SURVIVAL ANALYSIS OF TIME-TO-DEATH FOR UNDER-FIVE CHILDREN IN ETHIOPIA: USING PARAMETRIC SHARED FRAILTY MODELS

By

Masrie Getnet

A Thesis Submitted to the Department of Statistics, College of Natural Science, Jimma University as a Partial Fulfillment for the Requirements of Master of Science (M.Sc.) Degree in Biostatistics

Jimma, Ethiopia

June, 2016

Survival analysis of time-to-death for under-five children in Ethiopia: Using Parametric Shared Frailty Models.

By

Masrie Getnet

Advisor: Professsor Kadi S.

Co-advisor: Zelalem Mehari (M.Sc.)

Jimma, Ethiopia

June, 2016

DECLARATIONS

I declare that this thesis is a result of my genuine work and all sources of materials used, for writing it, have been duly acknowledged. I have submitted this thesis to Jimma University in the partial fulfillment for the Degree of Master of Science in Biostatistics. The thesis can be in the university library to be made available to borrowers for reference. I solemnly declare that I have not so far submitted this thesis to any other institution anywhere for that award of any academic degree, diploma or certificate. Brief quotations from this thesis are allowed without requiring special permission provided that an accurate acknowledgement of the source is made. Requisites for extended quotations for the reproduction of the thesis in whole or in part may be granted by the head of the department of statistics when in his or her judgment the proposed use of the material is for a scholarly interest. In all other instances, however, permission must be obtained from the author.

Masrie Getnet

Signature: _____

Date: _____

Jimma University

Jimma, Ethiopia

DEPARTMENT OF STATISTICS, SCHOOL OF GRADUATE STUDIES
JIMMA UNIVERSITY

As thesis research advisors, we her by certify that we have read the thesis prepared by Masrie Getnet under our guidance, which is entitled "Survival analysis of time-to-death for under-five children in Ethiopia: Using Parametric Shared Frailty Models", in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including tables and figures are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the university library.

Kadi S. (Professor)	_____	_____
Advisor	Signature	Date
Zelalem Mehari (M.Sc.)	_____	_____
Co-Advisor	Signature	Date

As the members of the board of examiners of M.Sc. thesis open defense examination, we certify that we have read and evaluated the thesis and examined the candidate. Hence, we recommend that the thesis be accepted as it fulfills the requirements for the degree of Master of Science in Biostatistics.

_____	_____	_____
Name of Chairman	Signature	Date
_____	_____	_____
Name of Advisor	Signature	Date
_____	_____	_____
Name of Co-Advisor	Signature	Date
_____	_____	_____
Name of Internal Examiner	Signature	Date
_____	_____	_____
Name of External Examiner	Signature	Date

ACKNOWLEDGMENTS

First, I would like to thank the Almighty God. I would like to express my sincere gratitude to my advisor Professor Kadi S. and co-advisor Mr.Zelalem Mehari (M.Sc.) for their valuable advices. I'm deeply indebted to Mr. Getachew Tefera (President of Debre Berhan University), Mr. Akalu Banbeta (Lecturer in Jimma University, PhD scholar) and Dr. Getachew Seyoum (Senior Registrar Director of Jimma University) contributes a lot for the success of my M.Sc. study. Last but not least, I want to thank my family, friends, staff member of department of statistics of Jimma University and classmates, for their support and encouragement during my study.

DEDICATION

This thesis is dedicated to my beloved mother Belaynesh Gebeyaw and father Getnet Abate.

ABSTRACT

Background: under-five child mortality indicates the probability of dying between birth and exactly five years of age, expressed per 1,000 live births. Under-five child mortality is considered to be one of the key health indicators in an economy. This study aimed to investigate the potential risk factors affecting time-to-death of under-five children in Ethiopia using parametric shared frailty models where region were used as a clustering effect in the model.

Methods: Parametric shared frailty models have been used with three baseline hazard function (Weibull, Log-logistic, Log-normal) and two frailty distributions (Gamma, Inverse-Gaussian). From 2011 Ethiopian Demographic Health Survey (EDHS) 9433 under-five children were included from nine regional states and two city administrations. Data were analyzed using statistical software such as: R version 3.2.5 and STATA version 12.0.

Results: The median death time of under-five children in Ethiopia was 12 months. The clustering effect was significant and Log-normal-Inverse Gaussian shared frailty model was preferred over Weibull and Log-logistic Gamma shared frailty models based on Akaike Information Criterion (AIC) and graphical evidence. The result showed women's educational level, wealth index, type of births, total children ever born, preceding birth intervals and place of delivery were significant, where as sex of household head and religion were not significant covariates for under-five child mortality in Ethiopia.

Conclusion: The result suggested that the timing of death of under-five children from different region had different pattern, since there was a frailty (clustering) effect on the time-to-death of under-five children among regions of Ethiopia.

Key Words: Survival data analysis, Parametric shared frailty models, Under-five mortality, Time-to-death, Clustering effect, Ethiopia.

ACRONYMS

AFT	Accelerated Failure Time
AIC	Akaike Information Criterion
CDF	Cumulative Density Function
CSA	Central Statistical Agency
DF	Degree of Freedom
DHS	Demographic and Health Survey
EDHS	Ethiopian Demographic and Health Survey
FMOH	Federal Ministry of Health
HR	Hazard Ratio
InvGau	Inverse Gaussian
KM	Kaplan and Meier
MDG	Millennium Development Goal
Pdf	Probability density function
PH	Proportional Hazard
UNICEF	United Nations Children's Fund
UN	United Nation
USAID	United States Agency for International Development
WHO	World Health Organization

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

1.1. Background

Under-five mortality is the probability that a child will die before reaching the age of five (IGME, 2015). Under-five mortality is a key indicator of child well-being, including health and nutrition status. It is also a key indicator of the coverage of child survival interventions, social and economic development (UNICEF, 2014). Bryce *et al.* (2006), Sewanyana and Younger (2008) observed that reducing under-five mortality is one of the Millennium Development Goals and in fact it is the fourth Millennium Development Goal (MDG4) which states that under-five mortality are to be reduced by two-thirds between 1990-2015. While birth history data have been widely used for estimating under-five mortality at a national level, there are relatively few instances (Bangha and Simelane, 2007; Storeygard *et al*., 2008; Singh *et al*., 2011; Bauze *et al.*, 2012) where they have been used to estimate mortality at a fine sub national level, due to primarily concerns about small sample sizes.

Globally, under-five deaths have dropped from 12.7 million in 1990 to 5.9 million in 2015. This is the first year that the figure has gone below the 6 million mark. New estimates in Levels and Trends in Child Mortality Report 2015 released by UNICEF, the World Health Organization, the World Bank Group, and the Population Division of UNDESA, indicate that although the global progress has been substantial, 16,000 under-five children still die every day and 53 percent drop in under-five mortality is not enough to meet the Millennium Development Goal of a two-thirds reduction between 1990 and 2015. Kyaddondo (2012) described the under-five child mortality rate in Sub-Saharan Africa as a high mortality rate and that of Southern Asia as moderate. The above mentioned concerns are some of the reasons why under-five mortality has attracted many researchers in order to identify the factors strongly associated with high under-five child mortality rate and to evaluate the various government interventions.

In Ethiopia, under-five mortality rate has declined by two thirds from the 1990 figure of 204/1,000 live births to 68/1,000 live births in 2012, thus meeting the target for Millennium Development Goal 4 (MDG 4) on child survival three years ahead of time. In absolute numbers the under-five deaths in Ethiopia has declined from nearly half a million 444,000 a year in 1990, to about 196,000 in 2013.

About 44% of the childhood deaths occur within the first 28 days of life, thus increasingly accounting for a larger proportion of the under-five deaths. Over two-thirds of under-five deaths in Ethiopia are caused by few and easily preventable conditions; mainly infections, neonatal conditions and malnutrition.

Kleinbaum DG. *et al*. (1996) and Hosmer, D., and Lemeshow *et al.* (1998), the origin of survival analysis goes back to mortality tables from centuries ago. Survival analysis is a statistical method for data analysis where the outcome variable of interest is the time to the occurrence of an event (Klembaum, 1996). Hence, survival analysis is also referred to as "time-to-event analysis", which is applied in a number of applied fields, such as Medicine, Public Health, Social Science, and Engineering. To measure heterogeneity caused by unobserved covariates it is necessary to include random effect term or frailty into the model. Thus the frailty model is a random effect model for time-to- event data which is an extension of the Cox proportional hazard model. Frailty models are substantially promoted by its applications to multivariate survival data in a seminal paper by (Clayton, 1978) without using the notion frailty. The term frailty was first coined by Vaupel *et al.* (1979).

In this study, parametric shared frailty models used, by assuming that time-to-death of under-five children within the same cluster (region) shares similar risk factors, which could be taken care of the frailty term at regional level. This model is a conditional independence model where the frailty is common to all individuals in a cluster and therefore responsible for creating dependence between event times. Also, parametric frailty models are used to investigate the relationship between different potential covariates and time-to-death of under-five children for clustered survival data with a random right censoring. And, accelerated failure time models also fit by using Weibull, Log-logistic and Log-normal baseline distributions to compare and get the best model which fits the time-to-death of under-five children data appropriately on 2011 EDHS dataset . For the frailty distribution that have been assumed Gamma, Inverse-Gaussian and the comparison of different distributions selected by using AIC. It also investigated the causes for the reduction of under-five child mortality and identifies the more important factors associated with the decrease of under-five mortality by using a survival analysis of parametric shared frailty models.

1.2. Statement of the Problem

The variation in under-five mortality rates between the developing and developed nations is more than 78-fold, from a high of 180 per 1,000 live births in Angola to only 2.31 per 1,000 live births in Singapore (World Fact book, 2011). Evidence shows that only about one-third of all countries in Africa show a decline of 30% or more in under-five mortality, while a number of countries sadly show a considerable increase (Becher, 2010). Sub-Saharan Africa has the world's highest child mortality rate, which is 86 deaths per 1,000 live births in 2015 (UN, 2015). Mortality trends from EDHS surveys conducted in 2000, 2005, and 2011 shows that under-five mortality rates obtained by the surveys evidence was a continuous declining trend in under-five child mortality. Under-five mortality decreased from 166 deaths per 1,000 live births in the 2000 survey to 88 deaths per 1,000 live births in 2011. Even there were a decline number of under-five child mortality, still the number in Ethiopia is 68 deaths per 1,000 live births.

As the era of the MDGs comes to an end in 2015, a new framework for global development will be put in place. The Post-2015 Development Agenda will culminate in the formulation of a new set of goals and targets. One goal of sustainable development is reducing the under-five mortality rate to 25 or less deaths per 1,000 live births (UNICEF, 2015). So, Ethiopia is the one to meet the Post-2015 Development Agenda.

Most researches were conducted by using the Cox PH model for time-to-death of under- five children. The model is used to show the effects of covariates with time. It does not control the risk factor for some relevant covariates that are often unobservable or difficult to measure even unknown (Wienke, 2010).

This research aimed to explore factors that affect time-to-death of under-five children in Ethiopia using parametric shared frailty models. Frailty term was added to account the correlation which comes from the cluster, accounts unobservable random effect. Thus, the study aimed to address the following research questions:

I. What are the important predictors of time-to-death of under-five children in Ethiopia?
II. Is there any heterogeneity of under-five children mortality in regional states of Ethiopia?
III. Which baseline distributional assumption among the Weibull, Log-normal and Log-logistic; as well as frailty distributions, the Gamma and Inverse-Gaussian distributions well describe the time-to-death of under-five children in Ethiopia?

1.3. Objectives of the Study

1.3.1. General Objective

The main aim of this study is to model time-to-death of under-five children in Ethiopia using Parametric Shared Frailty Models.

1.3.2. Specific Objectives

I. To determine the impact of important demographic, socio-economic and environmental variables on time-to-death of under-five mortality in Ethiopia.
II. To assess the clustering effect in determining the factors associated with time-to-death of under-five children in Ethiopia.
III. To estimate the survival time and compare survival curves among the different covariates of under-five children in Ethiopia.

1.4. Significance of the Study

The significance of this study will provide information on under-five child mortality in Ethiopia and its determinant factors. Specifically;

I. To provide information about the covariates or risk factors of under-five mortality and recommend the way for the government and stakeholders on which factor/s they give a better attention.
II. To provide information to government and concerned bodies in setting policies and strategies.
III. Useful for further studies related to under-five child mortality.

2. LITERATURE REVIEW

2.1. Under-five mortality

Child survival interventions were launched by the United Nations Children's Fund (UNICEF) and WHO in the 1980s after the world economic meltdown. Globally, tremendous progress has been made on the reduction of under-5 mortality. However, this has been unequally distributed. At the regional level, the decline in under-five mortality rates between 1990 and 2012 were over 60% for three WHO regions: the Americas, European and the Western Pacific regions. Mortality rates among children under the age of five remain strikingly high throughout the majority of Sub-Saharan Africa. This means that the African region has increasing share of under-five deaths (WHO, 2012).

By 2050, consequently, 37% of the world's children under age five will live in Sub-Saharan Africa; while close to 40% of all live births will take place in that region. This is very hazardous if the risk and the exposure rates are not addressed. There is a possibility that the mortality numbers might stagnate or even increase if no much progress will take place in the African region. Despite Sub-Saharan Africa's relatively high rates of under-five mortality, there are signs of progress in the region. The pace of decline in the under-five mortality rate has accelerated over time, with an increase from 0.8 % per year in 1990-1995 to 4.1% per year in 2000-2012. Currently, childhood mortality remains a big issue for these developing countries, especially as researchers attempt to distinguish what factors contribute to the high levels (WHO, 2012).

2.2. Determinants of under-five mortality

Mosley *et al.* (1984), an analytical framework for the study of child survival in developing countries proposed an analytical framework for the study of determinants of child survival in developing countries. The study incorporates both social and biological variables and integrates research methods used by social and medical scientists to study child survival. The frame work is based on the premise that all social and economic determinants of child mortality necessarily operate through a common set of biological mechanism or proximate determinants that exert an impact on mortality.

Mosley and Chen (1981) also viewed morbidity and mortality of the child as being influenced by underlying factors of both biological and socio-economic, operating through proximate determinants. Jinadu *et al. (1991),* in a study, found dirty feeding bottles and utensils, inadequate disposal of household refuse and poor storage of drinking water to be significantly related to the high incidence of diarrhea. Studies have also shown maternal education to be a significant factor influencing child survival (Caldwell, 1979; Orubuloye and Caldwell, 1975; Meegama, 1980; Tawiah, 1979; Adewuyi and Feyisetan, 1988).

Hobcraft *et al.* (1984), identified five main social-economic factors that influence under the age of five survival and these include mother's education, mother's work status, husband's occupation, husband's education and type of place of residence. They used a simple tabular analysis followed by a multivariate approach in order to assess the relative importance of each of the five variables. The study used the World Fertility Survey data that was based on enquiries from 28 developing countries. In Asian countries, mother's level of education was seen to be strongly associated with mortality of the child during the first five years of their life. In America, results indicated that the husband's education was most important and in a few African countries, infant mortality was relatively strongly associated to husband's occupation and education.

Sengonzi and Shannon (2002) examined the effect of female migration on the health and survival of the most vulnerable migrants (infants and children) in Uganda. He used the Log-logistic regression techniques to analyze the probability of a child surviving up to the age of five. Results showed that 10% of the children die before age five and within group difference in mortality exists in urban and rural children depending on their mother's migration status. Other variables like parent's education, household size, household hardship, and mother's age at first birth, duration of breast feeding and place of delivery were seen to be significant.

In the Matlab area of Bangladesh, DaVanzo *et al.* (2008) in an in-press article find that shorter intervals are associated with higher mortality after controlling for other correlates of under-five mortality. The effects after the first month appear due to sibling competition since effects of short intervals are greater if the older sibling was still alive but many relationships are found to be consistent with maternal depletion. Effects were also greater if the interval began with a live birth than with a non-live birth. When compared with inter-outcome (pregnancy to conception) intervals, significant results were found for intervals shorter than 24 months for early neonatal mortality, for intervals shorter than 36 months for late neonatal mortality, post-neonatal mortality

and child (age one to four years) mortality. These effects persist when potentially confounding factors (prematurity, breastfeeding, and immunizations) and demographic and socioeconomic variables are controlled. Short subsequent inter pregnancy intervals are also associated with a significantly higher risk of mortality for the index child. This study used a large, high-quality longitudinal dataset of 145,000 pregnancy outcomes gathered over a period of more than 20 years in an experimental setting.

The major causes of under-five mortality in Ethiopia were ARI/Pneumonia (21%), diarrhea (14%), complications of prematurity (12%), intra partum related events (birth asphyxia) (9%), meningitis (6%), and measles (4%). Other causes of death (including deaths due to severe malnutrition) accounted for 18% of under-five mortality (UNICEF, 2012).

2.3. Survival Analysis

Survival analysis is a statistical method or tool used to analyze time to events data. The most common event of interest in the earlier development of research was death; this therefore suggests the name of the research area Survival analysis. Survival analysis is a highly active area of research with application in many fields of study which include engineering, physical, biological and social sciences (Cleves *et al.*, 2008, Klein and Goel, 1992). An event is an outcome on an individual unit that is a scientific interest in different studies like sociology, biology, demography, medicine, employment among other fields.

2.3.1. Frailty Models

The notion of frailty provides a convenient way to introduce random effects, association and unobserved heterogeneity into models for survival data. In its simplest form, a frailty is an unobserved random proportionality factor that modifies the hazard function of an individual, or related individuals. In essence, the frailty concept goes back to work of Greenwood and Yule (1920) on "accident proneness’’.

The frailty distributions most often applied are the Gamma distribution (Clayton 1978; Vaupel *et al.* 1979), the positive stable distribution (Hougaard, 1986b), a three-parameter distribution (Hougaard, 1986a), the compound Poisson distribution (Aalen, 1988, 1992) and the Log-normal distribution (McGilchrist and Aisbett, 1991). Frailty models have been applied to the analysis of event history data, including the study of age at time of death for individuals in terms of population (Zelterman, 1992). Flinn and Heckman (1982) used a Log-normal distribution for

frailty, whereas Vaupel *et al*. (1979) assumed that frailty is distributed across individuals as a Gamma distribution. Recent research has addressed the problem of heterogeneity. Hougaard (1986) suggested the power variance function (PVF) distribution which includes Gamma, Inverse-Gaussian as frailty model. Hedeker *et al*. (1996) discussed a frailty regression model for the analysis of correlated grouped time survival data.

Multivariate frailty models have been used frequently for modeling dependence in multivariate time-to-event data (Clayton, 1978; Hougaard, 2000; Oakes, 1982a; Yashin *et al.,* 1995). The aim of the frailty is to take into account the presence of the correlation between the multivariate survival times. Kazembe *et al.* (2012) and Omariba *et al.* (2007) used the Weibull unobserved heterogeneity (frailty) survival model on the 1998 Kenya DHS data to analyze the determinants of under-five mortality in Kenya. They compared the results of the standard Weibull survival model to the frailty Weibull model. They also mentioned that non-frailty models are biased due to the violation of the statistical assumption of independence. The shared frailty model is relevant to event times of related individuals, similar organs and repeated measurements. Individuals in a cluster are assumed to share the same frailty, which is why this model is called shared frailty model. It was introduced by Clayton (1978) and extensively studied in Hougaard (2000).

The Logistic-model is the most popularly used model because it assumes that child survival is a binary response: child is dead or alive, Kazembe *et al*. (2012) . But it ignores time to event and therefore fails to include the exposure to the risk of the event overtime. Other models like the Cox proportional hazard model by Cox (1972) are widely used to deal with time-to-event data and their relevancy on research in survival analysis in demography and related fields has increased over the years. The Cox model has several advantages and some of them are; (a) ability to include analysis of censored and truncated data (b) ability to include analysis of time varying covariate effects and lastly (c) the extensions of the Cox regression models with the inclusion of random effects and flexible modeling through semi-parametric and non-parametric approach. There is an advantage of these models over the ordinary generalized linear models as demonstrated by Kazembe *et al*. (2012). The random effects allows for the modeling of the unobserved covariates (and inherent heterogeneity) or frailty. These factors may be at a family, district, community, regional or national level and these cannot be ignored because they have an effect on the outcome.

3. DATA AND METHODS

3.1. Study area

This study is conducted in the place where Ethiopia on under-five children surveyed in 2011 EDHS. Ethiopia is situated in the horn of Africa covering about 1.1 million square kilometers area. The country shares border with Djibouti, Eritrea, Kenya, Somalia, South Sudan and Sudan. It has great geographical diversity, with high peaks ranging from 4,550 m above sea level to low depressions of 110 m below sea level.

Ethiopia is the second most populous country in Africa with a total population of 90.1 million, of which more than 84% live in rural areas. It has a broad geographic spectrum and over 80 distinct ethnic groups. Ethiopia's population is young with 45% being under the age of 15 and 14.6% (13.2 million) being under the age of five. The average household size is 4.8 people, with the urban population having a smaller mean household size (3.6) than the rural population (5.1) (CSA, 2014). Life expectancy at birth is 64 for both sexes with 65 years for women and 62 years for men (WHO, 2014).

The country is divided into nine administrative regions, namely: Tigray, Affar, Amhara, Oromiya, Somali, Benishangul-Gumuz, Southern Nations Nationalities and Peoples (SNNP), Gambela and Harari regional states and two city administrations, namely: Addis Ababa and Dire Dawa. The regions are divided into zones, woredas and kebeles which are the lowest level of administration. The woreda is the most important local government structure, acting as the basis for most administration and management. Currently there are 956 woredas, representing around 100,000 people each and 16,541 kebele (FMOH, 2014/15), with average catchment populations of 5,000 people each.

Figure 3.1: The map of Ethiopia (Reinikka and Collier, 2001).

3.2. Data Source

The source of the data used in this study was the 2011 Ethiopia Demographic and Health Survey (EDHS, 2011) conducted in Ethiopia as part of the worldwide demographic and health survey project. The 2011 Ethiopia Demographic and Health Survey were conducted by the Central Statistical Agency (CSA) with the support of the Ministry of Health. This was the third

Demographic and Health Survey DHS conducted in Ethiopia, under the worldwide measure DHS project, a USAID-funded project providing support and technical assistance in the implementation of population and health surveys in countries worldwide. The primary objectives of the 2011 EDHS were to provide up-to-date information for planning, policy formulation, monitoring, and evaluation of population and health programs in the country.

3.3. Sampling 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. 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.The sample size in this study is 9433 total under-five children. Information on under-five child mortality was found from the birth histories those were included in the survey. Since the interest of this study is about under-five children.

3.4. Variables in the study

3.4.1. Dependant variable

The dependent variable of the study is the duration of time from date of birth until date of death, which is measured in months. The censored observations denoted by 0 (under-five children who survived in the past 59 months), whereas event indicated by 1 (under-five children who died before reaching fifth birth day).

3.4.2. Independent variables

The independent variables considered in this study to investigated time-to-death of under-five children were: women's education, wealth index, type of births, total children ever born, preceding birth intervals, place of delivery, sex of household head and religion. Table 3.1, describes these variables with their coding.

Table 3.1: Description of independent variables used in the analysis

Variables	Description	Categories
Women's education	Women's educational level	0= No education;1= Primary; 2= Secondary and above
Wealth index	Household wealth index	0= Poor; 1=Middle; 2=Rich
Type of births	Type of births	0= single birth, 1= multiple birth
Total children ever born	Total children ever born	0= 1-3 children ; 1= 4-6 children ; 2= 7-9 children ; 3= ≥ 10 children
Preceding birth intervals	Preceding birth intervals	< 24 months =0, 24-47 months =1,≥48 months =2
Place of delivery	Place of delivery	Health facility=0,elsewhere=1
Sex of household head	Sex of household head	0= male; 1=female
Religion	Religion	0= Muslim, 1= orthodox, 2= Protestant, 3= other

NB: For this research Region is considered as a clustering effect in frailty model.

3.5. Methods of Data Analysis

3.5.1. Survival Analysis

Survival analysis is used to describe the analysis of data in the form of times from a well-defined time origin until the occurrence of some particular event or end point. A survival time is censored if all is known that is began or ended within some particular interval of time, and thus the total spell length (from entry time until transition) is not known exactly (Klein and Moeschberger,2003). We may distinguish the following types of censoring:

- **Right censoring:** at the time of observation, the relevant event (transition out of the current state) had not yet occurred (the spell end date is unknown), and so the total length of time between entry to and exit from the state is unknown. Given entry at time 0 and observation at time t, that the completed spell is of length T > t.

- **Left censoring:** left-censored data are those for which it is known that exit from the state occurred at some time before the observation date, but it is not known exactly when.

- **Interval censoring:** Interval-censoring occurs when the event of interest is known only to occur within a given period of time. Both left-censored and right-censored data are special cases of interval-censored data, where the lower endpoint is 0 and the upper endpoint is ∞, respectively.

There are generally three reasons why censoring may occur:

(1) A person does not experience the event before the study ends.

(2) A person is lost to follow-up during the study period.

(3) A person withdraws from the study because of death (if death is not the event of interest).

There are two basic functions that are very important in the whole theory of survival analysis. These are the survival and hazard function.

3.5.1.1. Survival Functions

Given a random variable T that denotes the survival time, the basic quantity employed to describe time-to-event phenomenon is the Survival Function S(t), and it is defined as:

S(t) = P[T > t] = the probability that an individual survives beyond time t.

Since a unit either fails, or survives, and one of these two mutually exclusive alternatives must occur, the survival function is:

$$S(t) = 1 - F(t) \quad \ldots\ldots(1)$$

Where, F(t) is CDF. If T is a continuous random variable, then S(t) is a continuous, strictly decreasing function. The survival function is the integral of Pdf, that is:

$$S(t) = \int_t^{\infty} f(u)du \quad \ldots\ldots(2)$$

$$f(t) = -\frac{ds_{(t)}}{dt} \quad \ldots\ldots(3)$$

3.5.1.2. Hazard Function

The hazard function is the probability that an individual will experience an event (like, death) within a small time interval, given that the individual has survived up to the beginning of the interval. It is proportional to the instantaneous "risk of failing" at any time *t*, given that an individual has lived at least to time *t*. The hazard function is denoted by h(t) and is defined by the following equation:

$$h(t) = \lim_{h \to 0} \frac{P[t \le T \le t + h | T \ge t]}{h}$$

$$h(t) = f(t)/S(t) \quad \ldots\ldots\ldots\ldots(4)$$

Since h(t) is also equal to the negative of the derivative of ln{S(t)}, we have the useful identity:

$$S(t) = e^{-\int_0^t h(t)dt} \quad \ldots\ldots\ldots\ldots(5)$$

If we let

$$H(t) = \int_0^t h(t)dt \quad \ldots\ldots\ldots\ldots(6)$$

be the CDF, we then have S(t) = $e^{-H(t)}$. Two other useful identities that follow from these formulas are:

$$h(t) = -(d \ln S(t))/dt \quad \ldots\ldots\ldots\ldots (7)$$

$$H(t) = -\ln S(t) \quad \ldots\ldots\ldots\ldots(8)$$

3.5.1.3. Non-parametric Methods

Survival data are summarized through estimates of the hazard and survival function (Le and Le, 1997, Miller Jr, 2011). The methods used to estimate these functions are known as non-parametric or distribution free methods. The aim of non-parametric estimation of the survival function is to come up with graphical summaries of the survival times for a given group of individuals considered in the study. These graphical summaries are for the hazard and the survival function. After estimating the survival function, the median and other percentiles can be obtained which help to give a more detailed analysis (Cleves *et al*., 2008, Hanagal, 2011). Among the various non-parametric tests one can find in the statistical literature, the (Mantel- Haenzel, 1959) test, currently called the "log-rank" test will be used. Nowadays the Kaplan- Meier method for estimating survival curves and the log-rank test for comparing two estimated survival curves are the most frequently used statistical tools in medical reports on survival data.

3.5.1.3.1. Kaplan-Meier estimator

Kaplan and Meier (1958) proposed an estimator called as Kaplan-Meier or Product Limit estimator which provides quick, simple estimates of the survival function. It can be regarded as a point estimate of the survival function at any time t. The Kaplan-Meier estimator incorporates information from all of the observations available, both censored and uncensored, by considering any point in time as a series of steps defined by the observed survival and censored times. The survival curve describes the relationship between the probability of survival and time.

A general expression for the KM estimates can be written. Assume that we have n individuals on test and order the observed lifetimes for these n individuals from $t_{(1)}$ to $t_{(n)}$. Some of these are actual failure times and some are running times for individuals taken off test before they die. Suppose there are r deaths have occurred, and the ordered death times are $t_{(1)},\ldots, t_{(r)}$, where $r \leq n$ .The number of individuals who are alive just before time $t_{(j)}$, including those who are about to die at this time, will be denoted by n_j , j = 1,2,...,r, and d_j will denote the number who die at this time. The probability that an individual dies during the interval from $t_{(j)}- \delta$ to $t_{(j)}$ is estimated by $\frac{d_j}{n_j}$ where δ is an infinitesimal time interval. The corresponding estimated probability of survival through that interval is $\frac{n_j - d_j}{n_j}$. The probability of surviving through the interval from t(k) to t(k+1), and all preceding intervals, and leads to the Kaplan-Meier estimate of the survival function, which is given by:

$$\hat{S}_{(t)} = \prod_{j=1}^{k} \frac{n_j - d_j}{n_j} \quad \ldots\ldots(9)$$

for $t(k) \leq t < t(k+1)$; k = 1,.., r.

The estimated variance of the estimate of S(t) and is given by:

$$\mathrm{Var}(\hat{S}_{(t)}) \approx [\hat{S}_{(t)}]^2 \sum_{j=1}^{k} \frac{d_j}{n_j(n_j - d_j)} \quad \ldots\ldots(10)$$

The standard error of the KM estimate of survival function is:

$$\text{s.e}\,(\hat{S}_{(t)}) \approx \hat{S}_{(t)} \{\sum_{j=1}^{k} \frac{d_j}{n_j(n_j - d_j)}\}^{1/2} \quad \ldots\ldots(11)$$

for $t(k) \leq t < t(k+1)$; k = 1,.., r.

3.5.1.3.2. Log-rank test

The log rank test, developed by Mantel and Haenszel, is a non-parametric test for comparing two or more independent survival curves. It involves the calculation of observed and expected frequencies of failures in separate time intervals. 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. It can be generalized to accommodate other tests that are equally used sometime in practice such as Generalized Wilcoxon test, Tarone-Ware test, and Peto-Peto Prentice test. Each of these tests uses different weight to adjust for censoring that is often encountered in survival data. The log rank test statistic for comparing two groups is given by:

$$X_{LR} = \frac{\left(\sum_{i=1}^{m} d_{1i} - \sum_{i=1}^{m} \hat{e}_{1i}\right)^2}{\sum_{i=1}^{m} \hat{v}(\hat{e}_{1i})} \ldots\ldots(12)$$

Where: m is the number of rank ordered event (death) times, d_{ji} is the number of people experiencing the event at time $t_{(i)}$ in Group j, n_{ji} is the number of people at risk in group j at time $t_{(i)}$, d_i is the total number experiencing the event in both groups, $\hat{e}_{ji} = \frac{d_i n_{ji}}{n_i}$ is the estimated expected number of individuals experiencing the event at $t_{(i)}$ in group j, $\hat{v}_{(\hat{e}_{ji})} = \frac{n_{1i} n_{2i} d_i (n_i - d_i)}{n_i^2 \, (n_i - 1)}$ is the estimated variance of $\hat{e}_{ji}$, n_i is the number of individuals at risk in both groups 1 and 2 just prior to event time $t_{(i)}$.

3.5.1.4. Semi-parametric models

3.5.1.4.1. The Cox-proportional hazard model

A Cox model is a statistical technique for exploring the relationship between the survival time and several explanatory variables. The most commonly used regression model is the Cox-proportional hazard model. With this model the distribution for the baseline hazard function is not specified implies vary with time and that is why it is called a semi-parametric model. The Cox-proportional hazard model is a more general model in modeling the hazard and survival function because it does not place distributional assumptions on the baseline hazard. The Cox model was introduced by Cox (1972). It has the from:

$h_i(t \mid x) = h_o(t) \exp(X_i^T \beta)$……..(13)

Where , $h_o(t)$ is the baseline hazard function; X_i is a vector of covariates and β is a vector of parameters for fixed effects. The corresponding survival function for Cox-PH model is given by:

$S(t,X) = [S_o(t)]^{\exp\{\sum_{i=1}^{p} \beta_i X_i\}}$ ……..……(14)

where, $S_o(t)$ is the baseline survival function. The measure of the effect of the given covariates on survival time is given by the hazard ratio. Consider a categorical variable with two levels say X = 1 and X = 0, then the hazard ratio for the two groups is defined as:

$HR = \frac{h(t|X=1)}{h(t|X=0)} = \exp(\beta)$……..……(15)

When HR = 1, it implies that the individuals in the two categories are at the same risk of getting the event, when HR > 1, it implies that the individuals in the first category (X = 1) are at a high risk of getting the event and if HR < 1, the individuals in the second category (X = 0) are at a high risk of getting the event.

3.5.1.4.1.1. Parameter Estimation in Cox PH Model

The regression coefficients in the proportional hazards Cox model, which are the unknown parameters in the model, can be estimated using the method of maximum likelihood. In Cox proportional hazards model the vector of parameters β can be estimated without having any assumptions about the baseline hazard $h_{0(t)}$. Consider n independent individuals, the data that we need for the Cox proportional hazard model is represented by triplet (t_i, δ_i, x_i), i=1, 2, . . . n Where: t_i is the survival time for i^{th} individual, δ_i an indicator of censoring for the i^{th} individual given by 0 for censored and 1 for event/death, x_i a vector of covariates for individual *i*. Then, the full maximum likelihood is defined as:

$L(\beta) = \prod_{i=1}^{n} h(t_i, x_i, \beta)^{\delta_i} S(t_i, x_i, \beta)$ ……..……(16)

Where: $h(t_i, x_i, \beta) = h_o(t_i) e^{\beta' X_i}$ is the hazard function for individual i, $S(t_i, x_i, \beta) = S_o(t_o) e^{\beta' X_i}$ is the survival function for individual i. The maximum likelihood becomes:

$L(\beta) = \prod_{i=1}^{n} (h_o(t_i) e^{\beta' X_i})$ ……..……(17)

Full maximum likelihood requires that by maximize (17) with respect to the unknown parameter of interest β and unspecified baseline hazard and survival functions. This indicates that unless explicitly specify the baseline hazard $h_0(t)$. One cannot obtain the maximum likelihood estimators for the full likelihood. But, Cox (1972) proposed using an expression he called *"*partial likelihood function" that depends only on the parameter of interest.

3.5.1.4.1.2. Partial Likelihood

The general methodology used for proportional hazards which cancels out the baseline function is also used in determining the partial likelihood. To illustrate, the partial likelihood of an event occurring at time t for an individual can be written as:

P (individual *i* has experienced an event at time $t_{(i)}$ / one event at time $t_{(i)}$) = L

$$L = \frac{h(t,x_i)}{\sum j\epsilon R_t(i) h(t,x_i)} = \frac{h_o(t)e^{\beta' X_i}}{\sum j\epsilon R_t(t) h_o(t) e^{\beta' X_j}} \quad \text{(18)}$$

When there are no tied times assumed, the partial likelihood is defined over all failure time $t_{(i)}$ that i=1,2,. . ., m & given as:

$$L_p(\beta) = \prod_{i=1}^{m} \frac{\beta' X_i}{\sum j\epsilon R_t(i) e^{\beta' X_j}} \quad \text{(19)}$$

Where the product is over m distinct ordered failure times and $X_{(i)}$ denotes the value of the covariate for the subject with ordered survival time $t_{(i)}$. The log partial likelihood function is:

$$l_p(\beta) = \sum_{i=1}^{m} [\beta' X_i - \ln(\sum j\epsilon R_t(i) e^{\beta' X_j})] \quad \text{(20)}$$

The maximum partial likelihood estimator can be obtained by differentiating the right hand side of (20) with respect to the component of β, setting the derivative equal to zero and solving for the unknown parameters. However, this partial likelihood function methods are based on the assumption that there are no tied values among the observed survival times. But, in most real situations tied survival times are more likely to occur. In addition to the possibility of more than one death at a time, there might also be more than one censored observations at a time of death.

3.5.1.4.1.3. The Breslow approximation

This approximation is proposed by Breslow and Peto to modify the partial likelihood and has the form:

$$l_B(\beta) = \prod_{i=1}^{m} \frac{exp(\beta' S_i)}{[\sum l\epsilon R_t(i) e^{\beta' X_i}]^{d_i}} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(21)$$

Where: d the number of deaths occurred at time t_i, S the sum of covariates over d_i subjects at time t_i, then the partial log of (21) is given as:

$$l_B(\beta) = \sum_{i=1}^{m} [\beta' S_i - \mathrm{d_i} \ln(\sum j\epsilon R_t(i) e^{\beta^{'} X_j})] \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(22)$$

Breslow maximum partial likelihood estimator, adjusted for tied observation is obtained by differentiating equation (22) with respect to the components of β and setting the derivative equal to zero and solving for the unknown parameters.

A number of approaches to handle tied data have been suggested and, of these, three are used by software packages: an exact expression that is derived in Kalbfleisch and Prentice (1980) and approximations due to Breslow (1974) and Efron (1977). However, approximations derived by Breslow (1974) and Efron (1977) are designed to provide expressions that are more easily computed than the exact partial likelihood, yet that still account for the fact that ties are among the observed values of survival time. In many applied settings there is 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 and popular it is used mostly (Hosmer and Lemeshow, 1999).

Checking the assumption of proportional hazards

An important assumption of Cox PH is proportional hazard which means the hazard ratio is constant over time. To check it the estimated survival curves cross, if they do, then this an evidence that the hazards are not proportional.

3.5.1.4.2. Accelerated Failure Time Model

The second important regression model in survival analysis is the accelerated failure time (AFT) model (Lawless 1982, Kalbfleisch and Prentice 2002). It is an alternative if the proportional

hazards assumption does not hold. Denote the survival functions of two groups by $S_1(t)$ and $S_2(t)$, respectively, then the AFT model is given by:

$$S_1(t) = S_2(\phi t) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(23)$$

Where, $t \geq 0$ and ϕ is acceleration factor. This model implies that rate of group 1 is ϕ times as much as that of group 2. The hazard function of the i^{th} individuals at time t of the AFT regression model can be written in the form:

$$h_i(t) = e^{-\eta_i} h_o(t/e^{\eta_i}) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(24)$$

Where, $\eta_i = \alpha_1 x_{1i} + \alpha_2 x_{2i} +, \ldots, \alpha_p x_{pi}$ is the linear component of the model, in which x_{ji} *is* the value of the j^{th} explanatory variable. X_j, j = 1,2,…,p, for the i^{th} individual, i = 1,2,…,n. The baseline hazard function, $h_o(t)$ is the hazard of death at time t for an individual for whom the value of the p explanatory variables are all equal to zero.

The corresponding survivor function for the i^{th} individual is given by:

$$S_i(t) = S_o(t/e^{\eta_i}) = \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(25)$$

Where, $S_o(t)$ is the baseline survival function. Let $\eta_i = \alpha' x_i$, then $e^{-\alpha' x_i}$ is the acceleration factor.

Notice that:

$e^{-\alpha' x_i} > 1$ implies that there is an acceleration of endpoint (death).

$e^{-\alpha' x_i} < 1$ implies that there is a stretching or delay in endpoint (death).

The log-linear model for a random variable T_i associated with the lifetime of the i^{th} individual study, is given by;

$$\log_{T_i} = \mu + \alpha_1 x_{1i} + \alpha_2 x_{2i} +, \ldots, + \alpha_p x_{pi} + \delta \epsilon_i \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(26)$$

The survival function of the random variable ϵ_i is given by:

$$S_i(t) = S_{\epsilon_i}\left(\frac{\log t - \mu - \alpha_1 x_{1i} - \alpha_2 x_{2i} -, \ldots, - \alpha_p x_{pi}}{\delta}\right) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(27)$$

Where, μ is intercept, δ is scale parameter and ϵ is the error distribution assumed to have a particular parametric distribution.

Similarly, the hazard function of the random variable ϵ_i is given by:

$$h_i(t) = \frac{1}{\delta t} h_{\epsilon_i}\left(\frac{\log t - \mu - \alpha_1 x_{1i} - \alpha_2 x_{2i} -,\dots,- \alpha_p x_{pi}}{\delta}\right) \dots\dots\dots (28)$$

Where $h_{\epsilon_i(\epsilon)}$ is the hazard function of the distribution of ϵ_i.

3.5.1.4.2.1. Parametric accelerated failure time models

Parametric accelerated failure time models based on Weibull, Log-logistic and Log-normal distributions for survival time are the most commonly used.

3.5.1.4.2.1.1 Weibull Accelerated Failure Time model

The Weibull is a very flexible life distribution model. It has a hazard rate which is monotone increasing, decreasing, or constant. It is the only parametric regression model which has both a proportional hazards representation and an accelerated failure-time representation. The only difference between the Weibull model and the exponential model is that the scale parameter δ is estimated rather than being set to be one (Klein & Moeschberger, 2003). When T_i in (26) has a Weibull distribution then the survival function of the ϵ_i is given by:

$$S_{\epsilon_i}(\epsilon) = e^{(-e^{\epsilon})} \dots\dots\dots (29)$$

Where, $h_{\epsilon_i(\epsilon)} = e^{\epsilon}$. The survival function of the random variable T_i is given by:

$$S_i(t) = e^{(-\lambda_i t^{\frac{1}{\delta}})} \dots\dots\dots (30)$$

With $\lambda_i = e^{\left(\frac{-\mu - \alpha_1 x_{1i} - \alpha_2 x_{2i} -,\dots,- \alpha_p x_{pi}}{\delta}\right)}$ and where λ_i is scale parameter, δ^{-1} is shape parameter. The hazard function of T_i is given by:

$$h_i(t) = \frac{1}{\delta t}\left(\frac{\log t - \mu - \alpha_1 x_{1i} - \alpha_2 x_{2i} -,\dots,- \alpha_p x_{pi}}{\delta}\right) \dots\dots\dots (31)$$

3.5.1.4.2.1.2. Log-logistic Accelerated Failure Time model

When T_i in (26) has a Log-logistic distribution then the survival function of the ϵ_i is given by:

$$S_{\epsilon_i(\epsilon)} = \frac{1}{1 + e^{\epsilon}} \dots\dots\dots (32)$$

Where $h_{\epsilon_{i(\epsilon)}} = (1 + e^{-\epsilon})^{-1}$. The survival function for T_i is given by:

$$S_i(t) = \{1 + e^{(\frac{logt-\mu-\alpha_1 x_{1i}-\alpha_2 x_{2i}-,\ldots,-\alpha_p x_{pi}}{\delta})^{-1}} \ldots\ldots\ldots\ldots(33)$$

The hazard function of T_i for the i^th^ individuals is given by:

$$h_i(t) = \frac{1}{\delta t}\{1 + [e^{-(\frac{logt-\mu-\alpha_1 x_{1i}-\alpha_2 x_{2i}-,\ldots,-\alpha_p x_{pi}}{\delta})}]\}^{-1} \ldots\ldots\ldots\ldots(34)$$

3.5.1.4.2 .1 .3. Log-normal Accelerated Failure Time model

When T_i in (26) has a Log-normal distribution then the survival function of the ϵ_i is given by:

$$S_{\epsilon_{i(\epsilon)}} = 1 - \Phi(\epsilon) \ldots\ldots\ldots\ldots(35)$$

Where, $h_{\epsilon_{i(\epsilon)}} = \frac{e^{(-\epsilon^2/_2)}}{(1-\Phi(\epsilon))\sqrt{2\pi}}$. The survival function of T_i for the i^th^ individuals is given by:

$$S_i(t) = 1 - \Phi(\frac{logt-\eta_i-\mu}{\delta}) \ldots\ldots\ldots\ldots(36)$$

Where, with parameters $\eta_i - \mu$ and δ. The hazard function of T_i for the i^th^ individuals is given by (28).

3.5.1.4.2.1.4. Parameter Estimation

Accelerated failure time models are fitted using maximum likelihood estimation. The likelihood of the n observed survival time $t_{1,}t_2, \ldots, t_n$ is given by:

$$L(\alpha, \mu, \delta) = \prod_{i=1}^{n}[f_i(t_i)]^{\delta_i}[S_i(t_i)]^{1-\delta_i} \ldots\ldots\ldots\ldots(37)$$

The log likelihood function is then:

$$logL(\alpha, \mu, \delta) = \sum_{i=1}^{n}\{-\delta_i log(\delta t_i) + \delta_i log f_{\epsilon_i}(z_i) + (1-\delta_i) log S_{\epsilon_i}(z_i))\} \ldots\ldots(38)$$

Where, $z_i = \frac{logt-\mu-\alpha_1 x_{1i}-\alpha_2 x_{2i}-,\ldots,-\alpha_p x_{pi}}{\delta}$, $S_i(t_i) = S_{\epsilon_i}(z_i)$.

The maximum likelihood was manipulated by Newton-Raphson procedures using software.

3.5.1.5. The Frailty Concept

The concept of frailty provides a suitable way to introduce random effects in the model to account for association and unobserved heterogeneity. A random effect describes excess risk or frailty for distinct categories, such as individuals or families, over and above any measured covariates. Thus frailty or random effect models try to account for correlations within groups. Frailties are useful in modeling correlations in multivariate survival and event history data. A frailty model is a multiplicative hazard model consisting of three components: a frailty (random effect), a baseline hazard function (parametric or non-parametric), and a term modeling the influence of observed covariates (fixed effects). Frailty models provide a nice way to capture and to describe the dependence of observations within a cluster and/or the heterogeneity between clusters. Frailty models are hazard models having a multiplicative frailty factor (David D. Hanagal, 2011).

3.5.1.5.1. Shared Frailty Models

The shared frailty model is a mixture model because the common risk in each cluster (the frailty Z) is assumed to be random. The model assumes that all event times in a cluster are independent given the frailty variables. In other words, it is a conditional independence model where the frailty is common to all individuals in a cluster and therefore responsible for creating dependence between event times. This is the reason for the concept of shared frailty. A shared frailty model can be considered as a mixed (random effects) model in survival analysis with group variation (frailty) and individual variation described by the hazard function. Thus the frailty variable is associated with groups of individuals rather than individuals as such.

The shared frailty approach assumes that all failure times in a cluster are conditionally independent given the frailties. The value of the frailty term is constant over time and common to all individuals in the cluster, and thus it is responsible for creating dependence between event times in a cluster. This dependence is always positive in shared frailty models. Originally, the model was introduced to the literature by David Clayton and was considered in the bivariate case without using the notion of frailty (Clayton 1978), modeling the event times of sons and their fathers. The shared frailty model dominates the literature on multivariate frailty models and was extensively studied in the monographs by Hougaard (2000), Therneau and Grambsch (2000), and Duchateau and Janssen (2008).

For n clusters and that cluster i has n_i observations and associates with the unobserved frailty Z_i ($1 \leq i \leq n$). The vector X_{ij} ($1 \leq i \leq n$, $1 \leq j \leq n_i$) contains the covariate information of the event time T_{ij} of the j[th] observation in the i[th] cluster. Conditional on the frailty term Z_i, the survival times in cluster i ($1 \leq i \leq n$) are assumed to be independent and their hazard functions to be of the form:

$$h(t|X_{ij}, Z_i) = Z_i h_o(t) e^{\beta' X_{ij}} \quad \ldots\ldots(39)$$

Where $h_o(t)$ denotes the baseline hazard function and β is a vector of fixed effect parameters to be estimated. The frailties Z_i (i = 1, . . . , n) are independently and identically distributed random variables with density function f(z).

The main assumption of a shared frailty model is that all individuals in cluster i share the same value of frailty Z_i (i = 1, . . . , n), and this is why the model is called the shared frailty model. It was introduced by Clayton (1978) and extensively studied in Hougaard (2000), Therneau and Grambsch (2000), and Duchateau *et al.* (2007). Shared-frailty models are appropriate when we wish to model the frailties as being specific to groups of subjects, such as subjects within families, kebeles, regions, etc. Conditional on frailty Z_i which is shared by all individuals in cluster i, it holds that:

$$S(t_{i1}, \ldots, t_{ini}|X_i, Z_i) = S(t_{i1}|X_{i1}, Z_i), \ldots S(t_i n_i|X_i n_i, Z_i)$$

$$S(t_{i1}, \ldots, t_{ini}|X_i, Z_i) = e^{(-z_i \sum_{j=1}^{n_i} M_o(t_{ij}) e^{\beta' X_{ij}})} \quad \ldots\ldots(40)$$

Where $M_o(t) = \int_0^t h_o(s) ds$ denotes the cumulative baseline hazard function and $X_i = (X_{i1}, \ldots, X_i n_i)$ is the covariate matrix of the individuals in the i[th] clusters. Averaging expression (40) with respect to the frailty Z_i gives the marginal survival function:

$$S(t_{i1}, \ldots, t_{ini}|X_i) = L(\sum_{j=1}^{n_i} M_o t_{ij})\, e^{\beta' X_{ij}} \quad \ldots\ldots(41)$$

Where L denotes the Laplace transform of the frailty variable. Thus, the multivariate survival function is expressed as the Laplace transform of the frailty distribution, evaluated at the cumulative baseline hazard. The joint survival function for all event-time data is now the product of the survival functions of all the clusters because of the assumption about independence between clusters:

$$S(t_{11}, \dots, t_n n_n)|X_1, \dots, X_n) = \prod_{i=1}^{n} L(\sum_{j=1}^{n_i} M_o(t_{ij}) e^{\beta' X_{ij}}) \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots(42)$$

Where, L denotes the Laplace transform of the frailty variable.

Hougaard (1986) used several distributions for frailty including Gamma, Inverse Gaussian, and claimed that these two distributions are relevant and mathematically tractable as a frailty distribution for heterogeneous populations. Flinn and Heckman (1982) used a Log-normal distribution for frailty, whereas Vaupel *et al.* (1979) assumed that frailty is distributed across individuals as a Gamma distribution.

3.5.1.5.1.1. Shared Gamma Frailty Model

The standard assumption about frailty in shared frailty models is that it follows a Gamma distribution. The main reason for the popularity of the Gamma distribution is their nice mathematical properties, especially the simple form of the Laplace transform. In the shared frailty model, another aspect has to be considered additionally with respect to frailty distribution. Each frailty distribution implies a specific form of dependence between event times in clusters.

To make the model identifiable, it is better to restrict that expectation of the frailty equals one and variance be finite, so that only one parameter needs to be estimated. Thus, the distribution of frailty Z is the one parameter Gamma distribution. Under the restriction, the corresponding density function and Laplace transformation of Gamma distribution:

$$fz(z_i) = \frac{z_i^{(1/\theta)-1} exp(-z_i/\theta)}{\Gamma(1/\theta)\theta^{1/\theta}} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots(43)$$

Where,$\theta > 0$, $\Gamma(.)$ is Gamma function. It corresponds to a Gamma distribution Gamma (μ, θ) with mean 1 which is μ and its variance is finite which is θ. The associated Laplace transformation is:

$$L(s) = (1 + s/\theta)^{-\theta}, \theta > 0, \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots(44)$$

Note that if θ > 0, there is heterogeneity. So the large values of θ reflect a greater degree of heterogeneity among groups and a stronger association within groups. The conditional survival function of the Gamma frailty distribution is given by: (Gutierrez, 2002).

$$S_\theta(t) = [(1 - \theta ln\{S(t)\})]^{-1/\theta} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots(45)$$

Where $\theta > 0$. The conditional hazard function of the Gamma frailty distribution is given by: (Gutierrez, 2002)

$$h_\theta(t) = h(t)[1 - \theta \ln\{S(t)\}]^{-1} \quad \ldots\ldots(46)$$

where S (t) and h(t) are the survival and the hazard functions of the baseline distributions. Larger variance indicates a stronger association within groups. For the Gamma distribution, the Kendall's Tau (Hougaard, 2000), which measures the association between any two event times from the same cluster in the multivariate case. It is an overall measure of dependence .The associations within group members are measured by Kendall's, which is given by:

$$\tau = \frac{\theta}{(\theta+2)} \quad \ldots\ldots(47)$$

Where $\tau \epsilon (0,1)$.

3.5.1.5.1.2. Shared Inverse Gaussian Frailty Model

The Inverse Gaussian (inverse normal) distribution was introduced as a frailty distribution alternative to the Gamma distribution by Hougaard (1984) and was used, by Manton *et al.* (1986), Klein *et al.* (1992), Keiding et al. (1997), Price and Manatunga (2001), Economou and Caroni (2005), Kheiri *et al.* (2007), and Duchateau and Janssen (2008). Similar to the Gamma frailty model, simple closed-form expressions exist for the unconditional survival and hazard functions, this makes the model attractive. The probability density function of an Inverse Gaussian shared distributed random variable with parameter θ > 0 and z > 0 is given by:

$$fz(z_i) = \left(\frac{1}{2\pi\theta}\right)^{1/2} z_i^{-3/2} exp\left(\frac{-(z_i-1)^2}{2\theta z_i}\right) \quad \ldots\ldots(48)$$

With z has mean one and variance θ. The Laplace transformation of the inverse Gaussian distribution is:

$$L(s) = exp\left[\frac{1-(1+2\theta s)^{1/2}}{\theta}\right] \quad \ldots\ldots(49)$$

Where $\theta > 0, s > 0$. For the inverse Gaussian frailty distribution the conditional survival function is given by: (Gutierrez, 2002).

$$S_\theta(t) = exp\left\{\frac{1}{\theta}\left(1 - [1 - 2\theta ln\{S(t)\}]^{1/2}\right)\right\} \quad (50)$$

Where $\theta > 0$. For the inverse Gaussian frailty distribution the conditional hazard function is given by: (Gutierrez, 2002).

$$h_\theta(t) = h(t)[1 - 2\theta ln\{S(t)\}]^{-1/2} \quad (51)$$

Where $\theta > 0$, S(t) and h(t) are the survival and the hazard functions of the baseline distributions. With multivariate data, an Inverse Gaussian distributed frailty yields a Kendall's Tau given by:

$$\tau = \frac{1}{2} - \frac{1}{\theta} + 2\frac{\exp(2/\theta)}{\theta^2} \int_{2/\theta}^{\infty} \frac{\exp(-u)}{u} du \quad (52)$$

Where $\tau \epsilon (0, 1/2)$.

3.5.1.5.1.3. Parameter Estimation

Estimation of the frailty model can be parametric or semi-parametric. In the former case, a parametric density is assumed for the event times, resulting in a parametric baseline hazard function. Estimation is then conducted by maximizing the marginal log-likelihood (Munda *et al*, 2012). Frailty models account for the clustering present in grouped event time data. For a right-censored clustered survival data, the observation for subject j ϵ $J_{(i)} = \{1, ..., n_{(i)}\}$ from cluster i ϵ I $= \{1, ..., s\}$ is the couple (y_{ij}, δ_{ij}), where y_{ij} = min (t_{ij}, c_{ij}) is the minimum between the survival time t_{ij} and the censoring time c_{ij}, and the indicator $\delta_{ij} = I(t_{ij} \leq c_{ij})$ is one for a subject where the event has taken place, while $\delta ij = 0$ for a censored observation. When covariate information's been collected, the observation will be (y_{ij}, δ_{ij}, X_{ij}), where X_{ij} denote the vector of covariates for the ij^{th} observation. In the parametric setting, estimation is based on the marginal likelihood in which the frailties have been integrated out by averaging the conditional likelihood with respect to the frailty distribution.

Under the assumption of right-censoring, of independence between the censoring time and the survival time of random variables, given the covariate information, the marginal log-likelihood of the observed data can be:

$$lmarg(h_o, \beta, \theta; Z, X)$$

$$= \prod_{i=1}^{s}\left[\left(\prod_{j=1}^{ni}(h_o(yij)exp(xij^T\beta))^{\delta ij}\right)X\int_0^{\infty} Zi^{di}\, exp\left(-Zi\sum_{j=1}^{ni}H_o(yij)exp(Xij^T\beta)\right)f(zi)dzi\right]$$

$$= \prod_{i=1}^{s}\left[\left(\prod_{j=1}^{ni}(h_o(yij)exp(Xij^T\beta))^{\delta ij}\right)X(-1)^{di}L^{(di)}\left(\sum_{j=1}^{ni}H_0(yij)exp(xij^T\beta\right)\right]$$

Taking the logarithm, the marginal likelihood is:

$$l_{marg}(h_o(.), \beta, \theta; Z, X) = \sum_i^s\{\left[\sum_{j=1}^{ni}\delta ij\left(log\left(h_o(yij)\right) + {X_{ij}}^T\beta\right)\right] +$$
$$log\left[(-1)^{di}L^{(di)}\left(\left[\sum_{j=1}^{ni}H_o(yij)exp(xij^T\beta)\right]\right)\right]\}.....(53)$$

Here, di $= \sum_{\text{j=1}}^{\text{ni}}$ δij is the number of events in the i^{th} clusters and $L^{(q)}(.)$ is the q^{th}derivative. The Laplace transformation of the frailty distribution Z is defined as:

$$L_{(s)} = E[exp(-Zs)] = \int_0^{\infty} exp(Z_i s)f(Z_i)dz_i \text{ .....(54)}$$

Where, $s > 0$ and,

$$L^{(q)}(s) = (-1)^q \int_0^{\infty} Z^q exp(-Zs)f(z)dz \text{ .....(55)}$$

Where $q \geq 0$ and $h_o(.)$ represents a vector of parameters of the baseline hazard function, β the vector of regression coefficients and θ the variance of the random effect. The estimates of $h_o(.)$, β, θ are obtained by maximizing the marginal log-likelihood of the above. This can be done if one is able to compute higher order derivatives $L^{(q)}(.)$ of the Laplace transform up to q = max {d_1, ---, d_s}. Symbolic differentiation is performed in R, but is impractical here, mainly because this is very time consuming Munda *et al.* (2012).

3.6. Variable Selection

The methods of selecting a subset of covariates in a PHs regression model are essentially similar to those used in any other regression models. The most common methods are purposeful selection, step-wise (forward selection and backward elimination) and best sub-set selections. Survival analysis using Cox regression method begins with a thorough univariate analysis of the association between survival time and all important covariates (Hosmer and Lemeshow, 1999).

Recommendable procedure in selecting variables in the study Hosmer and Lemeshow (1999) and Collett (2003) recommended the following procedure in variable selection.

I. Include all variables that are significant in the univariable analysis and also any other variables which are presumed to be important to fit the initial multivariable model.

II. The variables that appear to be important from step (I) are then fitted together in multivariable model. In the presence of certain variables others may cease to be important. Consequently, backward elimination is used to omit non-significant variables from the model. Once a variable has been dropped, the effect of omitting each of the remaining variables in turn should be examined.

III. Variables, that were not important on their own, and so were not under consideration in step (II), may become important in the presence of others. These variables are therefore added to the model from step (II), with forward selection method. This process may result in terms in the model determined at step (II) ceasing to be significant.

IV. A final check is made to ensure that neither significant variable is eliminated from the model nor non-significant variable is included in the model. At this stage the interactions between any of the main effects currently in the model can be considered for inclusion if the inclusion significantly modifies the model.

3.7. Model Selection

Akaike's Information Criterion (AIC): can be used to compare models that are not nested. The minimum AIC indicates the model is the best.

AIC = -2 log(L) + kp

Where, p is the number of parameters in the model, L is the likelihood, K is the number of covariates.

3.8. Model Diagnosis

3.8.1. Asses the adequacy plots of Parametric Baselines

Weibull: plot the log-cumulative hazard versus log(t).

Log-logistic: plot logarithm of the failure odds versus log(t).

Log-normal: plot $\Phi^{-1}(1-S(t))$ versus log(t).

3.8.2. Asses the Cox Snell Residual plot

Cox–Snell residuals are useful for checking the overall fit of the final model (Klein and Moeschberger, 2003). The Cox-Snell residual for the individual with observed survival time is given by: $r_j = \widehat{H}(T_j/X_j)$, where $\widehat{H}$ is the cumulative hazard function of the fitted model. If the model fits the data, then r_j's should have a standard (λ =1) exponential distribution, so that a hazard plot of r_j versus the estimated cumulative hazard rate of r_j should be a straight line with slope 1.

4. RESULTS AND DISCUSSION

4.1. Descriptive Statistics

The response variable in this study is survival time measured in month from the date of birth to the date of death which is continuous. The censoring indicator (status) is 0 for censored observations and 1 for event occurred. The study included 9433 children under the age of five years, who were born during the five years preceding the date of the survey in Ethiopia. From the total number of under-five children 8591 (91.07%) were censored whereas 842 (8.93%) were event. Summary results of covariates of time-to-death for under-five children in Ethiopia dataset presented in Table 4.1 below.

Table 4.1: Summary results of covariates of time-to-death for under-five children in Ethiopia.

Covariates	Category	Status					
		Censored		Event		Total	
		Frequency	%	Frequency	%	Frequency	%
Women's education	No education	6459	68.47	618	6.55	7077	75.02
	Primary education	1878	19.91	203	2.15	2081	22.06
	Secondary& above	254	2.69	21	0.22	275	2.92
Wealth index	Poor	4396	46.6	653	6.92	5049	53.52
	Middle	1433	15.19	134	1.42	1567	16.61
	Rich	2762	29.28	55	0.58	2817	29.86
Types of births	single births	8358	88.6	743	7.88	9101	96.48
	multiple births	233	2.47	99	1.05	332	3.52

	1-3 children	2785	29.52	333	3.53	3118	33.05
Total children ever born	4-6 children	3655	38.75	304	3.22	3959	41.97
	7-9 children	1724	18.28	156	1.65	1880	19.93
	≥ 10 children	427	4.53	49	0.52	476	5.05
Preceding birth intervals	< 24 months	2083	22.08	457	4.84	2540	26.93
	24-47 months	4611	48.88	289	3.06	4900	51.95
	≥48 months	1897	20.11	96	1.02	1993	21.13
Place of delivery	Health facility	832	8.82	97	1.03	929	9.85
	elsewhere	7759	82.25	745	7.9	8504	90.15
Sex of household head	Male	7080	75.06	679	7.2	7759	82.25
	Female	1511	16.02	163	1.73	1674	17.75
Religion	Muslim	4103	43.5	399	4.23	4502	47.73
	Orthodox	2531	26.83	251	2.66	2782	29.49
	Protestant	1690	17.92	157	1.66	1847	19.58
	Other	267	2.83	35	0.37	302	3.20
	Grand Total	8591	91.07	842	8.93	9433	100

From the above summary table 4.1: 7077 (75.02%), 2081(22.06%), 275(2.92%) children under age of five born from women with their educational level were: no education, primary education and secondary& above respectively. Under-five children born from poor, middle and rich

economical status of women's were 5049(53.52%), 1567(16.61%) and 2817(29.86%) respectively. From the total of under-five children 9101(96.48%) births were single births, whereas 332(3.52%) births were twin. The total children ever born between (1 to 3) were 3118 (33.05%), between (4 to 6) were 3959(41.97%), between (7 to 9) were 1880(19.93%) and 10 and more were 476(5.05%) per household. The preceding birth intervals of under-five children were born less than 24 months, between (24 to 47) months and 48 months and more were 2540 (26.93%), 4900 (51.95%) and 1993 (21.13%) respectively. Under-five children born in the health facility were 929(9.85%) while 8504 (90.15%) were born out of the health facility. Under-five children were born from male house hold head 7759 (82.25%), whereas 1674 (17.75%) were born from female household head. Under-five children were born from Muslim, Orthodox, Protestant and other religion of women were 4502 (47.73%), 2782 (29.49%), 1847 (19.58%) and 302 (3.20%) respectively.

4.2. Non-parametric Survival Analysis

It is also imperative to do some basic descriptive analysis that will be used as initiation to our subsequent finding. The log-rank test and Kaplan-Meier survival estimates that have been used to glance the significance of the difference among the different groups of covariates.

4.2.1. Log rank test for under-five children

The result summarized in Table 4.2, the log-rank test was used at 5% level of significance to validate the differences in the survival time of each factor. There is no difference between the probabilities of an event occurring at any time point was the null hypothesis that has been tested.

Table 4.2: Log rank test of survival time among the different groups of covariates for under-five children in Ethiopia.

Groups	Chi-square	DF	Pr>Chi-square
Women's education	7.8	2	0.020
Wealth index	131	1	0.000
Types of births	160	1	0.000
Total children ever born	34.1	3	0.000
Preceding birth intervals	113	2	0.000
Place of delivery	17.2	1	0.000
Sex of household head	0	1	0.968

Religion	4.9	3	0.182

According to Table 4.2, women's educational level, wealth index, types of births, total children ever born, preceding birth intervals and place of delivery had statistically significant difference in experiencing death event, whereas sex of household head and religion had not statistically significant in experiencing death event.

4.2.2. The Kaplan- Meier Estimate for under-five children

Survival time distributions of time-to-death for under-five children were estimated for each group using the KM method in order to compare the survival curves of two or more groups. From figure 4.1 of KM curve, the horizontal axis shows that the time-to-death of under-five children, whereas the vertical axis shows the probability of survival. At the beginning, the survival curve is increasing, implies that during the time of post-neonatal, neonatal and infancy period there were high numbers of death, whereas at the end the survival curve is decreasing, implies that the death of under-five children decreases when age increases. For hazard plot of under-five children, the horizontal axis shows the time-to-death of under-five children, whereas the vertical axis shows the cumulative hazard. The curve implied that, the survival rate of under-five children were longer when the age of under-five children increases.

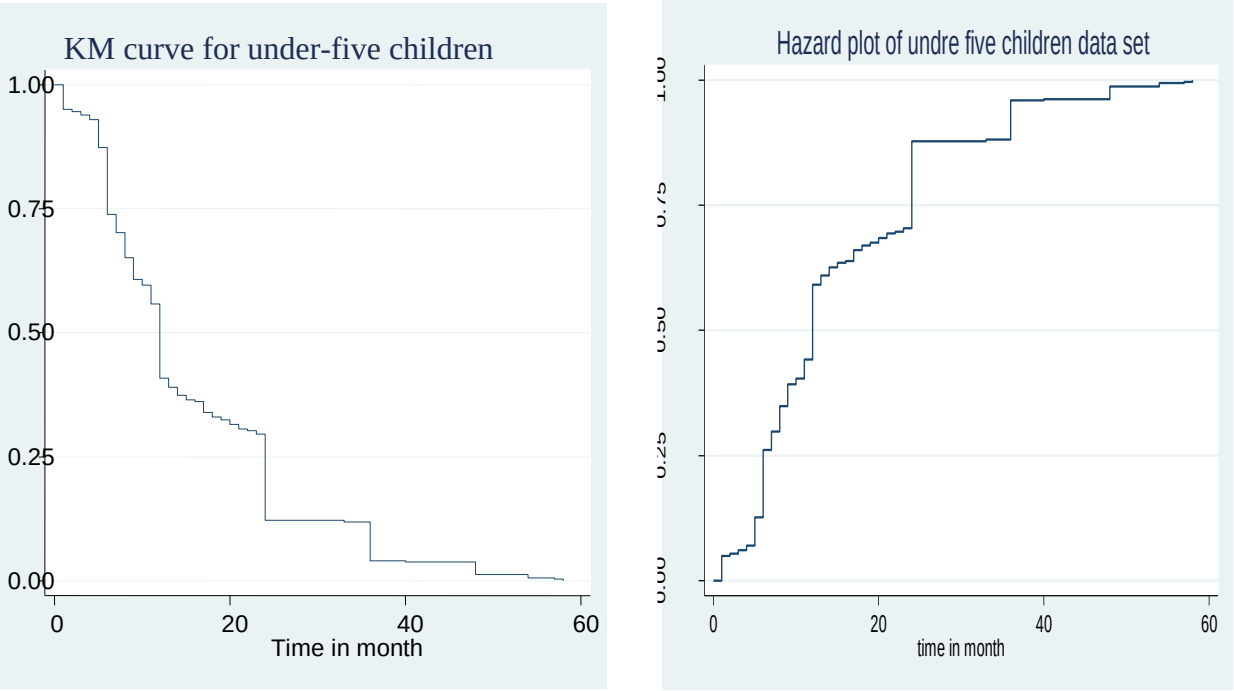

Figure 4.1: The K-M curve for survival and hazard functions of under-five children.

4.2.2.1. Kaplan-Meier curves of time-to-death for different groups

4.2.2.1.1. Kaplan-Meier curves of time-to-death for under-five children by women's educational level

The Kaplan-Meier curves of time-to-death for under-five children by women's educational level are shown by in Appendix 3 (figure 4.2). As it can be observed from the plot, under-five children from a better educated mother have a better survival rate. Also, from Table 4.2, the chi-square with 2 DF is 7.8 and p-value is 0.0204, implies that there is significance difference between the survival curves of three educational categories/groups.

4.2.2.1.2. Kaplan-Meier curves of time-to-death for under-five children by wealth index

The Kaplan-Meier curves of time-to-death for under-five children by wealth index shown by in Appendix 3 (figure 4.3). As it can be shown from the curves, that a mother those who have a better economical status had a better survivable rate of under-five children. Also, from Table 4.2, the chi-square with 2 DF is 131 and p-value is 0, implies that there is very high significance difference between the survival curves of three wealth index categories/groups.

4.2.2.1.3. Kaplan-Meier curves of time-to-death for under-five children by type of births

The Kaplan-Meier curves in figure 4.4: it has a clear difference in the way they lay. The above curve is for single births have a better survival rate than those twin births of under-five children. Also, from Table 4.2, the chi-square with 1 DF is 160 and p-value is 0, implies that there is very high significance difference between the survival curves of two types of births categories/groups.

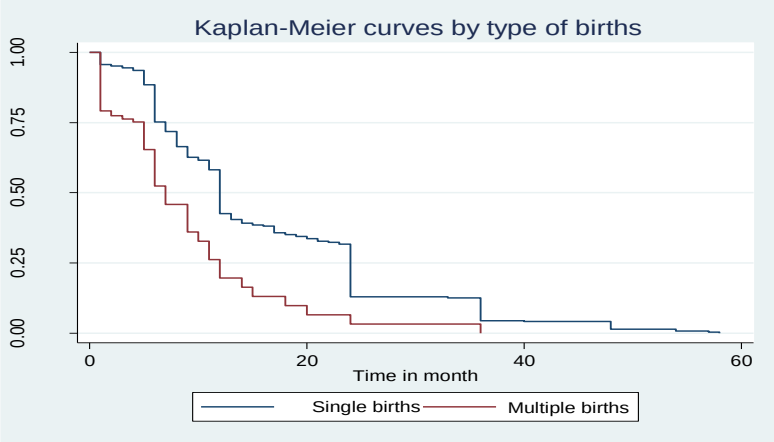

Figure 4.4: KM curves for survival of time-to-death for under-five children by type of births.

4.2.2.1.4. Kaplan-Meier curves of time-to-death for under-five children by total children ever born

The Kaplan-Meier curves by total children ever born in Appendix 3 (figure 4.5), as it can be observed from the curves, when the total children ever born increases the survival rate of under-five children decreases. Also, from Table 4.2, the chi-square with 3 DF is 34.1 and p-value is 0, implies that there is very high significance difference between the survival curves of four total children ever born categories/groups.

4.2.2.1.5. Kaplan-Meier curves of time-to-death for under-five children by preceding birth intervals

As it has been observed from appendix 3 (figure 4.6) Kaplan-Meier curves, under-five children who have longer preceding birth intervals had a better survival rate. Also, from Table 4.2, the chi-square with 2 DF is 113 and p-value is 0, implies that there is very high significance difference between the survival curves of three total preceding birth interval categories/groups.

4.2.2.1.6. Kaplan-Meier curves of time-to-death for under-five children by place of delivery

The Kaplan-Meier curves by place of delivery in Appendix 3 (figure 4.7), as it can be observed from the curves those under-five children born in health facility had a better survival rate. Also, from Table 4.2, the chi-square with 1 DF is 17.2 and p-value is 0, implies that there is very high significance difference between the survival curves of two places of delivery categories/groups.

4.2.2.1.7. Kaplan-Meier curves of time-to-death for under-five children by sex of household head

The Kaplan-Meier curves by sex of household head in Appendix 3 (figure 4.8), the survival curves overlaid one with other, implies that sex of household head is not significant factor of time-to-death for under-five children. Also, from Table 4.2, the chi-square with 1 DF is 0 and p-value is 0.968, implies that there is no significance difference between the survival curves of two sex of household head categories/groups.

4.2.2.1.8. Kaplan-Meier curves of time-to-death of under-five children by religion

The Kaplan-Meier curves by religion in Appendix 3 (figure 4.9), the survival curve have been observed that being Muslim, Orthodox, Protestant and other, one was not had better survival rate than others, implies religion was not significant factor for under-five children. Also, from table 4.2, the chi-square with 3 DF is 4.9 and p-value is 0.182, implies that there is no significance difference between the survival curves of four religion categories/groups.

The median survival time of time-to-death for under-five children from women those who had no education, primary education, and secondary& above were 12 months with 95% CI [12, 13], 11 months with 95% CI [9, 14] and 12 months with 95% CI [12, 13] respectively. The median survival time of time-to-death for under-five children from poor, middle and rich women were 12 months with 95% CI [11, 12] , 12 months with 95% CI [8, 24] and 12 months with 95% CI [7, 19] respectively. The median survival time of time-to-death for under-five children from single births was 12 months with 95% CI [12, 13], whereas from twin births was 7 months with 95% CI [6, 11]. In Appendix 4 (Table 4.3) shows the median survival time and the corresponding 95% confidence interval for the rest categorical variables.

4.3. Univariable Analysis

From the summary of univariate analysis given in appendix 1, we used univariate analysis in order to see the effect of each covariate on time-to-death of under-five children before proceeding to the multivariable analysis. The univariate analysis was fitted for every covariate by using different baseline distributions i.e. Weibull, Log-logistic, and Log-normal. In univariate analysis, women's educational level, wealth index, type of births, total children ever born, preceding birth

intervals and place of delivery were significantly associated with under-five children, whereas sex of household head and religion were not significant at 10% level of significance.

4.4. Multivariable Analysis

Under multivariable survival analysis the study was done by considering the three baseline hazard function such as Weibull, Log-logistic, Log-normal and two frailty distributions such as Gamma and Inverse-Gaussian using the six significant covariates in the univariable analysis.

Model comparisons were presented in Table 4.4: To compare the efficiency of different models, the AIC was used. It is the most common applicable criterion to select model. Based on AIC, a model having the minimum AIC value was preferred. Accordingly, Log-normal baseline (AIC = 6863.021) found to be the best model for the time-to-death of under-five children in Ethiopia dataset.

Table 4.4: Comparison of models with AIC.

Baseline	**Frailty**	
	Gamma	**invGau**
Weibull	6893.074	6893.047
Log logistic	7103.410	7102.410
Lognormal	6864.724	6863.021

The variance of the frailty were significant for all baseline hazard function with an inverse Gaussian shared frailty distribution in the models, whereas it was not significant in the Gamma shared frailty distribution using the same baseline as inverse Gaussian models at 5% level of significance. This indicates the presence of heterogeneity and necessitates the frailty models. The estimate for the variance parameter θ in a shared frailty models can be thought as a measure of the degree of correlation and provides information on the variability (the heterogeneity) in the population of clusters. The value of shared frailty distribution (θ) are 0.026, 0.030 and 0.025 for Weibull-Inverse Gaussian, Log-logistic-Inverse Gaussian and Log-normal-Inverse Gaussian respectively (see under Appendix 2 and table 4.5 E).The corresponding Kendall's tau (τ) values of shared frailty distribution are 0.223, 0.399 and 0.361 respectively. The Kendall's tau (τ) value is used to measure the dependence within the clusters (region).

Table 4.5: Results of the Multivariable Log-normal-Inverse Gaussian Shared Frailty Model for time-to-death dataset.

F. Multivariable analysis using the Log-normal -Inverse Gaussian frailty model

Variable	Coef	S.e(coef)	Φ	Chi-sq	95%CI		P-value
					LCL	UCL	
Women's Education							
(Intercept)	1.386	0.0126	1.115	120.85	1.090	1.140	*
No education	Ref						
Primary	-0.2279	0.0066	1.066	12.00	1.053	1.078	*
Secondary&above	-0.0679	0.0188	1.188	0.13	1.151	1.224	*
Wealth Index							
(Intercept)	1.386	0.0126	1.115	120.85	1.090	1.140	*
Poor	Ref						
Middle	0.2512	0.0070	1.070	12.79	1.056	1.084	*
Rich	1.2524	0.0092	1.091	186.73	1.073	1.109	*
Type of births							
(Intercept)	1.386	0.0126	1.115	120.85	1.090	1.140	*
Single	Ref						
Multiple	-1.0981	0.0098	1.098	126.26	1.078	1.117	*
Total children ever born							
(Intercept)	1.386	0.0126	1.115	120.85	1.090	1.140	*
1-3 children	Ref						
4-6 children	0.3924	0.0061	1.061	40.89	1.049	1.073	*
7-9 children	0.462	0.0077	1.076	36.50	1.061	1.091	*
≥ 10 children	0.2643	0.0117	1.117	5.12	1.094	1.140	*
Preceding birth intervals							
(Intercept)	1.386	0.0126	1.115	120.85	1.090	1.140	*
< 24 months	Ref						
24-47 months	0.5134	0.0058	1.058	77.33	1.047	1.070	*
≥48 months	0.5779	0.0082	1.082	50.05	1.066	1.098	*
Place of delivery							

(Intercept)	1.386	0.0126	1.115	120.85	1.090	1.140	*
Health facility	Ref						
Elsewhere	0.6331	0.0099	1.098	40.90	1.079	1.118	*
Frailty				19.47			*
τ= 0.361 θ= 0.0252 δ = 4.760 λ= 1.832							
Likelihood ratio test=625, df= 21.4, p=0.000							

*Coef= coefficient, S.e= standard error, ϕ = acceleration factor, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Chi-sq= Chi-square, Ref=Reference, θ = variance of the random effect, λ = scale parameter, δ= shape parameter, τ = Kendall's Tau., * = p-value < 0.05.*

The most important thing in the interpretation of acceleration factor is, if 1 is not included in the acceleration confidence interval then, the factors are statistically significant else insignificant. Hence, from Table 4.5 F, the acceleration factors and its 95% confidence interval for women's educational level for a group of primary and secondary & above are 1.066 (1.053, 1.078) and 1.1876 (1.151, 1.224) respectively, when compared to no education as reference category. In the confidence interval of acceleration factors 1 is not included, implies that women's educational level was statistically significant for time-to-death of under-five children in Ethiopia. The corresponding p-values are less than 0.05 which supports that women's educational level was significant.

The acceleration factors and its 95% confidence interval for wealth index are 1.070 (1.056, 1.084) and 1.091 (1.073, 1.109). In the 95% confidence interval of the acceleration factors 1 is not included, implies that wealth index or economical status of women's were determines the time-to-death of under-five children in Ethiopia. The p-values also support this, which are less than 0.05 for middle and rich wealth index, when compared to poor as reference category.

The types of births were statistically significant, which determines the time-to-death of under-five children in Ethiopia. The acceleration factors and its 95% confidence interval for a group of multiple births 1.098 (1.078, 1.117) when compared to single births as reference category with p-value is significant. The estimated coefficient of the parameters multiple births was -1.0981. The sign of the coefficient is negative which implies that decreasing logged of survival time and hence, shorter expected duration of time-to-death of under-five children.

Total children ever born were statistically significant factor for time-to-death of under-five children in Ethiopia, since 1 is not included in the 95% confidence interval of acceleration factors which are (1.049, 1.073), (1.061, 1.091) and (1.094, 1.140) for 4-6 children, 7-9 children and 10 and more children respectively, when compared to 1-3 children as reference category. The corresponding p-values are less than 0.05 which are significant and acceleration factors are 1.061, 1.076, 1.117 respectively.

Preceding birth intervals were significantly important factors for time-to-death of under-five children in Ethiopia. Accordingly, 1.058(1.047, 1.070) and 1.082(1.066, 1.098) are the acceleration factors and its 95% confidence interval in between (24 to 47) months and 48 and more months when compared to less than 24 months as reference category.

Place of delivery out of health facility were statistically determines the time-to-death of under-five children in Ethiopia. The 95% confidence interval of acceleration factors for a group of elsewhere (1.079, 1.118) when compared to health facility as reference category. The p-values are less than 0.05 which also supports this significance difference.

The estimate of shape parameter in the Log-normal-Inverse Gaussian shared frailty model is (δ= 4.760). This value shows the shape of hazard function is unimodal because the value is greater than unity i.e., it increases up to some time and then decreases. The heterogeneity in the population of the region which is used as a clusters are estimated by our selected model is θ= 0.0252 and the dependence within the clusters (region) is measured by Kendall's tau is τ= 0.361.

4.5. Model Diagnostics

4.5.1. Checking adequacy of parametric baselines using graphical methods

After the model has been fitted, it is desirable to determine whether a fitted parametric model adequately describes the data or not. Therefore, the appropriateness of model with Weibull baseline can be graphically evaluated by plotting log (-log(S(t)) versus log(time), the Log-logistic baseline by plotting $\log(\frac{\hat{S}_{(t)}}{1-\hat{S}_{(t)}})$ versus log(time) and the Log-normal baseline by plotting $(\phi^{-1}[1-S(t)]$ against log (t). If the plot is linear, the given baseline distribution is appropriate for the given dataset. Accordingly, their respective plots are given in figure 4.9 below and the plot for the Log-normal baseline distribution make straight line better than Weibull and Log-logistic baseline distribution. This evidence also strengthens the decision made by AIC value that Log-normal baseline distribution is appropriate for the given dataset.

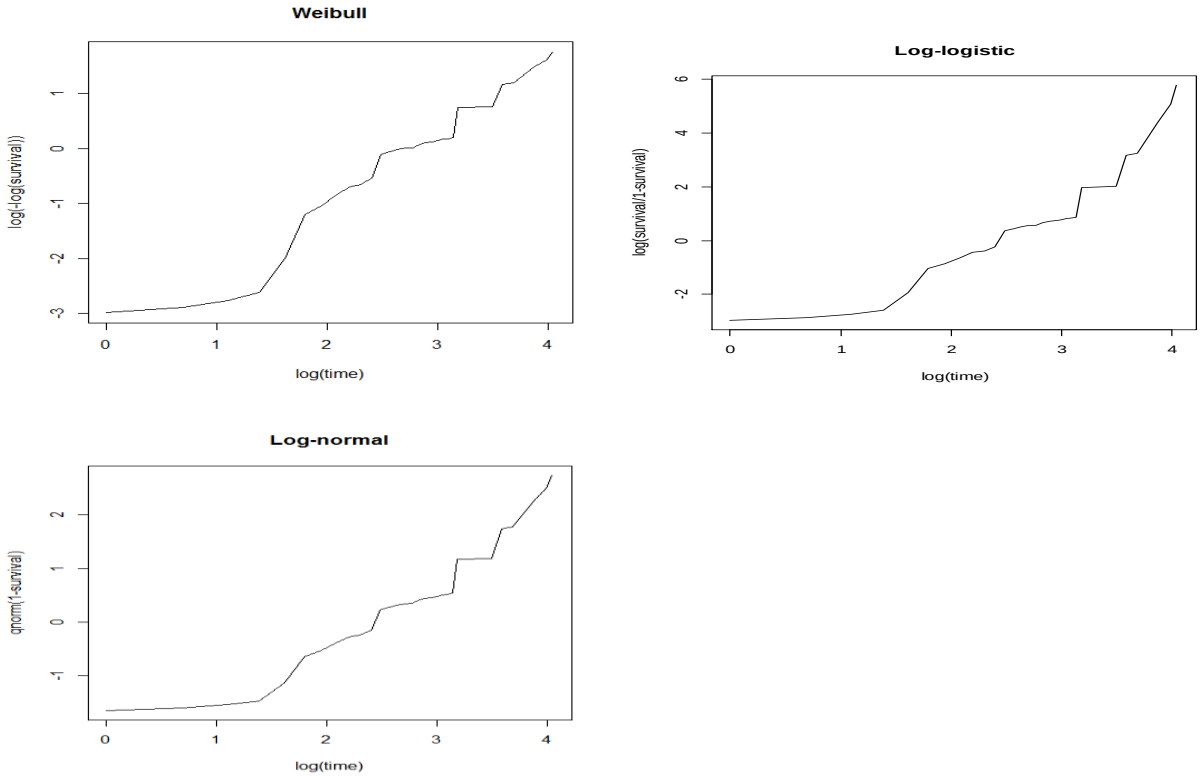

Fig 4.9: Graphs of Weibull, Log-logistic, and Log-normal baseline distributions for time-to-death of under-five children dataset.

4.5.2. Cox- Snell residuals plots

The Cox-Snell residuals are one way to investigate how well the model fits the data. The plot for fitted model of residuals for Log-normal to our data via maximum likelihood estimation with cumulative hazard functions given in figure 4.10 below. If the model fits the data, the plot of cumulative hazard function of residuals against Cox-Snell residuals should be approximately a straight line with slope 1. The plot makes straight lines through the origin for Log-normal baseline distribution suggesting that, it is appropriate for time-to-death of under-five children dataset.

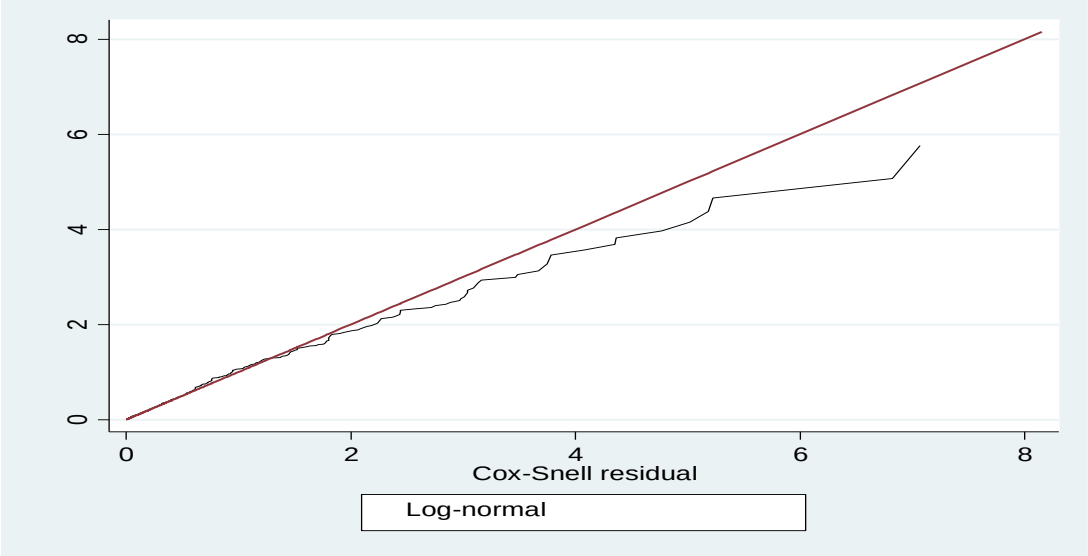

Figure 4.10: Cox- Snell residuals plots of Log-normal baseline distribution for time-to-death of under-five children in Ethiopia.

4.6. Discussion of the results

The main purpose of the study was modeling the determinants of time-to-death of under-five children in Ethiopia on EDHS 2011 using three baselines hazard function (Weibull, Log-logistic, Log-normal) and two parametric shared frailty distributions (Gamma, Inverse-Gaussian) in which the outcome variables measured in months. The study estimate and compare the survival time and the factors that have statistical significant by using univariable and multivariable shared frailty analysis. Factors that are concerned for our study were women's educational level, wealth index, type of births, total children ever born, preceding birth intervals, place of delivery, sex of household head and religion.

The univariate analysis (in Appendix 1) revealed that women's educational level, wealth index, type of births, total children ever born, preceding birth intervals and place of delivery were significantly associated with time-to-death of under-five children, whereas sex of household head and religion were not significant at 10% level of significance. All significant covariates in univariate analysis were included in all multivariable analysis and comparison was done within the models using Akaike Information Criteria (AIC), Introduced by Hitrotugu Akaike (1971), AIC measures the relative goodness of fit of statistical model ("Book Reviews," 1988). Boco (2010) noted that the lower value of AIC indicates a better fit. Log-normal-Inverse Gaussian shared frailty model was found to be the best model based on AIC value and graphical evidence (figure 4.9 and figure 10) to describe time-to-death of under-five children in Ethiopia.

From the R output the clustering effect were significant (p-value=0.000) in shared frailty models. This showed that there was heterogeneity between the regions on the time-to-death of under-five children in Ethiopia. The estimated median survival time of time-to-death of under-five children found to be 12 months with 95% confidence interval [11, 13].

The findings of this study revealed that mother's education level is an important factor for under-five child mortality reduction, as more education is associated with lower risk of under-five child death, implies that under-five children born from educated mothers had a lower mortality risk. A study conducted by (Woldemiceal, 2001) investigated morbidity being significantly lower among under-five children of more educated mothers (secondary or higher) than among under-five children of mothers with no or primary education. Similar study conducted by Goro (2007) used data from 1993, 1998, and 2003 DHS surveys in Ghana to examine the determinants of under-five child mortality and found that education of mothers is powerful significant determinants for under-five child mortality. Twum-Baah *et al* (1994) also indicated that children born to mothers with higher educational level associated with lower risk of under-five child mortality as compared to children born to mothers with primary education level or none educated. Other study in Kenya by Hill (2000) found that mother's educational levels have a significant impact on under-five child mortality. Children of mothers with primary (and secondary) education have a significant decreased mortality risk compared to those of mothers with no education EI-Zanaty F, (2001). Nath DC, Land KC, Singh KK, Worku Z, Deribew A, Tessema F, Girma B, Houweling TA, Kunst AE, Moser K, Mackenbach JP studies showed that child mortality rates are higher among less educated mothers compared with mothers who have higher levels of education. The

importance of maternal education is based on the fact that education increases a mother's level of knowledge and skills, thus enabling her to effectively understand and utilize available information and resources critical for child health and survival.

The results of this finding suggested that wealth index had a significant effect on under-five child mortality in Ethiopia. The study revealed higher deaths of under-five children were observed from a lowest household economical status. Children born to mothers in the lowest wealth index are at higher risk of dying than children born to mothers in the middle and highest wealth index (World Bank, 2007b). A study conducted by Doctor HV (2014) using Nigeria Demographic Health Survey for 2008 and found that the highest household's economical status was less likely to experience under five-child death than the poorest household's economical status in rural Nigeria.

The result of this finding suggested that type of births had a significant effect on under-five child mortality in Ethiopia. The study showed that those under-five children with multiple births had a higher risk of death than single births. A similar research which supports the result of this study conducted by Rathavuth Hong (2006) on 2004 Bangladesh DHS data suggested that multiple births have higher risk of mortality than singleton births. A similar study also conducted by Kembo and Ginneken (2009) address some important issues in under-five mortality in Zimbabwe in their study. They found that births of order 6+ with a short preceding interval had the highest risk of under-five mortality. The under-five mortality risk associated with multiple births was 2.08 times higher relative to singleton births.

The result of this finding suggested that high number of total children ever born in the household were more likely to die before their fifth birth day. A similar study was conducted by Aristide Romaric and Sathiya Susmuman (2015), in West African countries, the result showed that the probability of dying before the age of five year increased with household size.

The result of this finding suggested that place of delivery had a significant effect on under-five child mortality in Ethiopia. The study showed that those under-five children born out of health facility had a higher risk of death than born in health facility. A similar study conducted by Ettarh RR, Kimani J, (2014) women who deliver at health facilities have a lower chance of under-five child death as compared to those who deliver out of health facilities. A study conducted by Mwangi Reuben Wambugu (2014), place of delivery with children whose mothers delivered in their homes compared to those who deliver in the public and private health facilities was

significant in KDHS 2008/9 data and conclude that increased use of both public and health facilities turn down under-five mortality. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS conducted a study and suggest that women who deliver at health facilities have a lower chance of child death as compared to those who deliver at home due to the use of skilled delivery at health facilities and the none existence of such at home. Doctor HV (2014) conducted a study and suggested that the likelihood of under-five mortality has also been linked to place of delivery, with evidence indicating that women who deliver at health facilities have a lower probability of reporting child death compared with those delivering in home settings. These differences have largely been driven by the use of skilled delivery care at health facilities compared with the deliveries that occur at home, which in most cases are not attended to by skilled birth attendants.

The result of this finding suggested that the preceding birth intervals had a significant effect on under-five children in Ethiopia. Shea O. Rutstein (2008) conducted a similar study and suggested that the shorter the duration of the interval for intervals less than 24 months, the higher is the risk of dying of under-five children. Mohammad, Khwaja, Bashir, Iqbal, Fred, Pav, Shea and Rebecca (July 2013) were conducted a similar study in Afghanistan and suggested that, a higher proportion of children who died had a short birth interval of 0-23 months, at 42% compared with 33% among all children. For children who died, just over one-fifth of the preceding birth intervals were 24-35 months, and 18% had a previous birth interval of 36 or more months.

5. CONCLUSION AND RECOMMENDATION

5.1. Conclusion

This study was used under-five children dataset from Ethiopian Demographic Health Survey (EDHS 2011) with the main purpose of modeling time-to-death of under-five children in Ethiopia using parametric shared frailty models. Out of the total 9433 under-five children 8.93% were experienced an event (death) and 91.07% were not experienced an event (live). The estimated median death time of under-five children was 12 months.

To model the determinants of time-to-death of under-five children, three baseline hazard function (Weibull, Log-logistic, Log-normal) and two well known frailty distribution (Gamma, Inverse Gaussian) were used. By using AIC, Log-normal Inverse Gaussian shared frailty model is better fitted to time-to-death of under-five children dataset than other parametric shared frailty models. There was a frailty (clustering) effect on the time-to-death of under-five children among regions of Ethiopia. This indicates the presence of heterogeneity and necessitates the frailty models.

The result of Log-normal-Inverse Gaussian frailty models showed that women's educational level, wealth index, type of births, total children ever born, preceding birth intervals and place of delivery were found significant predictors to time-to-death of under-five children in Ethiopia, whereas sex of household head and religion were not statistically significant.

The graphical plots (Fig 4.9 and Fig 4.10) also showed that Log-normal distribution is better when compared to Weibull and Log-logistic baseline distributions to explain time-to-death of under-five children dataset.

5.2. Recommendation

From the study women's educational level, wealth index, type of births, total children ever born, preceding birth interval and place of delivery were the causes for the death of under-five children in Ethiopia on 2011 EDHS data set, so the government and other stakeholders take an action:

- On improving the women's educational level.
- On improving the economical status of women's.
- For women with twin children needs a special cares than women with one child.
- By minimizing the total number of children in the household.
- By increasing the gap of birth interval.

- By encouraging the women born in the health facility and discouraging the women born in out of the health facility.
- Giving an attention for children are a critical issues for one's own country. So, further research should be conduct on the area.

Ethical Considerations

Ethical issue (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or redundancy, etc.) have been completely observed by the author.

Limitation of the Study

- Somalia region is not included in the study because in the EDHS it was not included.

Software

Data were analyzed using R version 3.2.5 and STATA version 12.0 Software.

REFERENCES

Aristide, R., Bado, S., Susmuman ,A.(2015). Iran Public health.44(7), 465763.

Bangha,M, Simelane,S.(2007). Spatial differentials in childhood mortality in South Africa: e vidence from the 2001 census. African Population Study,22(2),3–21.

Bauze, A., Tran, L., Nguyen, K., Firth, S., Jimenez, E., Dwyer, L.,(2012). Equity and geography: t he case of child mortality in Papua New Guinea. PLoS ONE,7(5),37861.

Becher, H., Muller,O., Jahn, A., Gbangou, A., Kynast,G. and Kouyate, B. (2004). "Risk factors of infant and child mortality in rural Burkina Faso", Bulletin of the World Health Organiz atio, 82 (4).

Boco, Adébiyi, G. (2010). Individual and Community Level Effects on Child Mortality:Analysis of 28 Demographic and Health Surveys in Sub-Saharan Africa, 73, (Ed).

Book Reviews. (1988). Journal of the American Statistical Association, 83(403), 902-926.

Bryce, J., Terreri, N., Victora, G., Mason, E., Daelmans, B., Bhutta, A., Bustreo, F., Song Ane, F., Salama, P., and Wardlaw, T. (2015). Countdown to tracking intervention coverage for c hild survival. The Lancet, 368(9541),1067.

Le, T. and Le, C. (1997). Applied survival analysis. Wiley New York.

Caroni, C., Crowder, M., Kimbe,r A. (2010). Proportional hazards models with discrete frailty. Li fetime Data Analysis 16, 374–384.

Clayton, D. (1978). A model for association in bivariate life tables and its application in epidemi ological studies of familial tendency in chronic disease incidence. Biometrika ,65,141-15.

Cleves, M. A., Gould, W. W., and Gutierrez, R. G. An introduction to survival analysis.

Cox, D. R.(1972). Regression Models and Life Tables (with discussion), Journal of the Royal Stat istical Society, Series B, 34(2).CRC, 2003.

Collett,D.(2005). Modeling survival data in medical research, 57.

Chapman & Hall/Economoun , Caroni, P.,(2003).Graphical tests for the assumption of gamma a nd inverse Gaussian frailty distributions. Lifetime Data Analysis, 11, 565–582.

DaVanzo, J., Hale, L., Razzaque A., and Rahman, M.(2007). Effects of inter pregnancy interval and outcome of the preceding pregnancy on pregnancy outcomes in Matlab, Bangladesh BJOG: An International Journal of Obstetrics and Gynaecology,114(9),1079-1087.

Doctor HV (2011). Does living in a female-headed household lower child mortality? The case of r ural Nigeria. Rural and Remote Health 11: 1635.

Doctor HV(2011).Does living in female-headed household lower child mortality? The case of rural Nigeria. Rural Remote Health. 11: 163.

Duchateau, L.,and Janssen, P. (1977). The frailty model (statistics for biology and health), 2007. Efron B The efficiency of Cox's likelihood function for censored data. J Am Statistical A ssociation,72, 557-65.

EI-Zanaty, F., Way, A., Calverton, ,M. (2001). Minitry of Health and Population councel and OR C Macro Egypt demographic health survey 2000.

Ettarh, R., Kimani, J.(2012). Determinants of under-five mortality in rural and urban Kenya. Rur al Remote Health,12,1812-(Online) access on 16 January 2014 at http://www.rrh.org.au

Flinn, C. & Heckman, J. (1982). New methods for analyzing individual event histories, Sociologi cal methodology, 99-140.

Goro, M. (2007). The stalling child mortality: the case of three northern regions. The 5th conferece of union for Africa population, Tanzania.

Hanagal, D. (2011).Modeling Survival Data Using Frailty Models.

Hill, K., Bicego, G., Mahy, M. (2000). Childhood Mortality in Kenya: An Examination of Trends and Determinants in the Late 1980s to Mid 1990s, John Hopkins University/ Macro

Hill, K. (1991). Approaches to the measurement of childhood mortality: A comparative review. P opulation Index, 57(3),368-382.

Hosmer, D.W. and Lemeshow, S. (1998): Applied Survival Analysis: Regression Modeling of Tim e to Event Data; Wiley Series in Probability and Statistics. Canada.

Hougaard, P. (1986b). Survival models for heterogeneous populations derived from stable distr ibutions. Biometrika, 73, 387-396.

Hobcraft, J., McDonald, W., and Rutstein, O. (1984). Socio-economic factors in infant A cross-n ational comparison. Population studies,38(2),193-223.

Jones, G, Steketee ,W., Black, E., Bhutta, Z., Morris, S.(2003). The Bellagio Child Survival Study Group. How many child deaths can we prevent this year? Lancet, 36, 65–71.

Klein, J. P. and Goel, P. K. (1992). Survival analysis: state of the art, 2011.

Kalbfleisch, J. D. and Prentice, R. L. (1980). The Statistical Analysis of Failure Time Data. John Wiley & Sons, Inc.: New York.

Kaplan, E. L.,& Meier, P. (1958). Nonparametric estimation from incomplete observations. Journal of the American statistical association, 53(282), 457-481.

Keiding, N., Andersen, P., Klein, J. (1997). The role of frailty models and accelerated failure time models in describing heterogeneity due to omitted covariates. Statistics in Medicine ,16, 215–224.

Kheiri, S., Meshkani, M.R., Faghihzadeh, S. (2005). A correlated frailty model for analysing risk f actors in bilateral corneal graft rejection for Keratoconus: a Bayesian approach. Statist ic in Medicine 24, 2681–2693.

Kleinbaum, D. (1996). Survival Analysis: A self-Learning Text.New York: Springer-Verlag;child mortality: A cross-national comparison.

Klein, J. P., & Moeschberger, M. L. (2003). Survival analysis: techniques for censored and trunk ated data. Springer Science & Business Media.

Kazembe, L., Clarke, A. and Kandala, N.(2012). Childhood mortality in sub-Saharan Africa: cr oss-sectional insight into small-scale geographical inequalities from census data. BMJ o pen, 2(5).

Kyaddondo, B. (2012). Uganda population stabilisation report. Population Trends and Policy Op tions in Selected Developing Countries.

Manatunga, A.K., Oakes, D. (1999). Parametric analysis of matched pair survival data. Lifetime Data Analysis ,5, 371–387.

Manton, K., Stallard, E. (1981). Methods for evaluating the heterogeneity of aging processes in h uman populations using vital statistics data: Explaining the black/white mortality crosso ver by a model of mortality selection. Human Biology, 53, 47–67.

McGilchrist, C.A., Aisbett, C.W. (1991). Regression with Frailty in Survival Analysis. Biometrics, 47, 461-466.

Mohammad, Khwaja, Bashir, Iqbal, Fred, Pav, Shea and Rebecca (July 2013). The effects of birth intervals on the cause of under-five children In Afghanistan, ICF International Calverto ,Maryla nd, USA.

Mosley, W.H. and Chen, I.C. (1984). An analytical framework for the study of child survival in de veloping countries. Population and Development Review, A supplement to Vol.10.

Mosley, W. H., L. C. Chen, (1984). Child survival: strategies for research continued.

Mwangi, R., Alfred, A.,Samuel ,W. , (2014). A research Project on population studies, University of Nairobi.

Nielsen, G.G., Gill, R.D., Andersen, P.K., Sørensen, T.I.A. (1992). A counting process approach to maximum likelihood estimation in frailty models. Scandinavian Journal of Statistics,1

9, 25–43.

Oakes, D. (1977). The asymptotic information in censored survival data. Population and develop ment review, 10(Supplement), 1984. Biometrika, 64, 441-8.

Omariba, D., Beaujot, R. and Rajulton, F.(2007). Determinants of infant and child mortality in Kenya: an analysis controlling for frailty effects. Population Research and Policy Revie w,26,299-321.

Price, D., Manatunga, A. (2001). Modelling survival data with a cured fraction using frailty mode ls. Statistics in Medicine, 20, 1515–1527.

Rathavuth, H.(2006). Department of Global Health, School of Public Health and Health Service s, George Washington University, Washington, DC, USA , Journal of Paediatrics and C hild Health ,42 ,630–635.

Shea, O. Rutstein (2008). Further Evidence of the Effects of Preceding Birth Intervals on Neonat al, Infant, and Under-Five-Years Mortality and Nutritional Status in Developing Countr ies:Evidence from the Demographic and Health Surveys.

Sewanyana, S., and Younger,D. (2008). Infant mortality in uganda: Determinants, trends and the millennium development goals. Journal of African Economies,17(1),34-61.

Singh, A., Pathak, P., Chauhan,R., Pan, W. (2011). Infant and child mortality in India in the last t wo decades: a geospatial analysis, 6(11), 26856.

Spiegelhalter, D., Best, N., Carlin, B., Van DerLinde, A. (2002). Bayesian measures of model co mplexity and fit. J Roy Stat Soc: Ser B (Stat Methodol); 64(4):583–639.

Sengonzi, G. F., R. De Jong and S. C. Shannon. The effect of female migration on infant and child survival in uganda. Population Research and Policy Review, 21(5):403{431,2002.

Storeygard, A., Balk, D., Levy, M., Deane, G. (2008). The global distribution of infant mortality:a subnational spatial view. Popul Space Place;14(3):209–29.

Twum – Baah et al. (1994). A study of infant, child and maternal mortality in Ghana. Ghana stati stical service in collaboration with Ministry of Health and UNICEF, Accra, Ghana.

UNICEF, (2012). Pneumonia and diarrhoea: Tackling the deadliest diseases for the world' poor est children. Statistics and Monitoring Section – Division of Policy and Strategy, UNICE F, New York, NY.using Stata. Stata Corp, 2008.

Vaupel, J., Manton, K. and Stallard, E. (1979). The impact of heterogeneity on individual frailty on the dynamic of mortality. Demography,16(3), 439-54.

Wienke, A. (2010). Frailty models in survival analysis. CRC Press.

Woldemicael, G. (2001). Diarrhoeal morbidity among young children in Eritrea. Health Populati on and Nutrition, 2, 83-90.

World Bank, (2007b). Urban Labor Markets in Ethiopia: Challenges and Prospects Poverty Red uction and Economic Management Unit, Africa Region, Report No. 38665-ET, Washingt on DC: World Bank, (2).

World Factbook. (2011, Accessed on February 28, 2011.).

World Health Organization,(2014). Household Air Pollution and Health,WHO Fact Sheet no.292.

Yashin, A., Vaupel, J., Iachine, I. (1995). Correlated Individual Frailty: An Advantageous Appro ach to Survival Analysis of Bivariate data. Mathematical Population Studies,5,145 –159.

Zelterman, D. (1992). A statistical distribution with an unbounded hazard function and it's applic ation to a theory from demography. Biometrics, 807-818.

APPENDIX 1

Univariable analysis using Gamma and Inverse Gaussian parametric shared frailty models for time-to-death of under-five children in Ethiopia.

A. Weibull-Gamma Univariable Analysis

Variable	Coef	S.e(coef)	Φ	Chi-sq	95%CI		P-value
					LCL	UCL	
Women's Education							
(Intercept)	2.939	0.0042	1.037	5027.7	1.029	1.045	*
No education	Ref						
Primary	-0.160	0.0060	1.060	7.02	1.048	1.072	*
Secondary&above	-0.213	0.0165	1.164	1.68	1.132	1.196	*
Wealth Index							
(Intercept)	2.730	0.0023	1.038	139.70	1.033	1.042	*
Poor	Ref						
Middle	0.260	0.0076	1.076	11.68	1.061	1.091	*
Rich	1.250	0.0120	1.120	109.13	1.096	1.144	*
Type of births							
(Intercept)	2.990	0.0018	1.041	268.31	1.037	1.044	*
Single	Ref						
Multiple	-0.973	0.0082	1.082	139.86	1.066	1.098	*
Total children ever born							
(Intercept)	2.673	0.0097	1.046	754.40	1.027	1.065	*
1-3 children	Ref						
4-6 children	0.386	0.0059	1.059	42.70	1.047	1.071	*
7-9 children	0.375	0.0072	1.072	27.28	1.058	1.086	*
≥ 10 children	0.229	0.0114	1.114	4.06	1.091	1.136	*
Preceding birth intervals							
(Intercept)	2.672	0.0175	1.042	234.37	1.008	1.077	*
< 24 months	Ref						
24-47 months	0.536	0.0063	1.063	73.39	1.050	1.075	*
≥48 months	0.594	0.0091	1.091	42.26	1.073	1.109	*

Place of delivery							
(Intercept)	2.591	0.0081	1.078	1018.36	1.062	1.094	*
Health facility	Ref						
Elsewhere	0.343	0.0081	1.080	17.85	1.064	1.096	*
Sex of household head							
(Intercept)	2.900	0.0362	1.036	6425.07	0.965	1.107	*
Male	Ref						
Female	0.004	0.0346	1.065	0.00	0.997	1.132	
Religion							
(Intercept)	2.934	0.0466	1.043	3965.63	0.951	1.134	*
Muslim	Ref						
Orthodox	-0.102	0.0641	1.060	2.55	0.935	1.186	
Protestant	-0.026	0.0749	1.071	0.12	0.924	1.217	
Other	-0.018	0.1327	1.131	0.02	0.871	1.391	

*Where: coef=coefficient, s.e=standard error, ϕ=Acceleration Factor, Chi-sq=Chi-square, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Ref=Reference, *= p-value < 0.05.*

B. Weibull- Inverse-Gaussian Univariable Analysis

Variable	**Coef**	**S.e(coef)**	**Φ**	**Chi-sq**	**95%CI**		**P-value**
					LCL	**UCL**	
Women's Education							
(Intercept)	2.938	0.0039	1.037	5820.84	1.029	1.044	*
No education	Ref						
Primary	-0.160	0.0060	1.060	7.09	1.048	1.071	*
Secondary&above	-0.208	0.0641	1.164	1.61	1.038	1.289	*
Wealth Index							
(Intercept)	2.753	0.0046	1.036	3579.87	1.026	1.045	*
Poor	Ref						
Middle	0.234	0.0075	1.075	9.75	1.060	1.089	*
Rich	1.184	0.0160	1.115	104.23	1.084	1.147	*

Type of births							
(Intercept)	2.965	0.0037	1.035	6345.15	1.028	1.043	*
Single	Ref						
Multiple	-0.944	0.0081	1.081	135.74	1.065	1.097	*
Total children ever born							
(Intercept)	2.656	0.0455	1.044	3406.80	0.955	1.133	*
1-3 children	Ref						
4-6 children	0.381	0.0059	1.059	42.06	1.047	1.070	*
7-9 children	0.374	0.0072	1.072	27.26	1.058	1.086	*
≥ 10 children	0.223	0.0113	1.113	3.92	1.091	1.135	*
Preceding birth intervals							
(Intercept)	2.663	0.0046	1.038	3361.20	1.029	1.047	*
< 24 months	Ref						
24-47 months	0.517	0.0062	1.062	69.60	1.050	1.074	*
≥48 months	0.574	0.0091	1.090	40.20	1.072	1.108	*
Place of delivery							
(Intercept)	2.601	0.0079	1.078	1098.10	1.062	1.093	*
Health facility	Ref						
Elsewhere	0.327	0.0080	1.079	16.69	1.064	1.095	*
Sex of household head							
(Intercept)	2.900	0.0377	1.036	5926.53	0.962	1.110	*
Male	Ref						
Female	0.002	0.0648	1.065	0.00	0.937	1.192	
Religion							
(Intercept)	2.935	0.0447	1.043	4306.76	0.955	1.130	*
Muslim	Ref						
Orthodox	-0.102	0.0621	1.060	2.69	0.938	1.181	
Protestant	-0.031	0.0726	1.070	0.19	0.928	1.212	
Other	-0.026	0.1316	1.130	0.04	0.872	1.388	

*Where: coef=coefficient, s.e=standard error, ϕ=Acceleration Factor, Chi-sq=Chi-square, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Ref=Reference, * =p-value < 0.05.*

C. Log-logistic- Gamma Univariable Analysis

Variable	Coef	S.e(coef)	Φ	Chi-sq	95%CI		P-value
					LCL	UCL	
Women's Education							
(Intercept)	2.662	0.0005	1.044	2825.00	1.043	1.045	*
No education							
Primary	-0.187	0.0062	1.061	9.23	1.049	1.073	*
Secondary&above	-0.212	0.0159	1.158	1.78	1.127	1.189	*
Wealth Index							
(Intercept)	2.354	0.0025	1.044	89.10	1.039	1.048	*
Poor	Ref						
Middle	0.286	0.0075	1.075	14.40	1.060	1.090	*
Rich	1.254	0.0110	1.110	129.60	1.088	1.131	*
Type of births							
(Intercept)	2.700	0.0202	1.047	179.77	1.007	1.086	*
Single	Ref						
Multiple	-1.090	0.0091	1.091	143.17	1.073	1.109	*
Total children ever born							
(Intercept)	2.344	0.0132	1.052	316.24	1.026	1.078	*
1-3 children	Ref						
4-6 children	0.439	0.0059	1.059	54.56	1.048	1.071	*
7-9 children	0.422	0.0073	1.073	33.46	1.059	1.087	*
≥ 10 children	0.258	0.0115	1.115	5.05	1.092	1.137	*
Preceding birth intervals							
(Intercept)	2.293	0.0207	1.049	123.18	1.008	1.089	*
< 24 months	Ref				0.000	0.000	
24-47 months	0.606	0.0061	1.061	98.23	1.049	1.073	*
≥48 months	0.662	0.0087	1.087	58.20	1.070	1.104	*
Place of delivery							
(Intercept)	2.275	0.0085	1.079	714.56	1.063	1.096	*
Health facility	Ref						

Elsewhere	0.383	0.0081	1.079	22.42	1.064	1.095	*
Sex of household head							
(Intercept)	2.616	0.0503	1.043	2706.27	0.944	1.142	*
Male	Ref						
Female	0.009	0.0671	1.067	0.02	0.935	1.198	
Religion							
(Intercept)	2.659	0.0556	1.050	2283.15	0.941	1.159	*
Muslim							
Orthodox	-0.131	0.0682	1.062	3.70	0.929	1.196	
Protestant	-0.017	0.0793	1.073	0.05	0.917	1.228	
Other	-0.020	0.1475	1.144	0.02	0.855	1.434	

*Where: coef=coefficient, s.e=standard error, ϕ=Acceleration Factor, Chi-sq=Chi-square, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Ref=Reference, * =p-value < 0.05.*

D. Log-logistic- Inverse-Gaussian Univariable Analysis

Variable	**Coef**	**S.e(coef)**	**Φ**	**Chi-sq**	**95%CI**		**P-value**
					LCL	**UCL**	
Women's Education							
(Intercept)	2.662	0.0047	1.044	3261.02	1.034	1.053	*
No education	Ref						
Primary	-0.187	0.0061	1.061	9.38	1.049	1.073	*
Secondary&above	-0.209	0.0158	1.158	1.75	1.127	1.189	*
Wealth Index							
(Intercept)	2.364	0.0076	1.044	981.30	1.029	1.058	*
Poor	Ref						
Middle	0.274	0.0075	1.075	13.40	1.060	1.089	*
Rich	1.176	0.0104	1.103	128.00	1.082	1.123	*
Type of births							
(Intercept)	2.680	0.0050	1.042	2922.20	1.032	1.052	*
Single	Ref						
Multiple	-1.070	0.0091	1.091	140.23	1.073	1.108	*

Total children ever born							
(Intercept)	2.325	0.0051	1.050	2050.66	1.040	1.060	*
1-3 children							
4-6 children	0.437	0.0059	1.059	54.53	1.047	1.071	*
7-9 children	0.422	0.0073	1.073	33.78	1.058	1.087	*
≥ 10 children	0.263	0.0114	1.114	5.29	1.092	1.137	*
Preceding birth intervals							
(Intercept)	2.289	0.0060	1.046	1454.50	1.034	1.058	*
< 24 months							
24-47 months	0.593	0.0061	1.061	95.30	1.049	1.072	*
≥48 months	0.641	0.0086	1.086	55.70	1.069	1.102	*
Place of delivery							
(Intercept)	2.277	0.0083	1.079	754.43	1.063	1.095	*
Health facility							
Elsewhere	0.376	0.0080	1.079	21.93	1.063	1.095	*
Sex of household head							
(Intercept)	2.616	0.0463	1.043	3195.59	0.952	1.134	*
Male	Ref						
Female	0.012	0.0669	1.067	0.03	0.935	1.198	
Religion							
(Intercept)	2.663	0.0510	1.049	2727.04	0.949	1.149	*
Muslim							
Orthodox	-0.133	0.0630	1.061	4.45	0.937	1.184	
Protestant	-0.032	0.0733	1.070	0.19	0.927	1.214	
Other	-0.039	0.1445	1.143	0.07	0.860	1.426	

Where: coef=coefficient, s.e=standard error, ϕ=Acceleration Factor, Chi-sq=Chi-square, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Ref=Reference, =p-value < 0.05.*

E. Log-normal- Gamma Univariable Analysis

Variable	Coef	S.e(coef)	Φ	Chi-sq	95%CI		P-value
					LCL	UCL	
Women's Education							
(Intercept)	2.777	0.0058	1.050	2275.19	1.038	1.061	*
No education							
Primary	-0.179	0.0060	1.059	9.06	1.047	1.071	*
Secondary&above	-0.215	0.0150	1.148	2.07	1.119	1.178	*
Wealth Index							
(Intercept)	2.443	0.0257	1.048	90.26	0.998	1.099	*
Poor	Ref						
Middle	0.287	0.0070	1.070	16.67	1.057	1.084	*
Rich	1.161	0.0089	1.089	170.45	1.071	1.106	*
Type of births							
(Intercept)	2.800	0.0205	1.052	186.23	1.011	1.092	*
Single							
Multiple	-1.070	0.0095	1.095	126.16	1.077	1.114	*
Total children ever born							
(Intercept)	2.473	0.0137	1.057	327.31	1.030	1.083	*
1-3 children	Ref						
4-6 children	0.408	0.0057	1.057	51.38	1.046	1.068	*
7-9 children	0.405	0.0070	1.070	33.09	1.057	1.084	*
≥ 10 children	0.243	0.0112	1.112	4.76	1.090	1.133	*
Preceding birth intervals							
(Intercept)	2.389	0.0220	1.053	117.58	1.010	1.096	*
< 24 months	Ref						
24-47 months	0.609	0.0059	1.059	108.22	1.047	1.070	*
≥48 months	0.680	0.0081	1.081	70.66	1.065	1.097	*
Place of delivery							
(Intercept)	2.406	0.0097	1.082	613.80	1.063	1.101	*
Health facility	Ref						

Elsewhere	0.379	0.0081	1.079	22.00	1.063	1.095	*
Sex of household head							
(Intercept)	2.737	0.0597	1.049	2098.75	0.932	1.166	*
Male	Ref						
Female	-0.007	0.0650	1.065	0.01	0.937	1.192	
Religion							
(Intercept)	2.773	0.0627	1.055	1954.34	0.932	1.178	*
Muslim							
Orthodox	-0.130	0.0678	1.062	3.67	0.929	1.194	
Protestant	0.008	0.0796	1.072	0.01	0.916	1.228	
Other	-0.084	0.1414	1.138	0.35	0.861	1.415	

*Where: coef=coefficient, s.e=standard error, ϕ=Acceleration Factor, Chi-sq=Chi-square, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Ref=Reference, *= p-value < 0.05.*

F. Log-normal - Inverse-Gaussian Univariable Analysis

Variable	**Coef**	**S.e(coef)**	**Φ**	**Chi-sq**	**95%CI**		**P-value**
					LCL	**UCL**	
Women's Education							
(Intercept)	2.775	0.0055	1.050	2558.63	1.039	1.060	*
No education	Ref						
Primary	-0.180	0.0059	1.059	9.19	1.047	1.070	*
Secondary&above	-0.212	0.0149	1.148	2.03	1.119	1.177	*
Wealth Index							
(Intercept)	2.450	0.0073	1.048	1136.50	1.034	1.062	*
Poor	Ref						
Middle	0.276	0.0070	1.070	15.60	1.056	1.083	*
Rich	1.111	0.0086	1.085	168.40	1.068	1.102	*
Type of births							
(Intercept)	2.780	0.0056	1.048	2454.00	1.037	1.059	*
Single	Ref						
Multiple	-1.060	0.0095	1.095	125.00	1.076	1.113	*

Total children ever born							
(Intercept)	2.452	0.0059	1.055	1750.19	1.043	1.066	*
1-3 children	Ref						
4-6 children	0.407	0.0057	1.057	51.49	1.046	1.068	*
7-9 children	0.405	0.0070	1.070	33.41	1.056	1.084	*
≥ 10 children	0.244	0.0111	1.111	4.84	1.089	1.133	*
Preceding birth intervals							
(Intercept)	2.380	0.0066	1.051	1290.20	1.038	1.064	*
< 24 months							
24-47 months	0.597	0.0058	1.058	105.70	1.047	1.069	*
≥48 months	0.660	0.0080	1.080	68.40	1.064	1.095	*
Place of delivery							
(Intercept)	2.410	0.0087	1.082	759.70	1.065	1.099	*
Health facility	Ref						
Elsewhere	0.360	0.0079	1.078	20.70	1.062	1.093	*
Sex of household head							
(Intercept)	2.733	0.0550	1.049	2468.61	0.941	1.157	*
Male	Ref						
Female	-0.003	0.0648	1.065	0.00	0.937	1.192	
Religion							
(Intercept)	2.775	0.0597	1.055	2163.42	0.938	1.172	*
Muslim							
Orthodox	-0.133	0.0648	1.060	4.21	0.932	1.187	
Protestant	-0.002	0.0760	1.070	0.00	0.921	1.219	
Other	-0.096	0.1397	1.137	0.47	0.863	1.411	

*Where: coef=coefficient, s.e=standard error, ϕ=Acceleration Factor, Chi-sq=Chi-square, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Ref=Reference, * =p-value < 0.05.*

APPENDIX 2

Multivariate analysis using Gamma and Inverse Gaussian parametric shared frailty models for time-to-death of under five children in Ethiopia.

A. Weibull- Gamma Multivariate Analysis

Variable	Coef	S.e(coef)	Φ	Chi-sq	95%CI		P-value
					LCL	UCL	
Women's Education							
(Intercept)	1.797	0.0306	1.122	34.39	1.062	1.182	*
No education	Ref						
Primary	-0.238	0.0071	1.071	11.35	1.057	1.084	*
Secondary&above	-0.367	0.0204	1.204	3.22	1.164	1.244	*
Wealth Index							
(Intercept)	1.797	0.0306	1.122	34.39	1.062	1.182	*
Poor	Ref						
Middle	0.249	0.0079	1.079	10.03	1.063	1.094	*
Rich	1.490	0.0131	1.131	129.71	1.105	1.156	*
Type of births							
(Intercept)	1.797	0.0306	1.122	34.39	1.062	1.182	*
Single	Ref						
Multiple	-1.095	0.0094	1.094	136.82	1.075	1.112	*
Total children ever born							
(Intercept)	1.797	0.0306	1.122	34.39	1.062	1.182	*
1-3 children	Ref						
4-6 children	0.371	0.0067	1.067	30.56	1.054	1.080	*
7-9 children	0.498	0.0083	1.083	35.93	1.067	1.099	*
≥ 10 children	0.181	0.0125	1.125	2.08	1.101	1.150	*
Preceding birth intervals							
(Intercept)	1.797	0.0306	1.122	34.39	1.062	1.182	*
< 24 months	Ref						
24-47 months	0.458	0.0066	1.066	48.81	1.053	1.078	*
≥48 months	0.551	0.0096	1.096	32.92	1.077	1.115	*

Place of delivery							
(Intercept)	1.797	0.0306	1.122	34.39	1.062	1.182	*
Health facility	Ref						
Elsewhere	0.657	0.0106	1.106	38.69	1.085	1.126	*
Frailty				4.38			*
	$\theta = 0.868$ $\tau = 0.333$ $\delta = 1.250$ $\lambda = 0.098$						
	Likelihood ratio test of $\theta = 507$,df= 24, p-value=0.00						

*Coef= coefficient, Se= standard error, ϕ = acceleration factor, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Chi-sq=Chi-square, Ref=Reference, θ = variance of the random effect, λ = scale parameter, δ = shape parameter, τ = Kendall's Tau, * =p-value < 0.05.*

B. Weibull-Inverse Gaussian Multivariate Analysis

Variable	**Coef**	**S.e(coef)**	**Φ**	**Chi-sq**	**95%CI**		**P-value**
					LCL	**UCL**	
Women's Education							
(Intercept)	1.799	0.0130	1.118	192.49	1.092	1.143	*
No education	Ref						
Primary	-0.244	0.0070	1.070	12.14	1.056	1.083	*
Secondary&above	-0.361	0.0204	1.203	3.14	1.163	1.243	*
Wealth Index							
(Intercept)	1.799	0.0130	1.118	192.49	1.092	1.143	*
Poor	Ref						
Middle	0.233	0.0078	1.078	8.89	1.062	1.093	*
Rich	1.475	0.0130	1.129	129.00	1.104	1.155	*
Type of births							
(Intercept)	1.799	0.0130	1.118	192.49	1.092	1.143	*
Single	Ref						
Multiple	-1.083	0.0092	1.092	137.26	1.074	1.110	*
Total children ever born							
(Intercept)	1.799	0.0130	1.118	192.49	1.092	1.143	*
1-3 children	Ref						

4-6 children	0.373	0.0067	1.067	30.90	1.054	1.080	*
7-9 children	0.500	0.0083	1.082	36.60	1.066	1.098	*
≥ 10 children	0.177	0.0125	1.125	2.00	1.100	1.149	*
Preceding birth intervals							
(Intercept)	1.799	0.0130	1.118	192.49	1.092	1.143	*
< 24 months	Ref						
24-47 months	0.444	0.0065	1.065	46.35	1.052	1.078	*
≥48 months	0.537	0.0096	1.095	31.53	1.077	1.114	*
Place of delivery							
(Intercept)	1.799	0.0130	1.118	192.49	1.092	1.143	*
Health facility	Ref						
Elsewhere	0.642	0.0103	1.101	39.09	1.081	1.121	*
Frailty				17.12			*
	$\theta = 0.0264$ $\tau = 0.223$ $\delta = 1.250$ $\lambda = 0.098$						
	Likelihood ratio test of $\theta = 504$, df= 21.2 , p-value=0.00						

*Coef= coefficient, Se= standard error, ϕ = acceleration factor, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Chi-sq=Chi-square, Ref=Reference, θ = variance of the random effect, λ = scale parameter, δ = shape parameter, τ = Kendall's Tau, *= p-value < 0.05.*

C. Log-logistic-Gamma Multivariate Analysis

Variable	**Coef**	**S.e(coef)**	**Φ**	**Chi-sq**	**95%CI**		**P-value**
					LCL	**UCL**	
Women's Education							
(Intercept)	1.217	0.0311	1.125	15.29	1.064	1.186	*
No education	Ref						
Primary	-0.248	0.0071	1.071	12.39	1.057	1.084	*
Secondary&above	-0.0916	0.0201	1.201	-1.57	1.162	1.241	*
Wealth Index							
(Intercept)	1.217	0.0311	1.125	15.29	1.064	1.186	*
Poor	Ref						
Middle	0.274	0.0076	1.076	13.00	1.061	1.091	*

Rich	1.4347	0.0116	1.116	152.87	1.093	1.139	*
Type of births							
(Intercept)	1.217	0.0311	1.125	15.29	1.064	1.186	*
Single	Ref						
Multiple	-1.1436	0.0098	1.098	136.05	1.079	1.117	*
Total children ever born							
(Intercept)	1.217	0.0311	1.125	15.29	1.064	1.186	*
1-3 children	Ref						
4-6 children	0.4538	0.0066	1.066	47.64	1.053	1.079	*
7-9 children	0.4995	0.0081	1.081	37.67	1.065	1.097	*
≥ 10 children	0.2901	0.0122	1.122	5.69	1.098	1.145	*
Preceding birth intervals							
(Intercept)	1.217	0.0311	1.125	15.29	1.064	1.186	*
< 24 months	Ref						
24-47 months	0.5337	0.0062	1.062	74.17	1.050	1.074	*
≥48 months	0.595	0.0089	1.089	44.42	1.072	1.107	*
Place of delivery							
(Intercept)	1.217	0.0311	1.125	15.29	1.064	1.186	*
Health facility	Ref						
Elsewhere	0.7077	0.0108	1.108	42.98	1.087	1.129	*
Frailty				4.39			*

$\theta = 0.893$ $\tau = 0.395$ $\delta = -4.194$ $\lambda = 1.461$

Likelihood ratio test of $\theta = 604$, df= 24, p-value=0.00

*Coef= coefficient, Se= standard error, ϕ = acceleration factor, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Chi-sq=Chi-square, Ref=Reference, θ = variance of the random effect, λ = scale parameter, δ = shape parameter, τ = Kendall's Tau, * =p-value < 0.05.*

D. Log-logistic- Inverse Gaussian Multivariate Analysis

Variable	Coef	S.e(coef)	Φ	Chi-sq	95%CI		P-value
					LCL	UCL	
Women's Education							
(Intercept)	1.2191	0.0134	1.121	83.30	1.095	1.147	*
No education	Ref						
Primary	-0.2536	0.0070	1.070	13.09	1.056	1.084	*
Secondary&above	-0.1031	0.0200	1.200	0.27	1.160	1.239	*
Wealth Index							
(Intercept)	1.2191	0.0134	1.121	83.30	1.095	1.147	*
Poor	Ref						
Middle	0.2603	0.0076	1.075	11.88	1.060	1.090	*
Rich	1.4083	0.0113	1.112	154.98	1.090	1.134	*
Type of births							
(Intercept)	1.2191	0.0134	1.121	83.30	1.095	1.147	*
Single	Ref						
Multiple	-1.132	0.0098	1.097	134.69	1.078	1.117	*
Total children ever born							
(Intercept)	1.2191	0.0134	1.121	83.30	1.095	1.147	*
1-3 children	Ref						
4-6 children	0.4519	0.0066	1.066	47.39	1.053	1.078	*
7-9 children	0.498	0.0081	1.081	37.59	1.065	1.097	*
≥ 10 children	0.2873	0.0121	1.121	5.61	1.098	1.145	*
Preceding birth intervals							
(Intercept)	1.2191	0.0134	1.121	83.30	1.095	1.147	*
< 24 months	Ref						
24-47 months	0.5259	0.0062	1.062	72.60	1.050	1.074	*
≥48 months	0.5845	0.0089	1.089	43.33	1.071	1.106	*
Place of delivery							
(Intercept)	1.2191	0.0134	1.121	83.30	1.095	1.147	*
Health facility	Ref						

Elsewhere	0.7092	0.0106	1.106	44.55	1.085	1.126	*
Frailty				19.84			*
	θ= 0.03 τ=0.399 δ = -6.032 λ= 1.270						
	Likelihood ratio test of θ = 602,df= 21.4 , p-value=0.00						

*Coef= coefficient, Se= standard error, ϕ = acceleration factor, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Chi-sq=Chi-square, Ref=Reference, θ = variance of the random effect, λ = scale parameter, δ = shape parameter, τ = Kendall's Tau, * =p-value < 0.05.*

E. Log-normal-Gamma Multivariate Analysis

Variable	**Coef**	**S.e(coef)**	**Φ**	**Chi-sq**	**95%CI**		**P-value**
					LCL	**UCL**	
Women Education							
(Intercept)	1.3829	0.0309	1.118	19.99	1.058	1.179	*
No education	Ref						
Primary	-0.222	0.0066	1.066	11.25	1.053	1.079	*
Secondary&above	-0.0562	0.0190	1.190	0.09	1.153	1.227	*
Wealth Index							
(Intercept)	1.3829	0.0309	1.118	19.99	1.058	1.179	*
Poor	Ref						
Middle	0.2655	0.0071	1.071	14.08	1.057	1.085	*
Rich	1.2704	0.0093	1.093	185.95	1.075	1.111	*
Type of births							
(Intercept)	1.3829	0.0309	1.118	19.99	1.058	1.179	*
Single	Ref						
Multiple	-1.1085	0.0098	1.098	127.44	1.079	1.117	*
Total children ever born							
(Intercept)	1.3829	0.0309	1.118	19.99	1.058	1.179	*
1-3 children	Ref						
4-6 children	0.3943	0.0062	1.062	41.08	1.049	1.074	*
7-9 children	0.4644	0.0077	1.077	36.66	1.062	1.092	*
≥ 10 children	0.2651	0.0117	1.117	5.13	1.094	1.140	*

Preceding birth intervals							
(Intercept)	1.3829	0.0309	1.118	19.99	1.058	1.179	*
< 24 months	Ref						
24-47 months	0.5199	0.0059	1.059	78.52	1.047	1.070	*
≥48 months	0.5845	0.0082	1.082	50.60	1.066	1.098	*
Place of delivery							
(Intercept)	1.3829	0.0309	1.118	19.99	1.058	1.179	*
Health facility	Ref						
Elsewhere	0.6347	0.0101	1.101	39.64	1.081	1.120	*
Frailty				3.80			*
θ= 0.898 τ= 0.739 δ = 6.491 λ= 2.187							
Likelihood ratio test of θ = 625 ,df=21.4 , p-value=0.00							

*Coef= coefficient, Se= standard error, ϕ = acceleration factor, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Chi-sq=Chi-square, Ref=Reference, θ = variance of the random effect, λ = scale parameter, δ = shape parameter, τ = Kendall's Tau, * =p-value < 0.05.*

APPENDIX 3

Kaplan-Meier curves of time-to-death for different groups.

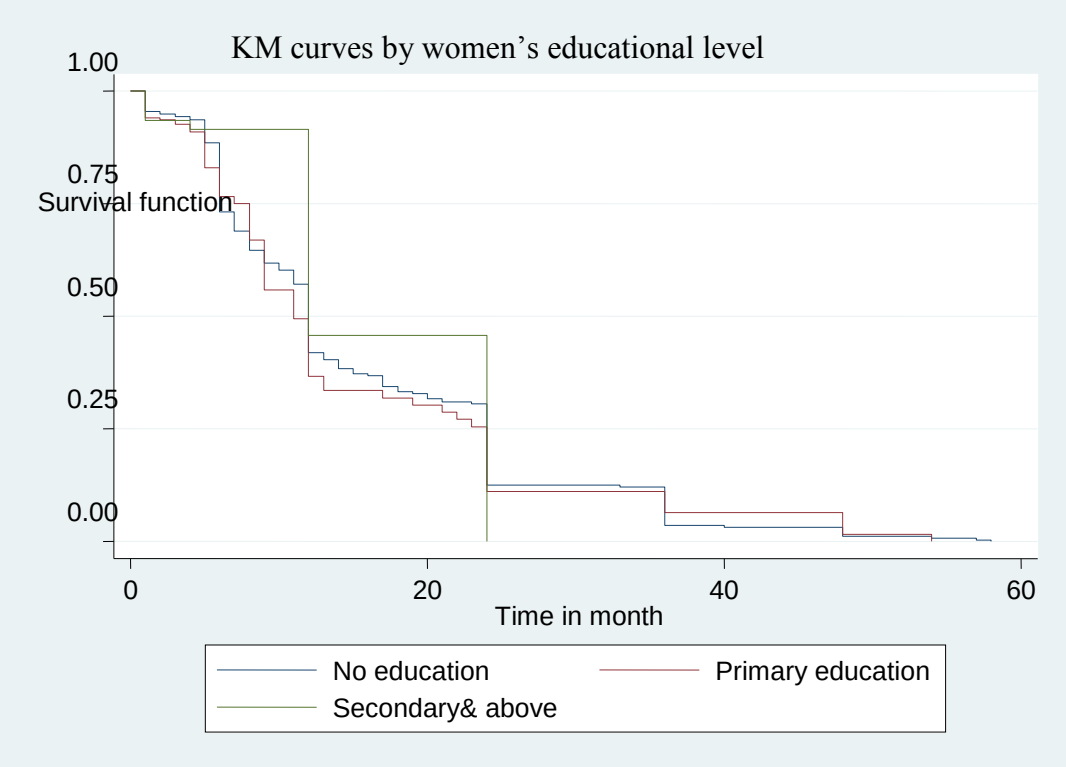

Figure 4.2: KM curves of time-to-death for under-five children by women's educational level.

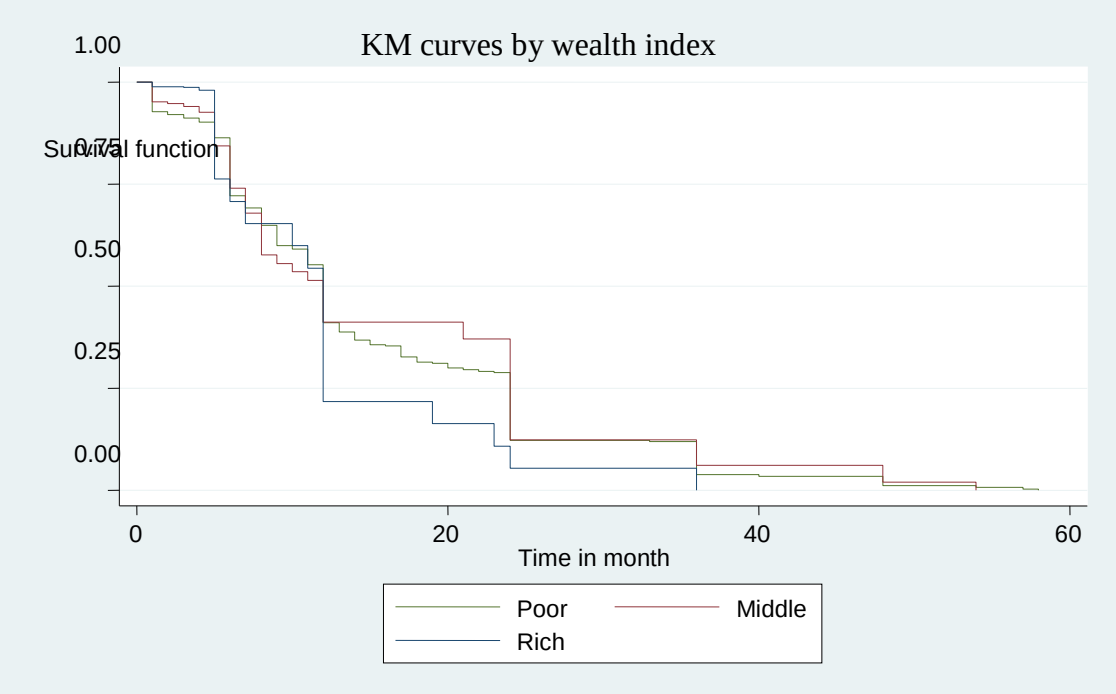

Figure 4.3: KM curves of time-to-death for under-five children by wealth index

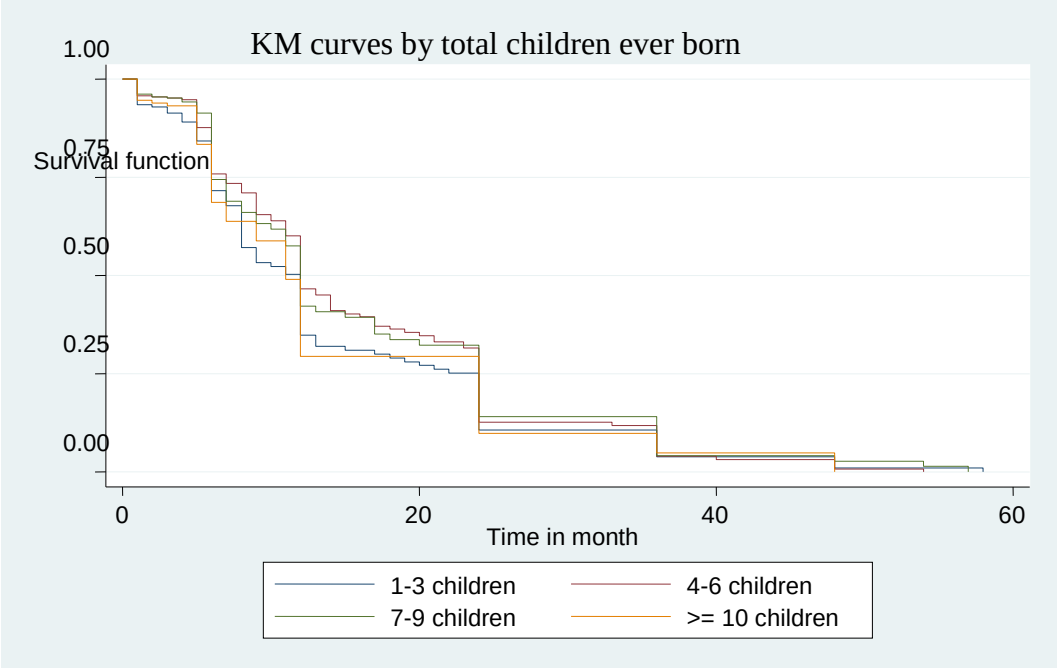

Figure 4.5: KM curves of time-to-death for under-five children by total children ever born

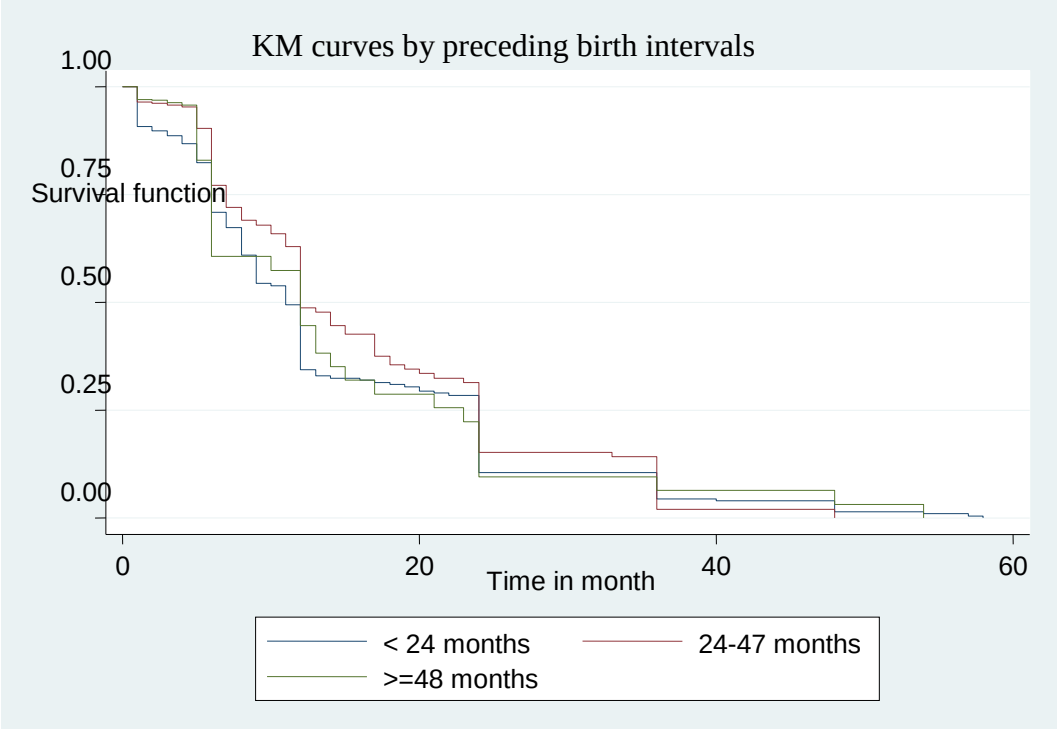

Figure 4.6: KM curves of time-to-death for under-five children by preceding birth intervals.

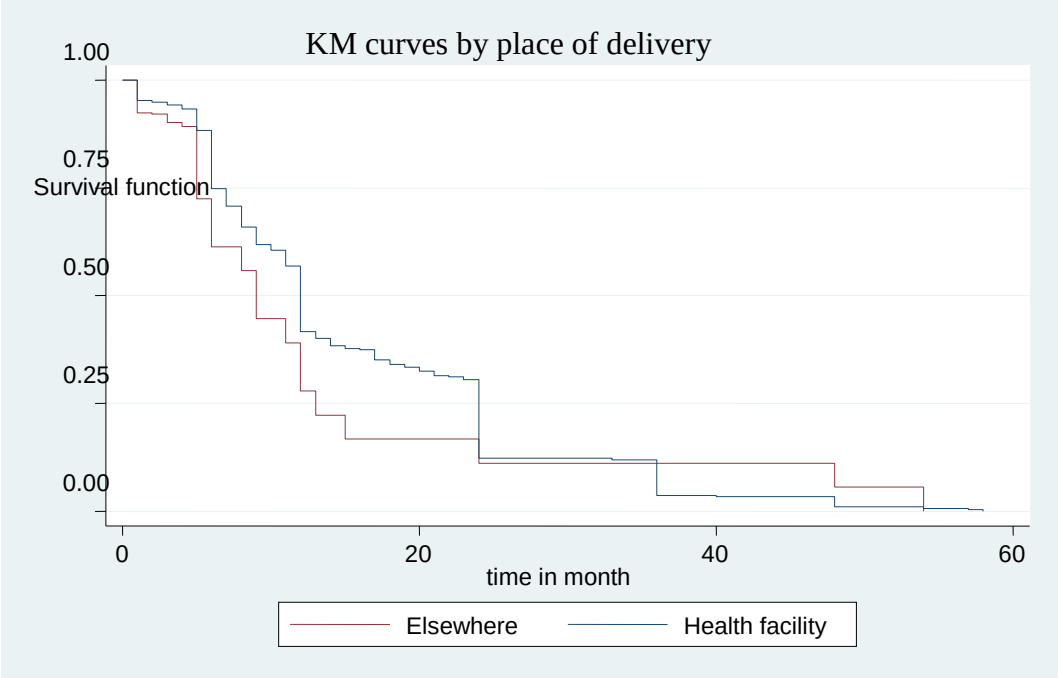

Figure 4.7: KM curves of time-to-death for under-five children by Place of delivery.

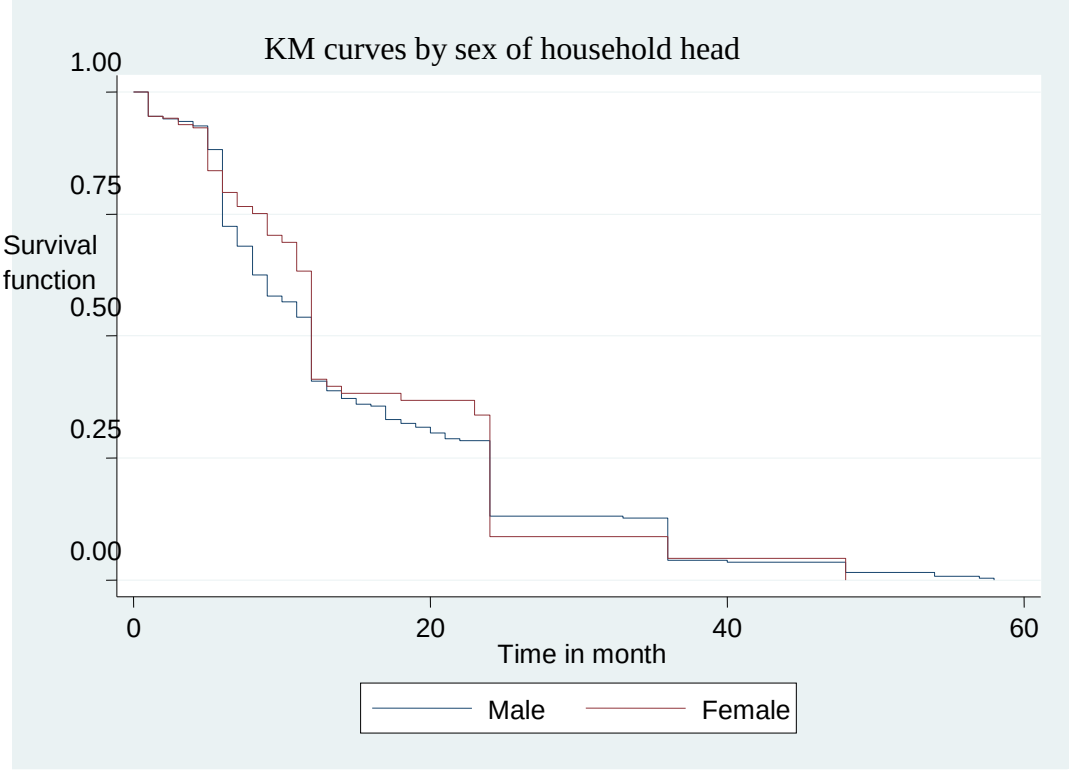

Figure 4.8: KM plot for survival of time-to-death for under-five children by sex of household head

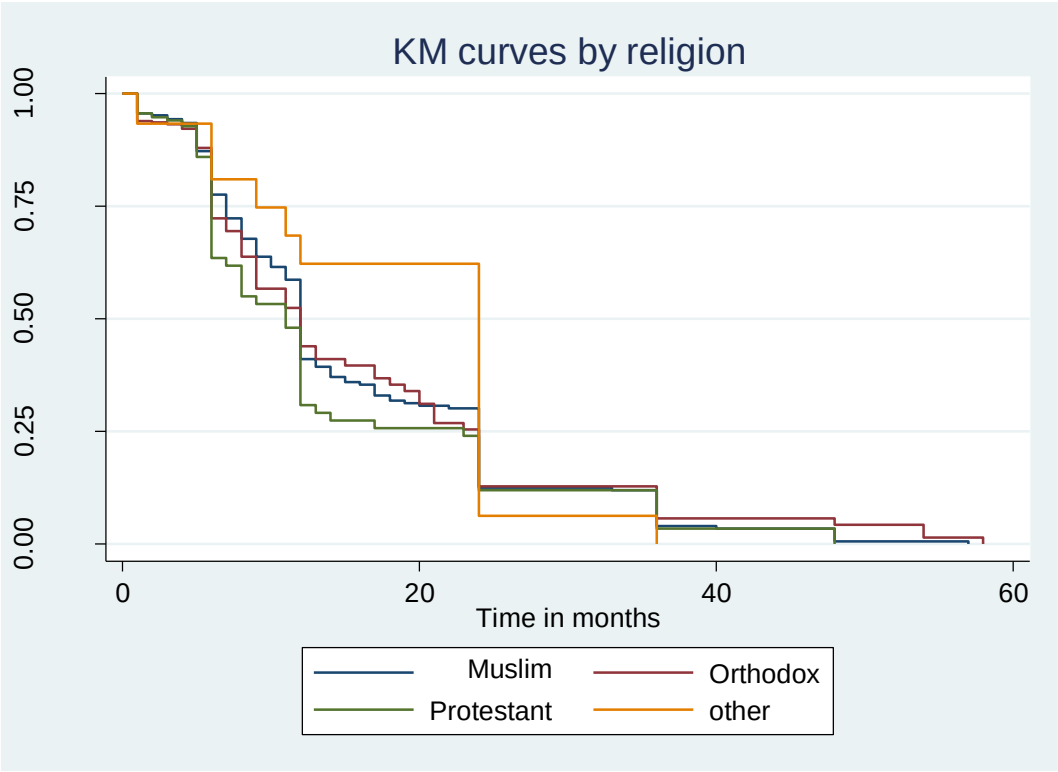

Figure 4.9: KM plot for survival of time-to-death for under-five children by sex of religion

APPENDIX 4

Table 4.3: Median time-to-death for under-five children and confidence interval by levels of Covariates

Category	Time-to-death		
		95% CI	
	Median (in months)	LCL	UCL
No education	12	12	13
Primary education	11	9	14
Secondary& above	12	12	13
Poor	12	11	12
Middle	12	8	24
Rich	12	7	19
Single	12	12	13
Multiple	7	6	11
1-3 children	12	8	12

4-6 children	12	12	15
7-9 children	12	11	17
>= 10 children	11	7	24
<24 months	11	9	12
24-47 months	12	12	17
>=48 months	12	6	17
Health facility	9	6	15
Elsewhere	12	12	13
Male	12	11	12
Female	12	12	18
Orthodox	12	12	13
Muslim	12	9	17
Protestant	11	8	12
Other	24	12	24

Table 4.6: Summary of quantitative variables

						95% CI	
Variable	Minimum	Maximum	Mean	median	Std.Deviation	LCL	UCL
time-to-death	1	58	11.5	12	3.62	11	13