ORIGINAL ARTICLE

The effect of hypoxic ischemic encephalopathy towards multi-organ complications and its early outcome at a Malaysian district hospital

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ABSTRACT

Introduction: Hypoxic ischemic encephalopathy (HIE) is a clinically defined syndrome of disturbed neurologic function in the newborn with evidence of perinatal asphyxia. Stages of HIE are categorised into mild, moderate or severe based on the Sarnat classification. Neurological dysfunction constitutes a part of the wide spectrum of hypoxic ischemic insult as affected infants can have co-existing multi-organ dysfunction which further contributes to morbidities and mortality. This study aims to determine the relationship between the severity of HIE with multi-organ complications and early clinical outcomes.

Materials and Methods: All neonates who were admitted to the NICU at Hospital Sultan Abdul Halim between January 2018 to December 2022, who fulfilled the inclusion criteria were included. Demographic data, clinical course and investigation results were retrospectively obtained from the medical records.

Results: From a total of 90 infants (n = 90) who fulfilled our inclusion criteria, 31 (34%) were mild, 31 (34%) were moderate and 28 (31%) were severe HIE. The mean maternal age was 27 years. Common antenatal issues include diabetes mellitus (37.8%) and anaemia (22.2%). The Apgar scores at 1 and 5 minutes, initial resuscitation requiring intubation, chest compression and adrenaline were associated with higher severity of HIE (p < 0.05). Coagulation dysfunction was the most common complication (79.7%), followed by respiratory dysfunction (33.3%), cardiac dysfunction (28.9%), renal dysfunction (16.1%), haematological dysfunction (15.6%) and hepatic dysfunction (12%). Respiratory and haematological dysfunctions were significantly associated with higher mortality (p < 0.05). There was a significant longer hospital stay (p = 0.023), longer duration of ventilation (p < 0.001) and increase in frequency of seizures (p < 0.001) when comparing moderate and severe HIE patients to mild HIE patients. With increasing severity of HIE, there was also statistically significant higher mortality (p < 0.001).

Conclusions: There is a significant relationship between multiorgan dysfunction, the severity of HIE and mortality. Early anticipation of multi-organ injury is crucial for optimal early management which would reduce the mortality and improve the neurological outcome of the patients.

KEYWORDS:
Hypoxic ischemic encephalopathy, term newborn, multiorgan dysfunction, early outcome, mortality

INTRODUCTION

Neonatal encephalopathy is a clinically defined syndrome of disturbed neurologic function in the earliest days of life in an infant born at or beyond 35 weeks of gestation.[1] The most prominent cause of neonatal encephalopathy is perinatal asphyxia, more appropriately called hypoxic ischemic encephalopathy (HIE). There is no gold standard test for the diagnosis of HIE and it is a diagnosis made based on the clinical evidence and markers of acute hypoxia-ischemia.[2]

The incidence of neonatal encephalopathy in the developed world is estimated at 2 to 6 per 1000 live term births, with HIE occurring in approximately 1.5 per 1000 live term births.[2] It is also very common in Malaysia and the incidence of HIE in Malaysia in 2012 was 2.59 per 1,000 live births.[3]

HIE is classified as mild, moderate or severe based on Sarnat criteria and infants with moderate to severe encephalopathy are more likely to develop the long-term neurologic morbidity.[4] An alternative scoring system for identifying HIE in Malaysia NICUs is the Thompson score. Thompson score is based on features of HIE and it can have a maximum (worst) score of 22.[5] It allows a very precise clinical description of infants by assigning a numeric score rather than 'mild', 'moderate' or 'severe'. Day 1 Thompson score showed statistically significant correlation with morbidity and mortality of HIE babies, p-values 0.024 and 0.001 respectively.[6]

Neurological dysfunction is only part of the spectrum of hypoxic ischemic insult, infants can have co-existing multi-organ dysfunction which further contributes to subsequent morbidities and mortality.[7] The underlying cause of cell damage in each organ is likely to be secondary to a mixture of reperfusion, direct reactive oxidative stress, and cytokine injury.[8]

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There are several studies evaluating organ(s) dysfunction in newborns with HIE. The prevalence of each organ involvement varies in previous literatures, with pulmonary involvement (26 to 86%), cardiac involvement (29 to 78%), renal involvement (15 to 72%), liver involvement (73.7 to 85%) and coagulopathy (41 to 50.9%).[9-12] A study by Michniewicz et al. (N = 57) comparing the incidence of end organ complications between stage II and stage III HIE patients showed that the latter had experienced significantly higher incidence of kidney and liver dysfunction, with thrombocytopaenia.[12] Sweetman et al. created a simple multi-organ dysfunction in neonatal encephalopathy scoring (MODE) system which include the cardiovascular, respiratory, gastrointestinal, haematological and neurological systems and found that neonates with higher MODE scores were significantly more likely to have moderate/severe NE (grade II/III) p-value ($p < 0.001$).[13]

The understanding of the relationship between organ dysfunction and HIE is lacking and there is currently no data available in the Malaysian population. The emergence of new biomarkers such as urinary cystatin C (CysC), kidney injury molecule-1, troponin T and brain natriuretic peptide showed good ability to predict early organ dysfunction involvement in neonatal encephalopathy.14,15 However, these biomarkers are not readily available in a developing country like Malaysia. Therefore, a good understanding of the co-existing and prevalence of organ dysfunction in newborns with HIE in Malaysia is important. The anticipation and early detection of cardiac, respiratory, hepatic, renal, haematological and coagulation dysfunction will assist the acute management and hopefully improve outcomes of these patients.

MATERIALS AND METHODS

We performed a retrospective study of 90 neonatal patients diagnosed with HIE in the neonatal intensive care unit (NICU), Hospital Sultan Abdul Halim between 2018 and 2022. Newborns with presumed HIE who fulfilled our eligibility criteria were included and we retrieved the relevant data from our hospital medical records.

Inclusion Criteria

We included late preterm and term infants born at or beyond 35 weeks of gestation who met all the diagnostic criteria for HIE:

(a) Any three features of encephalopathy within 72 hours of birth, such as abnormal level of consciousness (e.g. hyperalert state, lethargy, stupor or coma), abnormal muscle tone, abnormal deep tendon reflexes, seizure, abnormal Moro reflex, abnormal sucking reflex, abnormal respiratory pattern and oculomotor or pupillary abnormalities.
(b) Three or more findings of acute perinatal events, such as arterial cord pH < 7.00, Apgar score < 5 at 5 minutes of life, evidence of multi-organ system dysfunction within 72 hours of birth, evidence of foetal distress on antepartum monitoring, abnormal electroencephalogram and abnormal imaging of the brain showing ischaemia or oedema within seven days of birth.[16]

We further classify the severity of HIE newborns as mild, moderate or severe according to modified Sarnat's criteria[17,18] and Thompson score.[5] The highest Thompson score obtained for the infant was used as classification. Infants with score 1 to 10 were considered to have mild HIE, 11 to 14 have moderate HIE and 15 to 22 were considered to have severe HIE.[6] If the classification of the severity between the Sarnat staging and Thompson score is different, the more severe one would be chosen to classify the patient.

Exclusion Criteria

Patients with underlying congenital cerebral infections/abnormalities or inborn errors of metabolism that could account for the encephalopathy are excluded.

Criteria for Organ Dysfunction and Outcome

Although multi-organ dysfunction is well described and included in the criteria of HIE there are no standardised consensus definitions of individual organ dysfunction. We defined the criteria for involvement of each organ as follows based on previous literature.

Early outcomes are measured based on length of hospital stay, presence of clinical or subclinical neonatal seizures, in-hospital mortality and presence of MRI abnormalities done in 10 to 14 days of life.

Statistical Analysis

The data was analysed using SPSS version 29. Continuous data is presented as mean/SD or median/IQR while categorical data is presented as frequency/percentage. Categorical data was analysed using Chi-square or Fisher's exact test. The relationship between the three severities of HIE was analysed using one way ANOVA for normally distributed data or Kruskal Wallis test for non-normally distributed data. Post hoc Dunn-Bonferroni test was performed for two groups comparison. Independent T test was used to measure the differences between the survivor and non-survivor groups (normally distributed) or Mann-Whitney test for non-normally distributed data. A value of $p < 0.05$ is considered statistically significant.

RESULTS

A total of 98 newborns were identified with the diagnosis of neonatal encephalopathy. Two patients were excluded in view of prematurity at 33 weeks, five were excluded as they failed to meet the diagnosis criteria for HIE and one was excluded as he was diagnosed with Edward syndrome. The remaining 90 patients were eligible and subjected to this study.

Table II shows the maternal characteristics of the affected newborn. The mothers of the affected babies had a mean age of 27 (8) years, and the majority were of Malay ethnicity (77, 85.6%). 47 (52.2%) of them were primigravida. Diabetes mellitus (34, 37.8%) and anaemia (20, 22.2%) were the two most common maternal illnesses and none of them were affected by eclampsia, chorioamnionitis and placenta praevia. There was no significant difference in maternal age, ethnicity, primigravida, diabetes mellitus, hypertension, eclampsia, anaemia, abruptio placenta and obesity among the mothers of newborns with HIE.

Table I: Criteria for organ dysfunction

Cardiac dysfunction	Measured qualitatively by evaluating the heart haemodynamics and contractility using echocardiography.[19] Hypotension requiring inotropic support beyond 2 hours post birth was also included as having cardiac dysfunction.[10]
Respiratory dysfunction	Needed respiratory support with 40% oxygen for at least the first 4 hours after birth.[9]
Hepatic dysfunction	Liver enzymes aspartate aminotransferase >100 IU/l or alanine aminotransferase > 100 IU/l at any time during the first week after birth.[9]
Renal dysfunction*	Serum creatinine greater than 100 mm/L (1.5 mg/dL).[13] An increased of serum creatinine of at least 17 to 27 mm/L (0.2 to 0.3 mg/dL) per day from a previous lower value.[20]
Haematological dysfunction	Thrombocytopenia (platelet count (PLT) <100,000/mm3.[10] International normalized ratio (INR) >1.5, activated partial thromboplastin time (aPTT) >50 seconds or features of haemorrhagic diathesis.[12]
Multiorgan dysfunction	Involvement of two or more organ dysfunctions (cardiac, respiratory, hepatic, renal, haematological). Central nervous system dysfunction is excluded since it is considered a baseline characteristic for HIE.

*Blood for renal profile must be taken at least after 24 hours of life

Table II: Maternal characteristics of newborns with hypoxic ischaemic encephalopathy (n = 90)

Variable	No. (%)				
	Total (n = 90)	Mild HIE (n = 31)	Moderate HIE (n =31)	Severe HIE (n = 28)	*p*-value
Age*	27 (8)	26 (5)	27 (7)	29.5 (11)	0.667
Ethnicity					0.548
Malay	77 (85.6)	26 (83.9)	29 (93.5)	22 (78.6)	
Chinese	2 (2.2)	1 (3.2)	0 (0)	1 (3.6)	
Indian	6 (6.7)	2 (6.5)	2 (6.5)	2 (7.1)	
Others	5 (5.6)	2 (6.5)	0 (0)	3 (10.7)	
Primigravida	47 (52.2)	21 (67.7)	15 (48.4)	11 (39.3)	0.080
Diabetes mellitus	34 (37.8)	15 (48.4)	9 (29)	10 (35.7)	0.280
Hypertension	2 (2.2)	1 (3.2)	0 (0)	1 (3.6)	0.760
Eclampsia	0 (0)	0 (0)	0 (0)	0 (0)	NA
Chorioamnionitis	0 (0)	0 (0)	0 (0)	0 (0)	NA
Anaemia	20 (22.2)	6 (19.4)	7 (22.6)	7 (25.0)	0.872
Abruptio placentae	1 (1.1)	0 (0)	1 (3.2)	0 (0)	1.000
Placenta previa	0 (0)	0 (0)	0 (0)	0 (0)	NA
Obesity	14 (15.6)	4 (12.9)	5 (16.1)	5 (17.9)	0.935

*Data presented as median (interquartile range).

Table III shows that most babies affected were from the 37 weeks to 40 weeks gestation group (60, 66.7%) and they had a good weight of more than 2.5 kg (80, 88.9%). Statistically, there were no significant differences in terms of birth weight, gestational age, growth status, gender, mode of delivery or being inborn in the different HIE categories. The mean APGAR score at 1 and 5 minutes were 3.6 (2.2) and 5.6 (2.7) respectively. APGAR score was significantly lower as the severity of HIE increased ($p < 0.001$). The mean pH from cord blood gas or blood gas taken in 1 hour of life was 6.99 (SD 0.19). 89 (98.9%) of them required oxygen support at initial resuscitation and severe HIE neonates have significantly higher chance of ETT ventilation ($p = 0.038$), chest compression ($p < 0.001$) and adrenaline requirement ($p < 0.001$). There was also a higher proportion of them in increasing severity of HIE to receive cooling therapy ($p < 0.001$).

Table IV demonstrates that coagulation dysfunction was the most common complication (63, 79.7%), followed by respiratory dysfunction (30, 33.3%), cardiac dysfunction (26, 28.9%), renal dysfunction (14, 16.1%), haematological dysfunction (14, 15.6%) and hepatic dysfunction (9, 12%). Coagulation and haematological dysfunction showed a significant difference among the three groups with p-values of 0.006 and 0.019 respectively. Multi-organ dysfunction affected (41/90) 45.6% of the subjects and it showed significant differences among the three groups ($p = 0.011$). There was a significantly longer hospital stay ($p = 0.023$), longer duration of ventilation ($p < 0.001$) and increased in

Table III: Characteristics of newborns with hypoxic ischaemic encephalopathy (n = 90)

Variable	No. (%)				
	Total (n = 90)	Mild HIE (n = 31)	Moderate HIE (n = 31)	Severe HIE (n = 28)	*p*-value
Birth weight					0.766
≤1500 g	0 (0)	0 (0)	0 (0)	0 (0)	
1501 to 2500 g	10 (11.1)	4 (12.9)	4 (12.9)	2 (7.1)	
≥2501 g	80 (88.9)	27 (87.1)	27 (87.1)	26 (92.9)	
Gestational age					0.053
35 to 36weeks+ 6days	10 (11.1)	1 (3.2)	4 (12.9)	5 (17.9)	
37 to 40 weeks	60 (66.7)	26 (83.9)	16 (51.6)	18 (64.3)	
> 40 weeks	20 (22.2)	4 (12.9)	11 (35.5)	5 (17.9)	
Growth status					0.427
SGA	6 (6.7)	2 (6.5)	1 (3.2)	3 (10.7)	
AGA	81 (90)	29 (93.5)	29 (93.5)	23 (82.1)	
LGA	3 (3.3)	0 (0)	1 (3.2)	2 (7.1)	
Male	58 (64.4)	20 (64.5)	21 (67.7)	17 (60.7)	0.824
Singleton	90 (100)	31 (100)	31 (100)	28 (100)	NA
Mode of delivery					0.394
Vaginal	36 (40)	14 (45.2)	10 (32.3)	12 (42.9)	
Forceps	17 (18.9)	7 (22.6)	5 (16.1)	5 (17.9)	
Vacuum	7 (7.8)	1 (3.2)	4 (12.9)	2 (7.1)	
EMLSCS	28 (31.1)	9 (29.0)	10 (32.3)	9 (32.1)	
ELLSCS	2 (2.2)	0 (0)	2 (6.5)	0 (0)	
APGAR score					
at 1 min*	3.6 ± 2.2	4.4 ± 2.0	4.1 ± 1.9	2.1 ± 1.9	<0.001
at 5 min*†	5.6 ± 2.7	7.0 ± 2.5	6.4 ± 2.0	3.1 ± 2.0	<0.001
Blood gas pH*	6.99 ± 0.19	6.99 ± 0.18	7.03 ± 0.20	6.96 ± 0.18	0.313
Resuscitation at birth					
Oxygen	89 (98.9)	31 (100)	30 (96.8)	28 (100)	1.000
Bag-and-mask ventilation	85 (94.4)	28 (90.3)	29 (93.5)	28 (100)	0.365
Chest compression	27 (30)	5 (16.1)	4 (12.9)	18 (64.3)	<0.001
ETT ventilation	79 (87.8)	25 (80.6)	26 (83.9)	28 (100)	0.038
Adrenaline	19 (21.1)	3 (9.7)	3 (9.7)	13 (46.4)	<0.001
Inborn	76 (84.4)	30 (96.8)	24 (77.4)	22 (78.6)	0.051
Cooling therapy	68 (75.6)	12 (38.7)	28 (90.3)	28 (100)	<0.001

*Data presented as mean ± standard deviation. †n=76, after excluding missing data.
SGA: small for gestational age; AGA: appropriate for gestational age; LGA: large for gestational age; EMLSCS: emergency lower segment Caesarean section; ELLSCS: elective lower segment Caesarean section; ETT: endotracheal tube.

frequency of seizures ($p < 0.001$) when comparing moderate and severe HIE patients to mild HIE patients. However, post hoc analysis showed no statistically significant difference between moderate and severe HIE groups. With increasing severity of HIE, there was also statistically significance higher mortality ($p < 0.001$). 53 of the subjects underwent MRI at day 10 to 14 of life and 36/53 (67.9%) had evidence of HIE on the scan; however, no difference was found in the occurrence between the three groups.

Table V shows comparison of factors affecting survivors and non-survivors. Respiratory and haematological dysfunctions were significantly higher among non-survivor groups with the p-value of 0.018 and 0.019 respectively. All the non-survivors had multi-organ dysfunction and this was significantly higher ($p < 0.001$) compared to the survivors group. Lower APGAR scores at 1 and 5 minutes were observed among non-survivor group as well ($p < 0.001$). There were no statistically significant differences in seizure occurrence, cooling therapy requirement and being outborn among the two groups.

DISCUSSION

Antenatal, intrapartum and initial resuscitation affects the severity and outcome of newborns with HIE. Our study revealed diabetes mellitus, anaemia and obesity are the most common antenatal problems, and this finding is similar to our country's national data reported in 2012.[3] Gestational diabetes mellitus is common, with the recent meta-analysis in 2021 showing a prevalence of 21.5% among Malaysian women. Maternal hyperglycaemia significantly increases the risks of low Apgar scores and asphyxia-related neonatal complications in the infants.[21,22] A standardised screening for gestational diabetes mellitus and proper antenatal follow up are crucial to reduce the risk of HIE. Our current study did not reveal any maternal factor that significantly affected the severity of HIE. However, intrapartum factors including low APGAR, extensive initial resuscitation requiring intubation, CPR or adrenaline highly correlate with the severity of HIE; this is similar to observations in another study.[3]

In addition to CNS involvement, 81% of the subjects have at least 1 other organ involvement. Coagulation dysfunction was the most common complication (79.7%) and showed statistically significant differences among the different

Table IV: Clinical problems, organ(s) dysfunction and outcome of newborns with hypoxic ischaemic encephalopathy (n = 90)

Variable	No. (%)				
	Total (n = 90)	Mild HIE (n = 31)	Moderate HIE (n =31)	Severe HIE (n = 28)	*p*-value
Cardiac dysfunction	26 (28.9)	5 (16.1)	12 (38.7)	9 (32.1)	0.132
Respiratory dysfunction	30 (33.3)	7 (22.6)	12 (38.7)	11 (39.3)	0.292
Hepatic dysfunction*	9 (12)	3 (16.7)	3 (10.0)	3 (11.1)	0.816
Renal dysfunction†	14 (16.1)	2 (6.9)	5 (16.1)	7 (25.9)	0.163
Haematological dysfunction	14 (15.6)	2 (6.5)	3 (9.7)	9 (32.1)	0.019
Coagulopathy#	63 (79.7)	13 (59.1)	24 (80)	26 (96.3)	0.006
Multi-organ dysfunction	41 (45.6)	8 (25.8)	15 (48.4)	18 (64.3)	0.011
Number of organ(s) dysfunction≠	1 (2)	1 (2)	1 (2)	2 (2)	<0.001
Highest oxygen support					0.171
Nasal prong oxygen	1 (1.1)	1 (3.2)	0 (0)	0 (0)	
Non-invasive ventilation	3 (3.3)	3 (9.7)	0 (0)	0 (0)	
Conventional ventilation	80 (88.9)	24 (77.4)	30 (96.8)	26 (92.9)	
HFOV	6 (6.7)	3 (9.7)	1 (3.2)	2 (7.1)	
Length of hospital stay (day)≠	11 (10)	7 (9)	13 (13)	12 (13)	0.023
Ventilation duration (day)≠	4 (4)	1 (2)	4 (3)	5 (3)	<0.001
Seizures (clinical/subclinical)	36 (40)	4 (12.9)	16 (51.6)	16 (57.1)	<0.001
Positive MRI findings of HIEμ	36 (67.9)	6 (50)	20 (74.1)	10 (71.4)	0.343
Alive	78 (86.7)	31 (100)	30 (96.8)	17 (60.7)	<0.001

*n=75, after excluding missing data ; †n=87, after excluding missing data ; #n=79, after excluding missing data ;μ=53, after excluding missing data ; ≠Data presented as median (interquartile range). HFOV: high frequency oscillation ventilation ;MRI: magnetic resonance imaging.

Table V: Comparison of survivors and non-survivors of hypoxic ischaemic encephalopathy (n = 90)

Variable	No. (%)			
	Total (n = 90)	Survivor (n = 78)	Non-survivor (n = 12)	*p*-value
Cardiac dysfunction	26 (28.9)	20 (25.6)	6 (50)	0.097
Respiratory dysfunction	30 (33.3)	22 (28.2)	8 (66.7)	0.018
Hepatic dysfunction*	9 (12.0)	7 (10.9)	2 (18.2)	0.612
Renal dysfunction†	14 (16.1)	10 (13.2)	4 (36.4)	0.072
Haematological dysfunction	14 (15.6)	9 (11.5)	5 (41.7)	0.019
Coagulopathy#	63 (79.7)	51 (76.1)	12 (100)	0.112
Multi-organ dysfunction	41 (45.6)	29 (37.2)	12 (100)	<0.001
Number of organ(s) dysfunction≠	1 (2)	1 (1)	3 (1)	<0.001
Seizure	36 (40)	29 (37.2)	7 (58.3)	0.210
Cooling therapy				0.384
Completed active cooling	40 (44.4)	36 (46.2)	4 (33.3)	
Completed passive cooling	16 (17.8)	12 (15.4)	4 (33.3)	
No cooling/incomplete cooling	34 (37.8)	30 (38.5)	4 (33.3)	
APGAR score at 1 min≠	3 (3)	4 (2)	0.5 (2)	<0.001
APGAR score at 5 min≠&	6 (3)	6 (3)	2 (3)	<0.001
Outborn	14 (15.6)	10 (12.8)	4 (33.3)	0.088

*n = 75, after excluding missing data; †n = 87, after excluding missing data; #n = 79, after excluding missing data; and n = 76, after excluding missing data; ≠Data presented as median (interquartile range)

severities of HIE (p = 0.006), this result is comparable to a study by Michniewicz et al, which also showed highest incidence of coagulation dysfunction in their subjects.[12] Haematological dysfunction and thrombocytopenia, which are closely related to coagulopathy, also showed significant differences between different stages of HIE and between survivors and non-survivor groups (p = 0.019). The disturbance in haemostasis is due to various factors after birth asphyxia. Oxygen deprivation to the liver and bone marrow may suppress the coagulation factors and platelet production while disseminated intravascular coagulopathy may follow a severe asphyxial event.[23] In addition, hypothermia therapy, which was initiated in 75.6% of newborns in this current study may impair haemostasis by slowing enzymatic function of the coagulation cascade, impairing thrombin generation and further triggering DIC.[24]

Respiratory and cardiac dysfunctions were the next commonest complications following coagulopathy with involvement of 33.3% and 28.9% of the newborns. This was similar to other studies with reported incidences of between 20 to 30%.[11,12] 87.8% of the newborns in this study required intubation at birth but most of them were ventilated with low ventilation setting. However, some of them developed respiratory failure and this may be directly related to hypoxia induced persistent pulmonary hypertension (PPHN) or be indirectly associated with meconium aspiration syndrome or perinatal sepsis/pneumonia.[25]

Cardiovascular dysfunctions include myocardial damage, right ventricular (RV) dysfunction and altered transitional circulation, all of which will further lead to greater risk of adverse cerebral injury.[26] Giesinger et al,[27] suggested that a

complete haemodynamically assessment (including clinical evidence, biochemical evaluation and echocardiography) should not only be performed early in all infants with HIE treated with a cardiovascular agent, but also in infants with moderate to severe HIE before or at 24 hours after initiation of therapeutic hypothermia (TH) to identify myocardial dysfunction that may not be clinically apparent. Our incidence might underestimate the actual incidence as many of our subjects involved did not have a biochemical evaluation or echocardiography done in view of lack of resources and expertise.

Renal dysfunction affected 16.1% of HIE newborns in this study. This is lower compared to other studies, which varied from 22 to 70%.[28] This study also did not show significant differences of renal involvement in different stages of HIE. Urine output and serum creatinine were used to identify patients with renal injury in our study. However, creatinine is not an ideal biomarker of neonatal AKI as it peaks late (often lags 48 to 72 hours behind the onset of injury) and may reflect maternal creatinine level.[29] Cystatin C and Neutrophil gelatinase-associated lipocalin (NGAL) are better biomarkers to reflect renal injury but are not readily available in our center.[14,30]

Hepatic dysfunction is the least affected organ, with only 9/75 (12%) of newborns affected and it showed no significant differences among the different HIE severity. This is in contrast with previous studies which showed the incidence to be high at 80 to 85%.[9,10] This could be due to improvement in HIE management in terms of hypothermia therapy as both previous studies were done prior to the hypothermia era. The pathogenesis of liver injury is related to the hypoxic ischemic insult causing formation of blebs and ruptures of plasma membrane in the liver resulting in the release of intracellular enzymes (AST, ALT, ALP).[31]

This study also showed statistically significant relationship between the number of organ dysfunction, severity of HIE and infant death, which were also demonstrated in other studies.[11,23] With increasing severity of HIE, there was also statistically significant higher mortality. Moderate and severe HIE babies also had significantly longer hospital stay, longer duration of ventilation and higher rate of seizure activity when compared to mild HIE babies. However, there were no differences between moderate and severe HIE babies. This may be in part due to shorter durations of ventilation in severe HIE infants because of higher mortality.

MRI brain abnormality did not show a significant difference among the groups as there was much missing data, especially from the mild and severe HIE groups. We did not proceed with the MRI brain in some mild HIE babies due to cost limitations; whereas for the severe HIE babies, 11 babies passed away prior to the MRI brain, which was usually done at second week of life for better prognostication value.[32]

Several limitations were identified in this study. Our scales and criteria for organ dysfunction were selected based on previous studies and there were no standardized criteria for them. This may explain the inconsistent findings of the incidences in organ dysfunction among the studies. This was an observational study among HIE cohorts without having a normal control. The strength of this study was the use of readily available biomarkers and clinical criteria that could be applied to most hospitals with limited resources.

CONCLUSION

In conclusion, this study shows the relationship of multiorgan dysfunction with hypoxic ischemic encephalopathy (HIE) severity and outcome. Early anticipation of multi-organ injury is crucial for optimal early management which will reduce the mortality and improve the neurological outcome of the patients. In the absence of multiorgan dysfunction, the origin of neonatal encephalopathy should be carefully investigated as perinatal asphyxia might not be the underlying aetiology.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICAL APPROVAL

The study had been registered under National Medical Research Register (NMRR) and ethical approval by the Medical Research and Ethics Committee (MREC). Research ID: RSCH ID-23-02012-TYG.

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