RESEARCH PAPER

Survival Modelling Of Neonates With Perinatal Asphyxia In A Tertiary Care Hospital In Lucknow

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ABSTRACT

Perinatal asphyxia accounts for nearly one-quarter of neonatal complications worldwide, positioning as a primary driver of neonatal death and long-term health issues. For neonates identified with perinatal asphyxia, the probability of adverse outcomes fluctuates throughout their hospitalization, with distinct patient characteristics and medical variables impacting their recovery path differently at various points post-admission. Survival-based approaches that use duration of stay as the time scale are therefore essential for characterizing this time-varying risk in resource-limited settings. A study was conducted on neonates admitted to the Neonatal Intensive Care Unit (NICU) and Special Newborn Care Units (SNCU) at Dr. Ram Manohar Institute of Medical Sciences (RMLIMS) in Lucknow, Uttar Pradesh, from January 1, 2024, to December 31, 2024, covering the period from admission to discharge. The event of interest was on perinatal asphyxia morbidity in neonates. Neonates who were discharged alive were treated as censored observations. We used semi-parametric Cox proportional hazards regression and parametric Weibull, Exponential, log-logistic, and Gompertz survival models to identify key predictors of perinatal asphyxia. Among these applied models, the Weibull proportional hazards model showed the best fit. The model's adequacy was confirmed with the Cox-Snell residual plot. Key significant predictors of perinatal asphyxia included the absence of cry at birth, a low five-minute APGAR score (Appearance, Pulse, Grimace, Activity, and Respiration), preterm gestational age, prolonged labor, fetal distress, and the need for resuscitation at birth. Weibull parametric survival models offer a solid framework for understanding time-dependent perinatal asphyxia risk in resource-limited NICU settings. The identified predictors define a clinically actionable risk profile spanning intrapartum events, neonatal condition at birth, and gestational maturity.

Keywords: *Perinatal asphyxia, neonatal morbidities, Weibull survival model, proportional hazards, NICU.*

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INTRODUCTION

Perinatal asphyxia in neonates is a significant cause of newborn morbidity, long-term neurological developmental issues, and death worldwide[1]. Clinically, perinatal asphyxia is defined as the failure to establish spontaneous and regular breathing within one minute of birth. This leads to progressive hypoxaemia, hypercapnia, and metabolic acidosis, which together impair organ perfusion and cellular function[2]. In its most severe form, perinatal asphyxia can cause Hypoxic-Ischaemic Encephalopathy (HIE), multi-organ dysfunction, and death during the early neonatal period[3,4]. Data from the World Health Organization indicates that between 4 and 9 million infants are affected by this condition annually. It is responsible for nearly 23 percent of the total global neonatal death toll, with a staggering 98 percent of these fatalities concentrated in low- and middle-income nations (LMICs)[5,6].

In India, perinatal asphyxia accounts for roughly 16 to 21 percent of newborn deaths; specifically, Uttar Pradesh faces one of the country's heaviest burdens, as rising hospital birth rates have not been met with corresponding upgrades in the standard of care during labor[5,6]. The APGAR score at one and five minutes, the cry at birth, and the need for resuscitation are the most

common indicators used to identify asphyxiated neonates at the time of delivery[7,8,9].

Studies have also identified specific intrapartum and neonatal risk factors that are associated with the occurrence of perinatal asphyxia. These factors include foetal distress, prolonged labor, preterm birth, low birth weight, and obstetric issues like obstructed labor and meconium-stained amniotic fluid[10,11]. In resource-limited settings, systems-level determinants including delayed obstetric decision-making, inadequate skilled birth attendance, and suboptimal neonatal resuscitation capacity further amplifies biological risk and represent modifiable targets for preventive intervention[11,12].

Despite the clinical importance of characterizing time-dependent perinatal asphyxia risk, existing research predominantly employs logistic and multivariable regression models, which overlook the advantages of survival modeling in the early neonatal period. Neither approach adequately captures the specific distribution-based hazard structure typically observed in tertiary care NICU cohorts[11,13,14].

In this aspect, parametric survival models offer distinct methodological advantages by correctly specifying the baseline hazard distribution13. Furthermore, they provide highly interpretable time-dependent hazard ratios and achieve greater statistical efficiency for identifying moderate-magnitude predictors within smaller institutional cohorts[15].

The application of parametric survival modeling to perinatal asphyxia within Indian research on NICUs remains limited. Consequently, the present study employs both semi-parametric and parametric survival modelling techniques to characterize the time-to-perinatal asphyxia hazard structure and identify independent predictors of perinatal asphyxia morbidity in a tertiary care NICU in Uttar Pradesh, India. Furthermore, this study sought to determine the critical factors associated with perinatal asphyxia in neonates for targeted clinical interventions.

MATERIALS AND METHODS

In this research, we conducted a prospective study design to collect data from the NICU and SNCU of the Department of Pediatrics at Dr. Ram Manohar Lohia Institute of Medical Sciences (RMLIMS) in Lucknow, Uttar Pradesh. RMLIMS is a teaching hospital with 24 beds and has life-support technologies, including bubble Continuous Positive Airway Pressure (CPAP) units and invasive ventilation. Data was collected during the study period from January 1, 2024, to December 31, 2024. We used a pre-tested questionnaire that included both intramural cases (neonates born within the facility) and extramural cases (neonates referred from external facilities). The Institutional Ethics Committee (IEC) of RMLIMS in Lucknow approved the study (IEC: No. :184/22). Informed consent was also obtained from the guardians of the neonates included in the study.

All live-born neonates aged 0 to 27 days within the NICU and SNCU during the study period were eligible for inclusion. Neonates were excluded if they had incomplete clinical records (missing primary diagnosis, gestational age, or birth weight), were transferred within 24 hours of admission before outcomes could be ascertained, or if guardians declined consent. The final sample included 686 neonates, who were enrolled one after another. They were monitored from the time of admission until discharge. The main focus of this study is the neonates with perinatal asphyxia during their hospital stay. We coded the event as 1 for neonates with perinatal asphyxia and 0 for those with other health issues, treating them as censored observations. The time scale was the length of the hospital stay in days, calculated from the admission date to the discharge date. The analysis incorporated a wide range of maternal and newborn-related factors. The selection of prognostic variables was based on a comprehensive literature review to ensure the inclusion of key factors influencing perinatal asphyxia. Consequently, the predictor variables were categorized into three clinical domains: (i) maternal and antepartum factors, including maternal age (17–24, 25–30, >30 years), gravida of mother (primigravida vs. multigravida), pregnancy-induced hormone (PIH), type of delivery (Lower Segment Caesarean section(LSCS) and normal vaginal delivery (NVD)), amniotic fluid color (clear vs. stained), and preterm premature rupture of membranes (PPROM); (ii) intrapartum factors, including course of labor (uneventful, obstructed, or prolonged), type of labor (spontaneous vs. induced), and feotal distress (yes/no); and (iii) neonatal factors, including sex, gestational age (full term vs. preterm), birth weight (normal vs. low birth weight), breastfeeding initiation (yes/no), APGAR score at 5 minutes (more than equal to 7 vs. less than 7), cry immediately after birth (yes/no), and requirement for resuscitation at birth (yes/no)[9,10,11,12].

Bivariate associations between the outcome and prognostic factors were evaluated using chi-square tests. The Variance Inflation Factor (VIF) was used to assess multicollinearity among variables. The Cox

proportional hazard model and the parametric survival models were fitted to identify significant predictors of perinatal asphyxia. The Schoenfeld residuals test was employed to determine the proportional hazards (PH) assumption[15]. Overall model fit was assessed by plotting Cox-Snell residuals against the Nelson-Aalen cumulative hazard estimator. A line with a unit slope through the origin indicated a good fit. AIC and BIC were used to choose the best-fitting parametric models[16]. Statistical modelling was performed using Stata v.13 (StataCorp, 2013)[17].

The Cox Proportional Hazards Model

Within the Cox proportional hazards framework, the risk of an event occurring for a specific covariate vector $\mathbf{x}_i$ is characterized as the interaction between a flexible baseline hazard and the exponential of the linear predictors[18]. This relationship is formally expressed as:

$$h(t \mid \mathbf{x}_i) = h_0(t) \cdot \exp(\mathbf{x}_i{}^{\top}\boldsymbol{\beta}) \quad (1)$$

In this semi-parametric approach, $h_0(t)$ represents the baseline hazard function. By utilizing the partial likelihood estimation method, the vector of regression parameters β can be determined without the need to specify the functional form of $h_0(t)$, effectively treating it as a nuisance factor[13,18]. The likelihood function is defined as:

$$L(\beta) = \prod_{i:\delta_i=1} \frac{\exp(\mathbf{x}_i^{\top}\beta)}{\sum_{j\in\mathcal{R}(t_i)} \exp(\mathbf{x}_j^{\top}\beta)} \quad (2)$$

Here, $\mathcal{R}(t_j)$ encompasses all subjects remaining in the risk pool at time t_j. Furthermore, the Breslow method was implemented to account for any instances of simultaneous event occurrences[19].

Proportional Hazards (PH) Assumption Tests

The PH assumption that covariate effects are constant over time is evaluated using Schoenfeld residual. Schoenfeld residual for covariate k at the j-th event is

$$r_{k(i)} = x_{ki} - \frac{\sum_{j\in R(t_i)} x_{kj} \cdot \exp\left(\mathbf{x}_j^{\top}\hat{\boldsymbol{\beta}}\right)}{\sum_{j\in R(t_i)} \exp\left(\mathbf{x}_j^{\top}\hat{\boldsymbol{\beta}}\right)} \quad (3)$$

Under PH, $E\left[\tilde{r}_{jk}\right] = 0$ for all t. A statistically significant slope when $\tilde{r}_{jk}$ is regressed on a function of time ($p < 0.05$) indicates violation of PH[15].

Parametric Survival Models

Models using a parametric survival framework operate on the premise that the baseline hazard follows a predefined probability distribution. Adopting a proportional hazards (PH) structure, the hazard function for subject i at a given time t is expressed as

$$h(t \mid \mathbf{x}) = h_0(t;\theta)\exp(\mathbf{x}'\beta) \quad (4)$$

where $h_0(t)$ represents the underlying hazard, while $\mathbf{x}$ and β denote the vectors for covariates and their corresponding coefficients, respectively. To determine the model parameters, the maximum likelihood (ML) estimation method is applied. This study utilizes four distinct specifications for the parametric baseline hazard[14].

1. Exponential Distribution

The exponential model imposes a constant baseline hazard $h_0(t) = \lambda$, implying memorylessness and no duration dependence[13,14]. The hazard functions and log-likelihood are:

$$h(t) = \lambda\exp(\mathbf{x}^{\top}\boldsymbol{\beta}) \quad (5)$$

$$\ell(\boldsymbol{\beta},\lambda) = \sum_i [d_i(\ln\lambda + \mathbf{x}_i^{\top}\boldsymbol{\beta}) - \lambda t_i\exp(\mathbf{x}_i^{\top}\boldsymbol{\beta})] \quad (6)$$

where d_i is the event indicator and t_i the observed time for individual i.

2. Weibull Distribution

The Weibull model introduces a shape parameter $\gamma > 0$ allowing monotonically increasing ($\gamma > 1$), decreasing ($\gamma < 1$), or constant ($\gamma = 1$) hazard[13,14].

$$h(t) = \lambda\gamma\, t^{\gamma-1}\exp(\mathbf{x}^{\top}\boldsymbol{\beta}) \quad (7)$$

$$\ell(\boldsymbol{\beta},\lambda,\gamma) = \sum_i \{d_i[\ln(\lambda\gamma) + (\gamma-1)\ln t_i + \mathbf{x}_i^{\top}\boldsymbol{\beta}] - \lambda t_i^{\gamma}\exp(\mathbf{x}_i^{\top}\boldsymbol{\beta})\} \quad (8)$$

3. Gompertz Distribution

The Gompertz model specifies an exponentially increasing or decreasing baseline hazard $h_0(t) = \lambda e^{\gamma t}$ with shape parameter γ. Setting $\gamma = 0$ collapses the model to the exponential[13,14]:

$$h(t) = \lambda e^{\gamma t}\exp(\mathbf{x}^{\top}\boldsymbol{\beta}) \quad (9)$$

$$\ell(\boldsymbol{\beta},\lambda,\gamma) = \sum_i \left\{d_i[\ln\lambda + \gamma t_i + \mathbf{x}_i^{\top}\boldsymbol{\beta}] - \frac{\lambda}{\gamma}[e^{\gamma t_i} - 1]\exp(\mathbf{x}_i^{\top}\boldsymbol{\beta})\right\} \quad (10)$$

4. Log-Logistic Distribution

The log-logistic model accommodates a non-monotone hazard that first increases then decreases, suitable for processes with an internal peak risk[13,14]:

$$h(t) = \frac{\lambda\gamma(\lambda t)^{\gamma-1}}{1 + (\lambda t)^{\gamma}}, \quad (11)$$

To determine the most appropriate model, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were utilized for comparison. The mathematical definitions for these criteria are:

$$AIC = -2\ln(L) + 2k$$

$$BIC = -2\ln(L) + k\ln(n)$$

Within these equations, k signifies the quantity of parameters estimated, and n corresponds to the total observations in the sample. In this framework, the optimal model is identified by achieving the lowest possible values for both AIC and BIC[16].

RESULTS

The association between the event and prognostic variables was examined using the chi-square test. The sex of newborn, breastfeeding within one hour, birth weight, APGAR score at 5 minutes, course of labor, and amniotic fluid colour, cried immediately after birth, and resuscitation required were found to be associated with the perinatal asphyxia. The variance inflation factor (VIF) was employed to detect multicollinearity among predictor variables. With all VIF values below 3.0 and a mean VIF of 1.32, multicollinearity was deemed negligible.

The Schoenfeld residual test yielded a chi-square statistic of 16.69 (d.f. = 18, p = 0.544), showing that the proportional hazards assumption was satisfied across the neonatal follow-up period (Table 1). Among the fitted parametric Weibull, exponential, Gompertz, and loglogistic proportional hazards models, the Weibull model had the lowest AIC and BIC (Table 2). Six predictors were found to be significant for the perinatal asphyxia morbidity in the Weibull model. Absence of cry immediately after birth was identified as the strongest predictor of perinatal asphyxia, with affected neonates exhibiting 7.662 (95% CI: 4.135, 14.197) times the instantaneous hazard of experiencing perinatal asphyxia compared with those who cried at birth. A low 5-minute APGAR score was the second-strongest predictor. Neonates with an APGAR score below 7 faced 2.042 times the risk of perinatal asphyxia as compared to those with a normal score of 7 or above (95% CI: 1.406, 2.966, $p < 0.001$). Preterm birth was also a significant predictor, with preterm neonates showing 1.664 times the risk of perinatal asphyxia compared to term neonates. (Table 3)

Maternal and intrapartum factors contributed significantly to the risk. Neonates born after prolonged labor faced 1.745 times the risk of perinatal asphyxia compared to those born after normal labor. Foetal distress was identified as an independent and significant prognostic determinant of perinatal asphyxia in the Weibull model (HR = 1.640; 95% CI: 1.015, 2.652, $p < 0.05$). Neonates needing resuscitation right after birth had 1.760 times the risk of perinatal asphyxia with respect to those who did not require this intervention (95% CI: 1.026, 3.020, $p < 0.05$) (Table 3).

The sex of the neonate showed no independent association with perinatal asphyxia risk after adjustment for clinical and obstetric covariates, indicating that sex alone does not confer differential risk within this cohort. Furthermore, breastfeeding status, low birth weight, maternal multigravida status, caesarean section delivery, preterm premature rupture of membranes (PPROM), obstructed labor, induced labor, pregnancy-induced hormones, and stained amniotic fluid all had non-significant associations in the multivariate model. (Table 3).

Both the semi-parametric and parametric survival frameworks demonstrated strong predictive accuracy. Specifically, the Cox regression yielded a Harrell's C-statistic of 0.861 and a Somers' D of 0.722, which closely matched the Weibull model's scores of 0.860 and 0.721. Such high metrics, as detailed in Table 3, confirm that the chosen independent variables are highly effective at distinguishing the underlying factors associated with the onset of perinatal asphyxia.

Figures 1 and 2 show the overall goodness-of-fit for the models. For this cohort, the observed cumulative hazard in the Weibull model closely aligns with the reference line across the distribution, indicating that the Weibull distribution accurately captures the baseline hazard structure of Perinatal Asphyxia in this study. When comparing the two, the Weibull PH model (Figure 1) shows tighter, more consistent adherence to the reference line than the Cox PH model (Figure 2). This visual evidence, combined with the lower AIC and BIC values, confirms that the parametric Weibull model is a more robust and statistically efficient choice for identifying predictors of neonatal morbidity in this high-risk setting.

DISCUSSION

This study provides a comprehensive perspective on the occurrence of perinatal asphyxia in tertiary care NICU/SNCU in Uttar Pradesh. It uses both semi-parametric and parametric survival modeling. The preference for the Weibull model is justified by its ability to explicitly specify the baseline hazard, providing a more precise characterization of the accelerating risk during the immediate neonatal period than the distribution-free Cox method within a hospital-based cohort[9,10,11]. The factors that have emerged as

independent determinants of the perinatal asphyxia were immediate neonatal signs of depression (absence of cry at birth, low 5-minute APGAR), maternal-infant vulnerabilities linked to prematurity, intrapartum-care deficiencies reflected by prolonged labor and resuscitation requirements.

The absence of cry at birth conferred the highest hazard (HR = 7.66), indicating profound brainstem suppression of autonomous respiratory drive and placing the newborn in the most critical stage of asphyxia[20]. This finding is consistent with a study that observed that non-crying neonates require intensive, high-priority surveillance irrespective of eventual respiratory effort[4]. A low 5-minute APGAR score (HR = 2.04) captures persistent depression beyond the first minute and reflects the evolution of hypoxic-ischemic encephalopathy[4,21,22]. The APGAR score remains a pragmatic bedside tool for triaging neonates to higher levels of care; its prognostic utility is supported by numerous studies linking scores ≤ 3 at 5 minutes to increased mortality and neurodevelopmental disability, as shown in the study by Kawakami et al. (2021)[4]. Persistent low APGAR scores should therefore trigger rapid escalation to neonatal intensive care, including neuroprotective strategies such as therapeutic hypothermia when indicated.

Preterm birth was associated with an adjusted HR of 1.66, underscoring the physiological immaturity of respiratory surfactant systems and reduced pulmonary compliance[23,24]. In Uttar Pradesh, this vulnerability is often compounded by limited antenatal corticosteroid coverage and inadequate CPAP support[23]. Consequently, preterm asphyxiated neonates necessitate stratified management protocols that include early surfactant administration, gentle ventilation strategies, and vigilant monitoring for air-leak syndromes[23,24]. Tertiary NICUs, by virtue of their equipment and expertise, are uniquely positioned to mitigate the combined burden of prematurity and asphyxia. The association of prolonged labor and resuscitation requirements with perinatal asphyxia (HR = 1.76) likely reflects the high-risk referral pattern to tertiary centers, where fetal oxygen reserves have already been depleted prior to arrival[10,11]. Delayed emergency obstetric decisions or insufficiently skilled attendance in peripheral settings prolong the second stage of labor, exacerbating fetal acidosis[4,5,7]. Moreover, suboptimal delivery-room resuscitation manifested by inadequate mask ventilation, delayed chest compressions, or poor adherence to Helping Babies Breathe algorithms increases early mortality[24].

The study confirms that perinatal asphyxia in a tertiary NICU/SNCU is driven not only by intrinsic neonatal and maternal factors but also by modifiable health-system deficiencies. Addressing delays in obstetric care, ensuring essential neonatal therapies, and reinforcing resuscitation competence through Helping Babies Breathe and quality-improvement are critical steps to reduce the burden of perinatal asphyxia, especially among preterm and prolonged-labor neonates. Future research should evaluate the impact of integrated obstetric-neonatal quality-improvement bundles on perinatal asphyxia incidence and long-term neurodevelopmental outcomes in low-resource setting[22,23,24].

Methodologically, this study establishes the Weibull distribution as an appropriate specification for survival research in advanced Indian NICUs. While the retrospective design and single-center setting are noted limitations, the findings provide a robust benchmark for future prospective, multi-center studies aimed at validating these hazard structures across the regional healthcare hierarchy.

In conclusion, this study underscores that perinatal asphyxia in tertiary care settings in Uttar Pradesh is a multifaceted challenge driven by immediate neonatal depression, maternal-infant vulnerabilities, and systemic intrapartum-care deficiencies. The absence of a cry at birth and low 5-minute APGAR scores remain the most critical clinical predictors of hazard, necessitating rapid escalation to intensive care and neuroprotective strategies. Furthermore, the significant impact of prolonged labor and resuscitation requirements highlights the urgent need for modifiable health-system interventions, including reinforced Helping Babies Breathe training and streamlined obstetric referral chains. By integrating these clinical insights with the precision of Weibull survival modelling, this research provides a robust framework for future quality-improvement bundles aimed at reducing the long-term burden of neonatal mortality and disability in low-resource environments.

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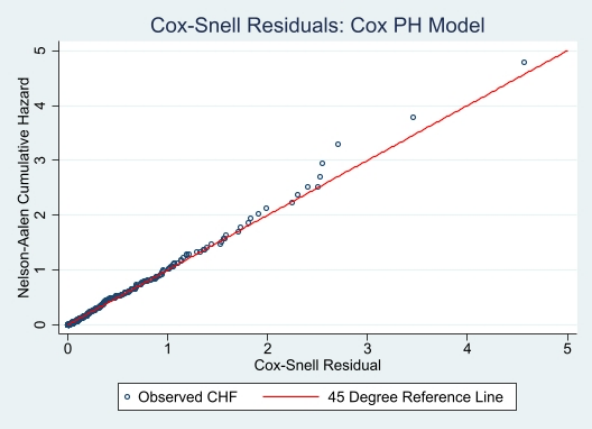
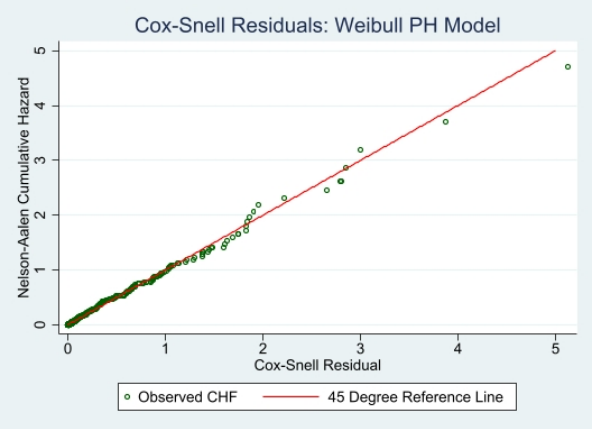
FIGURES AND TABLES





Note: These diagnostic plots were generated using Stata (Version 13) following estimation of the respective survival models.

Figure 1: Cox-Snell Residual Plot for the Cox PH Model

Figure 2: Cox-Snell Residual Plot for the Weibull PH Model

Table 1: Proportional Hazards Assumption Diagnostic Test (Schoenfeld Residuals)

Diagnostic Test	Statistic	d.f.	p-value
Global Test	16.69	18	0.5443

d.f. = Degrees of Freedom.

Table 2: Comparison of Parametric Survival Models for Model Selection

Model	Log-likelihood (Model)	d.f.	AIC	BIC
Weibull	**-287.99**	**20**	**615.99**	**706.61**
Log-normal	-290.6	20	621.2	711.82
Gompertz	-295.15	20	630.31	720.93
Exponential	-315.22	19	668.43	754.52

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

Table 3: Cox Proportional Hazards and Weibull Regression Models

Predictors	Cox PH HR (95% CI)	Weibull PH HR (95% CI)
Sex of Baby (Ref: Female)		
Male (Male)	0.837 (0.594-1.181)	0.839 (0.595-1.183)
Gestational Week (Ref: Full Term)		
Preterm	1.636* (1.026-2.606)	1.664* (1.040-2.662)
Breastfeeding within one hour (Ref: Yes)		
No	1.438 (0.700-2.951)	1.386 (0.676-2.842)
Birth Weight (Ref: Normal Birth Weight)		
Low Birth Weight	0.775 (0.495-1.212)	0.753 (0.479-1.184)
APGAR Score at 5 min (Ref: More than >=7)		
Less than 7	1.960*** (1.349-2.848)	2.042*** (1.406-2.966)
Maternal Age (Ref: 25-30 Years)		
17-24 Years	0.981(0.663-1.451)	0.982(0.664-1.453)
> 30 Years	0.936 (0.586-1.497)	0.934 (0.585-1.491)
Gravida of mother (Ref: Primigravida)		
Multigravida	0.797 (0.563-1.128)	0.810 (0.573-1.145)

Mode of Delivery (Ref: Normal Vaginal Delivery)		
Lower Segment Caesarian Section	1.257 (0.884-1.788)	1.298 (0.912-1.846)
Course of Labor (Ref: Uneventful)		
Obstructed	1.713 (0.912-3.218)	1.664 (0.881-3.143)
Prolonged	1.706* (1.045-2.787)	1.745* (1.072-2.840)
Labor (Ref: Spontaneous)		
Induced	1.241 (0.767-2.008)	1.280 (0.792-2.070)
Foetal Distress (Ref: No)		
Yes	1.613 (0.997-2.610)	1.640* (1.015-2.652)
Pregnancy Induced Hormone (Ref: No)		
Yes	1.130 (0.656-1.948)	1.245 (0.722-2.146)
Amniotic Fluid Color (Ref: Clear)		
Stained	1.193 (0.816-1.744)	1.203 (0.822-1.763)
Preterm Premature Rupture of Membranes (Ref: No)		
Yes	0.706 (0.457-1.091)	0.708 (0.457-1.095)
Cried immediately after birth (Ref: Yes)		
No	7.627*** (4.129-14.086)	7.662*** (4.135-14.197)
Resuscitation Required (Ref: No)		
Yes	1.732* (1.013-2.962)	1.760* (1.026-3.020)
Model Fit Statistics		
Log-likelihood	-757.08	-288
LR Chi-square (d.f.=18)	262.05***	269.53***
Shape Parameter (p)	—	1.664 (1.476-1.875) ***
Model Discriminatory Power		
Harrell's C-index	0.861	0.860
Somers' D	0.722	0.721

*HR: Hazard Ratio; CI: Confidence Interval; Ref: Reference Category; Significant at p < 0.05; ** Significant at p < 0.01; *** Significant at p < 0.001.*