

## Changes in Perinatal Care and Predictors of In-Hospital Mortality for Very Low Birth Weight Preterm Infants

Ying Dong<sup>1</sup>, MD; Guang Yue<sup>2</sup>, MD, and Jia-lin Yu\*<sup>1</sup>, PhD

1. Department of Neonatology, Children's Hospital of Chongqing Medical University, Chongqing, China
2. Department of Neonatology, Women and children's Hospital, Chengdu, China

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### Abstract

**Objective:** Mortality of very low birth weight premature infants is of great public health concern. To better guide local intervention program, it is essential that current and reliable statistics be collected to understand the factors associated with mortality of these infants.

**Methods:** Data of very low birth weight premature infants admitted to a neonatal unit during 2002-2009 was retrospectively collected. Changes in perinatal care between two halves of the study period (2002-2005 and 2006-2009) were identified. Factors associated with in-hospital mortality were found by logistic regression and a predictive score model was established.

**Findings:** A total of 475 cases were enrolled. In-hospital mortality decreased from 29.8% in 2002-2005 to 28.1% in 2006-2009 ( $P>0.05$ ). More infants born <28 gestational weeks survived to discharge in the latter epoch (38.1% vs 8.3%,  $P<0.05$ ). Persistent pulmonary hypertension of newborn, pulmonary hemorrhage, birth weight <000 grams, gestational age <33 weeks, feeding before 3 postnatal days and enteral feeding were found predictors of in-hospital mortality by logistic regression. The discriminating ability of the predictive model was 82.4% and the cutoff point was -0.56.

**Conclusion:** Survival of very low birth weight premature neonates was not significantly improved in 2006-2009 than 2002-2005. Infants with a score higher than -0.56 were assessed to be at high risk of in-hospital mortality. Multi-center studies of planned follow-up are needed to develop a comprehensive and applicable score system.

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**Key Words:** Premature Infant; Very Low Birth Weight; Mortality; Predictive Score Model

### Introduction

The World Health Organization defines preterm birth as the delivery of an infant between 20 and 37 gestational weeks. Premature infants with very low birth weight (VLBW) only account for a small proportion of the whole live births but are

responsible for a large part of neonatal mortality disproportionately<sup>[1]</sup>. It is estimated that 4%-7% of all live births are VLBW preterm infants and they contribute to nearly 30% of early neonatal deaths<sup>[2]</sup>. Additionally, VLBW preterm infants are increasing over the past two decades due to advances in obstetrical practice, bringing more

\* Corresponding Author;

Address: Children's Hospital of Chongqing Medical University, No.136 2<sup>nd</sup> Zhongshan Road, Yuzhong District, Chongqing, 400014, China

E-mail: yujialin486@sohu.com

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burden to public welfare<sup>[3]</sup>. The impact exerted by VLBW premature neonates on public health is tremendous and a full understanding of the factors affecting mortality rate of VLBW preterm infants is of great importance for improvement in perinatal care. So far, some researches have contributed to our knowledge of the factors associated with mortality of VLBW preterm infants<sup>[1,2,4-6]</sup>. However, data from developed regions comprise the majority of this knowledge and there is a lack of information from developing regions. Because approaches to care vary widely among centers, data from developed regions are not perfectly applicable to neonatal settings in developing regions. Therefore, it is essential that current and reliable statistics be collected locally to guide intervention programs, with the aim of reducing mortality rate of VLBW premature infants and improving perinatal care. The purpose of this study is to identify factors associated with in-hospital mortality of VLBW preterm infants, determine changes in perinatal care over a period of 8 years and establish a predictive score model by retrospectively reviewing case data relevant to a neonatal unit in Southwest China.

## Subjects and Methods

The investigation was retrospectively conducted and the study period was from January 2002 to December 2009. Inclusion criteria were: (1) neonates with a birth weight (BW) <1500 g and a gestational age (GA) <37 weeks; (2) neonates admitted within 24 hours of birth; (3) neonates without lethal congenital anomalies; (4) neonate whose case data was complete. This study was approved by the Institutional Review Board of our university.

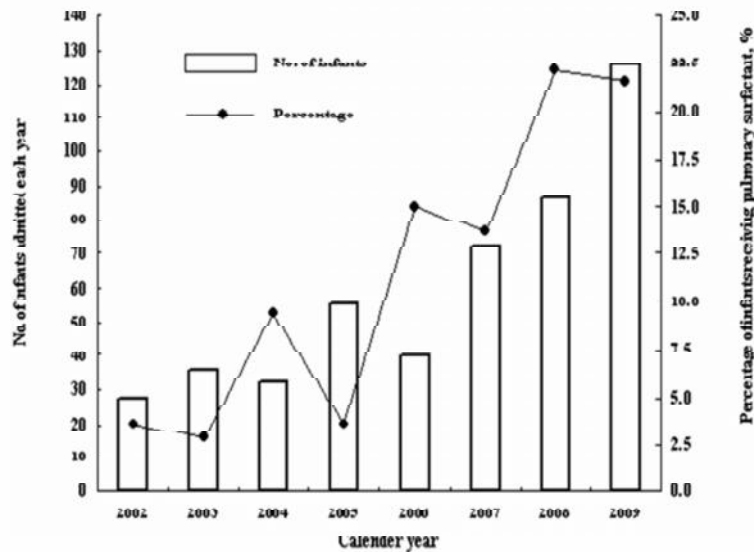
Data were retrospectively collected on precoded forms, including obstetric history, delivery, birth characteristics, neonatal morbidities and neonatal outcome at discharge from hospital. In addition, had all been collected, the forms were further verified by another senior neonatologist to guarantee the quality control.

Definitions: (1) GA and obstetric history were reported by attending obstetric staff or parents/guardians; (2) BW was measured within 1 hour of birth; (3) respiratory distress syndrome (RDS) was graded according to the radiographic manifestation<sup>[7]</sup>; (4) a full course of antenatal corticosteroid was defined as dexamethasone administered intramuscularly in 4 doses of 6mg every 12 hours for pregnancies with threatened preterm birth<sup>[8,9]</sup>; (5) outcome of neonates was dichotomous and encoded as deceased or survived at discharge; (6) a standardized list of definitions was compiled for neonatal disorders<sup>[10]</sup>.

Continuous variables were presented as mean±SD (median) or median (range), analyzed by Student's *t*- or Mann-Whitney *u* test. Categorical variables were expressed as number (percentage), analyzed by chi-square test. Associated factors of in-hospital mortality identified in univariate analysis were subjected to stepwise multiple logistic regression. A predictive score model was developed and a receiver operating characteristic curve (ROC) was constructed based on logistic regression analysis. The software employed was SPSS (version 18.0, Chicago, IL, USA) and statistical significance was set at  $P<0.05$ .

## Findings

A total of 475 VLBW premature infants were included. There was not an infant with a BW<500 grams or GA<24 weeks. The number of neonates admitted in 2002-2005 and in 2006-2009 was 151 and 324 respectively. The trend toward an increasing admission rate by year is presented in Fig 1. For infants born with a GA<35 completed weeks, administration of antenatal corticosteroid was increased insignificantly in 2006-2009 (34.6% vs 31.7%;  $P=0.308$ ). The proportion of infants receiving a full course of antenatal corticosteroids among all infants who received this medication was not statistically different between 2006-2009 and 2002-2005 (15.3% vs 23.9%;  $P=0.2$ ). Cesarean section occurred more frequently in 2006-2009 and the increase was



**Fig. 1:** Admission rate and pulmonary surfactant administration of very low birth weight preterm infants by calendar year, from 2002-2009

most dramatic for infants of GA <28 weeks (from 0 to 38.1%;  $P < 0.001$ ).

For infants of GA <35 completed weeks, the increase in the incidence of RDS was approximately 7% (15.5% vs 22.4%,  $P=0.08$ ). Administration of pulmonary surfactant (PS) increased with time (Fig. 1) and was significantly more frequent in 2006-2009 than in 2002-2005 for neonates with RDS (62.9% vs 27.3%,  $P=0.003$ ), but the initial dose ( $126.25 \pm 21.06$  vs  $74.05 \pm 37.63$ ,  $P=0.002$ ) was decreased. Use of surfactant was associated with the severity of RDS: in 2006-2009 59.2% of infants with RDS grade I to II received this medication as opposed to 71.4% with grade III to IV and 7.1% without RDS ( $P < 0.001$ ). Survival of neonates who developed RDS was improved on account of PS: 46.0% of treated infants survived to discharge as opposed to 40.5% of the untreated infants ( $P=0.6$ ), but in an insignificant way. In-hospital mortality was not significantly decreased in 2006-2009 than in 2002-2005 (28.1% vs 29.8%;  $P=0.7$ ), but more infants born very premature (with GA <28 weeks) survived to discharge (38.1% vs 8.3%;  $P < 0.05$ ). Withdrawal of treatment occurred in 44.5% and 46.2% of deaths in 2002-2005 and 2006-2009 respectively, on account of economical embarrassment or medical futility. The former reason accounted for 10.5% and 22.0% of withdrawal in 2002-2005 and 2006-

2009 respectively ( $P < 0.05$ ). Respiratory problems were the major cause of death in hospital.

Data of 475 VLBW premature infants were pooled to determine the predictors of in-hospital mortality. Results of univariate analysis are presented in Table 1.

The following factors were found to be statistically significant: birth asphyxia, RDS, pulmonary hemorrhage, persistent pulmonary hypertension of newborn (PPHN), feeding before 3 postnatal days and enteral feeding. The risk factors identified by multivariate logistic regression were: pulmonary hemorrhage ( $P < 0.001$ ;  $OR: 6.52$ ;  $95\% CI: 2.69-15.76$ ), PPHN ( $P=0.007$ ;  $OR: 4.98$ ;  $95\% CI: 1.56-15.88$ ), BW <1000 grams ( $P=0.003$ ;  $OR: 3.99$ ;  $95\% CI: 1.59-10.01$ ) and GA <33 weeks ( $P=0.001$ ;  $OR: 2.54$ ;  $95\% CI: 1.49-4.34$ ). Protective factors were: enteral feeding ( $P < 0.001$ ;  $OR: 0.13$ ;  $95\% CI: 0.08-0.22$ ) and feeding before 3 postnatal days ( $P=0.021$ ;  $OR: 0.37$ ;  $95\% CI: 0.16-0.87$ ). The developed model was Logistic =  $-0.583 + 1.871\chi_1 + 1.604\chi_2 + 0.934\chi_3 + 1.385\chi_4 - 0.984\chi_5 - 2.031\chi_6$ .

Based on the results from Table 2, we summed up the regression coefficients weighed by the code of each predictor to arrive at a final score for every particular neonate. The score ranged from -3.01 to 4.41 and the area under the ROC curve (Fig. 2) was 0.824. At the determined cutoff point of -0.56, the

**Table 1:** Univariate analysis of in-hospital mortality

Parameters, n(%)	Survived (n=339)	Deceased (n=136)	P value	
Cerebral injury	271 (79.9)	101 (74.3)	0.2	
Asphyxia	101 (29.8)	59 (43.4)	0.005	
Sepsis	19 (5.6)	8 (5.9)	0.05	
Intraventricular Hemorrhage	130 (38.3)	40 (29.4)	0.07	
Respiratory Distress Syndrome	40 (11.8)	52 (38.2)	<0.001	
Pneumonia	321 (94.7)	123 (90.4)	0.09	
Pulmonary Hemorrhage	10 (2.9)	34 (25.0)	<0.001	
Neonatal Necrotizing Enterocolitis	23 (6.8)	7 (5.1)	0.5	
Persistent Pulmonary Hypertension of Newborn	7 (2.1)	13 (9.6)	<0.001	
Pregnancy Induced Hypertension	55 (16.2)	20 (14.7)	0.7	
Intrahepatic Cholestasis of Pregnancy	13 (3.8)	2 (1.5)	0.3	
Gestational Cardiac Disease	5 (1.5)	3 (2.2)	0.9	
Birth Weight (g)	≥1000	328 (96.8)	113 (83.1)	<0.001
	<1000	11 (3.2)	23 (16.9)	
Gestational Age(wk)	33-36	83 (24.9)	15 (11.3)	<0.001
	28-32	242 (72.5)	94 (70.7)	
	<28	9 (2.7)	24 (18.0)	
Admitted in 2006-2009	233 (68.7)	91 (66.9)	0.7	
Feeding before 3 postnatal days	56 (16.5)	8 (5.8)	0.002	
Enteral feeding	303 (89.4)	67 (49.3)	<0.001	

sensitivity, specificity, positive and negative predictive value was 0.729, 0.832, 0.634 and 0.885 respectively.

## Discussion

This study retrospectively reviewed the data of 475 VLBW premature infants admitted over a period of 8 years. Consistent with other

researches<sup>[1,11]</sup>, our study noted a trend toward increasing admission rate of VLBW infants. Relative researches have reported a wide range of mortality rates (from 57% to less than 10%) of VLBW neonates<sup>[4,12-14]</sup>. In-hospital mortality of our unit in 2006-2009 was approximately equal to that from Banaras Hindu university hospital in India (28.1% vs 22.2%)<sup>[2]</sup>. Survival of VLBW premature infants was not significantly increased in 2006-2009 than in 2002-2005, however, progress was achieved in perinatal care of infants born very premature. It is noteworthy that a

**Table 2:** Multivariate logistic analysis of in-hospital mortality of very low birth weight preterm infants

Variable	Code	Regression coefficient	OR	95% CI
Pulmonary hemorrhage	No	0	1.00	2.69-15.76
	Yes	1	1.874	
persistent pulmonary hypertension of newborn	No	0	1.00	1.56-15.88
	Yes	1	1.604	
Birth weight(g)	≥1000	0	1.00	1.59-10.01
	<1000	1	0.934	
Gestational age(wk)	33-36	0	1.00	1.49-4.34
	28-32	1	1.385	
	<28	2	5.08	
Feeding before 3 postnatal days	No	0	1.00	0.16-0.87
	Yes	1	-0.984	
Enteral feeding	No	0	1.00	0.08-0.22
	Yes	1	-2.031	

CI: Confidence Interval; OR: Odds Ratio

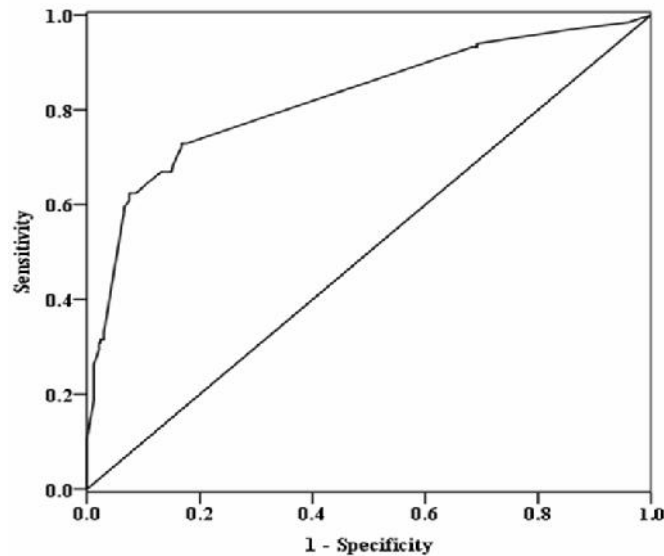


Fig. 2: ROC curve for in-hospital mortality of very low birth weight preterm infants

higher percentage of infants with  $GA < 28$  weeks were delivered by cesarean section in 2006-2009, demonstrating the better chance of survival that these infants now have<sup>[11]</sup>. Quite a proportion of treatment was given up due to economical embarrassment, and withdrawal occurred more frequently in 2006-2009. This might be explained by the fact that the degree of increase in health expenditure was more than that in the average personal income from 2004 to 2008, regionally (102.9% vs 42.1%)<sup>[15,16]</sup>. It was estimated that the cost for NICU hospitalization of VLBW infants is very high for the current level of economy, either in developed regions or developing regions<sup>[17-19]</sup>.

According to European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants - 2010 Update<sup>[9]</sup>, clinicians should offer a single course of antenatal steroids to all women at risk of preterm delivery from about 23 weeks up to 35 completed weeks' gestation. Guideline for the use of antenatal corticosteroids for fetal maturation suggested that babies with or at high risk of RDS should be given bovine or porcine surfactant with the recommended dose of 200mg/kg<sup>[8]</sup>. The low frequency and inadequate dose of antenatal corticosteroids as well as postnatal PS administration indicates several deficits in our perinatal care and may partly explain the increasing incidence of RDS. Inconsistent with researches demonstrating that antenatal

corticosteroids could decrease the risk of intraventricular hemorrhage (IVH)<sup>[11,20,21]</sup>, our study showed that 43.3% of infants treated with antenatal corticosteroids developed IVH as opposed to 32.1% of those untreated. This might be associated with the insufficient administration of antenatal corticosteroid.

Pulmonary hemorrhage, PPHN,  $BW < 1000$  grams and  $GA < 33$  weeks were risk factors of in-hospital mortality. Apart from these, illness severity was also demonstrated in other researches to associate with outcome of neonates. Clinical risk index for babies (CRIB), Score for neonatal acute physiology II (SNAP II) and Score for neonatal acute physiology-perinatal extension (SNAP-PE II) were most commonly used illness severity score models<sup>[22-24]</sup>. Calculation of these scores requires items such as  $FiO_2$ , blood pressure and arterial blood gas analysis within first 24 hours of life. On account of data missing or the lack of available monitoring facilities in 2002-2005, our study was not powered to estimate individual illness severity scores. Respiratory diseases were shown to be most responsible for mortality, therefore, generation of awareness among expectant mothers to seek prenatal care and effective respiratory management (e.g. early and adequate administration of antenatal corticosteroid and postnatal PS) are important to improve our perinatal care. Enteral feeding and feeding before 3 postnatal days were found to be

protective factors of in-hospital mortality. Early enteral feeding has been recommended by various guidelines and minimal enteral nutrition (MEN) was reported to improve gastrointestinal capacity, decrease side effects due to parenteral nutrition and reduce the risk of NEC<sup>[25-27]</sup>. Early feeding improves neonatal outcome through preventing catabolic disturbance and contributes to normal physiological development, however, controversies remain concerning the administration of MEN<sup>[28-30]</sup>. Progression rate and milk components are areas of active research.

We developed a prediction score model based on logistic regression analysis. Compared with other scoring models, we explored more perinatal factors such as feeding strategy while others were chiefly focused on physiologic status of neonates. Although the score model has good calibration and discrimination, its application in clinical practice might be prevented by the negative cutoff point.

The limitations of our study included the retrospective single center design and analysis of outcomes till discharge. Unfortunately, the ideal prospective multicenter study is very difficult to carry out in developing regions due to limited resources in money and manpower, and there is no reliable system to do post-discharge follow up currently. To get a more clearly defined clinical picture, multi-center studies of planned follow-up will be needed.

## Conclusion

Our study showed that perinatal care of VLBW premature infants still needs to be improved regardless of the progress achieved in certain aspects over a period of 8 years. PPHN, pulmonary hemorrhage, BW<1000g and GA<33 weeks were risk factors of in-hospital mortality while feeding before 3 postnatal days and enteral feeding favored good outcome. Infants with the score of more than - 0.56 were at high risk for death. Multi-center studies of planned follow-up are needed to develop a comprehensive score system for guiding our clinical practice.

## Acknowledgment

This study was approved by the Ethics Committee Review Board of Chongqing Medical University, China

**Conflict of Interest:** None

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