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Original article

Prognostic Factors for Neonatal Mortality with Perinatal Asphyxia in a Neonatal Intensive Care Unit

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Abstract Perinatal asphyxia is a complicated health problem in newborns and leads to increased neonatal mortality. In Thailand, perinatal asphyxia has been the most common cause of severe morbidity and mortality for the past 10 years. If the prognostic factors of death were known in severe perinatal asphyxia cases requiring neonatal intensive care unit (NICU) admission, the treatment could be planned more efficiently. The objective of this retrospective case-control research was to identify the prognostic factors of neonatal mortality with perinatal asphyxia in NICU. The study was conducted on 120 newborns (60 dead cases and 60 survived controls) undergoing treatment for perinatal asphyxia in the NICU of Chonburi Hospital from January 2018 to December 2021. The risk factors for perinatal asphyxia mortality were identified using multiple logistic regression. A prognostic model was created by using the coefficient of the regression weighted scores of significant risk factors to predict the chance of mortality. The results showed that the prognostic factors affecting mortality were: female (OR 3.60, 95%CI 1.21-10.65, p<0.05), requirement for advanced neonatal resuscitation (OR 3.72, 95%CI 1.14-12.17, p<0.05), and severe acidosis (OR 4.58, 95%CI 1.53-13.70, p<0.05). The predictive model was developed by applying scores of 1, 2 and 2, respectively, for these significant risk factors. With the cutoff point of 3 from the model, the probability of death within 28 days was approximately 60% with a hazard ratio of 6.82, 95%CI 3.82-12.20, and p<0.05.

***Keywords*: prognostic factors; perinatal asphyxia; neonatal mortality**

Introduction

Perinatal asphyxia is a complex health problem in newborns with a high contribution to the incidence of newborn mortality globally, with higher case fatality rates and consequent complications in developing countries due to poor health facilities. Globally, one study reported that perinatal asphyxia was associated with around 2,500,000 neonatal child deaths in 2018[1], with an incidence reported in another study of approximately 1 - 8 per 1,000 live births[2]. In Thailand, the incidence of hypoxia during birth during 2013-2016 was about 19-20 per 1,000 live births[3]. Perinatal asphyxia is defined as conditions caused by impaired gas exchange. This can lead to hypoxemia

and hypercapnia, and if the hypoxia is severe, it affects organs such as the heart and brain, which is the main cause of about 25% of newborn deaths[1].

The causes of perinatal asphyxia are diverse including various maternal illnesses, placental disorders, and other fetal health problems[4-8]. There have been many studies conducted on newborns with perinatal asphyxia treated in neonatal intensive care units and neonatal wards, which have reported risk factors for this condition of prolapsed cord, pregnancy-induced hypertension, maternal iron deficiency anemia, neonatal seizures[1], maternal infection, prematurity, and multiple births[5]. This study aimed to examine the factors affecting mortality in neonates treated in a neonatal intensive care unit, which admits only newborns with greater severity of disease, who need more treatment tools, require endotracheal intubation, ventilators and drugs, and have a higher risk of death. In Chonburi Hospital during 2018-2021, 55.27% of the NICU admission were for perinatal asphyxia, of whom 20.22% died. This research aimed to study the prognostic factors for neonatal mortality with perinatal asphyxia in a neonatal intensive care unit, because we felt that if the prognostic factors for death were known, the treatment may be planned more efficiently, and we could also provide better information to parents.

Materials and Method

The study used a case-control retrospective design that reviewed the records of all any gestation-age patients diagnosed with perinatal asphyxia (APGAR score ≤7) admitted to the neonatal intensive care unit of Chonburi Hospital from January 2018 to December 2021.

Perinatal asphyxia patients who were also diagnosed with a congenital anomaly, such as gastroschisis, chromosome abnormalities, congenital diaphragmatic hernia, or hydrops fetalis, or had incomplete data for any of the study variables were excluded.

Data collection

Details of the clinical data from the hospital's electronic charts were obtained for each patient, including perinatal history (maternal age, resuscitation at delivery room, type of delivery, sentinel events, and Apgar scores), neonatal variables (gestational age, birth weight, sex, and referral status), clinical and treatment data (encephalopathy, severe metabolic acidosis).

Statistical analysis

The statistical analysis used IBM SPSS Statistics Version 23 and STATA version 16. Categorical data were compared with the chi-square test or Fisher's exact test, and continuous data used the student t test or Mann-Whitney U test, as appropriate, for data distribution. The relations of the prognostic factors were assessed using multiple logistic regression. Beta coefficient was used to create a weighted score. The probability of death was assessed with a risk curve to select the appropriate cut off point for death prediction with the finding presented in the form of survival analysis and hazard ratios.

Ethical approval

This research was approved by the Human Subjects Committee, Chonburi Hospital, Research code 54/65/S/h3

Results

During the study period, 21,939 neonates were born in our hospital, of whom 435 were admitted to

the neonatal intensive care ward due to perinatal asphyxia, and 88 cases (20.22%) died within the first 28 days. Among the death group, 22 neonates were excluded because of anomalies and 6 due to missing data, leaving 60 cases in the study. In the survival group, 37 neonates were excluded due to anomalies and 8 for missing data, leaving 302 neonates, of whom 60 were randomly selected by the computer to create a 1:1 ratio of the death and the survival groups.

Maternal and newborn demographic data

There were no significant differences in average maternal age, antenatal care, maternal medical conditions, complications during birth, gestational age, birth weight or delivery method between the death and survival groups. Only neonates with fetal distress, female sex, and referral cases showed statistically significant differences between the groups ($p<0.001$, 0.014, and 0.036 respectively), as shown in Tables 1 and 2.

The prognostic factors for neonatal mortality in newborns with perinatal asphyxia from the neonatal intensive care unit data

Infants in the group who died had significantly lower APGAR scores at 1 and 5 minutes, significant-

Table 1 Maternal demographic and clinical data

Demographic and clinical data	Neonatal deaths (n=60)		Neonatal survivors (n=60)		p-value
	Number	%	Number	%	
Age (years)*	28.15±7.27		28.92±7.78		0.578
Thai Nationality	55	91.67	50	83.33	0.269
No antenatal care.	7	11.67	4	6.67	0.529
Number of antenatal visits**	6 (3,9)		6 (3,9)		0.849
Twin pregnancies	3	5.00	3	5.00	0.999
Maternal diseases	12	20.00	19	31.67	0.144
High blood pressure	7	11.67	13	21.67	0.142
Diabetes	5	8.33	4	6.67	0.999
Others	4	6.67	7	11.67	0.197
Complications during delivery	54	90.00	53	83.33	0.769
Meconium aspiration syndrome	8	13.33	10	16.67	0.609
Marternal fever (>38 degrees Celsius)	3	5.00	1	1.67	0.619
Chorioamnionitis	2	3.33	1	1.67	0.999
PPROM >18 hours	1	1.67	5	8.33	0.207
Maternal hemorrhage	4	6.67	5	8.33	0.999
Fetal distress	34	56.67	12	20.00	<0.001***
Shoulder dystocia	2	3.33	3	5.00	0.999
Others	35	58.33	29	48.33	0.335

* Mean±SD, ** Median (IQR), ***p<0.05, PPROM = preterm premature rupture of membranes

Table 2 Neonatal data

Neonatal data	Neonatal deaths (n=60)		Neonatal survivors (n=60)		p-value
	Number	%	Number	%	
Referral cases	27	45.00	16	26.67	0.036**
Average gestational age (weeks)*	34.40±4.13		34.62±4.05		0.772
Female	29	48.33	16	26.67	0.014**
Premature	37	61.67	37	61.67	0.999
Average birth weight(g)*	2214.45±946.65		2175.97±781.44		0.809
Average birth length(cm)*	44.32±6.53		44.19±5.25		0.908
Average newborn head circumference (cm)*	30.08±3.92		30.38±3.36		0.663
Size of gestational age					0.41
appropriate for gestational age (AGA)	47	78.33	52	86.67	
Small for gestational age (SGA)	10	16.67	7	11.67	
Large for gestational age (LGA)	3	5.00	1	1,67	
Mode of delivery					0.298
Vaginal birth	23	38.33	29	48.33	
Emergency cesarean section	37	61.67	30	50.00	
Non-emergency cesarean section	0	0.00	1	1.67	
Therapeutic hypothermia (n=27)***	9	15.00	18	30.00	0.07

* Mean±SD, ** Significant - p<0.05, *** a total of 27 patients met the treatment criteria

ly higher requirements for advanced neonatal resuscitation, significantly more sentinel events, incidence of severe acidosis, and moderate to severe encephalopathy (stage II to III encephalopathy) than in the survival group (p<0.05) as shown in Table 3. Neonates who met the criteria for moderate and severe encephalopathy were treated by therapeutic hypothermia, of whom there were 9 (15.00%) in the non-survival group and 18 in the survival group (30.00%).

Multiple logistic regression analysis of predictive factors for death in newborns with perinatal asphyxia

Multiple logistic regression analysis indicated that the prognostic factors associated with neonatal mortality from neonatal asphyxia were female gender (OR 3.66, 95%CI 1.217-10.654, p=0.021), requirement for advanced neonatal resuscitation (OR 3.727, 95%CI 1.141-12.174, p=0.029), and severe acidosis (OR 4.583, 95%CI 1.533-13.705, p=0.006), all of which showed statistically significant differences compared to the survival group, as shown in Table 4. All three significant factors were used to calculate a weighted score to create a predictive score for mortality. Female, requirement for advanced neonatal resuscitation, and severe acidosis were scored as 1, 2, and 2 points, respectively (Table 5), with a total possible score of 5, which had a predictive power represented by the area under the curve (AUC) of 0.866 and, an accuracy of 86% (Figure 1). The weighted scores of 1, 2, 3, 4 and 5 had probabilities of death of 20.89%, 39.66%, 62.10%, 80.30% and

Table 3 Prognostic factors affecting neonatal mortality

Factor	Death within 28 days (n=60)		Survived >28 days (n=60)		p-value
	Number	%	Number	%	
APGAR scores					
1 minute*	1.57±1.95		3.27±2.00		<0.001**
5 minutes*	3.42±2.55		5.05±2.13		<0.001**
Required advanced resuscitation					
PPV	46	76.67	13	21.67	<0.001**
CPAP	57	95	58	96.67	0.999
Intubation	7	11.67	16	26.67	0.062
Chest compression	60	100	60	100	0.999
Medication	46	76.67	13	21.67	<0.001**
PPV >10 minutes	32	53.33	8	13.33	<0.001**
Sentinel events	45	75	28	46.67	0.001**
Severe acidosis	50	83.33	9	15.00	<0.001**
pH*	7.16±0.19		7.33±0.12		<0.001**
Base excess*	-15.37±6.07		- 6.06±5.91		<0.001**
Encephalopathy	56	93.33	40	66.67	<0.001**
Mild (Stage I)	5	8.33	21	35.00	
Moderate (Stage II)	21	35.00	15	35.00	
Severe (Stage III)	30	50.00	4	66.67	
Stage II and III encephalopathy	51	85.00	19	31.67	<0.001**
Abnormal neuro signs	56	93.33	33	55.00	<0.001**
Alteration of consciousness	44	73.33	15	25.00	<0.001**
Seizure	33	55.00	8	13.33	<0.001**
Hypotonia	45	75.00	27	45.00	<0.001**
Decreased primitive reflex	55	91.67	32	53.33	<0.001**

*mean±SD, **p<0.05, PPV = Positive pressure ventilation, CPAP = Continuous positive airway pressure

Table 4 Multiple logistic regression of prognostic factors affecting the death of the study newborns with perinatal asphyxia.

Prognostic factor	Beta-Coefficient	Adjusted OR	95%CI	p-value
Female gender	1.53	3.6	1.22 – 10.65	0.021*
Referral case	0.63	2.15	0.69 – 6.70	0.190
Sentinel events	0.46	0.66	0.20 – 2.17	0.490
Requirement of advanced resuscitation	2.22	3.73	1.14 – 12.17	0.029*
APGAR at 1 minute	0.16	0.71	0.12 – 4.32	0.710
APGAR at 5 minutes	0.22	0.77	0.17 – 3.41	0.730
Encephalopathy stage II	0.53	1.71	0.31 – 9.44	0.540
Encephalopathy stage III	1.92	6.83	0.91 – 50.77	0.060
Encephalopathy stageII,III	1.68	3.22	0.93 – 11.13	0.060
Severe acidosis	2.02	4.58	1.53 – 13.71	0.006*

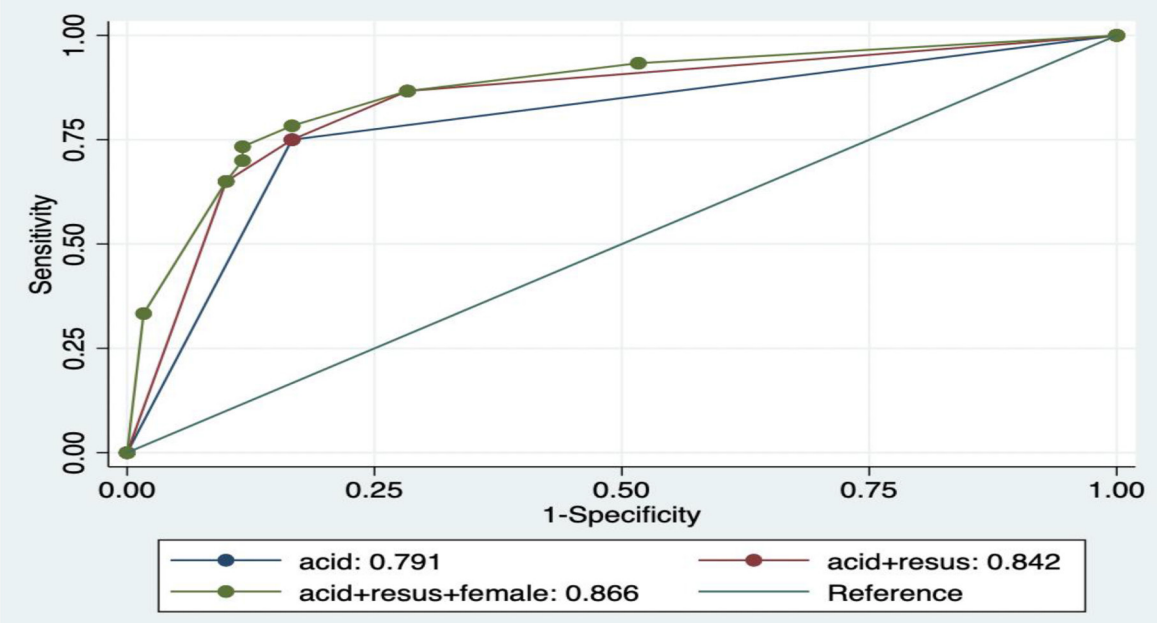
*p<0.05

Table 5 Weighted score of factors predicting the death of study newborns with perinatal asphyxia.

Prognostic factor	Weighted score*
Female gender	1
Requirement of advanced resuscitation	2
Severe acidosis	2
Total possible score	5

*Weighted scores based on Beta coefficient

Figure 1 Areas under the curves (AUC) of the prognostic factors associated with neonatal mortality with neonatal asphyxia



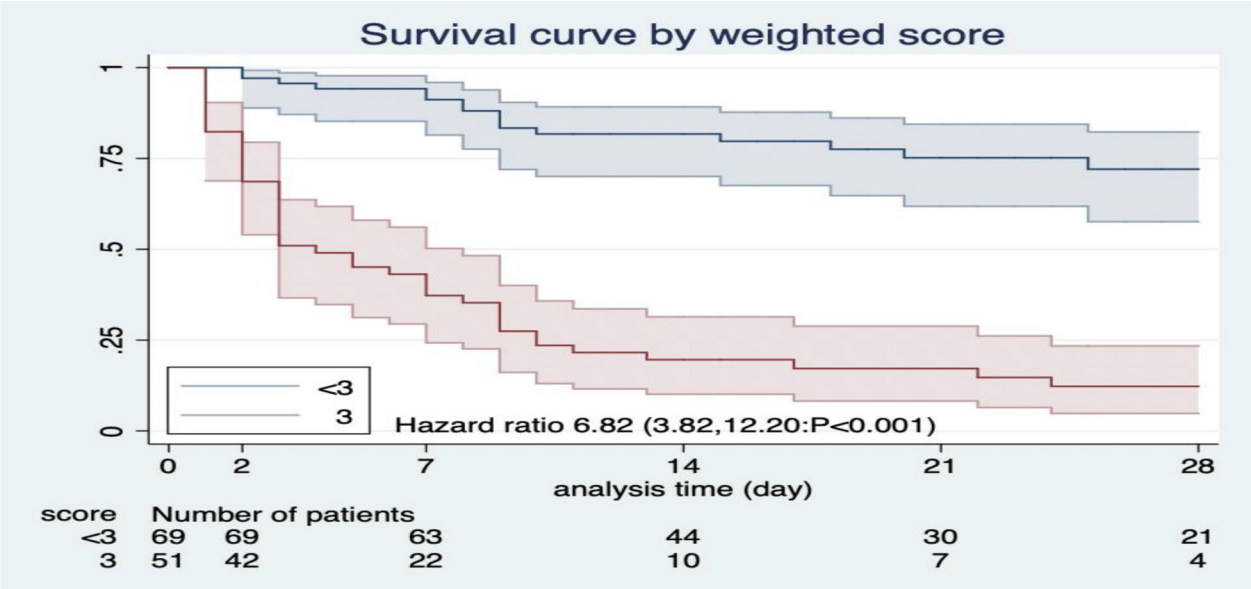
Remark: acid = severe acidosis, resus = advanced resuscitation, female = female sex

91.03%, respectively (Table 6). The cutoff point suitable for applying the weighted score was equal to or greater than 3 points, which had a probability of death of approximately 60%, which was greater than the incidence of mortality among newborns in this study (20.22%) (Table 6). Newborns with a score equal to or greater than 3 points had a 6.82-fold chance of neonatal death (HR 6.82, 95%CI 3.82-12.20, p<0.05), as shown in Figure 2.

Table 6 Correlation of deaths among newborns with perinatal hypoxia compared with weighted scores

Score	Probability of 28-day mortality (%)
0	9.58
1	20.89
2	39.66
3	62.1
4	80.3
5	91.03

Figure 2 **Survival analysis of newborns with perinatal asphyxia by comparing between the groups of newborns with a weighted score equal to or greater than 3 and the group of newborns with a weighted score less than 3**



Discussion

This study determined the prognostic factors for neonatal mortality in newborns with perinatal asphyxia in the Neonatal Intensive Care Unit at Chonburi Hospital, Thailand by comparing selected factors between infants who died within 28 days or survived beyond that time. Three important prognostic factors were identified:

Factor 1: female (OR 3.60, 95%CI 1.217-10.654, p=0.021). In the study, there were 45 females of 120 births (37.5%), of whom 29 were in the non-survival group (48.33%) and 16 in the survival group (26.67%), which was statistically significant, although this factor was not significant in previous studies[5,9,10], possibly due to ethnic differences between our study and earlier ones, sample size differences, or the fact that the newborns enrolled in both arms of this study had severe disease requiring greater respiration support (endotracheal tube and mechanical ventilator) and needed treatment in our neonatal intensive care unit, while other studies included almost neonates who did not require ICU admission. The survival group used randomization by computer and female may be accidental. However, future studies are needed to clarify this point.

Factor 2: requirement for advanced neonatal resuscitation (OR 3.727, 95%CI 1.141-12.174, p=0.029). This finding was similar to an earlier study conducted in Tehran, Iran[11]. The principle cause of perinatal asphyxia in this context was that all newborns in this study required early life support, intubation and requiring mechanical ventilator, chest compression or medications such as adrenaline, indicating a problem with the heart and blood pumping insufficiency, which in turn increased the chance of lack of oxygen for a longer time leading to ischemia in major organs such as the brain, kidneys or heart to have ischemia.

Factor 3: severe acidosis (pH <7 or BE <-12) (OR 4.583, 95%CI 1.533-13.705, p=0.006). The principal causes of perinatal asphyxia in this context was blood gas showing severe metabolic acidosis, which results from prolong asphyxia and the resulting anaerobic activity.

Sentinel events and moderate to severe encephalopathy (stages II or III) showed statistically significant differences ($p<0.05$) as shown in Table 3, but the multiple logistic regression revealed that these were not significant factors. This is because in this study, newborns met the inclusion criteria to be treated by therapeutic hypothermia which is used to treat hypoxic ischemic encephalopathy, which has been found to provide statistically significantly better outcomes than neonates not treated with this treatment[12], which may have increased the survival rate in these infants.

Our predictive model was developed by applying scores of 1, 2 and 2 for each of the above significant risk factors, respectively. With the cutoff point of 3 from the model, the probability of death within 28 days was approximately 60% with a Hazard ratio of 6.82, 95% CI 3.82-12.20, and $p<0.05$. If we use these prognostic factors (female neonate, requirement for advanced neonatal resuscitation, severe acidosis) in newborns with perinatal asphyxia in the neonatal intensive care unit, we can provide more accurate information to parents about the probability of death within 28 days by using the weighted scores and plan for intensive treatment for severe cases to increase the chance of survival.

Limitations

First, although the study had a large enough sample size, it was a retrospective study with the attendant problems of reliable data collection, etc. Second, the perinatal asphyxia patients in our study were enrolled from only a single center, and thus the results may lack generalizability. However, about one-tenth of the study patients were referred from other provinces in Eastern Thailand. Third, the study focused only on the short-term outcomes of death and survival, there are other outcomes and detailed long-term clinical data are needed to clarify the long-term effects of perinatal asphyxia in the early years of life in these patients.

Conclusion

Perinatal asphyxia mortality is an important problem that needs to be treated immediately with extreme care required for improvement of the survival rates, especially in neonates with perinatal asphyxia who need to be treated in a neonatal intensive care unit. This study found that female, requirement for advanced neonatal resuscitation and severe acidosis were statistically significant prognostic factors for neonatal mortality with perinatal asphyxia. When used to calculate weighted scores for predicting mortality of 1, 2 and 2, respectively, a score of 3 or higher had a probability of death of 60% or more and there was a 6.82-fold chance of neonatal mortality.

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บทคัดย่อ: ปัจจัยที่มีผลต่อการพยากรณ์การเสียชีวิตของทารกแรกเกิดที่มีภาวะขาดออกซิเจนปริกำเนิดในหอผู้ป่วยทารกแรกเกิดวิกฤติ

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ภาวะขาดออกซิเจนปริกำเนิด (perinatal asphyxia) เป็นปัญหาสุขภาพที่ซับซ้อนของทารกแรกเกิดและทำให้มีการเสียชีวิตของทารกแรกเกิดเพิ่มขึ้น ในประเทศไทยภาวะขาดออกซิเจนปริกำเนิดยังคงเป็นสาเหตุที่พบบ่อยของการเจ็บป่วยและการตายของทารกแรกเกิดในช่วงสิบปีที่ผ่านมา ดังนั้น หากทราบปัจจัยพยากรณ์การเสียชีวิตโดยเฉพาะในทารกแรกเกิดที่มีภาวะขาดออกซิเจนปริกำเนิดที่อาการรุนแรงที่จำเป็นต้องได้รับการรักษาในหอผู้ป่วยทารกแรกเกิดวิกฤติอาจทำให้มีการวางแผนการรักษาได้อย่างมีประสิทธิภาพมากยิ่งขึ้น การวิจัยนี้เป็นการศึกษาย้อนหลังแบบเชิงเปรียบเทียบโดยมีวัตถุประสงค์คือการระบุปัจจัยพยากรณ์การเสียชีวิตของทารกแรกเกิดที่มีภาวะขาดออกซิเจนปริกำเนิดในหอผู้ป่วยทารกแรกเกิดวิกฤติ การศึกษาดำเนินการกับทารกแรกเกิด 120 คน (กลุ่มเสียชีวิต 60 รายและกลุ่มรอดชีวิต 60 ราย) ที่เข้ารับการรักษาด้วยภาวะขาดออกซิเจนปริกำเนิดในหอผู้ป่วยทารกแรกเกิดวิกฤติในโรงพยาบาลชลบุรีตั้งแต่วันที่ 1 มกราคม 2561 ถึงวันที่ 31 ธันวาคม 2564 ปัจจัยเสี่ยงของภาวะขาดออกซิเจนปริกำเนิดประเมินโดยใช้การวิเคราะห์ด้วยสถิติ multiple logistic regression และรูปแบบการพยากรณ์ถูกสร้างขึ้นโดยใช้ coefficient of the regression weighted score ของปัจจัยเสี่ยงที่มีนัยสำคัญเพื่อใช้ในการทำนายโอกาสในการเสียชีวิต ผลการศึกษาพบว่า ปัจจัยพยากรณ์ที่มีผลต่อการเสียชีวิต มีเพศหญิง (OR 3.60, 95%CI 1.21-10.65, p<0.05) จำเป็นต้องได้รับ advanced resuscitation (OR 3.72, 95%CI 1.14-12.17, p<0.05) และมีภาวะ severe acidosis (OR 4.58, 95%CI 1.53-13.70, p<0.05) รูปแบบการพยากรณ์ได้สร้างเป็นคะแนนถ่วงน้ำหนักเพื่อทำนายการเสียชีวิตเท่ากับ 1, 2, และ 2 สำหรับแต่ละปัจจัยเสี่ยงที่มีนัยสำคัญตามลำดับ โดยมีค่า cut off point เท่ากับ 3 คะแนน มีความน่าจะเป็นของการเสียชีวิตใน 28 วันแรกของชีวิตประมาณ 60% โดยมี hazard ratio = 6.82, 95%CI 3.82-12.20, p<0.05.

คำสำคัญ: **ปัจจัยพยากรณ์; ภาวะขาดออกซิเจนปริกำเนิด; การเสียชีวิตในทารกแรกเกิด**