Risk factors associated with necrotising enterocolitis in very low birth weight infants in Malaysian neonatal intensive care units

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INTRODUCTION This study aimed to identify the risk factors associated with necrotising enterocolitis (NEC) in very low birth weight (VLBW; weight < 1,501 g) infants in Malaysian neonatal intensive care units (NICUs).

METHODS This was a retrospective study based on data collected in a standardised format for all VLBW infants born in 2007 (n = 3,601) and admitted to 31 NICUs in Malaysian public hospitals. A diagnosis of NEC was made based on clinical, radiological and/or histopathological evidence of stage II or III, according to Bell's criteria. Logistic regression analysis was performed to determine the significant risk factors associated with NEC.

RESULTS 222 (6.2%) infants developed NEC (stage II, n = 197; stage III, n = 25). 69 (31.3%) infants died (stage II, n = 58; stage III, n = 11). The significant risk factors associated with NEC were: maternal age (adjusted odds ratio [OR] 1.024, 95% confidence interval [CI] 1.003–1.046; p = 0.027), intrapartum antibiotics (OR 0.639, 95% CI 0.421–0.971; p = 0.036), birth weight (OR 0.999, 95% CI 0.998–0.999; p < 0.001), surfactant therapy (OR 1.590, 95% CI 1.170–2.161; p = 0.003), congenital pneumonia (OR 2.00, 95% CI 1.405–2.848; p < 0.001) and indomethacin therapy for the closure of patent ductus arteriosus (PDA) (OR 1.821, 95% CI 1.349–2.431; p = 0.001).

CONCLUSION Increasing maternal age, decreasing birth weight, surfactant therapy, congenital pneumonia and indomethacin therapy for the closure of PDA were associated with an increased risk of NEC in Malaysian VLBW infants. Infants that received intrapartum antibiotics were associated with a reduced risk of developing NEC.

Keywords: necrotising enterocolitis, risk factors
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INTRODUCTION

Necrotising enterocolitis (NEC) is a serious condition in preterm infants, which is associated with high mortality and morbidity. The incidence of NEC varies from country to country and between neonatal intensive care units (NICUs).[1-5] The Malaysian National Neonatal Registry (MNNR) was set-up in 2004 to study the outcome of critically ill and very low birth weight (VLBW; weight < 1,501 g) infants. NICUs in Malaysia were invited to participate in this registry, with the primary aim to improve the standard of neonatal intensive care in Malaysia. Based on the data collected for 2004,[6] 2005[7] and 2006[8] from the MNNR, the incidence of NEC among VLBW infants was reported to be 9%, 10% and 8%, respectively, with fatality rates for these years being very high at 26%, 34% and 34%, respectively. The present study was undertaken in an effort to reduce the incidence of NEC among VLBW infants in NICUs in Malaysia, with the objective to identify potentially preventable risk factors associated with the condition in Malaysian NICUs.

METHODS

This was a retrospective study based on the data of all VLBW infants born in 2007 and admitted to the NICUs of hospitals participating in the MNNR in 2007. Participating NICUs submitted data on these infants to the MNNR upon their discharge or death. A standardised format was used for data collection. Each infant was considered a unique case and not duplicated in the registry, irrespective of the number of admissions to different participating NICUs. Infants of birth weight < 501 g were excluded from the MNNR.

A diagnosis of NEC was made based on the presence of clinical, radiological and/or histopathological evidence that fulfilled the stage II or III of Bell's criteria.[9] Infants were defined as small for gestational age (birth weight < 10th percentile for respective gestational age), appropriate for gestational age (birth weight between 10th–90th percentile for respective gestational age), and large for gestational age (birth weight > 90th percentile for gestational age).[10]

Intrapartum antibiotics were considered to have been given if they were administered to the mothers of these infants within 24 hours prior to delivery. A diagnosis of respiratory distress syndrome (RDS) was made in the presence of a partial pressure of arterial oxygen (PaO_2) < 50 mmHg when breathing room air, central cyanosis in room air or a requirement for supplemental

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oxygen to maintain PaO_2 > 50 mmHg, as well as a chest radiograph showing low lung volumes and reticulogranular appearance in the lung fields, with or without air bronchogram signs. A diagnosis of patent ductus arteriosus (PDA) was made based on the presence of a continuous heart murmur in the left second intercostal space, hyperdynamic precordium, bounding pulses, wide pulse pressure, and an increased pulmonary vasculature or cardiomegaly in the chest radiograph, or echocardiographic evidence of PDA. A diagnosis of pneumothorax was made in the presence of extrapleural air detected by chest radiograph or needle aspiration (thoracocentesis). Intraventricular haemorrhage (IVH) was defined as the presence of haemorrhage in the subependymal, intraventricular or periventricular regions of the lateral ventricles of the brain, as detected by cranial ultrasonography.[11] Sepsis was defined as the presence of clinical evidence of sepsis with positive microbiological culture in aseptically collected blood or cerebrospinal fluid specimens. Congenital pneumonia was diagnosed in the presence of clinical and radiological evidence of pneumonia at birth or shortly after birth within 48 hours of life, with and without positive microbiological evidence. Chronic lung disease (CLD) was defined as needing oxygen therapy for more than 28 days and at 36 weeks of gestation.

Statistical analyses were performed using the statistical programme STATA version 10.0 (StataCorp LP, College Station, TX, USA). Comparisons were carried out for demographic and clinical data between infants with and without NEC, and those of survivors and nonsurvivors of NEC. Chi-square test (or Fisher's exact test for variables with expected values < 5) was used for univariate analysis of categorical variables. Student's *t*-test was used for univariate analysis of continuous variables with normal distribution while the Mann-Whitney U test was used for variables with skewed distribution. Backward logistic regression analysis was carried out using NEC as the dependent variable and the following as independent variables: maternal age, ethnic groups (with Malays as the reference group), birth weight, gestational age, multiplicity of pregnancy, intrapartum antibiotics, surfactant therapy, RDS, PDA, indomethacin for the closure of PDA, congenital pneumonia and congenital anomalies. Backward logistic regression analysis was also carried out using mortality in infants with NEC as the dependent variable and the following variables as independent variables: birth weight, gestation, intrauterine growth status, congenital anomalies, pneumothorax, sepsis, severe IVH of grade 3 or 4, NEC stage III, ventilator support and duration of ventilation. A p-value < 0.05 was considered statistically significant.

RESULTS

In 2007, 31 out of 40 NICUs in Malaysian public hospitals participated in the MNNR. These 31 NICUs accounted for more than 95% of the VLBW infants born in the 40 NICUs. The remaining nine nonparticipating NICUs were very small units with less than four beds and without neonatologists to coordinate data submission. There were 3,601 VLBW infants in the registry for 2007. The main ethnicities of these infants were Malay, Chinese, Sabahan, Sarawakian and Indian (Table I). Almost one-third (29.2%) of these infants were extremely low birth weight (ELBW; weight < 1,000 g), and 34.6% of infants were of gestation ≤ 28 weeks. A majority (87.3%) of the VLBW infants were born to inpatients. NEC of stages II (n = 197; 88.7%) and III (n = 25; 11.3%) were reported in 222 (6.2%) infants. The mean incidence of NEC among VLBW infants in the participating NICUs was 6.2% (range 0%–13.1%; 95% confidence intervals [CI] 4.7–7.6; p < 0.001). There was no correlation between the number of VLBW admitted and the incidence of NEC in these participating centres (r = –0.006; p = 1.0).

Univariate analysis showed no significant difference in the maternal and intrapartum factors between VLBW infants with and without NEC, except for the use of intrapartum antibiotics (Table I). The proportion of mothers receiving intrapartum antibiotics was significantly lower among infants with NEC. When compared to those without NEC, infants with NEC were of significantly lower birth weight and gestational age. A significantly higher proportion of these infants were ELBW and extremely premature, with gestation ≤ 28 weeks at birth. Variables such as a history of RDS, PDA, surfactant therapy, indomethacin therapy for closure of PDA and congenital pneumonia were significantly more common among infants with NEC. Logistic regression analysis showed that, after controlling for various potential confounders, the only significant risk factors associated with NEC among VLBW infants were: maternal age, history of not receiving intrapartum antibiotics, decreasing birth weight, congenital pneumonia, history of receiving surfactant therapy and history of having received indomethacin for the closure of PDA (Table II). Multiple pregnancies, ethnicity, gestational age, RDS, PDA and congenital anomalies were not significant risk factors.

Table III compares the outcome and treatment received by VLBW infants with and without NEC. Significantly higher proportions of infants with NEC had IVH, sepsis, CLD, total parenteral nutrition (TPN), ventilator support and nasal continuous positive airway pressure support (p < 0.001). These infants also needed a significantly longer duration of ventilator support and longer stay in the hospital (p < 0.05), and were of significantly lower body weight at the time of death or discharge (p = 0.04). The mortality rate of infants (n = 69; 31.1%) with NEC was significantly high. Even among survivors, infants with NEC had a significantly longer duration of hospital stay (p < 0.001) and a significantly higher proportion was small for gestation at discharge (p = 0.007) than those without NEC.

Among the 31 NICUs, the death rates of VLBW infants with NEC ranged from 0%–100%, with a median of 33.3% (interquartile range 16.8–50.0). Death was more common among infants of lower gestational age: 67% in infants with < 24 weeks gestation, 53% in infants with 24–26 weeks gestation, 23% in infants with 27–29 weeks gestation, 32% in those with 30–32 weeks gestation and 26% in those with > 32 weeks gestation. Mortality was also

Table I. Demographic and clinical characteristics of very low birth weight (weight < 1,501 g) infants (n = 3,601) with and without necrotising enterocolitis.

Characteristic	No. (%)			p-value
	Total	With NEC (n = 222)	Without NEC (n = 3,379)	
Maternal factors				
Maternal age* (yrs)	29 (24–34)	30 (24–35)	29 (24–34)	0.06
Ethnic groups				
Malay‡	2,223 (61.8)	125 (56.3)	2,098 (62.1)	
Chinese	393 (10.9)	34 (15.3)	359 (10.6)	0.08
Indian	238 (6.6)	10 (4.5)	228 (6.7)	
Sarawakian	211 (5.9)	17 (7.7)	194 (5.7)	
Sabahan	251 (7.0)	21 (9.5)	230 (6.8)	
Foreigner	208 (5.8)	11 (5.0)	197 (5.8)	
Others	75 (2.1)	4 (1.8)	73 (2.2)	
Singleton pregnancy	2,986 (82.9)	192 (86.5)	2,794 (82.7)	0.1
Lower-segment Caesarean section	1,686 (46.8)	112 (50.5)	1,574 (46.6)	0.6
Maternal insulin-dependent DM	118 (3.3)	7 (3.2)	111 (3.3)	0.9
Antenatal steroids	2,118 (58.8)	135 (60.8)	1,983 (58.7)	0.3
No intrapartum antibiotics	2,783 (77.3)	180 (81.1)	2,603 (77.0)	0.03†
Neonatal factors				
Born to inpatients	3,145 (87.3)	189 (85.1)	2,956 (87.5)	0.3
Male gender	1,876 (52.1)	123 (55.4)	1,753 (51.9)	0.4
Birth weight* (g)	1,190 (940–1,360)	1,013 (850–1,220)	1,200 (950–1,365)	< 0.001†
Birth weight < 1,000 g	1,051 (29.2)	98 (44.1)	953 (28.2)	< 0.001†
Gestation* (wks)	30 (28–32)	29 (27–31)	30 (28–32)	0.002†
Gestation ≤ 28 wks	1,246 (34.6)	98 (44.1)	1,148 (34.0)	0.002†
Growth status at birth				0.4
Appropriate for gestation	2,299 (63.8)	136 (61.3)	2,163 (64.0)	
Large for gestation	45 (1.2)	3 (1.4)	42 (1.2)	
Small for gestation	1,256 (34.9)	83 (37.4)	1,173 (34.7)	
Respiratory distress syndrome	2,600 (72.2)	183 (82.4)	2,417 (71.5)	< 0.001†
Given surfactant therapy	1,766 (49.0)	146 (65.8)	1,620 (47.9)	< 0.001†
PDA	1,295 (36.0)	108 (48.6)	1,187 (35.1)	< 0.001†
Indomethacin for closure of PDA	450 (12.5)	54 (24.3)	396 (11.7)	< 0.001†
Congenital pneumonia	445 (12.4)	51 (23.0)	394 (11.7)	< 0.001†
Pneumothorax	154 (4.3)	11 (5.0)	143 (4.2)	0.6
Congenital anomalies	257 (7.1)	11 (5.0)	246 (7.3)	0.2

*Data is presented as median (interquartile range). †p < 0.05 is statistically significant. ‡ Reference group.
DM: diabetes mellitus; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus

Table II. Multivariate logistic regression analysis of risk factors associated with necrotising enterocolitis among very low birth weight infants.

Risk factor	Coefficient (β)	OR (95% CI)	p-value*
Constant	−2.470	0.085	< 0.001
Birth weight (g)	−0.001	0.999 (0.998–0.999)	< 0.001
Congenital pneumonia	0.693	2.000 (1.405–2.848)	< 0.001
Indomethacin for closure of PDA	0.599	1.821 (1.278–2.593)	0.001
Surfactant therapy	0.464	1.590 (1.170–2.161)	0.003
Maternal age (yrs)	0.024	1.024 (1.003–1.046)	0.03
Received intrapartum antibiotics	−0.447	0.639 (0.421–0.971)	0.04

CI: confidence interval; OR: adjusted odds ratio; PDA: patent ductus arteriosus

more common in the lower birth weight groups: 64% among infants of birth weight 501–750 g, 38% in infants with birth weight 751–1,000 g, 24% in those with birth weight 1,001–1,250 g and 10% in those that weighed 1,251–1,500 g at birth.

Univariate analysis showed no significant difference in the maternal demographic, antenatal and intrapartum variables between survivors (n = 153) and nonsurvivors (n = 69) of NEC (p > 0.4). However, nonsurvivors had significantly lower birth weight (p < 0.001) and gestational age (p < 0.04). A significantly higher proportion of nonsurvivors were ELBW infants (62.3% vs. 35.9%; p < 0.0001) and had congenital anomalies (10.1% vs. 2.6%; p = 0.038), sepsis (49.3% vs. 32.0%; p = 0.01), IVH of grade 3 (18.3% vs. 7.8%; p = 0.02) or grade 4 (10.1% vs. 2.6%; p = 0.04), and longer median duration of ventilator support (19 days vs. 13 days; p = 0.01). There was no significant difference in the proportion of infants with stage III NEC, receiving TPN

Table III. Comparison of treatment received and outcome among very low birth weight infants with and without necrotising enterocolitis.

Parameter	No. (%)		p-value
	With NEC (n = 222)	Without NEC (n = 3,379)	
Treatment received			
Total parenteral nutrition	163 (73.4)	1,382 (40.9)	< 0.001†
Ventilator support	204 (91.9)	2,559 (75.7)	< 0.001†
Duration of ventilator support* (days)	15 (6–29)	5 (2–12)	< 0.001†
nCPAP therapy	133 (59.9)	1,627 (48.2)	0.001†
Outcome			
Developed chronic lung disease	29 (13.1)	206 (6.1)	< 0.001†
Intraventricular haemorrhage	93 (41.9)	766 (22.7)	< 0.001†
Developed sepsis	83 (37.4)	418 (12.4)	< 0.001†
Died	69 (31.1)	821 (24.3)	0.02†
Duration of hospital stay of infants**(days)	53.0 ± 34.3	37.0 ± 31.2	0.04†
Body weight at discharge/death**(g)	1,548.4 ± 486.1	1,616.2 ± 565.3	0.04†
Duration of hospital stay of survivors** (days)	64 ± 32.5	46 ± 26.5	< 0.001†
Weight of survivors at discharge** (g)	1,778 ± 327	1,828 ± 389	0.1
Growth status at discharge (%)			
Appropriate for gestation‡	89 (40.1)	1,680 (49.7)	
Large for gestation	11 (5.0)	92 (2.7)	
Small for gestation	122 (55.0)	1,606 (47.5)	0.007†

*Data is presented as median (interquartile range). **Data is presented as mean ± standard deviation. †p < 0.05 is statistically significant. ‡Reference group.
nCPAP: nasal continuous positive airway pressure; NEC: necrotising enterocolitis

Table IV. Multivariate logistic regression analysis of risk factors associated with mortality among infants with necrotising enterocolitis.

Risk factor	Coefficient (β)	OR (95% CI)	p-value*
Constant	3.674	39.39	< 0.001
Birth weight (g)	−0.004	0.996 (0.995–0.998)	< 0.001
Congenital anomalies	1.996	7.36 (1.58–34.34)	0.01
Confirmed sepsis	0.733	2.08 (1.07–4.06)	0.03

CI: confidence interval; OR: adjusted odds ratio

and surfactant therapy, with PDA, congenital pneumonia or CLD between survivors and nonsurvivors (p > 0.05).

Logistic regression analysis showed that, after controlling for various potential confounders, the only significant predictors of mortality in infants with NEC were decreasing birth weight, congenital anomalies and sepsis (Table IV). Variables such as gestational age, small size for gestational age, pneumothorax, NEC stage III, IVH grade 3 or 4, and need for ventilator support or duration of ventilator support were not significant risk factors.

DISCUSSION

While similar to those reported by some networks and large cohort studies,[1-5,12] We found that the incidence of NEC among VLBW infants in the MNNR in 2007, was much higher than three large cohort studies reported in Italy (3.1%),[13] Australia (3.8%)[14] and the United States (2.6%).[15] Although a wide variation was seen in the incidence of NEC among the various NICUs within the Malaysian network, it is unlikely that this difference was due to differences in patient load, as there was no correlation between the number of VLBW infants admitted to these NICUs and the incidence of NEC. Factors such as differences in feeding policy, infection control measures and different proportion of infants who were ELBW and of extreme prematurity admitted to the different NICUs could account for the differences in the incidence and mortality of NEC in the MNNR.

Similar to the findings of Kosloske[4] and Holman et al[5], the data from the MNNR for 2007 showed that decreasing birth weight was a significant risk factor associated with NEC. This was different from the findings of Canadian[2] and Australian[14] studies which reported decreasing gestation to be a significant risk factor. Despite the plurality of Malaysian society, ethnicity was not a significant independent risk factor associated with NEC. This is contrary to a report by Uauy et al, who found that black infants had significantly higher risk of developing NEC than nonblacks.[3]

Although RDS has been previously reported to be a significant risk factor associated with NEC,[14] it was not a significant factor in the present study. Instead, a history of having received surfactant therapy was a significant risk factor. As surfactant therapy is very costly in Malaysia, the only indication for this type of therapy for VLBW infants in the Malaysian NICUs was severe RDS. Our findings thus suggest that severe RDS was a significant risk factor associated with NEC. Given that the use of the antenatal steroid was low (range 59%–61%; Table I) among Malaysian VLBW infants, our study suggests a need to promote the use of antenatal steroids among high-risk pregnancies in Malaysia to help reduce the incidence of severe RDS and consequently, NEC.

Contrary to other cohort studies,[2,13,16] PDA was not a significant independent risk factor associated with NEC in Malaysian NICUs. Instead, the use of indomethacin for the closure of PDA was a significant independent risk factor, as also reported by Guthrie et al[15] and Grosfeld et al.[17] The latter showed that infants receiving indomethacin for the closure of PDA had higher risk of bowel perforation following the development of NEC. Major et al also

reported a significant increase in the incidence of NEC in low birth weight infants following antenatal exposure to indomethacin (for maternal tocolysis of labour) within 24 hours of delivery.[18]

Previously, a large Australian study[14] reported younger mothers to be a significant risk factor associated with NEC. Multivariate analysis in the present study, however, showed that older mothers were significant risk factors instead. However, without additional maternal data from the present study, it was not possible to determine the underlying reasons for this difference in findings.

Congenital pneumonia and a history of not having received intrapartum antibiotics were both novel significant risk factors identified in our study that have not been previously reported. These two factors suggest that intrapartum infections might play an important role in the pathogenesis of NEC in Malaysian VLBW infants. An important potential risk factor not included in the present study was the enteral feeding strategies followed in the participating NICUs. This is because information on the age of onset of feeding, rate of increment of the volume of enteral feed, types of feeds and age when full feed was established were potential risk factors associated with the development of NEC. Identification of such factors could help clinicians plan for preventive strategies that could reduce the incidence of NEC among VLBW infants in NICUs.

Only two maternal variables (maternal age and maternal insulin-dependent diabetes mellitus) were included in the MNNR database for 2007. Other maternal characteristics such as pregnancy-induced hypertension, antepartum haemorrhage, premature rupture of membrane, duration of antepartum antibiotics and use of indomethacin for tocolysis of preterm labour, as well as infant characteristics, such as Apgar scores, intubation in the delivery room, early use of antibiotics, use of umbilical arterial catheters, and details on indomethacin usage, were not included in the MNNR database for 2007. As a result, it was not possible to determine whether these variables were significant risk factors associated with NEC in VLBW infants in Malaysian NICUs.

Similar to the findings of other studies[1-5] and the MNNR data for previous years,[6-8] the mortality rate associated with NEC in 2007 was high. Our study showed that decreasing birth weight, sepsis and congenital anomalies were significant predictors of mortality. These findings suggest that prevention and aggressive treatment of sepsis could help to reduce the mortality rates in VLBW infants with NEC in Malaysia. In summary, NEC is still a common problem affecting VLBW infants in Malaysian NICUs, with high mortality being associated with the condition. A number of modifiable risk factors associated with NEC have been identified and it is possible that such factors might help us to plan preventive strategies to reduce the incidence of NEC in VLBW infants.

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