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ORIGINAL ARTICLE

Risk factors associated with outcomes of very low birthweight infants in four Asian countries

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Aim: The study aims to determine the risk factors associated with mortality and necrotising enterocolitis (NEC) among very low birthweight infants in 95 neonatal intensive care units in the Asian Network on Maternal and Newborn Health.

Methods: This is a cross-sectional study using an international collaborative database of 17 595 very low birthweight infants admitted within 28 days of birth between 2003 and 2006 in four Asian countries. Information on the mortality and morbidity of neonates admitted to the neonatal intensive care units was recorded. Factors associated with the death and diseases of infants were estimated using multilevel multivariate logistic regression. Random effects were included to account for the clustering of the observations.

Results: Overall discharge mortality was 15% and it was significantly different by countries and units. The mortality rate was found to be significantly higher in neonates with pulmonary haemorrhage (odds ratio 1.83, 95% confidence interval 1.63–2.04) and air leak syndrome (odds ratio 1.51, 95% confidence interval 1.30–1.72). The incidence of NEC was 4.3% and was strongly associated with other morbidities. Multivariate logistic regression showed that patent ductus arteriosus was the most significant risk factor associated with NEC.

Conclusions: Our analysis has highlighted the great potential that multi-country, collaborative datasets have in terms of epidemiologic research when it comes to identifying issues in perinatal health that are common throughout Asia, and in relation to particular issues pertaining to specific countries and neonatal units. Establishing collaborative networks, conducting analyses of common datasets and further epidemiologic research are now essential measures to improve newborn health in Asia.

Key words: Asia; necrotising enterocolitis; risk factor; very low birthweight infant.

What is already known on this topic

1 Improved perinatal health care through a health professionals' coordinated programme of research, education and quality improvement in regions other than Asia has significantly increased the survival rates of very low birthweight (VLBW) infants.
2 There have been no previous large-scale cross-country studies in Asia to determine factors associated with the medical outcomes of VLBW infants.
3 The incidence of complication associated with VLBW has remained stable.

What this paper adds

1 By using the Asian Network on Maternal and Neonatal Health datasets that exist across Asia which have large sample sizes, we determine the effect of multiple risk factors on medical outcomes for very low birthweight infants.
2 This is the first large-scale cross-country study in Asia to determine the risk factors associated with infant mortality and necrotising enterocolitis.
3 Infant mortality was different between countries and units.

Very low birthweight (VLBW) infants are those born weighing less than 1500 g, either because of prematurity or because of fetal growth retardation. They are at increased risk of neonatal morbidity and mortality. Despite improvements in the survival of VLBW infants in various countries, the incidence of most short-term major complications associated with prematurity has remained relatively stable.[1,2] Although survival rates have improved, the incidence of major morbidities of VLBW infants, whether short term or long term, including respiratory distress

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syndrome (RDS), chronic lung disease (CLD),[2,3] intraventricular haemorrhage (IVH),[2] patent ductus arteriosus (PDA),[4] retinopathy of prematurity and necrotizing enterocolitis (NEC),[2] remain a serious concern. Furthermore, neonatal risk factors related to prematurity and low birthweight persist and contribute significantly to infants' death. Among these outcomes, NEC, a syndrome of inflammation and necrosis of the gastrointestinal tract, remains one of the leading causes of morbidity and mortality in this population.[5,6]

Evidence-based approaches and the use of quality improvement cycles are keys to achieving better patient outcomes. Successful examples include the Vermont Oxford Network, the National Neonatal Audit Programme in the UK, and the Australian and New Zealand Neonatal Network, a collaborative network that is continuously registering neonatal data to improve perinatal health care in its region. However, these activities have not been extensively reported in Asia. Therefore, during the third annual meeting of the Asian Society of Pediatric Research (ASPR) in 2007 – a body that comprises active research paediatricians in Asia – the possibility of collaboration between perinatal facilities throughout Asia was discussed.

The Asian Network on Maternal and Newborn Health (ANMAN) was thus subsequently established with the primary objectives of promoting maternal and newborn health in Asia via the creation of networks and collaborations among neonatal care specialists in the region, and of improving the data collection systems in participating facilities. The present study (as the first step towards these goals) aimed to use the ANMAN datasets to assess factors associated with the mortality and morbidity of VLBW infants in the member neonatal intensive care units (NICUs) in Japan, Malaysia, Hong Kong and Singapore. A secondary aim was to determine which factors were associated with the incidence of NEC in these NICUs.

Methods

The ANMAN network was established in 2009 based on those member countries participating in the ASPR. The network collate data on neonatal clinical practice from each country based upon agreed definitions. This study is a cross-sectional data analysis of clinical data on all the infants participating in the network. The inclusion criteria were all VLBW infants born in the participating neonatal centres or that were admitted to these facilities within 28 days of birth between 2003 and 2006, including those who were born alive but died in the delivery room. Information on the mother was collected at the time of delivery, and information on the neonates was collected upon admission to the NICU. The progress of the infants was followed until death or discharge. Maternal and infant data were collected using a standardized form developed by the investigators similar to those of the Vermont Oxford Network. Information was collected on 17 595 VLBW infants from 95 NICUs in the four Asian countries that participate in this Network. This information came from 63 NICUs with 10 482 infants in Japan, 30 NICUs with 6670 infants in Malaysia, one NICU with 275 infants in Hong Kong SAR China and one NICU with 168 infants in Singapore.

The following definitions and categories were used to define the variables used in this study: the day of birth was defined as 'day 0'. VLBW infant mortality was defined as death occurring on or before 28 days of birth, and mortality before discharge as death occurring before discharge from participating NICUs. Gestational age (GA) was determined in the following order: by obstetric examination with ultrasonography, followed by obstetric history based on the last menstrual period and then by the postnatal physical examination of the neonates. Birthweight was recorded in grams and expressed in mean (standard deviation) scores. Infants weighing less than the 10th percentile in their corresponding region-specific birthweight growth curve at different GAs were defined as small-for-gestational age (SGA). Antenatal steroid use was defined as the administration of any corticosteroids to accelerate fetal lung maturity. RDS was diagnosed from clinical and radiographic findings. CLD was defined as the need for supplemental oxygen with chest X-ray changes at 36 weeks GA. Symptomatic PDA was diagnosed by both echocardiographic findings and clinical evidence of volume overload due to left-to-right shunt. IVH included subependymal and intraventricular and was diagnosed with the use of cranial ultrasonography, and graded according to the classification of Papile *et al*.[7] As for periventricular leukomalacia (PVL), only cystic PVL diagnosed by using either head ultrasound or cranial magnetic resonance imaging scans, performed after 2 weeks of age or later, was included. NEC was defined according to Bell *et al*.'s classification stage II or above.[8] Retinopathy was defined in accordance with the International Classification for Retinopathy of Prematurity.

Ethical consideration

Ethical approval for this study was obtained from the Tokyo Women's Medical University.

Statistical analysis

Multivariate logistic regression models were used to determine which factors were associated with the mortality and morbidity of VLBW infants, and to determine the association between infant diseases and the development of NEC. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the various demographic and clinical outcomes including birthweight, GA, death at discharge, RDS, air leak syndrome, pulmonary haemorrhage, PDA, IVH and NEC, using mixed-effects logistic regression model. Although CLD was considered to be associated with increased mortality and NEC, we excluded CLD in the logistic regression analysis because it was diagnosed at 36 weeks while the death of infants occurred within the first 28 days. Random effects were included in the model to account for the correlation of the clustered observations, by countries and by units separately, and for both between- and within-countries. A P-value of <0.05 was considered statistically significant. All analyses were performed using the statistical software package Stata 10.0 (StataCorp, College Station, TX, USA).

Results

Overview of the dataset

The mean age of the mothers was 30 $\pm$ 6 years (range 13–57). Primigavida mothers comprised 24% of all mothers (4111/

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Table 1 Clinical and demographic data of very low birthweight (<1500 g) infants

Variables	*N* = 17 595
Neonatal characteristics	
Born by caesarean section	65.8% (11 471/17 438)
Male	51.1% (8 988/17 593)
Gestational age (weeks, mean(SD))	29.3 (3.1) (N = 17 585)
Birthweight (g, mean(SD))	1 085.0 (274.7) (N = 17 595)
Small-for-gestational age	1.6% (230/14 674)
Neonatal outcomes	
Death at discharge	15.2% (2 547/16 803)
RDS	60.1% (9 950/16 561)
Air leak syndrome	3.7% (606/16 549)
Pulmonary haemorrhage	4.2% (667/15 917)
CLD	25.7% (3 723/15 133)
PDA	24.6% (4 575/17 362)
IVH	17.5% (2 856/16 309)
NEC	4.3% (707/16 540)

CLD, chronic lung disease; IVH, intraventricular haemorrhage; *N*, total number of participants; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; SD, standard deviation.

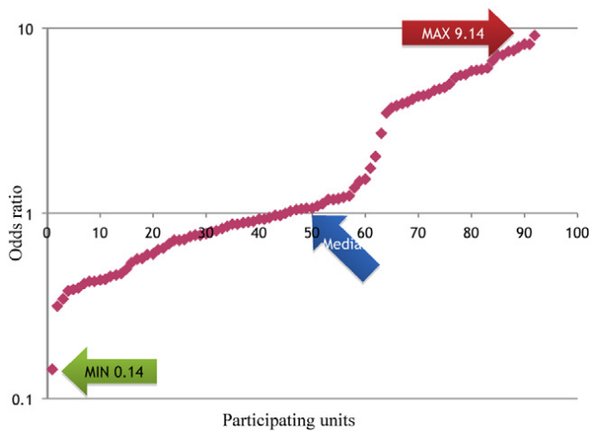

Fig. 1 Odds ratio for discharge mortality by participating units adjusted for birth weight. The median unit is the reference category.

16 829). The rate of pre-labour caesarean section was 66%. Of the 17 593 infants admitted to the 95 neonatal units in the four countries, 51% were males. Multiple births accounted for 23% of all births, of which 77% were monochorionic, and this was a significant predictor of discharge mortality ($P < 0.001$). The mean GA at birth was 29 ± 3 weeks (range 24–44). The mean birthweight was 1085 ± 275 g. SGA babies comprised 2% of all births. The management of SGA babies in this category in these countries is not substantially different from that appropriate for GA babies. Antenatal steroids were administered to 48% (8232/17 305) of mothers. Of all VLBW infants, 15% died in the NICUs before the age of 28 days. RDS was diagnosed in 60% of infants and pulmonary surfactants were administered to 53% (5316/10 131) of infants with RDS. A diagnosis of PDA was made in 25% of VLBW infants and ligation was performed in 10% (478/4575) of infants with PDA. CLD was diagnosed in 26% of infants. Severe IVH developed in 18% of infants, while the incidence of NEC was 4%. Pulmonary haemorrhage occurred in 4% of the infants. There was a low rate (4%) of air leak among all VLBW infants (Table 1).

Factors associated with infant mortality

The adjusted ORs of VLBW infants for discharge mortality by participating units adjusted for birthweight are shown in Figure 1. After excluding units with missing values, the adjusted OR associated with discharge mortality for birthweight of the 92 participating units ranged from 0.14 (95% CI 0.07 to 0.68) to 9.14 (95% CI 7.98 to 25.07) when compared with the units with the median mortality of 1.03 (95% CI 0.61 to 4.15). The adjusted OR associated with discharge mortality for the birthweight of VLBW showed an estimated variance of random effect by unit of 1.03 (95% CI 0.89 to 1.22) and 0.83 (95% CI 0.40 to 1.70) by countries. After adjusting for birthweight, an Apgar score at 1 min of life and the random effect by hospitals, and an Apgar score at 5 min ($P < 0.001$) and antenatal steroids ($P < 0.001$) were significant predictors associated with discharge mortality.

Table 2 Mixed-effects logistic regression analysis of factors associated with discharge mortality

Variables	Odds ratio	95% CI	*P*-value
Birthweight	0.00	0.00 to 0.04	<0.001
Gravida	0.05	0.01 to 0.08	0.004
Air leak	1.51	1.30 to 1.72	<0.001
Pulmonary haemorrhage	1.83	1.63 to 2.04	<0.001
IVH	0.31	0.19 to 0.44	<0.001
NEC	0.56	0.36 to 0.76	<0.001

CI, confidence interval; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis.

Mixed-effects logistic regression showed that lower birthweight ($P < 0.001$), pre-labour caesarean section ($P < 0.001$) and the gender of infants, that is, being a boy, ($P < 0.001$) had a significant effect in terms of increased mortality among VLBW infants. The use of antenatal steroids showed a significant association with an overall reduction in the mortality rates of VLBW infants ($P < 0.001$). The mortality rate was found to be significantly higher for infants with pulmonary haemorrhage (OR 1.83, 95% CI 1.63 to 2.04) and air leak syndrome (OR 1.51, 95% CI 1.30 to 1.72) (Table 2).

Factors associated with NEC

Table 3 shows the results of the multilevel multivariate logistic regression analysis of the factors associated with NEC among VLBW infants. After controlling for the year of birth, maternal

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Table 3 Multilevel logistic regression analysis of potential risk factors associated with necrotising enterocolitis

Variable	Odds ratio	95% CI	*P*-value
Mode of birth†	0.18	0.08 to 0.27	<0.001
RDS	0.34	0.11 to 0.57	0.002
PDA	0.67	0.50 to 0.86	<0.001
IVH	0.37	0.18 to 0.56	<0.001

†Born by caesarean section. CI, confidence interval; IVH, intraventricular haemorrhage; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome.

age, parity, multiplicity, gender and GA, infants who were delivered by caesarean section, the presence of PDA or presence of IVH were significantly associated with the development of NEC.

Discussion

In the context of very little data on VLBW infants in Asia, we analysed data on 17 595 VLBW infants from 95 units in four Asian countries using the ANMAN datasets. Our analysis showed that the proportion of deaths was 15%, much higher than that reported by the Vermont Oxford Network.[9] This study has highlighted differences in infant mortality between countries and units, after adjusting for birthweight. A plausible explanation for this is that the infant health outcomes within each unit or country are underpinned by their own unique factors. Moreover, the distribution of birthweight was significantly different by participating countries and units. In terms of the adjusted ORs for discharge mortality, only birthweight was used because no other risk factors were available.

We determined and quantified the factors that increased the risk of mortality and morbidity among VLBW infants. Mixed-effect logistic regression analysis substantially supported our hypothesis of these risk factors' effects. Infants with pulmonary haemorrhage had two times greater odds of death than those without this condition.[10,11] RDS remained the most common (60%) acute pulmonary disease in our target population. This finding was consistent with other studies conducted by Chinese and Taiwan collaborative study groups.[12,13] Surfactant therapy and conventional or high-frequency mechanical ventilation have been the standard form of care in the management of RDS. Other studies have shown that the incidence of RDS and mortality in VLBW infants decreases with the introduction of antenatal steroids.[14,15] Consistent with a published study using data from the Vermont Oxford Network database, where 62% of the 26 007 neonates weighing <1500 g were given surfactant which was associated with the improved survival of the infants,[16] 50% of the VLBW infants participating in our study received surfactant therapy which was also associated with a better prognosis. Our finding suggests that the use of surfactant therapy may therefore make a significant contribution to better health outcomes among VLBW infants in this region.

In this study, PDA was found to be the commonest cause of neonatal morbidity among VLBW infants (26%). This incidence was higher than that seen in the Swiss Neonatal Network which reported PDA in 20% of VLBW infants.[4] Furthermore, the Israel Neonatal Network have previously reported that PDA is a significant risk factor associated with the development of NEC in VLBW infants.[17] This suggests that variations between countries in the management of PDA and related outcomes are an important area for further investigation.

A secondary aim of using the ANMAN datasets was to determine potential risk factors for NEC. NEC is significantly associated with a fatal outcome and remains a leading cause of morbidity and mortality in our population. About 3–15% of all infants born at <30 weeks GA or <1500 g birthweight were afflicted with NEC.[1,6,14,18,19] The use of antenatal corticosteroid is one approach to enhance maturation of the fetus if preterm delivery is likely.[20,21] A meta-analysis indicated that the lower mortality associated with NEC in VLBW infants was linked to the shorter time to full feeds after administration of probiotic supplementation.[22] This might explain the negative relation observed in the current study between NEC and infant mortality at discharge.

Our analysis indicates that the incidence of NEC was strongly associated with other VLBW morbidities. PDA was thought to be an independent risk factor for the development of NEC in VLBW infants. Both NEC and PDA were interconnected as the incidence of NEC was significantly greater in neonates with PDA compared with the normal newborn population.[23] As medical and surgical advances allow for the palliation and correction of complex lesions in VLBW infants, the already alarmingly high risk of NEC in this population is likely to increase. This will require further in-depth study on the causal mechanisms of NEC in patients with PDA and as regards the development of preventative therapies to decrease the potential morbidity and mortality associated with the combination of these diseases.

Strengths and limitations of this study

To the best of our knowledge, this is the first large-scale study in Asia to determine factors associated with the medical outcomes of VLBW infants using data from numerous NICUs located in several Asian countries. We took advantage of good quality data and employed advanced statistical analysis to address confounding factors, and differences in hospital mortality between units and countries when doing this. This is the major strength of this study. Furthermore, the large sample size achieved as a result of this collaboration allowed us to analyse unit and country patterns on the effect of multiple risk factors on outcomes. This study therefore provides a good representative sample of VLBW infants across Asia.

The limitations of this study should also be kept in mind, however. First, our findings cannot be extrapolated to the entire VLBW population in Asia due to the use of a non-probability sample, which was the only possible method that was open to us for recruiting the study population. Second, there may be selection biases linked with the participating units. This being said, facility-based discharge data are a crucial resource for informing risk factor analyses, and our results provide an important evidence base for better clinical perinatal and neonatal care in the region.

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Conclusions

This study highlights the potential usefulness of multi-country datasets and epidemiologic research for identifying issues in perinatal health that are common throughout Asia, particularly issues pertaining to specific countries and neonatal units. The results from our analyses on the infant population supported the hypothesis that our datasets constitute a valuable resource for examining these issues. Expanding the current network and establishing other neonatal unit networks in addition to collecting and analysing the common datasets they can provide would be an important strategy when it comes to improving newborn health in Asia. This requires further epidemiologic research to identify independent predictive factors, and to develop a risk factor score for use in NICUs.

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References

1 Eichenwald EC, Stark AR. Management and outcomes of very low birth weight. *N. Engl. J. Med.* 2008; **358**: 1700–11.
2 Groenendaal F, Termote JUM, van der Heide-Jalving M, van Haastert IC, de Vries LS. Complications affecting preterm neonates from 1991 to 2006: what have we gained? *Acta Paediatr.* 2010; **99**: 354–8.
3 Hintz SR, Poole WK, Wright LL *et al*. Changes in mortality and morbidities among infants born at less than 25 weeks during the post-surfactant era. *Arch. Dis. Child. Fetal Neonatal Ed.* 2005; **90**: F1–28.
4 Ruegger C, Hegglin M, Adams M, Bucher HU. Population based trends in mortality, morbidity and treatment for very preterm- and very low birth weight infants over 12 years. *BMC Pediatr.* 2012; **12**: 17.
5 Luig M, Lui K; the NSW & ACT NICUS Group. Epidemiology of necrotizing enterocolitis – Part II: risk and susceptibility of premature infants during the surfactant era: a regional study. *J. Paediatr. Child Health* 2005; **41**: 174–9.
6 Westby WSH, Sommerfelt K, Reigstad H *et al*. Neonatal mortality and morbidity in extremely preterm small for gestational age infants: a population based study. *Arch. Dis. Child. Fetal Neonatal Ed.* 2009; **94**: F3 63–7.
7 Papile L, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 g. *J. Pediatr.* 1978; **92**: 529–34.
8 Bell MJ, Ternberg JL, Feigin RD *et al*. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann. Surg.* 1978; **187**: 1–7.
9 Morales LS, Staiger D, Horbar JD *et al*. Mortality among very low-birthweight infants in hospitals serving minority populations. *Am. J. Public Health* 2005; **95**: 2206–12.
10 Kluckow M, Evans N. Ductal shunting, high pulmonary blood flow, and pulmonary haemorrhage. *J. Pediatr.* 2000; **137**: 68–72.
11 Pandit PB, O'Brien K, Asztalos E, Colucci E, Dunn MS. Outcome following pulmonary haemorrhage in very low birthweight neonates treated with surfactant. *Arch. Dis. Child. Fetal Neonatal Ed.* 1999; **81**: F40–4.
12 Hu X, Qian S, Xu F *et al*.; Chinese Collaborative Study Group for Pediatric Respiratory Failure. Incidence, management and mortality of acute hypoxemic respiratory failure and acute respiratory distress syndrome from a prospective study of Chinese paediatric intensive care network. *Acta Paediatr.* 2010; **99**: 715–21.
13 Tsou KI, Tsao PN; Taiwan Infant Development Collaborative Study Group. The morbidity and survival of very-low-birth-weights infants in Taiwan. *Acta Paediatr. Taiwan.* 2003; **44**: 349–55.
14 Pantou K, Drougia A, Krallis N, Hotoura E, Papassava M, Andronikou S. Perinatal and neonatal mortality Nortwest Greece (1996–2004). *J. Matern. Fetal Neonatal Med.* 2010; **23**: 1237–43.
15 Jobe AH. Lung maturation: the survival miracle of very low birth weight infants. *Pediatr. Neonatol.* 2010; **51**: 7–13.
16 Horbar JD, Badger GJ, Carpenter JH *et al*. Trends in mortality and morbidity for very low birth weights infants, 1991–1999. *Pediatrics* 2002; **110**: 143–51.
17 Dollberg S, Lusky A, Reichman B. Patent ductus arteriosus, indomethacin and necrotizing enterocolitis in very low birth weight infants: a population-based study. *J. Pediatr. Gastroenterol. Nutr.* 2005; **40**: 184–8.
18 Guthrie SO, Gordon PV, Thomas V, Thorp JA, Peabody J, Clark RH. Necrotizing enerocolitis among neonates in the United States. *J. Perinatol.* 2003; **23**: 278–85.
19 Thompson AM, Bizzarro MJ. Necrotizing enterocolitis in newborn; pathogenesis, prevention and management. *Drugs* 2008; **68**: 1227–38.
20 Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst. Rev.* 2006; (3): CD004454.
21 Darlow BA, Cust AE, Donoghue DA on behalf of the Australian and New Zealand Neonatal Network (ANZNN). Improved outcomes for very low birthweight infants – evidence from New Zealand national population-based data. *Arch. Dis. Child. Fetal Neonatal Ed.* 2003; **88**: F23–8.
22 Boyd CA, Quigley MA, Brocklehurst P. Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis. *Arch. Dis. Child. Fetal Neonatal Ed.* 2007; **92**: F169–75.
23 Giannone PJ, Luce WA, Nankervis CA, Hoffman TM, World LE. Necrotizing enterocolitis in neonates with congenital heart disease. *Life Sci.* 2008; **82**: 341–7.

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