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Original Article

Competing Risk Analysis of the Health Status of Neonates with Respiratory Distress Syndrome

Zenaw Ayele, Mekonnen Tadesse* , Zelalem Tazu

Department of Statistics, Addis Ababa University, P.O.Box 1176, Addis Ababa, Ethiopia.

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ABSTRACT

Introduction: Respiratory distress syndrome (RDS) is not only the most common respiratory disorder in premature infants but also the main cause of neonatal mortality.
Methods: Competing risk framework was used to examine and identify potential prognostic factors of the health status of preterm infants with respiratory distress syndrome. Preterm infants with RDS admitted to the neonatal intensive care units (NICUs) of selected hospitals in Ethiopia were followed for 28 days and only neonates with complete cases were included in the analysis. The Fine-Gray or sub-distribution hazard model was used to identify significant prognostic factors. Three outcome variables (death due to RDS, death due to other causes and discharged alive) were considered.
Results: The Fine-Gray model fit results revealed that anemia, multiple pregnancies, birth-weight and gestational age were the prognostic factors significantly associated with the death of neonates due to Respiratory distress syndrome problem while Pneumonia, meningitis, anemia and gestational age of neonates were the significant prognostic factors for death of neonates due to other causes. Moreover, pneumonia, birth weight and gestational age were identified as the prognostic factors associated with neonates being discharged alive.
Conclusion: Offering intensive and adequate treatments for neonates with lowest birth-weights and gestational age may be useful to reduce neonatal mortality and increase the incidence of being discharged alive.

Introduction

Respiratory distress syndrome (RDS) is one of the neonatal health complications which call for a lot of tasks to be done targeting for the development of treatments and technology for neonatal intensive care (1). It frequently happened in premature infants and is the most common respiratory disorder in premature infants and cause of admission to the neonatal intensive care units (NICUs) with different clinical symptoms (2,3). Moreover, prematurity mainly increases the vulnerability of neonates in developing RDS (3).Globally, RDS is a main cause to neonatal mortality. Nevertheless, information about RDS-specific mortality rates and technologies for its treatment are rare in low-

* Corresponding author.Email:mekonnentadesse@yahoo.com or mekonnen.tadesse@aau.edu.et

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income countries leading towards inconsistent health care platform (1).

The neonatal mortality rate in developing countries continues to be an urgent global problem with over 4 million infants dying within the first month of life (4).Respiratory distress syndrome is one of the primary causes of death of neonates (5). There are different policies, strategies, and programs which work on prevention and care of preterm birth and its outcome including RDS. Among these are Sustainable Development Goals and Every Women and Every Child initiative. However, the etiologies and risk factors associated with RDS have not been well cited in low-income countries and particularly in sub-Saharan Africa (6).

In this study, we have focused on preterm infants with RDS problem which is the most common cause of morbidity and mortality of neonates admitted to NICUs. Neonates admitted to NICUs due to respiratory distress syndrome problem may die due to other causes or discharged alive from the NICUs in the follow-up days. Thus, the occurrence of neonatal death due to other causes or of those discharged alive from NICUs preclude the observation of death due to RDS.

A competing risk is an event that either hinders the observation of the event of interest or modifies the chance of the occurrence of this event (7). Equivalently, competing risk refers to a situation where an individual is exposed to two or more causes of failure, and its eventual failure can be attributed exactly to only one (8). In competing risk analysis, there is a distinct cause-specific hazard function for each of the distinct types of events and a distinct sub-distribution hazard function for each of the distinct types of events (9). In this study the events that may be observed, called competing risks, include death of neonates due to RDS which is our event of interest, death due to other causes and those discharged alive from hospital.

Ignoring the competing event(s) and using ordinary survival analysis methods may be inappropriate and alternative methods specifically designed for analyzing competing risks data should then be applied (7).

In this study, the proportion of preterm infants with the event of interest, death due to RDS was about one-fourth of the total preterm neonates admitted to NICUs. In view of that, the use of standard survival analysis methods would lead to censoring about three-fourth of the study participants resulting in statistical error and consequently leading to incorrect conclusions. These limitations could be handled using competing risk models/analysis methods. Therefore, the aim of this study was to examine and identify accurate prognostic factors associated with the health status of neonates with RDS through appropriate modeling approaches by accounting for the potential competing risks. Moreover, to the best of our knowledge there were no previous works that used competing risk analysis of Ethiopian neonates with RDS.

Materials and Methods

Data Source

The data considered in this study were obtained from a Study of Illness in Preterm (SIP) project that have compiled neonatal data from five public hospitals in Ethiopia which have Neonatal Intensive Care Units

(NICUs). The study subjects were preterm infants born before 37 completed weeks of gestation and admitted to neonatal intensive care units (NICUs) of one of the selected hospitals due to the problems of RDS. Neonates admitted to NICUs of the hospitals during July 1, 2016 to May 31, 2018 were followed for 28 days and relevant data were collected. Besides, consent was made with parents or caregivers for post-mortem examinations and whenever death occurred, the primary cause and date of death of the neonate were recorded.

Variables Used in the Study

The covariates considered in the study are: gender of preterm infant (male, female), gestational age in weeks (<28, 28-31, 32-34,>35), whether mothers had multiple pregnancy (yes, no), birth-weight of neonates at the time of birth in gram (<1000, 1000-1500, 1500-2000,>2000),mothers' age at birth in years (<20,20-34,>=35),having pneumonia (yes, no), having anemia (yes, no),existence of feeding problem (yes, no),mother has received antenatal care (yes, no),mother is diabetic (yes, no),C-section during delivery (yes, no),hypertensive disorder during pregnancy (yes, no).We have considered three outcome variables: death due to RDS, death due to other causes and discharged alive from the neonatal intensive care units. While death of neonates due to RDS is our event of interest, death due to other causes and neonates discharged alive from the units are competing risks. The outcome variable (health status) takes numeric values with 1=died due to RDS, 2= died due to other causes and 3=survived and discharged from NICU alive. Since neonates in the study experienced one of the possible outcomes, there were no censored observations in the current study. All neonates with health problem of RDS during the study period were included in the study. A neonate with incomplete data of its medical records was excluded from the analysis. Details of neonates admitted to NICUs are presented in Figure 1.

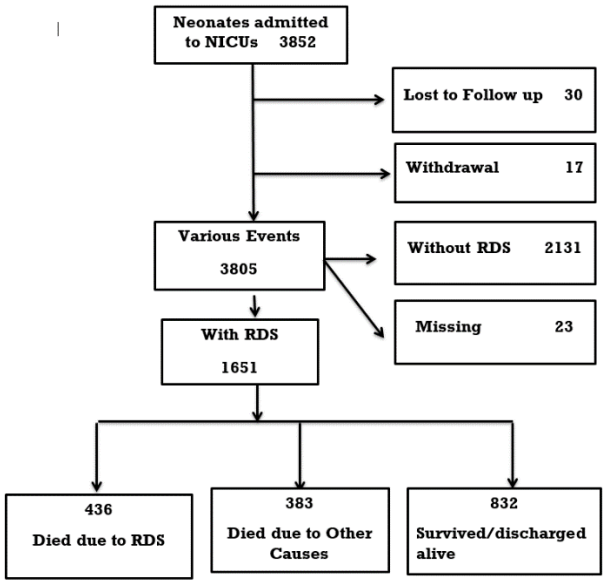


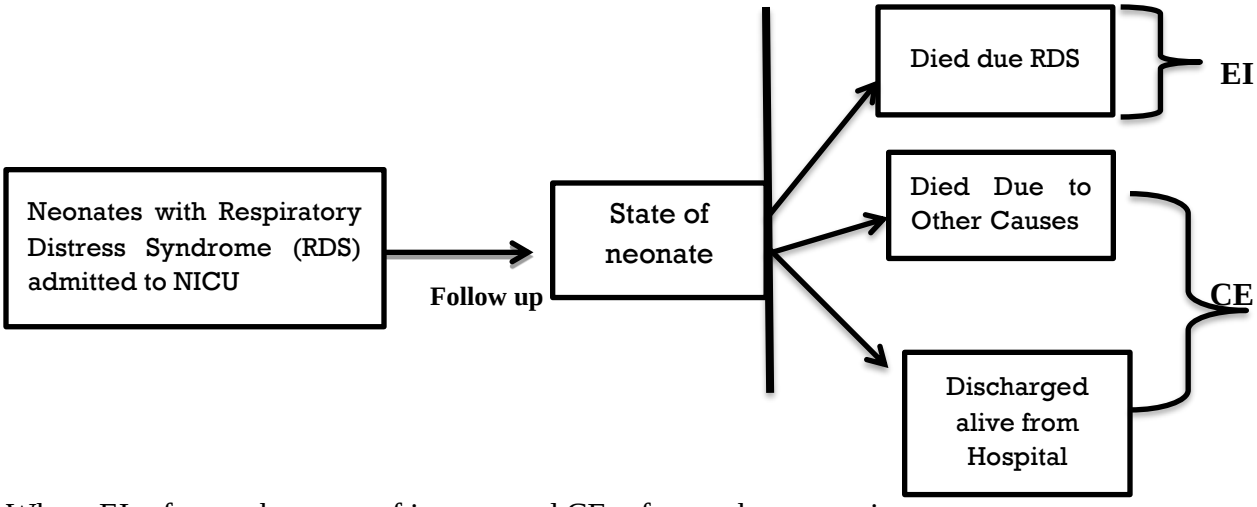
Figure 1. Particulars of Neonates admitted to NICUs

Competing Risk Analysis

Competing risk analysis refers to a special type of survival analysis that aims to correctly estimate marginal probability of an event in the presence of competing events. In fitting models in the presence of competing risks, one can choose from two different modeling approaches: cause-specific hazard or Sub distribution hazard model also known as Fine-Gray Model(8). The cause specific hazard model is used to estimate the effect of the covariates on the rate of occurrence of the outcome in those subjects who are currently event free. Nevertheless, the Fine-Gray Model allows us to estimate the effect of covariates on the absolute risk of the outcome over time (9).

The Fine-Gray model is based on a proportional hazards model for the sub-distribution of a competing risk where covariates under study directly affect the cumulative incidence function. The cumulative incidence function (CIF) for the kth failure or cause is given by Pr ($T \leq t$, $D= k$), where D is the type of event that happened from the possible event at time t. In standard survival analysis, we know that the survival function is given by $S(t) = P(T \geq t)$ and the incidence of the event over the duration of follow-up is given as $F(t) = 1-S(t) = Pr(T \leq t)$. Conversely, the CIF, as distinct from 1 – S (t), allows for estimation of the incidence of the occurrence of an event while taking competing risks into account.

The function CIFk (t) denotes the probability of experiencing the kth event before time t and before the occurrence of a different type of event. Unlike the survival function in the absence of competing risks, CIFk (t) will not necessarily approach unity as time becomes large because of the occurrence of competing events that preclude the occurrence of events of type k. The possible states of the neonates with RDS are depicted in Figure 2.



Where EI refers to the event of interest and CE refers to the competing events

Figure 2: Potential states of neonates with RDS

Basic Hazard Functions in Competing Risk Analysis

There are two common types of hazard functions in competing risk analysis. These are the cause-specific hazard and sub-distribution hazard (cumulative incidence) functions.

The cause-specific hazard function for the kth cause, (9) is defined as

$$\lambda_k{}^{cs}(t)=\lim_{\Delta t\to 0}\frac{\text{Prob}(t\le T<t+\Delta t, D=k|T\ge t)}{\Delta t} \quad k=1,\ldots, D$$

and represents the rate of occurrence of the k^{th} failure. In our case, k=1, 2, 3

It denotes the instantaneous rate of occurrence of the k^{th} event in subjects who are currently event free (i.e. in subjects who have not yet experienced any of the different types of events).

The sub-distribution function for the k^{th} type of event (9) is defined by

$$\lambda_k{}^{sd}(t)=\lim_{\Delta t\to 0}\frac{\text{Prob}(t\le T<t+\Delta t, D=k|T>t\cup(T<t\cap D\neq k))}{\Delta t}$$

where D is a variable denoting the type of event that occurred. This corresponds to the probability of a subject failing from cause kin the presence of all the competing risks. The CIF is used to model the risk of experiencing a specific event in subjects who have not yet experienced this event.It denotes the instantaneous risk of failure from the k^{th} event in subjects who have not yet experienced an event of type k. The basic difference between the two hazards is related to the risk sets.

For univariate analysis of each prognostic factor, cumulative incidence function was used and the value of the Gray's test was obtained to determine the extent of significant association between the outcome variable and the factors.

Regression Models of Competing Risks

In survival analysis with competing risks, there are two regression modelling approaches which depend on the above mentioned hazard functions: the cause-specific hazards model and the Sub-distribution hazard model also called Fine-Gray model (10).

CIF based proportional hazard model to analyze competing risk data was developed (11).In the competing risks setup, for each cause for the occurrence of an event of interest, a hazard function in the presence of covariates is considered (12).

In this study, we have applied the Fine-Gray modeling approaches to identify the potential prognostic factors of the health status of neonates with RDS.

Using the relationship between the survival, hazard and cumulative incidence function (13)

$$\lambda(\mathrm{t}) = \frac{f(t)}{S(t)} = \frac{f(t)}{1-F(t)}$$

the sub distribution hazard (hazard of the cumulative incidence) for each cause for an individual who either fails from cause k or does not, can be written as:

$$\lambda_k{}^*(\mathrm{t;X}) = \frac{f_k(t)}{1-F_k(t)}$$

Under the proportional hazard, Fine-Gray Model can be specified (13) as:

$$\lambda_k{}^*(\mathrm{t;X}) = \lambda_{0k}{}^*(\mathrm{t})\exp(\mathrm{X}\beta_k)$$

Where $\lambda_{0k}{}^*(\mathrm{t})$ is the baseline sub-distribution hazard for cause k Variable/Model Selection Methods in Competing Risks

In the Fine and Gray model, only subjects who experience the primary event contribute information to the partial likelihood. (14) proposed a new variable selection criteria called BICcr by changing the penalty to be the total number of primary events, denoted by n*.

$$\mathrm{BICcr} = -2\log L(\beta) + p\log(n^*).$$

In our analysis, we have used full range of potential prognostic factors through careful study of the literature in relation to the outcome variable. For each outcome variable (death due to RDS, death due to other causes and discharged alive), separate Fine-Gray model was fitted.

Methods of Parameter Estimation

The partial likelihood for the Fine-Gray model is given (14) as:

$$\mathrm{L}(\beta) = \prod_{k=1}^{r} \frac{\exp(\beta X_k)}{\sum_{i\in R^*(t_k)} w_{ki}\exp(\beta X_i)}$$

The product is taken over all r time points, ($t_1 < t_2 < \ldots < t_r$), where r is the total number of events of interest i.e. ($\sum_{i=1}^{n} I\{\in_i = 1\}$). The modified risk set, $R^*(t_k)$ is a set of subjects that are still at risk for the event of interest at time t (11). Thus, subjects that have experienced other types of events remain in the risk set all the time. Besides, the weight is defined as

$$w_{ki} = \frac{\hat{G}(t_k)}{\hat{G}(\min(t_k, t_i))}$$

Where $t_i = \min.(T_i, C_i)$ for i such that $\in_i \neq 1$ and t_k is the time of the k^{th} event. $\hat{G}$ is the KM estimate of the survivor function of the censoring distribution ($G(t) = P(C \geq t)$). The weight is 1 for the subjects who did not experience any type of event by time t_k and less than 1 for those who had a competing event before t_k. As a result, individuals who experience a competing event at time t_i do not participate fully in the partial likelihood; the further the time point (t_k) is from the time of the competing event (t_i), the smaller the weight. When there is only one event of interest, the weights are all equal to1, and the risk set contains only those at risk at the specified time point (14).

Results

Descriptive Results

A total of 1651 eligible neonates were enrolled to the NICUs due to the problem of RDS. Of the 1651 preterm newborns with RDS followed for 28 days, 436 (26.4%) died due to RDS, 383(23.2%) died due to other causes and 832(50.4%) survived and were discharged (discharged alive) from the units. The distributions of the clinical characteristics of the neonates are presented in Table 1.

Of the 1651 enrolled neonates, 913 (55.3%) were males making the sex ratio 1.24:1. The highest proportion (39.6%) of the preterm infants in this study had gestational age of 32 to 34 weeks.

Among the 82 neonates with RDS having gestational age of less than 28 weeks, 56.1% of them died due to RDS, 34.1 % died due to other causes and only 9.8 % were discharged alive from the hospitals. It was observed that the number of neonates being discharged alive from the hospitals increases as gestational age increases. Out of the 139 preterm newborns with birth-weight less than 1Kg, 52.5% of them died due to RDS while 33.8% of them died due to other causes. Details are shown in Table 1.

The mean and median follow up period of the study was about 9 and 6 days respectively. Moreover, the mean birth-weight of the preterm infants was 1.55kg and the median was 1.5 Kg. Similarly, the mean and median age of mothers who gave preterm birth was 26.3 and 26 years respectively.

Table 1. Distribution of Clinical Characteristics of Neonates

			Health status of neonate		
			Died due to RDS	**Died due to Other Cause**	**Discharged alive**
Covariate	**Category**	**Total**	**Percent**	**Percent**	**Percent**
Sex	Female	738	27.5	22.5	50
	Male	913	25.5	23.8	50.7
Gestational Age (in weeks)	< 28	82	56.1	34.1	9.8
	28-31	648	37	30.1	32.9
	32-34	654	19.6	16.8	63.6
	>=35	267	8.2	18.7	73
Multiple pregnancy	No	1111	28.1	23.2	48.7
	Yes	540	23	23.1	53.9
Birth weight (in Kilo grams)	<1	139	52.5	33.8	13.7
	1-1.5	610	34.9	28.9	36.2
	1.5-2	570	24.1	18.6	60
	>=2	332	8.4	16.3	75.3

		<20	130	27.7	23.1	49.2
Maternal Age(in Years)		20-34	1367	26.0	22.9	51.1
		>=35	154	28.6	26.0	45.5
Pneumonia		No	1611	26.6	22.7	50.7
		Yes	40	20	42.5	37.5
Antenatal Care		No	111	32.4	32.4	35.1
Received		Yes	1540	26	22.5	51.5
Diabetes mellitus		No	1631	26.5	23.3	50.2
		Yes	20	20	15	65
C-section		No	974	27.4	24.8	47.7
		Yes	677	25	20.8	54.2
Cardiac disease		No	1637	26.4	23.3	50.3
		Yes	14	28.6	7.1	64.3
Feeding Problems		No	1265	24.3	21.9	53.8
		Yes	386	33.4	27.5	39.1
Hypertensive disorder		No	1173	25.2	24.3	50.5
		Yes	478	29.3	20.5	50.2

A graph of the absolute probability of the cumulative incidence of the event of interest and competing risks against follow up times is presented in Figure 3 .Within the first 10 days of the follow up time, neonates admitted to NICUs had higher probability of death due to RDS than death due to other causes or being discharged alive from the centers. However, the probability of being discharged alive rose after this follow up time and was higher than the probability of death throughout the follow up period.

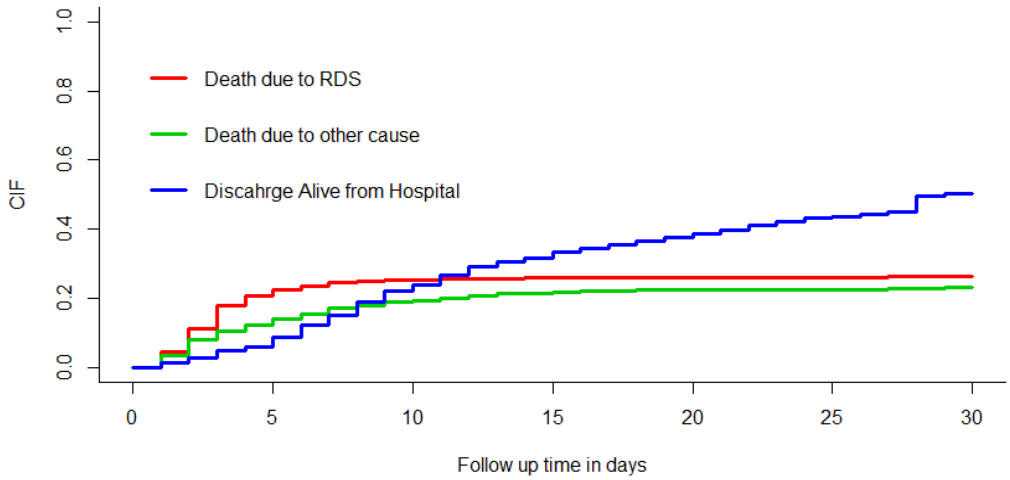


Figure 3. Plot of Cumulative incidence of the outcome Variables

Analytical Results

Gray's test was used to assess the association between each potential prognostic factor and the outcome variables considered in the study.

The Gray's test results showed that meningitis, anemia, multiple pregnancy, gestational age, birth-weight and feeding problem have a statistically significant association with death of preterm infants due to RDS while pneumonia, meningitis, anemia, antenatal care received, gestational age, birth-weight and feeding problem had statistically significant association with death of preterm infants due to other causes as presented in Table 2. Moreover, C-section, antenatal care received, birth-weight, feeding problem and gestational age have significant association with being discharged alive as shown in Table 3.

Table 2: Gray's Test Results for death due to RDS and Other Causes

Covariate	**Category**	**Death due to RDS**		**Death due to Other causes**	
		Gray's test	**P-value**	**Gray's test**	**P-value**
Pneumonia	No	0.95	0.33	8.33	0.004
	Yes				
Meningitis	No	4.54	0.03	16.1	0.00006
	Yes				
Anemia	No	11.0	0.0009	7.56	0.006
	Yes				
Multiple pregnancy	No	4.5	0.03	0.01	0.94
	Yes				
Sex	Male	0.52	0.47	0.55	0.46
	Female				
C-section	No	1.35	0.24	3.67	0.055
	Yes				
Diabetes mellitus	No	0.35	0.56	0.71	0.40
	Yes				
	Less than 1				
Birthweight (KG)	1.0-1.5	137.9	<0.0001	35.8	<0.0001
	1.5-2.0				
	2.0 or above				
Maternal age		29.62	0.43	35.4	0.19
Cardiac Disease	No				
	Yes	0.05	0.82	2.07	0.15
Antenatal Care Received	No	2.31	0.13	6.59	0.01
	Yes				

Hypertensive disorders	No	2.59	0.11	2.99	0.08
	Yes				
	Less than 28				
Gestational Age(in weeks)	28-31	145.3	<0.000!	41.5	<0.0001
	32-34				
	35 or above				
Feeding problem	No				
	Yes	12.7	0.00036	4.8	0.028

The assumption of proportionality was checked and the plots do not indicate violation of this assumption as shown in Figure 4, Figure 5 and the appendix.

Table 3. Gray's Test Results for discharged alive

		Survived to be Discharged alive	
Covariate	**Category**	**Gray's test**	**P-value**
Pneumonia	No	2.37	0.12
	Yes		
Meningitis	No	2.38	0.12
	Yes		
Anemia	No	0.89	0.344
	Yes		
Multiple pregnancy	No	2.75	0.097
	Yes		
Sex	Male	0.53	0.47
	Female		
C-section	No	6.15	0.01
	Yes		
Diabetes mellitus	No	1.39	0.24
	Yes		
	Less than 1		
Birthweight (KG)	1.0-1.5		
	1.5-2.0		
	2.0 or above	247.7	<0.0001
Maternal age		25.8	0.63
Cardiac Disease	No	0.41	0.52
	Yes		
Antenatal Care Received	No	6.51	0.01
	Yes		
Hypertensive disorders	No	0.37	0.54
	Yes		
	Less than 28		
Gestational Age(in weeks)	28-31	145.3	<0.0001
	32-34		
	35 or above		
Feeding problem	No		
	Yes	27.23	<0.0001

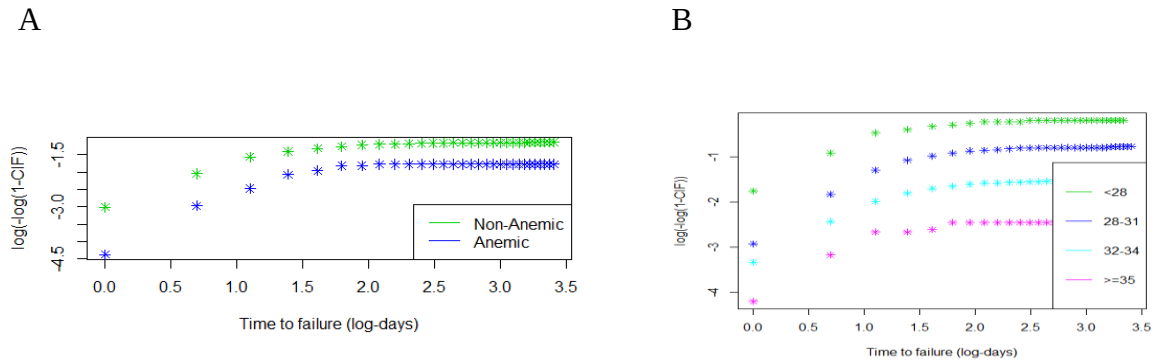


Figure 4. Plot of the Proportionality of the hazard of the CIF for Anemia (A) and Gestational Age (B)

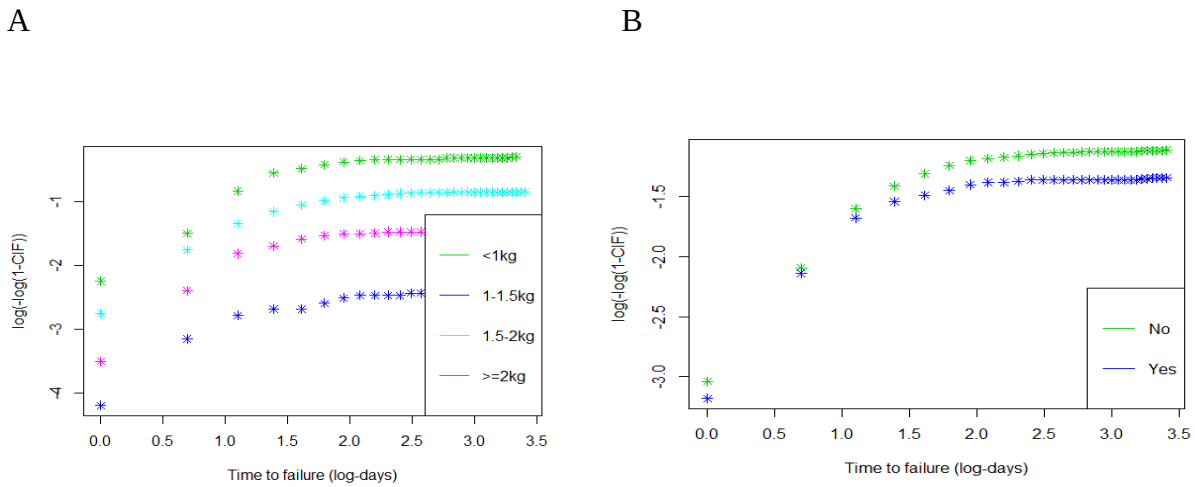


Figure 5. Plot of Proportionality of the hazard of the CIF for Birth-weight (A) and Multiple Pregnancies (B)

Sub-distribution hazard ratios (sHR) and 95% CIs for sHR obtained from the Fine-Gray model fit results are presented in Table 4 and Table 5. The results in Table 4 show that preterm infants who had pneumonia are 93% more likely to die due to other causes but 40% less likely to be discharged alive than those preterm infants who did not have pneumonia. Anemic preterm infants were 60% less likely to die due to RDS whereas they were 36% more likely to die due to other causes compared to those without anemia. For neonates with birth weight 1000-1500, 1500-2000 and 2000 g and above, the relative probabilities of failure or death due to RDS were 41%, 53% and 76% less than for those with birth weight of less than 1000g, respectively.

Conversely, the results in Table 5 show that preterm infants with birth weight 1000-1500, 1500-2000 and 2000g and above increased the cumulative incidence of being discharged

alive 2.06, 3.21 and 4.49times than that for those with birth weight of less than 1000g, respectively. Preterm infants with meningitis were 45% less likely tobe discharged alive than those without meningitis.

Mothers with multiple pregnancies had 22% lower risk of failure or death of neonates due to RDS than those mothers who have not experienced multiple pregnancies. Moreover, neonates with gestational age 28-31, 32-34 and 35 and above weeks had 21%, 50%, 70% lower risk of death due to RDS than preterm infants with gestational age less than 28 weeks, respectively. Conversely, neonates with gestational age 32-34 weeks had 43% lower risk of death due to other causes than those with gestational age of less than 28 weeks. Also, neonates with gestational age 28-31, 32-34 and 35 and above weeks were 2.39, 4.27, 5.0 times more likely to be discharged alive than preterm infants with gestational age less than 28 weeks, respectively.

Table 4.Results of the Fine-Gray Model fit for Death due to RDS and other causes

		Death due to RDS			**Death due to Other Causes**		
Covariate	**Category**	**sHR**	**95% CI**	**P-value**	**sHR**	**95% CI**	**p-value**
Pneumonia (Ref.=No)	Yes	0.81	0.42-1.56	0.53	1.93	1.23-3.05	0.0045
Meningitis(Ref.=No)	Yes	0.42	0.15-1.14	0.09	2.14	1.34-3.40	0.0014
Anemia (Ref.=No)	Yes	0.40	0.27-0.60	0.000013	1.36	1.00-1.84	0.0480
Multiple pregnancy (Ref.=No)	Yes	0.78	0.63-0.96	0.021	1.02	0.82-1.28	0.8500
Sex (Ref.=Female)	Male	1.06	0.88-1.14	0.54	1.18	0.97-1.45	0.1000
C-section (Ref.=No)	Yes	0.89	0.73-1.10	0.27	0.95	0.75-1.21	0.6800
Diabetes mellitus(Ref.=No)	Yes	0.75	0.30-1.87	0.53	0.75	0.24-2.33	0.6200
Birthweight (Ref.= less than 1Kg)	1.0-1.5	0.59	0.46-0.75	0.000014	1.04	0.77-1.41	0.7900
	1.5-2.0	0.47	0.35-0.64	0.0000015	0.74	0.50-1.10	0.1300
	2.0 or above	0.24	0.15-0.40	0.000000	0.67	0.41-1.10	0.1100
Maternal Age(Ref.=under20)	20-34	1.15	0.91-1.46	0.24	0.97	0.76-1.24	0.7900
	35 or above	1.17	0.76-1.80	0.48	1.06	0.64-1.76	0.8300
Cardiac disease (Ref.=No)	Yes	1.04	0.38-2.86	0.94	0.27	0.04-1.71	0.1700
Antenatal care received(Ref.=No)	Yes	0.95	0.68-1.33	0.76	0.72	0.51-1.03	0.0710
Hypertensive disorders (Ref.=No)	Yes	1.03	0.83-1.27	0.81	0.86	0.66-1.13	0.2800
Gestational Age(in weeks) (Ref.=less than 28)	28-31	0.79	0.56-1.10	0.16	0.89	0.58-1.37	0.5900
	32-34	0.50	0.34-0.74	0.00055	0.57	0.35-0.93	0.0240
	35 or above	0.30	0.16-0.55	0.00011	0.72	0.40-1.32	0.2900
Feeding problem(Ref.=No)	Yes	1.07	0.84-1.35	0.60	1.16	0.87-1.54	0.3100

Table 5: Results of the Fine-Gray Model fit for Discharged alive

		discharged alive from NICUs		
Covariate	**Category**	**sHR**	**95% CI**	**P-value**
Pneumonia (Ref: No)	Yes	0.60	0.38-0.97	0.036
Meningitis(Ref: No)	Yes	0.55	0.34-0.91	0.021
Anemia (Ref: No)	Yes	1.01	0.80-1.28	0.9
Multiple pregnancy (Ref: No)	Yes	1.13	0.98-1.31	0.098
Sex (Ref: Female)	Male	0.88	0.76-1.02	0.079
C-section (Ref: No)	Yes	1.09	0.94-1.28	0.25
Diabetes mellitus(Ref: No)	Yes	1.23	0.78-1.93	0.38
Birthweight (Ref: less than 1K g)	1.0-1.5	2.06	1.46-2.91	<0.0001
	1.5-2.0	3.21	2.23-4.62	<0.0001
	2.0 or above	4.49	3.05-6.60	<0.0001
Maternal Age (Ref: less than 20)	20-34	0.97	0.81-1.15	0.69
	35 or above	0.84	0.56-1.24	0.37
Cardiac disease (Ref: No)	Yes	1.22	0.59-2.51	0.59
Antenatal care received(Ref: No)	Yes	1.39	0.99-1.96	0.055
Hypertensive disorders (Ref: No)	Yes	1.03	0.87-1.22	0.71
Gestational Age(in weeks)	28-31	2.39	1.20-4.76	0.013
(Ref: less than 28)	32-34	4.27	2.14-8.54	<0.0001
	35 or above	5.00	2.45-10.22	<0.0001
Feeding problem (Ref: No)	Yes	0.85	0.69-1.06	0.14

Discussion

RDS has become one of the main health complications for preterm infants and it is considered to be the major cause of increased morbidity and mortality for neonates (15). The study of neonatal data has turn out to be one of the main research areas in developing countries like Ethiopia due to its paramount importance for the nation as a measure of achievement of global agenda like sustainable development goals (SDGs).

The current study indicated that 26.4% of the neonates admitted to NICU died due to respiratory distress syndrome. This result is comparable with the findings (16) that mortality rate of preterm infants due to respiratory distress syndrome was 22.86%.

In the present study, only about one-fourth of the total preterm neonates had the event of interest. Had we used the standard survival analysis methods, about three-fourth of the data on the study participants would have been treated as censored observations which would have led to statistical error and incorrect conclusions. These limitations were handled using a competing risk model which allowed us to acknowledge the possible competing events. Therefore, the current study aimed to identify accurate prognostic factors by accounting for the potential

competing risks. In particular, the Fine-Gray competing risk model was used to analyze the prognostic factors associated with the health status of neonates with respiratory distress syndrome.

The result of this study showed that preterm infants having mothers with multiple pregnancy problems had lower risk of dying due to RDS than neonates whose mothers did not experience multiple pregnancy. This result contradicts the findings (17) that multiple gestation pregnancy was associated with high risk of neonatal respiratory diseases.

The results of our study revealed that neonates with birth-weight 1000-1500, 1500-2000 and 2000 g and above had increased cumulative incidence of being discharged alive compared to those with birth-weightless than 1000g. This result is consistent with the finding by (18) that preterm infants with low birth weight had higher risk of death due to RDS than those with normal weight. Similar findings were observed in the study done by (16) that the frequency of RDS is inversely related to gestational age and birth weight. Moreover, the study by (6) showed that the probability of neonates that survived and were discharged alive from the NICUs increases with the increase of birth weight.(15) have also observed in their study that premature infants/neonates with extremely low birth-weight (<1000 g) had increased risk of death due to RDS.

The current study revealed that preterm infants with gestational age less than 28 weeks had a higher risk/probability of dying due to RDS than preterm infants with the gestational age 28-31, 32-34, or 34 and above weeks. Conversely, only preterm infants with gestational age 32-34 weeks had a lower risk/probability of dying due to other causes than preterm infants with gestational age less than 28 weeks. This result is consistent with findings by (19) that mortality and morbidity of neonates was higher for preterm infants with low gestational age and low birth weight. Another study had similar findings with the present study that infants with gestational age less than 25 weeks had increased neonatal mortality (20).

The result of the present study confirmed that preterm infants with anemia had lower risk of dying due to RDS but increased cumulative incidence of death due to other causes than neonates who do not have anemia. However, the findings by (3) showed that anemic neonates had higher incidence of RDS.

Our observation is consistent with the result of the study by (6) that the highest rate of neonatal mortality occurred in the first weeks of admission to the intensive care units. Likewise, our result also revealed that pneumonic neonates have a higher risk of dying due to other causes and reduced relative risk/ probability of being discharged alive than non- pneumonic neonates.

Conclusion

The main objective of the study was to examine and identify potential prognostic factors related to the health status of preterm infants with respiratory distress syndrome problem.

Competing risk modeling frame work helpful to have separate parameter estimates for each recognized competing event was applied. In particular, the Fine-Gray Model or sub-distribution hazard model was used to identify significant prognostic factors

associated with the health status of neonates with RDS.

Death of neonates due to RDS was the event of interest while death of neonates due to other causes and neonates being discharged alive were the competing events. The study revealed that anemia, multiple pregnancies, birthweight and gestational age are the prognostic factors significantly associated with the death of neonates due to RDS while pneumonia, meningitis, anemia and gestational age of neonates were the significant prognostic factors related to death of neonates due to other causes. Similarly, pneumonia meningitis, birthweight and gestational age were identified as the significant prognostic factors associated with neonates being discharged alive.

The results of this study are expected to provide information about prognostic factors of death of neonates (with RDS) admitted to NICUs by considering competing events which may in turn be essential for planning effective programs and evaluating the existing national health policy. In addition, the results of this study may be used as a basis for future studies in the area.

Desired treatments should be provided giving more attention for neonates diagnosed for health complication of anemia, pneumonia and meningitis in order to prolong their survival time which in turn reduces neonatal mortality. Offering intensive and adequate treatments for those critically exposed neonates with lowest birth-weight and gestational age could decrease the burden of neonatal mortality. Moreover, evaluating the existing neonatal health care modalities provided in intensive care units may help to increase neonates' incidence of being discharged alive. Further studies that consider more prognostic factors are recommended.

Declaration of Conflicts of Interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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