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Research Article

The Determinants of Survival Time of Premature Neonates at Shambu General Hospital

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Background. Premature birth occurs before 37 completed weeks of gestation. It has a greater risk of developmental disabilities, health, and growth problems than full birth. It is the second leading cause of morbidity and mortality among under-five children. Therefore, the aim of this study was to identify determinants of the survival time of premature neonates admitted to the neonatal intensive care unit (NICU) at Shambu General Hospital. *Methods*. A retrospective study design was used. Data were collected from medical records of premature neonates from January 2018 to March 2021. A total of 361 premature neonates were included in the study. Descriptive statistics, Kaplan–Meier (KM) curve and log-rank test were computed. The survival time of preterm neonates were compared for different categorical covariates. The Cox's proportional hazard model was fitted. The fitness and statistical assumptions of the model were checked. Parametric regression models were compared. Weibull regression model was fitted for premature data to identify the predictors of death time of the premature neonates. *Results*. The proportion of premature neonatal death was 23.3%. Gestational age, neonatal sex, place of residence, hemoglobin (Hb) level, hypertension status, HIV status, antenatal care, mode of delivery, birth weight, multiple pregnancies, perinatal asphyxia, and parity greater than 1 were significantly associated with the death time of premature neonates. *Conclusion*. Percentage of premature neonatal death in this study was 23.3. Improving mothers' Hb level through routine iron supplementation, encouraging mothers to have regular antenatal follow-up at health institution were recommended.

1. Introduction

Premature births are born fragile, small, and weigh less than full term birth. It is major determinant of neonatal morbidity and mortality. It can be divided into late preterm (34–37) weeks, moderate preterm (32–34) weeks, very preterm (28–32) weeks, and extremely preterm (less than 28) weeks [1, 2].

Preterm birth commonly occurs during the third trimester of pregnancy [3]. It is the major cause of perinatal morbidity [4] and is the second leading cause of neonatal death [5]. It accounts 75% of the deaths among premature neonates in the modern and developing countries [6] resulting in 80% of deaths of neonates without congenital abnormalities. Preterm birth accounts for 3.1% of all disability adjusted life years [5].

Globally, 15-million babies born before 37 completed weeks of gestation every year and more than 1-million die due to complications related to preterm birth [7, 8]. Rates are highest in low and middle income countries [9]. Sub-Saharan Africa and south Asia account for over 60% of preterm birth worldwide. In Ethiopia, preterm birth accounts for 28% of all other causes of neonatal death. From 320,000 babies born too soon each year 24,000 children under 5-year die due to preterm complication in Ethiopia [10].

Preterm neonates born within preterm category shares similar risk for death, weight, size, and are at higher risk for health and developmental problems compared to the neonates born full term. They experience difficulty in feeding, blood glucose control, jaundice, temperature instability, apnoea, respiratory distress and sepsis. Preterm neonates are at a higher risk of cognitive and behavioral disorders compared to the other newborns. These complications are associated with genetic influences, infertility treatments, multiple pregnancies, infections, and chronic conditions such as diabetes and high blood pressure, [11] environmental exposure, medical conditions of the mother or fetus, behavioral and socioeconomic factors [12].

2. Methodology

A retrospective study design was used. All medical records of premature neonates who were admitted to NICU at Shambu General Hospital from January 2018 to March 2021 were collected by medical professional. Data were extracted for 361 neonates using a structured checklist. The dependent variable is time from the beginning of follow-up until death occurs; the study ends or the participant is lost follow-up. The independent variables were place of residence, gestational age, neonatal sex, Hb level of mother, hypertension status of mother, antenatal care of mother during pregnancy, jaundice, HIV status of mother, mode of delivery, multiple pregnancy, perinatal asphyxia (PNA), weight of neonate during birth, parity, hypothermia, sepsis, gravidity, and breast feed initiated within 1 hr. Data were analyzed by R statistical package.

2.1. Survival Analysis. Survival model is a method of data analysis where the outcome variable is time from the beginning of follow-up until an event occurs [13]. It takes into account when some subjects are lost to follow-up or when the period of observation is finite and certain subjects may not experience the event of interest over the study period.

2.1.1. The Survivor Function S (t). Let T be a random variable associated with the survival times of premature neonates and $f(t)$ be the probability density function of the survival time. The cumulative distribution function $F(t)$ represents the probability that premature neonate selected at random will have a survival time less than t is given by:

$$F(t) = P(<t) = \int_0^t f(u)\, du, \qquad t>0. \tag{1}$$

The survivor function $S(t)$ is the probability that the survival time of a randomly selected premature neonate is greater than or equal to some specified time t.

$$S(t) = P(T \geq t) = 1 - F(t), \qquad t \geq 0\ . \tag{2}$$

2.1.2. The Hazard Function. The hazard function is the risk of death at time t, and is obtained from the probability that a preterm neonate dies at time t given that it has survived up to time t. The hazard function $\lambda(t \geq 0)\mathrm{h}(\mathrm{t}) \geq 0,$ is given as follows:

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{P\left(\begin{array}{c} a \text{ premature neonatedies in time} \\ \text{, interval}(t, t+\Delta t) | \text{it survives until time } t \end{array}\right)}{\Delta t}\ , \tag{3}$$

$$= \lim_{\Delta t \to 0} \frac{P(t \leq T \leq t+\Delta t | T>t)}{\Delta t}. \tag{4}$$

The hazard function can be expressed in terms of probability density function and the survivor function as follows:

$$\lambda(t) = \frac{f(t)}{S(t)} = \frac{-d}{dt} \ln S(t). \tag{5}$$

2.1.3. Kaplan–Meier (KM) Estimator. Suppose that $t_1,\ \ t_2, \ldots,$ t_n be the survival time of n independent premature neonates and $t_1 \leq t_2 \leq \ldots \leq t_m\ m \leq n$ be the m distinct ordered death times. The KM estimates of survival time t is given by [14]:

$$S(t) = \prod_{t=1}^{k} \left(\frac{n_t - d_t}{n_t}\right), t_{(k)}\ < t_{(k+1)} k = 1, 2, \ldots,\ \ m\ , \tag{6}$$

with the convention that $S(t) = 1$ for $t<t_1$ where n_t is the number of premature neonates who are at the risk of dying at time t and d_t is the number of premature neonates died at time t. The variance of the KM estimate is [15]:

$$\mathrm{Var}(S(t)) = (S(t))^2 \sum_{i=1}^{k} \frac{d_t}{n_t(n_t - d_t)},\ t_k \leq t \leq t_{k+1}\ . \tag{7}$$

2.2. Comparison of Survival Curves. The survival time of premature neonates for the different groups can be compared by plotting the KM estimators of the groups on the same axes. The graph shows that the survival curve lying above had more survival experience than the group defined by the lower curve. The test statistics for the comparison of survival time between groups can be defined as follows:

$$Q = \frac{[\sum_{i=1}^{m} w_i(d_{1i} - \widehat{e}_{1i})]^2}{\sum_{i=1}^{m} w_i{}^2 \widehat{\nu}_{1i}}, \tag{8}$$

where m is the number of rank-ordered survival times. d_{1i} is the observed number of death in Group 1 at failure time t_i.

$$\widehat{e}_{1i} = \frac{n_{1i} \times d_{1i}}{n_i} \widehat{e}_{1i} = \frac{n_{1i} X d_i}{n_i}, \tag{9}$$

is the expected number of deaths corresponding in Group 1 at time t_i.

$$\widehat{\nu}_{1i} = \frac{n_{1i} n_{2i} d_i (n_i - d_i)}{n_i{}^2 (n_1 - 1)}, \tag{10}$$

is the variance of the number of deaths in Group 1 at time t_i.

The test statistic Q has χ^2 distribution when the total number of observed events and sum of expected number of events are large and assuming that the censoring experience is independent of group [16, 17].

2.2.1. Cox Proportional Hazard Model. Cox proportional hazard model gives a hazard at time t for a premature neonate with a given specification of a set of explanatory variables denoted by X and it is generally given by:

$$\lambda(t, X, \beta) = \lambda_0(t)\exp(\beta^t X)h(t, x, \beta) = h_0(t)\exp(\beta^T x), \tag{11}$$

where $\lambda_0(t)$ is a baseline hazard function which is obtained when all X's are set to zero, $X = (x_1, x_2, \ldots, x_p)^t$ is a vector of explanatory variables associated with the premature neonate and $\beta = (\beta_1, \beta_2, \ldots, \beta_p)^t$ is a vector of unknown regression parameters that are assumed to be the same for premature neonates, which measures the influence of the covariate.

The Cox model can also be regarded as a linear model for the logarithm of the relative hazard that is

$$\ln\left(\frac{\lambda(t, X, \beta)}{\lambda_0(t)}\right) = \beta^t X. \tag{12}$$

The logarithm of the hazard ratio for two individuals having two distinct covariate values x_j and x_i can be expressed as follows:

$$\ln\left(\frac{\lambda(t, x_j, \beta)}{\lambda(t, x_i, \beta)}\right) = \ln\left(\frac{\lambda_0(t)\exp(\beta^t x_j)}{\lambda_0(t)\exp(\beta^t x_i)}\right) = \beta^t(x_j - x_i)\ . \tag{13}$$

2.3. Parametric Regression Modeling. A parametric survival model assumes that the survival time follows a known distribution. Many models using different distributions have been developed.

2.4. The Weibull Regression Model. The survival time t is a positive random variable having Weibull probability density function can be expressed as follows:

$$f(t:\mu, \alpha) = \frac{\alpha}{\mu}\left(\frac{t}{\mu}\right)^{\alpha-1}\exp\left(\left(-\frac{t}{\mu}\right)^{\alpha}\right), \tag{14}$$

where $\mu > 0, \alpha > 0$ and the hazard function of the distribution becomes $\lambda(t:\mu, \alpha) = \frac{\alpha}{\mu}\left(\frac{t}{\mu}\right)^{\alpha-1}$ yielding in survivor function $S(t) = \exp(-\left(\frac{t}{\mu}\right)^{\alpha})$ and cumulative hazard function $\lambda(t) = \left(\frac{t}{\mu}\right)^{\alpha}$. Now incorporating covariates X in the hazard function, the Weibull regression models become:

$$\lambda(t:X, \beta) = \lambda\alpha t^{\alpha-1}\exp(X\beta). \tag{15}$$

The model assumes that individual i and j with covariates x_i and x_j have proportional hazard function of the form:

$$\frac{\lambda(t; x_i)}{\lambda(t; x_j)} = \frac{\exp(x_i\beta)}{\exp(x_j\beta)} = \exp\big((x_i - x_j)\beta\big). \tag{16}$$

The quantity $\exp(\beta)$ can be interpreted as hazard ratios.

2.5. The Exponential Regression Model. For the time data and skewed to the right, with distribution of the time is exponential, the survival of time for a single covariate x, which is called, accelerated failure time, expressed as follows:

$$T = \exp(\beta_0 + \beta_1 x + \varepsilon). \tag{17}$$

This model can be linearized by taking the natural log of each side of the equation as follows:

$$\ln T = \beta_0 + \beta_1 x + \varepsilon^*, \tag{18}$$

where ε^* is the error component. The exponential model ($t \sim Exp(\alpha)$) is the simplest parametric model and assumes a constant hazard over time, which reflects the "memory less" property of the exponential distribution. The survivorship function may be obtained by expressing in terms of time as follows:

$$S(t, x, \beta) = \exp\left(\frac{-t}{e^{\beta_0+\beta_1 x}}\right). \tag{19}$$

And the hazard function of the exponential regression model is:

$$\lambda(t, x, \beta) = e^{(\beta_0+\beta_1 x)}. \tag{20}$$

The exponential regression model for the k covariates and i^{th} individual preterm neonate is expressed as follows:

$$\lambda_i(t, x_i, \beta) = \lambda_0\exp(\beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \ldots + \beta_k x_{ik}), \tag{21}$$

For exponential regression survival model the hazard ratio for the dichotomous covariate is

$$HR\ \ (x = 1, x = 0) = e^{\beta_1}. \tag{22}$$

2.6. The Log-Logistic Regression Model. Single covariate log-logistic accelerated failure time may be expressed as follows:

$$\ln T = \beta_0 + \beta_1 x + \sigma\varepsilon\ . \tag{23}$$

The survivorship function for the model is:

$$S(t, x, \beta, \sigma) = [1 + \exp(z)]^{-1}, \tag{24}$$

where z is the standardized log-time outcome variable, that is;

$$z = \frac{(y - \beta_0 - \beta_1 x)}{\sigma} \text{ and } y = \ln(t)\ . \tag{25}$$

The odds of a survival time of at least t are, $OR = \frac{S(t,x,\beta,\sigma)}{1-S(t,x,\beta,\sigma)} = \exp(-z)$ assumes that the covariate is dichotomous and coded 0 or 1. The odds-ratio at time t from the ratio the odds of a survival time evaluated at $x = 0$ and $x = 1$ is:

$$\begin{aligned} \text{OR}\ (X = 1, X = 0) &= \frac{\exp\left[\frac{-(y-\beta_0-\beta_1\times 1)}{\sigma}\right]}{\exp\left(\frac{-(y-\beta_0-\beta_1\times 0)}{\sigma}\right)}\ , \\ &= \exp\left(\frac{\beta_1}{\sigma}\right) \end{aligned} \tag{26}$$

which is independent of time.

3. Results

Among 361 preterm neonates admitted to Shambu General Hospital, 76.7% were discharged and 23.3% premature neonates died. The mean and median length of hospital stay was 16.8 (95% CI: 16.12, 17.49) and 18 days, respectively. The minimum and maximum time of hospital stay was 1 and 28 days, respectively. The result in Table 1 revealed that about 64.8% and 62.3% of premature neonates were female and rural resident, respectively. The proportion of premature neonatal death born in gestational age less than 28, (28–32), (32–34), and (34–37) weeks were 59%, 23%, 11.8%, and 6.7%, respectively. From 50.4% of premature neonates weighting greater than or equal to 1,600 g at the time of birth 35.7% were died. More than 37% and 24% of premature neonates delivered from HIV positive and HIV negative mothers were died.

Majority of premature neonates (70.6%) were delivered from mother who had Hb level greater than or equal to 11 g/dl. About 35.8% and 23.5% of premature neonates delivered from mothers who had Hb level less than and more than 11 g/dl were died, respectively. Majority of mothers (81.4%) followed antenatal visit during pregnancy. About 26.9% premature neonates delivered from mothers who did not have antenatal care visit during pregnancy were died. Rate of neonatal death varies for the different type delivery method. Among preterm neonates, 78.9% were born via spontaneous vaginal delivery (SVD). About 27.3% and 27% of premature neonates delivered by vaginal and Caesarian section (C/S) were died, respectively. Majority of premature neonates (87%) were delivered singleton. 27.1 and 27.7% of premature neonates delivered singleton and delivered twins were died, respectively. About 29.7% of premature neonates delivered from hypertensive mothers were died.

3.1. Comparison of Survivor Function. KM curve is a decreasing step functions as time increases illustrated Figure 1. It gives the probability that the survival time of premature neonate exceeds the specified day. During the first day of hospital stay the maximum survival probability of 0.994 (95% CI: 0.987–1.000) was observed with a standard error of 0.00391, at the 26th days of hospital stay the probability of survival time of premature neonates was 0.409 (95% CI: 0.299, 0.519) with a standard error of 0.05625. Separate KM curve were shown for different categorical covariates as shown in Figures 2–10.

KM curves of neonatal sex, Hb level of mothers, multiple pregnancies, HIV status of mother, weight of neonate, PNA, mode of delivery, hypertension status of mother, and gestational age were shown in Figures 2–10. The survival time of premature neonates who are female, had weight ≥1,600 g, high-gestational age, whose mother had Hb level ≥11 g/dl, had PNA, born singleton, delivered by C/S, delivered from HIV negative, and nonhypertensive mothers were consistently greater than the male premature neonates, weight less 1,600 g and lower gestational age, Hb level less than 11 g/dl, did not have PNA, born multiple, delivered with SVD, delivered from HIV positive, and hypertensive mothers, respectively.

Log-rank test evaluates whether KM curves of categories of covariates are statistically equivalent or not. This is used to test the hypothesis that survival time of premature neonates for the different categories of predictor variables are equal. Both log-rank and Generalized Wilcoxon test given in Table 2 revealed that there is a significant difference in survival experience among categories of place of residence, gestational age, neonatal sex, Hb level of mother, hypertension status of mother, antenatal care, jaundice, HIV status of mother, mode of delivery, multiple pregnancy, PNA, weight of neonate during birth, and parity at 5% level of significance.

This mean that the hypothesis of equal survival time is rejected and we have enough evidence to say that the KM curves of different categories of covariates are significantly different at 5%.

But there is no difference in survival experience of premature neonates among groups of hypothermia, sepsis, gravidity, and breast feed initiated within 1 hr.

3.2. Cox's Proportional Hazard Model. The Cox's proportional hazard model was used to identify factors associated with the survival time of preterm neonates. The results of multivariate Cox Proportional hazard model in Table 3 revealed that gestational age, neonatal sex, place of residence, Hb level of mother, hypertension status of mother, HIV status mother, antenatal care, mode of delivery, birth weight, multiple pregnancy, parity (2–4), and PNA were significantly related with the survival time of premature neonates. However, jaundice, hypothermia, sepsis, parity > 5, gravidity, and breast feed initiated within 1 hr were not significant at 5%.

The hazard ratio (95% CI) for premature neonates who are female and lives in rural were 0.498 (0.272–0.912) and 1.733 (1.044–2.878) compared to the male premature neonates and premature who lives in urban, respectively. The risk of death of premature neonates who lives in rural is 1.733 times higher than premature neonates who reside in urban. Female premature neonates were 50.2% times less likely die compared to the male premature neonates.

The hazard ratio (95% CI) for premature neonates who were born in between gestational age (28–32), (32–34), and

Table 1: Descriptive statistics of premature neonates at Shambu General Hospital from January 2018 to March 2021 ($n = 361$).

Variable	Category	Death		Live		Total	
		N	Percentage (%)	*N*	Percentage (%)	*N*	Percentage (%)
Residence	Urban	127	35.3	234	64.7	136	37.7
	Rural	80	22.2	281	77.8	225	62.3
Gestational age	≤28	213	59	148	41	105	29.1
	(28–32)	83	23	278	77	100	27.7
	(32–34)	43	11.8	318	88.2	105	29.1
	(34–37)	24	6.7	337	93.3	51	14.1
Neonatal sex	Male	136	37.8	225	62.2	127	35.2
	Female	77	21.4	284	78.6	234	64.8
Hb level	<11 g/dl	129	35.8	232	64.2	106	29.4
	≥11 g/dl	85	23.5	276	76.5	255	70.6
Hypertension	Yes	107	29.7	254	70.3	118	32.7
	No	93	25.9	268	74.1	243	67.3
Antenatal care	Yes	99	27.4	262	72.8	294	81.4
	No	97	26.9	264	73.1	67	18.6
Jaundice	Yes	40	11.1	321	88.9	63	17.5
	No	110	30.5	251	69.5	298	82.5
Hypothermia	Yes	103	28.5	258	71.5	170	47.1
	No	102	28.3	259	71.7	191	52.9
Sepsis	Yes	99	27.5	262	72.5	324	89.8
	No	88	24.3	273	75.7	37	10.2
HIV status	Yes	134	37.2	227	62.8	42	11.6
	No	88	24.4	273	75.6	319	88.4
Mode of delivery	SVD	99	27.3	262	72.7	285	78.9
	C/S	97	27	264	73	76	21.1
Multiple pregnancy	No	98	27.1	263	72.9	314	87
	Yes	100	27.7	261	72.3	47	13
PNA	No	53	14.8	308	85.2	149	41.3
	Yes	129	35.8	232	64.2	212	58.7
Weight	<1,600	66	18.4	295	81.6	179	49.6
	≥1,600	129	35.7	232	64.3	182	50.4
Breast feed within 1 hr	Yes	83	22.9	278	77.1	230	63.7
	No	107	29.6	254	70.4	131	36.3
Parity	1	24	6.6	337	93.4	70	19.4
	2–4	36	10	325	90	139	38.4
	>4	101	28	260	72	152	42.2
Gravidity	1	63	17.4	298	82.6	179	49.6
	2–5	88	24.3	273	75.7	76	21
	6–10	129	35.8	232	64.2	106	29.4

(34–37) weeks compared to those who were born at gestational age less than or equal to 28 weeks were 0.217 (0.078–0.601), 0.300 (0.159–0.569), and 0.285 (0.098–0.829), respectively. That is, premature neonates who were born in between gestational age (28–32), (32–34), and (34–37) weeks were 78.3, 70, and 71.5% less likely die compared to the premature neonates who were born at less than or equal to 28 weeks of gestation, respectively.

The hazard ratio (95% CI) for premature neonates who were born from mothers who had antenatal care, hypertension, Hb level greater than or equal to 11 g/dl and HIV Positive were 0.363 (0.206–0.637), 2.789 (1.456–5.343), 0.433 (0.273–0.688), and 2.527 (1.356–4.707), respectively, compared to the neonates who were born from mothers who did not have antenatal care, not hypertensive, Hb level less than 11 g/dl, and HIV negative. This means that premature neonates who were born from mothers who had antenatal follow-up were 63.7% less likely die compared to the premature neonates whose mother did not have antenatal care. The risk of death of premature neonates who were born from mothers who had hypertension was 2.789 times higher than premature neonates who were born from

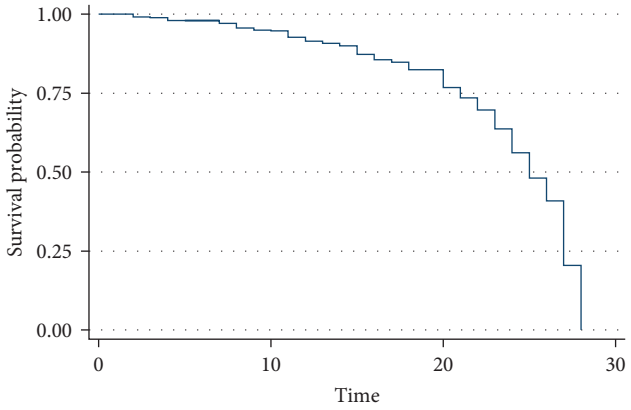

Figure 1: KM curve for premature neonates.

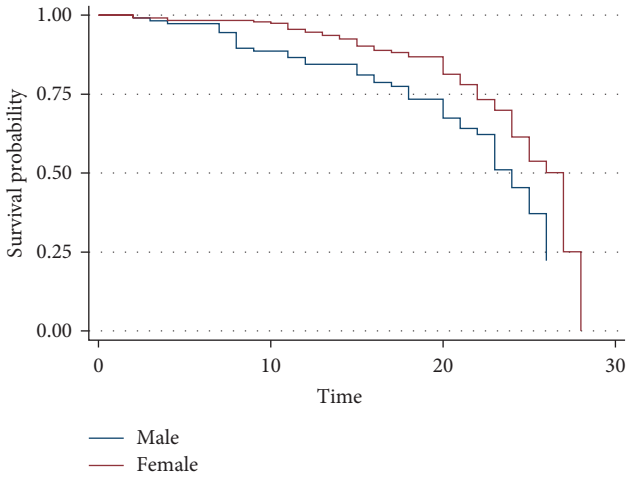

Figure 2: KM curve for premature neonates by sex.

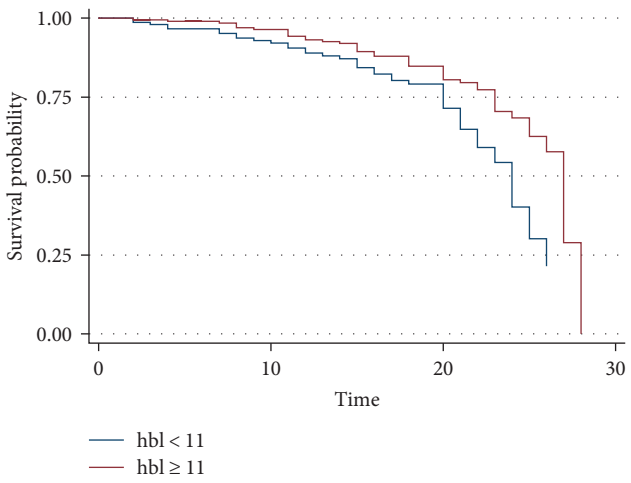

Figure 3: KM curve for premature neonates by hemoglobin level of mother.

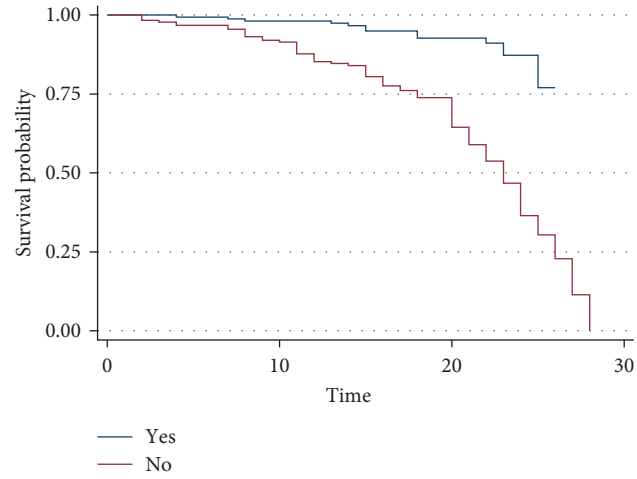

Figure 4: KM curve for premature neonates by multiple pregnancy.

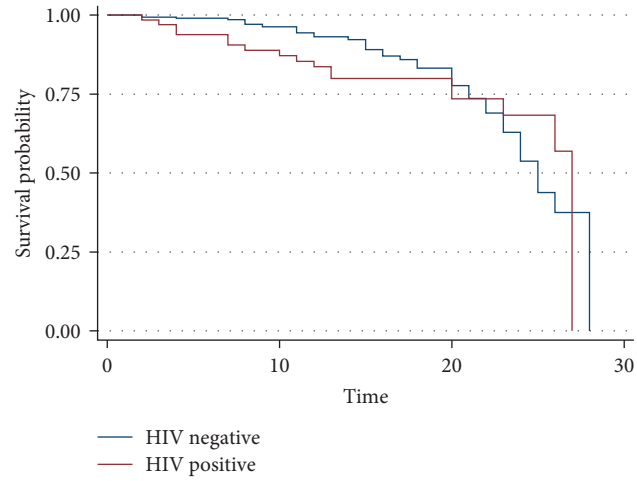

Figure 5: KM curve for premature neonates by HIV status of mother.

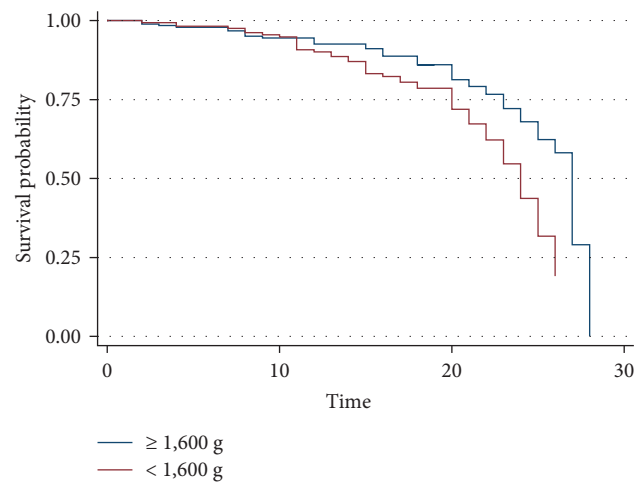

Figure 6: KM curve for premature neonates by weight.

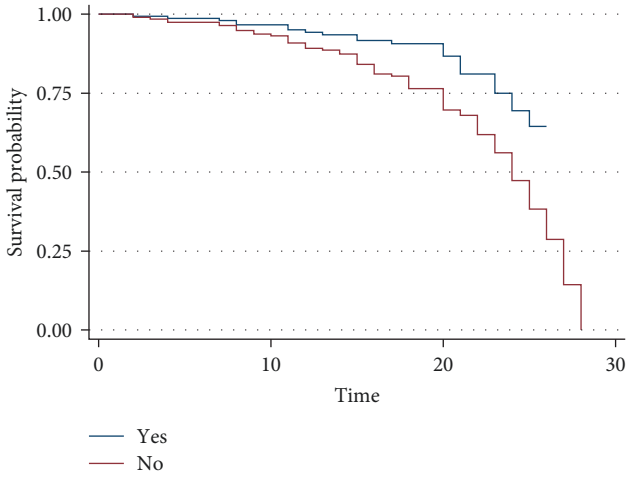

Figure 7: KM curve for premature neonates by perinatal asphyxia.

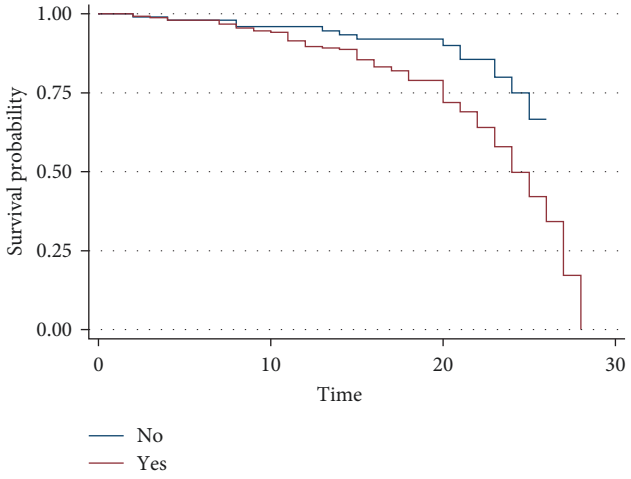

Figure 8: KM curve for premature neonates by hypertension status of mother.

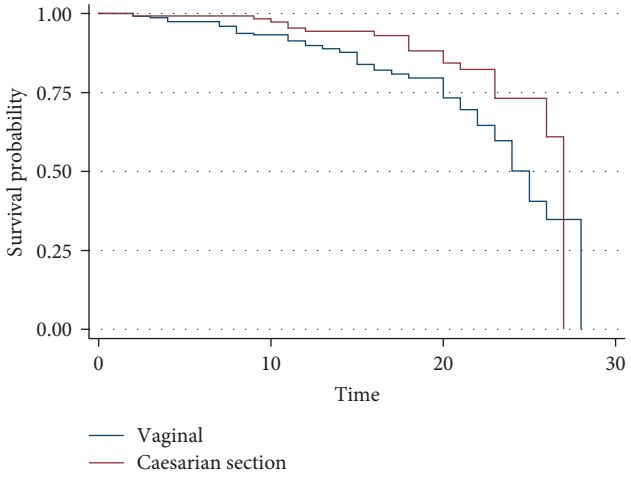

Figure 9: KM curve for premature neonates by mode of delivery.

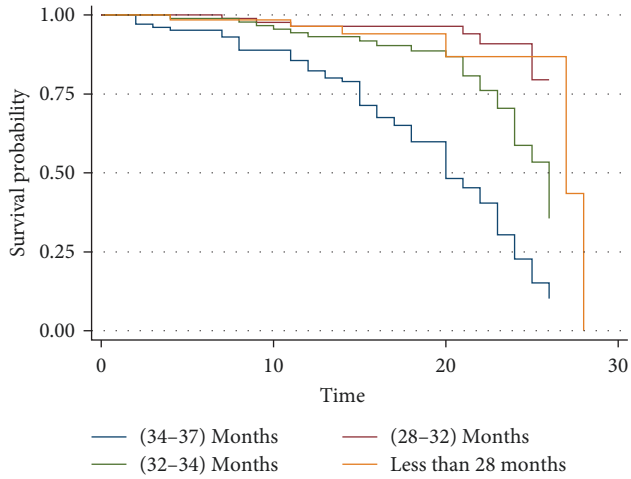

Figure 10: KM curve for premature neonates by gestational age.

Table 2: Comparison of survival experience of premature neonates at Shambu General Hospital from January 2018 to March 2021 ($n = 361$).

Variable	Log rank test			Generalized Wilcoxon test		
	DF	$\chi 2$	Sign	*DF*	$\chi 2$	Sign
Residence	1	10.8	0.010	1	10.3	0.010
Gestational age	3	82	0.000	3	79.2	0.000
Neonatal sex	1	9.9	0.000	1	10.1	0.001
Hb level	1	12.3	0.000	1	10.4	0.001
Hypertension	1	9.6	0.002	1	9.2	0.002
Antenatal care	1	0.3	0.000	1	0.2	0.000
Jaundice	1	53.5	0.006	1	50.8	0.000
Hypothermia	1	0.5	0.500	1	0.6	0.400
Sepsis	1	0.6	0.400	1	0.5	0.500
HIV status	1	4.2	0.000	1	3.6	0.000
Mode of delivery	1	7.5	0.006	1	7.8	0.005
Multiple pregnancy	1	45.3	0.000	1	43.8	0.000
PNA	1	12.3	0.000	1	11.5	0.000
Weight	1	10.8	0.001	1	88	0.003
Breast Feed within 1 hr	1	0.4	0.500	1	0.2	0.600
Parity	2	14.3	0.000	2	12.2	0.002
Gravidity	2	0.6	0.700	2	0.6	0.700

mothers who did not have hypertension. Premature neonates who were born from mothers who had Hb level greater than or equal to 11 g/dl were 56.7% less likely die than neonates whose mother had Hb less than 11 g/dl. Premature neonates who were born from mothers with HIV positive were 52.7% more likely die than neonates born from HIV negative mothers.

The hazard ratio (95% CI) for premature neonates who had weight less than 1,600 g, PNA, born multiple and parity (2–4) were 1.775 (1.088–2.898), 1.914 (1.125–3.256), 2.872

Table 3: The results of cox proportional hazard model of premature neonates at Shambu General Hospital from January 2018 to March 2021 ($n = 361$).

Variable	Coef	Exp (coef)	SE (β)	Z	Sign	HR (95%CI)
Residence Ref (urban) rural	0.55	1.733	0.2588	2.126	0.034	1.044, 2.878
Gestational Age ref (≤28)						
(28–32) weeks	−1.53	0.217	0.521	−2.839	0.003	0.078, 0.601
(32–34) weeks	−1.203	0.300	0.326	−3.692	0.000	0.159, 0.569
(34–37) weeks	−1.255	0.285	0.545	−2.3	0.021	0.098, 0.829
Sex ref (male) female	−0.698	0.498	0.309	−2.258	0.024	0.272, 0.912
Hb ref (<11) ≥11	−0.835	0.433	0.236	−3.545	0.000	0.273, 0.688
Hypertension ref (no) yes	1.026	2.789	0.332	3.093	0.002	1.456, 5.343
HIV ref (no) yes	0.927	2.527	0.318	2.92	0.004	1.356, 4.707
Antenatal care ref (no) yes	−1.014	0.363	0.287	−3.529	0.000	0.206, 0.637
Mode of delivery ref (C/S) SVD	−0.931	0.394	0.304	−3.068	0.002	0.217, 0.714
Jaundice ref (no) yes	−1.031	0.357	0.265	−3.897	0.072	0.212, 0.599
Hypothermia ref (no) yes	0.162	1.176	0.245	0.664	0.507	0.728, 1.899
Sepsis ref (no) yes	−0.528	0.590	0.259	−2.036	0.142	0.355, 0.980
Multiple pregnancy ref (no)yes	1.055	2.872	0.336	3.143	0.002	1.488, 5.546
PNA ref (no) yes	0.649	1.914	0.271	2.393	0.017	1.125, 3.256
Breast feed 1 hr ref (no) yes	−0.168	0.845	0.249	−0.676	0.499	0.519, 1.376
Weight ref (≥1,600) <1,600	0.574	1.775	0.25	2.296	0.022	1.088, 2.898
Parity ref (I) II–IV	0.748	2.113	0.36	2.079	0.038	1.044,4.279
>IV	0.308	1.361	0.479	0.644	0.520	0.533,3.475
Gravidity ref (I) II–V	0.951	2.589	0.528	1.803	0.071	0.920, 7.282
>V	0.548	1.730	0.325	1.69	0.091	0.916, 3.269

(1.488–5.546), and 2.113 (1.044–4.279) compared to the premature neonates who had weight greater than or equal to 1,600 g, who did not have PNA, born single and parity 1, respectively. That is, the risk of death of premature neonates who had weight less than 1,600 g, who had PNA, twin and parity 1 were 1.775, 1.94, 2.872, and 2.133 times higher than premature neonates who weights greater than or equal to 1,600g, who did not have PNA, singleton and parity 1, respectively.

Hazard ratio (95% CI) for premature neonates delivered by spontaneous vertex were 0.394 (0.217–0.714) compared to the premature neonates delivered by C/S. This means, premature neonates delivered by spontaneous vertex were 60.6% less likely die compared with the premature neonates delivered by C/S.

3.3. Assessment of Model Assumption. The assumptions of proportional hazard were checked by χ^2 test based on the Schoenfeld residuals for each explanatory variables and globally ($\chi^2 = 20.41$, p-value = 0.495). In addition, the assumption of proportionality was assessed graphically by plotting the Schoenfeld residuals of each covariate against log time. There were no covariates which show a pattern with time indicating the hazard ratio was constant for time.

3.4. Model Comparison Criteria. Based on the Akaike information criterion (AIC), Weibull model (AIC = 781.1) was more efficient than exponential (AIC = 903.4), log logistic (AIC = 799.1), and lognormal (AIC = 828.3) models.

3.5. Multivariate Weibull Regression Model. The Weibull regression model in Table 4 showed that gestational age, neonatal sex, Hb level of mother, hypertension status of mother, HIV status of mother, antenatal care, mode of delivery, multiple pregnancy, birth weight, and PNA were significant determinants of the survival time premature neonatal death. Breast feed within 1 hr, place of residence, jaundice, sepsis, gravidity, parity, and hypothermia were not significant at 5%.

The hazard ratio (95% CI) for premature neonates who had gestational age between (28–32), (32–34), and (34–37) weeks and whose mother had Hb level greater than or equal to 11 g/dl compared to the premature neonates who were born at gestational age less than or equal to 28 weeks and whose mother had Hb level less than 11 g/dl were 0.758 (0.544–1.056), 0.944 (0.772–1.156), 0.790 (0.585–1.0660, and 0.816 (0.707–0.941), respectively. Premature neonates who had gestational age between (28–32), (32–34), and (34–37) weeks and whose mother had Hb level greater than or equal to 11 g/dl were 24.2, 5.6, 21, and 18.4% less likely die compared to the premature neonates born at gestational age less than or equal to 28 weeks and whose mother had Hb level less than 11 g/dl, respectively.

The hazard ratio (95% CI) for preterm neonates who were born from HIV positive mothers and whose mother had antenatal care compared to the premature neonates who were born from HIV negative mothers and whose mother did not have antenatal care were 3.284 (2.678–4.026) and 0.661 (0.558–0.784), respectively. This mean that premature neonate

Table 4: Parameter estimates, standard errors, and the hazard ratios in the final Weibull regression model at Shambu General Hospital from January 2018 to March 2021 ($n = 361$).

Variables	β	SE	Z	Sign	HR	HR (95% CI)
Intercept	3.546	0.226	15.7	0.000	34.754	22.32, 54.12
Residence ref (urban) rural	0.638	0.080	7.978	0.065	1.893	1.618, 2.214
Gestational age ref (≤28)						
(28–32) Weeks	−0.277	0.169	−1.638	0.003	0.758	0.544, 1.056
(32–34) Weeks	−0.057	0.103	−0.554	0.002	0.944	0.772, 1.156
(34–37) Weeks	−0.236	0.153	−1.542	0.076	0.790	0.585, 1.066
Sex ref (male) female	−0.195	0.094	−2.071	0.049	0.823	0.685, 0.990
Hb ref (<11) ≥11 g/dl	−0.204	0.073	−2.793	0.005	0.816	0.707, 0.941
Hypertension ref (no) yes	1.302	0.106	12.287	0.005	3.678	2.988, 4.527
HIV status ref (no) yes	1.189	0.104	11.433	0.002	3.284	2.678, 4.026
Antenatal care ref (no) yes	−0.414	0.087	−4.753	0.005	0.661	0.558, 0.784
Mode of delivery ref (C/S) SVD	−0.246	0.094	−2.615	0.009	0.782	0.650, 0.940
Jaundice ref (no) yes	−0.265	0.086	−3.086	0.202	0.767	0.648, 0.908
Hypothermia ref (no) yes	−0.055	0.077	−0.72	0.473	0.946	0.814, 1.101
Sepsis ref (no) yes	0.169	0.08	2.09	0.076	1.184	1.012, 1.385
Multiple pregnancy ref (no) yes	1.470	0.111	13.247	0.001	4.351	3.500, 5.408
PNA ref (no) yes	0.763	0.087	8.772	0.019	2.145	1.809, 2.544
Breast feed 1 hr ref (no) yes	0.032	0.078	0.4	0.686	1.033	0.886, 1.203
Weight ref (≥1,600) <1,600	0.952	0.078	12.201	0.042	2.590	2.223, 3.018
Parity ref (I) II–V	0.985	0.113	8.719	0.169	2.679	2.146, 3.343
>V	0.793	0.145	5.471	0.714	2.211	1.664, 2.937
Gravidity ref (I) II–V	−0.274	0.158	−1.74	0.082	0.760	0.558, 1.036
>V	−0.095	0.096	−0.99	0.322	0.909	0.753, 1.098
Log (scale)	−1.137	0.087	−13.06	0.000	0.321	0.271, 0.381

who were born from HIV positive mother were 3.284 more likely die than premature neonates who were born HIV negative mothers. Premature neonates who were born from mothers who had antenatal follow-up were 33.9% less likely to die compared to premature neonates who were born from mothers who did not have antenatal care. The hazard ratio (95% CI) for premature neonates who had PNA, whose mother have hypertension and born twin compared to premature neonates who did not have PNA, whose mother did not have hypertension and single were 2.145 (1.809–2.544), 3.678 (2.988–4.527), and 4.351 (3.5–5.408), respectively. That is, the risk of death of premature neonates who had PNA, whose mother had hypertension and born twin were 2.145 and 3.678; and 4.351 times higher than premature neonates did not have PNA, whose mother did not have hypertension and singleton, respectively.

The hazard ratio (95% CI) for female premature neonate and premature neonates who weight less than 1,600 g were 0.823 (0.685–0.990) and 2.59 (2.223–3.018), respectively, compared to the male premature neonate and premature neonates whose weights greater than or equal to 1,600 g. That is, the risks of death of female premature neonates were decreased by 17.7% compared with male premature neonates.

The risk of death of premature neonates weighting less than 1,600g was increased by 59% compared with the premature neonates whose weight greater than or equal to 1,600 g.

4. Discussion

During the study period, 361 premature neonates were admitted to the NICU at Shambu General Hospital.

The proportion of premature neonatal death was 23.3%. This finding is in line with studies conducted in northern Ethiopia 25.2% [18], in Addis Ababa 25.3% [19], in urban Pakistan 34% [20], in Tigray region 34% [21], and in Jimma 34.9% [22]. The overall mean (95% CI) and median length of hospital stay was 16.8 (95% CI: 16.12, 17.49) and 18 days, respectively.

The log-rank test and KM curves show that categories of place of residence, gestational age, neonatal sex, Hb level of mothers, hypertension status of mothers, jaundice, HIV status of mothers, mode of delivery, multiple pregnancy, PNA, antenatal care, birth weight, and parity were statistically difference in experiencing death event at 5% level of significance. But sepsis, breast feed within 1-hr hypothermia, and gravidity were not clearly experiencing significance differences in the death of premature neonates.

Cox proportional hazard and Weibull regression models were used to estimate the risk of death of premature neonates. Gestational age, neonatal sex, place of residence, Hb level of mother, hypertension status of mother, HIV status of mother, antenatal care visit, mode of delivery, birth weight, multiple pregnancy, parity 2–5, and PNA were identified as significant determinants of the survival time premature

neonates in both Cox proportional hazard and Weibull regression models.

Birth weight affects survival time of premature neonates. Both Cox's proportional hazard model and Weibull regression model show that the risk of death of premature neonates who had weight less than 1,600 g is about 1.775 and 2.59 higher than the premature neonates who had weight greater than 1,600 g, respectively. This result is in accordance with the previous studies conducted in northern west and central parts of the country [19, 23].

Gestational age is prognostic factor that significantly predicts the survival time of premature neonates. The risk of death of premature neonates with gestation (28–32), (32–34), and (34–37) weeks were 0.217, 0.300, 0.285 and 0.758, 0.944, 0.79 times lower than the hazard of death premature neonates with gestational age less than 28 weeks, respectively, in both Cox's proportional hazard and Weibull regression models. This result is comparable with earlier studies conducted in Jimma University [22] Gondar University [18] and Moi University Hospital in Kenya [24]. This is because as fetal maturity increases risk of premature neonatal death will decrease.

The risk of death of premature neonates who had PNA is about 1.914 and 2.145 times higher than premature neonates who did not have PNA, respectively, in both Cox's proportional hazard and Weibull regression models. This result is in accordance with the studies done by Yehuala et al. [18] and Wesenu et al. [22]. This is because PNA is causes of premature neonatal death where neonatal care not adequate.

Mother's HIV status is predictor of death time of premature neonates. This study revealed that the risk of death of premature neonates whose mother had HIV was 2.527 and 3.284 higher than premature neonates whose mother was HIV negative, respectively, in both Cox's and Weibull regression models. The present result concords with earlier study conducted in Ethiopian [18, 25] and in Uganda [26].

The survival time of premature neonate whose mother had received antenatal care were 63.7 and 33.9% lower than premature neonates whose mother did not have received antenatal care in both Cox's and Weibull regression models, respectively. This finding is consistent with the report of the previous study having antenatal care visit significantly reduces premature neonatal death [18, 24].

Hypertension is related to the time to death of premature neonates. In both Cox's and Weibull regression models hazard of death of premature neonate whose mother had hypertension were 2.789 and 2.988 higher than premature neonate whose mother did not have hypertension, respectively. This is similar to reports by Gebreslasie [25]. This might be because, the complications of pregnancy induced hypertension can cause vascular damage to placenta.

Hb level of mother significantly predicts the survival time of premature neonates. The hazard of death of premature neonate whose mother had Hb level less than 11 g/dl is about 56.7% and 18.4% higher than premature neonates whose mother had Hb greater than 11 g/dl in both Cox's proportional hazard and Weibull regression model, respectively. This result is in accordance with the previous study [18].

Survival prognosis of premature neonate was lower for twins. The risk of death of premature twins were 2.872 and 4.351 higher compared to singleton, respectively, in both Cox's and Weibull parametric models. This find was in line with studies conducted in northern Ethiopia [18].

This study indicates that hazard of death for premature neonates delivered by SVD were 0.394 and 0.782 compared to premature neonates delivered by C/S in both Cox's proportional hazard and Weibull models. The finding was supported by [24, 27]. But this finding was contrary to the other studies where C/S was associated with better survival [18]. The variation in the results of our study is probably related to different environments of the countries that affected the variables.

There is a significant relationship between neonatal sex and survival time. Female preterm neonates had 0.498 and 0.823 times lower risk of death compared to the male premature neonates, respectively in both Cox's proportional hazard and Weibull regression models. This find was in line with study conducted by Nalini et al. [28].

The hazard rate of premature neonates who live in rural was 1.733 times higher than the premature neonates who reside in urban in Cox's proportional model. This result is in accordance with the study conducted in iran [28]. But the relationship between neonatal sex and death time of premature neonate was insignificant at 5% in Weibull regression model.

5. Conclusions

The main factors of preterm death were gestational age, being HIV positive, hypertension, Hb level, antenatal care, PNA, place of delivery, multiple pregnancy, and birth weight of neonates. Efforts have to be made to decrease the prevalence of preterm death. Health workers should work on encouraging mothers to have regular antenatal follow-up, improving mothers' Hb level, controlling of hypertension, providing quality of healthcare may decrease the rate of preterm birth and its consequences.

Data Availability

Data were extracted from neonates' records using a pretested structured checklist.

Additional Points

Limitation. There was a lack some important variables affecting the outcome variables and missing values.

Conflicts of Interest

The author declares that there is no conflicts of interest.

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