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The burden of hypoxic-ischaemic encephalopathy in Malaysian neonatal intensive care units

Nem-Yun Boo[1], MBBS, FRCPCH, *Irene Guat-Sim Cheah*[2], MBBS, FRCPCH

INTRODUCTION This study aimed to determine the incidence of hypoxic-ischaemic encephalopathy (HIE) and predictors of HIE mortality in Malaysian neonatal intensive care units (NICUs).

METHODS This was a retrospective study of data from 37 NICUs in the Malaysian National Neonatal Registry in 2012. All newborns with gestational age ≥ 36 weeks, without major congenital malformations and fulfilling the criteria of HIE were included.

RESULTS There were 285,454 live births in these hospitals. HIE was reported in 919 newborns and 768 of them were inborn, with a HIE incidence of 2.59 per 1,000 live births/hospital (95% confidence interval [CI] 2.03, 3.14). A total of 144 (15.7%) affected newborns died. Logistic regression analysis showed that the significant predictors of death were: chest compression at birth (adjusted odds ratio [OR] 2.27, 95% CI 1.27, 4.05; p = 0.003), being outborn (adjusted OR 2.65, 95% CI 1.36, 5.13; p = 0.004), meconium aspiration syndrome (MAS) (adjusted OR 2.16, 95% CI 1.05, 4.47; p = 0.038), persistent pulmonary hypertension of the newborn (PPHN) (adjusted OR 4.39, 95% CI 1.85, 10.43; p = 0.001), sepsis (adjusted OR 4.46, 95% CI 1.38, 14.40; p = 0.013), pneumothorax (adjusted OR 4.77, 95% CI 1.76, 12.95; p = 0.002) and severe HIE (adjusted OR 42.41, 95% CI 18.55, 96.96; p < 0.0001).

CONCLUSION The incidence of HIE in Malaysian NICUs was similar to that reported in developed countries. Affected newborns with severe grade of HIE, chest compression at birth, MAS, PPHN, sepsis or pneumothorax, and those who were outborn were more likely to die before discharge.

Keywords: hypoxic-ischaemic encephalopathy, predictors of early mortality, term newborns

INTRODUCTION

Hypoxic-ischaemic encephalopathy (HIE) is a serious condition that affects newborns. The incidence of HIE in developed countries was reported to range from 0.97 to 2.5 per 1,000 live births in the 1990s.[1-4] Randomised controlled studies showed that early cooling therapy improved neurodevelopmental outcomes of newborns with HIE.[5] To the best of our knowledge, the incidence, clinical characteristics and predictors of early outcome of HIE patients in Malaysia have not previously been reported. To address this gap in knowledge and assist Malaysian neonatologists in planning strategies to improve outcomes for this group of newborns, the Malaysian National Neonatal Registry (MNNR), which had a membership of 37 member neonatal intensive care units (NICUs) in 2012, included in its database all newborns diagnosed with HIE and admitted to their NICUs. We herein present the incidence, clinical characteristics and predictors of early outcome of newborns diagnosed to have HIE.

METHODS

This was a retrospective study using data collected prospectively from the MNNR of newborns delivered in the year 2012. We included all newborns who had a gestational age ≥ 36 completed weeks, were diagnosed with HIE and were admitted to NICUs in the member hospitals. Preterm newborns with gestational age < 36 completed weeks, and term newborns with major congenital malformations or inborn errors of metabolism were excluded.

HIE was diagnosed if all of the following three criteria were met: (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 five minutes of life, evidence of multi-organ system dysfunction within 72 hours of birth, evidence of fetal distress on antepartum monitoring, abnormal electroencephalogram, and abnormal imaging of the brain showing ischaemia or oedema within seven days of birth; and (c) the absence of any underlying congenital cerebral infections/abnormalities or inborn errors of metabolism that could account for the encephalopathy.[6] The severity of HIE was graded as: mild when the newborn was alert or hyperalert with either normal or exaggerated response to arousal; moderate when the newborn was lethargic with diminished response to arousal manoeuvres; and severe when the newborn was in a deep stupor or coma at birth and not arousable in response to appropriate manoeuvres.

Newborns were categorised as appropriate for gestational age, small for gestational age and large for gestational age when their birth weights were in the 10th–90th percentile, < 10th percentile

[1]Department of Population Medicine, Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Selangor, [2]Department of Paediatrics, Paediatric Institute, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Correspondence: Dr Nem-Yun Boo, Senior Professor, Department of Population Medicine, Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Jalan Sungai Long, Bandar Sungai Long, 43000 Kajang, Selangor, Malaysia. boony@utar.edu.my

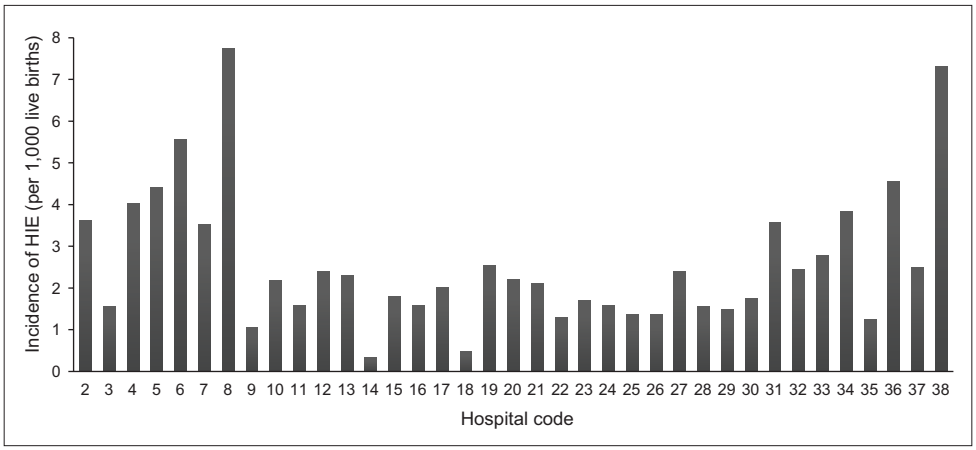

Fig. 1 Graph shows the incidence of hypoxic-ischaemic encephalopathy (HIE) in 37 Malaysian hospitals in 2012.

and > 90th percentile for their gestational age, respectively.[7] Meconium aspiration syndrome (MAS) was diagnosed when the following five criteria were met: (a) meconium-stained amniotic fluid at birth; (b) onset of respiratory distress within one hour of birth; (c) partial pressure of oxygen in arterial blood (PaO_2) < 50 mmHg, central cyanosis on room air or requiring supplemental oxygen to maintain PaO_2 > 50 mmHg; (d) an abnormal chest radiograph showing either coarse irregular or nodular pulmonary densities, areas of diminished aeration or consolidation alternating with areas of hyperinflation, or generalised hyperinflation; and (e) absence of culture-proven, early-onset bacterial sepsis or pneumonia. Pneumothorax was diagnosed based on radiological evidence. Sepsis was diagnosed given the presence of clinical signs and positive culture in the blood or cerebral spinal fluid.

The live birth census from each member hospital, organised according to mode of delivery, gestation and birth weight categories, was submitted to the MNNR at the end of each calendar month. At the end of the study, an online survey was conducted to identify the hospitals that had facilities for cooling therapy and cerebral function monitoring (CFM) during the study period and those that did not. The number of newborns with HIE and their outcomes in these two groups of hospitals were compared.

The incidence of HIE at each hospital was calculated by dividing the number of inborn newborns with HIE by the total number of live births at the respective hospital in 2012 and multiplying by 1,000. Descriptive statistics were reported as percentage for categorical variables, mean ± standard deviation for continuous variables with normal distribution and median (lower quartile, upper quartile) for skewed distributions. Chi-square test (or Fisher's exact test for expected sample size < 5) was used for analysis of categorical variables, Student's *t*-test for continuous variables between groups, one-way analysis of variance for continuous variables with normal distribution for multiple groups and Kruskal-Wallis test for skewed distributions. Linear regression analysis was used to identify multicollinearity among potential predictors that were subsequently excluded from multivariate analysis. Logistic regression analysis was carried out to determine significant predictors associated with mortality of HIE newborns at discharge. The following independent variables used were identified based on the results of univariate analysis of survivors and non-survivors with p-values < 0.001, and after excluding variables with multicollinearity: abruptio placentae, mode of delivery, gestational age, chest compression at birth, admission temperature, outborn status, severity of HIE, MAS, persistent pulmonary hypertension of the newborn (PPHN), sepsis, conventional ventilation and pneumothorax. A p-value < 0.05 was considered statistically significant.

RESULTS

HIE was reported in a total of 919 newborns, 768 (83.6%) of whom were inborn. There were 285,454 live births at the participating hospitals. The mean incidence of HIE was 2.59 per 1,000 live births/hospital (95% confidence interval [CI] 2.03, 3.14) (Fig. 1). Table I shows the incidence of HIE according to ethnicity, mode of delivery, gestational age and birth weight. HIE was most common in foreigners (with Sabah natives having the highest incidence among Malaysians), newborns delivered by forceps, and term newborns with higher birth weight and lower gestational age. The incidence of HIE was lowest in newborns delivered by elective lower segment Caesarean section (LSCS). Of the 919 newborns with HIE, 307 (33.4%), 423 (46.0%) and 189 (20.6%) had mild, moderate and severe HIE, respectively (Table II).

The mothers of the affected newborns had a mean age of 27.7 years (Table II). Anaemia and diabetes mellitus were the most common maternal illnesses. There was no significant difference in maternal age, ethnicity, anaemia, hypertension, eclampsia, chorioamnionitis, placenta previa, cord prolapse and use of intrapartum antibiotics among the mothers of newborns of different HIE grades. However, mothers of newborns with severe HIE had significantly higher gravid and parity status, and higher rates of abruptio placentae than those with moderate HIE.

Table III shows the neonatal characteristics of the newborns with HIE. About one-third of all newborns with HIE were born via LSCS and more than 95% of these births occurred in emergency situations. The median Apgar score was less than 6. More than 80% of them received oxygen therapy, bag-and-mask ventilation and/or endotracheal ventilation at birth. A significantly higher proportion of newborns with severe HIE were delivered by LSCS compared to those with moderate HIE (p = 0.024). Apgar scores

Table I. Incidence of hypoxic-ischaemic encephalopathy (HIE) among newborns in the 2012 Malaysian National Neonatal Registry.

Variable	No.		
	Total live births (n = 285,454)	Inborn newborns with HIE (n = 768)	Incidence of HIE*
Ethnicity†			
Malay	188,578	477	2.53
Chinese	22,927	39	1.70
Indian	14,294	33	2.31
Aboriginal	2,388	1	0.42
Sabah native	15,624	50	3.20
Sarawak native	14,915	27	1.81
Foreigner	22,646	133	5.87
Other Malaysian	4,080	8	1.96
Mode of delivery			
SVD	201,620	316	1.57
Breech	1,311	15	11.44
Forceps	1,189	23	19.34
Vacuum extraction	10,226	166	16.23
LSCS			
Emergency	17,438	240	13.76
Elective	53,670	8	0.15
Gestational age‡ (wk)			
36	12,768	39	3.05
37–40	216,494	690	3.19
> 40	39,245	39	0.99
Birth weight§ (g)			
1,501–2,000	7,954	12¶	1.51
2,001–2,500	32,314	82	2.54
> 2,500	240,676	674	2.80

*No. of inborn newborns with HIE per 1,000 live births. †Ethnicity of 2 newborns not reported. ‡16,947 live births not included, as they were of gestational age < 36 weeks. §4,510 newborns were of birth weight < 1,501 g. ¶One of these newborn weighed 1,408 g. LSCS: lower segment Caesarean section; SVD: spontaneous vertex delivery

at one minute and five minutes were significantly lower as the severity of HIE increased. Higher proportions of newborns with severe HIE received chest compressions when compared to newborns with moderate ($p < 0.001$) and mild HIE ($p < 0.001$). More newborns with severe ($p < 0.001$) and moderate HIE ($p < 0.0001$) needed endotracheal tube ventilation at birth when compared to those with mild HIE. More newborns with severe HIE ($p < 0.001$) received adrenaline at birth than those with mild and moderate HIE.

Seizures and MAS were common among all affected newborns. More than 90% of all newborns required respiratory support and the total mortality (15.7%) was high (Table IV). When compared to newborns with mild and moderate HIE, those with severe HIE had significantly lower admission temperatures; significantly higher rates of seizures, PPHN, sepsis and respiratory support; significantly longer duration on all types of ventilation, including conventional ventilation; significantly higher mortality; and longer hospital stays among survivors ($p < 0.01$).

Table V shows a comparison of intrapartum, perinatal and neonatal factors between non-survivors and survivors of HIE. Univariate analysis showed that non-survivors had significantly higher proportions of abruptio placentae and LSCS; lower Apgar scores; lower admission temperatures; higher proportions of outborns, MAS, PPHN, respiratory support, pneumothorax, sepsis and severe HIE; and received more resuscitation at birth with oxygen, chest compression and adrenaline.

After excluding variables with multicollinearity (i.e. Apgar scores at one and five minutes, adrenaline at birth and high-frequency ventilation), logistic regression analysis showed that the only significant predictors of mortality before discharge were: chest compression at birth (adjusted odds ratio [OR] 2.27, 95% CI 1.27, 4.05; $p = 0.003$), outborn (adjusted OR 2.65, 95% CI 1.36, 5.13; $p = 0.004$), MAS (adjusted OR 2.16, 95% CI 1.05, 4.47; $p = 0.038$), PPHN (adjusted OR 4.39, 95% CI 1.85, 10.43; $p = 0.001$), sepsis (adjusted OR 4.46, 95% CI 1.38, 14.40; $p = 0.013$), pneumothorax (adjusted OR 4.77, 95% CI 1.76, 12.95; $p = 0.002$) and severe HIE (adjusted OR 42.41, 95% CI 18.55, 96.96; $p < 0.0001$). The Nagelkerke R^2 value of the model was 0.582.

During the study period, only seven of the NICUs were each equipped with one set of facilities for cooling therapy. Although these NICUs had a higher number of newborns with HIE (median 26.0, IQR 11.0–50.0) than centres without cooling facilities (median 15.5, IQR 13.0–22.3), this difference was not statistically significant ($p = 0.26$). Furthermore, although the mortality rates of these NICUs were lower (median 14.3%, IQR 8.3%–21.4%) than those of NICUs without cooling facilities (median 20.0%, IQR 11.0%–29.9%), this difference was also not statistically significant ($p = 0.24$).

DISCUSSION

The MNNR was set up in 2004 with the aim of improving the standard of neonatal care in Malaysian NICUs. Participation in the registry was voluntary. During the early years of the MNNR, the inclusion criteria for newborns were: very low birth weight (< 1,500 g) or preterm with gestational age > 32 weeks; the presence of major congenital malformations; and requiring respiratory support. In 2012, all newborns diagnosed to have HIE were included in the database to aid in determining the extent of the morbidity and mortality of this condition in Malaysia. The findings in this study were representative of the majority of Malaysian NICUs in 2012, as 37 out of 40 NICUs in Malaysian public hospitals participated. Furthermore, the majority of the NICUs in Malaysian private hospitals had very small NICUs and were known to have transferred their seriously ill neonates to these public hospitals.

Although the incidence of HIE varied widely among these 37 Malaysian hospitals, the mean incidence of HIE per hospital (2.59 per 1,000 live births) was higher than the population-based incidence reported in the United Kingdom (1.94 per 1,000 live births),[1] Western Australia (0.97 per 1,000 live births),[2] and Sweden (1.75 per 1,000 live births).[3] However, when compared with the hospital-based or region-based incidence reported in

Table II. Maternal characteristics of newborns with hypoxic-ischaemic encephalopathy (HIE) in the 2012 Malaysian National Neonatal Registry.

Variable	No. (%)			
	Total (n = 919)	Mild HIE (n = 307)	Moderate HIE (n = 423)	Severe HIE (n = 189)
Age* (yr)	27.7 ± 5.8	27.7 ± 5.6	27.7 ± 5.8	27.7 ± 6.0
Ethnicity				
Malay	575 (62.6)	193 (62.9)	277 (65.5)	105 (55.6)
Chinese	47 (5.1)	14 (4.6)	21 (5.0)	12 (6.3)
Indian	40 (4.4)	14 (4.6)	13 (3.1)	13 (6.9)
Aboriginal	4 (0.4)	0	2 (0.5)	2 (1.1)
Sabah native	60 (6.5)	27 (8.8)	18 (4.3)	15 (7.9)
Sarawak native	35 (3.8)	8 (2.6)	18 (4.3)	9 (4.8)
Foreigner	150 (16.3)	47 (15.3)	71 (16.8)	32 (16.9)
Other Malaysian	8 (0.9)	4 (1.3)	3 (0.7)	1 (0.5)
Gravida†	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 3)‡
Parity†	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 2)§
Diabetes mellitus	130/884 (14.7)	56/300 (18.7)	46/409 (11.2)‡	28/175 (16.0)
Anaemia	181/887 (20.4)	70/301 (23.3)	72/409 (17.6)	39/177 (22.0)
Hypertension	74/889 (8.3)	27/302 (8.9)	30/411 (7.3)	17/176 (9.7)
Eclampsia	18/897 (2.0)	9/303 (3.0)	7/415 (1.7)	2/179 (1.1)
Chorioamnionitis	11/895 (1.2)	3/303 (1.0)	5/414 (1.2)	3/178 (1.7)
Abruptio placentae	24/918 (2.6)	8 (2.6)	5 (1.2)	11/188 (5.9)‖
Placenta previa	3/917 (0.3)	3/306 (1.0)	0	0/188
Cord prolapse	27/918 (2.9)	11 (3.6)	9 (2.1)	7/188 (3.7)
Intrapartum antibiotics	80/901 (8.9)	25/302 (8.3)	40/414 (9.7)	15/185 (8.1)

Value of n is provided for variables with missing data. *Data presented as mean ± standard deviation. †Data presented as median (lower quartile, upper quartile). ‡moderate vs. severe HIE: p = 0.031. §severe vs. moderate HIE: p = 0.009. moderate vs. mild HIE: p = 0.027. ‖severe vs. moderate HIE: p = 0.0048.

Table III. Characteristics of newborns with hypoxic-ischaemic encephalopathy (HIE) in the 2012 Malaysian National Neonatal Registry.

Variable	No. (%)				p-value*
	Total (n = 919)	Mild HIE (n = 307)	Moderate HIE (n = 423)	Severe HIE (n = 189)	
Birth weight† (g)	3,065 ± 486	3,051 ± 481	3,084 ± 497	3,048 ± 470	0.582
Gestational age† (wk)	38.8 ± 1.3	38.8 ± 1.3	38.9 ± 1.2	38.7 ± 1.3	0.086
Growth status					0.596
AGA	751 (81.7)	259 (84.4)	338 (79.9)	154 (81.5)	
LGA	34 (3.7)	11 (3.6)	17 (4.0)	6 (3.2)	
SGA	134 (14.6)	37 (12.1)	68 (16.1)	29 (15.3)	
Male	592 (64.4)	198 (64.5)	289 (68.3)	105 (55.6)	0.010‡
Singleton	904 (98.4)	300 (97.7)	418 (98.8)	186 (98.4)	0.512
Mode of delivery					< 0.0001‡
Vaginal	430 (46.8)	118 (38.4)	234 (55.3)	78 (41.3)	
Instrumental	202 (22.0)	85 (27.7)	93 (22.0)	24 (12.7)	
All LSCS	287 (31.2)	104 (33.9)	96 (22.7)	87 (46.0)	
Emergency	275 (95.8)	97 (93.3)	94 (97.9)	84 (96.6)	0.239
Apgar score†					
At 1 min	3.5 ± 2.2 (n = 895)	4.1 ± 2.1 (n = 300)	3.5 ± 1.9 (n = 414)	2.4 ± 2.3 (n = 181)	< 0.0001‡
At 5 min	5.4 ± 2.4 (n = 856)	6.3 ± 2.2 (n = 292)	5.5 ± 2.0 (n = 396)	3.6 ± 2.8 (n = 168)	< 0.0001‡
Resuscitation at birth					
Oxygen	852/890 (95.7)	282/300 (94.0)	394/404 (97.5)	176/186 (94.6)	0.051
Bag-and-mask ventilation	799/890 (89.8)	260/300 (86.7)	369/404 (91.3)	170/186 (91.4)	0.092
Chest compression	171/888 (19.3)	30/300 (10.0)	59/404 (14.6)	82/184 (44.6)	< 0.0001‡
ETT ventilation	748/890 (84.0)	224/300 (74.7)	354/404 (87.6)	170/186 (91.4)	< 0.0001‡
Adrenaline	105/887 (11.8)	13/300 (4.3)	23/403 (5.7)	69/184 (37.5)	< 0.0001‡
Outborn	151 (16.4)	35 (11.4)	78 (18.4)	38 (20.1)	0.013‡

Value of n is provided for variables with missing data. *Comparison among newborns with mild, moderate and severe HIE. †Data presented as mean ± standard deviation. ‡p-value is statistically significant. AGA: appropriate for gestational age; ETT: endotracheal tube; LGA: large for gestational age; LSCS: lower segment Caesarean section; SGA: small for gestational age

Table IV. Clinical problems and outcomes of newborns with hypoxic-ischaemic encephalopathy (HIE) in the 2012 Malaysian National Neonatal Registry.

Variable	No. (%)				p-value*
	Total (n = 919)	Mild HIE (n = 307)	Moderate HIE (n = 423)	Severe HIE (n = 189)	
Admission temperature† (°C)	36.2 (35.6, 36.6)	36.5 (36.0, 36.6)	36.2 (35.6, 36.7)	36.0 (35.0, 36.5)	< 0.0001§
Seizures	487 (53.0)	52 (16.9)	317 (74.9)	118 (62.4)	< 0.0001§
MAS	167 (18.2)	52 (16.9)	84 (19.9)	31 (16.4)	0.467
PPHN	71/914 (7.8)	11/305 (3.6)	39/422 (9.2)	21/187 (11.2)	0.003§
Sepsis	29 (3.2)	5 (1.6)	12 (2.8)	12 (6.3)	0.012§
Early onset	13 (44.8)	2 (40.0)	8 (66.7)	3 (25.0)	0.118
Late onset	16 (55.2)	3 (60.0)	4 (33.3)	9 (75.0)	
Respiratory support‡	858 (93.4)	262 (85.3)	410 (96.9)	186 (98.4)	< 0.0001§
CPAP	245 (28.6)	90 (34.4)	115 (28.0)	40 (21.5)	0.012§
Conventional ventilation	777 (90.6)	212 (80.9)	387 (94.4)	178 (95.7)	< 0.0001§
HFV	59 (6.9)	11 (4.2)	25 (6.1)	23 (12.4)	0.002§
iNO therapy	20 (2.3)	5 (1.9)	9 (2.2)	6 (3.2)	0.640
Duration on ventilation† (day)					
All types	2 (1, 5) (n = 897)	1 (0, 2) (n = 291)	3 (2, 5) (n = 419)	4 (1, 7) (n = 187)	< 0.0001§
Conventional	3 (1, 5)	1 (1, 3)	3 (2, 5)	4 (2, 7)	< 0.0001§
Pneumothorax	45 (4.9)	13 (4.2)	22 (5.2)	10 (5.3)	0.804
Died	144 (15.7)	9 (2.9)	22 (5.2)	113 (59.8)	< 0.0001§
Length of hospital stay† (day)	7 (4, 12)	5 (4, 8)	8 (6, 13)	7 (2, 19)	< 0.0001§
Survivor	8 (5, 12) (n = 775)	5 (4, 8) (n = 298)	9 (6, 13) (n = 401)	20 (10, 29) (n = 76)	< 0.0001§

Value of n is provided for variables with missing data. *Comparison among newborns with mild, moderate and severe HIE. †Data presented as median (lower quartile, upper quartile). ‡More than one type of respiratory support was used for some newborns. §p-value is statistically significant. CPAP: continuous positive airway pressure; HFV: high-frequency ventilation; iNO: inhaled nitric oxide; MAS: meconium aspiration syndrome; PPHN: persistent pulmonary hypertension of the newborn

the 1980s and 1990s in countries such as the United Kingdom (4.6–6.0 per 1,000 live births in the 1980s),[8,9] Sweden (1.8 per 1,000 live births in 1985–1991),[4] the United States (4.5 per 1,000 live births in the 1990s)[10] and Saudi Arabia (5.5 per 1,000 live births in the 1990s),[11] our incidence was lower.

A system for referring high-risk pregnancies to major government hospitals has been in place in Malaysia for more than two decades. Since September 1996, neonatal resuscitation training programmes based on the American Heart Association and American Academy of Paediatrics' Neonatal Resuscitation Program (NRP) have been systematically implemented in all government hospitals in Malaysia. All paediatric and obstetric medical and nursing staff in all Malaysian government hospitals are trained in the NRP.[12,13] However, recertification training for the NRP, which should be conducted every two years, has not been stringently implemented.

The difference in HIE incidence among the 37 hospitals in the MNNR could be due to many factors, such as differences in patient profiles, and antenatal, intrapartum and resuscitation care. In the case-control studies reported previously by other investigators,[3,4,14] maternal diabetes mellitus, anaemia and hypertension were reported to be significant risk factors associated with HIE. In the present study, we were unable to identify risk factors associated with HIE in these Malaysian hospitals, as the 2012 MNNR database included only term newborns diagnosed to have HIE and those requiring respiratory support. All term newborns without HIE born in these participating hospitals were not included in the database. Nevertheless, the high incidence of HIE among newborns with instrumental deliveries and emergency LSCS (Table I), and the high proportions of HIE newborns with low Apgar scores requiring extensive resuscitation at birth (Table III) in this study suggest that intrapartum factors could be significant risk factors associated with HIE in Malaysian hospitals; this is similar to observations by investigators elsewhere.[15,16] Further studies are urgently needed to identify these risk factors and determine whether earlier recognition of obstetric problems and increasing the frequency of intrapartum monitoring could help to improve the incidence of HIE. Studies are also needed to determine the competence of NRP-certified staff in performing newborn resuscitation in labour rooms in Malaysia, as training does not imply competence and systematic retraining may be needed for NRP-certified staff.[17]

In 2012, only six NICUs in the MNNR were able to perform amplitude integrated electroencephalography (aEEG) for CFM. Few NICUs (n = 4) had ready access to electroencephalography (EEG) in their hospitals. In 2012, the severity of HIE in the MNNR was graded based solely on the level of consciousness and muscle tone of newborns on admission, instead of the presence or absence of seizures and EEG changes as required in the original criteria by Sarnat and Sarnat.[18] Based on our modified method of grading HIE, 16.9% of newborns categorised under mild HIE in the present study had seizures and would be classified as having

Table V. Comparison of non-survivors and survivors of hypoxic-ischaemic encephalopathy (HIE) in the 2012 Malaysian National Neonatal Registry (n = 919).

Variable	No. (%)		p-value
	Non-survivors (n = 144)	Survivors (n = 775)	
Maternal			
Age* (yr)	28 (24, 33)	27 (24, 31)	0.941
Gravid*	2 (1, 3)	1 (1, 2)	0.051
Parity*	0 (0, 2)	0 (0, 1)	0.014
Malay ethnicity	85 (59.0)	490 (63.2)	0.189
Diabetes mellitus	20/127 (15.7)	110/757 (14.5)	0.720
Hypertension	15/128 (11.7)	59/761 (7.8)	0.095
Eclampsia	2/131 (1.5)	16/766 (2.1)	1.00
Chorioamnionitis	2/130 (1.5)	9/765 (1.2)	0.667
Anaemia	25/129 (19.4)	156/758 (20.6)	0.754
Abruptio placentae	10/143 (7.0)	14 (1.8)	0.002‡
Placenta previa	0	3/774 (0.4)	1.00
Cord prolapse	4/143 (2.8)	23 (3.0)	1.000
Intrapartum antibiotics	9/139 (6.5)	71/762 (9.3)	0.279
LSCS delivery	71 (49.3)	216 (27.9)	< 0.0001‡
Birth weight† (g)	3,030 ± 481	3,072 ± 486	0.346
Gestational age (wk)	38.6 ± 1.4	38.8 ± 1.3	0.044
SGA	25 (17.4)	109 (14.1)	0.587
Apgar score*			
At 1 min	2 (0, 4) (n = 133)	4 (2, 5) (n = 762)	< 0.001‡
At 5 min	4 (1, 6) (n = 127)	6 (4, 7) (n = 729)	< 0.001‡
Resuscitation at birth			
Oxygen at birth	128/139 (92.1)	724/751 (96.4)	0.036‡
Bag-and-mask ventilation	122/139 (87.8)	677/751 (90.1)	0.445
Chest compression	66/138 (47.8)	105/750 (14.0)	< 0.001‡
ETT ventilation	122/139 (87.8)	626/751 (83.4)	0.192
Adrenaline	55/137 (40.1)	50/750 (6.7)	< 0.001‡
Outborn	38 (26.5)	113 (14.6)	< 0.001‡
Admission temperature* (ºC)	36.0 (34.9, 36.5)	36.3 (35.7, 36.6)	< 0.0001‡
Seizures	73 (50.7)	414 (53.4)	0.547
MAS	40 (27.8)	127 (16.4)	0.001‡
PPHN	31 (21.5)	40/770 (5.2)	< 0.0001‡
Respiratory support	141 (97.9)	717 (92.5)	0.017‡
CPAP	8/141 (5.7)	237/717 (33.1)	< 0.0001‡
Conventional ventilation	134 (95.0)	643 (89.7)	0.047‡
High-frequency ventilation	35 (24.8)	24 (3.3)	< 0.0001‡
iNO therapy	9/141 (6.4)	11/717 (1.5)	0.002‡
Pneumothorax	17 (11.8)	28 (3.6)	< 0.0001‡
Sepsis	12 (8.3)	17 (2.2)	< 0.0001‡
Late onset	9 (75.0)	7 (41.2)	0.076
HIE stage			< 0.0001‡
Mild	9 (6.3)	298 (38.5)	
Moderate	22 (15.3)	401 (51.7)	
Severe	113 (78.5)	76 (9.8)	

*Data presented as median (lower quartile, upper quartile). †Data presented as mean ± standard deviation. ‡p-value is statistically significant. CPAP: continuous positive airway pressure; ETT: endotracheal tube; iNO: inhaled nitric oxide; LSCS: lower segment Caesarean section; MAS: meconium aspiration syndrome; PPHN: persistent hypertension of newborn; SGA: small for gestational age

at least moderate HIE according to Sarnat and Sarnat's criteria. Hence, our method could have resulted in underdiagnosis of the severity of HIE. These findings provide evidence of the need to adopt the full criteria from Sarnat and Sarnat to categorise the severity of HIE. In addition, equipping all Malaysian NICUs with aEEG capabilities would help staff to detect clinically subtle seizures and confirm obvious ones for staging, management and prediction of outcome.

Our data revealed that a majority of HIE newborns were seriously ill after admission, as more than 90% of them needed ventilator support. Furthermore, the more severe the HIE, the higher the morbidity and mortality among these HIE newborns. A number of significant predictors were identified. Univariate analysis showed that besides Apgar scores and adrenaline at birth (similar to a report by Toh in a previous study with a small sample size),[19] chest compression, PPHN and MAS were significant predictors. However, in the present study, Apgar scores and adrenaline were found to be highly correlated with chest compression, PPHN and MAS in tests of multicollinearity. These two factors (Apgar scores and adrenaline at birth) were therefore not included in the logistic regression analysis. After controlling for various potential confounders, logistic regression analysis showed that newborns in our NICUs who had severe HIE, chest compression at birth, MAS, PPHN, sepsis and pneumothorax, and were outborn were more likely to die before discharge, confirming Toh's findings to some extent.[19]

In 2012, only seven NICUs in the MNNR were equipped with a set of facilities for cooling therapy and only one affected newborn could receive cooling therapy at a time in each centre. Numerous studies have shown that cooling therapy improves the early and long-term outcome of newborns with HIE.[1,20-23] Given the large number of newborns in the MNNR who were graded with moderate and severe HIE, facilities for cooling therapy should be provided to all Malaysian NICUs and in an adequate number in order to reduce the morbidity and mortality associated with this condition.

Apart from our possible misclassification of HIE severity, this study had a few other limitations. Risk factors associated with HIE in the NICUs could not be identified because the perinatal and neonatal data of all term newborns with and without HIE in these hospitals was not included in the MNNR database. The criteria for newborns to receive cooling therapy in centres with cooling facilities were also not identified in the database; hence, we could not determine whether cooling made a difference in their outcome compared with newborns in the same centre who did not receive cooling therapy.

In conclusion, the incidence of HIE in Malaysian NICUs was similar to that reported in developed countries in the 1990s. The morbidity and mortality of HIE newborns were high in Malaysian NICUs. There is an urgent need to identify the risk factors associated with this problem for effective preventive steps to be taken, and to equip all Malaysian NICUs with CFM and facilities for cooling therapy, so as to improve the diagnosis and management of this group of high-risk newborns.

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