scientific reports

Check for updates

OPEN

# The significance of glycemic variability in conjunction with lactate metabolism levels in the clinical assessment of neonatal hypoxic-ischemic encephalopathy

Lili Zhang[1,3], Chuanhua Wang[1,3], Qi Jia[1,3], Hui Li[2], Fudong Wang[1] & Lijun Jiang[1]✉

**The disruption of cerebral cellular energy metabolism represents the initial phase in the pathogenesis of neonatal hypoxic-ischemic encephalopathy (HIE). This study aimed to investigate the significance of glycemic variability (GV) and lactate (LAC) metabolic levels for early assessment of HIE. A retrospective study was conducted on asphyxiated neonates admitted to our hospital from January 2018 to January 2024. Neonates ultimately diagnosed with HIE were categorized into the HIE group, while those excluded from the HIE diagnosis were allocated to the control group. GV was assessed using the difference between maximum and minimum (max-min), standard deviation (SD), and coefficient of variation (CV). Lactate clearance rate (LCR) was used as an indicator of lactate metabolism. We found that GLU CV and LCR were independent risk factors for brain injury following asphyxia. The combination of GLU CV and LCR demonstrated a sensitivity of 84.2% and specificity of 78.6% in predicting HIE, and achieved a sensitivity of 90.0% and specificity of 61.1% in predicting moderate-severe HIE. Early monitoring of GV and LAC levels can serve as valuable indicators for predicting neonatal HIE and assessing disease severity.**

**Keywords** Newborn, Hypoxic-ischemic encephalopathy, Asphyxia, Glycemic variability, Lactic acid, Lactate clearance rate

Neonatal hypoxic-ischemic encephalopathy (HIE) is a perinatal brain injury resulting from hypoxia and ischemia affecting fetal or neonatal brain tissue due to various perinatal factors. This condition represents a prevalent form of neonatal central nervous system injury, with severe cases leading to varying degrees of long-term sequelae and, in extreme instances, neonatal mortality[1–4].

The pathogenesis of HIE encompasses a multitude of intricate pathophysiological processes, with the disruption of cerebral cellular energy metabolism being the predominant factor contributing to post-hypoxic-ischemic brain injury[5,6]. During hypoxia-ischemia, aerobic metabolism is compromised, leading to an increase in anaerobic metabolism, elevated lactate production, and subsequent tissue acidosis[7]. Stress factors such as hypoxia and acidosis can also induce abnormal fluctuations in glucose levels[8]characterized by early stress-induced hyperglycemia followed by significant glycogen depletion at a later stage. Studies have demonstrated that stress-induced hyperglycemia is a significant risk factor for multi-organ damage[9,10]and neonatal hypoglycemia in the context of hypoxia can result in more severe brain injury[11]. Consequently, monitoring only hypoglycemia or hyperglycemia does not adequately capture the impact of glucose fluctuations on brain injury following asphyxia. In recent years, with the progressive refinement of glucose management protocols, it has become increasingly evident that controlling the magnitude of GV is more critical than managing glucose levels at isolated time points[12]. Elevated levels of GV and LAC have been found to be associated with brain injury in adults, as well as increased mortality in critically ill patients[13–16]. Consequently, it is reasonable to hypothesize that monitoring GV and LAC levels may offer a valuable reference for the early prediction and severity assessment of neonatal HIE. The aim of this study was to investigate the significance of GV and LAC metabolic levels in the early evaluation of HIE, thereby providing a reference for clinical management.

[1]Department of Neonatology, Affiliated Hospital of Yangzhou University, Yangzhou 225000, Jiangsu, China. [2]Department of Interventional Medicine, Yangzhou Hongquan Hospital, Yangzhou 225200, Jiangsu, China. [3]Lili Zhang, Chuanhua Wang and Qi Jia contributed equally to this work. ✉email: lijun-jiang80@163.com

## Materials and methods

### Patient selection

A retrospective study was conducted on 136 full-term neonates diagnosed with asphyxia who were admitted to the Neonatal Intensive Care Unit (NICU) of the Affiliated Hospital of Yangzhou University between January 2018 and January 2024. To establish the diagnosis and severity of encephalopathy, a neurological examination was performed within 6 h of birth according to the National Institute of Child Health and Human Development (NICHD) classification for modified Sarnat staging[17]. Simultaneously, the data from brain computed tomography (CT) or magnetic resonance imaging (MRI) as well as amplitude-integrated electroencephalogram (aEEG) were retrospectively analyzed and utilized for reference. The brain CT and MRI imaging results, as well as the aEEG findings, were evaluated by radiologists and electroencephalographers who were blinded to the study details. In accordance with the established inclusion and exclusion criteria, a total of 38 asphyxiated neonates diagnosed with HIE were categorized into the HIE group, while 56 neonates not diagnosed with HIE were allocated to the control group (Fig. 1). The HIE group was further subdivided into mild, moderate, and severe subgroups based on clinical grading. Neonates with moderate and severe HIE received therapeutic hypothermia (TH) initiated within the first 6 h of life and maintained for a duration of 72 h. This study adhered to medical ethical standards and received approval from the Institutional Review Board (IRB) of the Affiliated Hospital of Yangzhou University (No. 2022-YKL3-06-006). All methods were performed in compliance with the relevant guidelines and regulations established by the hospital's IRB. Due to the retrospective nature of the study, the IRB of the Affiliated Hospital of Yangzhou University waived the need of obtaining informed consent. The inclusion criteria were as follows: gestational age of 37 to 42 weeks, birth weight ≥ 1800 g, admission to the NICU within 0.5 h postpartum, no prior exposure to medications that could influence blood glucose and LAC levels such as

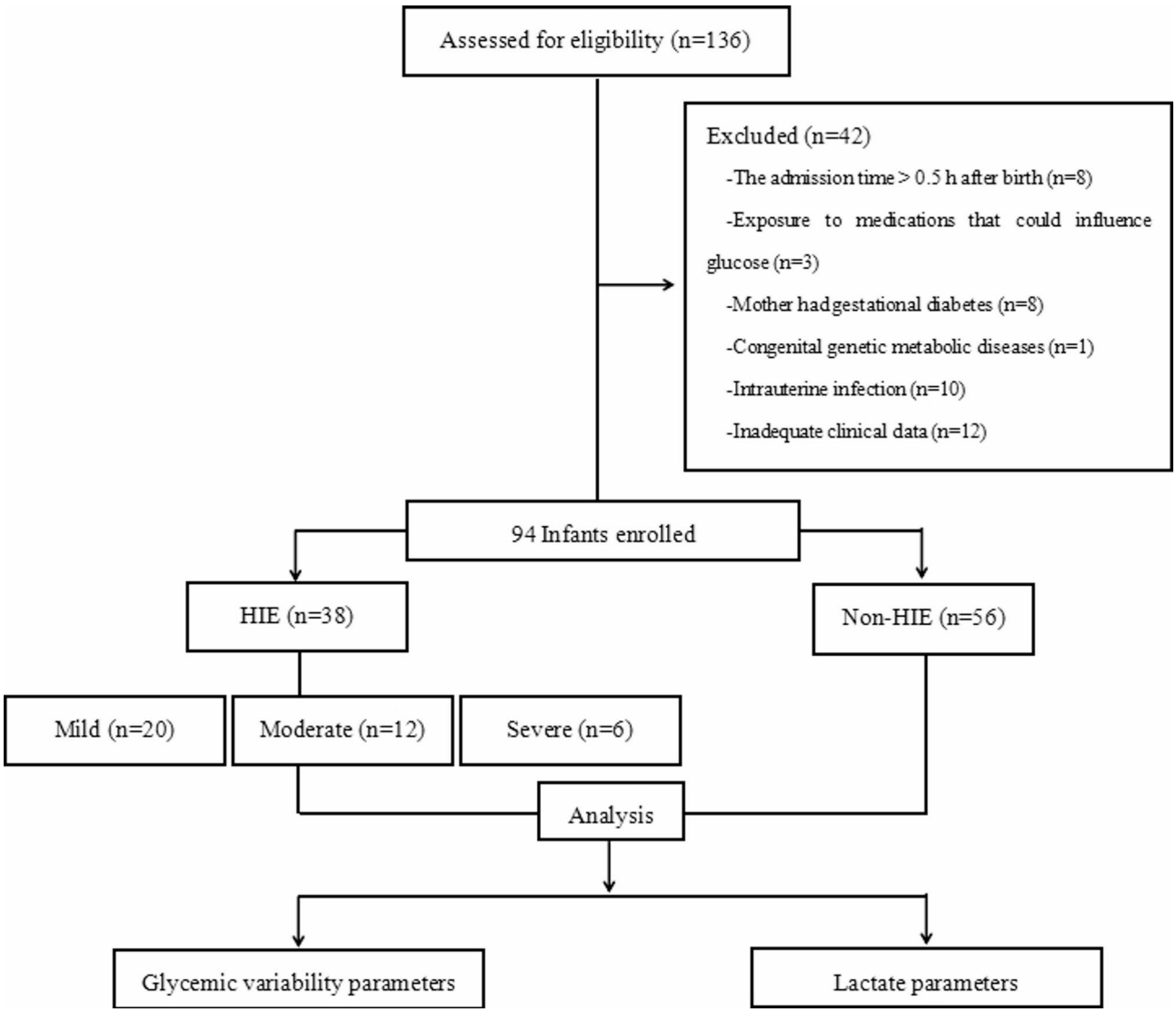


**Fig. 1**. Study flow chart. HIE, hypoxic-ischemic encephalopathy.

glucocorticoids, catecholamines, and maternal absence of gestational diabetes. Exclusion criteria encompassed conditions such as congenital genetic metabolic diseases, intrauterine infection, and congenital malformations.

### General data

Demographic and clinical information were collected for all enrolled infants, including gender, gestational age, birth weight, mode of delivery, and perinatal medical history.

### Arterial lactate data collection

Arterial blood gas analysis was conducted to measure the arterial LAC levels at admission ($LAC_{TP0}$) and 6 h thereafter ($LAC_{TP6}$). The LCR was subsequently calculated using the formula: LCR = [($LAC_{TP0}$ - $LAC_{TP6}$) / $LAC_{TP0}$] × 100%[18].

### Glucose monitoring

All included infants underwent glucose monitoring at 3-hour intervals throughout the first day of life. If the glucose levels fell below 2.6 mmol/L or exceeded 8.3 mmol/L, the monitoring frequency was increased to every 30 min to 1 h, and appropriate interventions were initiated. Specifically, when the blood glucose level was below 2.6 mmol/L, an intravenous bolus of 10% glucose (2 ml/kg) was administered, followed by an increase in the glucose infusion rate. When the blood glucose level exceeded 8.3 mmol/L, the glucose infusion rate was decreased. Notably, none of the infants developed hyperglycemia requiring insulin therapy. Data from glucose monitoring within the first 24 h post-admission were collected. The following metrics were calculated: average glucose (GLU ave), the difference between the maximum and minimum of glucose values (GLU max-min), standard deviation of glucose (GLU SD), and coefficient of variation of glucose (GLU CV). GLU max-min, GLU SD, and GLU CV were utilized as indicators of GV[19].

### Statistical analysis

All statistical analyses were performed using SPSS software (version 26.0, IBM Corporation, Armonk, NY, USA). For continuous variables, the Student's t-test was used for parametric testing and the Mann-Whitney U-test was used for nonparametric testing. Analysis of variance (ANOVA) was employed to conduct comparisons among multiple groups. For categorical variables, the chi-square test was used. Univariate analyses were performed to identify possible risk factors that might be associated with HIE individually. Multicollinearity was tested among all factors identified as possibly associated with HIE ($P<0.05$). In the multivariate analysis, the variables were further entered into the logistic regression model to determine independent predictors of HIE. The performance of factors identified as significantly related to HIE development from the regression analysis was assessed by receiver operating characteristic (ROC) curve analysis and estimation of the corresponding AUC.

## Results

### Demographic and clinical data of the control and HIE groups

A total of 136 asphyxiated neonates were admitted during the research window, of whom 94 met the inclusion criteria and had comprehensive clinical data. Among these neonates, 38 infants diagnosed with HIE were assigned to the HIE group, while 56 infants who were not diagnosed with HIE were allocated to the control group (Fig. 1). There were no significant differences in the demographic and general clinical characteristics between the two groups (Table 1).

### Arterial lactate and the development of HIE

According to the inclusion criteria, all newborns were admitted to NICU within 0.5 h after birth. Consequently, the timing of $LAC_{TP0}$ corresponded to within 0.5 h post-birth, while $LAC_{TP6}$ corresponded to approximately 6 h post-birth. TH was initiated 4.6 ± 1.1 h post-birth, thereby minimizing its influence on $LAC_{TP6}$ measurements. There was no significant difference in the $LAC_{TP0}$ levels between the two groups ($P>0.05$). However, 6 h after admission, the $LAC_{TP6}$ levels were significantly higher, and the LCR levels were significantly lower in the HIE group compared to the control group ($P<0.05$) (Table 2).

| | HIE $n=38$ | | | | | | |
|---|---|---|---|---|---|---|---|
| | Total $n=38$ | Mild $n=20$ | Moderate $n=12$ | Severe $n=6$ | Control $n=56$ | $t/\chi^2$ | $P$-value[a] |
| Male sex, n(%) | 24 (63.2) | 12 (60) | 8 (66.7) | 4 (66.7) | 34 (60.7) | 0.057 | 0.811 |
| Birth weight (g) | 3453 g ± 452 | 3355 ± 425 | 3592 ± 538 | 3500 ± 316 | 3577 g ± 383 | 1.455 | 0.231 |
| Gestational age (weeks) | 38.68 ± 1.21 | 38.35 ± 1.14 | 39.17 ± 1.03 | 38.83 ± 1.60 | 39.11 ± 1.20 | 2.789 | 0.098 |
| Umbilical arterial cord pH | 6.97 ± 0.06 | 6.98 ± 0.08 | 6.92 ± 0.06 | 6.93 ± 0.05 | 7.01 ± 0.11 | 3.366 | 0.070 |
| 5-min Apgar (IQR) | 5 (4,5) | 5 (5,5) | 4 (4,5) | 4 (3,5) | 5 (4,6) | 3.744 | 0.053 |
| Vaginal delivery, n(%) | 20 (52.6) | 11 (55.0) | 5 (41.7) | 4 (66.7) | 34 (60.7) | 0.605 | 0.437 |
| Gestational hypertension, n(%) | 9 (23.7) | 4 (20.0) | 3 (25.0) | 2 (33.3) | 6 (10.7) | 2.840 | 0.092 |
| Parenteral nutrition, n(%) | 36(94.7) | 18(90.0) | 12(100.0) | 6(100.0) | 51(91.1) | 0.070 | 0.792 |

**Table 1**. Demographic and clinical data of the control and HIE groups. [a]Comparision between the control and HIE groups; HIE, hypoxic-ischemic encephalopathy.

| | HIE $n=38$ | Control $n=56$ | t | *P*-value |
|---|---|---|---|---|
| $LAC_{TP0}$ (mmol/L) | 7.4 ± 3.0 | 6.1 ± 3.3 | 1.978 | 0.060 |
| $LAC_{TP6}$ (mmol/L) | 4.5 ± 2.7 | 2.8 ± 1.7 | 3.365 | 0.001 |
| LCR (%) | 36.1 ± 15.7 | 48.4 ± 22.5 | 2.902 | 0.005 |

**Table 2**. Arterial lactate and the development of HIE. HIE, hypoxic-ischemic encephalopathy; LAC, lactate; TP0, time point of admission, the timing of $LAC_{TP0}$ corresponded to within 0.5 h post-birth; TP6, time point 6 h after admission, the timing of $LAC_{TP6}$ corresponded to approximately 6 h post-birth; LCR, lactate clearance rate.

| | HIE $n=38$ | Control $n=56$ | t | *P*-value |
|---|---|---|---|---|
| GLU ave (mmol/L) | 4.9 ± 1.7 | 4.9 ± 1.2 | 0.062 | 0.951 |
| GLU max-min | 5.3 ± 2.1 | 3.4 ± 1.1 | 5.200 | 0.001 |
| GLU SD | 1.6 ± 0.7 | 1.0 ± 0.3 | 5.432 | 0.001 |
| GLU CV (%) | 33.68 ± 10.0 | 21.2 ± 6.4 | 6.827 | 0.001 |

**Table 3**. Glycemic variability and the development of HIE. HIE, hypoxic-ischemic encephalopathy; GLU, Glucose; ave, average; max, maximum; min, minimum; SD, standard deviation; CV, coefficient of variation.

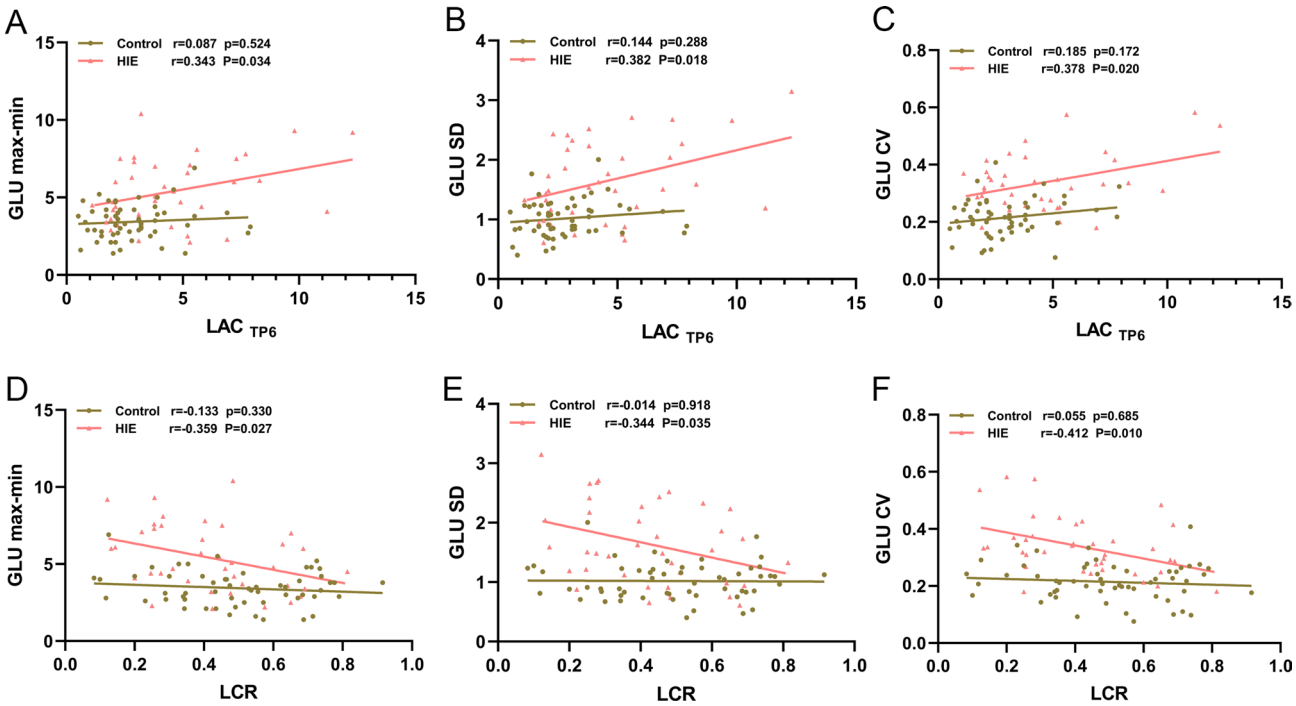


**Fig. 2**. Relationship between GV and LAC metabolic levels. GV, glycemic variability; LAC, lactate; TP6, time point 6 h after admission; LCR, lactate clearance rate; GLU, Glucose; max, maximum; min, minimum; SD, standard deviation; CV, coefficient of variation.

## Glycemic variability and the development of HIE

There was no significant difference in the GLU ave levels between the two groups ($P>0.05$). In comparison to the control group, the HIE group exhibited significantly higher values for GLU max-min, GLU SD, and GLU CV ($P<0.05$) (Table 3).

## Relationship between GV and LAC metabolic levels

In the HIE group, GLU max-min, GLU SD, and GLU CV exhibited significant positive correlations with $LAC_{TP6}$ and significant negative correlations with LCR ($p<0.05$). In contrast, GV showed no significant correlation with lactate in the control group ($p>0.05$) (Fig. 2).

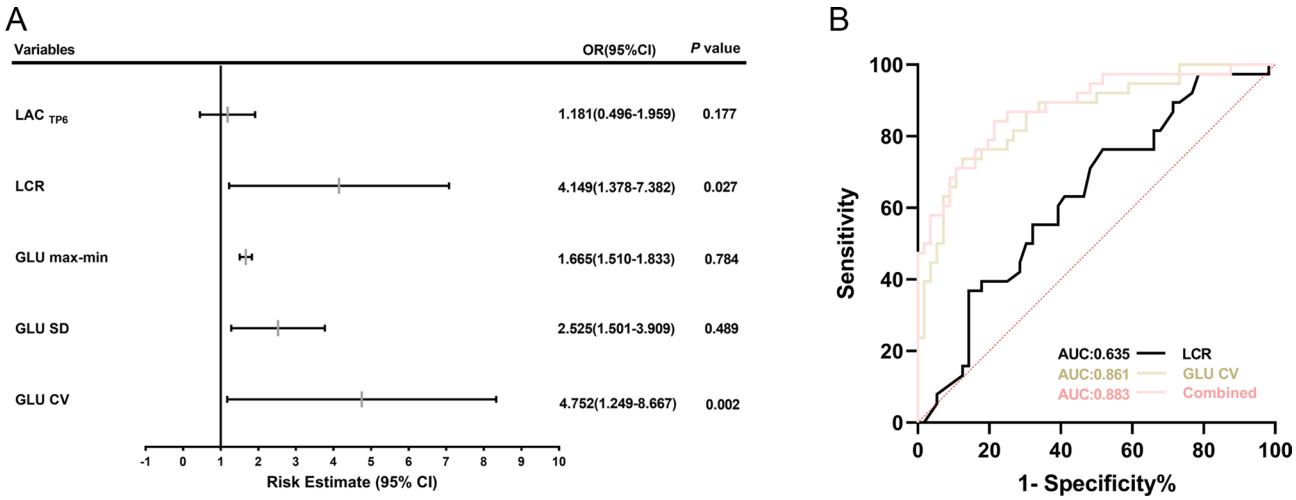


**Fig. 3**. Analysis of risk factors for HIE. HIE, hypoxic-ischemic encephalopathy; LAC, lactate; TP6, time point 6 h after admission; LCR, lactate clearance rate; GLU, Glucose; max, maximum; min, minimum; SD, standard deviation; CV, coefficient of variation; Combined = LCR + GLU CV.

| | Mild $n=20$ | Moderate $n=12$ | Severe $n=6$ | Moderate-severe $n=18$ | $F/\chi^2$ | *P*-value |
|---|---|---|---|---|---|---|
| Male sex, n(%) | 12 (60) | 8 (66.7) | 4 (66.7) | 12 (66.7) | 0.249 | 0.969 |
| Birth weight (g) | 3355 ± 425 | 3592 ± 538 | 3500 ± 316 | 3564 ± 373 | 1.618 | 0.196 |
| Gestational age (weeks) | 38.35 ± 1.14 | 39.17 ± 1.03 | 38.83 ± 1.60 | 39.06 ± 1.21 | 1.603 | 0.200 |
| Umbilical arterial cord pH | 6.98 ± 0.08 | 6.92 ± 0.06 | 6.93 ± 0.05 | 6.93 ± 0.06 | 2.735 | 0.053 |
| 5-min Apgar (IQR) | 5 (5,5) | 4 (4,5) | 4 (3,5) | 4 (4,5) | 11.520 | 0.003 |
| Vaginal delivery, n(%) | 11 (55.0) | 5 (41.7) | 4 (66.7) | 9 (50.0) | 1.130 | 0.770 |
| Gestational hypertension, n(%) | 4 (20.0) | 3 (25.0) | 2 (33.3) | 5 (27.8) | 0.563 | 0.905 |
| Parenteral nutrition, n(%) | 18(90.0) | 12(100.0) | 6(100.0) | 18(100.0) | 3.733 | 0.292 |
| MRI scan, n(%) | 15(75.0) | 12(100.0) | 6(100.0) | 18(100.0) | 9.882 | 0.020 |
| Age at MRI scan (days) | 4.9 ± 1.4 | 5.6 ± 1.4 | 7.0 ± 2.7 | 6.0 ± 2.0 | 2.770 | 0.051 |
| Abnormalities on MRI, n(%) | 13(86.7) | 12(100.0) | 6(100.0) | 18(100.0) | 4.996 | 0.172 |

**Table 4**. General clinical data of different clinical grading groups for HIE. HIE, hypoxic-ischemic encephalopathy; MRI, magnetic resonance imaging.

## Logistic regression analysis of risk factors for the development of HIE

Elevated GLU CV and reduced LCR were identified as independent risk factors associated with HIE, with an OR (95% CI) of 4.752 (1.249–8.667) and 4.149 (1.378–7.382), respectively (Fig. 3A).

## ROC curve analysis of risk factors for the development of HIE

The ROC curve analysis showed that in predicting HIE, the combined detection of GLU CV and LCR yielded the highest AUC of 0.883, and the Youden index was the largest when the cut-off value was 0.71, with a sensitivity and specificity of 84.2% and 78.6%, respectively (Fig. 3B).

## General clinical data of different clinical grading groups for HIE

The HIE group was further subdivided into mild ($n=20$), moderate ($n=12$), and severe ($n=6$) subgroups based on clinical grading. In order to identify moderate and severe HIE and initiate brain protection strategies as soon as possible, moderate and severe HIE were combined as a moderate-severe HIE group for analysis. There were no significant differences in the demographic and general data across all clinical grading groups ($P>0.05$), with the exception of the 5-minute Apgar score and the proportion of patients undergoing brain MRI scanning ($p<0.05$) (Table 4).

## Arterial lactate and clinical severity of HIE

There were no significant differences in the $LAC_{TP0}$ levels among the groups ($P>0.05$). However, at 6 h post-admission, the $LAC_{TP6}$ levels increased, while LCR decreased as the severity of HIE worsened ($P<0.05$) (Table 5).

| | Mild $n=20$ | Moderate $n=12$ | Severe $n=6$ | Moderate-severe $n=18$ | F | *P*-value |
|---|---|---|---|---|---|---|
| $LAC_{TP0}$ (mmol/L) | 6.9 ± 2.7 | 7.7 ± 2.6 | 8.7 ± 4.6 | 8.0 ± 3.3 | 0.701 | 0.556 |
| $LAC_{TP6}$ (mmol/L) | 3.6 ± 2.4 | 4.7 ± 1.7 | 7.1 ± 4.0 | 5.6 ± 2.8 | 3.496 | 0.022 |
| LCR (%) | 49.0 ± 16.7 | 36.6 ± 17.5 | 19.8 ± 7.2 | 31.0 ± 16.7 | 6.705 | 0.001 |

**Table 5**. Arterial lactate and clinical severity of HIE. HIE, hypoxic-ischemic encephalopathy; LAC, lactate; TP0, time point of admission, the timing of $LAC_{TP0}$ corresponded to within 0.5 h post-birth; TP6, time point 6 h after admission, the timing of $LAC_{TP6}$ corresponded to approximately 6 h post-birth; LCR, lactate clearance rate.

| | Mild $n=20$ | Moderate $n=12$ | Severe $n=6$ | Moderate-severe $n=18$ | F | *P*-value |
|---|---|---|---|---|---|---|
| GLU ave (mmol/L) | 5.6 ± 1.8 | 5.6 ± 1.6 | 4.5 ± 1.1 | 5.1 ± 1.5 | 1.177 | 0.328 |
| GLU max-min | 4.7 ± 2.0 | 6.4 ± 1.9 | 7.2 ± 0.7 | 6.1 ± 2.0 | 3.725 | 0.017 |
| GLU SD | 1.4 ± 0.6 | 2.0 ± 0.6 | 2.2 ± 0.3 | 1.9 ± 0.7 | 4.088 | 0.011 |
| GLU CV (%) | 31.1 ± 9.6 | 35.2 ± 4.0 | 50.7 ± 6.9 | 36.5 ± 9.8 | 8.096 | 0.001 |

**Table 6**. Glycemic variability and clinical severity of HIE. HIE, hypoxic-ischemic encephalopathy; GLU, Glucose; ave, average; max, maximum; min, minimum; SD, standard deviation; CV, coefficient of variation.

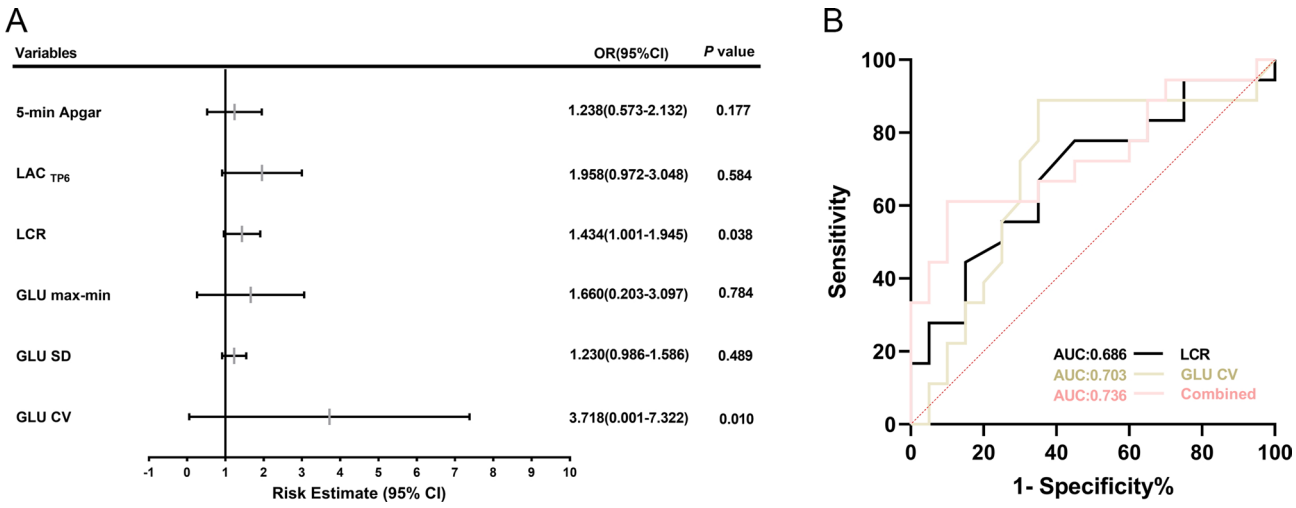


**Fig. 4**. Analysis of risk factors for moderate-severe HIE. HIE, hypoxic-ischemic encephalopathy; LAC, lactate; TP6, time point 6 h after admission; LCR, lactate clearance rate; GLU, Glucose; max, maximum; min, minimum; SD, standard deviation; CV, coefficient of variation; Combined = LCR + GLU CV.

## Glycemic variability and clinical severity of HIE

There was no significant difference in the GLU ave levels among the groups ($P > 0.05$). However, GLU max-min, GLU SD, and GLU CV showed an increasing trend with the severity of HIE, and these differences were statistically significant ($P < 0.05$) (Table 6).

## Logistic regression analysis of risk factors for the severity of HIE

In multiple regression analysis, GLU CV and LCR were identified as significant risk factors for moderate-severe HIE, with an OR (95% CI) of 3.718 (0.001–7.322) and 1.434 (1.001–1.945), respectively (Fig. 4A).

## ROC curve analysis of risk factors for the severity of HIE

The ROC curve analysis showed that in predicting moderate-severe HIE, the combined detection of GLU CV and LCR yielded the highest AUC of 0.736, and the Youden index was the largest when the cutoff value was 0.51, with a sensitivity and specificity of 90.0% and 61.1%, respectively (Fig. 4B).

## Discussion

In this study, we have demonstrated a significant association between elevated GV levels and reduced LCR levels and the development and severity of brain injury in neonates with HIE following asphyxia. Furthermore, our findings suggest that the combined detection of GV and LCR holds potential predictive value for the early identification and evaluation of HIE.

The impairment of energy metabolism in cerebral cells following hypoxic-ischemia represents the initial stage in the progression of HIE. The accumulation of LAC in tissues during anaerobic metabolism, along with fluctuations in glucose levels under stress conditions, is closely associated with brain injury. Consequently, maintaining homeostasis and stabilizing glucose levels are crucial for mitigating brain injury after hypoxic-ischemia[5–7]. Research has demonstrated that the metabolic interplay between glucose and LAC is disrupted following HIE, leading to disorders in LAC and glucose metabolism[20]. Both hyperglycemia and hypoglycemia are prevalent among asphyxiated neonates[21]. While hypoglycemia is a significant risk factor for hypoxic-ischemic brain injury[22]hyperglycemia and erratic glucose fluctuations also impair cerebral cell energy metabolism, contributing to neurological damage[23,24]. Therefore, this retrospective study aims to predict the risk of HIE and evaluate its severity by monitoring changes in LAC and glucose levels.

GV represents the magnitude of glucose fluctuation within a given time period, reflecting an unstable condition where glucose levels oscillate between maximum and minimum values. Research has demonstrated that maintaining long-term stable glucose levels can decrease the incidence of brain injury and mortality risk[25,26]. Currently, GV has gained widespread application in adult endocrinology research; however, its utility in predicting neonatal HIE remains unreported. In this study, we found that the levels of GLU max-min, GLU SD, and GLU CV in the HIE group were significantly higher than those in the non-HIE group ($P<0.05$). It is hypothesized that asphyxia-induced elevation in stress hormone secretion stimulated increased glycogenolysis and gluconeogenesis, leading to stress hyperglycemia. If hypoxia remains uncorrected, anaerobic metabolism intensifies, resulting in glycogen depletion and subsequent hypoglycemia. The significant fluctuations in glucose caused by this neuroendocrine response are closely associated with the development of hypoxic-ischemic brain injury[19]. Further comparative analysis of GV indexes among neonates in different clinical grading groups revealed that GLU max-min, GLU SD, and GLU CV progressively increased with the severity of HIE ($P<0.05$). This observation is consistent with previous studies[27,28]which have demonstrated that significant fluctuations in glucose levels, particularly extreme highs and lows, can lead to abnormal cerebral blood flow and neuronal stress damage, thereby supporting our findings.

Changes in LAC levels serve as sensitive indicators of the degree of tissue and cellular hypoxia. Research has confirmed that neonates experiencing hypoxic-ischemic events exhibit increased anaerobic metabolism, which can lead to hyperlactatemia and accumulation of LAC in the brain. This process is closely associated with the onset and progression of HIE[29]. We observed that at 6 h post-admission, the LAC levels in the HIE group were significantly higher compared to the control group, whereas the LCR levels were notably lower. The LAC and LCR levels at 6 h post-admission were correlated with disease severity ($P<0.05$), which was consistent with prior research[29].

In the metabolic processes of neonatal HIE, glucose and LAC exhibit interactive relationships that collectively influence cerebral cellular energy metabolism[20]. This study further investigated the correlation between GV and LAC indices. The results demonstrated that no significant correlation was observed between GV and the lactate indices in the control group ($p>0.05$). In contrast, within the HIE group, GLU max-min, GLU SD, and GLU CV were positively correlated with the LAC levels and negatively correlated with LCR ($p<0.05$). Although the association within the HIE group was not very pronounced, potentially due to the low proportion of neonates with severe HIE, we hypothesize that this association may become stronger as the proportion of neonates with increasing HIE severity rises. It is hypothesized that following hypoxic-ischemic injury, neurons are unable to secure a stable energy supply due to erratic fluctuations in glucose levels, and LAC can serve as an alternative energy source, which has been termed "alternative brain fuel"[30]. Consequently, there exists a compensatory relationship between LAC and glucose in the metabolic alterations observed in HIE.

Therefore, GV and LAC levels are intricately associated with brain injury following hypoxic-ischemic events. It is crucial to maintain the homeostasis of glucose and LAC metabolism in the clinical management of asphyxiated neonates to mitigate the risk of brain injury. Multivariate logistic regression analysis revealed that increased GLU CV (OR: 4.752, 95% CI: 1.249–8.667) and decreased LCR (OR: 4.149, 95% CI: 1.378–7.382) were independent risk factors for HIE following asphyxia. Additionally, elevated GLU CV (OR: 3.718, 95% CI: 0.001–7.322) and reduced LCR (OR: 1.434, 95% CI: 1.001–1.945) were associated with an increased risk of moderate-severe HIE. These findings suggest that higher GV and lower LCR levels may play partial roles in the development and progression of HIE. However, GLU CV for moderate-severe HIE exhibit imprecision (owing to wide 95% CI), potentially influenced by the proportion of HIE severity. Consequently, these findings should be interpreted with clinical prudence and in conjunction with neuroimaging and neuroelectrophysiological data. Further analysis of the ROC curve demonstrated that the combination of GLU CV and LCR achieved the highest diagnostic efficiency for both the occurrence and severity of HIE. Specifically, the AUC for predicting HIE was 0.883, with a sensitivity of 84.2% and a specificity of 78.6%. For moderate-severe HIE, the AUC was 0.736, with a sensitivity of 90.0% and a specificity of 61.1%.

Our study has some limitations. First it is a single center study, with a relatively small sample size that precluded more in-depth analyses. Second, given that blood glucose monitoring was performed intermittently rather than continuously, the available blood glucose data fail to comprehensively capture the trends of blood glucose fluctuations following asphyxia. Furthermore, owing to the scarcity of blood glucose data within the first six hours postpartum, it was not feasible to analyze the significance of GV during the TH therapeutic intervention window for clinical decision-making purposes. Finally, this study did not evaluate the long-term neurodevelopmental outcomes in infants with HIE.

## Conclusions

Our study indicates that elevated GV and reduced LCR are indicative of cellular energy depletion and impaired homeostasis in neonatal HIE. The concurrent evaluation of GV and LCR may serve as a valuable tool for the early prediction and assessment of HIE severity. Prompt monitoring of glucose fluctuations and LAC metabolism could offer novel insights for the prevention and management of brain injury following hypoxic-ischemic events.

## Data availability

The original rearch data presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Received: 12 March 2025; Accepted: 4 August 2025
Published online: 08 August 2025

## References

1. Gale, C., Statnikov, Y., Jawad, S., Uthaya, S. N. & Modi, N. Neonatal brain injuries in england: population-based incidence derived from routinely recorded clinical data held in the National neonatal research database. *Arch. Dis. Child. Fetal Neonatal Ed.* **103**(4), F301–F306. https://doi.org/10.1136/archdischild-2017-313707 (2018).
2. Bruns, N. et al. Short-term outcomes of asphyxiated neonates depending on requirement for transfer in the first 24 h of life. *Resuscitation* **202**(0), 110309. https://doi.org/10.1016/j.resuscitation.2024.110309 (2024).
3. Glass, H. C. et al. Predictors of death or severe impairment in neonates with Hypoxic-Ischemic encephalopathy. *JAMA Netw. Open.* **7**(12), e2449188. https://doi.org/10.1001/jamanetworkopen.2024.49188 (2024).
4. Bonifacio, S. L., Liu, J., Lee, H. C., Hintz, S. R. & Profit, J. Trends in HIE and use of hypothermia in California: opportunities for improvement. *Pediatrics* **154**(3), e2023063032. https://doi.org/10.1542/peds.2023-063032 (2024).
5. Yang, M., Wang, K., Liu, B., Shen, Y. & Liu, G. Hypoxic-Ischemic encephalopathy: pathogenesis and promising therapies. *Mol. Neurobiol.* **62**(2), 2105–2122. https://doi.org/10.1007/s12035-024-04398-9 (2025).
6. Greco, P. et al. Pathophysiology of hypoxic-ischemic encephalopathy: a review of the past and a view on the future. *Acta Neurol. Belg.* **120**(2), 277–288. https://doi.org/10.1007/s13760-020-01308-3 (2020).
7. Olofsson, P. Umbilical cord pH, blood gases, and lactate at birth: normal values, interpretation, and clinical utility. *Am. J. Obstet. Gynecol.* **228**(0), S1222–S1240. https://doi.org/10.1016/j.ajog.2022.07.001 (2023).
8. Liu, C. H. et al. Effect of birth asphyxia on neonatal blood glucose during the early postnatal life: A multi-center study in Hubei province, China. *Pediatr. Neonatol.* **64**(5), 562–569. https://doi.org/10.1016/j.pedneo.2021.11.016 (2023).
9. Sperry, J. L. et al. Early hyperglycemia predicts multiple organ failure and mortality but not infection. *J. Trauma.* **63**(3), 487–493. https://doi.org/10.1097/TA.0b013e31812e51fc (2007).
10. Garcia Whitlock, A. E. et al. Loss of FOXO transcription factors in the liver mitigates stress-induced hyperglycemia. *Mol. Metab.* **51**(0), 101246. https://doi.org/10.1016/j.molmet.2021.101246 (2021).
11. Mietzsch, U. et al. Early glycemic state and outcomes of neonates with hypoxic-Ischemic encephalopathy. *Pediatrics* **152**(4), e2022060965. https://doi.org/10.1542/peds.2022-060965 (2023).
12. See, K. C. Glycemic targets in critically ill adults: A mini-review. *World J. Diabetes.* **12**(10), 1719–1730. https://doi.org/10.4239/wjd.v12.i10.1719 (2021).
13. Qi, L. et al. Association of glycemic variability and prognosis in patients with traumatic brain injury: A retrospective study from the MIMIC-IV database. *Diabetes Res. Clin. Pract.* **217**(0), 111869. https://doi.org/10.1016/j.diabres.2024.111869 (2024).
14. Bagshaw, S. M., Egi, M., George, C. & Bellomo, R. Early blood glucose control and mortality in critically ill patients in Australia. *Crit. Care Med.* **37**(2), 463–470. https://doi.org/10.1097/CCM.0b013e318194b097 (2009).
15. Schurr, A. Lactate: A major and crucial player in normal functioning of the brain and in brain pathological conditions. *J. Physiol.* **586**(11), 2665–2666. https://doi.org/10.1113/jphysiol.2008.155416 (2008).
16. Andersson, M. et al. Prehospital lactate analysis in suspected sepsis improves detection of patients with increased mortality risk: an observational study. *Crit. Care.* **29**(1), 38. https://doi.org/10.1186/s13054-024-05225-2 (2025).
17. Sarnat, H. B. & Sarnat, M. S. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Arch. Neurol.* **33**, 696–705. https://doi.org/10.1001/archneur.1976.00500100030012 (1976).
18. Abdelaziz, T. A., Karam, N. A., Ismail, W. I., Askary, N. M. A. & Baz, E. G. Lactate dynamics in paediatric patients with severe sepsis: insights from a prospective cohort study. *BMC Pediatr.* **24**(1), 345. https://doi.org/10.1186/s12887-024-04809-9 (2024).
19. Fuentes, B. et al. Glucemie variability: prognostic impact on acute ischemic stroke and the impact of corrective treatment for huperalycemia. The GLIAS-III translational study. *J. Trans. Med.* **18**(1), 414. https://doi.org/10.1186/s12967-020-02586-4 (2020).
20. Galderisi, A. et al. Glucose-to-lactate ratio and neurodevelopment in infants with hypoxic-ischemic encephalopathy: an observational study. *Eur. J. Pediatr.* **182**(2), 837–844. https://doi.org/10.1007/s00431-022-04694-3 (2023).
21. Basu, S. K. et al. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap study. *Arch. Dis. Child. Fetal Neonatal Ed.* **101**(2), F149–155. https://doi.org/10.1136/archdischild-2015-308733 (2016).
22. Basu, S. K., Salemi, J. L., Gunn, A. J. & Kaiser, J. R. Hyperglycaemia in infants with hypoxic-ischaemic encephalopathy is associated with improved outcomes after therapeutic hypothermia: a post hoc analysis of the CoolCap study. *Arch. Dis. Child. Fetal Neonatal Ed.* **102**(4), F299–F306. https://doi.org/10.1136/archdischild-2016-311385 (2017).
23. Gao, X. et al. Hyperglycemia aggravates the cerebral ischemia injury via protein O-GlcNAcylation. *J. Alzheimers Dis.* **94**(2), 651–668. https://doi.org/10.3233/JAD-230264 (2023).
24. Ali, M. A. M. et al. Glucose instability and outcomes of neonates with hypoxic ischemic encephalopathy undergoing therapeutic hypothermia. *Brain Dev.* **46**(8), 262–267. https://doi.org/10.1016/j.braindev.2024.05.003 (2024).
25. Kramer, A. H., Roberts, D. J. & Zygun, D. A. Optimal glycemic control in neurocritical care patients: a systematic review and meta-analysis. *Crit. Care.* **16**(5), R203. https://doi.org/10.1186/cc11812 (2012).
26. Panayi, A. C. et al. Effect of Liberal glucose control on critically ill patients: a systematic review and meta-analysis. *BMC Endocr. Disord.* **25**(1), 36. https://doi.org/10.1186/s12902-025-01864-w (2025).
27. Lei, H. & Gruetter, R. Metabolic and perfusion responses to acute hypoglycemia in the rat cortex: A non-invasive magnetic resonance approach. *J. Neurochem.* **154**(1), 71–83. https://doi.org/10.1111/jnc.15028 (2020).
28. Yang, W. et al. NLRP3 inhibitor alleviates glycemic variability-induced cognitive impairment in aged rats with type 2 diabetes mellitus. *Mol. Cell. Endocrinol.* **595**(0), 112406. https://doi.org/10.1016/j.mce.2024.112406 (2025).
29. Wu, T. W. et al. Cerebral lactate concentration in neonatal hypoxic-ischemic encephalopathy: in relation to time, characteristic of injury, and serum lactate concentration. *Front. Neurol.* **9**(0), 293. https://doi.org/10.3389/fneur.2018.00293 (2018).
30. Harris, D. L., Weston, P. J. & Harding, J. E. Alternative cerebral fuels in the first five days in healthy term infants: the glucose in well babies (GLOW) study. *J. Pediatr.* **231**(0), 81–86e2. https://doi.org/10.1016/j.jpeds.2020.12.063 (2021).

## Acknowledgements
We are grateful to the participants and the staff of the NICU for their support and assistance in this study.

## Author contributions
LZ and CW contributed to the conception and design of the study and wrote the manuscript. QJ and LJ contributed to the design of the study and reviewed the manuscript. FW, HL and LJ corrected the draft. QJ and HL completed the statistical analysis. All authors contributed to the article and approved the submitted version.

## Funding
This study was funded by Maternal and Child Health Research Project of Jiangsu Province (F202071) and Maternal and Child Health Outstanding Talent Project of Jiangsu Province (SWBFY 2021-9).

## Declarations

## Ethics statement
This study adhered to medical ethical standards and received approval from the Institutional Review Board (IRB) of the Affiliated Hospital of Yangzhou University (No. 2022-YKL3-06-006). Due to the retrospective nature of the study, the IRB of the Affiliated Hospital of Yangzhou University waived the need of obtaining informed consent.

## Competing interests
The authors declare no competing interests.

## Additional information
**Correspondence** and requests for materials should be addressed to L.J.