

Hepatic Injury in Neonates with Perinatal Asphyxia

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ABSTRACT

Background: Perinatal asphyxia is a major cause of neonatal morbidity and mortality and frequently results in multiorgan dysfunction. The liver is particularly susceptible to hypoxic injury because of reduced hepatic perfusion during oxygen deprivation.

Objectives: To determine the frequency of liver dysfunction in neonates with birth asphyxia and to compare the frequency of liver dysfunction according to the severity of hypoxic-ischemic encephalopathy (HIE).

Study Design & Setting: This analytical cross-sectional study was conducted in the Neonatal Intensive Care Unit (NICU), Fauji Foundation Hospital, Rawalpindi from 21 February 2026 to 21 May 2026.

Methodology: A total of 95 full-term neonates with birth asphyxia were enrolled using a non-probability consecutive sampling technique. HIE was staged according to the Sarnat classification. Liver dysfunction was diagnosed when two or more predefined biochemical abnormalities were present. Demographic, clinical, and laboratory data were collected using a structured proforma. Data were analyzed using IBM SPSS Statistics version 23. Continuous variables were expressed as mean $\pm$ standard deviation, while categorical variables were presented as frequencies and percentages. The Independent Samples *t*-test, One-Way ANOVA, Pearson Chi-square test, and binary logistic regression were applied where appropriate, with a *p*-value <0.05 considered statistically significant.

Results: The mean gestational age was 38.52 ± 1.21 weeks, and the mean birth weight was 2.94 ± 0.41 kg. Liver dysfunction was identified in 39 (41.1%) neonates. HIE Stage I, II, and III were observed in 36.8%, 43.2%, and 20.0% of neonates, respectively. Liver dysfunction increased significantly with HIE severity, occurring in 14.3%, 43.9%, and 84.2% of Stage I, II, and III cases, respectively ($p < 0.001$). Stage III HIE, lower cord blood pH, and lower birth weight were independent predictors of liver dysfunction.

Conclusion: Liver dysfunction was common among neonates with birth asphyxia and was significantly associated with increasing severity of hypoxic-ischemic encephalopathy. Early assessment of liver function may facilitate prompt identification of high-risk neonates and improve clinical management.

Keywords: Birth asphyxia; Hepatic injury; Hypoxic-ischemic encephalopathy; Liver dysfunction; Neonate; Perinatal asphyxia.

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INTRODUCTION

Over the past decade, neonatal care in Pakistan has seen notable improvements, including wider availability of neonatal intensive care units (NICUs), better resuscitation protocols, enhanced monitoring technologies, and increased awareness of early intervention strategies. These advancements have contributed to improved survival rates among neonates suffering from birth asphyxia.¹

However, with increased survival comes the responsibility to recognize and manage secondary complications that may affect long-term outcomes. Perinatal hypoxia is diagnosed when a neonate exhibits all of the following: (a)

profound metabolic or mixed acidemia (pH <7.00) on umbilical arterial blood sample, if available; (b) an Apgar score of 0–3 for more than five minutes; (c) neurological manifestations such as seizures, coma, or hypotonia; and (d) evidence of multiorgan dysfunction. Additional criteria include prolonged antenatal acidosis (>1 hour), fetal heart rate <60 bpm, Apgar score ≤ 3 at ≥ 10 minutes, delayed first cry (>5 minutes), need for positive pressure ventilation >1 minute, seizures within 12–24 hours of birth, and abnormal EEG or aEEG patterns such as burst suppression or suppressed background activity.^{2,3}

Hypoxia can affect nearly every organ system. In response to oxygen deprivation, the fetus initiates protective

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mechanisms—known as the "diving reflex"—to prioritize blood flow to vital organs like the brain, heart, and adrenal glands, while reducing perfusion to less critical organs such as the kidneys, lungs, gastrointestinal tract, liver, and spleen.^{4,5} The liver, being central to metabolism, detoxification, and coagulation, is particularly vulnerable to hypoxic injury. Hepatic involvement in birth asphyxia often resembles shock liver syndrome and typically presents within 24–72 hours of birth as a sharp rise in aminotransferases (AST and ALT), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH). These levels usually normalize within 10 days, and while hypoxic hepatitis rarely progresses to liver failure, its early recognition is essential.^{6,7} However, hepatic dysfunction often goes unnoticed, which can lead to bleeding disorders, poor metabolic regulation, and increased risk of infection. Perinatal hypoxia, defined by profound acidemia (pH <7.00), low Apgar scores, neurological symptoms, and multiorgan dysfunction, frequently affects the liver due to blood flow redistribution during hypoxic insult.^{8,9}

Perinatal asphyxia is a major cause of neonatal morbidity and frequently results in hepatic injury, yet liver dysfunction is often under-recognized during the early management of affected neonates. Although international studies have demonstrated an association between hepatic dysfunction and the severity of hypoxic-ischemic encephalopathy (HIE), evidence from Pakistan remains limited, with only a few local studies addressing this relationship.^{10,11}

This study provided local data on the frequency of liver dysfunction and its association with HIE severity in neonates with birth asphyxia, helping to address an important gap in the Pakistani literature. The findings may support the routine assessment of liver function in neonates with perinatal asphyxia and contribute to earlier risk stratification and improved clinical management. The objectives of the study were to determine the frequency of liver dysfunction in neonates with birth asphyxia and to compare the frequency of liver dysfunction according to the severity of hypoxic-ischemic encephalopathy (HIE) among neonates with birth asphyxia.

METHODS

After obtaining ethical approval was obtained from the Institutional Ethics Committee & Synopsis approval from CPSP the study was conducted at Neonatal Intensive Care Unit (NICU) Fauji Foundation Hospital, Rawalpindi from 21 February 2026 to 21 May 2026. An analytical cross-sectional study design was used. The sample size was 95, calculated using the WHO sample size formula with a 95% confidence level, an anticipated population proportion of 42.85%, and an absolute precision of 10%.¹⁵ A non-probability consecutive sampling technique was followed. The study included full-term neonates (gestational age ≥ 37 weeks) with birth asphyxia. Neonates were excluded if they had congenital malformations, particularly involving the liver or biliary tract, evidence of neonatal sepsis or systemic bacterial infection, exposure to potentially hepatotoxic medications such as

anticonvulsants or antibiotics, or incomplete clinical or biochemical records. Preterm neonates (gestational age <37 weeks) were also excluded to ensure uniformity in developmental maturity and liver function assessment.

A trained resident pediatrician was responsible for systematic data collection throughout the study. Upon delivery, each neonate was assessed for gestational age using the Ballard scoring system, and Apgar scores were recorded at one and five minutes. Neonates fulfilling the inclusion criteria were enrolled after informed parental consent had been obtained. Birth asphyxia was documented, and hypoxic-ischemic encephalopathy (HIE) was staged according to the Sarnat and Sarnat classification based on neurological examination performed within the first six hours of life. Blood samples were collected aseptically on day 1, day 3, and day 10 to measure liver function parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total protein, serum albumin, total and direct bilirubin, prothrombin time (PT), international normalized ratio (INR), and serum creatinine. Cord blood pH was recorded immediately after birth. Ultrasound findings were documented by a radiologist and reviewed by the resident pediatrician. Demographic and clinical variables, including sex, birth weight, mode of delivery, and neonatal outcome, were recorded on a pre-designed data collection proforma. Double data entry and periodic cross-checking with source documents were performed to ensure data accuracy.

To minimize collection bias, the resident pediatrician was blinded to the biochemical analysis results and followed standardized protocols for clinical assessment. All measurements were obtained using calibrated equipment and interpreted according to uniform reference ranges. The operational definitions of the study were as follows. Birth asphyxia was defined as an Apgar score of ≤ 7 at five minutes of life, indicating impaired respiratory effort and oxygenation requiring resuscitative measures. Hypoxic-ischemic encephalopathy (HIE) was defined as neurological dysfunction resulting from perinatal hypoxia and was staged according to the Sarnat classification as Stage I (irritability, jitteriness, normal EEG, and no seizures), Stage II (lethargy, hypotonia, abnormal EEG, and seizures within 12 hours), and Stage III (stupor, absent reflexes, isoelectric EEG, and prolonged or refractory seizures).⁸ Liver dysfunction was diagnosed when two or more of the following criteria were present on the first day of life: alanine aminotransferase (ALT) >50 U/L, aspartate aminotransferase (AST) >140 U/L, alkaline phosphatase (ALP) >420 U/L, lactate dehydrogenase (LDH) >580 U/L, total protein <4.5 g/dL, serum albumin <2.5 g/dL, prothrombin time >20 seconds, or an international normalized ratio (INR) >1.2.

Data were analyzed using IBM SPSS Statistics version 23. Categorical variables, including birth asphyxia severity, sex, mode of delivery, liver dysfunction, HIE stage, and neonatal outcome, were summarized as frequencies and percentages. Associations between categorical variables

were assessed using the Pearson Chi-square test. Continuous variables, including Apgar score, gestational age, birth weight, cord blood pH, and liver function parameters (ALT, AST, ALP, LDH, total protein, serum albumin, bilirubin, PT, INR, and serum creatinine), were summarized as mean $\pm$ standard deviation. The Independent Samples t-test was used to compare continuous variables between neonates with and without liver dysfunction, while One-Way Analysis of Variance (ANOVA) was used to compare mean values across different HIE stages. Binary logistic regression was performed, where appropriate, to adjust for potential confounding variables such as gestational age and birth weight. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 95 neonates with birth asphyxia were included in the study. The mean gestational age was 38.52 ± 1.21 weeks, the mean birth weight was 2.94 ± 0.41 kg, and the mean cord blood pH was 6.96 ± 0.11 . The mean Apgar scores at 1 minute and 5 minutes were 3.18 ± 1.09 and 5.24 ± 1.16 , respectively, as given in Table 1.

Table 1. Baseline Characteristics of Neonates with Birth Asphyxia (n = 95)

Variable	Value
Gestational age (weeks), Mean $\pm$ SD	38.52 ± 1.21
Birth weight (kg), Mean $\pm$ SD	2.94 ± 0.41
Cord blood pH, Mean $\pm$ SD	6.96 ± 0.11
Apgar score at 1 minute, Mean $\pm$ SD	3.18 ± 1.09
Apgar score at 5 minutes, Mean $\pm$ SD	5.24 ± 1.16

Among the 95 neonates, 56 (58.9%) were males and 39 (41.1%) were females. Vaginal delivery was observed in 49 (51.6%) neonates, while 46 (48.4%) were delivered by caesarean section. Moderate birth asphyxia was present in 61 (64.2%) neonates, whereas 34 (35.8%) had severe birth asphyxia. Most neonates (86, 90.5%) survived, while 9 (9.5%) expired, as given in Table 2.

Table 2. Demographic and Clinical Characteristics of Neonates (n = 95)

Variables	Type	Frequency (n)	Percentage (%)
Gender	Male	56	58.9
	Female	39	41.1
Mode of Delivery	Vaginal delivery	49	51.6
	Caesarean section	46	48.4
Severity of Birth Asphyxia	Moderate	61	64.2
	Severe	34	35.8
Neonatal Outcome	Survived	86	90.5
	Expired	9	9.5

Regarding the severity of hypoxic-ischemic encephalopathy, 35 (36.8%) neonates had Stage I HIE, 41

(43.2%) had Stage II HIE, and 19 (20.0%) had Stage III HIE. Stage II was the most frequently observed stage among the study participants, as given in figure 1.

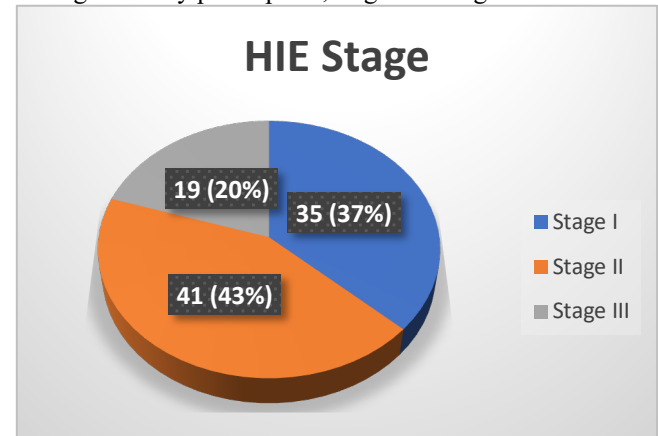


Figure 1. Distribution of Hypoxic-Ischemic Encephalopathy (HIE) Stages (n = 95)

Liver dysfunction was identified in 39 (41.1%) of the neonates with birth asphyxia, whereas 56 (58.9%) did not demonstrate evidence of liver dysfunction. Thus, approximately two-fifths of the study population developed hepatic involvement following birth asphyxia, as given in figure 2.

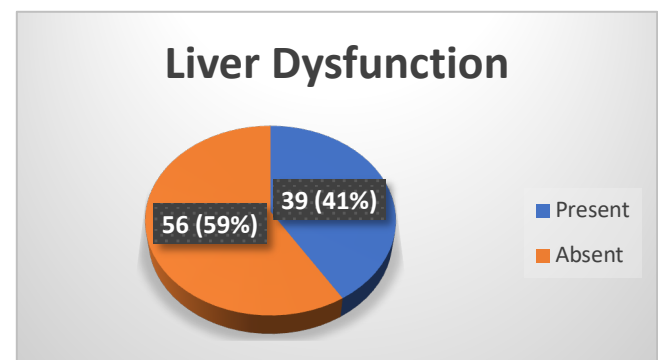


Figure 2. Frequency of Liver Dysfunction among Neonates with Birth Asphyxia (n = 95)

The mean liver function parameters among the study participants were 54.82 ± 18.63 U/L for ALT, 149.57 ± 48.29 U/L for AST, 391.84 ± 91.75 U/L for ALP, 628.53 ± 165.42 U/L for LDH, 5.06 ± 0.74 g/dL for total protein, 2.91 ± 0.48 g/dL for serum albumin, 5.92 ± 2.03 mg/dL for total bilirubin, 0.88 ± 0.36 mg/dL for direct bilirubin, 18.67 ± 4.21 seconds for prothrombin time, 1.19 ± 0.24 for INR, and 0.93 ± 0.27 mg/dL for serum creatinine, as given in Table 3.

Table 3. Liver Function Parameters among Neonates (n = 95)

Variable	Mean $\pm$ SD
ALT (U/L)	54.82 ± 18.63
AST (U/L)	149.57 ± 48.29
ALP (U/L)	391.84 ± 91.75
LDH (U/L)	628.53 ± 165.42
Total Protein (g/dL)	5.06 ± 0.74

Serum Albumin (g/dL)	2.91 ± 0.48
Total Bilirubin (mg/dL)	5.92 ± 2.03
Direct Bilirubin (mg/dL)	0.88 ± 0.36
Prothrombin Time (seconds)	18.67 ± 4.21
INR	1.19 ± 0.24
Serum Creatinine (mg/dL)	0.93 ± 0.27

The frequency of liver dysfunction increased significantly with increasing severity of hypoxic-ischemic encephalopathy. Liver dysfunction was present in 5 (14.3%) neonates with Stage I HIE, 18 (43.9%) with Stage II HIE, and 16 (84.2%) with Stage III HIE. This association was statistically significant ($p < 0.001$), indicating that more severe HIE was associated with a higher frequency of liver dysfunction, as given in Table 4.

Table 4. Comparison of Liver Dysfunction According to HIE Stage (n = 95)

HIE Stage	Liver Dysfunction Present (%)	Liver Dysfunction Absent (%)	Total n	p-value
Stage I (n=35)	5 (14.3)	30 (85.7)	35	<0.001
Stage II (n=41)	18 (43.9)	23 (56.1)	41	
Stage III (n=19)	16 (84.2)	3 (15.8)	19	

Pearson Chi-square test applied

Neonates with liver dysfunction had significantly lower mean gestational age (38.21 ± 1.18 vs. 38.74 ± 1.19 weeks; $p=0.031$), lower birth weight (2.79 ± 0.39 vs. 3.05 ± 0.38 kg; $p=0.002$), lower cord blood pH (6.88 ± 0.09 vs. 7.01 ± 0.08 ; $p<0.001$), lower Apgar score at 1 minute (2.67 ± 0.91 vs. 3.54 ± 1.03 ; $p<0.001$), and lower Apgar score at 5 minutes (4.62 ± 1.02 vs. 5.67 ± 1.03 ; $p<0.001$) compared with neonates without liver dysfunction, as given in Table 5.

Table 5. Comparison of Clinical Characteristics According to Liver Dysfunction (n = 95)

Variable	Liver Dysfunction Present (n=39) Mean ± SD	Liver Dysfunction Absent (n=56) Mean ± SD	p-value
Gestational age (weeks)	38.21 ± 1.18	38.74 ± 1.19	0.031
Birth weight (kg)	2.79 ± 0.39	3.05 ± 0.38	0.002
Cord blood pH	6.88 ± 0.09	7.01 ± 0.08	<0.001

Apgar score at 1 minute	2.67 ± 0.91	3.54 ± 1.03	<0.001
Apgar score at 5 minutes	4.62 ± 1.02	5.67 ± 1.03	<0.001

Independent Samples t-test applied

Binary logistic regression analysis demonstrated that Stage III HIE was independently associated with increased odds of liver dysfunction (adjusted OR = 7.84, 95% CI: 2.11–29.12, $p=0.002$). Lower cord blood pH (adjusted OR = 0.12, 95% CI: 0.03–0.49, $p=0.003$) and lower birth weight (adjusted OR = 0.41, 95% CI: 0.19–0.89, $p=0.024$) were also significant independent predictors of liver dysfunction, whereas gender was not significantly associated with liver dysfunction ($p=0.586$), as given in Table 6.

Table 6. Logistic Regression Analysis for Factors Associated with Liver Dysfunction (n = 95)

Variable	Adjusted OR	95% CI	p-value
Stage III HIE	7.84	2.11–29.12	0.002
Cord blood pH	0.12	0.03–0.49	0.003
Birth weight	0.41	0.19–0.89	0.024
Male gender	1.27	0.54–2.97	0.586

DISCUSSION

Perinatal asphyxia is a major cause of neonatal morbidity and mortality, particularly in developing countries.¹² Hypoxic injury resulting from birth asphyxia affects multiple organs, with the liver being one of the most vulnerable because of reduced hepatic blood flow during hypoxia. Hepatic injury is characterized by elevated liver enzymes and impaired synthetic function, reflecting the severity of hypoxic insult.^{13,14} Early recognition of liver dysfunction may facilitate timely management and improve neonatal outcomes. Therefore, assessing hepatic injury in neonates with perinatal asphyxia is important for evaluating disease severity and guiding clinical care.

The findings of the present study are comparable with those reported by Choudhary et al. (2015), who evaluated hepatic dysfunction in asphyxiated neonates and found that 22.8% had severe, 47.1% moderate, and 30% mild birth asphyxia. They reported HIE Stage I in 14.28%, Stage II in 25.73%, and Stage III in 11.42% of neonates, while 48.57% had no evidence of HIE. The prevalence of liver dysfunction was 42.85%, which is remarkably similar to the 41.1% observed in the present study.¹⁵ The results of the present study also agree with those of Elsadek et al. (2021), who reported 25% severe, 43% moderate, and 32% mild perinatal asphyxia. HIE was present in 39% of affected neonates, with 25.7% classified as Stage I, 41% as Stage II, and 33.3% as Stage III. Impaired liver function was detected in 48% of cases,

slightly higher than the 41.1% observed in the present study. They also found significantly elevated ALT, AST, ALP, LDH, PT, and INR levels together with significantly reduced total protein and serum albumin.¹⁶ Likewise, Prasad et al. (2021) reported significantly higher AST, ALT, LDH, and ALP levels among asphyxiated neonates compared with controls ($p < 0.05$), whereas differences in total protein and total bilirubin were not statistically significant. They further observed significant differences in AST, ALT, and LDH between HIE Stage I and Stage II and between Stage I and Stage III, although the difference between Stage II and Stage III was not significant.¹⁷ Similar observations were reported by Samad et al. (2016), who demonstrated that asphyxiated neonates had significantly higher LDH, ALT, AST, bilirubin, creatinine, and urea levels together with lower platelet counts compared with healthy newborns. Their study highlighted that biochemical evidence of hepatic and renal injury reflected the extent of multiorgan damage caused by hypoxic insult.¹⁸

More recently, Yasin et al. (2025) demonstrated that serum ALT, AST, and LDH levels increased significantly with increasing severity of perinatal asphyxia, with the highest values recorded among severely affected neonates. Hepatic dysfunction was more frequent in severe cases, and the authors concluded that liver enzyme measurements could serve as early indicators of disease severity. The present study supports these observations, as liver dysfunction was identified in more than four-fifths (84.2%) of neonates with Stage III HIE compared with only 14.3% of those with Stage I HIE, indicating a strong relationship between hepatic injury and the severity of hypoxic insult.¹⁹ Comparable findings were also reported by Hussain et al. (2025), who demonstrated that increasing severity of perinatal asphyxia was significantly associated with organ damage. Elevated serum creatinine was present in 36%, elevated ALT in 40%, and elevated CK-MB in 46% of neonates. They concluded that prompt recognition of organ dysfunction and early intervention could improve neonatal outcomes. Their observation of elevated ALT in 40% of neonates is almost identical to the 41.1% frequency of liver dysfunction documented in the present study, further supporting the importance of routine biochemical assessment for early detection of hepatic injury in neonates with birth asphyxia.²⁰

STUDY LIMITATIONS

This study was conducted at a single tertiary care center with a relatively small sample size, which may limit the generalizability of the findings. Long-term follow-up of hepatic function and neurodevelopmental outcomes was not performed. Additionally, the cross-sectional design did not allow assessment of causal relationships between perinatal asphyxia and hepatic injury.

CONCLUSION

Liver dysfunction was a frequent finding among neonates with perinatal asphyxia and was significantly associated with increasing severity of hypoxic-ischemic

encephalopathy. Early assessment of hepatic function may help identify neonates at greater risk of adverse outcomes. Routine liver function evaluation should be considered in the management of neonates with birth asphyxia.

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