ADDIS ABABA UNIVERSITY

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RISK FACTORS OF NEONATAL MORTALITY IN ETHIOPIA: APPLICATIONS OF SURVIVAL ANALYSIS METHODS

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ACRONYMS

AIC	Akaike's information criterion
BIC	Bayesian Information Criterion
CI	Confidence Interval
CSA	Central Statistical Agency
EA	Enumeration Area
EAG	Empowered Action Group
EDHS	Ethiopia Demographic and Health Survey
HR	Hazard Ratio
KM	Kaplan-Meier
LR	Likelihood Ratio
MDG	Millennium Development Goal
NFHS	National Family and Health Survey
PH	Proportional Hazards
SRS	Sample Registration System
UNICEF	United Nations Children's Fund
UN-IGME	United Nations Inter-agency Group Child Mortality Estimation
WHO	World Health Organization

ABSTRACT

Neonatal mortality accounts for almost 40 percent of under-five child mortality, globally (WHO 2005). An understanding of risk factors related to neonatal mortality is important to guide the development of focused and evidence-based health interventions to reduce neonatal deaths. This study aimed to identify the risk factors of neonatal mortality in Ethiopia. The data source for the analysis was the 2011 EDHS data from which survival information of 8,651 live-born neonates born five years before the survey was examined. Stratified Cox-proportional hazards model was employed to analyze risk factors associated with neonatal deaths, using socio-economic, demographic and maternal health service factors. About 71% and 79% of the neonatal deaths occurred within the first and second weeks of follow-up time, respectively. The estimated hazard ratios of mortality were higher for twins or multiple births (HR=3.728, 95% CI: 2.813-4.942), first order birth (HR=1.675, 95% CI: 1.252-2.242), male sex (HR=1.26, 95% CI: 1.057-1.501), birth interval shorter than 24 months (HR=1.633, 95% CI:1.312-2.032), very small and very large sized neonates at birth, (HR=1.833, 95% CI:1.457-2.305) and (HR=1.966, 95% CI:1.535-2.519), respectively, neonates born to mothers aged less than 20 years and above 34 years, (HR=1.382, 95% CI:1.051-1.818) and (HR=1.323, 95% CI:1.060-2.799), respectively, and neonates whose mothers had a history of pregnancy complications (HR = 1.732, 95% CI:1.266-2.239). The risk of dying were lower for neonates whose mothers attended antenatal visits (HR=0.716, 95% CI: 0.577-0.889) and neonates put to breast immediately upon birth (HR=0.828, 95% CI: 0.693-0.989). Thus, public health interventions directed at reducing neonatal death should address demographic and maternal health service factors which significantly influence neonatal mortality in Ethiopia.

CHAPTER ONE
INTRODUCTION

1.1 Background of the study

Neonatal mortality (NN) is the probability of dying within the first month of life and is expressed as a rate per 1000 live births. Neonatal deaths account for 40% of deaths under the age of 5 worldwide and it has been estimated that, each year, 8 million neonates died within the first 28 days of life (WHO 2005) and the relative importance of these deaths increased as child mortality reduced. The vast majority of these events occur in low-income countries, including those in Sub-Saharan Africa (Lopez et al, 2001). Despite the reduction in under-five mortality over the past years, it has become evident that the Millennium Development Goal 4 that targets reduction of under five mortality by two thirds by 2015 is unlikely to be achieved if neonatal survival chances do not improve (Lawn et al, 2005). Reduction of neonatal death is a high priority, and it is an international mission to achieve the Millennium Development Goals (UN 2002). Thus, it is crucial that health policy makers and programme managers pay attention to the epidemiology of neonatal deaths, mainly in low-income countries where the vast majority of neonatal mortality occurs.

The first month of life, the neonatal period, carries one of the highest risks of death of any month in the human lifespan (Lawn et al, 2005). In high-income countries, neonates are now a major focus of child health both for mortality and morbidity reduction. However, in lower-income countries neonatal mortality rates, trends, and causes have attracted relatively little attention compared to maternal deaths or deaths among older children under 5 and in international public health policy and programmes, neonatal deaths still do not receive attention commensurate with their burden (Shiffman 2010). A specific focus on neonatal mortality is required as the epidemiology, cause-of-death distribution, and health interventions differ from those of older children. Child survival programmes have typically focused on diseases affecting children aged over 1 month primarily pneumonia, malaria, diarrhea, and vaccine preventable diseases and safe motherhood programmes have tended to focus on the mother and not her newborn (Tinker et al, 2005).

Ethiopia is the second most populous country in Africa after Nigeria with a population of nearly 83 million in 2010 (World Bank, 2013). The population grows at a rate of 2.6 percent per annum which is slightly greater than the sub-Saharan African countries average growth of 2.5 percent and the majority of people (84%) reside in rural areas, with agriculture being the major source of livelihood. The age structures suggest nearly 45 percent of the populations are under age 15 and the percentages of the population above age 65 are only about 3.2 percent. High mortality, high fertility and low life expectancy characterize the demography, as in most sub-Saharan African countries (Ringheim *et al,* 2009).

In Ethiopia, results from the 2011 EDHS data showed a remarkable decline in all levels of childhood mortality. The same report showed that infant mortality has declined by 42 percent over the 15-year period preceding the survey from 101 deaths per 1,000 live births to 59 deaths per 1,000 live births. Furthermore, under-five mortality has declined by 47 percent over the same period from 166 deaths per 1,000 live births to 88 deaths per 1,000 live births. Even though not to the same extent, the neonatal mortality has also decreased over the 15-year period preceding the survey by 31 percent from 54 deaths per 1,000 live births to 37 deaths per 1,000 live births. This reduction in neonatal mortality, as in other parts of the world, was slower than for infant, and under-five mortality, which fell by 42 percent and 47 percent respectively over the 15 year period (EDHS Report 2011). In addition, the country is experiencing a high neonatal mortality rate at 37 per 1000 live births, comparable to the average rate of 35.9 per 1000 live births for the African region overall (Oestergaard *et.al*, 2011).

There is limited research conducted on neonatal mortality in Ethiopia. Most of the information for any program planning and implementation has been based on Ethiopian Demographic and Health Survey (EDHS) conducted every five years. EDHS describes only the rate of mortality and does not provide information on the causes of death distribution, and health interventions differ from older children. This study focused on the determinants and risk factors associated with neonatal mortality in Ethiopia. We are particularly interested in how neonatal survival is affected by household's socio-economic, demographic and maternal health service characteristics.

Previous reviews of the causes of neonatal deaths from 75 countries have demonstrated that up to 70 percent of neonatal mortality could be prevented using evidence-based interventions (Darmstadt et al, 2005). To adopt a focused, evidence-based approach to reduce neonatal mortality in Ethiopia, a clear understanding of the associated factors is necessary. Using the 2011 Ethiopia Demographic and Health Survey data, this study examined the determinants of neonatal mortality for all neonates of the sampled women who were born five years before 2011 survey.

Currently more than half of all infant death occurs during the first week of life largely as a result of poorly managed pregnancies and births, or because of the absence of a few simple life-saving gestures during the first critical moments of life, neither mother nor infant will need high technology interventions or expensive drugs or equipment (WHO, 1996).

Antenatal care that women receive during pregnancy is an important opportunity providing a pregnant woman with vaccinations to prevent tetanus, screening her for anemia, enrolling her in the prevention of mother to child transmission of HIV, and providing her with counseling for safe delivery. All these factors help ensure that the mother remains healthy during childbirth and give her healthy neonates (Taddele, 2010). Proper medical attention and hygienic conditions during delivery can reduce the risks of complications and infections that may cause death or serious illness to either the mother or the baby or both (EDHS, 2000).

Poverty is one of the most important factors affecting the infant mortality rate in Africa. Ethiopia is one of the poorest African countries with, according to UNICEF (2009) report, with a Gross National Income per capita of about USD 220 in 2007. The impact of poverty on the health of children is due to lack of access to a variety of material and non-material resources, as well as environmental and psychological deprivation at cultural, social and health levels. Low socio-economic position has been found to be associated with low birth weight and increased neonatal mortality (Bradley and Corwyn 2002). While medical interventions can in principle prevent most early child deaths, they cannot eliminate the underlying causes of poor health, which are linked directly to those severely deprived or 30 percent of the world's children living in absolute poor conditions (UNICEF 2004). Eliminating extreme poverty is the key to improving global infant survival rates, particularly over the long term.

1.2 Statement of the problem

One of the targets of the Millennium Development Goals (MDGs) is to reduce the under-five mortality rate by two-thirds between 1990 and 2015. Since 1990 the under-five mortality rate has dropped 35 percent, with every developing region seeing at least a 30 percent reduction. However, at the global level progress is behind schedule, and the target is at risk of being missed by 2015. The global under-five mortality rate needs to be halved from 57 deaths per 1,000 live births to 29 that imply an average rate of reduction of 13.5 percent a year, much higher than the 2.2 percent a year (UN-IGME, 2011).

A recent review of child mortality has revealed that the proportion of under-five child deaths occurring in the first month of life has been increasing (Black *et al,* 2003), accounting for almost 40 percent of all under-five child deaths and more than half of infant deaths, neonatal mortality are not a target of the Millennium Development Goals (MDGs) (UN 2001). In Ethiopia, approximately 42% of the under-5 mortality is attributable to neonatal deaths. However, if the MDG target of a two-thirds reduction in child mortality by 2015 is to be achieved then neonatal mortality must be addressed.

The mortality trends in Ethiopia can be examined by comparing data from DHS surveys conducted in 2000, 2005, and 2011. Infant and under-five mortality rates obtained by these surveys evidence a continuous declining trend in mortality. Under-five mortality decreased from 166 deaths per 1,000 live births in the 2000 survey to 88 in 2011, while infant mortality decreased from 97 deaths per 1,000 live births in the 2000 survey to 59 in the 2011 survey. On the other hand, even though neonatal mortality rate decreased from 49 deaths per 1,000 live births in 2000 to 39 deaths per 1,000 live births in 2005, it has since remained stable at 37 deaths per 1,000, as reported in the 2011 EDHS (DHS 2011 Report). From the result acceleration in progress towards MDG 4 has been observed, but less attention has been paid to neonates compared to older children under the age of 5. The reduction rate in neonates remained stagnant over the last two surveys.

Hence, to achieve MDG 4 a planning and policy intervention program is necessary to reduce the current rates of neonatal mortality. This research is undertaken with the aim to identify factors that have effect on neonatal mortality. The study focuses on an analysis of the impact of demographic, socioeconomic and maternal health service factors on neonatal mortality. The research question is:-

What are the key socio-economic, demographic and maternal health service predictors of mortality amongst neonates in Ethiopia?

1.3 Objectives of the study

1.3.1 General objective

The general objective of the study is to identify the key socio-economic, demographic and maternal health service determinant factors of neonatal mortality in Ethiopia by using survival analysis based on non-parametric and semi-parametric methods.

1.3.2 Specific objectives

The specific objectives of the study are:-

- To compare survival experience of neonates in various categories of covariates.
- To identify the levels of significant risk factors that affect survival times of neonates.
- Make relevant recommendations for policy makers, program managers as well as development planners.

1.4 Significance of the study

The results of this study may provide information on causes of high risk neonatal mortality in Ethiopia by analyzing the impact of different variables on survival of neonates.

Specifically;

1. The results are expected to give some knowledge about determinants and risk factors of neonatal mortality in Ethiopia.
2. The results of this study could be used as input for other studies related to neonatal death.
3. This study could provide information to government and other concerned bodies in setting policies, strategies, and further investigation for reducing neonatal mortality.

1.5 Limitations of the study

- The estimates of neonatal mortality are based on retrospective birth histories which are subject to possible reporting errors that may affect the quality of the data. A lack of accurate information on the age at death may distort the age pattern of mortality.
- The study is based on only the set of data for which complete information on survival times are available because of missing values.
- Variables such as gestational age and birth weight were not considered in this study even though they were potential predictors of neonatal mortality in the literature. The record on gestational age was not available in 2011 EDHS data. Birth weight was omitted from this study since about 87.5% of neonates at birth were not weighted.

CHAPTER TWO
LITERATURE REVIEW

2.1 Theoretical Literature

Researchers used a number of different theoretical frameworks to analyze the impact of different risk factors on infant and child survivals. Among these researchers Mosley and Chen (1984) and Schultz (1984), classified the determinants of infant and child mortality as exogenous (socioeconomic or extrinsic) such as socioeconomic, community and regional determinants and endogenous (bio-medical or intrinsic) such as maternal, environmental, nutrition, injuries and personal illness. The effects of the exogenous variables are considered indirect because they operate through the endogenous biomedical factors. Likewise, bio-medical factors are called intermediate variables or proximate determinants because they constitute the middle step between the exogenous variables and child mortality (Mosey and Chen, 1984; Schultz, 1984).

Mosley and Chen (1984) were among the first to study the intermediate biomedical factors affecting child mortality, labeled 'proximate determinants'. They identified fourteen proximate determinants and categorized them into four groups: maternal (fertility) factors, environmental sanitation factors, availability of nutrients to the foetus and infant, injuries, and personal illness control factors.

Cramer (1987) developed a conceptual model of infant mortality with the objective to use a causal modeling approach in order to detect direct and indirect effects of socio-economic factors. More precisely he considered that maternal age, marital status and education (socio-economic factors) influence birth order, birth weight and antenatal care (intervening variables which finally influence the infant mortality).

Regarding the association between socioeconomic status and infant and child mortality, Caldwell (1979) reported on the effect of mother's education on reducing child mortality. He put up a theory that mother's education works through changing feeding and care practices, leading to better health seeking behavior and by changing the traditional familial relationships. In supporting Caldwell's explanation, Hobcraft (1993) explained that education can contribute to child survival by making women more likely to marry and enter motherhood later and have fewer children, utilize prenatal care and immunize their children. The results also, however, showed mysterious conclusion that the effect of maternal education on child survival is weaker in Sub-Saharan Africa.

Galster's (2010) work on the mechanisms of neighborhood effects theory observed a link between residential environment and health. Evidence suggested that living in an economically and socially deprived community or neighbourhood was associated with increased risk of under-five mortality (Antai and Moradi, 2010); and children from the same community tend to share the same environmental conditions. For instance, children raised in a community that lacks electricity, good drinking water and health facility are likely to suffer from the same deprivation which can directly or indirectly influence their health outcomes.

However, Whitworth and Stephenson (2002) maintain that two neonates with similar characteristics may experience a different neonatal mortality risk because of the community contextual effects. The authors argue that these differentials in mortality risks may be as a result of differences in the provision of antenatal and obstetric health care or the effects of environmental conditions the children are exposed to.

Further the WHO Commission established that reducing child mortality is a key to economic growth, for a variety of reasons. Societies with high rates of infant and child mortality have higher rates of fertility, and large numbers of children reduce the ability of poor families to invest in health and education, resulting in an under-trained productive work force (WHO, 2001).

In addition to its effect on fertility, child mortality is also important for the human capital investment decision of parents. Lower mortality implies a higher rate of return to education, and thus declining child and youth mortality provides an important incentive to increase investment in the education of each child (Kalemli-Ozcan, 2002). Heckman

(2000) also argues that the return to human capital investment is highest before age five. Secondly, lowering infant mortality rates tends to lower, not raise, population growth over the long run, as people adjust to having smaller families.

2.2 Empirical Literature

Empirically, many studies have shown that neonatal mortality is influenced by a number of socio-economic, demographic and maternal health service factors. For instance, Titaley et al. (2008) used data from the Indonesian Demographic and Health Survey conducted in 2002/03 to identify the determinants of neonatal mortality in Indonesia. Multilevel logistic regression using a hierarchical approach was performed to analyze the factors associated with neonatal deaths, using community, socio-economic status and proximate determinants. Results revealed that the odds of neonatal death were higher for infants with a short birth interval, male infants, very small-sized infants and infants whose mothers had a history of delivery complications. Furthermore, infants receiving any postnatal care were significantly protected from neonatal death. The study concluded that low birth weight and short birth interval infants as well as prenatal health service factors such as the availability of skilled birth attendance and postnatal care utilization should be taken into account when planning the interventions to neonatal mortality.

Another study in Indonesia, by Dakhi (2012) used data from Indonesian Demographic and Health Surveys 2002-2003 and 2007 to determine contribution of delivery assistance by skilled attendants on the risk reduction of neonatal mortality. The Cox proportional hazards model was used for data analysis. Results showed that in the period of 2002-2003, the risk of neonatal mortality was significantly lower in delivery attended by skilled attendants compared to unskilled attendants (HR=0.6; 95% CI=0.4 to 0.9). In the period of 2007, it was found that the risk of neonatal death was lower in delivery attended by skilled attendants compared to unskilled attendants, but the difference was not statistically significant (HR=0.8; 95% CI=0.5 to1.1). Furthermore, the risk of neonatal death was higher among women who received antenatal care less than 4 times during the pregnancy, infants who did not receive any postnatal care, infants whose mother's age was above 34 years, infants born at gestational age of less than or equal to 37 weeks, birth below 2500 gram, and male infants. But, socio-economic status had no effect on neonatal mortality.

In Tanzania, Nathan and Mwanyangala (2012) used longitudinal data generated in a Health and Demographic Surveillance System in rural Southern Tanzania to assess associations of neonatal mortality and place of delivery. Poisson regression was used to estimate crude relative risks of neonatal death by place of birth. The results showed that neonates born in a health facility had similar chances of dying as those born in the community. From the study they found no evidence to suggest that delivery in health facilities was associated with better survival chances of the neonates. However, another study in Brazil concluded that children who were not born in a hospital had 1.9 times increased risk of neonatal death. Mothers, who delivered at home were of low socio economic status and had a lower education level (Almeida et al, 1999).

Arokiasamy and Gautam (2007) examined the level and trends in neonatal mortality in the Empowered Action Group (EAG) states of India. They used data from India's Sample Registration System (SRS) and National Family and Health Survey (NFHS-2, 1998–99). Cox proportional hazard model was used to estimate adjusted neonatal mortality rates by health care and bio-demographic determinants. Variations in neonatal mortality by these determinants suggested that universal coverage of all pregnant women with full antenatal care and providing assistance at delivery including emergency care were critical inputs for achieving a reduction in neonatal mortality. From the result they found that health interventions should focus on curtailing the high risk of neonatal deaths arising from the mothers' young age at birth, first and higher order births and short birth intervals is required.

Rutstein (2008) studied the pooled birth history data from all 52 countries surveyed in the DHS program between 2000 and 2005 to see the effects of the preceding birth interval on infant and child mortality, broken down into several periods – early neonatal, neonatal, post-neonatal, infant, child (one to four years), and under-age five years. Life tables and Cox hazard multivariate regression were used to analyze the data. The results revealed that the risk of neonatal mortality by preceding birth-to-pregnancy interval was U-shaped with the lowest point at the reference group (24-47 months). All interval groups outside the period 24 to 47 months had adjusted relative risks that were significantly higher than that of the reference group. Furthermore, intervals shorter than 24 months have adjusted relative risks that are from 19 percent to 146 percent higher than the risk of the reference group's mortality. Intervals longer than the reference group have risks that are from 20 percent to 79 percent higher than the risk of the reference group's mortality.

Mustafa and Odimegwu (2008) used the 2003 DHS data set for children by using logistic regression models in Kenya to examine socioeconomic determinants of neonatal and post-neonatal mortality rate both in urban and rural settings. They found that there was regional variation in infant mortality rate within different provinces of Kenya. Most of the socioeconomic factors were not found to be associated with the risk of infant mortality while infants born in rich household had lower probability of infant mortality relative to infants born in poor households. However, ethnicity and breast feeding had a significant influence on infant mortality. Also first order birth and birth intervals less than two years were found as important determinants for the risk of neonatal mortality.

Chaman *et al.* (2009) investigated neonatal mortality risk factors in rural part of Iran based on nested case-control design. The neonates born in rural areas of Kohgiluyeh and Boyerahmad province (South of Iran) were followed up till the end of neonatal period and the outcome of interest was neonatal death. The study concluded that preterm birth, low birth weight, birth spacing less than 24 months and birth order higher than 4 were found to be important risk factors for neonatal mortality.

Susman (2012) analyzed data from the Ethiopian Demographic and Health Surveys 2000 and 2005 using indirect estimation of Brass and Trussell. The results showed that neonatal and post-neonatal mortality declined gradually. Birth intervals shorter than 2 years led to higher neonatal mortality rates than higher birth intervals. The study concluded that proper spacing of births would provide more time for childcare by making more maternal resources available for the care of the child and mother.

Tesfaye (2003) conducted a cross sectional comparative study to assess pregnancy and birth outcome with emphasis on perinatal and neonatal mortality by delivery place and its associated factors in Dire Dawa, Ethiopia[1]. Logistic regression was employed to analyze the data collected on 1462 mothers who had children or had been pregnant in the last five years before the study. It was found out that very small and smaller than average size of the neonates at birth had more risk of neonatal mortality than neonates who had average birth size at birth (OR 3.61, 95% CI 1.75 - 7.43). Furthermore, neonates born to mothers whose income was under 300 birr per month and neonates born to mothers whose income was 300-600 birr per month had more risk to neonatal mortality than those neonates born to mothers whose income was more than 600 birr per month.

A birth cohort study was conducted by Makonnen et al. (2002) to investigate risk factors associated with neonatal and post-neonatal mortality in Jimma, Keffa and Illubabor zones of Southwest Ethiopia. Cox proportional hazards model was used to analyze the data collected on socio-economic, biological, and environmental factors. Infant mortality rate was estimated as 106.2 per 1000, with estimates of 97.0 per 1000 and 113.5 per 1000 for urban and rural areas, respectively. The results revealed that mortality was associated with mothers' education and with antenatal care follow-up: there was better survival with at least one antenatal care follow-up. Furthermore, twins were much more likely to die than singletons, even after taking their birth weight into account in neonatal age.

Mondal et al. (2009) used the logistic regression model, investigated factors influencing neonatal, post-neonatal and child mortality in Rajshahi District of Bangladesh. The findings revealed that the most significant predictors of neonatal, post-neonatal and child mortality levels were immunization, ever breastfeeding, mother's age at birth and birth interval. In a similar vein, Chowdhury et al. (2010) in their study on Bangladesh examined the effects of socio-economic factors on neonatal, post-neonatal, infant and child mortality using multivariate analysis. They found that mother's education, types of latrine and electricity had significant association with neonatal, post neonatal, infant and child mortality.

[1]perinatal mortality includes both deaths in the first week of life and fetal deaths (stillbirths)

Kamal (2012) investigated the effect of maternal education on neonatal mortality in Bangladesh using data from the 2007 Bangladesh Demographic and Health Survey. Both bivariate and multivariate statistical analyses were used to assess the relationship between neonatal mortality and contextual factors focusing on maternal education. The results revealed that the sequential multivariate logistic regression analyses yielded a strong significant negative association between maternal education and neonatal mortality. Furthermore, maternal age less than 20 years, religion, birth order and antenatal care seeking were identified as important determinants of neonatal death.

Another study in Jimma town, south west Ethiopia, conducted by Tsinuel and Hailu (2008) to assess traditional care given to newborns in Jimma town found out that home delivered babies were exposed to harmful practices and small babies did not receive special care.

In addition, delivery in medical institutions and with professional health assistance during delivery was determining factors of neonatal mortality rate. A higher level of institutional delivery uptake was associated with reductions of neonatal mortality in developing countries (Claeson and Waldman, 2000).

Wang (2003) used data from 2000 DHS in Ethiopia to examine the effect of environmental factors on infant and child mortality by using three hazard models (the Weibull, the Piece-wise Weibull and the Cox model) and to investigate three age-specific mortality rates: neonatal (under-one month), infant (under-one year) and under-five mortality by location (urban/rural), female education attainment, religion affiliation, and access to basic environmental services (water, sanitation and electricity). The findings were that infant and child mortality was higher in rural areas than urban areas, and that poor environmental conditions were related to high risk of infant and child mortality. But the effects of environmental conditions were not significant on neonatal mortality.

A community-based study was conducted in a rural area, El-Minia governorate, Egypt by Seedhom and Kamal (2008) to determine the neonatal mortality rate and risk factors. The results showed that neonatal mortality rate was 24/1000 live births. Maternal demographic characteristics were associated significantly with neonatal mortality. About 27%, 83%, and 79% of neonatal deaths were associated with maternal age less than 20 years, maternal illiteracy, and no breast feeding respectively.

Joshi (2003) studied social and biomedical risk factors attributable to perinatal and neonatal mortality in rural Punjab, India using a community based case control study. The results showed that households with a low socio-economic status had a 5 times higher risk of having perinatal or neonatal mortality compared to households in higher socioeconomic status.

Kamal et al. (2012) used data from the 2007 Bangladesh Demographic and Health Survey to identify the risk factors of neonatal mortality. Bivariate and multivariate statistical analyses were used to assess the relationship between neonatal mortality and risk factors. The study showed that the prevalence of neonatal mortality was 37 per 1,000. Increased risk of neonatal mortality was associated with children whose mothers had no formal education, were adolescents of age 15-19 and first born child.

A case-control study was conducted in the Gaza Strip, occupied Palestinian territory, by Awour et al. (2012), to identify risk factors affecting neonatal mortality. Multilevel logistic regression was employed to assess differences in exposures between surviving and deceased neonates. The results have shown that cases whose mothers had more than four dependants were at a higher risk than were controls whose mothers had fewer dependants (OR: 1.56, 1.07-2.27; p=0.05), and newborn babies born to mothers who attended fewer than four antenatal sessions during pregnancy had a risk of dying that was almost twice that of those born to mothers who attended antenatal session four or more times (OR: 1.99, 1.04–3.45 p=0.03). Furthermore, the risk of death in neonates who were breastfed within the first hour of delivery was much lower than among those who were not breastfed in the first hour (OR: 0·12, 0·06–0·22; p<0·0001).

Araújo et al. (2000) employed multiple logistic regressions to study neonatal death in Caxias do Sul city, Brazil. The study found out that mother's age at birth, gestational age, male infants and multiplicity of birth were significantly related to neonatal death.

The above literature search was used to further understanding of the risk factors affecting neonatal mortality and to select the variables that would be important to include in this research. It is hoped that this review will serve as a standard for comparison for the intended analyses.

CHAPTER THREE
DATA AND METHODOLOGY

3.1 Data source

The dataset used in this study was obtained from Demographic and Health Survey data conducted in Ethiopia in 2011, which is the third comprehensive survey conducted as part of the worldwide Demographic and Health Surveys project. The data provide in-depth information on fertility, family planning, infant, child, adult and maternal mortality, maternal and child health, nutrition and knowledge of HIV/AIDS and other sexually transmitted diseases.

3.2 Sample design

The sample for the 2011 EDHS was designed to provide population and health indicators at the national (urban and rural) and regional levels. The 2007 Population and Housing Census, conducted by the CSA, provided the sampling frame from which the 2011 EDHS sample was drawn. Administratively, regions in Ethiopia are divided into zones, and zones, into administrative units called *weredas*. Each *wereda* is further subdivided into the lowest administrative unit, called *kebele*. During the 2007 census each *kebele* was subdivided into census enumeration areas (EAs), which were convenient for the implementation of the census.

The 2011 EDHS sample was selected using a stratified, two-stage cluster design and EAs were the sampling units for the first stage. The sample included 624 EAs, 187 in urban areas and 437 in rural areas. Households comprised the second stage of sampling. A complete listing of households was carried out in each of the 624 selected EAs from September 2010 through January 2011. A representative sample of 17,817 households was selected for the 2011 EDHS, of these, 16,702 were successfully interviewed. In the interviewed households 17,385 eligible women were identified for individual interview; complete interviews were conducted for 16,515.

The number of children at this level was 11,654 representing the number of live births born to the interviewed mothers in the period of five years preceding the date of the survey. After a certain rearrangement, reorganization and removal of missing values the total number of children with complete information became 8,651.

3.3 Variables in the study

The response (dependent) variable

The dependent variable used in the hazard model analysis is neonatal survival time. It is measured as the duration starting from date of birth of neonate to the date of death/censor measured in days.

Predictor (independent) variables

The predictors considered in this study are categorized as socio-economic, demographic and maternal health service factors/variables.

Table 3.1: Operational definition and categorization of the variables

Variables	Definition and Categorization
Socioeconomic factors	
Region	Administrative regions (1=Tigray;2=Affar;3=Amhara;4=Oromiya; 5=Somali;6=Benishangul-Gumuz;7=SNNP;8=Gambela;9=Harari; 10=Addis Ababa;11=Dire Dawa)
Residence	Place of residence (1=Urban;2=Rural)
Wealth index	Household wealth index (1= Poor; 2=Medium; 3=Rich)
Maternal education	Mother's level of education (0= No education;1= Primary; 2= Secondary and Higher)
Maternal marital status	Marital status of the mother (1=Never in union; 2=Married; 3=Widowed/divorced/separated)
Demographic factors	
Maternal age	Mother's age at child birth in years (1=<20; 2 =20-34; 3 =>34).
Birth order	Birth rank of child (1=First birth;2=2-4 births;3=Fifth or above)
Sex	Sex of neonates (0=Female;1=Male)
Multiple births	Whether neonate is twin (1=Single;2=Multiple)

Birth interval	Preceding birth interval in months (1=<24;2=24-47;3=>47)
Birth size	Subjective assessment of the respondent on the birth size (1=Very large;2=Larger than average;3=Average;4=Smaller than average;5=Very small)
When neonate put to breast	Neonate put to breast immediately upon birth (0=No;1=Yes)
Maternal health service factors	
Antenatal care seeking	Sought antenatal care services during pregnancy (0=No;1=Yes)
Place of delivery	Place of delivery (1 = Home; 2 = Health facility)
Delivery assistance	Birth attendant during delivery (1= Unskilled birth attendant; 2=Skilled birth attendant)
Pregnancy complications	Pregnancy complications during delivery (0=No;1=Yes)

3.4 Methodology: Survival data analysis

Survival analysis is a collection of statistical procedures for data analysis for which the outcome variable of interest is time until an event occurs. It involves the modeling and analysis of data that have a principal end point, the time until an event occurs (time-to-event data). By time, we mean years, months, weeks, or days from the beginning of follow-up of an individual until an event occurs. In survival analysis, we usually refer to the time variable as survival time, because it gives the time that an individual has 'survived' over some follow-up period. We also use the term `failure' to define the occurrence of the event of interest (even though the event may actually be a `success' such as recovery from therapy) (Kleinbaum and Klein, 2005).

Survival analysis is different from the other statistical procedures due to following reasons.

1. In survival analysis, the response variable is time.
2. Staggered entries are more common in medical research. By staggered entries we mean that all individuals in the study do not have the same entrance time. This does not affect the survival analysis, as the analysis deals with the length of the observation time and not based on the same entrance.

3. The assumption of normality does not hold in survival analysis, as survival data are generally skewed.
4. The covariates can be time dependent.

One of the most important differences between the outcome variables modeled via linear and logistic regression analyses and the time variable in the survival data is the fact that we may only observe the survival time partially. The variable time actually records two different things. For those subjects who died, it is the outcome variable of interest, the actual survival time. However, for subjects who were alive at the end of the study, or for subjects who were lost to follow-up, time indicates the length of follow-up (which is a partial or incomplete observation of survival time). These incomplete observations are referred to as being censored. Censoring may occur when a person does not experience the event before the study ends, a person is lost to follow-up during the study period, and a person withdraws from the study.

There are three common forms of censoring:

a. Right Censoring: The most common form of incomplete data is right censoring. A survival time is said to be right censored if it is recorded from its beginning until a well defined time before its end time. It means a subject's follow-up time terminates before the outcome of interest is observed.
b. Left Censoring: A survival time is said to be left censored if an individual developed the event of interest prior to the beginning of the study. This situation is less common in survival studies and is often not a focus.
c. Interval Censoring: A survival time is categorized as interval censored if it is only known that the event of interest occurs within an interval of time without the knowledge of when exactly it occurs. Interval censoring can occur in clinical trials, industrial experiments, etc.

The focus of this study is on right censoring. We consider an observation as right censored if the subject did not experience the event during study period. In our dataset the event of interest was rare in that there were a high percentage of censored observations (about 94%). For such data proportional hazards and Poisson models are the preferred choices than other statistical models. But selecting between these two can be based on convenience in most circumstance (Callas *et al.,* 1998 and Stewart, 2010). Hence to incorporate survival time into the analysis we used proportional hazards model in the study.

3.4.1 Descriptive methods for survival data

Descriptive analysis for survival data is to present numerical or graphical summaries of the survival times in a particular group. In general, a statistical analysis should begin with a thoughtful and thorough univariate description of the data. The survivor function and hazard function are the two functions of central interest in summarizing survival data.

Survivor function

Let T be a random variable associated with the survival times, t be the realization of the random variable T and $f(t)$ be the underlying probability density function of the survival time t. The cumulative distribution function $F(t)$, which represents the probability that a subject selected at random will have a survival time less than some stated value t, is then given by:

$$F(t) = P(T \leq t) = \int_0^t f(u)du, t \geq 0 \tag{1}$$

The survivor function, denoted by $S(t)$, is defined to be the probability of an individual surviving or being event-free beyond time t (experiencing the event after time t). It is defined as $S(t) = P(T > t)$. The survival function is merely the complement of the cumulative distribution function, that is

$$S(t) = 1 - F(t) \tag{2}$$

Since $S(t)$ is a probability, $S(0) = 1$ and as t approaches ∞, $S(t)$ approaches 0. From equations (1) and (2) the relationship between $f(t)$ and $S(t)$ can be given as:

$$f(t) = -\frac{dS(t)}{dt}, \quad t \geq 0 \tag{3}$$

Hazard function

The hazard function is a measure of the probability of failure during a very small interval, assuming that the individual has survived at the beginning of the interval. It is defined as

$\lambda(t) = \lim_{\Delta t \to 0}$ P (an individual who survive to time t fails in (t, t+ Δt))/Δt

$$\lambda(t) = \frac{f(t)}{S(t)} = \frac{-d\ln S(t)}{dt} \quad (4)$$

Survival model is usually expressed in terms of hazard function. The cumulative hazard function is defined as

$$\Lambda(t) = \int_0^t \lambda(u)du \quad (5)$$

Similarly, the survival function can be given in terms of the hazard function as:

$S(t)$=exp (- Λ (t)), consequently $f(t) = \lambda(t)$ exp (- Λ (t)). (6)

Estimation of the survivor function

Among the other estimators of the survivor function the Kaplan-Meier estimator is the most common one. The Kaplan-Meier or product limit estimator is the limit of the life-table estimator when intervals are taken so small that only at most one distinct observation occurs within an interval. Kaplan and Meier (1958) demonstrated that this estimator is a "maximum likelihood estimator". The estimator incorporates information from all of the observations available, both uncensored and censored, by considering survival to any point in time as a series of steps defined by the observed survival and censored times. This method is non-parametric or distribution-free, since it does not require specific assumptions to be made about the underlying distribution of the survival times (Hosmer and Lemeshow, 1999).

Let $d(x)$ denote the number of deaths at time x. Generally $d(x)$ is either zero or one, but we allow the possibility of tied survival times in which case $d(x)$ may be greater than one. Let $n(x)$ denote the number of individuals at risk just prior to time x; *i.e.*, number of individuals in the sample who neither died nor were censored prior to time x. Then the Kaplan-Meier estimator of the survival function at time t is obtained from the equation;

$$\hat{S}_{KM}(t) = \prod_{x \le t} \left(1 - \frac{d(x)}{n(x)}\right) \tag{7}$$

with the convention that $\hat{S}_{KM} = 1$ if $t < t_{(1)}$

In the notation above, the product changes only at times x where $d(x) \geq 1$; *i.e.*, only at times where we observed deaths.

From equation (6) the KM estimator of the cumulative hazard function can be estimated

$$\hat{\Lambda}_{KM}(t) = -\ln(\hat{S}_{KM}(t) \tag{8}$$

The variance of the Kaplan-Meier estimators which is referred to as Greenwood's formula is given as:

$$V\hat{a}r(\hat{S}_{KM}(t)) = \left(\hat{S}_{KM}(t)\right)^2 \sum_{x \le t} \frac{d(x)}{n(x)[n(x) - d(x)]} \tag{9}$$

Another alternative estimator of the survival function and the corresponding commutative hazard function at time t due to Nelson and Aalen as stated in Collett (2003), which is based on the individual failure times is given by;

$$\tilde{\Lambda}_{NA}(t) = \sum_{x \le t} \frac{d(x)}{n(x)} \text{ and it implies } \tilde{S}_{NA}(t) = \exp(-\tilde{\Lambda}(t)) = \prod_{x \le t} \exp\left(-\frac{d(x)}{n(x)}\right) \tag{10}$$

It is merely in the case of small samples that the Nelson-Aalen estimate of the survivor function prevails over the KM estimate (Hosmer and Lemeshow, 1999).

Comparison of survivorship functions

After providing a description of the overall survival experience in the study, we turn our attention to a comparison of the survivorship experience in key subjects in the data. The simplest way of comparing the survival times obtained from two or more groups is to plot the Kaplan-Meier curves for these groups on the same graph. However, this graph does not allow us to say, with any confidence, whether or not there is a real difference between the groups. The observed difference may be a true difference, but equally, it could also be due merely to chance variation. Assessing whether or not there is a real difference between groups can only be done, with any degree of confidence, by utilizing statistical tests.

The standard statistical procedures may be used when there are no censored observations. But modifications of these procedures are required when censored observations are present in the data. In comparing groups of subjects, it is always a good idea to begin with a graphical display of the data in each group. The figure in general shows if the pattern of one survivorship function lies above another, meaning that the group defined by the upper curve lived longer, or had a more favorable survival experience, than the group defined by the lower curve. In other words, at any point in time the proportion of subjects estimated to be alive is greater for one group (represented by the upper curve) than the other (represented by the lower curve). Now the statistical question is whether the observed difference seen in the figure is significant. A number of statistical tests have been proposed to answer this question such as Log-rank, Gehan's generalization of Wilcoxon test, and Peto-Peto-Prentice's test and so on.

The calculation of each test is based on a contingency table of groups by status at each observed survival time. The general form of these test statistics for the comparison of survival functions between two groups can be defined as follows:

$$Q = \frac{\left\{ \sum_x w(x) \left[dN_1(x) - \frac{dN(x) * Y_1(x)}{Y(x)} \right] \right\}^2}{\sum_x w^2(x) \left[\frac{Y_1(x) Y_0(x) dN(x) [Y(x) - dN(x)]}{Y^2(x) [Y(x) - 1]} \right]} \tag{11}$$

where

$Y_0(x)$ is the number of individuals at risk at time x from group 0

$Y_1(x)$ is the number of individuals at risk at time x from group 1

$Y(x)$ is the total number of individuals at risk at time x from both groups

$dN_0(x)$ is the number of observed deaths from group 0 at time x

$dN_1(x)$ is the number of observed deaths from group 1 at time x

$dN(x)$ is the total number of deaths observed at time x

$w(x)$ is the weight for censor adjustment at failure time x

The test statistic Q has chi-square distribution with 1 degree of freedom under the null hypothesis that the two survivorship functions are the same 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. The statistic Q can be extended for comparing more than two groups of survival experience (Collett, 2003).

The weight function $w(x)$ can be used to emphasize differences in the hazard rates over time according to their relative values. The most commonly used test is the log-rank test where $w(x) = 1$ for all x. The log-rank test is a non-parametric test for comparing two or more survival curves. Since it is a non-parametric test, no assumptions about the distributional form of the data need to be made. This test is however most powerful when used for non-overlapping survival curves. This test can be generalized to accommodate other tests that are equally used sometime in practice such as Generalized Wilcoxon test, and Peto-Peto-Prentice test. Each of these tests uses different weights to adjust for censoring that is often encountered in survival data. For instance, the Wilcoxon test weights the j^{th} failure time by $Y(x)$ (the number still at risk), and the Peto-Peto-Prentice test weights the j^{th} failure time by the survival estimate $\widetilde{S}(x)$ calculated over all groups combined. Since both $Y(x)$ and $\widetilde{S}(x)$ are non-increasing functions of x, both tests emphasize the difference early in the survival curves (Kleinbaum and Klein, 2005).

3.4.2 Regression Models for Survival Data

In modeling survival data we will explore how the survival experience of a group of individuals depends on the values of one or more explanatory variables, whose values have been recorded for each individual at the time origin. The hazard function is modeled directly in survival analysis. There are two broad reasons to model survival data. One objective of the modeling process is to determine which combinations of potential explanatory variables affect the form of the hazard function. Another reason for modeling the hazard function is to obtain an estimate of the hazard function itself. This may be of interest in its own right, but in addition, from the relationship between the survivor function and hazard function an estimate of the survivor function can be found (Klein and Moeschberger, 1998).

A variety of models and methods have been developed for doing this sort of survival analysis using either parametric or semi-parametric approaches. Semi-parametric models are models that parametrically specify the functional relationship between the lifetime of an individual and his/her characteristics (demographic, socio-economic, etc.) but leave the actual distribution of lifetimes arbitrary. The most popular of the semi-parametric models is the proportional hazards model. It has the property that the ratio of the hazards depends on the values of their explanatory variables but does not depend on time t. A hazard model is a regression model in which the "risk" of experiencing an event (death in our case) at a certain time point is predicted with a set of covariates.

Cox-proportional Hazards Model

This model was proposed by Cox (1972) and has also come to be known as the Cox regression model. Cox introduced the model to cater for covariate effects for single event failures. This model is valid under the assumption of proportional hazards (PH). Cox observed that if proportional hazards assumption holds (or is assumed to be hold), then it is possible to estimate the effect of parameter(s) without any consideration of the hazard function. Although the model is based on the assumption of proportional hazards, no particular form of probability distribution is assumed for the survival times.

Suppose the set of values of the explanatory variables in the PH model will be represented by a vector X. Let $\lambda_o(t)$ be the hazard function for an individual for whom the values of all explanatory variables that make up the vector X are zero. The function λ_o(t) is called the baseline hazard function. The hazard function for the individual can then be written as

$$\lambda(t, X, \beta) = \lambda_0(t)\exp(\beta' X) \qquad (12)$$

where $\boldsymbol{\beta}$ is a p x 1 vector of unknown regression parameters that are assumed to be the same for all individuals in the study and measure the influence of the covariate on the survival experience with β_i representing increase in the log hazards as x_i increases one unit relative to the baseline hazard function. **X** is a $p \times 1$ vector of covariates such as treatment indicators, prognostic factors, and etc. The baseline hazard function $\lambda_o(t)$ can take any shape as a function of t. The only requirement is that $\lambda_o(t) > 0$. This is the nonparametric part of the model and $\boldsymbol{\beta}'\mathbf{X}$ is the parametric part of the model. So Cox's proportional hazards model is a semi parametric model.

A key reason for the popularity of the Cox model is that, even though the baseline hazard is not specified, reasonably good estimates of regression coefficients, hazard ratios of interest, and survival curves can be obtained for a wide variety of data situations. Another way of saying this is that the Cox PH model is a "robust" model, so that the results from using the Cox model will closely approximate the results for the correct parametric model (Kleinbaum and Klein, 2005).

An important feature of the Cox proportional hazards model, which concerns the proportional hazards assumption, is that the baseline hazard is a function of t, but does not involve the **X**'s. In contrast, the exponential expression, involves the **X**'s, but does not involve t. The **X**'s, here, are assumed to be time-independent. The other assumption of the proportional hazards refers to the fact that the effects of covariates are the same for all values of t. Putting it in other words, the Cox proportional hazards model assumes that changes in the hazard of any subject over time will always be proportional to changes in the hazard of any other subject and to changes in the underlying hazard over time (Kleinbaum and Klein, 2005).

From equation (11) one can notice a couple of features. First, if the vector of covariate is a zero vector, then the hazard function for the i^{th} individual is the baseline hazard function. It is the hazard function in the absence of covariates or when all of the coefficients of the covariates are assumed to be zero. Second, if we divide both sides by $\lambda_o(t)$, we get equation (12) below that indicates where the term proportional comes from. Since for each individual, $\exp(\beta' x_i)$ is constant across time, equation (14) below shows that at every value of t, the i^{th} individual's log hazard ratio is constant. This implies that each individual's hazard function is parallel to the $\lambda_o(t)$.

$$\frac{\lambda(t,x_i,\beta)}{\lambda_0(t,x_i=0,\beta)}=\frac{\lambda_0(t)\exp(\beta' x_i)}{\lambda_0(t)}=\exp(\beta' x_i) \tag{13}$$

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

$$\ln\left(\frac{\lambda(t,x_j,\beta}{\lambda(t,x_i,\beta)}\right)=\ln\left(\frac{\lambda_0(t)\exp(\beta' x_j)}{\lambda_0(t)\exp(\beta' x_i)}\right)=\beta'(x_j-x_i) \tag{14}$$

Clearly the above ratio is independent of time which means that the log hazard ratio is constant at any given time. Moreover, the hazard ratio does not depend on the value of the covariate; rather it depends on the difference between the covariate values. The Cox proportional hazards model can equally be regarded as linear model, as a linear combination of the covariates for the logarithm transformation of the hazard ratio given by:

$$\ln\left(\frac{\lambda(t,X,\beta)}{\lambda_0(t)}\right)=\beta' X \tag{15}$$

The cumulative hazard functions at time t for a subject with covariate x is given by:

$$\Lambda(t,X,\beta)=\Lambda_0(t)\exp(\beta' X) \tag{16}$$

Consequently, from the proportional hazard function, we obtain the survivor function given by:

$$S(t,X,\beta)=[S_0(t)]^{\exp(\beta' X)} \tag{17}$$

where $S_0(t)$ is the baseline survival function (Hosmer and Lemeshow, 1999).

Fitting the Proportional Hazards Model

Fitting the proportional hazards model to observed survival data entails estimating the unknown regression coefficients. Since the baseline hazard $\lambda_0(t)$ is left completely unspecified, ordinary likelihood methods can't be used to estimate β. Cox conceived of the idea of a partial likelihood to remove the nuisance parameter $\lambda_0(t)$ from the proposed equation.

Suppose we have a random sample of individuals of size n from a specific population whose true survival times are $Z_1, Z_2, ..., Z_n$. Denote by C the censoring process and by $C_1, C_2, ..., C_n$ the (potential) censoring times. The observed data are the minimum of the survival time and censoring time for each subject in the sample and the indication whether or not the subject is censored. Statistically, we have observed triplet data (t_i, δ_i, X_i) where $t_i = \min(Z_i, C_i)$, δ_i is the event indicator δ_i=1 if the event has occurred and δ_i=0 if it is censored, and X_i is the vector of covariates or the risk factors for the i^{th} individual. Under the assumption of independent observations, the full likelihood function is obtained by multiplying the respective contributions of the observed triplets, a value of $f(t, X, \beta)$ for uncensored observation and a value of $S(t, X, \beta)$ for censored observations. Thus, the contribution of each triplet to the likelihood is the expression

$$[f(t, X, \beta]^{\delta_i} \times [S(t, X, \beta]^{1-\delta_i} \tag{18}$$

Since the observations are assumed to be independent, the likelihood function is the product of the expression in (17) over the entire sample and is formulated as:

$$l(\beta) = \prod_{i=1}^{n} \left\{ [f(t_i, X_i, \beta]^{\delta_i} \times [S(t_i, X_i, \beta]^{1-\delta_i} \right\} \tag{19}$$

It can be further simplified as

$$l(\beta) = \prod_{i=1}^{n} \left\{ [\lambda(t_i, X_i, \beta]^{\delta_i} \times [S(t_i, X_i, \beta] \right\} \tag{20}$$

Cox showed that the relevant likelihood function which considers the baseline hazard rate as a nuisance parameter; he called it a partial likelihood function, for the proportional hazards model assuming no tied survival times is given by (Hosmer and Lemeshow, 1999)

$$l_p(\beta) = \prod_{i=1}^{n} \left(\frac{e^{x_{(i)}\beta}}{\sum_{j \in R(t_{(i)})} e^{x_j} \beta} \right)^{\delta_i} \tag{21}$$

where, $R(t_{(i)})$ represents the risk set just prior to time $t_{(i)}$. The corresponding log-partial likelihood function is given by

$$L_p(\beta)=\sum_{i=1}^{n}\delta_i\left\{X_{(i)}\beta-\ln\left[\sum_{j\in R(t_{(i)})}exp(X_j\beta)\right]\right\} \quad (22)$$

We obtain the maximum partial likelihood estimator (MPLE) by differentiating the right hand side of (22) with respect to β, setting the derivatives equal to zero and solving for the unknown parameters. This is using iterative numerical analysis techniques such as Newton-Raphson which make use of the efficient scores and the observed information matrix. Let $U(\beta)$ be the p×1 vectors of first derivatives of the log-likelihood function with respect to the β -parameters. This quantity is known as the vector of efficient scores. The negative of the second derivative of the log-partial likelihood is known as the observed information matrix (Hessian matrix) and denoted by

$$I(\beta)=-\frac{\partial^2 L_p(\beta)}{\partial\beta\partial\beta'} \quad (23)$$

According to the Newton-Raphson procedure an estimate of β at the $(k+1)^{th}$ cycle of the iterative procedure, $\hat{\beta}_{k+1}$, is $\hat{\beta}_{k+1}=\hat{\beta}_k+I^{-1}(\hat{\beta}_k)U(\hat{\beta}_k), k=1, 2, ...$ .The process can be started by taking $\hat{\beta}_0=(0,0,........,0)'$ and continue until the change in the likelihood function is sufficiently low. The estimator of the covariance matrix of the MPLE can be approximated by the inverse of the observed information matrix, evaluated at $\hat{\beta}$, that is

$$\hat{Var}(\hat{\beta})=I(\hat{\beta})^{-1} \quad (24)$$

The partial likelihood function methods described above are based on the assumption that there were no tied values among observed survival times. Hence to incorporate tied survival times in analyses there are two approaches. These are the Breslow[2] and the Efron approximations. The MPLE for β in the presence of ties is obtained in the same manner as in the non-tied data case, with exception that derivates are taken with respect to the

[2]Breslow (1974) approximation to the partial likelihood function in case of tied survival time is given as:

$$l_p(\beta)=\prod_{j=1}^{D}\frac{\exp\left(\beta\sum_{l\in D_j}x_l\right)}{\left[\sum_{l\in R_j}\exp(x_l\beta)\right]^{d_j}},$$

where d_j is the number of tied survival times at the j^{th} distinct survival time, D_j is the event (death) set at the j^{th} distinct survival time, and D is the total distinct events.

unknown parameters in the log of either the Breslow or Efron approximation to the partial likelihood. In many applied settings there will be little or no practical difference between the estimators obtained from the two approximations. Because of this, and since the Breslow approximation is more commonly available in many software packages, unless stated otherwise, analysis presented in this study will be based on it (Hosmer and Lemeshow, 1999).

After estimation of the regression coefficients, we go for assessing the significance of the coefficients and the construction of the confidence interval as well. The three different tests used to assess the significance of the coefficients are explained below.

a) The partial likelihood ratio test

It is used for testing the significance of a subset of q explanatory variables from p explanatory variables, and fit both the unrestricted and the restricted models. Then we obtain the value of the log-partial likelihood function $L_p(\hat{\beta}_{p-q})$ in the unrestricted model and $L_p(\hat{\beta}_p)$ when the model imposes the restrictions under H_0. The partial likelihood ratio test statistic is given by:

$$Q_{LR} = 2\left(L_p(\hat{\beta}_p) - L_p(\hat{\beta}_{p-q})\right) \tag{25}$$

Under the null hypothesis H_0 for large sample size the statistic Q_{LR} is asymptotically distributed as chi-squared with q degrees of freedom.

b) The Wald test

To test $H_0 = (0,0,...,0)'$, we use the multivariable Wald statistic

$$Q_w = \hat{\beta}'_q \left[I_q(\hat{\beta})\right]^{-1} \hat{\beta}_q' \tag{26}$$

where $\hat{\beta}_q$ and $I_q(\hat{\beta})$ are the corresponding estimates of β_q and sub matrix of the inverse of the observed information matrix from the full model. Under H_0 and for large sample size the statistic $Q_W \sim \chi^2_{(q)}$ at α level of significance. The Wald test can also be used to test the significance of individual variables. The Wald test statistic is

$$Z = \frac{\hat{\beta}_j}{se(\hat{\beta}_j)} \tag{27}$$

Under the null hypothesis $H_0 : \beta_j = 0$ the statistic $Z \sim N(0,1)$. Consequently, the $100(1-\alpha)\%$ Wald statistic-based confidence interval for β_j is $\hat{\beta}_j \mp Z_{\alpha/2} se(\hat{\beta}_j)$ where, $Z_{\alpha/2}$ is the upper $\alpha/2$ percentile of the standard normal distribution.

c) The Score test

The score test statistic, to test $H_0 : \beta_q = (0,0,...,0)'$ is defined as:

$$Q_S = U'(\beta_q, \hat{\beta}_{p-q}) I^{-1}(\beta_q, \hat{\beta}_{p-q}) U(\beta_q, \beta_{p-q}) \tag{28}$$

where $U(\beta_q, \hat{\beta}_{p-q})$ and $I^{-1}(\beta_q, \hat{\beta}_{p-q})$ are the score vectors and inverse of the observed information matrix evaluated at the hypothesized value of β_q and the restricted partial maximum likelihood estimator of β_{p-q}. Under the null hypothesis and for large sample, $Q_S \sim \chi^2(q)$.

When there is a disagreement among the three tests of the significance of the coefficient, the partial likelihood ratio test will prevail.

Interpretation of the coefficients

Interpretation involves two issues, determining the functional relationship between the outcome variable and the covariate and appropriately defining the unit of change for the predictor variable. For instance, when a covariate is dichotomous, say gender, with a value of $x_1 = 1$ for male $x_0 = 0$ for females, the hazard ratio becomes e^{β}. If the value of the coefficient is $\beta = \ln(2)$ or ($e^{\beta} = 2$), then it is simply saying that males are *dying* at twice the rate of females. If $\beta = 0$ (or $e^{\beta} = 1$), then **x** has no effect on the hazard. $e^{\beta} > 1$ implies that the group with **x** =1 has a higher hazard, or shorter event time, than the group with **x** = 0. By the same token, $e^{\beta} < 1$ implies that the hazard is higher among the group with **x**=0. For covariates having L levels ($L > 2$), similarly interpretations can made by taking one of the L-levels as a reference category (Hosmer and Lemeshow, 1999).

3.4.3. Variable Selection Procedures

The variable selection procedures in proportional hazards regression analysis requires critical decisions in selecting subsets of covariates. The methods available to select a subset of the covariates to include in a proportional hazards regression model are essentially the same as those used in the other regression models, like purposeful selection, stepwise (forward selection and backward elimination) and best subsets selection. When the number of variables is relatively large, it can be computationally expensive to fit all possible models. In this situation, automatic routines for variable selection that are available in many software packages might seem an attractive prospect. But they lead to the identification of one particular subset, rather than a set of equally good ones. The subsets found by these routines often depend on the variable selection process that has been used, that is, whether it is forward selection, backward elimination or the stepwise procedure, and generally tend not to take any account of the hierarchic principle. They also depend on the stopping rule that is used to determine whether a term should be included in or excluded from a model.

Thus, instead of using automatic variable selection procedures, the following general strategy for model selection is recommended by Collet (2003).

1. The first step is to fit models that contain each of the variables one at a time. The values of $-2\hat{L}_p$ for these models are then compared with that for the null model to determine which variable on their own significantly reduce the value of this statistic. A significance level from 20% to 25% is recommended in Hosmer and Lemeshow (1999).
2. The variables which appear to be important from Step 1 are then fitted together. In the presence of certain variables others may cease to be important. As a result, backward elimination is used to omit non-significant variables (i.e., those variables that do not significantly increase the value of $-2\hat{L}_p$ from the model). Only those that lead to a significant increase in the value of $-2\hat{L}_p$ are retained in the model.

3. Variables that were not important on their own, and so were not under consideration in step 2, may become important in the presence of others. These variables are therefore added the model from step 2 with forward selection method (i.e., any that reduce $-2\hat{L}_p$ significantly are retained in the model).
4. A final check is made to ensure that no term in the model can be omitted without significantly increasing the value of $-2\hat{L}_p$, and that no term not included significantly reduces the value of $-2\hat{L}_p$[3].

3.4.4 Assessment of Model Adequacy

After a model has been fitted, the adequacy of the fitted model needs to be assessed. Model-based inferences depend completely on the fitted statistical model. For these inferences to be *valid* in any sense of the word, the fitted model must provide an adequate summary of the data upon which it is based.

Many model checking procedures are based on residuals. A residual is the difference between the observed value of the outcome variable and that value predicted by the model. The two key assumptions in the definition of a residual are the value of the outcome is known and the fitted model provides an estimate of the mean of the dependent variable or systematic component of the model. However, the two assumptions are not valid when using partial likelihood to fit the proportional hazards model to censored survival data. The absence of an obvious residual has lead to the development of several different residuals, each of which plays an important role in examining some aspect of the fit of the proportional hazard model. These include the Cox-Snell, martingale and Schoenfeld residuals.

[3] $\hat{L}_p$ denote the maximized partial log likelihood under assumed model and computed by replacing the β 's by Maximum partial likelihood estimate (MPLE) under the model.

Cox-Snell residuals: The Cox-Snell residual for the i^{th} individual with observed survival time t_i is given by

$$rc_i = \hat{\Lambda}_i(t_i) = -\hat{S}_i(t_i), \tag{29}$$

where $\hat{\Lambda}_i(t_i)$ and $\hat{S}_i(t_i)$ are the estimated values of the cumulative hazard and survivor functions of the i^{th} subject at time t_i respectively. In general, Cox-Snell residuals are useful in assessing an overall model fit (Cox and Snell, 1968)

Martingale residuals (rM_i) are also called modified Cox-Snell residuals and, expressed as:

$$rM_i = \delta_i - \hat{\Lambda}_i(t) = \delta_i - rc_i \tag{30}$$

where $\delta_i = 1$ for uncensored observations and zero otherwise, and rc_i are Cox-Snell residuals. The martingale residuals take values between negative infinity and unity. They have a skewed distribution with mean zero. In large samples, the martingale residuals are uncorrelated with one another and have an expected value of zero. However, the martingale residuals are not symmetrically distributed about zero (Barlow and Prentice, 1988)

Schoenfeld residuals: All the above residuals are residuals for each individual. We will describe covariate-wise residuals: Schoenfeld residuals. These residuals are calculated for each individual and for each covariate (Schoenfeld, 1982). Thus, the Schoenfeld residual for the i^{th} individual on the k^{th} covariate is given by:

$$rs_{ik} = \delta_i(x_{ik} - \bar{\hat{x}}_{w_i k}) \tag{31}$$

where $\bar{\hat{x}}_{w_i k} = \dfrac{\sum_{j \in R(t_{(i)})} x_{jk} \exp(x'_j \hat{\beta})}{\sum_{j \in R(t_{(i)})} \exp(x'_j \hat{\beta})}$, is a weighted mean of covariate value for those in the risk set at the given event time.

The sum of these residuals is zero and they have a large sample property that, their expected value is zero and they are uncorrelated with one another. The vector of these residuals for the i^{th} observation can be written as $rs_i = (rs_{i1}, rs_{i2}, ..., rs_{ip})'$ and the convention is that rs_{ik} is set to be missing for censored observations. Scaling a vector of Schoenfeld residuals by an estimator of its variance is more effective in detecting departures from the assumed model. The vector of the scaled Schoenfeld residuals is then given by:

$$rs_i^* = \left[\text{var}(rs_i)\right]^{-1} rs_i \approx m\,\text{var}(\hat{\beta}) rs_i \qquad (32)$$

where, m is the number of events (deaths) (Grambsch and Therneau,1994).

Each of these residuals provides a useful tool for examining one or more aspects of model adequacy.

1. **Testing for the form (linearity) of covariates**

After identification of a particular set of explanatory variables on which the hazard function depends, it is important to check that the correct functional form has been adopted for the continuous covariates. Linearity assumption can be checked by using the plot of martingale residuals. The plot of martingale residuals obtained from fitting the model, excluding the covariate whose functional form needs to be determined, against the excluded covariate display the functional form required for the covariate. In such a way that, LOESS smoothed curve can be superimposed on the scatter plots to give interpretation. If the resulting plot is showing no systematic pattern and the smoothed plot is a horizontal straight line through zero. This indicates that the covariate is linear in the model.

2. **Subject-wise diagnostic measures**

In the assessment of model adequacy, it is important to determine whether there are any subjects have an unusual configuration of covariates, exert an undue influence on the estimates of the parameters or have an undue influence on the fit of the model. Such observations may be termed as influential observations and the data from such individuals will need to be the subject of further analysis. Conclusions from survival analyses are often framed in terms of estimates of the relative hazard, which depends on the estimated values of the coefficients in the Cox regression model. For that reason, it has particular importance to examine the influence of each observation on these estimates (Hosmer and Lemeshow, 1999).

It may happen that the structure of the fitted model is particularly sensitive to one or more observations in the data set. Such observations can be analyzed through diagnostics that are designed to highlight observations that influence the complete set of parameter estimates in the linear predictor. This could be done by fitting the model to all n observations in the data set, and then fitting the same model to the sets of n-1 observations obtained by omitting each of the n observations in turn.

Suppose that $\hat{\beta}_k$ denotes the partial likelihood estimator of the coefficient computed using the entire sample of size n and $\hat{\beta}_{k(-i)}$ denotes the value of the estimator if the i^{th} subject is removed. Thus, the DFBETA statistic, which can be used as a measure of how the j^{th} parameter estimate would change if the i^{th} observation was deleted from the data set, is defined as:

$$\Delta\hat{\beta}_{ki} \approx \hat{\beta}_k - \hat{\beta}_{k(-i)} \tag{33}$$

Observations that influence a particular parameter estimate have a large absolute value of DFBETA than for other observations in the data set. However, this procedure involves a significant amount of computation if the sample size is large. We would like to use an alternative approximate value that does not involve an iterative refitting of the model. To check the influence of observations on a parameter estimate, an approximate estimator of (33) is the k^{th} element of the vector of coefficient changes

$$\Delta\hat{\beta}_i = (\hat{\beta} - \beta_{(-i)}) = \hat{Var}(\hat{\beta})\hat{L}_i \tag{34}$$

where $\hat{L}_i$ is the vector of score residuals which are modifications of Schoenfeld residuals and are defined for all the observations, and $\hat{Var}(\hat{\beta})$ is the estimator of the covariance matrix of the estimated coefficients. These are commonly referred to as the scaled Schoenfeld residuals.

3. **Methods for Assessing the Proportional Hazards Assumption**

The main assumption of the Cox hazards model is the proportionality of hazard. The assumption is vital to the interpretation and use of a fitted proportional hazards model. If hazards are not proportional, this means that the linear component of the fitted model varies with time in some manner. As a result, we need to plot the logarithm of the Kaplan-Meier cumulative hazards function based on different factors so that it helps in assessing the proportional hazards assumption before fitting a Cox model. If this assumption is met, then the plots will be more or less parallel. However, looking at the plot is not enough to be certain of proportionality since they are univariate analysis and do not shows whether hazards will still be proportional when a model includes many other predictors. But they support our argument for proportionality (Hosmer and Lemeshow, 1999).

The other method, which could be used after the fit of the model, is extending the proportional hazards model by defining several product terms involving each time independent variable with some function of time. That is, if the j^{th} time-independent variable is denoted as x_j, then we can define the j^{th} product term as $x_j \times g_j(t)$ where $g_j(t)$ is some function of time for the j^{th} variable. Usually the function $g_j(t)$ is chosen to be the natural logarithm of survival time i.e. $g_j(t) = \ln(t)$. Likewise, Grambsch and Therneau (1994) also considered a specific form of time-varying coefficient as:

$$\beta_j(t) = \beta_j + \theta_j x_j g_j(t) \tag{35}$$

where θ_j is a coefficient of the product term.

Thus, the extended Cox model that simultaneously considers all time-independent variables of interest can be formulated as:

$$\lambda(t, x, \beta) = \lambda_0(t)\exp\left(\sum_{j=1}^{p}\beta_j x_j + \sum_{j=1}^{p}\theta_j x_j g_j(t)\right) \tag{36}$$

To check the proportional hazards assumption, we consider the null hypothesis that all the θ_j terms are equal to zero so that the model reduces to the proportional hazards model. The hypothesis all θ_j's are zero ($H_0 : \theta_j = 0$) is tested via the partial likelihood ratio test, score test or Wald test. If the time-dependent covariate is insignificant then the assumption of proportionality is satisfied for that particular covariate. Moreover, the other statistical test of the proportional hazards assumption is based on the scaled Schoenfeld residual. If the PH assumption holds for a particular covariate then the scaled Schoenfeld residual for that covariate will not be related to survival time. So this test is accomplished by finding the correlation between the scaled Schoenfeld residuals for a particular covariate and the ranking of individual survival times. The null hypothesis is that the correlation between the scaled Schoenfeld residuals and the ranked survival time is zero. Rejection of null hypothesis concludes that PH assumption is violated.

4. Overall Goodness of Fit

Residual plots can be used in the graphical assessment of the adequacy of a fitted model. For instance, if the fitted model is adequate, the Cox-Snell residuals will behave as n observations from a unit exponential distribution. Thus, the plot of the estimated hazard rate of the Cox-Snell residuals $\hat{\Lambda}_i(t)$, versus r_{ci} will give a straight line with unit slope and zero intercept if the fitted model is correct. However, the drawback is that they do not indicate the particular departure from the model fitted, if there is any.

3.4.5 Extensions of the proportional Hazards model

The Cox regression model relies on the hazards being proportional, i.e. on the effect of a given covariate not changing over time. We have used a model with a common unspecified baseline hazard function where all the study covariates had values that remained fixed over the follow-up period. If these assumptions are violated, the proportional hazard model is invalid and more complicated analysis is required. One way of overcoming the problem is using the extended Cox regression model. In this model, the Cox regression model is extending to a model which contains time-dependent covariates and the product of these covariates with a function of time. However, this model building results in a loss of parsimony with results that may be difficult to interpret and difficult to explain to your collaborators. Another alternative is to use a stratified proportional hazards model. When we are considering many covariates in a model, we may find that most of the covariates follow a proportional hazards relationship and only a few of the covariates do not. If this is the case, we may stratify our study population into categories obtained by different combinations of the covariates and then use a stratified proportional hazards model.

The Stratified Proportional Hazards Model

The stratified Cox PH model is a modification of the Cox PH model by the stratification of a covariate that does not satisfy the proportional hazards assumption. Covariates that are assumed to satisfy the proportional hazards assumption are included in the model, whereas the predictor being stratified is not included. The strata divide the subjects into disjoint groups, each of which has a distinct (arbitrary) baseline hazard function but common values for the coefficients β (Therneau and Grambsch, 2000). If we denote the number of strata by K and let l index the strata, where $l = 1,..., K$ then the stratified proportional hazards model is given by

$$\lambda_l(t, Z, \beta) = \lambda_{0l}(t)\exp(\beta' Z), \tag{37}$$

where $Z = (Z_1,..., Z_p)'$ is a p dimensional vector of covariates that satisfy proportional hazards. In the above model, there are K unspecified baseline hazard functions for each stratum; *i.e.*, $\lambda_{0l}(t), l = 1,..., K; t \geq 0$, and within each stratum, the covariates Z satisfy proportional hazards assumption and the "effect" of the covariates Z is the same across K strata.

The interpretation of $\beta = (\beta_1,..., \beta_p)'$ is exactly the same as in an unstratified proportional hazards model. Namely, if we consider the hazard ratio resulting from an increase of one unit in the covariate Z_j, keeping all other covariates fixed (including those used to construct the strata), we get:

$$\frac{\lambda_l(t|Z_j = z_j + 1)}{\lambda_l(t|Z_j = z_j)} = \exp(\beta_j), \tag{38}$$

which is independent of time t.

To obtain estimates for β we only need a slight modification to the partial likelihood. For stratum l, denote the data within that stratum by $(X_{li}, \Delta_{li}, Z_{li}), i = 1,...,n_l, l = 1,...,K$. The total sample size $n = \sum_{l=1}^{K} n_l$.

The modified partial likelihood of β is given by

$$PL(\beta) = \prod_{l=1}^{K} PL_l(\beta) \tag{39}$$

where $PL(\beta)$ is the partial likelihood of β contributed by the data from the l^{th} stratum:

$$PL_l(\beta) = \prod_u \left[\frac{\exp(\beta^T Z_{l[i(u)]}}{\sum_{i=1}^{n_l} \exp(\beta^T Z_{li}) Y_{li}(u)} \right]^{dN_l(u)} \tag{40}$$

where $dN_l(u)$ is the number of deaths observed in time interval $[u, u + \Delta u)$ in the l^{th} stratum, $Y_{li}(u) = I(X_{li} \geq u)$ is the indicator indicating whether or not subject i in stratum l is at risk at time u. The maximum stratified partial likelihood estimator of the parameter vector, β, in equation (39) is obtained by solving the p equations obtained by differentiating the $\log(PL(\beta))$ with respect to the p unknown parameters and setting the derivatives equal to zero. Finally, all inferential methods derived previously for the unstratified PH model can be used with this stratified PH model (see details in Therneau and Grambsch, 2000).

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1. Introduction

The response variable, survival time measured in days from date of birth of neonate to the date of death/censor is continuous. The censoring indicator (status) is 0 for censored observations and 1 for event, in our case death. In this study the proportional hazards model was used to study the relationship between the explanatory variables introduced earlier and the response variable. We begin our data analysis by giving descriptive statistics. We then proceed to the univariate analysis, model diagnostic checking and then provide the final model in multivariate analysis.

4.2. Baseline summary statistics of covariates

A total of 8,651 neonates, who were born during the five years preceding the date of the survey, were included in the study. Summary results for socio-economic, demographic and maternal related health factors included in this study are presented in Table 1A (Appendix). Of the total of 8,651 neonates included in the study, 48.5% were females, 3.6% were multiple births, 83.2% were born in rural parts of Ethiopia, 14.2% were born in health facilities and only 53.3% were put to breast immediately upon birth. About 15.5% of neonates were first births, 20.2% had preceding birth intervals less than 24 months, and 23.2% had very small size and 16.9 % had very large size at birth. Among the neonate's mothers, 88% were currently married, 0.6% was never in union and 11.4% were classified as widowed/separated/divorced. The table shows that 10.7% of neonate mothers were below 20 years old of age, 73.6% neonate mothers were between 20-34 years, and the remaining 15.7% were older than 34 years when they gave birth. Only 33.5% neonate mothers sought antenatal visits, 25.4% of the visits were by skilled birth attendants, and 8% faced pregnancy complication during delivery. With regard to educational attainment, about 70 % of the mothers had no education while 25% of the mothers had primary education and the remaining 5% had attended secondary and higher education. About 49.6% of the households were classified as poor while 16.4% had medium income and 34% were rich. Furthermore, the highest percentages of neonatal births were observed in Oromiya (15.5%) whereas the lowest births observed in Addis Ababa (3.4%).

4.3. Descriptive survival analyses

In order to get a closer look at estimate of the survival time we use the Kaplan-Meier and Nelson-Aalen estimation techniques. These estimators incorporate information from all of the observations available, both uncensored and censored, by considering survival to any point in time as a series of steps defined by the observed survival and censored times. The graph of neonatal hazard function is given in Figure 4.1 below showing that an increase in the hazard rate has direct relation with the increase of time.

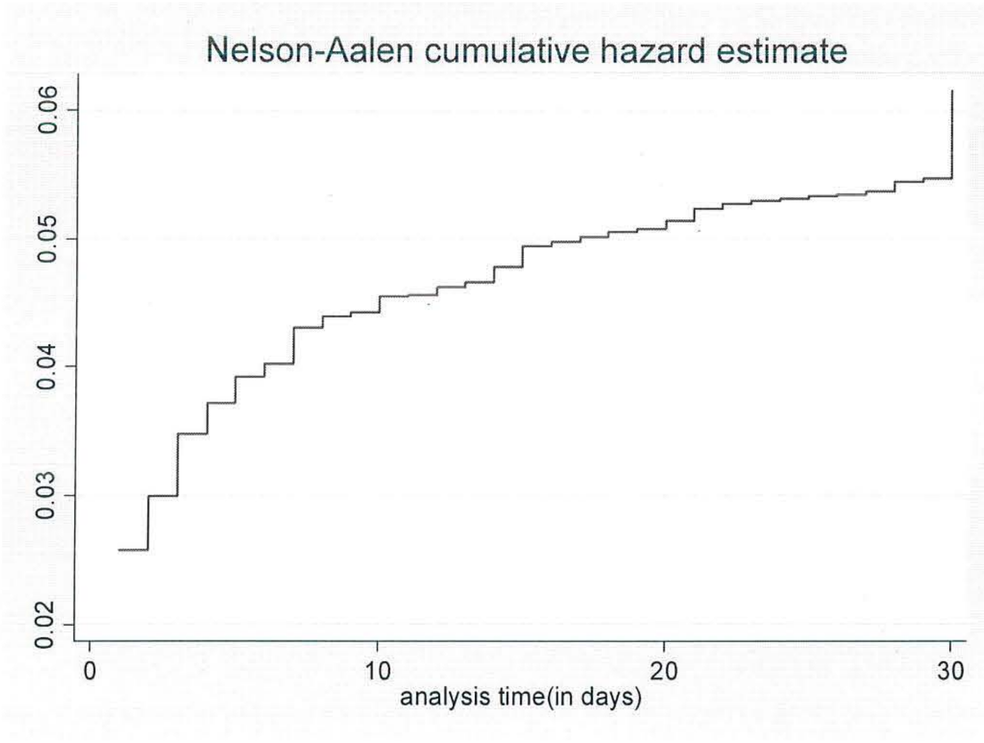

Figure 4.1: The Nelson-Aalen estimated cumulative hazard function of neonatal mortality

The graph of the estimate of overall Kaplan-Meier survivor function Table 2A (Appendix) and Figure 1A (Appendix) show that most deaths occurred in the earlier days of life and it declined in the later days of follow up time. From Table 2A, about 71% and 79% of the neonatal `deaths occurred within the first and second weeks of follow-up period, respectively. Separate graphs of the estimates of the Kaplan-Meier survivor functions have been constructed for different covariates so that it would be possible to assess whether there were differences in survival experience between the indicated categories of individuals. In general, the pattern of one survivorship function lying above another means that the group defined by the upper curve had better survival than the group defined by the lower curve. The graphs of Kaplan-Meier survival estimates based on different categories of covariates are displayed in Figure 2A of the Appendix. Some of the graphs did not show clear differences between the intended categories. However, relatively speaking graphs of multiplicity of birth, pregnancy complication, mothers age at child birth, birth order and preceding birth interval showed larger gaps and convey similar information as Table 4.1. Thus, the graph of single and multiple births show that the upper curve of the survival functions is for neonates, who were single births, indicating greater survival experience compared to neonates who were multiple births. Moreover, the graphs of the survival functions for neonates who had preceding birth intervals less than 24 months and longer than 47 months had lower survival probability than those neonates between 24-47 months.

We would like to point out that comparing the differences among survival curves utilizing graphical method is more or less subjective and we need formal statistical tests to assess the observed difference is the real difference between groups. Hence, we employed log-rank statistical test to check for significance differences among different categories of factors that had been demonstrated by using the Kaplan-Meier estimates of the survivor functions. The results of the log-rank test for categorical variables are given in Table 4.1. The table shows that there was no significant difference in survival experience between the various categories of place of residence, marital status, wealth index, mother education, delivery place and delivery assistance during child birth. However, the p-values of the log-rank test showed that the survival experience of neonates in the various categories of single versus multiple births, birth order, sex of neonate, preceding birth interval, antenatal visits, birth size, pregnancy complication, mothers age at birth, region and when child put to breast upon birth differ significantly (i.e. all of these covariates have P-value less than 0.05).

Table 4.1: Results of the Log-rank test for the categorical variables

Covariate / factor	DF	Chi-square	P-Value
Residence	1	2.82	0.093
Marital status	2	2.20	0.333
Wealth index	2	2.72	0.257
Mother education	2	0.99	0.609
Birth order	2	17.97	0.000
Multiplicity of birth	1	92.13	0.000
Sex of neonate	1	6.35	0.012
Birth interval	2	20.37	0.000
Sought antenatal visits	1	6.77	0.009
Delivery place	1	1.95	0.163
Birth size	4	41.11	0.000
Pregnancy complication	1	4.52	0.034
Mother age at birth	2	32.02	0.000
Delivery assistance	1	0.95	0.330
Child put to breast immediately	1	8.99	0.003
Region	10	20.86	0.022

4.4. Results of the Cox proportional hazards model

The Cox proportional hazard model is the most widely used procedure for modelling the relationship of covariates to a survival time by incorporating censored outcome in the analysis. It can be employed for estimating the regression coefficients, conducting statistical tests, constructing confidence intervals and making interpretation based on the hazard function. Checking the adequacy of model and its development precede interpretation of results obtained from the fitted model.

In model development procedures, to fit all possible models is computationally expensive when the number of covariates considered in study is relatively large. For this reason, the variable selection procedures given by Collet (2003) are used to select the important predictor variables utilizing SAS 9.2 and STATA 11 software (details of the procedures are given in Section 3.4.3). The first step is to select covariates which are important in a study at some relaxed level of significance. Results from univariable proportional hazards Cox regression model are presented in Table 3A (Appendix). From the table, variables which are significant in relation to the time to death of neonates at the 20-25 percent level of significance were included in multivariable analysis. The univariable analysis showed that not all of the 16 explanatory variables are statistically important to be included in the multivariable analysis stage. Among these, the candidate predictors for further analysis are residence, multiplicity, mother's age, birth order, sex, birth interval, antenatal visits, pregnancy complication, birth size, region and breast feeding.

Thus, the most appropriate subset of these covariates to be included in the multivariable model will be selected based on their contribution to the maximized log- partial likelihood of the model $(-2L)$. The value of $-2L(\hat{\beta})$ for the null or empty model is 9343.923. Therefore, inclusion of covariates will be based on the amount of reduction of this value. Based on Table 3A, the highest reduction in $-2L(\hat{\beta})$ is observed for multiplicity of births. It reduces the value from 9343.923 to 9285.756. This difference is 58.167 and it is statistically significant (P-value <0.0001) when compared with percentage points of the χ^2 distribution on 1 degree of freedom. The next highest change is obtained for birth size where the difference equal to 41.317 and statistically significant. All potential variables that are supposed to have statistically significant impact (at P-value < 0.25) at univariable analysis will be included in the initial multivariable proportional hazards model which led to a value of $-2L(\hat{\beta})$ to 9129.710 (Table 4A Appendix).

Thus, removal of variables from the model will be based on the increasing $-2L(\hat{\beta})$ and P-value. Results from Table 4A indicate that the least important covariate in the model was place of residence since the removal of this covariate led to insignificant increment (P-value is 0.773) in the value of $-2L(\hat{\beta})$. Continuing the fitting processes by eliminating the variable residence, the model consisted of the remaining ten variables was fitted and the effect of eliminating variables from the model was assessed. Table 5A (Appendix) shows the increase in $-2L(\hat{\beta})$ and P-values after eliminating the variable residence from the model. All of the covariates included in this table were significant at 5% level of significance. Hence, we obtained a multivariable model that included ten covariates, namely birth order, multiplicity of birth, sex, antenatal visits, breast feeding, pregnancy complication, birth interval, birth size, region and mother's age at birth.

The next important step is to consider variables that are non-significant at univariable and multivariable analyses for possibility of confounders. This can be checked by considering the change in coefficients of variables remaining in the multivariable model when those insignificant variables are added one at the time. A value of 20% change is generally considered as an important change in a coefficient (Hosmer and Lemeshow, 1999). Thus, the variables marital status, residence, wealth index, mother's education, delivery place and delivery assistance were included one at a time; the change in the coefficients of the significant variables is depicted in Table 6A (Appendix). Results from the Table 6A show that the percentage changes in the coefficients of the variables were by far less than 20% revealing that none of them was a significant confounder. Hence, variables that were neither significant at univariable analysis nor at multivariable analysis were not confounders of the main factors in the, preliminary, model of Table 5A.

Although the model developing process identified a particular set of covariates to be included in a multivariable model, it is important to check that the correct functional form has been adopted for continuous covariates. Thus, the plots of the martingale residuals are used to demonstrate the linearity of continuous covariates (in this case age is the only continuous covariate) after excluding the covariate for which we are checking the assumption of linearity. The resulting plot, for ungrouped mother age, together with LOESS smoothed curve superimposed to ease interpretation as given in Figure 4.2 below. It can be seen that the plots of martingale residuals are random showing no systematic pattern, and the LOESS smoothed curve appears approximately a horizontal line through zero. As a result the continuous covariate ungrouped mother age is linear in the model. Since the remaining covariates are not continuous there is no need for checking linearity.

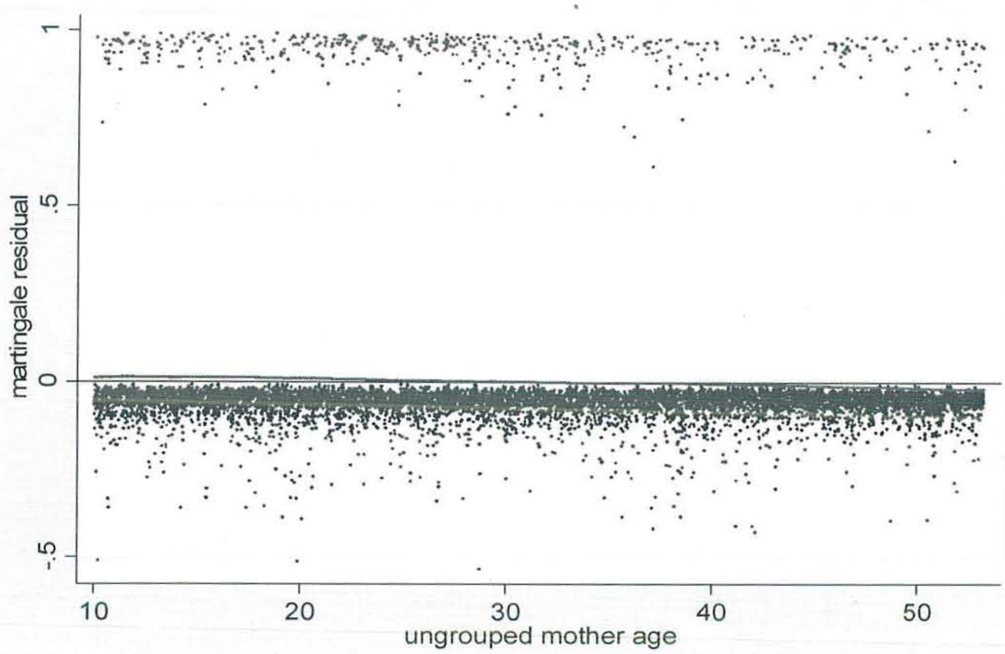

Figure 4.2: Plot of the martingale residuals against ungrouped mother age, with LOESS smoothed curve superimposed.

The last step in model development strategy is consideration of interaction terms that may be useful in the improvement of the model fit. Thus, all possible interactions among covariates that are significant at multivariable level of analysis are formed and the significance of adding each of the interaction terms in the main effects model, one at a time, is checked using the Wald test. The results from Wald test P-values in Table 7A indicate that none of the interaction terms were significant at 5% level. Hence, the last model will be the one which contains only the main effects in Table 8A.The parameter estimates and hazard ratios of the covariates are given in Table 8A(Appendix). However, the interpretation based on this model should not be made until the basic assumptions associated with the proportional hazards Cox regression model have been checked.

4.5. Model adequacy checking

After a model has been fitted, it is desirable to determine whether a fitted Cox regression model adequately describes the data or not. In this section we will deal with three kinds of diagnostics for the final Cox proportional hazards model: for violation of assumption of proportional hazards, checking for the presence of influential observations and measuring the overall goodness of fit of the model.

4.5.1. Checking the proportional hazards assumption

The proportional hazards assumption is vital to the interpretation and use of a fitted proportional hazards model. The basic assumption of proportional hazards model is that the hazard ratios are constant overtime. That means the risk of failure is the same no matter how long subjects have been followed. There are two methods of checking the proportional hazard assumption (Therneau and Grambsch, 2000). The first method draws plot of scaled Schoenfeld residuals versus time variable. If a horizontal line passes through the plots then it can be concluded that proportional hazard assumption is satisfied. Figure 3A (Appendix) shows the plots of the scaled Schoenfeld residuals for a covariate against time for the final model. The residuals look random showing no trend with time. Since the decision based on plots of scaled Schoenfeld residuals as graphical display requires subjective judgment, we perform a formal test of the proportional hazards assumption based on the scaled Schoenfeld residual. This test is accomplished by finding the correlation between the scaled Schoenfeld residuals for a particular covariate and the ranking of individual survival times. Results from Table 9A (Appendix) indicate that the correlation between scaled Schoenfeld residuals and log-time for some categories of region is statistically significant at 5% level. This implies that the proportionality assumption is not supported for the covariate region. But, before using this result it is better to consider another approach of checking proportionality. And this approach involves time-dependent covariates. The method adds a time-dependent variable to the last model. In this case, product of a variable of interest and logarithm of time variable was added for each covariate. If such a variable is statistically significant then it can be concluded that the assumption of proportional hazards is not satisfied for the given covariate. Thus, all interactions of covariates with the logarithm of survival times are modeled together with the main effects; and likelihood ratio statistic was used to test the significance of the interaction terms at 5% level of significance. Table 4.2 below presents likelihood ratio statistic value and corresponding P-values for each covariate. All of the covariates that interacted with log-time were insignificant except for region at 5%

level. Therefore, there is no sufficient evidence to reject the null hypothesis that the coefficients of the time varying variables (interaction terms) are zero for other covariates except region.

Table 4.2: Results of the multivariable proportional hazards Cox regression model containing the variables in Table 8A and their interaction with log-time (in days).

Covariates interacted with log time	df	LR χ^2	Sig.
Birth order	2	4.722	0.094
Multiple births	1	0.230	0.635
Sex	1	0.271	0.606
Antenatal visits	1	2.876	0.090
Breast feeding	1	0.240	0.626
Pregnancy complication	1	3.460	0.063
Birth interval	2	4.170	0.124
Birth size	4	7.301	0.121
Mother's age	2	2.120	0.347
Region	10	18.960	0.040

The P-value=0.040 of likelihood ratio test is less than 0.05 for region covariate which suggests assumption of proportional hazard is not satisfied for region covariate. This result confirms the result we obtained using scaled Schoenfeld residuals. But, we will deal with non-proportionality problem later in Section 4.6.

4.5.2 Assessing for influential observations

In evaluating the adequacy of the fitted model, we must determine if any one subject has a disproportionate influence on the estimated parameters. This is known as influence or leverage analysis. The preferred method of performing influence or leverage analysis is to compute DFBETA statistic which is used to examine if there is undue influence of an observation on the parameter estimate in the fitted Cox regression model (Collet,2003).

The first five largest changes in parameter estimates are shown in Table 10A of the Appendix. The largest difference for multiplicity of birth occurred for neonate 1,434 and 747. The result revealed that the changes in the parameter estimate (DFBETA) if the data for these neonates were omitted is 0.01751. Clearly, the omission of these neonates increases the hazard rate in relation to the baseline hazard rate. However, the question to be raised is whether the increment in the hazard rate is striking or not. This can be judged by considering standard error of the parameter estimate of the multiplicity of birth (0.144) taking the full data set into account. That is the percentage change in parameter estimate if the observation was removed is about 12.16% of the standard error (i.e., less than one standard error). Thus, removing this observation could not bring a significant change on multiplicity of birth.

Similarly, omitting the data for neonate 162 and neonate 7,395 from the dataset brought the largest change in parameter estimates of birth order and sex, respectively. But, the largest changes in the parameter estimates for birth order and sex when the said observation had been omitted in turn were 0.02818 (16.29% of the standard error) and 0.005343 (6% of the standard error), respectively. Since the percentage changes in parameter estimates are within one standard error, this is an indication that there is no high leverage value for both birth order and sex of neonate. Moreover, the maximum change in the parameter estimates, if the observation corresponding to the largest difference were removed for birth interval, antenatal visits, birth size, pregnancy complication, mother's age, breast feeding and region were 12.36%, 10.12%, 13.26%, 15.98%, 14.80%, 6.56% and 20.95% of their respective standard error, respectively. The largest difference is less than a quarter of the standard error of the corresponding estimate. Thus, removing the observations of the highest difference in parameter estimates had no significant impact on the parameters of the covariates and on the fit of the model. Hence, it can be concluded that there was no aberrant observation in the data set that illegitimately inflated the estimates of the parameters of the covariates in the final model.

4.5.3 Assessment for overall goodness of fit

The last step in the process of assessment of model adequacy is an overall assessment of the model. For this purpose, we use the Cox-Snell residuals to assess the overall goodness of fit of the model. The plot of the cumulative hazard function of the Cox-Snell residuals against the Cox-Snell residuals is presented in Figure 4.3 below.

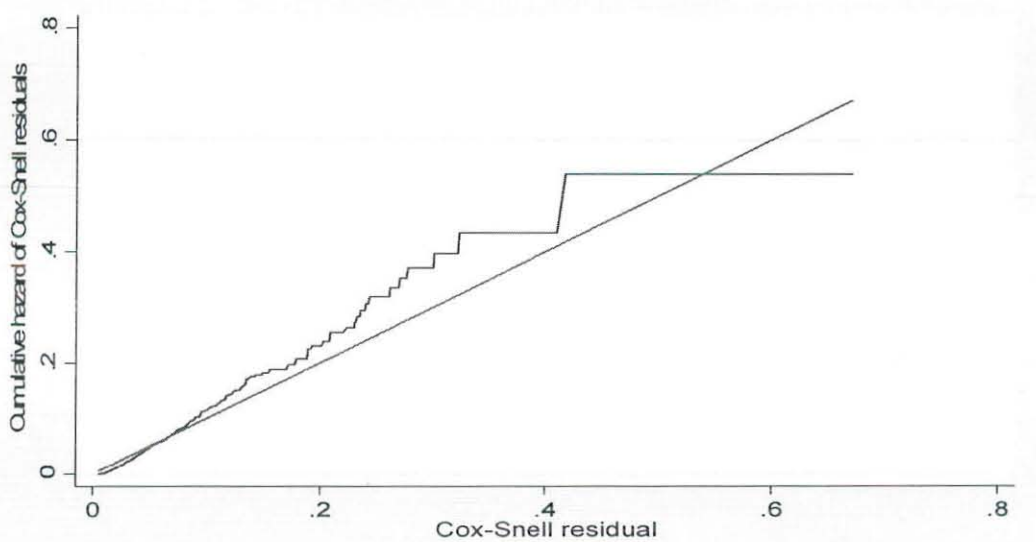

Figure 4.3: Cumulative hazard plot of the Cox-Snell residuals of the proportional hazards Cox regression model in Table 8A.The 45°-straight line through the origin is drawn for reference.

It can be seen that the plot of cumulative hazard against Cox-Snell residuals in Figure 4.3 above is in the lower part fairly close to the 45° straight line through the origin. This suggests that the model fitted to the data is satisfactory. But, the little departure from straight line may be due to non-proportionality in the dataset. Therefore, we use the Stratified Cox PH model to overcome this deficiency.

4.6. Results of the Stratified Cox proportional hazards model

One way of accommodating non-proportional hazards in model is to use the Stratified Cox proportional hazards model. Stratification entails fitting separate baseline hazard functions across strata (in this case region category). A baseline hazard function represents the hazard rate over time for an individual with all modeled covariates set to zero. With a Stratified Cox model, a proportional hazards structure does not necessarily hold for the combined data, but is assumed to hold within each region. However, the coefficients on the included covariates are common across region categories so that the relative effect of each predictor is the same across region.

The estimated coefficients of a Stratified Cox model are computed using the entire data set. Thus, the assumption is that we are fitting separate models for each categories of covariate region under the constraint that the coefficients are equal but the baseline hazard functions are not equal. As we attempted to show in the previous section, the proportional hazards assumption is not satisfied for the covariate region. Hence, the Stratified proportional hazards model is used to obtain the estimated coefficients of the remaining covariates after stratification by region. Table 4.3 below shows parameter estimates and hazard ratios on fitting Stratified Cox proportional hazards model to neonatal data. The Wald statistic P-value from the model indicates all of the coefficients included were significantly associated to neonatal survival time at 5% level. But, before using this result for interpretation and discussion, we need to check proportional hazards assumption once again.

The assumption of PH within strata can be checked using time-varying coefficients as in Section 4.5.1.The formal test based on scaled Schoenfeld residuals can be used to test the significance of the correlation between scaled Schoenfeld residuals and ordered survival times. However, the computation of scaled Schoenfeld residuals requires a modification given in Therneau and Grambsch (2000). The modification uses a within-stratum variance to compute the scaled Schoenfeld residuals within each stratum. Table 11A (Appendix) presents test of PH assumption after stratifying on region covariate. Based on P-value of correlations between scaled Schoenfeld residuals and ordered survival times, all of the correlations were insignificant at 5% level. Thus, there is no sufficient evidence to reject the null hypothesis that the correlation between the scaled Schoenfeld residuals and the ranked survival time is zero. This ascertains the validity of the assumption of the proportional hazards after stratification for region holds. In the next section we use criteria to compare PH and stratified PH models.

Table 4.3: Estimated values of the coefficients, hazard ratios, 95% CI for the hazard ratio and P- values of the explanatory variables on fitting the Stratified Cox proportional hazard model

Covariates/ factors	Parameter estimate	SE	Wald χ^2	df	P- value	Hazard ratio	95% Hazard ratio CI	
							Lower	Upper
Multiple births	1.316	0.144	83.765	1	<.0001	3.728	2.813	4.942
Birth order			12.332	2	0.002			
First birth	0.516	0.149	12.051	1	0.001	1.675	1.252	2.242
2-4	reference							
>4	0.004	0.115	0.001	1	0.971	1.004	0.802	1.258
Sex	0.231	0.089	6.650	1	0.010	1.260	1.057	1.501
Birth interval			23.778	2	<.0001			
<24	0.490	0.112	19.267	1	0.000	1.633	1.312	2.032
24-47	reference							
>47	-0.020	0.123	0.026	1	0.870	0.980	0.770	1.245
Antenatal visits	-0.334	0.110	9.124	1	0.002	0.716	0.577	0.889
Size at birth			41.616	4	<.0001			
Very small	0.606	0.117	26.807	1	0.000	1.833	1.457	2.305
Smaller than average	0.241	0.163	2.186	1	0.139	1.246	0.973	1.173
average	reference							
Larger than average	0.121	0.170	0.502	1	0.478	1.128	0.808	1.575
Very large	0.676	0.126	28.672	1	0.000	1.966	1.535	2.519
Pregnancy complication	0.549	0.160	11.818	1	0.001	1.732	1.266	2.239
Mother's age			10.810	2	0.004			
<20	0.323	0.140	5.348	1	0.021	1.382	1.051	1.818
20-34	reference							
>34	0.280	0.119	5.538	1	0.019	1.323	1.060	1.799
Breastfeeding	-0.189	0.091	4.339	1	0.037	0.828	0.693	0.989

*[4]The reference category in this table is selected based on guidelines by Garson (2006).

[4]The guidelines are: first, using categories such as *miscellaneous* or *other* is not recommended. Second, the reference category should not be a category with few cases. Third, theory may suggest which category we compare to a particular category.

4.7 Model comparison

In survival analysis, comparisons between a numbers of possible models can also be made based on the Akaike's information criterion (AIC) and Bayesian Information Criterion (BIC) [5]. The guiding principle is that the smaller the value of AIC and BIC the better fit the model. The values of AIC and BIC can be compared across different models. The values of AIC and BIC for the Cox PH model and stratified PH model are given in Table 4.4.

Table 4.4: Model information criteria

Model	AIC	BIC	No. of parameters
Cox PH model	9179.793	9285.994	25
Stratified Cox PH model	6803.084	6866.805	15

It can be seen from the Table 4.4 that the Stratified Cox PH model had a smaller value of both criteria (AIC and BIC). Since a lower value of these statistics indicates a better fitting model by adjusting for the number of explanatory variables and the number of observations used in the model, the Stratified Cox PH model gives better results compared to Cox PH model. This shows that using the Stratified Cox PH model gives more suitable results for survival data in the presence of non-proportional hazards. Thus, the Stratified Cox PH model with estimates as given in Table 4.3 is the final model. Now, we are in position to give interpretation and discussion based on Stratified PH model.

4.8. Interpretation and discussion of results

4.8.1 Interpretation

The coefficients of categorical explanatory variables in Stratified Cox PH model interpreted in the same way as in the Cox PH model. The comparison is made with the reference category and between groups for the categorical covariates. Thus, the estimates of hazard ratio and corresponding confidence interval can easily be found from the fitted model. Then, the interpretation of parameters corresponding to different variables which are found significant in the final model is presented as follows.

[5] $AIC = -2L(\hat{\beta}) + 2p$ and $BIC = -2L(\hat{\beta}) + p\log(n)$; p is the number of parameters in the model, and n is the number of observations in the data set.

The estimated hazard ratio for multiple birth neonates in relation to those who are single birth (reference category) is 3.728 (95% CI: 2.813-4.942). It means the twin or multiple births were 3.728 times as likely as to be dying at neonatal period than that of the singleton birth. The 95% confidence interval indicated that the hazard rate goes to a maximum of 4.942 and a minimum of 2.813.

The estimated hazard ratios for a neonate with first birth order and higher order births compared with birth order 2-4 (reference group) are 1.675 (95% CI:1.252-2.242) and 1.004 (95% CI:0.802-1.258), respectively. As compared to birth order 2-4, the first order birth has 67.5% higher risk of neonatal death, whereas the difference in the likelihood of neonatal death between higher order births and the birth order 2-4 is not significant. The 95% confidence interval for first order birth implies that the rate could be as low as 1.252 and as high as 2.242.

The hazard ratio for male neonate was 1.26. This implies male neonates have 26% higher risk of neonatal deaths when compared to female neonates (reference category). The confidence interval indicated that the risk of death for male neonates could be as low as 1.057 and as high as 1.501.

The estimated hazard ratio for neonates whose mother's attended antenatal visits during pregnancy when compared to those mother's who did not attend antenatal visit was 0.716 (95% CI:0.577-0.889). That is, neonates whose mother's attended antenatal visits during pregnancy had 28.4% lower risk of neonatal mortality than those who did not attend antenatal visits.

The risk of dying for neonates with preceding birth interval less than 24 months is higher by 63.3% relative to those neonates with birth interval between 24-47 months (reference category). The relative risk of death for neonates with preceding birth interval greater than 47 months compared to reference category is 0.98 (95% CI: 0.77-1.2447, P-value=0.869). The P-value for this category is greater than 0.05 and the confidence interval contain one, this indicates there is no statistically significant difference between estimated risks of death for neonates with preceding birth interval greater than 47 months compared to neonates with preceding birth interval 24-47 months.

The estimated hazard ratios for a neonate with very large size and very small size at birth in comparison with average size neonate at birth are 1.966 (95% CI: 1.535-2.519) and 1.833 (95% CI: 1.457-2.305), respectively. The risk of death for neonates with very large and very small size at birth are 96.6 % and 83.3% higher respectively than neonates with average size at birth (reference category).

The reference category for the mother age group is age 20-34. The estimated hazard ratio for mother age less than 20 is 1.382.This implies that neonates who are born to mothers of age group of less than 20 years are dying at a rate 38.2% higher than those who are in age group 20-34. The confidence interval suggests that the hazard ratios are as low as 1.051 and as high as 1.818.The hazard ratio for the mother age greater than 34 is 1.323. That is, neonates who are born to mothers of age above 34 years are dying at a rate 32.3% higher than those who are in the reference category. The 95% confidence interval implies that the rate could be as low as 1.060 and as high as 1.799.

The estimated hazard ratio for neonates born to mothers experiencing complication during delivery compared to neonates born to mother's not experiencing complication is 1.732 (95% CI: 1.266-2.239). It means neonates born to mothers experiencing pregnancy complication have about 73.2% higher mortality risk than those born to mother's not experiencing pregnancy complication during delivery. The 95% confidence interval indicated that the hazard rate goes to a maximum of 2.239 and a minimum of 1.266.

The estimated hazard ratio for neonate put to breast is 0.828 (95% CI: 0.693-0.989). The interpretation is that the neonates put to breast immediately upon birth had a 17.2 % lower risk of neonatal mortality than those not put to breast immediately. The confidence interval suggests that the risk could be as low as 1.1% and as high as 30.7%.

4.8.2 Discussion of the results

The main aim of this study was to identify risk factors of neonatal mortality in Ethiopia using the nationally representative 2011 EDHS data. Both univariate and multivariate statistical analyses were employed to examine factors affecting neonatal mortality. Our analyses revealed that demographic and some maternal health service factors rather than socioeconomic factors had statistically significant effect on neonatal mortality. The variables influencing neonatal mortality are multiplicity of birth, birth order, sex, birth interval, antenatal visits, birth size, pregnancy complication, mother's age at birth, and whether a child was put to breast.

The findings of this study revealed that the risk of neonatal death is higher among neonates who are twin or multiple births than those single births. A study in southwest Ethiopia by Makonnen et al. (2002) investigated risk factors associated with neonatal and post-neonatal mortality. The result suggested that twins were much more likely to die than singletons, even after taking their birth weight into account. A similar study in Brazil by Araújo et al. (2011) also found that multiplicity of birth was significantly associated with neonatal mortality. One possible reason for this observed association was that multi-foetal pregnancy and multiple births including twins and higher order multiples such as triplets and quadruplets were high-risk pregnancy and birth. These high-risk births were frequently accompanied by a number of associated foetal and neonatal complications that required special and expensive medical care (Ananth *et al.*, 2005). Thus, mortality among these high risk groups contributed to the higher rate of neonatal mortality.

Birth order of a neonate brought to light controversial results about neonatal mortality. Some studies showed that first order births were at higher risk of neonatal mortality, whereas some others showed that higher order births were at increased risk of neonatal mortality. For instance, in a study to identify the risk factors of neonatal mortality in Bangladesh, infants of first birth had higher risk of neonatal mortality (Kamal *et al.*, 2012). A study conducted in Empowered Action Group (EAG) states of India, Arokiasamy and Gautam (2007) showed that neonates with first and higher order births were at higher risk of neonatal deaths, while in rural part of Iran (Chaman *et al.*, 2009), the neonates with four or higher order births were at increased risk of neonatal mortality. Another study in Kenya by Mustafa and Odimegwu (2008) found that increased risk of neonatal mortality was associated with first born child. The current study showed that neonates with first order birth are significantly at increased risk of dying than birth orders two through four or higher order births agreeing with most of the studies mentioned above.

The observed higher risk of dying in neonatal period for males compared to females in this study was consistent with other studies conducted elsewhere. For instance, a study by Titaley *et al.* (2008) to indentify the determinants of neonatal mortality in Indonesia showed that the odds of neonatal death were higher for male infants. A study in Indonesia by Dakhi (2012) also showed that the risk of neonatal death was higher for male infants. A similar study in Brazil revealed that the risks of dying for male infants were significantly associated to neonatal death (Araújo *et al.,* 2011). A possible explanation for the findings might be biological factors like immunodeficiency, late maturity and congenital malformations of the urogenital system that increased risk of neonatal death in male infants.

The results of this study suggest that the risk of neonatal death is higher for neonates with preceding birth interval less than two years. Titaley *et al.* (2008) also revealed that the risk of neonatal death were higher for neonates with short birth interval. Rutstein (2008) pooled the birth history data from 52 countries to see the effect of preceding birth intervals on neonatal mortality. The results showed that the risk of neonatal mortality were higher for birth intervals shorter than 24 months and longer than 47 months compared to the reference group (24-47 months). But the departure from our result may be due to an aggregate effect of birth interval from 52 countries on neonatal death. Similar to our finding, studies by Arokiasamy and Gautam (2007), Mustafa and Odimegwu (2008), and Chaman *et al.* (2009) provided evidence that the risk of dying were higher for neonates with birth spacing less than 24 months. A study in Ethiopia showed that birth intervals less than two years led to higher neonatal mortality rates than higher birth intervals (Susman, 2012).

Our findings showed that neonates whose mothers attended antenatal visits during pregnancy had lower risk of neonatal mortality than those who did not attend antenatal visits. A study in the Gaza Strip, occupied Palestinian territory, by Awour *et al.* (2012) found that newborn babies born to mothers who attended fewer than four antenatal sessions during pregnancy had a risk of dying that was almost twice that of those born to mothers who attended antenatal session four or more times. A study in Indonesia also revealed that the risk of neonatal death was higher among women who did not attend antenatal care visits during pregnancy (Dakhi, 2012). A study in Ethiopia by Makonnen *et al.* (2002) showed that neonatal mortality was associated with antenatal care follow-up: there was better survival with at least one antenatal care follow-up. Thus, antenatal care follow-up is a prominent predictor of survival time of neonates.

Birth size was found to be one of the statistically significant predictors of neonatal death in our study. It showed that the risk of death for neonates with very large and very small size at birth was higher than neonates with average size at birth (reference category) whereas the risk of death for neonates with smaller than average and larger than average at birth are statistically insignificant compared to the reference category. A study in Indonesia revealed that the odds of neonatal death were higher with very small-sized infants (Titaley *et al.,* 2008). Similarly, a study in Dire Dawa, Ethiopia by Tesfaye (2003) found out that very small and smaller than average size of the neonates at birth had higher risk of neonatal mortality than neonates who had average birth size at birth.

We expect that neonates born to young mothers (age below 20 years) and those born to older mothers (age above 34 years) would have higher mortality than those born to mothers aged 20-34 years. The higher risks of neonatal death among neonates born to mothers aged less than 20 years and above 34 years found in this paper were as the expected mortality pattern. Mondal *et al.* (2009) in Bangladesh also showed that the mother's age at birth was the most significant predictors of neonatal mortality. The studies by Seedhom and Kamal (2008), Arokiasamy and Gautam (2007) and Kamal (2012) provided evidence that the risk of dying was higher for neonates whose mother's age was younger than 20 years. A study in Indonesia also revealed that the risk of neonatal death was higher among neonates whose mother's age was above 34 years. Thus, as expected, in this study neonates born to mothers aged 20-34 years are at a lower risk of mortality.

This study revealed that neonates born to mothers experiencing complications during childbirth had remarkably higher hazards of dying compared to those born to mothers without any complications. This result is similar to the finding of a study in Indonesia which showed that neonates born to mothers with delivery complications had lower survival than those born to mothers without delivery complications (Titaley *et al.,* 2008). Appropriate antenatal care can play a role by educating women and their families to recognize delivery complications that require referral to health care services to achieve a better health outcome for both mothers and neonates.

Another important predictor of neonatal mortality is the time neonates are put to breast upon birth. Our findings showed that the neonates put to breast immediately upon birth had lower risk of neonatal mortality than those not put to breast immediately upon birth. A study by Awour *et al.* (2012) found that the risk of death in neonates who were breastfed within the first hour of delivery was much lower than among those who were not breastfed in the first hour.

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

The study employed survival statistical analysis to determine risk factors associated with neonatal mortality in Ethiopia. The results from the Kaplan-Meier estimate showed that most of the deaths occurred during the earlier days of life, that is, from birth to the first week of life and it declined slowly in the later days of follow-up. About 71% and 79% of the neonatal deaths occurred within the first and second weeks of follow-up time, respectively. This study had also examined socio-economic, demographic and maternal health service determinants of neonatal mortality in Ethiopia. Results based on Stratified Proportional Hazards model revealed that demographic and some maternal health service factors rather than socio-economic factors had statistically significant effect on neonatal mortality. Specifically, the study demonstrated that various factors such as multiplicity of birth, birth order, sex, birth interval, sought antenatal visits, birth size, pregnancy complication, mother's age at birth, and whether a child was put to breast upon birth had statistically significant impacts on the survival experience of neonates.

Furthermore, the findings suggested the following: multiplicity of birth and birth order number had a significant effect on survival of neonates, that is, neonates who were twin or multiple births and first order birth were at higher risk of dying at neonatal period. Neonates who were male had higher risk of death and neonates whose mother's attended antenatal visits during pregnancy were at lower risk of mortality. Preceding birth interval and birth size were significantly related to neonatal mortality, that is, neonates with preceding birth interval less than two years were at higher risk of death, and very small and very large sized neonates at birth were more likely to face the risk of death. Also, neonates born to mothers aged 20-34 years were at a lower risk of mortality. The study also showed that pregnancy complication and the time when neonates were put to breast upon birth were associated with neonatal mortality. Neonates born to mothers experiencing pregnancy complications were more likely to face risk of death and neonates put to breast immediately upon birth were at lower risk of mortality. In general, addressing short birth interval, preventing younger and older mother pregnancy, putting the neonates to breast immediately upon birth and child birth through effective antenatal care programs need to be considered among neonatal survival interventions. Health interventions should also focus on curtailing the high risk of neonatal deaths arising from the pregnancy complication, twin or multiple births, and first order birth is required.

5.2 Recommendations

Based on the study findings and keeping the limitations in mind, the study puts forward the following recommendations.

- Neonates from birth to the first week of life had increased risk of neonatal mortality. This finding reinforces that improving the early-postnatal visits for both mothers and babies with effective care. This is an important finding for planners and policy makers as it indicates the age group with high risk of mortality.
- It is recommended that pregnant women should receive antenatal care during their pregnancy such that pregnant women at risk be identified early, when receiving antenatal care, and that they receive special attention during pregnancy and delivery. Health interventions should be directed preferably at these groups, since these women are the ones who give birth to high-risk newborns, who may die during the first days of life.
- In general, the government policies should focus on improving neonatal survival and health intervention policies should revise and implement to achieve the Millennium Development Goals (MDGs) of reducing under-five mortality by 2015.

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APPENDIX

Table 1A: Distribution of socio-economic, demographic and maternal health factors characteristics of neonates in Ethiopia.

Covariate/factor	Category	Censored	Dead	Total (%)
Residence	Urban	1381	73	1454(16.8)
	Rural	6753	444	7197(83.2)
Marital status	Never in union	48	5	53(0.6)
	Married	7164	446	7610(88.0)
	Widowed/divorced separated	922	66	988(11.4)
Wealth index	Poor	4022	271	4293(49.6)
	Medium	1329	87	1416(16.4)
	Rich	2783	159	2942(34.0)
Mother's education	No education	5706	356	6062(70.1)
	Primary	2024	138	2162(25.0)
	Secondary & above	404	23	427(4.9)
Birth order	First birth	1231	112	1343(15.5)
	2-4	3815	210	4025(46.5)
	> 4	3088	195	3283(38.0)
Multiple births	Single	7878	460	8338(96.4)
	Multiple	256	57	313(3.6)
Sex	Female	3975	223	4198(48.5)
	Male	4159	294	4453(51.5)
Birth interval (in months)	<24	1608	141	1749(20.2)
	24-47	3960	210	4170(48.2)
	>47	2566	166	2732(31.6)
Antenatal visits	No	5385	371	5756(66.5)
	Yes	2749	146	2895(33.5)
Delivery place	Home	6989	433	7422(85.8)
	Health facility	1145	84	1229(14.2)
Size of child at birth	Very small	1859	152	2011(23.2)
	Smaller than average	702	28	730(8.4)
	Average	3277	151	3428(39.6)
	Larger than average	948	71	1019(11.8)
	Very large	1348	115	1463(16.9)
Pregnancy complication	No	7493	463	7956(92.0)
	Yes	641	54	695(8.0)
Mother's age (in years)	<20	832	90	922(10.7)
	20-34	6029	334	6363(73.6)
	>34	1273	93	1366(15.7)
Delivery assistance	Unskilled	6071	396	6467(74.6)
	Skilled	2063	121	2184(25.4)
Child put to breast upon birth	No	3766	274	4040(46.7)
	Yes	4368	243	4611(53.3)

Region	Tigray	906	53	959(11.1)
	Affar	754	40	794(9.2)
	Amhara	936	73	1009(11.7)
	Oromiya	1269	75	1344(15.5)
	Somali	694	41	735(8.5)
	Benishangul-Gumuz	701	65	766(8.9)
	SNNP	1083	73	1156(13.4)
	Gambela	604	40	644(7.4)
	Harari	423	27	450(5.2)
	Addis Ababa	286	11	297(3.4)
	Dire Dawa	478	19	497(5.7)

Table 2A: Results of the Kaplan-Meier Estimates of neonatal survival function.

Time	Beg. Total	Fail	Net Lost	Survivor function	Std error	[95% Conf.Int.]	
1	8651	223	63	0.9742	0.0017	0.9707	0.9771
2	8365	35	0	0.9701	0.0018	0.9663	0.9735
3	8330	40	1	0.9655	0.0020	0.9614	0.9691
4	8289	20	2	0.9632	0.0020	0.9590	0.9669
5	8267	17	2	0.9612	0.0021	0.9569	0.9651
6	8248	8	0	0.9602	0.0021	0.9559	0.9642
7	8240	24	0	0.9574	0.0022	0.9530	0.9615
8	8216	7	0	0.9566	0.0022	0.9521	0.9607
9	8209	3	0	0.9563	0.0022	0.9518	0.9604
10	8206	10	2	0.9551	0.0022	0.9505	0.9593
11	8194	1	1	0.9550	0.0020	0.9504	0.9592
12	8192	5	3	0.9544	0.0022	0.9498	0.9586
13	8184	3	0	0.9541	0.0023	0.9494	0.9583
14	8181	10	0	0.9529	0.0023	0.9482	0.9572
15	8171	13	0	0.9514	0.0023	0.9466	0.9557
16	8158	3	0	0.9510	0.0023	0.9463	0.9554
17	8155	3	0	0.9507	0.0023	0.9459	0.9551
18	8152	3	0	0.9503	0.0023	0.9455	0.9547
19	8149	2	0	0.9501	0.0023	0.9453	0.9545
20	8147	5	0	0.9495	0.0024	0.9447	0.9539
21	8142	8	0	0.9486	0.0024	0.9437	0.9531
22	8134	3	0	0.9482	0.0024	0.9433	0.9527
23	8131	2	0	0.9480	0.0024	0.9431	0.9525
24	8129	1	1	0.9479	0.0023	0.9430	0.9524
25	8127	2	1	0.9477	0.0024	0.9427	0.9522
26	8124	1	0	0.9475	0.0024	0.9426	0.9520
27	8123	2	0	0.9473	0.0024	0.9424	0.9518
28	8121	6	0	0.9466	0.0024	0.9416	0.9512
29	8115	2	0	0.9464	0.0024	0.9414	0.9509
30	8113	55	8058	0.9400	0.0026	0.9347	0.9448

Table 3A: Results of the univariable proportional hazards Cox regression model

Covariates/factors	B	SE	Wald χ^2	df	Sig.	HR	LR(Sig	-2L
Residence	0.210	0.126	2.771	1	0.096	1.234	0.088	9341.1
Wealth index			2.678	2	0.262		0.256	9341.2
Medium	-0.029	0.123	0.057	1	0.811	0.971		
Rich	-0.161	0.099	2.612	1	0.106	0.851		
Marital status			2.148	2	0.342		0.3751	9341.9
Married	-0.494	0.450	1.207	1	0.272	0.610		
Widowed/divorced/ separated	-0.361	0.464	0.605	1	0.437	0.697		
Mother education			0.979	2	0.613		0.614	9342.9
Primary	-0.085	0.100	0.722	1	0.395	0.908		
Secondary and higher	-0.084	0.215	0.153	1	0.695	0.919		
Birth order			17.465	2	0.000		0.0003	9327.5
2-4	-0.487	0.117	17.319	1	0.000	0.614		
>4	-0.352	0.119	8.826	1	0.003	0.703		
Multiple births	1.255	0.140	79.864	1	0.000	3.508	0.000	9285.7
Sex of neonate	0.222	0.088	6.245	1	0.013	1.248	0.012	9337.6
Antenatal visits	-0.252	0.098	6.642	1	0.010	0.777	0.009	9337.0
Delivery place	0.029	0.123	0.057	1	0.812	1.030	0.814	9343.8 67
Breast feeding	-0.262	0.088	8.828	1	0.003	0.770	0.003	9335.0
Pregnancy complication	0.303	0.144	4.450	1	0.035	1.354	0.043	9339.8
Assistance at delivery	-0.100	0.104	0.934	1	0.333	0.904	0.330	9342.9
Birth interval			19.847	2	0.000		0.000	9324.8
24-47	-0.485	0.109	19.846	1	0.000	0.616		
>47	-0.288	0.115	6.316	1	0.012	0.750		
Birth size			39.405	4	0.000		0.000	9302.6
Very small	0.553	0.115	23.129	1	0.000	1.738		
Smaller than	-0.142	0.206	0.4755	1	0.490	0.868		
average	0.470	0.144	10.655	1	0.001	1.600		
Larger than average	0.595	0.124	23.071	1	0.000	1.812		
Very large								
Mother's age at			30.707	2	0.000		0.000	9316.2
birth	-0.644	0.148	29.357	1	0.000	0.525		
20-34	-0.374		6.393	1	0.011	0.688		
>34								

Region			20.159	10	0.028		0.0248	9323.4
Affar	0.284	0.279	1.043	1	0.307	1.329		
Amhara	0.657	0.258	6.523	1	0.011	1.931		
Oromiya	0.388	0.257	2.283	1	0.131	1.474		
Somali	0.391	0.278	1.982	1	0.159	1.478		
Benshangul-Gumuz	0.821	0.261	9.903	1	0.002	2.272		
SNNP	0.513	0.258	3.975	1	0.046	1.671		
Gambela	0.500	0.278	3.223	1	0.072	1.649		
Harari	0.468	0.299	2.447	1	0.118	1.598		
Addis Ababa	-0.024	0.379	0.004	1	0.949	0.976		
Dire Dawa	0.379	0.267	2.011	1	0.156	1046		

Remark: The value of -2L for the null model is 9343.923

Table 4A: Results of the multivariable proportional hazards Cox regression model containing the variables significant at 20-25% level in the univariable PH Cox regression model

Covariates/factors	df	Wald χ^2	Sig.	LR χ^2	Sig.
Residence	1	0.083	0.774	0.08	0.773
Birth order	2	12.468	0.002	12.05	0.003
Multiple births	1	84.914	0.000	62.02	0.000
Sex	1	6.54	0.010	6.80	0.009
Antenatal visits	1	10.486	0.001	11.06	0.001
Breast feeding	1	5.192	0.023	5.204	0.023
Pregnancy complication	1	10.122	0.002	9.297	0.002
Birth interval	2	25.053	0.000	23.248	0.000
Birth size	4	36.508	0.000	38.366	0.000
Mother's age	2	13.439	0.001	13.039	0.001
Region	10	23.840	0.008	24.880	0.005

Remark: The value of -2L for the model containing all the covariates in this table is 9129.710

Table 5A: Results of the multivariable PH Cox regression model after eliminating variable residence from the multivariable PH Cox regression model in Table 4A

Covariates/factors	df	Wald χ^2	Sig.	LR χ^2	Sig.
Birth order	2	12.397	0.002	11.970	0.003
Multiple births	1	84.828	0.000	62.120	0.000
Sex	1	6.721	0.009	6.780	0.009

Antenatal visits	1	9.220	0.002	9.650	0.002
Breast feeding	1	4.471	0.034	4.480	0.034
Pregnancy complication	1	11.890	0.000	10.790	0.001
Birth interval	2	23.747	0.000	22.080	0.000
Birth size	4	41.770	0.000	43.260	0.000
Mother's age	2	10.868	0.004	10.590	0.005
Region	10	25.608	0.004	27.310	0.002

Remark: The value of -2L for the model containing all the covariates is 9129.793

Table 6A: Percentage changes in the coefficients of the variables included in Table 5A, when the variables that were not significant in the univariable and multivariable proportional hazards Cox regression models are added one at a time.

Covariates/factors	Residence	Marital status	Wealth index	Mother's education	Delivery assistance	Delivery place
Birth order						
2-4	-0.16	0.72	-0.08	-1.22	-0.22	1.44
>4	-0.83	0.95	-0.72	-1.794	-0.72	1.90
Multiple births	-0.07	0.09	0.32	0.82	0.71	-0.64
Sex	0.11	0.08	-0.23	-0.06	-0.21	-0.09
Antenatal visits	1.29	-0.17	1.84	0.66	1.26	-1.54
Breast feeding	0.32	0.19	0.06	0.02	-0.26	0.02
Pregnancy complication	2.26	-0.07	1.90	2.37	0.93	-1.68
Birth interval						
24-47	-0.11	0.19	-0.05	-0.15	-0.10	0.13
>47	0.31	-0.30	0.55	0.03	0.22	-0.49
Birth size						
Very small	-0.43	-0.20	-0.76	-0.44	-0.90	0.32
Smaller than	-0.71	0.04	-0.75	-0.00	-0.12	-0.22
average	-0.61	0.00	-0.24	-0.11	0.27	-0.23
Larger than average	-0.19	-0.27	0.31	-0.11	0.05	0.41
Very large						
Mother's age						
20-34	1.08	0.09	0.47	1.15	0.50	-1.12
>34	1.26	0.22	0.58	1.24	0.62	-1.00
Region						
Affar	1.89	0.61	-4.95	0.39	-0.87	3.08
Amhara	-3.91	-0.13	-2.63	0.24	3.74	2.95
Oromiya	-3.59	0.25	-1.02	0.17	-2.88	2.88
Somali	-3.93	0.53	-1.51	0.21	-2.05	2.70

Benishangul-Gumuz	-4.37	0.29	-2.62	-0.37	4.85	1.86
SNNP	-4.03	-0.01	-1.86	-0.07	-3.86	3.21
Gambela	-3.58	-1.04	-4.36	0.22	-3.85	2.23
Harari	-0.61	0.13	3.07	-2.06	2.51	-0.02
Addis Ababa	5.52	-0.54	2.52	-3.67	-1.20	-3.94
Dire Dawa	-3.66	-0.49	2.52	0.22	-3.95	2.93

Table 7A: Values of Wald statistic and corresponding P-values of possible interaction terms, added one at a time, to the main effects variables included in Table 5A

Interaction b/n	Covariates	Wald χ^2	df	P-value
Birth order	Multiple births	0.463	2	0.793
	Sex	1.269	2	0.530
	Antenatal visits	2.623	2	0.269
	Breast feeding	3.347	2	0.188
	Pregnancy complication	5.857	2	0.054
	Birth size	12.960	8	0.110
	Mother's age	9.435	4	0.051
	Region	29.342	20	0.081
Multiple birth	Sex	1.729	1	0.189
	Antenatal visits	2.154	1	0.142
	Breast feeding	1.411	1	0.235
	Birth interval	5.278	2	0.071
	Birth size	4.249	4	0.373
	Mother's age	1.009	2	0.604
	Region	7.072	10	0.719
Sex	Antenatal visits	0.179	1	0.672
	Breast feeding	0.522	1	0.470
	Pregnancy complication	0.482	1	0.487
	Birth interval	0.367	1	0.833
	Mother's age	2.098	2	0.350
	Region	9.266	10	0.507
Antenatal visits	Breast feeding	0.046	1	0.829
	Pregnancy complication	3.803	1	0.051
	Birth interval	1.332	2	0.514
	Birth size	2.081	4	0.721
	Mother's age	4.723	2	0.094
	Region	9.435	10	0.491
Breast feeding	Pregnancy complication	2.853	1	0.091
	Birth interval	3.670	2	0.159
	Birth size	6.764	4	0.149
	Mother's age	1.899	2	0.387
	Region	14.811	10	0.139

Pregnancy complication	Birth interval	1.616	2	0.446
	Birth size	1.389	4	0.846
	Mother's age	3.604	2	0.165
	Region	13.618	10	0.191
Birth interval	Birth size	4.211	8	0.378
	Mother's age	2.261	4	0.688
	Region	22.502	20	0.313
Birth size	Mother's age	6.809	8	0.557
	Region	49.876	40	0.136
Mother's age	Region	14.542	20	0.802

Table 8A: Estimated values of the coefficients, hazard ratios and P-values of explanatory variables on fitting multivariable Cox proportional hazards model

Covariates/ factors	Parameter estimates	SE	Wald χ^2	df	P-value	Hazard ratio
Birth order			12.397	2	0.002	
2-4	-0.518	0.149	12.141	1	0.001	0.596
>4	-0.511	0.173	8.67	1	0.003	0.600
Multiple births	1.323	0.144	84.828	1	<.0001	3.756
Sex	0.232	0.089	6.721	1	0.009	1.261
Birth interval			23.747	2	<.0001	
24-47	-0.490	0.112	19.229	1	0.000	0.613
>47	-0.510	0.128	15.786	1	0.000	0.600
Antenatal visits	-0.336	0.111	9.218	1	0.002	0.715
Size at birth			41.770	4	<.0001	
Very small	0.605	0.117	26.816	1	<.0001	1.833
Smaller than	0.280	0.163	2.951	1	0.086	1.213
average	0.121	0.170	0.510	1	0.475	1.129
Larger than average	0.679	0.126	28.877	1	<.0001	1.971
Very large						
Pregnancy complication	0.551	0.160	11.890	1	0.001	1.735
Mother's age			10.869	2	0.004	
20-34	-0.327	0.140	5.448	1	0.019	0.721
>34	-0.005	0.192	0.001	1	0.978	0.995
Breast feeding	-0.192	0.091	4.471	1	0.034	0.825
Region			25.608	10	0.004	
Affar	-0.493	0.211	5.458	1	0.019	0.611
Amhara	-0.058	0.178	0.109	1	0.741	0.943
Oromiya	-0.364	0.178	4.182	1	0.041	0.695

Somali	-0.260	0.198	1.742	1	0.187	0.770
Benshangul-Gumuz	0.146	0.179	0.657	1	0.417	1.157
SNNP	-0.261	0.177	0.131	1	0.717	0.938
Gambela	-0.249	0.207	1.456	1	0.227	0.779
Harari	-0.134	0.224	0.355	1	0.551	0.875
Addis Ababa	-1.031	0.384	7.215	1	0.007	0.357
Dire Dawa	-0.595	0.264	5.065	1	0.024	0.552

Table 9A: Test of proportional-hazards assumption based on schoenfeld residuals for the variables included in the model in Table 8A

Covariates	rho	Chi-square	df	Sig.
Birth order				
2-4	0.015	0.13	1	0.722
>4	-0.031	0.61	1	0.433
sex	0.001	0.001	1	0.978
Birth interval				
24-47	0.069	2.53	1	0.112
>47	0.006	0.02	1	0.888
Multiple births	-0.040	0.80	1	0.372
Pregnancy complication	-0.042	0.92	1	0.337
Antenatal visits	0.082	3.51	1	0.061
Size at birth	0.046	1.10	1	0.294
Larger than average	0.053	1.47	1	0.224
Average	0.084	3.67	1	0.055
Smaller than average	0.069	2.53	1	0.112
Very small				
Mother's age				
20-34	0.057	1.93	1	0.164
>34	0.036	0.87	1	0.350
Breast feeding	0.003	0.01	1	0.938
Region				
Affar	0.086	3.86	1	0.042
Amhara	0.063	2.11	1	0.146
Oromiya	0.063	2.18	1	0.140
Somali	0.029	0.48	1	0.487
Benshangul-Gumuz	0.050	3.84	1	0.048
SNNP	0.089	4.24	1	0.039
Gambela	-0.015	0.12	1	0.723
Harari	-0.085	3.92	1	0.040
Addis Ababa	0.005	0.01	1	0.905
Dire Dawa	0.090	4.50	1	0.037
Global test	32.34	26	1	0.182

Table 10A: The five highest differences of the parameter estimates of the variables included in the model in Table 8A when the data value for each neonate is in turn deleted from the model

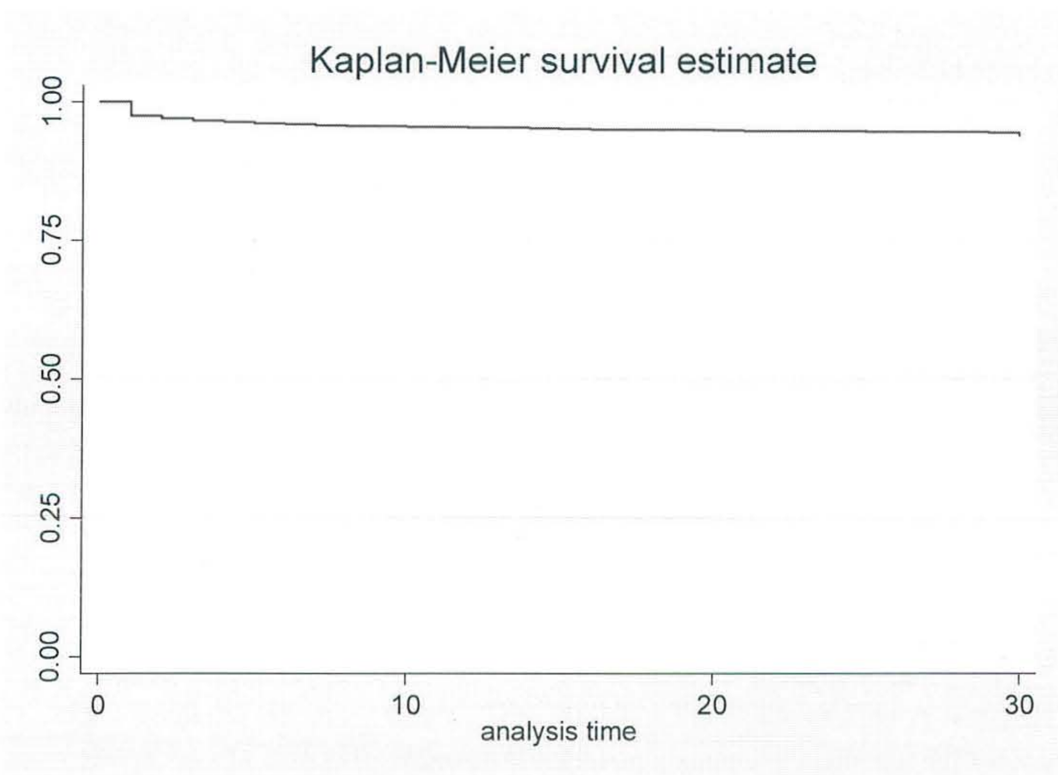
Covariates/ factors	Deleted observation(i)	$\Delta_{j(-i)} = \hat{\beta}_j - \hat{\beta}_{j(-i)}$	$\lvert \Delta_{j(-i)} = \hat{\beta}_j - \hat{\beta}_{j(-i)} \rvert$
Multiple births	1434	0.01751	0.01751
	747	0.01751	0.01751
	2795	0.01723	0.01723
	2436	0.01713	0.01713
	7516	0.01698	0.01698
Birth order	162	-0.02818	0.02818
	125	-0.02749	0.02749
	666	0.02545	0.02545
	598	0.02534	0.02534
	620	-0.02267	0.02267
Sex	7395	-0.005343	0.005343
	2401	-0.005341	0.005341
	1104	-0.005299	0.005299
	2009	-0.005203	0.005203
	3766	-0.005197	0.005197
Birth interval	125	-0.01521	0.01521
	4053	-0.01333	0.01333
	162	-0.01287	0.01287
	5870	-0.01280	0.01280
	6325	-0.01243	0.01243
Antenatal visits	495	0.01123	0.01123
	2613	0.01106	0.01106
	3869	0.01096	0.01096
	3795	0.01067	0.01067
	994	0.01055	0.01055
Birth size	2356	0.02254	0.02254
	2574	0.02235	0.02235
	4016	0.02219	0.02219
	3567	0.02200	0.02200
	1104	0.02189	0.02189
Pregnancy complication	3397	0.02557	0.02557
	5542	0.02474	0.02474
	3446	0.02450	0.02450
	5760	0.02446	0.02446
	2943	0.02383	0.02383
Mother's age	162	0.02842	0.02842
	666	-0.02800	0.02800
	608	0.02768	0.02768
	125	0.02746	0.02746
	620	0.02738	0.02738

Breast feeding	1020 5573 7697 2361 6496	0.00597 0.00576 0.00575 0.00569 0.00567	0.00597 0.00576 0.00575 0.00569 0.00567
Region	4305 1130 2689 2694 4311	0.05531 0.05488 0.05336 0.05304 0.05236	0.05531 0.05488 0.05336 0.05304 0.05236

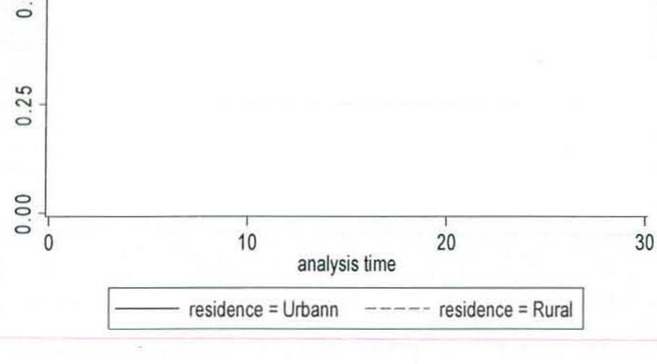
Table 11A: Test of proportional hazards assumption after stratified by region for the variables included in Table 4.3

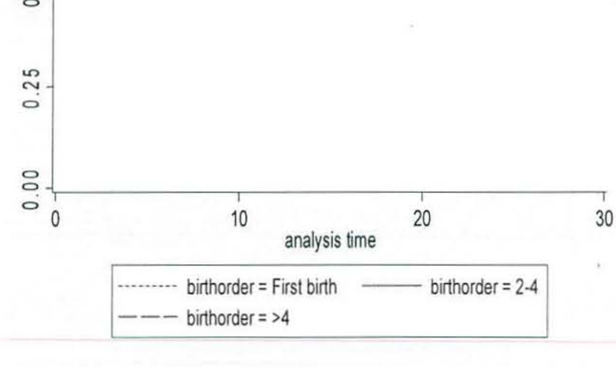
Covariates	rho	Chi-square	df	Sig.
Birth order				
First birth	0.014	0.12	1	0.725
>4	-0.031	0.61	1	0.433
sex	0.002	0.001	1	0.969
Birth interval				
<24	0.069	2.52	1	0.112
>47	0.006	0.02	1	0.891
Multiple births	-0.042	0.89	1	0.345
Pregnancy complication	-0.044	1.02	1	0.313
Antenatal visits	0.081	3.51	1	0.063
Size at birth				
Larger than average	0.045	1.10	1	0.294
Very large	0.053	1.48	1	0.224
Smaller than average	0.084	3.66	1	0.065
Very small	0.068	2.52	1	0.112
Mother's age				
<20	0.057	1.99	1	0.159
>34	0.036	0.88	1	0.349
Breast feeding	0.004	0.01	1	0.928
Global test		18.71	15	0.227

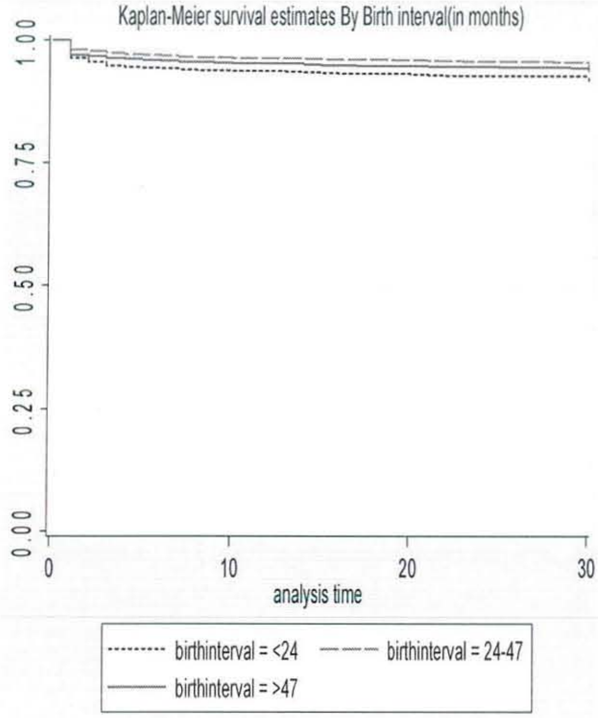
Figure 1A: The plot of the overall estimate of Kaplan-Meier survivor function

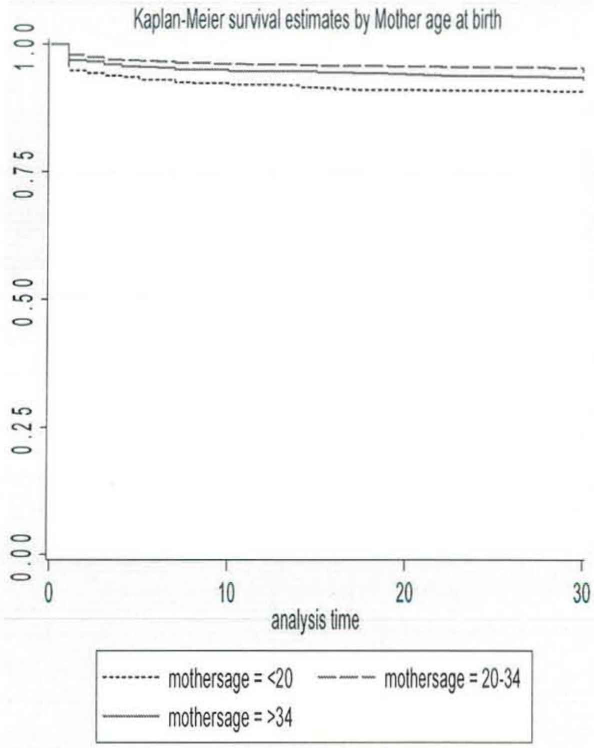


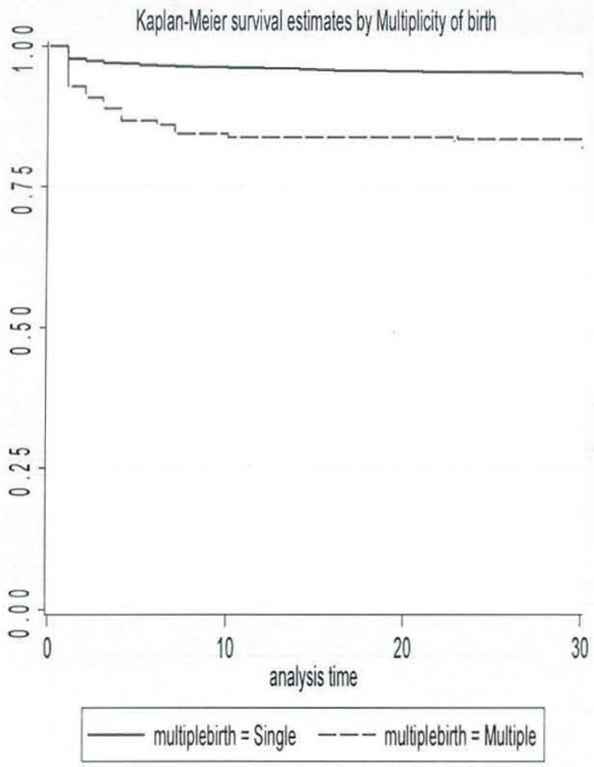
Figures 2A: Plots of Kaplan-Meier survivor functions, based on different covariates






Kaplan-Meier survival estimates By Birth interval(in months)
0.00
0.25
0.50
0.75
1.00
0
10
20
30
analysis time
birthinterval = <24
birthinterval = 24-47
birthinterval = >47


Kaplan-Meier survival estimates by Mother age at birth
0.00
0.25
0.50
0.75
1.00
0
10
20
30
analysis time
mothersage = <20
mothersage = 20-34
mothersage = >34


Kaplan-Meier survival estimates by Multiplicity of birth
0.00
0.25
0.50
0.75
1.00
0
10
20
30
analysis time
multiplebirth = Single
multiplebirth = Multiple

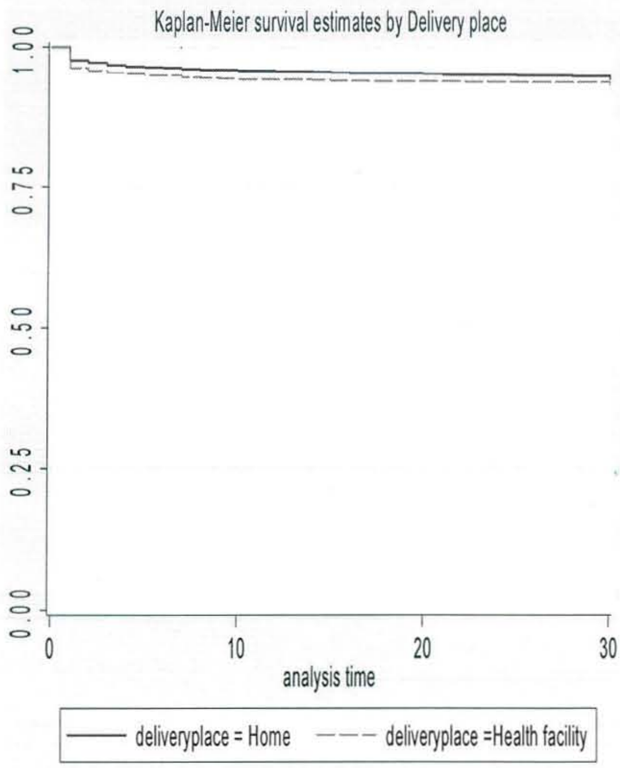
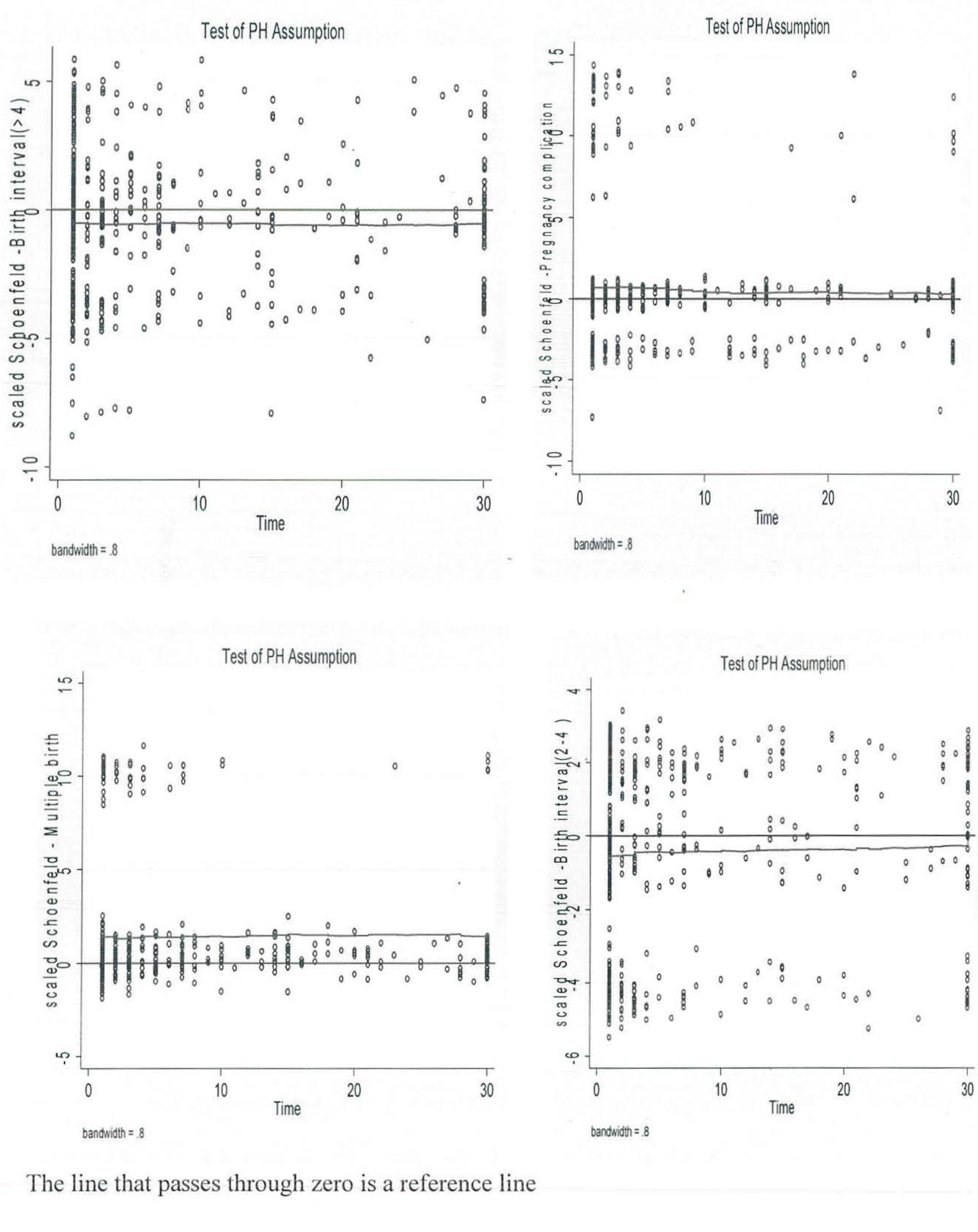
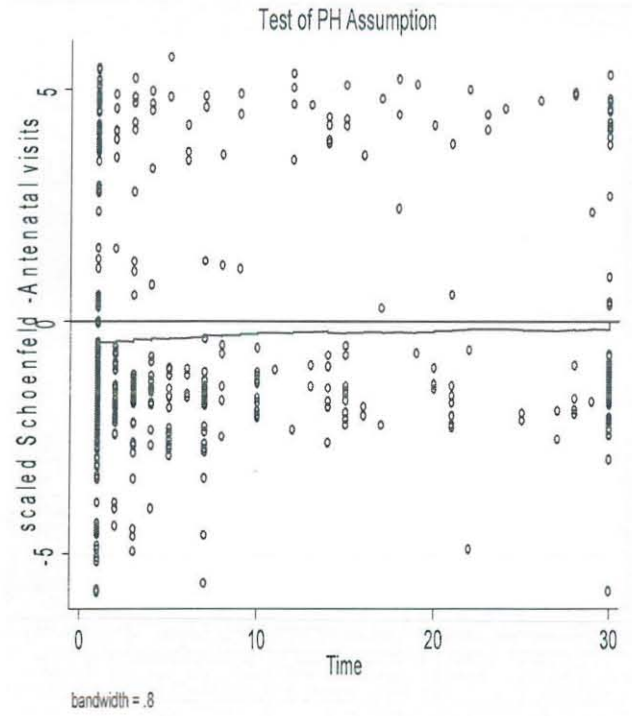
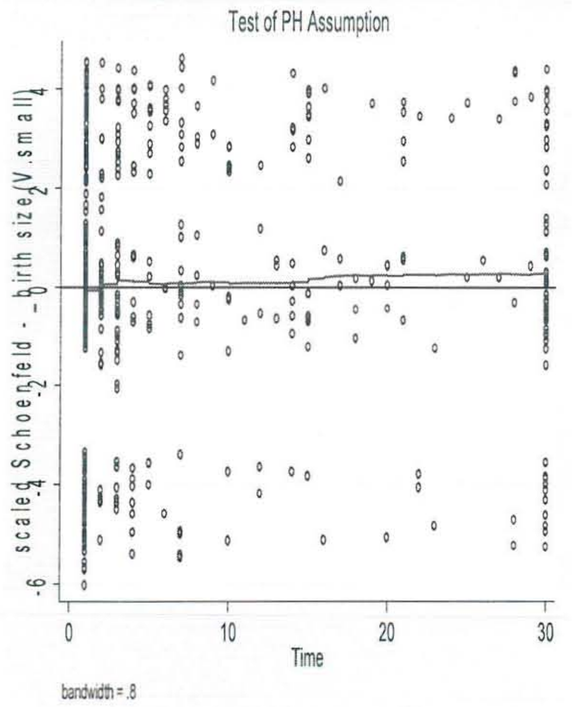

Kaplan-Meier survival estimates by Delivery place
0.00
0.25
0.50
0.75
1.00
0
10
20
30
analysis time
deliveryplace = Home
deliveryplace =Health facility

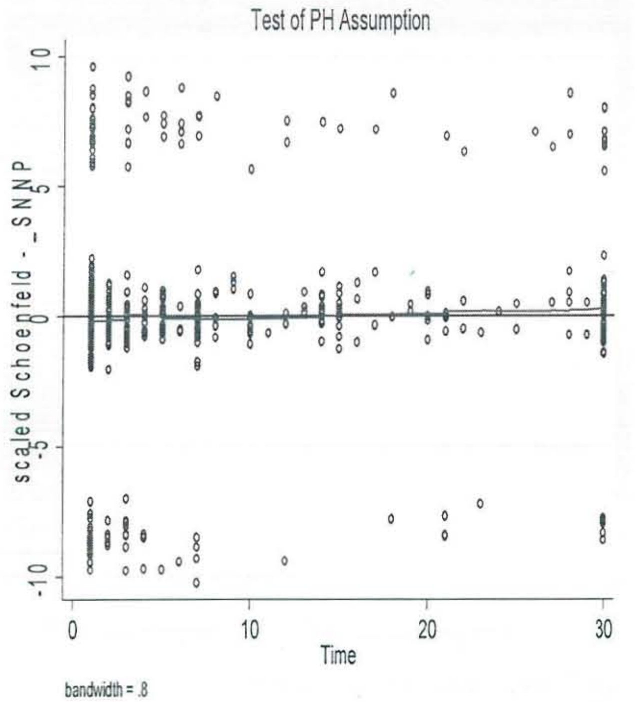
Figure 3A: Graphs of the Scaled Schoenfeld residuals and their lowess smooth obtained from the model in Table 8A for the some covariates.

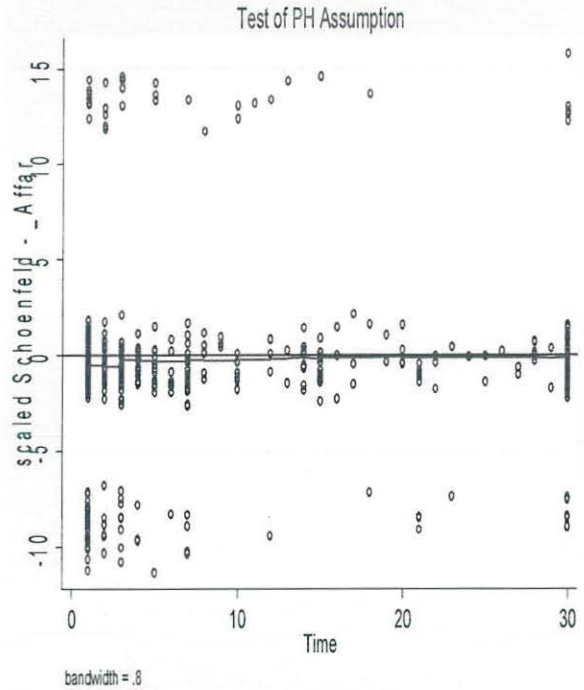


The line that passes through zero is a reference line









The line that passes through zero is a reference line