# Hepatic Injury in Neonates with Perinatal Asphyxia

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## Abstract

*Background:* Perinatal asphyxia (PA) is a major cause of morbidity and mortality in which dramatic transient impairment in liver functions occurs in some patients. *Objectives:* We aimed to evaluate the state of the liver in cases of Perinatal asphyxia and to assess the severity of hepatic impairment in relation to different grades of HIE. *Patients and Methods:* This case-control study was conducted on 100 full-term newborns with perinatal asphyxia (Group I) and 50 healthy neonates served as controls (Group II). All biochemical parameters of liver function were measured on the 1st, 3rd, and 10th day after birth. These parameters include serum alanine transferase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total protein, serum albumin, serum bilirubin (total and direct), and international normalized ratio (INR), in both cases and controls. *Results:* Among babies with PA, 25 (25%) had an Apgar score of 0 to 3 (severe PA), 43 (43%) had an Apgar score of 4 to 5 (moderate PA) and 32 (32%) had an Apgar score of 6 to 7 (mild PA) at 5 minutes of life. HIE was found in 39% among cases of PA and the remaining 61% were normal. Among babies with PA and HIE; 25.7% had stage I, 41% had stage II and 33.3% had stage III. Impaired liver function was reported in 48% of asphyxiated babies. On the first day of life, ALT, AST, ALP, LDH, PT, and INR were significantly higher in Group I compared to Group II. However, total protein and serum albumin were significantly lower in Group I compared to Group II. ALT and AST showed a positive correlation with the severity of HIE. On the third day of life, LDH rises as the stage of HIE progressed from stage 0 to stage 3. The difference in LDH among most stages of HIE was statistically significant. *Conclusion:* Liver enzymes can be used as an easy early diagnostic marker to differentiate between babies with asphyxia and those without asphyxia. Also, liver enzymes can be used for the detection of the severity of PA.

## Keywords

perinatal asphyxia, hypoxic-ischemic encephalopathy, hepatic injury

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## Introduction

Perinatal asphyxia (PA) is caused by a lack of oxygen supply to various organ systems in a neonate, due to a hypoxic or ischemic insult that occurs within proximity to labor (peripartum) and delivery (intrapartum). The lack of oxygen supply may lead to multi-organ failure with brain involvement as the major organ of concern (hypoxic-ischemic encephalopathy [HIE]). In cases of HIE, injury to other organ occurs, including the heart,

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**Table 1.** Sarnat Clinical Staging of HIE.

| Features | Stage I | Stage II | Stage III |
|---|---|---|---|
| Severity | Mild degree | Moderate degree | Severe degree |
| Consciousness | Hyper alert and irritable | Lethargic and obtunded | Comatosed |
| Pupils | Dilated | Constricted | Dilated |
| Tone | Normal tone | Marked hypotonia | Flaccidity |
| Reflexes | Normal or increased | Sluggish | Absent |
| Seizures | No seizures and symptoms usually resolve in less than 24 hours | Seizures are common | Seizures are frequently seen and more resistant to treat with anticonvulsants |
| EEG | Normal | Abnormal | abnormal with decreased background activity |
| Apgar score | 5 to 7 | 3 to 4 | 1 to 2 |

kidney, lung, and liver.[1,2] Despite advances in neonatal medicine, hypoxic–ischemic encephalopathy (HIE) remains a major cause of mortality and long-term morbidity among the survivors. Approximately 23% of neonatal deaths are due to PA.[3] The classification of birth asphyxia is based on 1-minute Apgar score.[4]

Severe PA when Apgar score of 0 to 3 while mild-to-moderate PA is considered with a score of 4 to 7. The American Academy of Pediatrics considers a neonate as having severe PA when all the following conditions are met:

(1) Arterial pH in the cord blood is less than 7;
(2) Apgar score of <3 for more than 5 minutes;
(3) Neurological manifestations (eg, seizures, coma, or hypotonia); and
(4) Multisystem organ dysfunction (MOD), involving many organ systems for example, cardiovascular, pulmonary, gastrointestinal, hematological, and renal systems.[5]

Hypoxia can cause damage to all body systems. In response to a hypoxic-ischemic insult to the fetus, a series of reflexes and events occur to prevent damage to vital organs [brain, heart and adrenals] at the expense of other organs [gastrointestinal tract, kidneys, lungs, liver, and spleen] via redistribution of cardiac output.[6] The most sensitive organs to asphyxia are those with a high energy needs and a high metabolic rate; as central nervous system (CNS), myocardium, and liver.[7]

Over the past decade, therapeutic hypothermia (TH) becomes the most promising of the neuroprotective therapies that had emerged and is rapidly becoming standard of care in neonates with moderate to severe HIE.[2] The role of TH in limiting neuronal injury is well recognized, but its effect on hepatic injury which occurs frequently in neonatal HIE is not known. TH is thought to modulate hepatic injury and affects hepatic biomarkers.[8]

The liver is involved in many metabolic processes. So, hepatic involvement is often reported in cases of PA. The condition is termed ischemic hepatitis or hypoxic hepatopathy.[9] Circulating enzymes provide evidence of cell injury that can be used to identify babies with MOD, especially hypoxic-ischemic encephalopathy (HIE).

The most commonly affected organs are the lungs in 86%, the liver in 85%, kidneys in 70%, and heart in 62% of cases.[10] Hepatic aminotransferases [AST and ALT] and LDH plasma activity showed a dramatic and transient elevation in cases of hypoxic hepatic injury (HHI).[10]

We aimed to evaluate hepatic state in neonates with birth asphyxia and to assess the severity of hepatic impairment in relation to different grades of HIE.

## Patients and Methods

This prospective cohort study was conducted on a cohort of 100 full-term neonates (Group I) with PA. Cases were recruited from Neonatal Intensive Care Unit, Prince Sultan Military hospital and Al hada Military hospital, Taif region, Saudi Arabia as well as from Benha University hospital, Benha, Egypt in the period from October 2018 to March 2020. Their gestational ages were ≥37 weeks. Their Apgar score <7 at 5 minutes after birth. We included all cases of HIE mild, moderate, or severe according to Sarnat and Sarnat clinical staging.[9] For inclusion in the study, there should be at least one of the following criteria:

Baby needs resuscitation with more than 3 minutes of positive pressure ventilation before spontaneous breathing. PH of umbilical cord blood (arterial) <7.20.[11] According to Sarnat and Sarnat clinical staging, babies with HIE were classified into 3 stages (Table 1).

## Exclusion Criteria Include

- Baby with a major congenital anomaly.
- Primary liver disease.
- History of hepatotoxic drugs.
- Neonatal sepsis
- Cases of inborn error of metabolism or congenital infection.
- Hemolytic disorders or condition of shock.

Within 24 hours of birth, Liver was observed for the presence of congenital malformation or abnormality of biliary system by an ultrasound. Neonates who developed liver dysfunction were managed conservatively according to the standard protocol.

We included 50 healthy newborns with Apgar score >7 at 5 minutes who serve as a control group (Group II).

All subjects included in our study were subjected to:

- **Complete history taking**: Antenatal, natal and postnatal histories with special stress on history of fetal distress, antepartum hemorrhage, type of anesthesia, and any drug taken by mother and infant.
- **Thorough clinical examination**: Determination of conscious level, Apgar score, heart rate, muscle tone, neonatal reflexes, and systemic examination, to determine the stage of HIE.
- **Laboratory investigation**: Blood samples were taken from all cases as well as controls for assay of serum enzymes namely aspartate transferase (AST) (normal value 35-140 U/L), alanine transferase (ALT) (normal value 6-50 U/L), alkaline phosphatase (ALP) (normal value 150-400 U/L), and lactate dehydrogenase (LDH) (normal value 160-450 U/L), total protein (normal value 4.5-8.4 g/dL), serum albumin (normal value 2.5-3.6 g/dL), serum bilirubin (total and direct) (normal value <2 mg/dL), and International Normalized Ratio (INR). All parameters were measured on the 1st, 3rd, and 10th days of life in all subjects enrolled in the study.

According to the criteria of hepatic injury that were applied on the first day of life, cases of PA were subdivided into 2 groups:

Group 1A: Included babies with PA and normal hepatic function.
Group 1B: Included babies with PA and impaired hepatic function.

These criteria include ALT >50 U/L, AST >140 U/L, ALP >420 U/L, LDH >580 U/L, total protein <4.5 g/dL, serum albumin <2.5 g/dL, prothrombin time >20 seconds, and/or INR >1.2. All babies with hepatic injury were managed according to a standardized protocol.

## Blood Sampling

A blood sample of 5 mL was withdrawn from each subject in the study into a plain tube from a venous or arterial umbilical catheter or during venipuncture at 3-time points (1st, 3rd, and 10th days of life).

All blood samples were separated immediately after collection, for the estimation of all liver parameters. Enzymatic assays (ALT, AST, and LDH) were performed using an ultraviolet spectrophotometer.

**Abdominal ultrasonography**: Liver was observed for hepatic or biliary tract anomalies within 24 hours of birth by an ultrasound

## Statistical Analysis

We used the SPSS software package (version 10.0, Chicago, IL, USA) for data analysis. Unpaired t-test [student's *t*-test] was used to compare quantitative variables while Chi-square test [$\chi 2$] was used to compare qualitative variables between 2 independent groups. The correlation between different variables was assessed using Pearson correlation test. *P*-value < .05 was considered significant.

## Ethical Approval and Informed Consent

The study was carried after written informed consent from concerned parents. Ethical clearance was obtained for the research study. The IRB of Faculty of medicine, Taif University, Saudi Arabia (#34721973R) and the IRB Faculty of medicine, Benha University, Egypt (#86372019) had approved the study. The study protocol conforms to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments.

## Results

Our study was conducted on 150 babies recruited during the study period. They included 100 babies with PA and 50 controls.

Among the babies with PA, 56(56%) were males and 44 were females (44%) Their gestational ages were 38.4 ± 1.2.

The gestation ages of babies with PA and controls were 38.4 ± 1.2 and 37.8 ± 1.4 weeks respectively, *P* < .05. This difference was statistically not significant.

The birth weight of babies with asphyxia was 3.3 ± 0.62 kg compared to 3.1 (0.58) kg in the control

**Table 2.** Correlation of Liver Enzymes (ALT and AST) with HIE Staging.

| HIE staging | No. | ALT | P-value | AST | P-value |
|---|---|---|---|---|---|
| 0 | 61 | 41.12 ± 20.22 | P < .01 | 73.05 ± 31.89 | P < .01 |
| I | 10 | 50.0 ± 30.32 | P < .05 | 91.03 ± 47.81 | P < .01 |
| II | 13 | 52.18 ± 31.22 | P < .01 | 99.23 ± 44.78 | P < .05 |
| III | 16 | 71.25 ± 28.89 | P < .001 | 141.95 ± 0.75 | P < .001 |
| Total | 100 | 47.95 ± 29.82 | P < .001 | 95.79 ± 47.35 | P < .001 |
| Controls (Group II) | 50 | 30.22 ± 14.36 | | 66.86 ± 36.40 | |

group, $P < .05$. This difference was statistically not significant. The Apgar score at 5 minutes after birth was $4.4 \pm 1.4$ minutes and $8.6 \pm 1.5$ minutes in cases and controls respectively, $P < .01$ with a highly significant statistical difference between them.

Among babies with PA, 25 (25%) had an Apgar score of 0 to 3 (severe PA), 43 (43%) had an Apgar score of 4 to 5 (moderate PA) and 32 (32%) had an Apgar score of 6 to 7 (mild PA) at 5 minutes of life.

Babies with PA that required parenteral nutrition were 12 (12%).

HIE was found in 39% among cases of PA and the remaining 61% were normal.

None of the 32 babies with mild PA developed HIE, while 18 (41.6%) of the 43 babies with moderate PA had HIE and 21 (84%) of the 25 babies with severe PA had HIE. Ten (25.7%) of the babies with HIE had a mild form (Stage I), 16(41%) had moderate (Stage II) and 13 (33.3%) had severe HIE (Stage III).

Among babies with HIE, 15 (38.4%) infants were managed at normal temperature (n = 8 HIE grade 1; n = 4 HIE grade 2; n = 3 HIE grade 3), and 24 (61.6%) received therapeutic hypothermia (TH) (n = 2 HIE grade 1; n = 12 HIE grade 2; and n = 10 HIE grade 3).

On the first day of life, ALT was significantly higher in cases (Group I) compared to controls (Group II) (respectively, $47.95 \pm 29.82$ U/L, $30.22 \pm 14.36$ U/L, $P < .001$). Also, AST was significantly higher in cases (Group I) compared to controls (Group II) (respectively, $95.79 \pm 47.35$ U/L, $66.86 \pm 36.40$, $P < .001$).

We observed a tendency of ALT and AST to rise with the progression of HIE staging from HIE stage 0 (respectively, $40.82.0 \pm 20.74$ U/L, $73.24 \pm 36.47$ U/L) to HIE stage III (respectively, $71.67 \pm 29.89$ U/L and AST $149.88 \pm 0.48$ U/L).

When ALT and AST levels were classified according to 5 minutes Apgar score, we found a similar correlation. The lower the values of 5 minutes Apgar score were observed with the higher values of ALT and AST (Table 2).

On the first day of life, LDH was significantly higher in Group I, Group IA, and Group IB compared to Group II (respectively, $455.27 \pm 305.83$ U/L, $383.4 \pm 216.35$ U/L,

**Table 3.** Correlation of LDH with HIE Staging.

| HIE staging | No. | LDH | P-value |
|---|---|---|---|
| 0 | 61 | 920.12 ± 335.43 | P < .01 |
| I | 10 | 1120.43 ± 285.58 | P < .001 |
| II | 16 | 1920.74 ± 387.98 | P < .001 |
| III | 13 | 2430.43 ± 285.58 | P < .001 |
| Total | 100 | 1128.71 ± 795.67 | P < .001 |
| Controls (Group II) | 50 | 334.67 ± 116.23 | |

The difference was significant between HIE 0 to II, HIE 0 to III, HIE I to II, and HIE I to III (P < .001), while it was insignificant between HIE 0 to I and HIE II to III (P > .1).

$551.1 \pm 373.85$ U/L, $329.40 \pm 154.89$ U/L, $P < .001$). Also, Serum ALP was significantly higher in Group I, Group IA, and Group IB compared to Group II (respectively, $341.01 \pm 98.65$ U/L, $286.67 \pm 68.70$ U/L, $413.43 \pm 85.06$ U/L, $254.8 \pm 96.77$ U/L, $P < .001$). We found no significant correlation between serum levels of LDH and ALP and various stages of HIE and form of asphyxia on the first day of life.

On the third day of life, LDH showed a significant elevation in Group I compared to Group II (respectively, $1128.71 \pm 595.53$ U/L, to $334.67 \pm 116.23$ U/L, $P < .001$).

We observed the mean concentration of LDH rises as the stage of HIE progressed from stage 0 to stage 3 on the third day of life. The difference in LDH among various stages of HIE was statistically significant between HIE 0 to II ($P < .001$), HIE 0 to III ($P < .001$), HIE I to II ($P < 0.001$), and HIE I to III ($P < .001$), while it was statistically insignificant when compared between HIE 0 to I and HIE II to III ($P > .1$) and according to the Apgar score (Table 3).

Total protein was $5.26 \pm 07.3$ g/dL in Group I ($5.52 \pm 0.47$ g/dL in Group IA; $4.78 \pm 0.45$ g/dL in Group IB) and $5.60 \pm 0.36$ g/dL in Group II, the difference being significant ($P < .001$).

Serum albumin was $3.02 \pm 0.59$ g/dL in Group I ($3.08 \pm 0.45$ g/dL in Group IA; $2.60 \pm 0.37$ g/dL in Group IB) as compared to $3.20 \pm 0.39$ g/dL in Group II, which was statistically significant ($P < .05$).

Total serum bilirubin (TSB) was $4.49 \pm 1.68$ mg/dL in Group I ($4.19 \pm 1.66$ mg/dL in Group IA; $4.85 \pm 1.61$ mg/dL in Group IB) and $3.42 \pm 1.79$ mg/dL in Group II, the difference being statistically significant ($P < .01$).

Direct serum bilirubin (DSB) was $1.18 \pm 0.66$ mg/dL in Group I ($1.14 \pm 0.67$ mg/dL in Group IA; $1.24 \pm 0.64$ mg/dL in Group IB) as compared to $1.04 \pm 0.46$ mg/dL in Group II, which was insignificant ($P < .05$).

TSB and DSB levels were comparable to the controls and in between the stages of HIE. Prothrombin time (PT) was $15.58 \pm 1.83$ seconds in Group I as compared to $14.32 \pm 1.6$ seconds in Group II, which was highly significant ($P < .001$). The INR was $1.47 \pm 0.13$ in Group I and $1.14 \pm 0.06$ in Group II, the difference being statistically significant ($P < .001$). In Group I, PT and INR values were higher in babies with asphyxia than those of controls, but these values were insignificant in between stages of HIE (Table 4).

Among 100 babies with PA enrolled in our study (Group I), 52 (52%) had a normal liver function (Group IA) and 48 (48%) had hepatic impairment (Group IB). In Group IA, ALT, AST, LDH, ALP, PT, and INR values were significantly higher in babies in all stages of HIE than those of controls, but the findings were not statistically significant. In Group IB, the above-mentioned parameters were significantly higher than those of controls in babies in HIE stages I, II, and III, which was statistically highly significant. However, observed ALT, AST, and LDH levels were statistically significant in HIE stage III when compared with those of HIE stage 0 and HIE stage I. LDH was the only enzyme that was significantly higher in newborns with HIE on the third day of life, and the deviation observed between HIE stage 0 and stage III ($P < .05$), and HIE stage I and stage III ($P < .02$) was statistically significant, while the difference between other HIE stages was statistically insignificant.

Babies with hepatic injury were comparable to those without hepatic injury in various clinical characteristics except more prevalence and higher grades of HIE were reported more frequently in babies with hepatic injury. Also, the unfavorable outcome was more frequent in babies with hepatic injury compared to those without hepatic injury (Table 5).

Out of 48 babies with PA and hepatic impairment, 6 (12.5%) died (5 were having HIE grade III and 1 had HIE grade II) and 3 (6.2%) had a persistent abnormal liver function on the 10th day, later this was normalized during a period of follow-up. However, among 52 babies with PA and without hepatic impairment, 2 (3.8%) died (they were HIE grade III) and 1 (1.9%) discharged against medical advice.

As regards hepatic ultrasonography done on babies with PA, we found 10 cases with hepatic abnormalities in the form of altered echotexture and hypoechogenic irregularities.

## Discussion

The value of Apgar score for detection of prognosis of HIE during the first hour is insufficient, as it can be affected by maternal drugs, trauma, metabolic disorders and/or infectious diseases. Thus, a biochemical parameter that correlates well with stages of HIE is of major interest.[12]

Many markers have been studied to identify PA, including electronic fetal heart rate monitoring, cord pH, electroencephalograms, and Doppler flow studies.[6]

It is known that PA can cause hepatic hypoxic injury (HHI) in newborn infants.[12]

The activity of serum liver enzymes is one of the more specific parameters of liver cell injury both in adults and the pediatric age group.[13,14] Few studies have discussed the pattern of hepatic enzymes in PA.[12]

In our study, we aimed to assess hepatic impairment can be used as a prognostic tool for assessment of the level of HIE during the beginning hours of life.

We found 48% of babies with PA had hepatic impairment. Our finding lies within the range of previous studies of 39% to 85% prevalence of this condition.[6,10,12,15-18] This wide range of observations could be attributed to variations in diagnostic criteria of PA and HHI that was used in different studies. Also, differences in severity of PA, time of estimation of serum transaminase, and cut-off point used for liver enzyme elevation. These observations suggest that HHI is common in babies with PA.

Serum levels of liver enzymes (ALT, AST) increase as a result of hypoxia and damage of liver parenchyma. Increased activities of these liver enzymes are sensitive markers of the impaired liver membrane. In babies with PA and hepatic dysfunction, serum levels of ALT and AST showed a significant rise on the first day after birth, peaked at the third day of life, and then declined sharply on the 10th day of life because of stabilization of the babies and normalization of their liver functions.

This time-trend pattern of changes in these liver enzymes was comparable to previous observations in adults[19] and neonates.[12]

The degree of rising in serum levels of ALT, AST was much lower than that reported in adults with HHI. This could be due to the smaller size or immaturity of infant's liver, or a milder degree of hepatic injury in infants with PA than that observed in adults with HHI which is usually caused by systemic hypotension.

**Table 4.** Liver Function Test on the first day of Life.

| | ALT (U/L) | AST (U/L) | LDH (U/L) | ALP (U/L) | TP (g/dl) | Albumin (g/dl) | TSB (mg/dl) | DSB (mg/dl) | PT (sec) | INR |
|---|---|---|---|---|---|---|---|---|---|---|
| Group I (No=100) | 47.95 ± 29.82 | 95.79 ± 47.35 | 455.27 ± 305.83 | 341.01 ± 98.65 | 5.26 ± 07.3 | 3.02 ± 0.59 | 4.49 ± 1.68 | 1.18 ± 0.66 | 15.58 ± 1.83 | 1.47 ± 0.13 |
| Group II (No=50) | 30.22 ± 14.36 | 66.86 ± 36.40 | 329.40 ± 154.89 | 254.8 ± 96.77 | 5.60 ± 0.36 | 3.20 ± 0.39 | 3.42 ± 1.79 | 1.04 ± 0.46 | 14.32 ± 1.60 | 1.14 ± 0.06 |
| Group IA (No=52) | 31.29 ± 9.28 | 86.16 ± 20.10 | 383.4 ± 216.35 | 286.67 ± 68.70 | 5.52 ± 0.47 | 3.08 ± 0.45 | 4.19 ± 1.66 | 1.14 ± 0.67 | 14.87 ± 1.62 | 1.12 ± 0.05 |
| Group IB (No=48) | 73.18 ± 25.17 | 144.81 ± 28.52 | 551.1 ± 373.85 | 413.43 ± 85.06 | 4.78 ± 0.45 | 2.60 ± 0.37 | 4.85 ± 1.61 | 1.24 ± 0.64 | 17.04 ± 1.54 | 1.22 ± 0.11 |
| P-value | $P < .001$ | $P < .001$ | $P < .001$ | $P < .001$ | $P < .001$ | $P < .05$ | $P < .01$ | $P < .05$ | $P < .001$ | $P < .001$ |

Group IA: Babies with PA and normal hepatic function; Group IB: Babies with PA and impaired hepatic function; Group II: Controls.
Comparison of groups:
IA vs II: No significant difference.
IB vs II: All parameters showed significant difference except TSB and DSB.
IA vs IB.

**Table 5.** Babies with PA, with and Without Hepatic Impairment.

| Feature | PA with hepatic impairment (No = 48) | PA without hepatic impairment (No = 52) | *P*-value |
|---|---|---|---|
| Gestational age | 37.4 ± 0.2 | 37.2 ± 0.3 | P > .05 |
| Sex (Boys/Girls) | 35/13 | 33/19 | P > .05 |
| Birth weight | 3.150 ± 255 | 3.230 ± 215 | P > .05 |
| Apgar score at 5 minute | 4(0-8) | 5 (0-8) | P > .05* |
| HIE grade I/II/III | 6/13/11 | 4/ 3/ 2 | P < .01 |
| Favorable outcome(yes/no)* | /939 | 49/ 3 | P < .05 |

Data are expressed as mean ± SD.
*Data are expressed as median (IQR).
Unfavorable outcome indicates death or discharge against medical advice.

We observed that the rise in serum levels of ALT and AST on the first day of life correlates strongly with the severity of HIE, and the poor degree of correlation was noticed with the severity of asphyxia according to the Apgar score.

Our findings are consistent with other studies.[12,13,16-18,20]

Babies with PA and hepatic impairment had statistically significant higher grades of HIE but did not have an unfavorable outcome than those with PA without hepatic impairment. However, serum levels of liver enzymes had no correlation with the highest grades of HIE. So, we suggest that babies with more severe PA develop HHI, but that their outcome is determined by HIE and not by HHI.

It is known that serum ALT and AST do not correlate with the severity of primary hepatic injury in contrast to cases of acute viral hepatitis.[21] Shah et al,[10] and Tarcan et al.[16] reported contradictory results. Karlsson et al[12] found a significant correlation of HHI with HIE.

Our study showed significantly increased serum ALP in babies with asphyxia and hepatic impairment than other groups but no significant correlation with stages of HIE was found.

In a study conducted by Islam et al.[20] they reported mean ALP similar to our study in PA but showed significant correlation with stages of HIE.

ALP reaches the circulation via leakage from the bile canaliculi into hepatic sinusoids that result from leaky tight junctions. So, the estimation of ALP levels can suggest any kind of liver injury. The rise in levels of LDH in the first few days of life indicates hepatic impairment. LDH levels increased in response to hypoxic-ischemic insult.

Our study showed a significant increase in LDH levels in babies with PA. This was supported by Karlsson et al,[12] Sánchez-Nava et al,[14] Lackmann and Töller,[22] and Reddy et al,[23] who reported higher mean LDH in asphyxiated neonates.

LDH reaches a peak level on the third day of life and then declined to normal values.

There was a significant positive correlation between LDH versus the HIE stage. These findings were supported by Choudhary et al[6] and El-Kabbany et al.[18]

In the present study, total protein and serum albumin showed significantly lower values in babies with PA and that they correlate poorly with the severity of birth asphyxia as assessed by HIE stage and Apgar score.

Similar findings were reported by other studies.[6,20] Hypoproteinemia has a prevalence rate of 23% in our babies with PA.

Choudhary et al[6] reported a prevalence of hypoproteinemia of 20% while Godambe et al[17] reported it in 34% in asphyxiated newborns. It was stated that hypoproteinemia is not an accurate index of the severity of liver damage in birth asphyxia owing to a long life of serum proteins, capillary leakage as a source of protein and hepatic immaturity in preterm babies.[16]

The liver is responsible for the clearing of bilirubin which is a breakdown product of hemoglobin. In the current study, TSB was significantly elevated in babies with PA compared to controls. Similar findings were reported by Islam et al,[20] and Choudhary et al.[6]

It was reported that serum billirubin levels are higher in patients with severe and moderate hypoxemia compared to mild hypoxemia patients.[24,25]

In our babies with PA who were treated by anticonvulsant drugs [n = 22; 22% of cases], there was no increase in serum bilirubin. This was supported by Karlsson et al[12] who reported bilirubin conjugating enzymes induced by anticonvulsant drugs.

The major site of synthesis of blood coagulation factors in the liver. Liver impairment can manifest by abnormalities in the coagulation system. We found Prothrombin time and INR were significantly higher in babies with PA. Other studies reported similar findings.[6,18,26] Another study showed that Prothrombin Index [PI] was reduced in all grades of asphyxia.[17]

The most important factors predicting mortality in our patients were hypoproteinemia, prolonged PT and INR as reported in other studies.[6]

In our study, most infants with moderate and severe HIE received TH as a standard protocol of management. However, we cannot clarify the effects of TH on hepatic biomarkers in this cohort of infants. This was a limitation in our study, that was attributed to a small sample of infants with HIE who have undergone TH and lack of daily monitoring of hepatic biomarkers. Recent studies showed controversial findings on the role of TH on liver biomarkers.[27,28]

The advantages of our study being a prospective one with the inclusion of healthy controls and relatively larger sample size. However, we have some limitations in our study; we include babies from many centers that made the study sample non-homogeneous, failure to measure blood pressure accurately, inability to detect the role of TH on hepatic biomarkers, and inability to detect subtle hepatic injury using liver biopsy(not available invasive and costly) for detection of histopathological changes.

## Conclusion

Elevation of serum liver enzymes is common in babies with PA. Assay of liver enzymes can be used as an easy early diagnostic marker to differentiate between babies with asphyxia and those without asphyxia. Also, liver enzymes can be used for the detection of the severity of PA and thus early intervention can be provided according to results of liver function tests.

## Author Contributions

HHE conceived the study, NFB, NMK, IMT, AEE, YHA, AHA, WEA, HAS, WAA, AMA, and AOI participated in its design and coordination. HHE, NFB, AEE,WAA and NMK, provided key technical guidance.HHE, NFB, NMK, WAA, YHA, HAS, AMA and IMT, drafted the manuscript, and AEE, AHA, WEA, and AOI critically revised the manuscript for important intellectual content.

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