaluated at discharge or follow-up using standardized assessments of cognitive, motor, receptive, and expressive domains. NDD assessments were conducted at 18 months of corrected age using the Bayley Infant NDD Screener (BINS III) [23], a validated tool designed to identify infants at risk for developmental delays. BINS III evaluate cognitive, motor, and expressive/receptive language skills through structured tasks and caregiver-reported observations. Infants were categorized as follows based on standardized cutoff scores. Infants were categorized as low risk (scores within age expectations), moderate risk (1–2 SD below the mean), or high risk ($>$ 2 SD below the mean/failed critical items) for NDD delay, enabling identification of those who need early intervention.

2.1.5. Statistical Analysis

Continuous variables were summarized as mean \pm SD and compared using t-tests. Categorical variables are expressed as counts and percentages and compared using χ^2 or Fisher's exact test, as appropriate. Associations between NH and outcomes were reported as odds ratios (ORs) or mean differences with 95% confidence intervals (CI). Sensitivity analyses included multivariable logistic regression to adjust for potential residual confounding and exploratory models assessing glucose variability and duration of hyperglycemia. Statistical significance was defined as a two-sided p-value $<$ 0.05. Analyses were performed using SPSS v29.

To minimize confounding, we used PSM. For NH, outcomes were calculated using logistic regression, including gestational age, birth weight, sex, antenatal steroid use, DR intervention, and key perinatal covariates. We performed 1:1 nearest-neighbor matching without replacement, using a caliper of 0.2 of the logit of the propensity score. Balance was assessed using standardized mean differences (SMD), with an SMD $<$ 0.10, indicating an acceptable balance. "Before matching" refers to the original sample; "after matching" refers to the matched pairs used for outcome comparisons.

Ethical approval was obtained from the Institutional Review Board, and informed consent was waived due to the study's retrospective nature.

3. Results

3.1. Cohort Characteristics

Among 225 infants, 131 (58.2%) developed NH during the first postnatal week, while 94 (41.8%) did not. Of the 131 infants, 20.91% developed any hyperglycemia, 11.47% mild NH, 4.34% moderate NH, and 5.10% severe NH.

3.1.1. Table 1: Maternal and Neonatal Characteristics

Before matching, infants with hyperglycemia were more premature (25.34 vs 25.8 weeks, $p=0.004$), had lower birth weight (803 g vs 914 g, $p<0.001$), and smaller head circumference (22.8 vs 23.95 cm, $p<0.001$). Maternal PPRM was significantly less frequent (20.6% vs 33.0%, $p=0.036$), and surfactant use in the delivery room was higher (63.4% vs 50.0%, $p=0.045$). After matching, none of these differences remained significant, indicating that maternal and neonatal characteristics were balanced between the two groups. Other maternal and neonatal baseline demographics did not differ significantly between groups.

Table 1. Maternal and Neonatal Characteristics.

Variable	Before Matching				After Matching			
	No HG (n = 94)	HG (n = 131)	Odds Ratio (95% CI) / Mean Difference (95% CI)	P-value	No HG (n = 54)	HG (n = 55)	Odds Ratio (95% CI) / Mean Difference (95% CI)	P-value
Maternal								
Hypertension, n (%)	12 (13.8%)	15 (11.8%)	0.84 (0.37 – 1.88)	0.668	11 (20.4%)	5 (9.1%)	0.39 (0.12 – 1.21)	0.096
Hyperglycemia / Diabetes, n (%)	15 (16.0%)	19 (14.8%)	0.92 (0.44 – 1.91)	0.820	7 (13%)	6 (11.1%)	0.83 (0.26 – 2.68)	0.767
Chorioamnionitis, n (%)	17 (18.1%)	16 (12.2%)	0.63 (0.30 – 1.32)	0.220	6 (11.1%)	10 (18.2%)	1.77 (0.59 – 5.29)	0.297
PPROM, n (%)	31 (33.0%)	27 (20.6%)	0.53 (0.28 – 0.96)	0.036	12 (22.2%)	14 (25.5%)	1.19 (0.49 – 2.89)	0.692
Antenatal steroids, n (%)	76 (80.9%)	114 (87.0%)	1.59 (0.77 – 3.27)	0.208	42 (77.8%)	48 (87.3%)	1.95 (0.70 – 5.43)	0.191
Maternal BMI (value)	29.86 ± 6.57	28.93 ± 5.40	0.93 (–0.67 – 2.53)	0.253	31.47 ± 7.72	29.22 ± 6.04	2.25 (–0.43 – 4.93)	0.098
Maternal HbA1c (%)	5.27 ± 0.47	5.30 ± 0.35	–0.04 (–0.19 – 0.12)	0.658	5.07 ± 0.24	5.25 ± 0.36	–0.176 (–0.367 – 0.0148)	0.070
Neonatal								
SGA, n (%)	3 (3.2%)	8 (6.1%)	1.97 (0.50 – 7.64)	0.367	3 (5.6%)	1 (1.8%)	0.32 (0.03 – 3.12)	0.363
LGA, n (%)	11 (11.7%)	13 (9.9%)	0.83 (0.35 – 1.94)	0.670	4 (7.4%)	3 (5.5%)	0.72 (0.15 – 3.38)	0.716
Male gender, n (%)	53 (56.4%)	73 (55.7%)	0.97 (0.57 – 1.66)	0.922	29 (53.7%)	26 (47.3%)	0.77 (0.36 – 1.64)	0.502
Birth weight (g)	913.82 ± 187.2	803.02 ± 164.3	110.79 (64.38 – 157.21)	<0.001	885.46 ± 169.62	850.2 ± 159.3	35.28 (–27.22 – 97.78)	0.266
Gestational age (weeks)	25.82 ± 1.16	25.34 ± 1.25	0.47 (0.15 – 0.80)	0.004	25.85 ± 1.14	25.58 ± 1.34	0.27 (–0.16 – 0.70)	0.218
Head circumference (cm)	23.95 ± 1.81	22.828 ± 1.76	1.13 (0.59 – 1.66)	<0.001	23.75 ± 1.93	23.36 ± 2.08	0.39 (–0.37 – 1.15)	0.312
BW Z score	0.34 ± 0.89	0.036 ± 0.90	0.30 (0.06 – 0.54)	0.013	0.188 ± 0.89	0.14 ± 0.72	0.04 (–2.66 – 0.35)	0.777
Intubation in DR, n (%)	69 (73.4%)	106 (80.9%)	1.53 (0.81 – 2.89)	0.181	45 (83.3%)	40 (72.7%)	0.53 (0.21 – 1.35)	0.182
Surfactant in DR, n (%)	47 (50.0%)	83 (63.4%)	1.73 (1.00 – 2.96)	0.045	26 (48.1%)	29 (52.7%)	1.20 (0.56 – 2.54)	0.633

This table compares baseline characteristics of mothers and their extremely preterm infants in the no-hyperglycemia and hyperglycemia groups, both before and after propensity score matching. Maternal variables include hypertension, diabetes, chorioamnionitis, preterm premature rupture of membranes (PPROM), antenatal steroid use, maternal body-mass index and HbA1c levels. Neonatal characteristics include small-for-gestational-age and large-for-gestational-age status, sex, birthweight, gestational age, head circumference, birth-weight z-score, delivery-room intubation and surfactant use. Each row reports counts (or means) for the two groups, the corresponding odds ratio or mean difference with 95 % confidence interval, and a P-value, both before and after matching. *Missing data: maternal hypertension (N=11), maternal BMI (N=7), maternal Hb A1C (N=113), head circumference (N= 42).

Table 2: Clinical Parameters in the NICU

Before matching, infants in the hyperglycemia group had a more intensive respiratory course. High-frequency ventilation was significantly more common (44.5% vs 20.5%; $p < 0.001$). The duration of invasive ventilation was longer (17.94 ± 23.2 vs 6.13 ± 20.0 days; mean difference 11.80 days, 95% CI 5.30–18.29; $p < 0.001$). Early physiological markers were also worse, with higher mean FiO_2 during the first week (45.54 vs 37.48; $p = 0.007$). Postnatal steroids were used more frequently in infants with hyperglycemia (20.2% vs 5.1%; $p = 0.003$). Hyperglycemia persisting beyond the first week was also more frequent (19.5% vs 3.4%; $p < 0.001$), and insulin therapy was required more often (9.9% vs 2.1%; $p = 0.021$). Other variables, including surfactant use, initial invasive ventilation rates, base excess, and discharge PMA, were not significantly different.

After matching, most early physiological differences diminished. High-frequency ventilation, week-1 FiO_2 , and base excess were no longer significantly different between groups (all $p > 0.20$). However, the duration of invasive ventilation remained longer in the hyperglycemia group (19.8 ± 25.3 vs 8.9 ± 24.8 days; mean difference 10.94 days, $p = 0.042$). Postnatal steroid exposure remained higher (18.2% vs 5.5%; $p = 0.040$), and persistent hyperglycemia beyond the first week was more common in the hyperglycemia group (27.3% vs 6.1%; $p = 0.004$). Discharge PMA was similar across groups, and insulin use after matching could not be reliably estimated due to sparse data.

Table 2. Comparison of Clinical Parameters in the NICU.

Variables	Before Matching				After Matching			
	No HG (n=94)	HG (n=131)	Odds ratio / Mean difference (95% CI)	P- value	No HG (n=54)	HG (n=55)	Odds ratio / Mean difference (95% CI)	P- value
Surfactant, n (%)	73 (82.0%)	114 (89.1%)	1.78 (0.82– 3.87)	0.139	52 (96.3%)	48 (87.3%)	0.26 (0.05– 1.33)	0.161
Invasive ventilation, n (%)	76 (85.4%)	119 (93.0%)	2.26 (0.92– 5.54)	0.069	52 (96.3%)	51 (92.7%)	0.49 (0.08– 2.79)	0.679
High frequency ventilation, n (%)	18 (20.5%)	57 (44.5%)	3.12 (1.67– 5.82)	<0.001	10 (18.5%)	15 (27.3%)	1.56 (0.66– 4.08)	0.277
Invasive ventilation, days	$6.13 \pm$ 20.0	$17.94 \pm$ 23.2	-11.80 (-18.29 to -5.30)	<0.001	$8.9 \pm$ 24.8	$19.8 \pm$ 25.3	-10.94 (-21.47 to -0.42)	0.042
High FiO_2 (first week)	$37.48 \pm$ 21.55	$45.54 \pm$ 22.04	-8.05 (-13.91 to -2.00)	0.007	$37.86 \pm$ 20.17	$35.92 \pm$ 18.45	1.93 (-5.49 – 9.28)	0.602
High lactate (first week)	$3.60 \pm$ 3.66	$4.87 \pm$ 5.0	-1.27 (-2.51 to -0.02)	0.045	$3.38 \pm$ 3.2	$3.12 \pm$ 2.08	0.25 (-0.77 – 1.29)	0.623
High Base Excess (first week), n	$7.89 \pm$ 4.51	$10.41 \pm$ 12.03	-2.52 (-5.18 - 0.13)	0.063	$7.91 \pm$ 4.7	$7.79 \pm$ 3.14	0.11 (-1.41 – 1.63)	0.882
Postnatal steroids, n (%)	4 (5.1%)	22 (20.2%)	4.74 (1.56 – 14.37)	0.003	3 (5.5%)	10 (18.2%)	4.64 (1.56 – 14.37)	0.040
Discharge PMA, weeks	$39.86 \pm$ 7.33	$41.84 \pm$ 6.96	-1.98 (-4.15 to - 0.18)	0.073	$38.5 \pm$ 5.13	$40.9 \pm$ 7.81	-2.44 (-5.27 - 0.38)	0.090
Hyperglycemia beyond first	3 (3.4%)	25 (19.5%)	6.79 (1.98 – 23.29)	<0.001	3 (6.1%)	15 (27.3%)	5.75 (1.55 – 21.31)	0.004

week of life, n (%)								
Insulin used, n (%)	2 (2.1%)	13 (9.9%)	5.07 (1.11–23.02)	0.021	–	–	–	–

This table summarises the major clinical interventions and metabolic parameters during the neonatal intensive care unit stay for infants with and without early hyperglycemia. It includes surfactant use, invasive ventilation (presence and duration), high-frequency ventilation, exposure to high FiO₂, high lactate levels, and high base-excess within the first week, administration of postnatal steroids, post-menstrual age at discharge, persistence of hyperglycemia beyond the first week, and insulin therapy. For each variable, counts or means are presented for the two groups before matching (n=94 vs. n=131) and after matching (n=54 vs. n=55), along with the odds ratio or mean difference (95 % CI) and P-value. Missing data: Surfactant administration (N=8), ventilation (N=8), HFO (N=9), VENT days (N= 36), postnatal steroids (N=37), D/C PMA (N=51), hyperglycemia beyond 1 week (N=10).

Table 3: Major Morbidities and Complications

Before matching, infants in the NH group had markedly higher respiratory and ophthalmologic morbidity. VAP was significantly more frequent in the hyperglycemia group (28.2% vs 6.4%; OR 5.77, 95% CI 2.32–14.34; p < 0.001). Any ROP was also more common (66.9% vs 46.5%; p = 0.003), as was severe ROP (26.3% vs 10.5%; OR 3.04, 95% CI 1.36–6.80; p = 0.006). Similarly, the incidence of BPD was higher among infants with hyperglycemia (58.9% vs 28.2%; OR 3.18, 95% CI 1.68–6.67; p < 0.001), as was moderate–severe BPD (46.8% vs 22.2%; OR 3.03, 95% CI 1.59–5.76; p < 0.001). Other complications, including early-onset and late-onset sepsis, NEC, IVH (including severe IVH), pneumothorax, PVL, PDA, and PDA device closure, did not differ significantly between groups.

After matching, most between-group differences were attenuated, but two key associations persisted. VAP remained significantly more frequent in the hyperglycemia group (23.6% vs 3.7%; OR 8.04, 95% CI 1.72–37.66; p = 0.003), and severe ROP continued to occur more often (21.6% vs 6.4%; OR 4.03, 95% CI 1.04–15.50; p = 0.032). Rates of any ROP, BPD, moderate–severe BPD, sepsis, NEC, IVH, pneumothorax, PVL, PDA, and PDA device closure were no longer statistically different after matching, although point estimates for BPD and moderate–severe BPD continued to trend higher in the hyperglycemia group.

Table 3. Major Morbidities and Complications.

Variables	Before Matching				After Matching			
	No HG (n = 94)	HG (n = 131)	Odds Ratio (95 % CI) / Mean Difference (95 % CI)	P-value	No HG (n = 54)	HG (n = 55)	Odds Ratio (95 % CI) / Mean Difference (95 % CI)	P-value
Early onset sepsis, n (%)	2 (2.1 %)	1 (0.8 %)	0.35 (0.03 – 3.96)	0.573	1 (1.9 %)	0 (0.0 %)	0.49 (0.40 – 0.59)	0.495
Late onset sepsis, n (%)	13 (13.8 %)	23 (17.6 %)	1.33 (0.63 – 2.77)	0.452	10 (18.5 %)	16 (29.1 %)	1.80 (0.73 – 4.44)	0.195
First sepsis episode DOL, days	16.33 ± 12.05	20.63 ± 16.97	–4.29 (–14.49 – 5.91)	0.4	16.64 ± 12.59	20.25 ± 14.64	–3.61 (–14.7 – 7.56)	0.512
UTI, n (%)	2 (2.1 %)	5 (3.8 %)	1.83 (0.34 – 9.61)	0.702	0 (0 %)	1 (1.8 %)	0.50 (0.41 – 0.60)	0.100

IVH, n (%)	19 (20.2 %)	39 (30 %)	1.69 (0.90 – 3.16)	0.099	12 (22.2%)	16 (29.1 %)	1.43 (0.60 – 3.41)	0.412
Severe IVH, n (%)	2 (2.1 %)	9 (6.9 %)	3.42 (0.72 – 16.21)	0.125	2 (3.7 %)	3 (5.5 %)	1.50 (0.24 – 9.35)	0.100
NEC, n (%)	4 (4.5 %)	11 (8.6 %)	1.97 (0.60 – 6.41)	0.250	3 (5.6 %)	6 (10.9 %)	2.08 (0.49 – 8.78)	0.489
VAP, n (%)	6 (6.4 %)	37 (28.2%)	5.77 (2.32 – 14.34)	< 0.001	2 (3.7 %)	13 (23.6 %)	8.04 (1.72 – 37.66)	0.003
Pneumothorax, n (%)	2 (2.2 %)	8 (6.3 %)	2.90 (0.60 – 13.99)	0.204	1 (1.9 %)	1 (1.8 %)	0.98 (0.06 – 16.10)	0.100
PVL, n (%)	1 (1.1 %)	6 (4.7 %)	4.46 (0.52 – 37.72)	0.243	1 (1.9 %)	2 (3.7 %)	2.03 (0.17 – 23.17)	0.100
PDA, n (%)	44 (52.4 %)	76 (62.8 %)	1.53 (0.87 – 2.70)	0.136	25 (52.1 %)	25 (50.0 %)	0.92 (0.41 – 2.03)	0.837
ROP, n (%)	40 (46.5 %)	79 (66.9 %)	2.32 (1.31 – 4.12)	0.003	21 (44.7 %)	28 (54.9 %)	1.50 (0.67 – 3.34)	0.312
Severe ROP, n (%)	9 (10.5 %)	31 (26.3 %)	3.04 (1.36 – 6.80)	0.005	3 (6.4 %)	11 (21.6 %)	4.03 (1.04 – 15.50)	0.032
BPD, n (%)	23 (28.2 %)	66 (58.9 %)	3.17 (1.96 – 6.67)	< 0.001	11 (25.0 %)	21 (43.8 %)	2.33 (0.95 – 5.67)	0.059
Moderate–severe BPD, n (%)	18 (22.2 %)	52 (46.4 %)	3.03 (1.59 – 5.76)	< 0.001	7 (15.9 %)	16 (33.3 %)	2.64 (0.96 – 7.23)	0.054
PDA device closure, n (%)	5 (6.9 %)	6 (5.8 %)	0.83 (0.24 – 2.82)	0.762	2 (4.8 %)	2 (4.3 %)	0.90 (0.12 – 6.75)	0.100

This table reports the incidence of major complications among the study infants with and without hyperglycemia. Outcomes include early and late-onset sepsis, day of first sepsis episode, urinary tract infection, intraventricular hemorrhage (IVH) and severe IVH, necrotising enterocolitis (NEC), ventilator-associated pneumonia (VAP), pneumothorax, periventricular leukomalacia (PVL), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP) and severe ROP, bronchopulmonary dysplasia (BPD) and moderate-to-severe BPD, and PDA device closure. The table lists counts and percentages for each group before and after matching, together with the odds ratio or mean difference (95 % CI) and P-value. Missing data: first sepsis DOL (N=107), PDA (N=20), PDA device closure (N=50), BPD (N=32).

Table 4: Hospital Stay, Clinical Outcomes, and Morbidities

Before matching, infants with early hyperglycemia had a longer NICU admission (mean difference 17.76 days, 95% CI 2.38–33.14; $p = 0.024$). They were less likely to be discharged before 36 weeks PMA (13.9% vs 36.7%; $p < 0.001$) and more likely to be discharged after 36 weeks (85.5% vs 64.2%; $p < 0.001$). Hospital stay was significantly longer overall (mean difference 24.85 days, $p = 0.001$). Death occurred at later postnatal ages in the hyperglycemia group (mean difference 24.98 days, 95% CI 1.44–48.51; $p = 0.038$), although the mortality rate itself did not differ significantly. NDD assessments were completed in 79/94 (84.0%) of infants in the NH group and 108/131 (82.4%) in the HG group. Infants without follow-up data were excluded. Hyperglycemia is associated with almost double the odds of any NDD risk (49.1% vs 32.9%; OR 1.96, 95% CI 1.07–3.58; $p = 0.027$). High-risk scores are more frequent, with odds 3.16 times higher (17.6% vs 6.3%; OR 3.16, 95% CI 1.12–8.87; $p = 0.023$). Motor-domain abnormalities (fine and gross motor) were also more frequent in the

hyperglycemia group (25.9% vs 13.9%; OR 2.16, 95% CI 1.00–4.66; $p = 0.036$). Other NDD domains (cognitive, receptive, and expressive) showed no significant differences before matching.

After matching, most differences were attenuated. NICU stay, and discharge timing were no longer significantly different (both $p > 0.05$), although the age at death remained later in infants with NH (mean difference 25.93 days, 95% CI 5.81–46.06; $p = 0.015$). Persistent differences in mortality rate, total hospital stay, and NDD outcomes did not meet statistical significance after matching, including any NDD risk, high-risk scores, or domain-specific delays. Overall, after balancing for baseline characteristics, only the age at death remained significantly different between groups.

Table 4. Hospital Stay, Clinical Outcomes, and Morbidities.

Variables	Before Matching				After Matching			
	No HG (n=94)	HG (n=131)	Odds ratio / Mean difference (95% CI)	P-value	No HG (n=54)	HG (n=55)	Odds ratio / Mean difference (95% CI)	P-value
NICU stay, days	97.73 ± 51.41	115.50 ± 49.8	-17.76 (-33.14 to -2.38)	0.024	88.21 ± 36.12	107.26 ± 53.11	-19.04 (-38.4 - 0.38)	0.055
Discharge before 36 weeks PMA, n (%)	29 (36.7%)	15 (13.9%)	0.28 (0.13 - 0.56)	<0.001	14 (32.6%)	9 (18.8%)	0.47 (0.18 - 1.25)	0.130
Discharge after 36 weeks, n (%)	52 (64.2%)	94 (85.5%)	3.27 (1.63 - 6.58)	<0.001	30 (68.2%)	38 (79.2%)	1.77 (0.69 - 4.55)	0.231
Discharge PMA, weeks	39.86 ± 7.33	41.84 ± 6.96	-1.98 (-4.15 to -0.18)	0.073	38.5 ± 5.13	40.9 ± 7.81	-2.44 (-5.27 - 0.38)	0.090
Death, n (%)	13 (13.8%)	21 (16.0%)	1.19 (0.56 - 2.51)	0.649	10 (18.5%)	7 (12.7%)	0.64 (0.22 - 1.83)	0.405
Death DOL, days	12.14 ± 12.13	37.12 ± 40.3	-24.98 (-48.51 to -1.44)	0.038	13.49 ± 13.45	39.42 ± 25.42	-25.93 (-46.06 to -5.81)	0.015
Hospital stays, days	90.47 ± 30.64	115.32 ± 59.99	-24.85 (-39.45 to -10.24)	<0.001	88.21 ± 36.12	107.26 ± 53.11	-19.04 (-38.48 - 0.38)	0.055
Any NDD risk, n (%)	26 (32.9%)	53 (49.1%)	1.96 (1.07 - 3.58)	0.027	15 (34.9%)	21 (43.8%)	1.45 (0.62 - 3.38)	0.388
High NDD, n (%)	5 (6.3%)	19 (17.6%)	3.16 (1.12 - 8.87)	0.023	2 (4.7%)	5 (10.4%)	2.38 (0.43 - 12.98)	0.265
Cognitive, n (%)	6 (7.6%)	9 (8.3%)	1.11 (0.37 - 3.24)	0.854	3 (7.0%)	1 (2.1%)	0.28 (0.02 - 2.83)	0.268
Neurologic (fine and gross motor), n (%)	11 (13.9%)	28 (25.9%)	2.16 (1.00 - 4.66)	0.046	6 (14.0%)	11 (22.9%)	1.83 (0.61 - 5.47)	0.273
Receptive, n (%)	15 (19.0%)	16 (14.8%)	0.74 (0.34 - 1.60)	0.449	9 (20.9%)	8 (16.7%)	0.75 (0.26 - 2.17)	0.602
Expressive, n (%)	20 (25.3%)	37 (34.3%)	1.54 (0.80 - 2.92)	0.189	15 (31.3%)	15 (13.3%)	—*	—*

This table compares overall clinical outcomes and hospital course variables between infants with and without hyperglycemia. Variables include length of NICU stay, discharge before or after 36 weeks' post-menstrual age, discharge post-menstrual age in weeks, mortality and age at death, total hospital stay, and NDD outcomes at follow-up. NDD outcomes include any risk of developmental delay, high risk of developmental delay, and domain-specific outcomes (cognitive, fine and gross motor, receptive language, and expressive language). Data are presented as means or counts for each group before and after matching, along with the corresponding mean differences or odds ratios (95 % CI) and P values. * Missing data: Stay days 51, hospital stays 38, discharge before 36 weeks: 38, discharge after 36 weeks: 34, neurodevelopmental assessment: 38 (died).

4. Discussion

In our study of EP infants, we found that early NH affected more than half of the population and was associated with a specific pattern of adverse outcomes. Before adjusting for baseline differences, these infants tended to be smaller, less mature, and more clinically unstable. They needed more respiratory support and higher oxygen levels, and they showed metabolic stress with elevated lactate levels. Even after carefully matching gestational age, birth weight, and perinatal factors, hyperglycemia itself remained an independent risk factor for several serious outcomes: VAP, severe ROP, prolonged invasive ventilation, persistent dysglycemia beyond the first week, and a possible increase in moderate-severe BPD. This suggests that NH is not simply a marker of illness severity; it may actively contribute to respiratory and retinal disease.

Our incidence of early NH (58%) aligns with reports indicating that 20–80% of very preterm or ELBW infants develop NH during the first week of life, especially within the context of aggressive

parenteral nutrition and critical illness. [4]. Recent cohort studies and systematic reviews have shown that NH is related to increased major morbidities and mortality, including IVH, ROP, NEC, and prolonged ventilation [5,6]. Our results demonstrate that hyperglycemic infants required much longer invasive ventilation and experienced greater early respiratory instability, even after matching. The ongoing need for prolonged ventilation and increased postnatal steroid exposure suggests that early dysglycemia may contribute to a more severe course of BPD.

The strong and consistent correlation between early NH and VAP in our cohort is noteworthy. After matching, infants with early NH had about eight times higher odds of developing VAP. This builds on previous research linking NH to late-onset sepsis and culture-confirmed infections [7], which makes biological sense, as hyperglycemia impairs neutrophil chemotaxis, phagocytosis, cytokine signaling, and mucosal immunity. Both adult and pediatric ICUs regularly recognize hyperglycemia as a risk factor for nosocomial infections and VAP; our results indicate a similar trend in EP infants, who are especially susceptible due to prolonged ventilation and invasive monitoring.

Our study further supports the growing evidence that early NH, is linked to ROP, especially in severe cases. Many observational cohorts and meta-analyses have shown an association between NH and increased risk of any ROP and ROP requiring treatment [9]. Kermorvant-Duchémin and colleagues showed that cumulative exposure above glycemic thresholds of 7–13 mmol/L (126–234 mg/dL) strongly predicts severe ROP [15]. Movsas et al. recently confirmed that early NH raises the risk of severe ROP and suggested glucose-based thresholds for risk stratification [16]. Our matched analysis—demonstrating a fourfold higher odd of severe ROP among hyperglycemic infants—aligns with these findings. The association between NH, higher early FiO₂ requirements, and elevated lactate levels suggests that metabolic stress and fluctuating oxygen delivery may synergize to accelerate abnormal retinal blood vessel growth.

BPD is another significant outcome where our findings align with current evidence. Before matching, early NH was linked to higher rates of BPD and moderate–severe BPD. After matching using the Jensen 2019 support-based definition, the effect size diminished but remained clinically relevant, showing a trend toward a two- to threefold increased risk. The Jensen system classifies BPD severity based on respiratory support at 36 weeks PMA and strongly correlates with long-term respiratory and NDD outcomes [21]. Our results indicate that although much of the connection between NH and BPD is due to overall illness severity, early dysglycemia may still biologically contribute through inflammatory and oxidative pathways. This perspective aligns with recent cohorts and meta-analyses [6,10,24,25] that emphasize the difficulty of entirely distinguishing glycemic effects from underlying immaturity.

Unlike earlier studies that indicated higher mortality rates in hyperglycemic infants [6,24], our matched cohort showed similar mortality across groups. However, hyperglycemic infants experienced later deaths and generally longer NICU stays. This pattern suggests that NH may be more closely associated with chronic respiratory and eye health issues than with immediate mortality, possibly because improvements in supportive care, nutrition, and infection prevention have reduced mortality. Severe ROP and BPD are important factors connecting early physiological instability with later death and NDD challenges [16,17], consistent with the profiles seen in our hyperglycemic infants.

It is still unclear how early NH affects long-term NDD. Before matching, infants with NH were more likely to experience motor and cognitive problems, consistent with research linking poorer white matter development [4–9]. Point estimates continued to favor the normoglycemic group, but these differences were no longer statistically significant after matching. These differences might be due to a small sample size, a short follow-up period, and reliance on early screening tools. Continuous glucose monitoring studies indicate that both hyperglycemia and glycemic variability can contribute to neurological injury, including severe IVH and PVL [2,9,10]. Our results support the idea that early NH is part of a broader dysglycemic pattern, indirectly linked to NDI through severe chronic conditions.

Finally, our findings highlight the importance of how we define and manage NH. In the first week, we used a threshold of >8.3 mmol/L (>150 mg/dL), and infants with NH were more likely to experience persistent hyperglycemia beyond that period. This was supported by Kermorvant-Duchémin and Movsas work [15,16], which shows that cumulative exposure to hyperglycemia above certain thresholds predicts severe ROP more accurately than isolated peaks. Other studies using continuous glucose monitoring suggest that glycemic variability may be equally important [2,9], suggesting that both burden and chronicity matter and that binary thresholds could underestimate total risk.

From a therapeutic perspective, our findings reinforce the need for careful prevention and monitoring of hyperglycemia rather than aggressive insulin-based tight glycemic control. Trials of early insulin therapy show reduced hyperglycemia and increased IGF-1 but at the cost of more hypoglycemia and no proven benefit for survival, ROP, or NDD [3]. Current expert recommendations support optimizing glucose infusion rates, carefully titrating parenteral nutrition, and, when available, using continuous glucose monitoring to reduce periods of severe dysglycemia. [2,17,26,27]. Our findings support this balanced approach: early NH identifies a high-risk phenotype with greater respiratory and retinal morbidity, but not an independent mortality signal that would justify aggressive insulin therapy.

4. Strengths and Limitations

The major strengths of this study are a large, current cohort of EP infants, standardized ROP screening, classification of BPD according to the Jensen 2019 framework, and use of PSM to reduce confounding. Limitations of this study include its single-center, retrospective design, possible residual confounding, reliance on intermittent glucose samples (which cannot detect variability), and early NDD screening rather than long-term standardized evaluations.

5. Conclusions

Early NH in EP infants was associated with greater respiratory morbidity, higher rates of VAP and severe ROP, prolonged invasive ventilation, and longer hospital stays. After adjusting for baseline differences, NH remained independently linked to VAP, severe ROP, and delayed mortality, indicating that early dysglycemia reflects not only underlying illness severity. Still, it may also contribute to specific adverse outcomes. NDD differences observed before matching were no longer significant after adjustment. These findings highlight the importance of early glycemic monitoring and targeted metabolic management in this high-risk population.

Author Contributions: Conceptualization, A.G.; methodology, A.G.; software, A.G.; validation, S.M.G.A.A., N.N. and A.G.; formal analysis, A.G.; investigation, S.M.G.A.A.; resources, A.A., M.T.H., O.N.H. and A.A.A.; data curation, S.M.G.A.A.; writing—original draft preparation, S.M.G.A.A.; writing—review and editing, N.N. and A.G.; visualization, S.M.G.A.A.; supervision, N.N.; project administration, S.M.G.A.A.; funding acquisition, A.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was approved by the Medical Research Center of Hamad Medical Corporation (MRC-01-21-975). Ethical approval included a waiver of informed consent due to the retrospective design and use of de-identified data.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data underlying this study are stored at the Hamad Medical Corporation and contain confidential patient information. Due to institutional and ethical restrictions, the dataset cannot be made publicly available. De-identified data may be obtained from the corresponding author upon reasonable request, following approval from the Institutional Review Board.

Acknowledgments: The authors have reviewed and edited the output and accept full responsibility for the content of this publication. We confirm that no generative AI tools were used in the writing, analysis, or preparation of this manuscript. The authors thank the NICU staff and research coordinators at the Women's Wellness and Research Center for their support in data collection and patient care.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

EP – Extremely Preterm

NH – Neonatal Hyperglycemia

NICU – Neonatal Intensive Care Unit

NDI – Neurodevelopmental Impairment

NDD – Neurodevelopmental

HG – Hyperglycemia Group

PSM – Propensity Score Matching

OR – Odds Ratio

CI – Confidence Interval

SD – Standard Deviation

SMD – Standardized Mean Difference

DR – Delivery Room

PMA – Postmenstrual Age

DOL – Day of Life

Bayley-III – Bayley Scales of Infant and Toddler Development, Third Edition

Bayley-4 – Bayley Scales of Infant and Toddler Development, Fourth Edition

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