Modeling Time-to-Recovery from Obstetric Fistula in Jimma University Medical Center, South West, Ethiopia

By

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STATEMENT OF AUTHOR

I declare that this thesis is a result of my genuine work and all sources of materials used 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 deposited 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.

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As thesis advisors, we here by certify that we have read the thesis prepared by Abriham Shiferaw under our guidance, which is entitled **"Modeling Time-to-Recovery from Obstetric Fistula in Jimma University Medical Center",** 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 ready for submission to the university library.

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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.

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My Father, Shiferaw Areba

&

Mother, Kasho Dabe

ABSTRACT

Obstetric fistula affects an estimated 50, 000 to 100,000 women around the world every year and is particularly common in sub-Saharan Africa, where populations face challenges to obtaining quality health care. The World Health Organization estimates that 9,000 Ethiopian women develop new fistulas every year.The general objective of this study is modeling time-to-recovery from obstetric fistula in Jimma University Medical Center, Ethiopia.Retrospective study was conducted in Jimma University Medical Center from January 2011to February2017.The Kaplan-Meierestimation method, Cox proportional hazard model, accelerated failure time and parametric frailty models were applied.The finding of this study showed that out of 270 obstetric fistula patients 81.4% of them were physically cured while the rest 18.6% were censored.Thelognormal inverse Gaussian frailty model has theminimum AIC value among accelerated failure time and other frailty models.The clustering effect is significant on modeling time-to-recovery from OBF.The result showed that Patients with weight ≥50kg (Φ=0.86), divorced(Φ=1.2), incontinence of urine >3months(Φ=1.2), residence at urban (Φ=1.56), no follow-up of antenatal care(Φ=1.189), duration of labor<2days(Φ=0.86), delivery at Health center(Φ=0.76), vaginal delivery(Φ=1.5), partially damaged urethra(Φ=1.59) and Vesico-vaginal fistula(Φ=0.735) were significantly affect recovery time of a fistula.The results suggested that patients from different zone had different pattern in their timing of fistula recovery. The study suggested that Patients with incontinence of urine > 3months, residence at urban, no follow-up of antenatal care, vaginal delivery, divorced and status of urethra partially damaged were prolonged time-to-recovery from OBF while weight ≥50kg, delivery at health center, duration of labor <2days and Vesico vaginal fistula were shorter time-to-recovery from OBF.The researcher recommends that the people should aware of the burden of those risk factors and well informed about the fistula.

Key words: *Obstetric Fistula, Time-to-recovery, Frailty Model, SurvivalAnalysis*

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LIST OF ACRONYMS

AFT Accelerated Failure Time

AIC Akaikie Information Criterion

ANC Antenatal Care

CIConfidence interval

CSCesarean Section

JUMCJimma University Medical Center

HRHazard Ratio

KM Kaplan-Meier

LR Likelihood ratio

MLE Maximum Likelihood Estimation

OBF Obstetric Fistula

PH Proportional Hazard

RVF Recto-Vaginal Fistula

SE Standard Error

UNFPA United Nation Population Fund

VVF Vesico-Vaginal Fistula

WHO World Health Organization

CHAPTER ONE
INTRODUCTION

1.1 Background of the study

The word "fistula" is a collective medical term for an abnormal connection between two bodily organs. In the case of obstetric fistula, it is the result of pressure exerted by the fetal head in the pelvis during obstructed labor, a force that interrupts the blood flow to nearby tissues in the mother's pelvis, resulting in two classifications Vesico vaginal fistula and Recto vaginal fistula. VVF occurs when the blood supply to the tissues of the vagina and the bladder is restricted during prolonged obstructed labor, the tissues die between these organs, forming holes through which urine can pass uncontrollably. RVF occurs in a similar way to VVF however, holes form between the tissues of the vagina and rectum, leading to uncontrollable leakage of faces (WHO, 2014).

Obstetric fistula is a maternal morbidity with devastating effects on a woman's life, persisting in low-income countries but virtually eliminated from the morbidity burden in high and middle-income countries. UNFPA (2012) estimates 2 to 3.5 million women currently suffer untreated fistula worldwide; and at least 50,000 to 100,000 women develop a fistula every year.OBF commonly results from child birth injuries that occur when labor does not progress normally, and the fetal presenting part becomes impacted within the birth canal. OBF like many other maternal mortalities and morbidities is almost inexistent in developed countries because emergency obstetric care is never far from a woman in labor. OBF sometimes occurs in developed countries as a complication of interventions like cancer treatment and pelvic surgery, for instance, post-hysterectomy (Wall, 2012).

Obstetric fistula is predominant in Africa with about 100,000 new cases occurring yearly (Tuncalp, et al., 2015; Wall, 2014). The event of OBF in these areas is typically preceded by a long hard labor that is unrelieved because the hospital where a cesarean section could be done is out of reach, either physically, financially, or socially (Maine, 1999). OBF all the maternal morbidities in sub-Saharan Africa, OBF receives the most attention because it has the most debilitating effect on women's lives (Hardee & Blanc, 2012). Also, theaccompanying problems are instituted by sociocultural and political conditions that perpetuate health inequities and injustices.

The incidence of OBF particularly in sub-Saharan Africa is an indicator of the poor state of maternal health coverage and, existing inequities in access to health care for women. The accompanying social and psychological impact of OBF on the woman is an even more significant cause for concern. According to Amodu (2016), these social problems can be worse than death. These issues for women are yet worsened by societal hegemonies and traditions related to reproductive health ideals.

In Ethiopia, it is estimated that 9,000 women annually develop a fistula, of which only 1,200 are treated (WHO, 2014). In Ethiopia, where 94% of births occur in the home without any medical care the risk of death and fistulas for women in child birth is enormous. Of the 3 million women who gave birth every year in Ethiopia, an estimated 8, 500 to 9,000 will develop the obstetric fistula. In Ethiopia 95% of VVF is obstetrics. The main cause in over 85% of OBF is obstructed labor that is not relieved in time by performing the caesarean section.

The Addis Ababa Fistula Hospital and its five outreach centers located in different regions have treated over 35,000 women in the last 35 years. Every year, doctors at the hospital and outreach centers operate on less than 2500 fistula patients (Hamlin Fistula Ethiopia 2010). Most fistula sufferers are young women; many still live with their condition for upwards of 25 years (Muleta et al 2008). It has been observed over the last 35 years that most women coming to seek treatment have had the problem for many years.

The Hamlin Fistula Ethiopia has been engaged for more than 35 years in the treatment of women with obstetric fistula and in the past seven years in various activities to minimize the incidence of fistula and increase awareness on early seeking of medical care. This has resulted in larger numbers of women with obstetric fistula seeking treatment. Some of the women lived for more than 30 to 40 years with the problem; some were hidden in monasteries where their lifestyle was completely changed. Despite a lot of effort to bring women early to the treatment centers and hospitals, still, many women continue to live with the problem. Eventually the source of the problem is the fact that delayed treatmenthas become too common and that this delayed pattern of seeking help has a detrimental health impact. Women's health is one of the major health issues in Ethiopia and obstetric fistula is a major contributor. Poverty, malnutrition, a poor access to health services and early marriage all play a role in the development of obstetric fistula in the rural settings of Ethiopia (Woldeamanuel, S. A. 2012).

Survival analysis is a statistical method for data analysis where the response variable is the time to the occurrence of an event, time-to-recovery from OBF in this study. In this study time-to-recovery from OBF was clustered by the zone. Hence, the effect of the zone was assessed by introducing the frailty term in the survival model. The study used parametric shared frailty model in determining the factors which affect the time-to-recovery from OBF. Also, Cox PH and accelerated failure time models fitted using Weibull, log-logistic and lognormal baseline distributions to compare and get the best model which fits the time-to-recovery from OBF data appropriately in JUMC.

1.2 Statements of the Problem

The problem of obstetric fistula is rare in developed and industrialized countries but remains a public health problem in developing countries with poor access to health facilities. It is one of the evilest morbidities associated with delivery. Although obstetric fistula is preventable and treatable conditions, the untreated condition remains prevalent in developing countries. Ethiopia is one of the developing countries with, poor maternal health care that leads over 100,000 girls and women living with a fistula, and further 9000 cases develop annually(WHO, 2014).

A large number of factors have been identified which may be associated with obstetric fistulae, such as early marriage, childhood, gender inequality, malnutrition, poor of education, lack of access to the health center and removal of the reproductive body are some of the socio-cultural factors. In the developing countries, factors such as lack of access to maternal health services and emergency obstetric care are contributing to the silent epidemic (Geta A., 2011). Obstetric fistula affects numerous girls and women. Women affected by obstetric fistula have to suffer not only the consequence of losing their children, physical, psychological and but also subjected to social humiliation and shame.They become outcasts due to pungent smell and wetness from urinary incontinence (Wall et al., 2004).

Despite the Addis Ababa Fistula Hospital and its five outreach centers dedication to treating women with obstetric fistula and massive community awareness activities for promoting treatment, there were only 1477 new fistula cases repaired in the year 2010, only 16.4% of new patients (Hamlin Fistula Ethiopia 2010).

Patients in the same cluster (community) usually share certain unobserved characteristics and as a result patients of the same cluster tend to be correlated. Some studies have been conducted on obstetric fistula in the context of Ethiopia, but none of them was not considered heterogeneity due to sampling design in the analysis. Therefore, this study is unique in that, the researchers used and compared for their efficiency, the parametric model (without taking into account the clustering of the data) and its extension parametric frailty model to investigate the pattern of obstetric fistula in Jimma University medical center using important covariates. Ignoring the dependencies among the observations, obtained from a cluster sampling scheme, can lead to incorrect standard errors of the estimates of the parameters of interest (Sastry, 1998). Frailty modeling approach accounts for this problem by specifying independence among observed data items conditional on a set of unobserved or latent variables. Frailty term was added to account the correlation which comes from the cluster, accounts unobservable random effect. In general, the motivation behind this study is to address the following major research questions:

- Which factors significantly affect time-to-recovery from obstetric fistula in Jimma University Medical Center?
- Is there a significant effect of unobserved heterogeneity in obstetric fistula patients in Jimma University Medical Center?
- Which type of survival model, AFT or parametric frailty model, predicts well the covariate that is associated with high risk of time-to-recovery from OBF in JUMC?

1.3 Objectives of the Study

1.3.1 General Objectives of the Study

The general objective of this study is modelingtime-to-recovery from obstetric fistula inJimma University Medical Center.

1.3.2 Specific Objectives

To:

- Identify factors associated with time-to-recovery from obstetric fistula inJimma University Medical Centerpatients.
- Test whether there is a clustering effect on modeling time-to-recovery from OBF, which might be due to the heterogeneity in Zones of fistula patients.
- Compare AFTand parametric frailty model in modeling time-to-recovery dataset in Jimma University Medical Center.

1.4 Significances of the Study

The result of this study will provide information on time to recovery from obstetric fistula among patients and its determinant factors. Specifically:

- To provide information about the covariates or risk factors of time-to-recovery from obstetric fistula.
- Provide information to government and concerned bodies in setting policies and strategies.
- The results of this study provide better opportunity for further studies in future.

1.5 Scope of the Study

The study would have been covered recovery obstetric fistula patients from 1st January 2011 to 1st February 2017, in Jimma University Medical Center. However, it is limited to identify the risk factors and compare models in JUMCfistula data.

CHAPTER TWO

LITERACTURE REVIEW

2.1 Overview of Obstetric Fistula

According to the World Health Organization, obstetric fistula is an abnormal connection between a women's vagina, rectum, and bladder which may develop after prolonged and obstructed labor and lead to continuous urinary or feces incontinence. A hole between the urinary bladder and the vagina is regarded as vesicovaginal fistula whereas a hole between the rectum and the vagina is known as the recto-vaginal fistula (Tuncalp 2015).

Obstructed labor is one of the leading causes of maternal mortality in developing countries and with it, comes other morbidities, the most devastating being obstetric fistula. It is estimated that for every maternal death, 20-30 women develop serious obstetric complications including fistula. These women, apart from surviving the ordeal of obstructed labor, face the physical and psychosocial challenges of living with obstetric fistula (Ahmed 2015).

Generally accepted estimates suggest that 2-3.5 million women live with obstetric fistula in the developing world, and between 50,000 and 100,000 new cases develop each year. All but eliminated from the developed world, obstetric fistula continues to affect the poorest of the poor: women and girls living in some of the most resource-starved remote regions in the world; of these, between 26,000 and 40,000 live in Ethiopia, 100,000 to 1,000,000 live in Northern Nigeria, and over 70,000 live in Bangladesh (UNFPA, 2012; WHO, 2014).

Reports from Sub Saharan Africa and the Middle East, 79.4% to 100% of reported fistula cases were obstetrical while the remaining cases were from other causes. Recto-vaginal fistulae accounted for 1% to 8%, vesicovaginal fistulae for 79% to 100% of cases (Tebeu 2012). The success rate of obstetric fistula repair is in general in the 80 to 90 percentile; however, there is a difference between completely cured and completely closed fistula. A patient who is completely cured is successfully closed and continent; whereas a patient with a closed fistula might still suffer from incontinence (Kelly J. 1995).

2.2Literature Related to the Obstetric Fistula

Biadgilign, S. et al., used logistic regression model in Prevalence and determinants of Obstetric Fistula in Ethiopia. The result showed that place of residence and parity(birth 10 or more) significantly affects OBF. The mean age of women who reported OBF was 32.9.

Marit L.(2016) using logistic regression prevention obstetric fistula in Addis Ababa. The result showed that married, formal education, delivery at home statistical significant effect on obstetric fistula but antenatal care, divorced are not significant.

Tukur et al. (2015) from 1st April to 31st October 2013, a total of 137 cases of obstetric fistula that satisfied the inclusion criteria were recruited at three fistula centers in north west Nigeria. Patients with Vesico-vaginal fistula alone accounted for 88% of cases, while patients with Recto-vaginal fistula, accounted for 12% of cases. Only half of the patients remained married at presentation, while 38 (27.7%) were divorced. Ninety two patients (67.2%) had no form of education and six patients (4.3%) had Primary/secondary education and39(28.5%) had some formal education.

Roka et al. (2013) seventy cases and 140 controls were included in the study, of the 70 cases, 38(54%) were married and 14(20%) were divorced compared to controls where 110/140 (79%) were married and 6/140(4.3%) were divorced. All the women with fistula who were divorced attributed the divorce to the fistula onset. Forty six percent (64/140) of the controls had labor duration of less than 12 hours and 39% (54/140) had duration of 12–24 hours. Seventy three percent (51/70) of cases and 84% (118/120) of controls delivered in a health facility. Seventy four percent (52/70) of cases and 94% (121/140) of controls had attended antenatal clinic at least once in the last pregnancy or the pregnancy associated with fistula.

Sori et al. (2016) patients with obstetric Vesico-vaginal fistula were repaired in Jimma University Specialized hospital, of 10.1% were younger than 18 years, 80% of patients were laboring for two or more days, 46.4 % delivered abdominally (cesarean section 24.4 %, hysterectomy for uterine rupture 22 %), and 85.7 % ended up in stillbirth. Most patients (56 %) had mid-vaginal Vesico-vaginal fistula. Route of repair was vaginal among 95.8 % of patients, and spinal anesthesia was applied among 70.8% of patients. Out of 93.4 % patients who had successful closure of their fistula, 84.5%of patients had their fistula healed and continent, 8.9 % of them developed urinary incontinence while 6.5 % of fistula repair had failed at the time of discharge.

Holme et al., (2007) reported that obstetrical fistula is most often the result of prolonged and obstructed labor. Up to 95.5% of 259 cases of obstetrical fistula reported in Zambia occurred following labor for more than 24 hours before the completion of delivery. Ninety two percent of 201 fistula cases reported in northern Ethiopian women did not have any antenatal care (Gessessew et al., 2003). Eighty-five percent of the 52 fistula patients in a Niger series delivered at home (Haroun et al., 2001).

Michele et al. (2013) on the long term outcomes of vaginal mesh versus native tissue repair for anterior vaginal wall prolapsed, from this a five year surgery for recurrent prolapse was similar between vaginal mesh and native tissue groups (10.4% vs 9.3%), P = 0.70 and the result of adjusted cox model were similar(HR=0.93, 95% CI: 0.83, 1.05). It shows that the use of mesh for anterior prolapsed was associated with an increased risk of repeat surgery.

WHO (1994) suggested that, when women try to labor at home unsuccessfully, they are more likely to come to the hospital at a late stage. This may be further delayed by the absence of transportation, poor roads, heavy rains, and great distances to the health facility. In many developing countries, patients have to use their own money to pay for health care, and this may further delay treatment.

The study conducted obstetric fistula in developing countries revealed that the mean age of fistula patients who admitted to the hospital was 22 years, age at first marriage was 14.7 and mean age at the causative delivery was 17.8. The result revealed that early marriages are more likely to expose to obstetric fistula (Muleta 2004). Early childbearing has been identified as one of the factors leading to increasing risks of fistula with particular reference to adolescents' women (12-19 years). This is prominent where early marriages are common for socio-cultural and religious reasons (Ampofo, K, 1990).

According to studies (Jonas et al., 1984; Symmonds, 1984; Lee et al., 1988 and Tancer, 1992) the most common cause of Vesico-vaginal fistula in most industrial countries is routine abdominal or vaginal hysterectomies. All major studies have shown that 75-90% of Vesico vaginal fistula in developing countries is due to obstetric etiology. Arshad et al. (2009) found that of 86 fistula cases maximum number of fistula were between 1-2 cm in size (44.18%), very few were less than 0.5 cm (4.65%) and above 4 cm (6.97%), multiple factors must be considered including the a etiology and duration of fistula, quality of tissues available for repair and probably most importantly the experience and training of the surgeon.

The mean duration of labor in fistula patients ranged from 2.5 to 4 days. Twenty to 95.7% of these women had labored for more than 24 hours, and operative delivery was performed in 11% to 60% of the indexed deliveries leading to fistula formation. Cephalopelvic disproportionwas the most common indication for cesarean delivery in sub-Saharan Africa. Studies have found Cephalopelvic disproportion as the primary indication in 30%, 33%, and 34% of cesarean deliveries in Senegal, Cameroon, and Namibia, respectively (Cisse et al., 1998; Van Dillen et al., 2007, Tebeu et al., 2008)

Wall and Karshima, (2004) found that of 899 fistula cases, 75% had a height less than 150cm and a weight less than 50kg. The body of literature suggests that malnutrition in childhood and adolescence might interfere with growth, leading to stunted stature and under-development of the pelvis, which in turn can impede pregnancy outcomes (Lawson,1989; Hamlin et al., 1996; Karshima et al., 2004; Ahmed et al., 2007).

Wall, karshima et al. (2004) conduct obstetric fistula patients from Jos, Plateau State, Nigeria and found with fistulas tended to have been married early, to be short (nearly 80% less than 150cm tall), small(mean weight less than 44kg), to be impoverished, poorly educated, and to come from rural agricultural families.

Feysal K., (2014) the study conducted on the Vesico-vaginal obstetric fistula in Metu Hamlin fistula hospital using Cox PH and Weibull regression models. The Cox PH results showed that weight, divorced, antenatal care, duration of incontinence of urine, duration of labor, place of delivery, mode of delivery and status of urethra were found as significant determinants. The result from Weibull regression analysis showed that recovery of VVOF patients was significantly related to age at first marriage, duration of incontinence of urine, duration of labor, place of delivery, mode of delivery, and status of the urethra. The log-rank test revealed that weight, antenatal care, duration of labor, place of delivery, mode of delivery and status of urethra. Out of 206 VVOF patients, 76.2% of them were physically cured while the rest 23.8% were censored.

Getachew, T., (2015) conducted the study on the obstetric fistula in Yirgalem Hamlin Fistula Hospital using Cox PH and Weibull regression model. The Cox PH results showed that weight, antenatal care, duration of incontinence of urine, duration of labor, place of delivery, mode of delivery and status of urethra were significantly affect recovery. The result from Weibull regression analysis showed that recovery of OBF patients was significantly related to weight, antenatal care, place of delivery, duration of labor, mode of delivery, status of urethra are statistical significant effect on obstetric fistula. The log-rank test revealed that antenatal care, place of delivery, mode of delivery, duration of incontinence of urine and status of urethra significant difference at 5% level. Among the patients with obstetric fistula considered, 81.7% of them were physically cured while the rest 18.3% were censored.

The study conducted in Prevalence of obstetric fistula and symptomatic pelvic organ prolapse in rural Ethiopia. The mean age of women was 29.5 years (SD 8.05). Just under a quarter (22%) of the women stated that they were aware of the symptoms of fistula, although there were considerable regional differences, with just 11% awareness in Eastern Harraghe, 31% awareness in West Gojjam and 21% in South Gondor(Ballard, K., Ayenachew, F., Wright, J., & Atnafu, H. 2016)

2.3Frailty Models

The concept of frailty provides a suitable way to introduce random effects in the model to account for the association and unobserved heterogeneity. In its simplest form, a frailty is an unobserved random factor that modifies multiplicatively the hazard function of an individual or a group or cluster of individuals (Wintrebert, 2007). Models constructed in terms of group level frailties are sometimes referred to as 'shared' frailty models because of observations within a subgroup share unmeasured 'risk factors' that prompt them to exit earlier than other subgroups.

Frailty models (Clayton and Cuzick, 1985) are increasingly popular for analyzing clustered survival data, where frailties or random effects often enter into the baseline hazard multiplicatively to model the correlation among observations within the same cluster (YI, 2000). We should be aware that, neither theory nor data typically provide much guidance for choosing a specific distribution from which to draw the frailty term and the parameter estimates can be very sensitive to the assumed parametric form (Zorn et al, 2000). The better model, the less unobserved heterogeneity there would be used. It is argued that the less heterogeneity in the model, the more appropriate it is to interpret any observed duration dependence in substantive terms (Zorn et al., 2000).

The more frail subjects experience on average the event earlier than the less fails subjects (Duchateau and Janssen, 2008). 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 (Gutierrez, 2002). In the second case, the baseline hazard is left unspecified and more complex techniques are available to approach that situation (Abrahantes et al., 2007) Even though semi-parametric estimation offers more flexibility, the parametric estimation will be more powerful if the form of the baseline hazard is somehow known in advance (Munda, 2012).

This study gives particularly a new approach to knowing the presence of unobserved factors (heterogeneity) with the help of observed prognostic factors. Various studies have been conducted to study the effects of prognostic factors incorporating frailty effect in different diseases like kidney transplant, waiting time to first pregnancy, genetic trait, birth interval etc. but its application on obstetric fistula is still an unexplored avenue. A number of works on the analysis of correlated survival data have appeared recently in the demographic literature.

S. Mahmood et al (2013) studied Frailty modeling for clustered survival data: an application to the birth interval in Bangladesh. The data used in this study are collected from a nation-wide survey (NIPORT, 2007), where multi-stage cluster sampling was used for the sampling design. The clusters were defined as small geographical regions and it is assumed that birth intervals for the women residing in the same cluster (community) are correlated because they share the same environment.

Yenefenta w.(2015) Modeling birth interval of women in Ethiopia: a comparison of Cox proportional hazards and shared gamma frailty models. The clusters were defined as small geographical regions and it is assumed that birth intervals for the women residing in the same cluster (community) are correlated because they share the same environment.

Ayele G. (2015) Survival Analysis of Time-to-First Birth after Marriage among Women in Ethiopia: Application of Parametric Shared Frailty Model. The clusters were defined as small geographical regions and it is assumed that birth intervals for the women residing in the same cluster (community) are correlated because they share the same environment. Banbeta, A. (2015) Modeling time-to-cure from severe acute malnutrition: a comparison of various parametric frailty models. The clusters were defined as Kebles and it is assumed that severe acute malnutrition for the children residing in the same cluster (community) are correlated because they share the same environment.

CHAPTER THREE

DATA AND METHODOLOGY

3.1 Data Source and Design

This study is a retrospective study (i.e. all the events-exposure had already occurred in the past) based on data from the OBF in Jimma University Medical Center, South West of Ethiopia. The survival data would be extracted from the patient's chart which contains epidemiological, laboratory and clinical information of all obstetric fistula patients initial date of entry to follow-up.

3.2 Study Area and Period

The study was conducted in Jimma University Medical Center, from 1st January 2011 to 1stFebruary 2017. It is currently administered by Jimma University and situated in Jimma town. Jimma town, the Capital of Jimma Zone, is located in southwest Ethiopia 335km away from Addis Ababa. The town is located at an average altitude of 1700 meter above sea level. Jimma Hospital which was established before 60 years during Italian Invasion is the only specialized referral Hospital in Southwest Ethiopia situated to the east of the town at about 3km from the town, Jimma Municipality.

3.3 Study Pupation

The study population includes all women who visited JUMC having OBF case only during the study period. Our inclusion criterion is to include all women who are admitted in JUMC from the year January, 2011 to February, 2017 G.C having OBF with complete information. Therefore, among the total of 350 OBF patients registered in the given year, only 270 OBF patients satisfy inclusion criteria and hence are included in this study.

3.4 Data Collection procedures

In this study, we incorporate secondary data. The hospital's registry was used to retrieve data on obstetric fistula and patients'initial date of entry to follow-up. During the study period, the hospital's record logbook also would be used in order to select the patients.

The completed data collection forms are examined for completeness and consistency during data management, storage and analysis. The data are collected by data clerks working in the clinic and coded and analyzed using the statistical softwareSTATA and R.

3.5Variables in the Study

The response and predictors variables used in the model for the estimation of parameters are defined as follows.

3.5.1 Response Variable

The response variable is the time-to-recovery from obstetric fistula, the length of time from obstetric fistula start diagnosis date until the date of recovery or censored(1st January 2011 to 1st February 2017), which is measured by weeks.A patient is said to be recovered if she physically cured from her sickness and no requirement for intervention of health care professionals.

3.5.2 Explanatory Variables

Several predictors wereconsidered in this study to investigate the determinant factors of time-to-recovery from OBF. These are age at first marriage, age of occurrence, weight, height, accompanying person, marital status, parity, fetal outcome, place of residence, education level, duration of incontinence of urine, antenatal care, place of duration of labor, delivery, mode of delivery, length of fistula, width of fistula, surgery approach, duration of Catheter, status of urethra and types of fistula. But for this thesis among these variables, the following are the only covariates used in table 3.1. The others are unfortunately not recorded on the patients' history card in the Hospital.

Table 3.1: Description of independent variables used in the study

Covariates	Description	Categories
Age	Age of Patient	0 = <20, 1 = 20 -30, 2 = >30
Zone	Zone of Patient live	0= Jimma, 1=Bench Majji, 2 =Bonga, 3=Yem, 4= Konta, 5=Gambela, 6=Bedele, 7=Tep
Residence	Residence of Patient live	1 = Urban 2=Rural

Education level	Education of Patient	0 = Illiterate, 1 = Literate
Weight	Weight of Patient	0= <50kg, 1= ≥50kg
Marital status	Marital status of Patient	0= Married, 1 = Divorced, 2=Others
Parity	No. of children born	0=1 child, 1=2-4 children, 2=≥ 5 children
Incontinence	Dur. of incontinence	0=≤3 months, 1= >3 months
ANC	Follow-up ANC	0=Yes, 1=No
Labor	Duration of labor	0=≥2 days, 1=<2 days
Place of delivery	Place of delivery	0=Home,1=Health Center
Delivery mode	Mode of delivery	0= Cesarean section, 1 = Vaginal
Surgery	Surgery approach	0= Abdominal, 1= Vaginal
Catheter	Duration of Catheter	0= ≤14 days, 1= 21 days
Urethra	Status of urethra	0= Not damaged , 1= Partially damaged
Type of fistula	Types of obstetric Fistula	0= VVF, 1=RVF

Others include: single & widowed.* Zone of the patients was considered as a clustering effect in frailty model.

3.6 Method of Survival Analysis

Most survival analyses consider a key analytical problem of censoring. In essence, censoring occurs when we have some information about individual survival time, but we do not know the survival time exactly(Aalen et al., 2008). In reality, such situation can occur due to the following reasons:

- A patient does not experience the event before the study ends
- A patient is lost to follow-up during the study period and
- A patient withdraws from the study for unknown/known reasons.

There are three categories of censoring.

1. **Right Censoring:** Survival time is said to be right-censored when it is recorded from its beginning to a defined time before its end time. This type of censoring is commonly recognized survival analysis and also considered in this study. Let C denote the censoring time, that is, the time beyond which the study subject cannot be observed. The observed survival time is also referred to as follow up time. It starts at time 0 and continues until the event T or a censoring time C, whichever

comes first. Let C1, C_2,...,C_n be a sample of censoring times. And T_1, T_2, ...,T_n be event times. We observe a sample of couples, (y_1, δ_1), (y_2, δ_2),...,(y_n, δ_n), where for i=1,2,....n(Cox,1984).

$$Y_i = \min(T_i, C_i) = \begin{cases} T_i \; if \; T_i \leq C_i \\ C_i \; if \; T_i > C_i \end{cases}$$

$$\delta_i = I(T_i, C_i) = \begin{cases} 1 \quad if \; T_i \leq C_i \\ 0 \quad if \; T_i > C_i \end{cases}$$

2. **Left Censoring**: Survival time is said to be left censored if an individual develops anevent of interest prior to the beginning of the study time but the exact time of its occurrence isn't known.
3. **Interval Censoring:** Survival time is said to be interval censored when it is only known that the event of interest occurs within an interval of time but the exact time of itsoccurrence is not known.

3.6.1 Survival Functions

The survivor function is defined to be the probability that the survival time of a randomly selected subject is greater than or equal to some specified time. Thus, it gives the probability that an individual surviving beyond a specified time. Let T be a continuous random variable associated with the survival times, t be the specified value of the random variable T and f(t) be the underlying probability density function of the survival time T. The cumulative distribution function F(t), which represents the probability that a subject selected at random will have a survival time less than some stated value t, is given by (Cox,1984);

$$F(t) = P(T < t) = \int_0^t f(u)du, \;\; where; \;\; t \geq 0 \quad 3.1$$

Survival function S(t), is given by;

$$S(t) = P(T \geq t) = 1 - P(T < t) = 1 - F(t), \;\; where; \; t \geq 0 \quad 3.2$$

The relationship between the probability density function f(t) and S(t) will be:

$$f(t) = \frac{d\left(1 - s(t)\right)}{dt} = \frac{-dS(t)}{dt} = \frac{d}{dt}F(t) \qquad 3.3$$

Characteristics of S(t):

a. Survival function is non-increasing
b. At time t=0, S(0)=1; that is, at the start of the study, since no one has experienced the event yet, the probability of surviving past time 0 is one and
c. At $t\to\infty$, $S(\infty)\to 0$; that is, theoretically, if the study period increased without limit, eventually nobody would survive, so the survivor curve must eventually converge to zero.

3.6.2 Hazard Function

The hazard function h(t) gives the instantaneous potential for failing at time t, given the individual has survived up to time t. This is the conditional probability of experiencing the event of interest within a very small time interval of size Δt having survived up to time t. It is a measure of the probability of failure during a very small interval, assuming that the individual has survived at the beginning of the interval. In addition, it is not a probability as it does not lie between 0 and 1. The hazard function, h(t) ≥0 is given as (Cox, 1984);

$$h(t) = \lim_{\Delta t\to 0} \frac{P(an\ individual\ fails\ in\ the\ time\ interval\ (t, \Delta t) given\ survivals\ until\ time\ t)}{\Delta t}$$

$$h(t) = \lim_{\Delta t\to 0} \frac{P(t \le T \le t + \Delta t / T \ge t)}{\Delta t} \qquad 3.4$$

Applying the conditional probability theory to know the relationship in probability density function, hazard function and survival function becomes:

$$h(t) = \frac{f(t)}{S(t)} \qquad 3.5$$

The corresponding cumulative hazard function, H(t) is defined as:

$$H(t) = \int_0^t h(u)du \qquad 3.6$$

Then $S(t) = \exp\big(-H(t)\big) \quad and\ \ f(t) = h(t) * s(t) \qquad 3.7$

The survival function is most useful for comparing the survival progress of two or more groups while hazard function gives a more useful description of the risk of failure at any time point.

3.6.3 Non-parametric Survival Methods

Survival data are conveniently summarized through estimates of the survival function and hazard function. The estimation of the survival distribution provides estimates of descriptive statistics such as the median survival time. These methods are said to be non-parametric methods since they require no assumptions about the distribution of survival time. Preliminary analysis of the data using non-parametric methods provides insight into the shape of the survival function for each group and get an idea of whether or not the groups are proportional, i.e., if the estimated survival functions for two groups are approximately parallel(do not cross).

3.6.3.1 Kaplan-Meier Estimator of Survival Function

The Kaplan-Meier (KM) estimator is the standard non parametric estimator of the survival function, S(t), proposed by Kaplan and Meier(1958) which is not based on the actual observed event and censoring times, but rather on the ordered in which events occur. It is also called the Product-Limit estimator. KM 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. When there is no censoring, the estimator is simply the sample proportion of observations with event times greater than t. The technique becomes a little more complicated but still manageable when censored times are included. Let ordered survival times are given by $0 \leq t_1 \leq t_2 \leq t_j \leq \infty$, then (Kaplan &Meier, 1958) .The KM estimator of the survival function at time t is given by:

$$\hat{s}(t) = \prod_{t_i < t} \left(\frac{n_i - r_i}{n_i}\right) = \prod_{t_i < t} \left(1 - \frac{r_i}{n_i}\right) \qquad 3.8$$

It was obvious from KM estimator, $\hat{s}(t) = 1$ if $t < t_i$ and when $r_i = n_i$ $\hat{s}(t) = 0$ for $t \geq t_i$
Where $r_{(i)}$ is the number of individuals who experience the recovery at $t_{(i)}$ and $n_{(i)}$ is the number of individuals at risk right before $t_{(i)}$. After providing a description of the overall survival experience in the study, we usually turn our attention to a comparison of the survivorship experience in key subjects in the data.

3.6.3.2 Comparison of Survivorship Functions

The simplest way of comparing the survival times obtained from two or more groups is to plot the Kaplan-Meier curves for these groups on the same graph. However, this graph does not allow us to say, with any confidence, whether or not there is a real difference between the groups. The observed difference may be a true difference, but equally, it could also be due merely to chance variation. Assessing whether or not there is a real difference between groups can only be done, with any degree of confidence, by utilizing statistical tests. Among the various non-parametric tests one can find in the statistical literature, the Mantel-Haenzel test, currently called the "log-rank" is the one commonly used non-parametric tests for comparison of two or more survival distributions. The log-rank test statistic for comparing two groups is given by (Cox, 1984):

$$Q=\frac{\left[\sum_{i=1}^{m} w_{i(r_{li}-\hat{e}_{li})}\right]^2}{\sum_{i}^{m} w_i^2 \hat{V}1i} \sim X^2{}_{k-1} \quad 3.9$$

Where $\hat{e}_{li}= \frac{n_{li} r_{li}}{n_i}$ is the expected number of events (recovery) corresponding to r_{li}.

$\hat{V}_{1i} = \frac{n_{li}\, n_{0i}(n_i - r_i)}{n_i^2 (n_i - 1)}$ is the variance of the number of events r_i at time t_i

n_{0i} is the number at risk at observed survival time t_i in group 0, n_{1i} is the number at risk at observed survival time t_i in the group l, r_{0i} is the number of observed recovery in group 0, r_{li} is the number of observed recovery in group 1, n_i is the total number of individuals or risk before time t_i, r_i is the total number of recovery at t_i, w_i is the weighted given for i^{th} individuals.

3.6.4 The Cox proportional Hazards Regression model

Survival models relate the time that passes before the recovery from obstetric fistula occurs to one or more covariates which may influence the proportional quantity. One of the most popular types of regression models used in survival analysis is the Cox proportional hazards regression model. Cox (1972) proposed a semi-parametric model for the hazard function that allows the addition of covariates, while keeping the baseline hazards unspecified and takes only positive values. With this parameterization the Cox-hazard regression model is:

$$h(t, x, \beta) = h_{o(t)} \exp(\beta' X) \quad 3.10$$

Where:

- ✓ $h(t, x, \beta)$ Represents the hazard function at time t for an individual with covariates ($X_1, X_2, \ldots, X_P$).
- ✓ $h_o(t)$ is a base line hazard function that characterizes how the hazard function changes as of survival time- t, the recovery time after treatment of the patients.
- ✓ $\beta' = (\beta_1, \beta_2 \ldots, \beta p)$ is a column vector of p unknown regression parameters.
- ✓ $\exp(\beta X)$ Characterizes how the hazard function changes as a function of subject covariates.

The survival time of each member of the sampled OBF patients is assumed to follow their own hazard function. In such case the above equation will become:

$$h(t, x, \beta) = h_{o(t)} \exp(\beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_p x_{ip}) \quad 3.11$$

i= 1, 2,…, n, where n is the total number of OBF patients that are included in the study.

The corresponding survival function for Cox PH model is given by:

$$S(t, x) = [S_0(t)]^{\exp(\sum \beta_i' x_i)} \quad 3.12$$

Where So(t) is the baseline survival function.

In this model, no distributional assumption is made for the survival time; the only assumption is that the hazards ratio does not change over time (i.e., proportional hazards) that is why this model is also known as semi-parametric model. Even though the baseline hazard is not specified, we can still get a good estimate for regression coefficients β, hazard ratio, and adjusted hazard curves.

The measure of effect is called hazard ratio. The hazard ratios of two individuals with different covariates X and $X^*$is given by:

$$\widehat{HR} = \frac{h_{o(t)} \exp(\beta' X)}{h_{o(t)} \exp(\beta' X^*)} = exp\{\sum \widehat{\beta'} (X - X^*)\} \quad 3.13$$

3.6.4.1 Fitting Cox Proportional Hazard Model

Fitting the Cox PH model, we estimate $h_o(t)$ and β. A more popular approach is proposed by Cox (1972) in which a partial likelihood function that does not depend on $h_o(t)$ is obtained for β. Partial likelihood is a technique developed to make inference about the regression parameters in the presence of nuisance parameters ($h_o(t)$) in the cox PH model. In this part, we construct the partial likelihood function based on the PH model. Suppose we have m distinct recovery time and X_i be the vector of expected variables at order recovery t_i . Partial likelihood is defined as:

$$L^{Partial}\ (\beta) = \prod_{i=1}^{m} \left[\frac{e^{\beta^t X_i}}{\sum_{j \epsilon R\ (ti)} e^{\beta^t X_j}}\right]^{r_i} \quad 3.14$$

Where r_i is the number of recovery's, r_i=1 we assume there are not tied observations and so r_i=0, $R(t_i)$ is the set of subjects at risk at time just prior to t_i. Once the likelihood function is formed for a given model, the next step for the computer is to maximize this function. This is generally done by maximizing the natural log of L, which is computationally easier. The log partial likely function is given by:

$$\ln(L^{Partial}\ (\beta)) = \sum_{i=1}^{m} \left\{\beta^t X_{(i)} - ln\left[\sum_{j \epsilon\ R_{(t(j))}} e^{\beta^t X_j}\right]\right\}$$

The maximization of $L^{Partial}\ (\beta)$ is carried out by taking partial derivatives of the log of $L^{Partial}\ (\beta)$with respect to each parameter in the model. This can be carried out using the statistical packages R.

3.6.4.2Testing the Assumption of Cox PH Model

The proportional hazards assumptions are vital to use in a fitted proportional hazards model. Variable adds significant information. If the newly added variable is not significant, it can be taken as the assumptions of the proportional hazard assumptions are satisfied. The method of checking the assumption of the Cox proportional hazards model is scatter plots using the Schoenfeld residual (Schoenfeld, 1982). The residuals constructed for each covariate that are included in the model which are expected to predict the recovery time of patient with obstetric fistula. Under the proportional hazard assumption for the respective covariate, a scatter plot of Schoenfeld residuals against event times is expected to scatter in a nonsystematic way about the zero line, and the Lowess curve connecting the values of the smoothed residuals should have a zero slope and cross the zero line several times (Klein &Moeschberger., 2003). If this plot shows some trend the assumption is violated, where as if the plot demonstrates randomly distributed around the reference line then the assumption is satisfied.

3.6.5Accelerated Failure Time Model

The accelerated failure time model (AFT) is an alternative to the PH model for the analysis of survival time data. Under AFT models we measured the direct effect of the explanatory variables on the survival time instead of hazard. This characteristic allows for an easier interpretation of the results because the parameters measure the effect of the correspondent covariate on the mean survival time. The AFT model states that the survival function of an individual with covariate X at time t is the same as the survival function of an individual with a baseline survival function at a time ($t * \exp(\beta' X)$), where β' =(β1, β2, ..., βp) is a vector of regression coefficients. In other words, the accelerated failure-time model is defined by the relationship (Klein & Moeschberger, 2003):

$S(t/x) = S_0\{t * \exp(\beta' X)\}$, for all X3.15

Hereby we can consider on a log-scale of the AFT model with respect to time is given analogous to the classical linear regression approach. In this approach, the natural logarithm of the survival time Y =log (T) is modeled. This is the natural transformation made in linear models to convert positive variables to observations on the entire real line. A linear model is assumed for Y;

$$Y = \log(T) = \mu + \beta' X + \sigma\varepsilon$$

Where β' = (β1, β2,..., βp) is a vector of regression coefficients

μ= intercept

σ = is scale parameter and

ε = is the error distribution assumed to have a particular parametric distribution

When we denote by S_0 the survival function when X = 0 then we find that

$$P(T > t/X) = P\left(Y > \frac{Log\,(t)}{X}\right)$$

$$= P\{\mu + \sigma\varepsilon > \log(t) - \beta' X/X\}$$

$$= P\{\exp(\mu + \sigma\varepsilon) > t * \exp(-\beta' X)/X\}$$

$$= S_0\{t * \exp(-\beta' X)/X\}$$

The effect of the covariates on the survival function is that the time scale is changed by a factor$\exp(-\beta' X)$, and we call this an acceleration factor.

We note that when

$\exp(-\beta' X) > 1$ → the survival process accelerates(i.e. time-to-recover accelerates).

$\exp(-\beta' X) < 1$ → the survival process decelerates(i.e. time-to-recovery decelerates).

If X is an indicator variable, this is equivalent to

$\beta > 1$ → Time shrinks

$\beta < 1$ → Time accelerates

For each distribution of ε there is a corresponding distribution for T. The members of the AFT model considered in this study are the Weibull, log-logistic, and log-normal AFT models. The AFT models are named for the distribution of T rather than the distribution of log T.

3.6.5.1 Weibull Accelerated Failure Time model

The Weibull distribution (including the exponential distribution as a special case) as shown above can also be parameterized as an AFT model, and they are the only family of distributions to have this property. The results of fitting a Weibull model can therefore beinterpreted in either framework (Klein & Moeschberger, 2003). Then the Weibull distribution is very flexible model for time-to-event data. It has a hazard rate which is monotone increasing, decreasing, or constant. The AFT representation of the survival and hazard function of the Weibull model with scale parameter and shape parameter is given by:

$$f(t,\mu,\alpha) = \frac{\alpha}{\mu}\left(\frac{t}{\mu}\right)^{\alpha-1} exp\left(\left(-\frac{t}{\mu}\right)\right)^{\alpha} \quad 3.16$$

Where $\mu > 0$ and $\alpha > 0$ and the baseline hazard function of the distribution becomes:

$$h_0(t,\mu,\alpha) = \frac{\alpha}{\mu}\left(\frac{t}{\mu}\right)^{\alpha-1} \quad 3.17$$

Reparameterizing the Weibull distribution using $\rho = \sigma^{-1}, \lambda = \mu^{-\alpha}, then\ h_0(t) = \lambda\rho t^{\rho-1}$ would be the baseline hazard function. Now incorporate covariates matrix X in the hazard function, the Weibull regression model becomes:

$$h_i(t,\beta,X_i) = \lambda\rho t^{p-1}\exp(\beta_0 + \beta_1 X_{11} + \cdots + \beta_1 X_{1k})$$

The event time of the i[th] subject is then characterized by the weibull distribution with scale parameter λ and shape parameter ρ. The shape of the hazard function critically depends up on the values of ρthat means: the model assumes that individual i and j with covariates X_i and X_j have proportional hazard function of the forms. A different parameterization is used with intercept v and covariate effects γ_i having relationship with original parameterization as$\beta_i = \frac{-\gamma_i}{\sigma}$ and $\mu = \exp(v)$.

$\frac{h(t,X_i)}{h(t,X_i)} = \frac{\exp(\beta' X_i)}{\exp(\beta' X_j)} = exp\left(\beta'\left(X_i - X_j\right)\right)$, the quantities $\exp(\beta)$ can be interpreted HR

3.6.5.2 Log-logistic Survival Regression Model

The log-logistic model assumes that the disturbance term, in an accelerated failure time, has a standard logistic distribution. Covariate incorporated log logistic accelerated failure time may be expressed as:

$$T = exp\left((\mu + \beta' X_i) + \varepsilon\sigma\right) \quad 3.18$$

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

$$lnT = \mu + \beta' X_i + \varepsilon\sigma \quad 3.19$$

Where, $\beta' = (\beta_1, \beta_2, \dots, \beta_p)$, μ is intercept, $\sigma$is scale parameter andε_i is a random variable used to model the deviation of values of $logT_i$from the linear part of the model.Suppose a random variable T, representing survival time, follows Log-Logistic distribution with shape parameter ρ and scale parameter λ with probability distribution.

$$f(t) = \frac{\lambda\rho\, t^{\rho-1}}{(1+\lambda t^{\rho})^2} \qquad 3.20$$

Where λ> 0 and $\rho > 0$, the corresponding survival and hazard functions are given by:

$$S(t) = \frac{1}{1+\lambda t^{\rho}} \qquad 3.21$$

$$h(t) = \frac{\lambda\rho\, t^{\rho}}{1+\lambda t^{\rho}} 3.22$$

When$\rho \leq 1$the hazard rate decreases monotonically and when $\rho > 1$, it increases from zero to its maximum point and then decreases to zero (Collett 2003).

To interpret the factor$\exp(\beta' X)$ for log-logistic model, one can notice that the odd of survival beyond time t for log-logistic model is given by:

$$\frac{S(t)}{1-S(t)} = \frac{\frac{1}{1+\lambda\rho\, t^{\rho}}}{1-\frac{1}{1+\lambda\rho\, t^{\rho}}} = \frac{1}{\lambda t^{\rho}} 3.23$$

3.6.5.3Lognormal Survival Regression Model

When a random variable T is said to have a lognormal distribution with parameters μ &σ^2 the probability density function is given as follows:

$$f(t, \mu, \sigma^2) = \frac{1}{\sigma\sqrt{2\pi}} t^{-1} exp\left\{-\left(\frac{(logt-\mu)^2}{2\sigma^2}\right)\right\}, for\ 0 \leq t < \infty, \sigma > 0 \qquad 3.24$$

From which the survivor and hazard functions can be derived. The survivor function is given by

$$S(t, \mu, \sigma^2) = 1 - \Phi\left(\frac{\log(t)-\mu}{\sigma}\right), \qquad h_0(t) = \frac{\Phi\left(\frac{\log(t)}{\sigma}\right)}{\left(\frac{\log(t)}{\sigma}\right)\sigma t} 3.25$$

Where $\Phi(.)$is the cumulative density function of the standard distribution.The survival function for the i^{th}individual is:

$S_i(t) = S_0(t * \exp(\mu + \beta' X_i)) = 1 - \phi\left(\frac{\log(t) - \beta' X_i - \mu}{\sigma}\right)$ 3.26

Therefore the log survival time for the i^th individual has normal($\mu + \beta' X_i,\ \sigma$). The log normal distribution has the AFT property. In a two group study:

We can easily get

$$\phi^{-1}(1 - S(t)) = \frac{1}{\phi}(logt - \beta' X_i - \mu)$$

Where, X_i is the value of categorical variables which value 0 in one group and 1 in the other group. This implies that the plot $\phi^{-1}(1 - S(t))$against log(t) will be linear if the lognormal distribution is appropriate for the given data set.

3.6.5.4 Estimation of parametric Survival Regression Models

Parameters in survival regression models can be estimated by maximum likelihood method. Suppose we have a censored sample $(Y_1, \delta_i), \ldots, (Y_n, \delta_n)$where $Y_i = \min(T_i, C_i)$ and $\delta_i = I(T_i \le C_i)$, i=1... n, with a $T_1, \ldots, T_n \sim f(t)$ and survival function by $S(t)$and T_i and C_i are independent and let β be the unknown parameter. The likelihood function for right censored data is given by:

$L(\beta) = \prod_{i=1}^{n} f(y_i, \beta)^{\delta_i} S(y_i, \beta)^{1-\delta_i}$ 3.27

$$= \prod_{i=1}^{n} \left(\frac{f(y_i, \beta)}{S(y_i, \beta)}\right)^{\delta_i} S(y_i, \beta)$$

$$= \prod_{i=1}^{n} \left(h(y_i, \beta)\right)^{\delta_i} S(y_i, \beta)$$

Take both sides by logarithm

$$\log(L(\beta)) = \delta_i \sum_{i=1}^{n} logh(y_i, \beta) + \sum_{i=1}^{n} S(y_i, \beta) \qquad 3.28$$

Maximum likelihood estimators can be obtained by equating thefirst derivatives of log-likelihood with respect to β is equal to zero.

3.6.6 Shared Frailty Model

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, zone, regions, etc. In this study Zoneof the patients was considered as a clustering effect in frailty model. The Zones are, Jimma, Bench Majji, Bonga, Yem, Konta, Gambela, Bedele, and Tep. Here a shared frailty model may be used to model the degree of correlation within groups; i.e., the subjects within a group are correlated because they share the same common frailty. Conditional on the frailty, the survival times in cluster i ($1 \le i \le n$) are assumed to be independent. And the proportional hazard frailty model assumes (wienke, 2010);

$$h_{ij}\left(t/X_{ij}, u_i\right) = \exp\left(\beta' X_{ij} + u_i\right) h_0(t) = Z_i h_0(t) \exp(\beta' X_{ij}) \quad 3.29$$

Where as an alternative if the proportional hazards assumption does not hold is the accelerated failure time frailty model which assumes.

$$h_{ij}\left(t/X_{ij}, u_i\right) = \exp\left(\beta' X_{ij} + u_i\right) h_0\left(\exp\left(\beta' X_{ij} + u_i\right) t\right) = Z_i h_0\left(Z_i \exp(\beta' X_{ij}) t\right) \exp(\beta' X_{ij})$$

Where i indicates the i^{th} cluster and j indicates the j^{th} individual for the i^{th} cluster, h0(.) is the baseline hazard, $u_i$the random term of all the subjects in cluster i, X_{ij} the vector of covariates for subject j in cluster i, and β the vector of regression coefficients. $Z_i=\exp(u_i)$the frailties $Z_i$are assumed to be identically and independentlydistributed random variables with common density function, f(z, θ), where θ is the parameter of the frailty distribution.The variability of Z_i determines the degree of heterogeneity among the groups.In empirical applications, the observed survival data are used toestimate the parameters of the distribution of frailty f(z, θ), and to actually predict the individual frailties.

3.6.6.1 The Frailty Distributions

The frailty denoted by z_i is an unobservable realization of a random variable Z with probability density function f(.), the frailty distribution. Since z_i multiplies the hazard function, Z has to be non-negative. In this research, frailty distributions namely the gamma and the inverse Gaussian were used. In both cases, as a single heterogeneity parameter (denoted by θ) indexes the degree of independence.

3.6.6.2 The Gamma Frailty Distribution

Gamma fit very well into survival models, because it is easy to derive the formulas for any number of events. This is due to the simplicity of the derivatives of the Laplace transform. The gamma frailty distribution has been widely used in parametric modeling of intra-cluster dependency because of its simple interpretation, flexibility and mathematical tractability (Vaupel, J. W., & Missov, T. I. 2014). The density of a gamma-distributed random variable with parameter θ is given by

$$f(z) = \frac{{z_i}^{\frac{1}{\theta}} \exp\left({-zi}/{\theta}\right)}{\theta^{\frac{1}{\theta}}\Gamma\left(\frac{1}{\theta}\right)},\ \theta > 0 \quad 3.30$$

Where $\Gamma(.)$ is the gamma function, it corresponds to a Gamma distribution Gam (μ, θ) with μ fixed to 1 for identifiability. Its variance is then θ, with Laplace transform

$$L(u) = \left(1 + \frac{u}{\theta}\right)^{-\theta} \quad 3.31$$

The conditional survival function and hazard function of the gamma frailty distribution is given by: (Gutierrez, 2002)

$$S_\theta(t) = [1 - \theta ln(S(t))]^{-1/\theta} \quad 3.32$$

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

Where S(t) and h(t) are the survival and the hazard functions of the baseline distributions. 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, can be compute by:

$$\tau = \frac{\theta}{\theta+2} \epsilon (0,1) \quad 3.33$$

3.6.6.3 The Inverse Gaussian Frailty Distribution

The inverse Gaussian (inverse normal) distribution was introduced as a frailty distribution alternative to the gamma distribution by (Hougaard, 1984). 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 distributed random variable with parameter θ > 0 is given by

$$f(z) = \frac{1}{\sqrt{2\pi\theta}} z^{-3/2} exp\left(-\frac{1}{2\theta z}(z-1)^2\right) \qquad 3.34$$

The mean and the variance are 1 and θ, respectively with Laplace transform

$$L(s) = exp\left(\frac{1}{\theta}\left(1-\sqrt{1+2\theta s}\right)\right) \quad s \geq 0 \qquad 3.35$$

For the inverse Gaussian frailty distribution the conditional survival function is given by:

$$S_\theta(t) = exp\left\{\frac{1}{\theta}\left(1-[1-2\theta \ln\{S(t)\}]^{1/2}\right)\right\} 3.36$$

And the conditional hazard function is given by:

$$h_\theta(t) = h(t)[1-2\theta \ln(S(t))]^{-1/2} 3.37$$

Where 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\left(2/\theta\right)}{\theta^2}\int_{2/\theta}^{\infty}\frac{\exp(-u)}{u}du \, \epsilon \left(0, 1/2\right)$3.38

3.6.6.4 Parameter Estimation for SharedFrailty Model

For right-censored clustered survival data, the observation for subject $j \epsilon J_i = \{1, \ldots, n_i\}$ from cluster $i \epsilon$ 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 where $\delta_{ij} = I(t_{ij} \leq c_{ij})$ is the event indicator. When covariate information are been collected the observation will be $(y_{ij}, \delta_{ij}, X_{ij})$, 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 assumptions of non-informative right-censoring and of independence between the censoring time and the survival time random variables, given the covariate information, the marginal log-likelihood of the observed data can be written as.

$$l_{marg}\,(\psi,\beta,\theta,Z,X)$$

$$= \prod_{i=1}^{s}\left[\left(\prod_{j=1}^{n_i} h_0(y_{ij})exp\left(X_{ij}^{t}\beta\right)\right)^{\delta_{ij}}\right) X \int_{0}^{\infty} Z_i^{di}\, exp\left(-Z_i \sum_{j=1}^{n_i} h_0\left(y_{ij}\exp(X_{ij\beta}^{T}\,)\right)\right) f(Z_i)dzi\right]$$

$$= \prod_{i=1}^{s}\left[\left(\prod_{j=1}^{n_i} h_0(y_{ij})exp\left(X_{ij}^{t}\beta\right)\right)^{\delta_{ij}}\right) X(-1)^{di} L^{(di)}\left(\sum_{j=1}^{n_i} H_0(y_{ij})\exp(X_{ij}^{T}\beta)\right)\right]$$

Taking the logarithm, the marginal likelihood is

$$l_{marg}\,(\psi,\beta,\theta,Z,X) = \sum_{i=1}^{s}\left\{\left[\delta_{ij}\left(\log h_0(y_{ij}) + X_{ij}^{T}\beta\right)\right] + log\left[(-1)^{di} L^{(d)}\left(\sum_{j=1}^{ni} \exp H_0(y_{ij})(X_{ij}^{T}\beta)\right)\right]\right\} \quad 3.39$$

Where $d_i = \sum_{j=1}^{ni} \delta_{ij}$ is the number of events in the i^{th} cluster, and $L^{(q)}(.)$ the q^{th} derivativeof the Laplace transform of the frailty distribution defined as

$$L(s) = E[\exp(-Z_i s)] = \int_0^{\infty} \exp(-Z_i s) f(Z_i) dz_i \quad s \geq 0, \quad 3.40$$

Where, ψ represents parameters of the baseline hazard function, β the vector of regression coefficients and θ the variance of the random effect.Estimates of ψ, β, θ are obtained by maximizing the marginal log-likelihood above. This can be done if one is able to compute higher order derivatives $L^{(q)}$ (.) of the Laplace transform up to q = max {d1, …, ds}. Symbolic differentiation might be performed in R.

3.6.7Model Development

Survival analysis begins with a thorough univariate analysis of the association between survival time and all important covariates (Stevenson M., 2009)
According to (Stevenson M., 2009), it is recommended to follow the steps given below.

- A multivariable model should contain at the outset all covariates significant in the univariate analyses at the P = 0.20 to 0.25 level and any others that are thought to be of clinical importance. You should also include any covariate that has the potential to be an important confounder (Stevenson 2009).

- The variables that appear to be important from step one are then fitted together in a model. In the presence of certain variables others may cease to be important. As a result, backward elimination is used to omit non-significant variables from the model.

3.6.8 Model SelectionMethods

To select the model that can predict the time to recovery from obstetric fistula patients, we used Cox-Snell residuals plot and AIC to compare different models. The first is graphical approach. For this method the Cox-Snell residual plot is the common one. It is used to determine how well a specific distribution fits the observed data. This plot will be approximately linear if the specified theoretical distribution is the correct model. Easy fit displays the reference diagonal line along which the graph points should fall along with the goodness of fit tests; the distribution plots can be helpful to determine the best fitting model. The Cox–Snell residual, r_j, is defined by:

$r_j = \widehat{H}(T_j / X_j)$Where, $\widehat{H}$is the cumulative hazard function of the fitted model.

Akaikie (1974) proposed an information criterion (AIC) statistic to compare different models and/or models with different numbers of parameters. For each model the value is computed as:

$$AIC = -2\log(likelihood) + 2(p + s) \qquad 3.41$$

Where p denotes the number of covariates in the model without including the constant term and s is the number of parameters minus one i.e. s=0 for the exponential regression model and s=1 for Weibull, log-logistic and lognormal regression models. According to the criterion, a model with small AIC value will be considered as a best fit to the data.

3.6.9Diagnostic methods for the models

After the model has been fitted, it is desirable to determine whether a fitted parametric model adequately describes the data or not.

3.6.9.1 Checking the Adequacy of Parametric Baselines

The graphical methods can be used to check if a parametric distribution fits the observed data. Model with the weibull baseline has a property that the log (-log(S(t)) is linear with the log of time, where $s(t) = \exp(-\lambda t^{\rho})$. Then, $log\left(-log(S(t))\right) = \log(\lambda) + \rho\log(t)$, this property allows a graphical evaluation of the appropriateness of a Weibull model by plotting log(–log($\hat{S}$(t))) versus log(t) where $\hat{S}$(t) is Kaplan-Meier survival estimate (Datwyler and Stucki, 2009). The log-failure odd versus log time of the log-logistic model is linear. Where the failure odds of log-logistic survival model can be computed as:

$\frac{1-S(t)}{S(t)} = \frac{\frac{\lambda t^{\rho}}{1+\lambda t^{\rho}}}{\frac{1}{1+\lambda t^{\rho}}} = \lambda t^{\rho}$, the log-failure odds can be written as:

$$Log\left(\frac{1-S(t)}{S(t)}\right) = \log(\lambda t^{\rho}) = \log(\lambda) + \rho\log(t)$$

Therefore, the appropriateness of model with the log-logistic baseline can graphically be evaluated by plotting $Log\left(\frac{1-S(t)}{S(t)}\right)$ versus log(time) where $\hat{S}$(t) is Kaplan-Meier survival estimate (Datwyler and Stucki, 2009). If the plot is straight line, log-logistic distribution fitted the given dataset well. If the plot $\phi^{-1}(1-S(t))$ against log (t) is linear, the log-normal distribution is appropriate for the given data set.

3.10 Ethical Considerations

The Research Ethics Review Board of Jimma University has provided an ethical clearance for the study. The data was collected from Jimma Medical center, and to do the department of statistics asked to write an official co-operation letter to the Hospital from where data was obtained. The study conducted without individual informed consent because it relied on retrospective data. In this research, the information obtained from log book and patients' card kept secured.

CHAPTER FOUR
RESULTS AND DISCUSSION

4.1 Descriptive Statistics

This section reports the descriptive results of the factors for time-to-recovery from obstetric fistula at the hospital treatment period. The average mean recovery time of obstetric fistula patient stay in the hospital to be physically cured is 6.56 weeks with standard deviation is 0.286. Among the patients with obstetric fistula considered in the study, 81.4% of them were physically cured while the rest 18.6% were censored. The descriptive statistics were presented in Table 4.1 below. Out of patients in the study 67(24.8%), 137(50.8%) and 66(24%) were in age groups found less 20, between21 and 30 and greater than 30 respectively. For weight, there are 197(73%) less than 50kg and 73(27%) were greater than or equal to 50kg. Among the number of children 83(30.7%), 101(37.4%) and 86(31.9%) patients were 1child, 2-4 children, and >5children respectively. Out of the study patients, 171(63.4%) were married, 90(33.3%) divorced and 9(3.3%) of them were others(single and widowed).

Table 4.1: Descriptive summaries of time-to-recovery from OBF in JUMC

Covariates	Categories	Frequency	Percent (%)
Age	<20	67	24.8
	21-30	137	50.8
	>30	66	24.4
Weight	< 50kg	197	73
	≥50kg	73	27
Marital status	Married	171	63.4
	Divorced	90	33.3
	Others	9	3.3
Parity	1 child	83	30.7
	2-4 children	101	37.4
	>5 children	86	31.9
Place of Residence	Rural	25995.9	

	Urban	11	4.1
Education Level	Illiterate	17966.7	
	Literate	9133.3	
Duration of Incontinence of urine	>3 months	136	50.4
	≤ 3 months	134	49.6
Antenatal care	No	172	63.7
	Yes	98	36.3
Duration of labor	<2days	8330.7	
	≥2days	18769.3	
Place of delivery	Home	177	65.6
	Health center	93	34.4
Mode of delivery	Vaginal	182	67.4
	CS	88	32.6
Surgery Approach	Vaginal	183	67.8
	Abdominal	87	32.2
Duration of Catheter	≤14 days	201	74.4
	>21 days	69	25.6
Status of Urethra	Not damaged	214	79.3
	P. damaged	56	20.7
Types of Fistula	RVF	34	12.6
	VVF	236	87.4

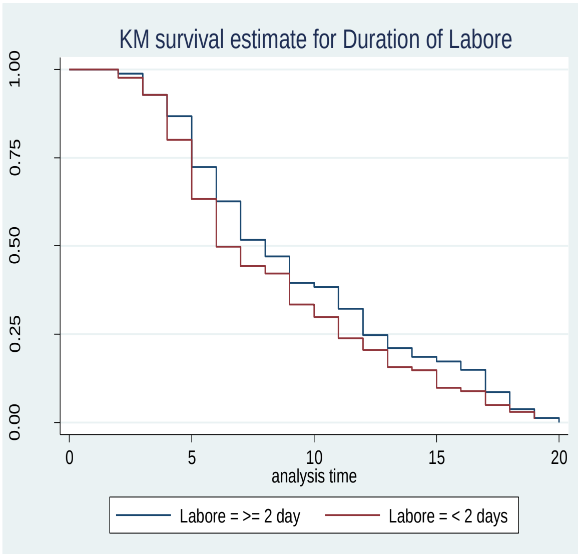
In the study, 259(95.9%) were lived rural while 11(4.1%) of them lived urban. Out of patients in this study, 180(66.3%) of the patients were illiterate whereas 90(33.7%) were literate. From the above table 4.1, patients who have no antenatal care follow-up were 172(67.3%) and who have antenatal care follow-up are 98(36.3%). Another factor considered under this study was the duration of incontinence of urine, under these 136(50.4%) and 134(49.6%) of the patients came to the health center after urine incontinence of ≤ 3 and > 3 months, respectively. Among duration of labor, 83(30.7%) and 187(69.3%) patients were labored for <2 days and ≥ 2 days, respectively.

From the study 177(65.6%) of the patients had delivered at home and 93(34.4%) were delivered at the health center. There were 182(67.4%) patients delivered vaginal and 88(32.6%) patients delivered cesarean section. The surgery approach found in the study, 183(67.8%) are vaginal and 87(32.2%) are abdominal. For the duration of the catheter of the patients, 201(74.4%) were ≤14 days and 69(25.6%) were >21 days. When we see the status of the urethra, patients with intact urethra were 214 (79.3%) and those partially damaged of the urethra was 56(20.7%). Finally, for types of fistula, there were 34(12.6%) of patients are RVF and 236(87.4%) are VVF.

4.1.1 Comparison of Survival Experiences of OBF Patients

The Kaplan-Meier survivor estimator is used to investigate the significant differences between the survival probabilities of different categories. From the overall graph of the Kaplan-Meier survivor function in figure 4.1 in the appendix showed that the most recovery is occurred at the beginning up to the fifth (5) weeks after entry and then the recovery decreases. The survival curve approaches to zero as the time goes to infinity and at the beginning, the survival distribution approximated to one. This shows the properties of Kaplan Meier survival curve i.e. $S(0) = 1$ and $S(\infty) = 0$.

The figure 4.2 below shows that the recovery time similar for both groups at the beginning and at the middle at two weeks. But the difference becomes at the middle of the curve. Generally, patients with duration of labor < 2days had better recovery time than labor ≥2 days. The log-rank test also in table 4.2 shows that labor had no significant association to time-to-recovery ($p = 0.157$). Among different place of delivery, patients who had delivered at health institutional had better recovery time than those who delivered at home. The log-rank test also table 4.2 blow revealed that difference had the significant association with time-to-recovery ($p=0.0395$).



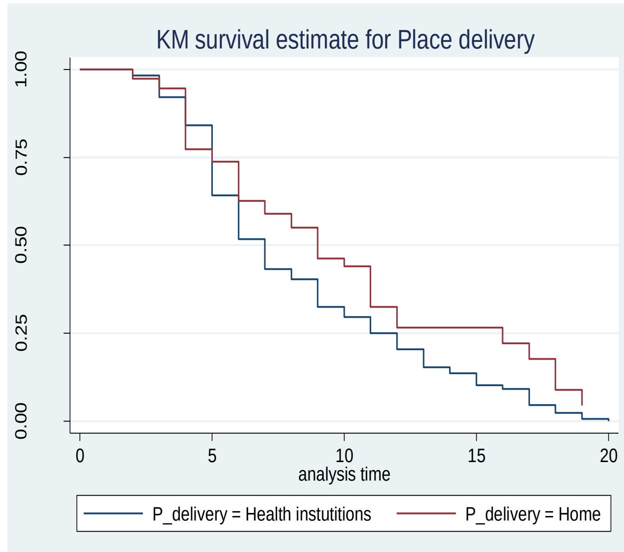
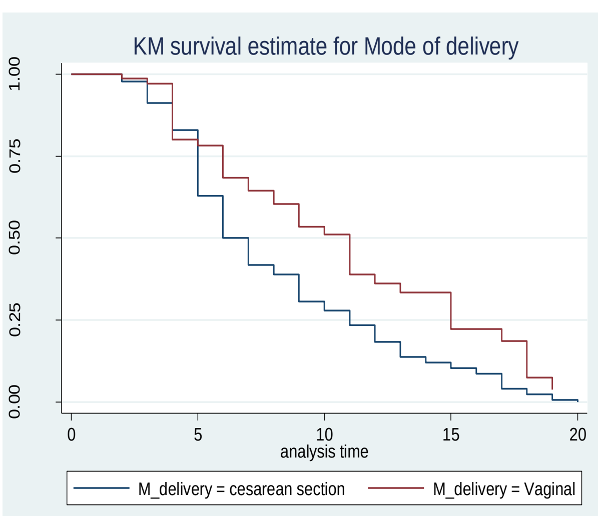


Figure 4.2: K-M plot of time-to-recovery by Duration of labor and Place of delivery.

The figures 4.3 below suggested that time-to-recovery are similar at the beginning of both curves groups. But patients with fast recovery are the mode of delivery at cesarean section, surgery approach at abdominal compared with vaginal delivery and vaginal approach respectively. The log-rank test also in table 4.2 shows that there was statistical significance on the difference in the physically cured of patients (with p=0.0022, 0.012 respectively).



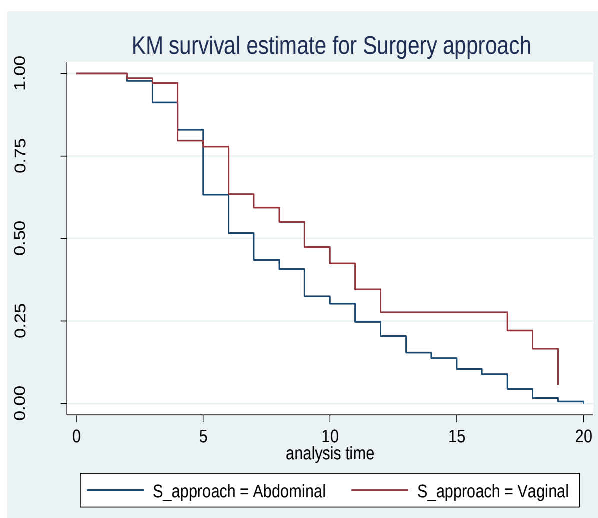


Figure 4.3: K-M plot of time-to-recovery by Mode of delivery and Surgery approach

The survival plot of time-to-recovery by age is shown in figure 4.4 in the appendix. As it can be observed from the plot, the survival curve for the age groups is overlapped from the beginning to the end. This implied that the recovery time for patients had the same at age groups. The log-rank test also revealed that age had no significant association to time-to-recovery from OBF ($p = 0.957$). The survival plot for time-to-recovery from OBF by weight is shown in figure 4.4. This figure shows that patients weight ≥ 50kg had better time-to-recovery compared with patients whose weight is <50kg. Statistical test using log-rank shows that difference was significant (p=1.84e-05).

The survival plot of time-to-recovery by marital status is shown in figure 4.5 in theappendix. This plot suggested that patients with others (i.e. single and widowed) had shorter time-to-recovery than the married and divorced. The log-rank test also revealed that difference had the significant association with time-to-recovery (p=6.04e-05). The survival plot of time-to-recovery by parity is shown in figure 4.5 in the appendix. This plot suggested that the time-to-recovery is similar for all groups (1 child, 2-4 children, and 5 children) at the beginning and at the end of the plot. But the difference is observed at the middle of the curve. At the middle point of the curve, the survival plot time-to-recovery for 2-4 children arelonger time-to-recovery than that of the one child and 5 children. The result of the log-rank test also significant (p= 0.0263) means this difference is significant at 5% level of significance.

The survival plot of time-to-recovery by place of residence is shown in figure 4.6 in the appendix. This plot suggested that patients lived in urban had better time-to-recovery than patients lived in rural. The result of the log-rank test also the difference is statistically significant (p= 4.29e-05). The survival plot of time-to-recovery by education level is shown in figure 4.6 in the appendix. This Figure shows that the curves overlap each other indicating that the recovery time may be identical for these groups. Log-rank also shows that; there was no statistical significance on the difference in the physically cured of patients (0.607).

The survival plot of time-to-recovery by the duration of incontinence and antenatal care is shown in figure 4.7 in the appendix. The figures show that among different duration of incontinence and antenatal care of a patient who had incontinence ≤ 3 months and those who follow up of antenatal care had short recovery time than those had duration of urine incontinence above three months and no follow-up of antenatal care service. This impression was confirmed using formal hypothesis tests in Table 4.2 below shows; log-rank test tests identify significant (P =3.16e-06, 0.0023) difference in recovery time.

The survival plot of time-to-recovery by the duration of the catheter, status of urethra and types of fistula is shown in figure 4.8 and 4.9 in the appendix. The figures suggested that among different duration of catheter, status of urethra and types of fistula of patient who had catheter 14 days, those who status of urethra not partially damaged and those whose Visco-vaginal fistula had lower recovery time than those had duration of catheter 21 days, that status of urethra partially damaged and those had recto-vaginal fistula. The log-rank test also identifies significant difference for both status of urethra and types of fistula in recovery time. But the duration of the catheter is not significant in recovery timeof fistula.

Table 4.2: Log-rank test for equality of survival time among the differentgroups of covariates for OBF in JUMC

Covariates	Observed	Expected	$(O-E)^2/E$	$(O-E)^2/V$	Chisq	Df	P-value
Age group							
< 20	55	56.6	4.73e-02	0.076814			
21-30	112	110.3	2.61e-02	0.063578	0.1	2	0.957
>30	53	53.1	7.22e-05	0.000116			
Weight							
<50kg	150	173.3	3.14	18.3	18.3	1	1.84e-05
≥50kg	70	46.7	11.67	18.3			
Marital status							
Married	163	139.97	3.79	12.78	19.4	2	6.04e-05
Divorced	48	74.68	9.53	17.81			
Others	9	5.35	2.49	2.99			

Parity							
1child	39	54.2	4.248	6.900			
2-4 children	98	93.2	0.246	0.525	7.3	2	0.0263
>5 children	83	72.6	1.485	2.678			
Place of Residence							
Rural	214	199.1	1.12	16.7	16.7	1	4.29e-05
Urban	6	20.9	10.65	16.7			
Education Level							
Illiterate	95.6	97.5	0.0379	0.265	0.3	1	0.607
Literate	29.3	27.4	0.1349	0.265			
Incontinence ofurine							
>3 months	134	113	3.71	9.33	9.3	1	0.00226
≤ 3 months	86	107	3.95	9.33			
Antenatal care							
No	171	141.3	6.23	21.7	21.7	1	3.16e-06
Yes	49	78.7	11.19	21.7			
Duration of labor							
<2days	82	91.3	0.946	2	2	1	0.157
≥2days	138	128.7	0.671	2			
Place of delivery							
Home	176	163.9	0.89	4.24	4.2	1	0.0395
Health center	44	56.1	2.60	4.24			
Mode of delivery							
Vaginal	179	160.7	2.08	9.4	9.4	1	0.00217
Cesarean section	41	59.3	5.63	9.4			
Surgery Approach							
Vaginal	182	167.7	1.22	6.29	6.3	1	0.0121
Abdominal	38	52.3	3.91	6.29			
Duration of Catheter							
≤14 days	198	189.1	0.419	3.56	3.6	1	0.0593
>21 days	22	30.9	2.565	3.56			
Status of Urethra							
Not damaged	213	193.2	2.03	20.1	20.1	1	7.52e-06
Partially damaged	7	26.8	14.65	20.1			
Types of Fistula							
RVF	33	56.4	9.69	17.6	17.6	1	2.77e-05
VVF	187	163.6	3.34	17.6			

Df= Degrees of freedom

4.2 Cox proportional Hazards Regression Model

4.2.1 Univariable Analysis of Cox PH Regression Model

Single covariate Cox proportional hazards model analysis is an appropriate procedure that is used to screen out potentially important variables before directly included in the multivariate model. The relationship between each covariate and survival time of obstetric fistula patients was presented in table 3.3 in the appendix. From table 3.3 survival of the patients was significantly related to weight, marital status, parity, place of residence, duration of incontinence of urine, antenatal care, duration of labor, place of delivery, mode of delivery, surgery approach, duration of catheter, status of urethra and types of fistula were significantly associated with survival time of OBF patients but age and level of education were not significant at modest level of significance at 0.25.

4.2.2 Multivariable Analysis of Cox PH Regression Model

One problem of single covariate approach is that it ignores the possibility that a collection of variables, each of which is weakly associated with the outcome, can become an important predictor of the outcome when taken together. It is for this reason that we used p-value of 0.25 for selection of variables that are candidates for the multiple covariate analysis from single covariate findings. Results presented in table 4.4 indicate the parameter estimates of coefficients β_i for the covariates in the final model along with the associated standard error, Wald statistic, significance level, hazard ratio and 95% confidence interval for the hazard ratio.

In order to decide whether or not a variable is significant, the p-value associated with each parameter has beenestimated and variables that have p-value less than 0.05 are considered as important variables and hence, are included in the study.

Table 4.4: Results of multivariable Cox PH Model time-to-recovery from OBF in JUMC

Covariates	Category	$\hat{\beta}$	SE	Wald	P-value	HR	95% CI for HR
Weight	< 50kg®						
	≥50kg	0.412	0.159	2.59	0.0095	1.51	[1.11, 2.06]
Place of Residence	Rural®						
	Urban	-0.97	0.457	-2.12	0.034	0.379	[0.155, 0.93]
Incontinence of Urine	≤3 months®						
	> 3 months	-0.297	0.147	-2.02	0.044	0.743	[0.556, 0.992]
Antenatal care	Yes®						
	No	-0.35	0.175	-1.99	0.046	0.71	[0.50, 0.994]
Mode of delivery	Cesarean section®						
	Vaginal	-0.576	0.28	-2.06	0.04	0.562	[0.325, 0.97]
Status of Urethra	not P. damaged®						
	P. damaged	-0.978	0.406	-2.41	0.016	0.376	[0.1696, 0.83]

** **SE:** Standard Error, **CI:**Confidence Interval, ®= Reference group**

Survival of obstetric fistula patients was significantly affected by weight, place of residence, duration of incontinence of urine, antenatal care, mode of delivery and status of urethra.The values of the Wald statistic for individual coefficients support that the estimated values$\widehat{\beta_i}$ are significant different from zero at α= 5% level of significance for all the above covariates.

4.2.3 Assessment of Model Adequacy of Cox PH Model

To check the PH assumption for covariates included in the fitted model, we used the ln (-ln (survival probability)) plot versus ln survival time figures 4.10 in appendix suggested that two lines corresponding to ln[-ln[S(t)]] versus ln(time) are not distributed parallel, the distance is changing over time and cross each other which suggests violation from PH assumption for covariates weight, incontinence of urine, antenatal care, mode of delivery and status of urethra. Table 4.5 shows the time-dependent covariates (interaction of covariates with the logarithm of time) was not significant for a place of residence which means the proportional hazard assumption was not violated for a place of residents. But newly added covariates were statistically significant which indicates that proportional hazard assumptions were not satisfied with weight, incontinence of urine, antenatal care, mode of delivery and status of the urethra.

Table 4.5: Statistical test for PH assumption of the covariates and their interaction with log time for time-to-recovery from OBF in JUMC

Covariates	$\hat{\beta}$	HR	SE	Wald	P-value
Weight	3.4427	31.27	0.6988	4.93	8.4e-07
Place of Residence	1.966	7.144	2.9361	0.67	0.50308
Incontinence of Urine	2.884	17.8765	0.5996	4.81	0.50308
Antenatal care	3.336	28.102	0.6496	5.14	1.5e-06
Mode of delivery	2.437	11.441	0.6913	3.53	0.00042
Status of Urethra	-5.844	0.0029	1.6532	-3.53	0.00041
Weight*ln(t)	-1.583	0.205	0.3514	-4.51	6.6e-06
Place of Residence *ln(t)	-1.182	0.3066	1.0812	-1.09	0.27419
Incontinence of Urine*ln(t)	-1.373	0.2535	0.2715	-5.06	4.3e-07
Antenatal care*ln(t)	-1.582	0.2056	0.2926	-5.41	6.4e-08
Mode of delivery*ln(t)	-1.196	0.3024	0.3182	-3.76	0.00017
Status of Urethra*ln(t)	1.885	6.5837	0.6822	2.76	0.00574

$\hat{\beta}$: Regression coefficient, *HR: hazard ratio***,** *SE***:** *Standard Error*

The plot of Schoenfeld residuals in Appendix figure 4.11 shows that distributes in nonsystematic way about the reference line (without definite increment or decrement), but the Lowess curve connecting the values of the smoothed residuals is slightly upward and down ward (not horizontally) for the covariates weight, incontinence of urine, antenatal care, mode of delivery and status of urethra i.e. Schoenfeld Residuals do not give straight forward answer, however they might suggest violation from PH assumption for those covariates. Thus, the researcher doubts the accuracy of the PH assumption and considers the AFT model for this data set.

4.3 Accelerated Failure Time Model Results

4.3.1 Univariable Analysis

This study used univariate analysis in order to see the effect of each covariate on time-to recovery from OBF before proceeding to the multivariable analysis. The univariate analyses was fitted for every covariate by AFT models using different baseline distributions i.e. weibull, log-logistic, and lognormalin table 4.6 in appendix. In candidate covariates for further analysis of AFT model are weight, marital status, parity, place of residence, duration of incontinence of urine, antenatal care, duration of labor, place of delivery, mode of delivery, surgery approach, duration of catheter, status of urethra and types of fistula were significantly associated with survival time of OBF patients but age and level of education were not significant at modest level of significance at 0.25.

4.3.2 Multivariable AFT Model Analysis

For survival time of OBF patients data, the multivariable AFT models are weibull, log-logistic, and lognormal distribution were fitted by including all the covariates p-value less than 0.25 in the Univariable analysis at modest level. 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, lognormal AFT model (AIC = 1206) found to be the best for the survival time of OBF data set from the given alternatives when we include all the covariate those are significant in the univariate analysis.Covariates which become insignificant in the multivariate analysis were removed from the model by using backward elimination technique. Accordingly, parity, surgery approach and duration of catheter were excluded in multivariate AFT model. The final model kept the main effect of the covariate weight, marital status, place of residence, duration ofincontinence of urine, antenatal care, duration of labor, place of delivery, mode of delivery, status urethra and types of fistula. AFT models in this study and the corresponding AIC values are displayed in table 4.7

Table4.7:AIC value of parametric AFT model for time-to-recovery from OBF in JUMC

Baseline Distribution	AIC
Weibull	1223.792
Lognormal	1206.000
Log- logistic	1210.215

AIC=Akaike's information criteria

4.3.3 Interpretation and presentation of the final AFT model

From table 4.8 showed patients with weight, marital status, place of residence, duration of incontinence of urine, antenatal care, duration of labor, place of delivery, mode of delivery, status urethra and types of fistula were statistically significant with survival time of OBF patients in JUMC.

Table 4.8: Results of multivariable lognormal AFT model for time-to-recovery from OBF

Covariates	Coef.	SE	Wald	P-value	Φ	95% CI for Φ
Weight						
<50kg®						
≥50kg	-0.1496	0.072	-2.078	0.038	0.86	[0.748, 0.992]
Marital status						
Married®						
Divorce	0.1868	0.0811	2.303	0.021	1.2	[1.03, 1.413]
Others	-0.187	0.1645	-1.112	0.26	0.83	[0.601, 1.145]
Place of residence						
Rural ®						
Urban	0.446	0.203	2.197	0.028	1.56	[1.049, 2.325]
Dur. of incontinence urine						
≤3 months®						
>3 months	0.182	0.0666	2.732	0.006	1.2	[1.053, 1.367]
Antenatal care						
Yes®						
No	0.1736	0.0768	2.26	0.024	1.19	[1.023, 1.383]
Duration of labor						
≥2days®						
<2days	-0.1449	0.0671	-2.158	0.031	0.865	[0.758, 0.987]
Place of delivery						
Home®						
Health center	-0.2803	0.1378	-2.034	0.042	0.76	[0.576, 0.9897]

Mode of delivery						
Cesarean section®						
Vaginal	0.4043	0.1463	2.764	0.0057	1.5	[1.125, 1.996]
Status of urethra						
Not damaged®						
Partial damaged	0.4671	0.1578	3.013	0.0031	1.6	[1.171, 2.174]
Types of Fistula						
VVF®						
RVF	-0.3083	0.0100	-3.083	0.0021	0.735	[0.604, 0.894]
Scale = 0.477	AIC=1206					

AIC=Akaike's information criteria, ***SE****: standard error; ϕ: acceleration factor;* ***95% CI ϕ:*** *95% confidence interval for acceleration factor,* **®:***Reference*.

Under the lognormal AFT model, when the effect of other factor keep fixed, the estimated acceleration factor for patients weight ≥ 50kg is estimated to be 0.86 with [95% CI: 0.748, 0.992] by using <50kg as the reference category. The confidence interval for the acceleration factor did not include one and P-value is smaller than 0.05. This result shows that weight ≥50kg patient is short time-to-recovery from obstetric fistula than weight < 50kg patient. The acceleration factor for divorce patients was estimated to be 1.21 with [95% CI: 1.03, 1.413] by using married as the reference category. This result suggested that divorce patients had prolonged time-to-recovery from obstetric fistula than married patients.

The acceleration factor for patients from urban is estimated to be 1.57 with [95% CI: 1.049, 2.325] by using rural as the reference category. The confidence interval for the acceleration factor did not include one. This result showed that a patient from urban has accelerated time-to-recovery from obstetric fistula than rural patients. The acceleration factor for patients who had the duration of incontinence of urine >3 months is estimated to be 1.185 with [95% CI: 1.053, 1.367] by using incontinence of urine ≤3 months as the reference category. The confidence interval for the acceleration factor did not include one and P-value smaller than 0.05. This implies that duration of incontinence of urine >3 months patients had longer time-to-recovery from obstetric fistula than the duration of incontinence of urine ≤3 months.

The acceleration factor of patients who had to no follow-up with antenatal care was 1.194 with [95% CI: 1.023, 1.383 and P=0.021] which shows that patients who had no follow-up with antenatal care have prolonged time-to-recovery from OBF than follow-up of antenatal care service. The acceleration factor of patients for the duration of labor < 2days was 0.87 with[95% CI: 0.758, 0.987 and P=0.0389] by using labor ≥ 2days as the reference category. This implied that duration of labor <2days patient is fast time-to-recovery from OBF than the duration of labor ≥ 2days. Similarly, the estimated acceleration factor for patients mode of delivery with vaginal was 1.5 with [1.125, 1.996 and P =0.006] mode of cesarean section as the reference, which shows that mode of delivery with vaginal patients had prolonged time-to-recovery from obstetric fistula than the mode of delivery with cesarean section.

The estimated acceleration factor for the place of delivery at Health centerwas 0.76 with [0.576, 0.9897 and P =0.0026] which shows that patients who place of delivery at Health centerhad better time-to-recovery from obstetric fistula than that of delivery at home. The estimated acceleration factor for patients partially damaged of the urethra was 1.607 with [1.171, 2.174 and P =0.0026] which shows that not damaged of urethra patients have accelerated time-to-recovery from obstetric fistula than partially damaged of the urethra. And the estimated acceleration factor for patients vesicovaginal fistula was 0.736 with [0.604, 0.894 and P =0.0026] by using VVF as the reference category, which shows that recto-vaginal fistula is better time-to-recovery from obstetric fistula thanVesicovaginal fistula patients.

4.3.4 Parametric Shared Frailty Model Results

The main focus of this study is to investigate risk factors associated with time-to recoveryusing parametric shared frailty model. The AIC value for both gamma and inverse Gaussian parametric shared frailty models with three baseline distribution is summarized in table 4.9. The AIC value of the lognormal inverse-Gaussian model is1199.655, whichis the minimum from all the other AIC values of the models which indicates that it is the most efficient model to describe the OBF dataset among the various parametric frailty models.

Table 4.9:AIC value of parametric frailty modelfor time-to-recovery from OBF in JUMC

Baseline Distribution	Frailty Distribution	AIC
Weibull	Gamma	1212.534
	Inverse-Gaussian	1209.693
Lognormal	Gamma	1204.017
	Inverse-Gaussian	1199.655*
Log-logistic	Gamma	1201.315
	Inverse-Gaussian	1205.697

AIC=Akaike's information criteria

3.4.5 Lognormal Inverse-Gaussian Frailty Model Result

This model is the same asthe log-normal AFT model discussed inthe previous section, except that a frailty component has been included. The estimated value of theta (θ) is 0.186. A variance of zero (θ = 0) would indicate that the frailty component does not contribute to the model. A likelihood ratio test for the hypothesis θ = 0 is shown in the table 4.10 below indicates a chi-square value of 92.15 with P-value of 7.1e-13 resulted in a highly significant. This implied that the frailty component had the significant contribution to the model. And Kendall's tau (τ), which measures dependence within clusters, is estimated to be 0.074. The estimated value of the shape parameter in the log-normal-inverse Gaussian frailty model is 1.527 (ρ = 1.527). This value showed the shape of hazard function is uni-modal because the value is greater than unity implies it increases up to its maximum point and then decreases.

Table 4.10: Results of Lognormal Inverse-Gaussian Frailty Model for Time-to-recovery from obstetric fistula in JUMC

Covariate	**Coef.**	**SE**	**Wald**	**P-value**	**Φ**	**95% CI for Φ**
Weight						
< 50kg®						
≥50kg	-0.1505	0.0719	-2.094	0.036	0.86	[0.747, 0.99]
Marital status						
Married®						
Divorced	0.1867	0.081	2.304	0.021	1.2	[1.028, 1.413]
Others	-0.187	0.1642	-1.137	0.26	0.83	[0.601, 1.14]

Place of Residence						
Rural ®						
Urban	0.4428	0.2029	2.183	0.029	1.56	[1.046, 2.317]
Urine incontinence						
≤ 3 months®						
>3 months	0.1848	0.0666	2.772	0.0056	1.2	[1.056, 1.371]
Antenatal care						
Yes®						
No	0.1732	0.0767	2.258	0.024	1.189	[1.023, 1.382]
Duration of labor						
≥2 days®						
<2days	-0.1456	0.0671	-2.171	0.03	0.86	[0.758, 0.986]
Place of delivery						
Home ®						
Health center	-0.2809	0.1377	-2.04	0.041	0.76	[0.576, 0.989]
Mode of delivery						
Cesarean section®						
Vaginal	0.4044	0.1464	2.763	0.0057	1.5	[1.125, 1.996]
Status of urethra						
Not damaged®						
Partially damaged	0.4639	0.1577	2.942	0.0033	1.59	[1.168, 2.166]
Types of Fistula						
VVF®						
RVF	-0.3077	0.0998	-3.083	0.0021	0.735	[0.6045, 0.894]
θ =0.186			AIC = 1199.655			
τ = 0.074				ρ = 1.527		
Likelihood-ratio test of θ= 0: Chi-square = 92.15 P = 7.1e-13						

***SE** =standard error; ϕ=acceleration factor; **95% CI ϕ:** 95% confidence interval for acceleration factor, θ=Variance of the random effect, τ= Kendall's tau, AIC=Akaike's Information Criteria,ρ= shape, **®** = Reference*

From above table 4.10, the confidence intervals of the acceleration factor for all significant categorical covariates do not include one at 5% level of significance. This showed that they are significant factors for determining time-to-recovery among patients in JUMC. However, from the covariate others (single and widowed) is not significant by taking married as reference (P-value = 0.26, ϕ = 0.83, 95% CI= 0.601, 1.14). The acceleration factor for divorced patients was estimated to be 1.2 with [95% CI: 1.028, 1.413]. This result showed that the recovery time for divorced patients is increased time-to-recovery by a factor of 1.2 compared to the married patients. The estimated acceleration factor for patients weight ≥50kg to less than 50kg was 0.86 with [95% CI = 0.216, 1.656]. This suggested that the time-to-recovery for weight ≥50kg is deceleratedby a factor of 0.86 compared to the weight <50kg group.

The acceleration factor for the patient who has lived in urban was accelerated time-to-recovery by a factor of 1.56 than those who were lived in rural (rural as a reference; ϕ: 1.56, 95%CI: 1.046, 2.317), this indicates that time-to-recovery for living urban patients were prolonging than rural patients. The estimated acceleration factor comparing for patients who had urine incontinence ≤ 3 months to >3 months is 1.2 with [95% CI:1.056, 1.371]. This implies that patients who had urine incontinence >3 months were loner recovery time than that of urine incontinence ≤3 months.

The estimated acceleration factor comparing for patients who had to no follow-up with antenatal care to follow-up of antenatal care is 1.189 with [95% CI: 1.023, 1.382]. This implies that patients who had to no follow-up with antenatal care were longertime-to-recovery than that of follow-up of antenatal care. The acceleration factor comparing for duration of labor less than 2days to ≥2 days was 0.87 with [95% CI: 0.758, 0.986 and P=0.0389]. This suggested that duration labor <2days patients short time-to-recovery from OBF by a factor of 0.87 compared to the duration labor ≥2days. The estimated acceleration factor for patients place of delivery at health center to home was 0.76 with [95%CI: 0.576, 0.989] which shows that patients for the place of delivery at home had prolongedtime-to-recovery from obstetric fistula than that of delivery at health institution.

Similarly, the estimated acceleration factor for patients mode of delivery at the vaginal to cesarean section was 1.5 with [95% CI: 0.565, 1.645], which shows that the recovery time for the mode of delivery with vaginal patients was increased by a factor of 1.5 compared to the mode of delivery with cesarean section. The patients recovery time for partially damaged is increased by factor of 1.56 compared to the notdamaged. Finally, the estimated acceleration factor comparing the recto-vaginal fistula patient to Vesco-vaginal fistula patients was 0.735 with [0.6045, 0.894] which suggested that patients time-to-recovery from obstetric fistula for VVF had longer compared to the RVF group i.e. patients who had RVF is shorter recovery time than patients those who had VVF.

4.3.6 Comparison of Lognormal AFT and Lognormal Inverse-Gaussian Frailty Model

The comparison of lognormal AFT and inverse-Gaussian frailty model is shown table 4.14 in appendix, we can observe that the results from the lognormal AFT and lognormal inverse Gaussian frailty model are quite similar but not identical. In this study, in order to compare the efficiency of the models, the AIC was used. The lognormal inverse Gaussian shared frailty model has a minimum (AIC=1199.655) than lognormal AFT (AIC =1206), indicating that lognormal inverse Gaussian frailty model fitted the survival time of fistula data better than the lognormal AFT model, which did not take into account the clustering effect. When we look at the estimated value of coefficients of the covariate, they are altered with the inclusion of the frailty component and the confidence interval for the acceleration factor is a little beat narrower for lognormal inverse Gaussian frailty model. Furthermore, the variance of random effect (frailty) was significant at 5% level of significance which indicates that the parametric shared frailty model fits the given dataset better than AFT model. In general lognormal inverse Gaussian, frailty model is preferred over lognormal AFT for modeling of time-to-recovery from OBF dataset.

4.5 Model Diagnostics

After the model has been fitted, it is desirable to determine whether a fitted parametric model adequately describes the data or not.

4.5.1. Checking Adequacy of Parametric Baselines using Graphical Methods

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 $\log\left(\frac{\hat{s}(t)}{1-\hat{s}(t)}\right)$ versus log (time) and the lognormal 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 the 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.

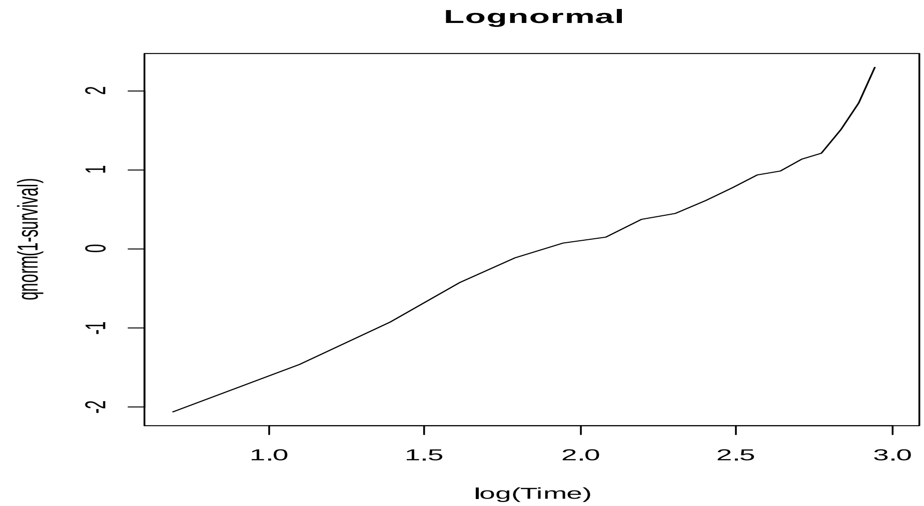


Figure 4.12: Graphs of Lognormal distributions for time-to-recovery from fistula data set.

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 fitting of residuals for weibull, lognormal and log-logistic models to our data via maximum likelihood estimation with cumulative hazard functions is given in figure 4.13 below. The plot shows that the line related to the Cox-Snell residuals of the lognormal models were better than weibull and log-logistic baseline distribution nearest to the line through the origin, this indicating that this model describes the time-to-recovery from obstetric fistula dataset well.

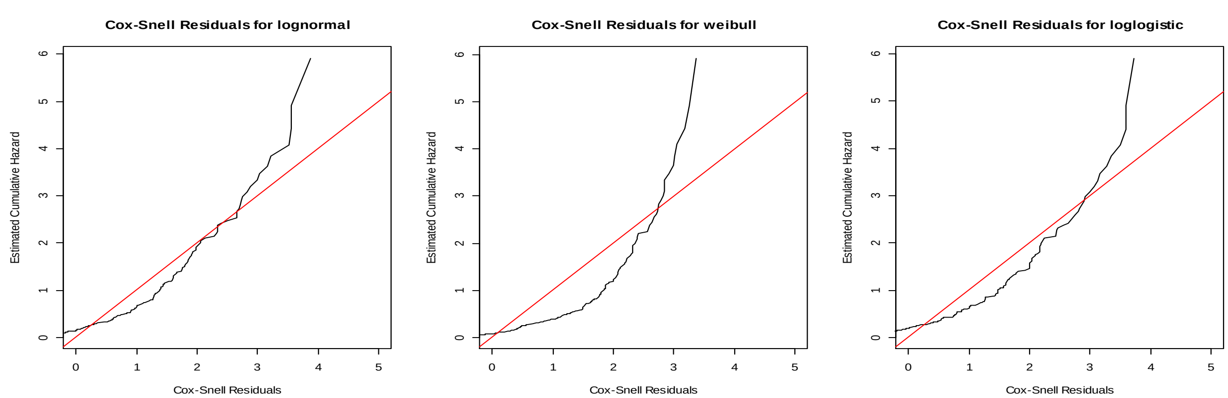


Figure 4.13: Cox-Snell residuals obtained by fitting lognormal, weibull and log-logistic models to the time-to-recovery from OBF dataset

4.6Discussion

The objective of the study was to identify significant risk factors that affect time-to-recovery from obstetric fistula patients in JUMC. For determining the risk factors for the physically cured obstetric fistula patients and modeling the survival time, a total of 270 patients were included in the study out of which 81.4% were physically cured and the rest 18.6% were censored.In a study done in southern part of Ethiopia at Yirgalem Hamlin Fistula Hospital, 81.7% were physically cured and the rest 18.3% were censored, which is almost similar what was observed by the current study.

The log-rank test revealed that weight, marital status, parity, place of residence duration of incontinence of urine, antenatal care, place of delivery, mode of delivery, status of urethra, Surgery Approach, types of fistula identify significant difference in recovery time.This result is in line with other studies (Feysal K., 2014, Getachew, T., 2015)

The main aim of the study was to modeling time-to-recovery from OBF using appropriate survival models. The comparison of distributions of the models was done using the AIC criteria, where a model with minimum AIC is accepted to be the best (Munda, 2012). In this study, lognormal inverse Gaussian frailty model which had AIC value is 1199.655 was the most appropriate model to describe the obstetric fistula data set. This study showed that there was heterogeneity between the Zones on the timing of recovery obstetric fistula among patients. Assuming patients coming from the same zone share similar risk factors related to obstetric fistula. This finding is similar to finding of (Ballard, K., Ayenachew, F., Wright, J., & Atnafu, H. 2016)

One of the factors that affect time-to-recovery from obstetric fistula is the weight of the patients. This study shows that the accelerated factor a patient with weight ≥50kg [Φ=0.86, 95%CI: 0.747, 0.99] is fast as compared to those whose weight <50kg. This indicates that larger weight shorter the chance of recovery as compared to smaller weight. The result is in accordance with the earlier studies (Ahmed et al., 2007; Wall and Karshima, 2004, Feysal K., 2014, Getachew, T., 2015). Marital status is an important predictor for the recovery of obstetric fistula patient with [Φ=1.2, 95%CI: 1.028, 1.413], which suggested that the survival time of divorced patients had prolonged time-to-recovery from obstetric fistula than married patients. This result is in line with the study by (Feysal K., 2014).

The place of residence is another prognostic factor that significantly predicts the recovery time of obstetric fistula patient at [Φ=1.56, 95%CI: 1.046, 2.317]. The study revealed that the survival time for patients living at urban is increased by a factor of 1.56 compared to the living at rural. The result is similar to earlier study (Biadgilign, S. et al). Duration of incontinence of urine is also other factors with accelerated factor 1.2 with [1.056, 1.371] which indicates that the survival time for patient's incontinence of urine > 3 months is longer time-to-recovery than that of patient's incontinence of urine≤ 3 months. This implies that shorter time of incontinence of urine fast the chance of recovery time as compared to the longer time of incontinence of urine. This result is consistent with (Getachew, T., 2015, Feysal K., 2014).

The results of this study suggested that antenatal care was the significant predictive factor for time-to-recovery from obstetric fistula with estimated accelerated factor 1.189 with [1.023, 1.382]. Patients who had no follow-up with antenatal care have prolonged time-to-recovery from OBF than follow-up of antenatal care service. Uses of antenatal care service improve the chance of recovery than no ANC. This result confirms the result obtained from the previous studies with (Gessessew et al., 2003, Getachew, T., 2015 and Feysal K., 2014).Duration of labor is also an important predictor for the recovery of obstetric fistula patient with [Φ=0.86, 95%CI: 0.758, 0.986]. This study suggested that the patient's whose labor <2 days were fast time-to-recovery compared with that of patient's labor ≥2 days. That is, a short time of obstructed labor is better time-to-recover than long time labored patient. This result is in accordance with the studies of (Cisse et al., 1998; Van Dillen et al., 2007; Tebeu et al., 2008, Getachew, T., 2015 and Feysal K., 2014).

Place of delivery has been observed to have the significant factor with [Φ=0.76, 95%CI: 0.576, 0.989]. The time-to-recovery for the delivery at home is longer compared to the delivery at the health center. This result is similar to the studies from Niger by Haroun et al., 2001; Getachew, T., 2015, Feysal K., 2014, Marit, 2016). The mode of delivery is another prognostic factor that significantly predicts the recovery time of obstetric fistula patient.

The result obtained from this study indicates the accelerated factor of CS [Φ=1.5, 95%CI: 1.125, 1.996] is accelerated by a factor of 1.5 compared to the delivered vaginally. This shows that Mode of delivery with vaginal had increased time-to-recovery than CS delivery. This result confirms the result obtained from the previous studies (Jonas et al., 1984; Symmonds, 1984; Haroun et al., 2001; Getachew, T., 2015, Feysal K., 2014).

In addition to those factors status of urethra also had a significant effect on the recovery time of obstetric fistula patient. Being havingpartiallydamaged status of urethra has longer recovery time than those who have not damaged status of urethra[Φ=1.59, 95%CI: 1.168, 2.166]. This result in line result obtained from the previous finding (Getachew, T., 2015, Feysal K., 2014). Finally, the types of fistula were the significant factor with [Φ=0.736, 95%CI: 0.6045, 0.894] for time-to-recovery from obstetric fistula in JUMC. The survival time for the VVF is prolonged compared to the RVF i.e. patients who had VVF is longer recovery time than patients those had RVF. This result confirms the result obtained from the previous studies (Tukur et al., 2015).

CHAPTER FIVE
CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

This study used survival times of Obstetric fistula patients' dataset of those patients who started their fistula treatment from January, 2011 to February, 2017 with the aim of modeling time-to-recovery from obstetric fistula in JUMC. A total of 270 patients were included in the study out of which 81.4% were physically cured and the rest 18.6% were censored.In assessing the significant risk factors the Log-Rank test revealed that, weight, marital status, place of residence, parity, duration of incontinence of urine, antenatal care, place of delivery, mode of delivery, surgery approach, status of urethra and types of fistula had significant survival probability difference for time-to-recovery from obstetric fistula.

To model the determinants of time-to-recovery, different parametric shared frailty, and AFT models by using different baseline distributions were applied. Among this using AIC, lognormal inverse Gaussian shared frailty model is better fitted to time-to-recovery dataset than other parametric shared frailty and AFT models. There is a frailty (clustering) effect on the time-to-recovery that arises due to differences in the distribution of timing of recovery among zones of OBF. This indicates the presence of heterogeneity and necessitates the frailty models.

The result of lognormal AFT and lognormal inverse Gaussian frailty models showed that the major factors that affect the time-to-recovery from OBF patients are weight, marital status, duration of incontinence of urine, place of residence, antenatal care, duration of labor, place of delivery, mode of delivery, status of urethra and types of fistula were found significant predictors to time-to-recovery from obstetric fistula in JUMC. Among these significant predictors, weight ≥50kg, delivery at health center, duration of labor <2days and recto-vaginal fistula were shorter time-to-recovery from OBF while incontinence of urine > 3 months, residence at urban, no follow-up of antenatal care, vaginal delivery, divorced and status of urethra partially damaged were prolonged time-to-recovery from OBF.

The goodness of the fit of baseline distribution by means of the graphical method and Cox-Snell residuals plots in figure 4.12 and 4.13 revealed that lognormal distribution is better when compared to Weibull and log-logistic baseline distributions to explain time-to-recovery dataset.

5.2 Recommendations

Based on the result of the study different factors are identified for the recovery of fistula patients. The following recommendations are made for health policy makers, clinicians and the community at large.

- Obstetricians and Gynecologists should work on perception about the problem and its risk factors, so that patients should be well informed about the problem and early diagnose to make a patient physically cured and to stop isolation and social humiliation of patient from community.

- Obstetricians, Gynecologists and all concerning health staff should work on early detection and intervention of obstructed labor.

- Government and concerning bodies should work a lot on giving health information and awareness for the community on:
  - ✓ Antenatal care follow-up
  - ✓ About obstructed labor
  - ✓ Intuitional delivery
  - ✓ Perception and attitude of fistula,especially for weight <50kg peopleand to seek early health service.

- The Ministry of Health need to equip health centers with necessary materials and human power to perform caesarian section at health center level.

- Patients with Vesicovaginal fistula have prolonged time-to-recovery. Sospecial attention should be given to Vesicovaginal fistulapatients to shorter time-to-recovery from their disease.

- Jimma University Medical Center need to improve public and professional awareness, early detection and prompt treatment using feasible, effective regimens and include detailed patients characteristics in the fistula registry data. This hospital based fistula patient's registry is older which need integration with computerized system.

5.3 Limitation of the Study

This study had some limitations: the first is that the study used data from single hospital. Thus, the findings of this study should be interpreted very carefully when they are inferred to the national level. The second limitation is lack of published literature on our country related to the time-to-recovery from OBF. Finally as different literature pointed out; there are different factors that are assumed to have factors on the survival of fistula patients such as age at first marriage, accompanying, fetal outcome, height,length of fistula and width offistula. However, data on these variables could not be available in hospital records, so these variables were not integrated in this study. May better if it done prospectively.

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APPENDIXIES

Kaplan Meier plot of time-to-recovery from OBF Patients by Different Covariates

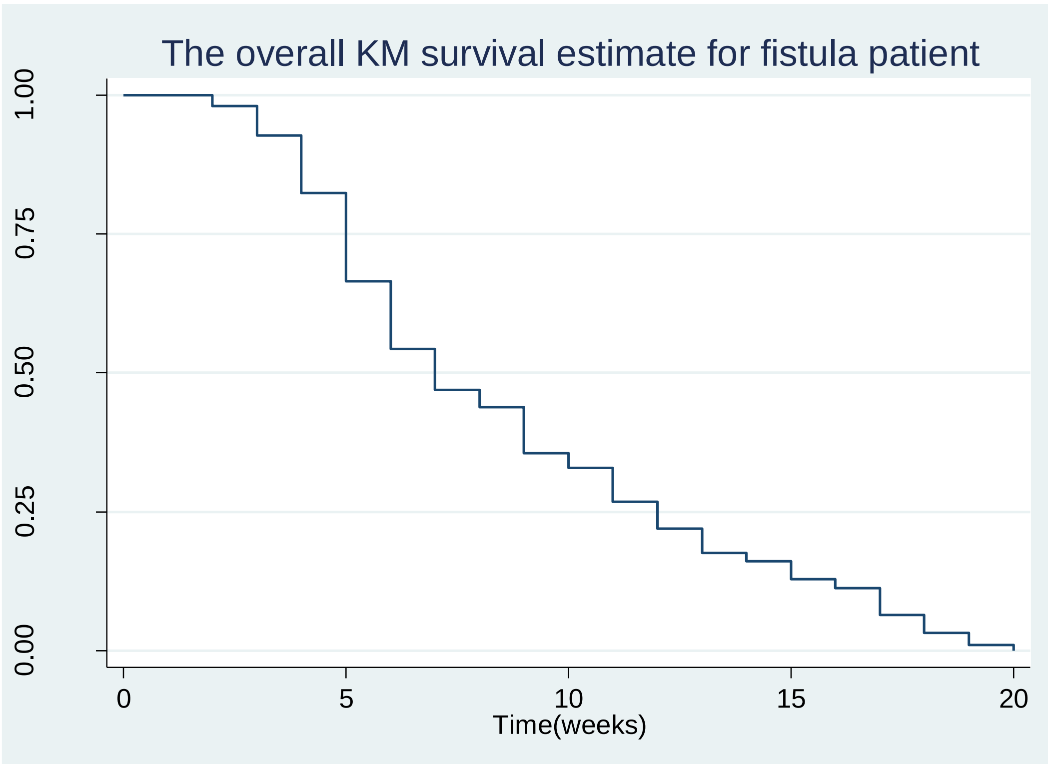


Figure 4.1: The overall estimate of Kaplan-Meier survival function of Fistula patients.

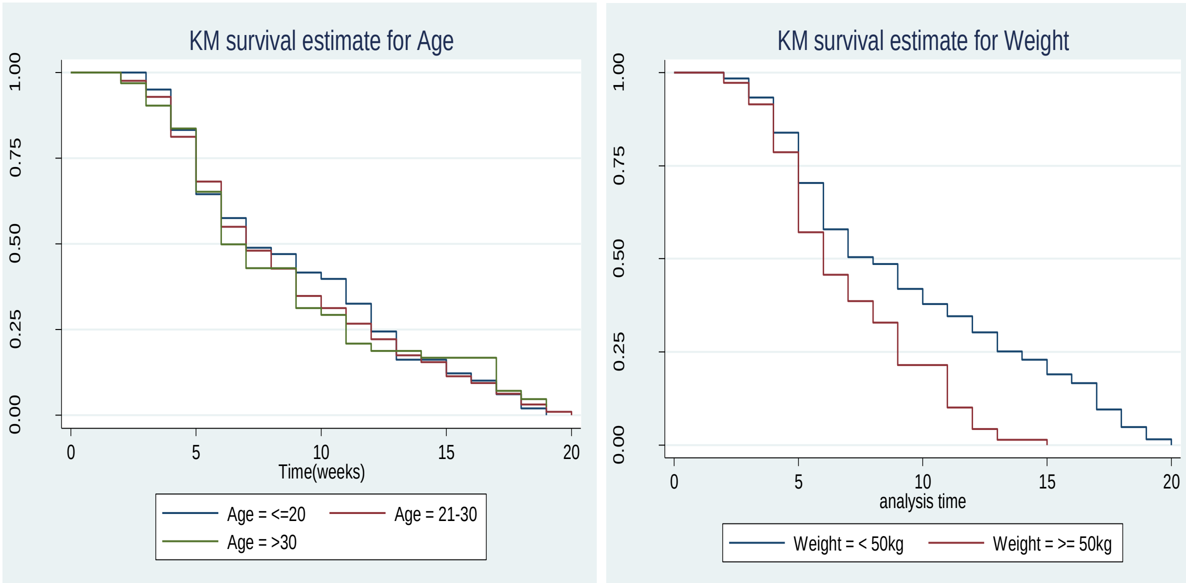


Figure 4.4: K-M plot of survival of time-to-recovery by Age and Weight

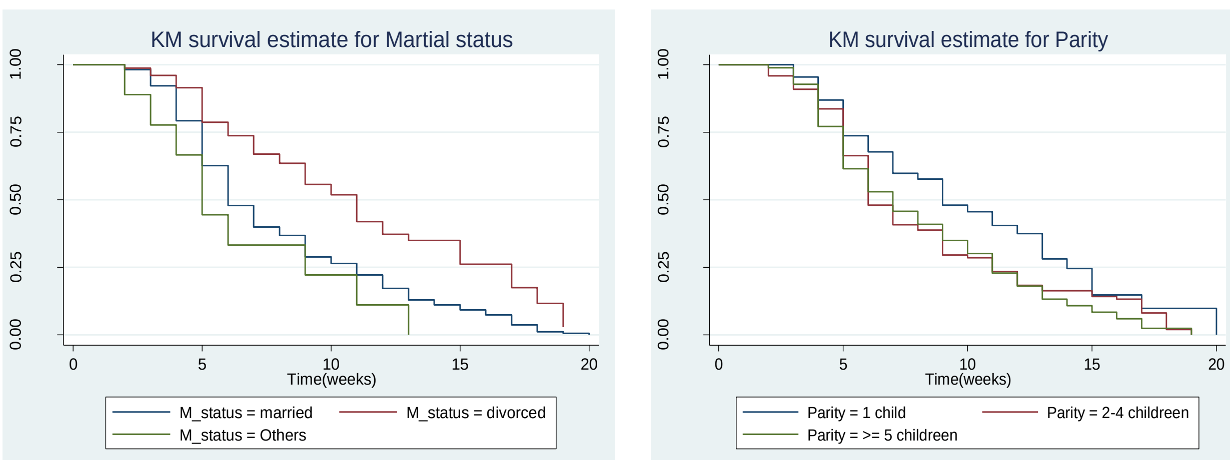


Figure 4.5:K-M plot of survival of time-to-recovery by Marital status and Parity

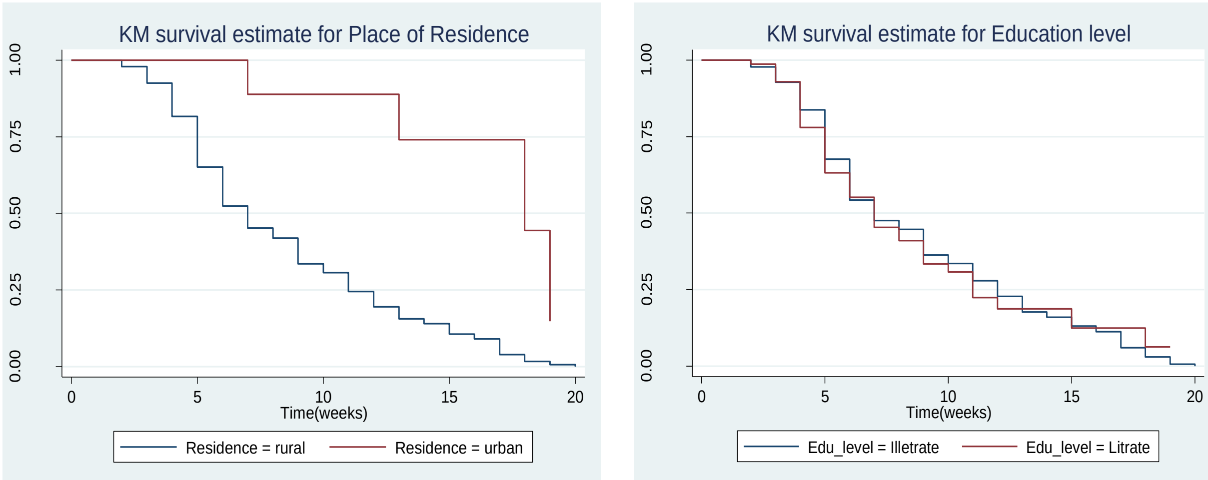


Figure 4.6:K-M plot of time-to-recovery by Education level andPlace of residence.

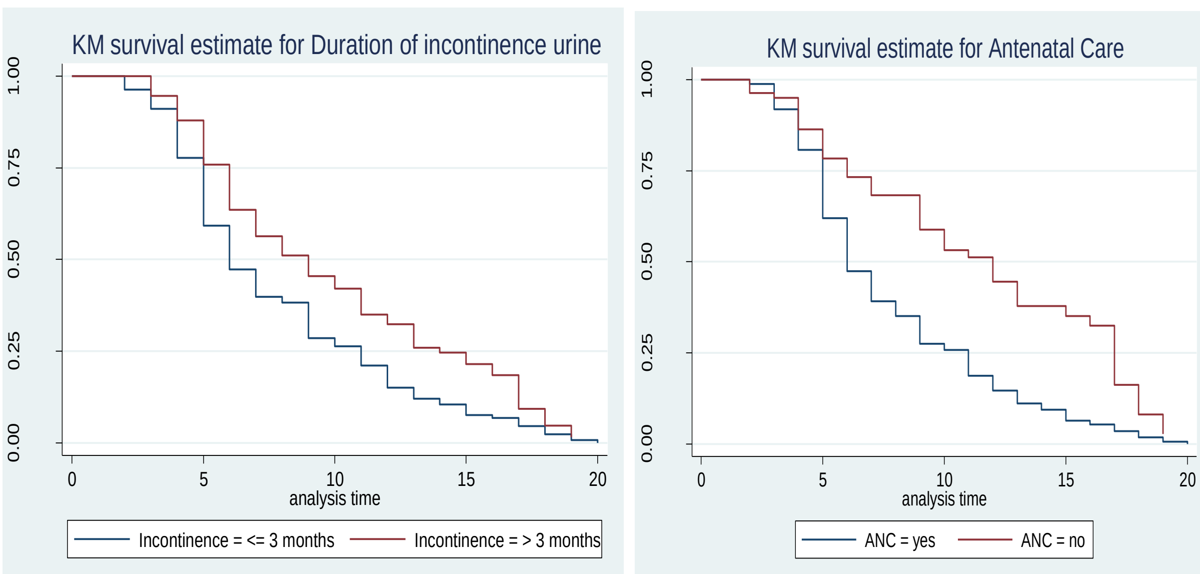


Figure 4.7:K-M plot of survival of time-to-recovery by Duration of incontinence and ANC

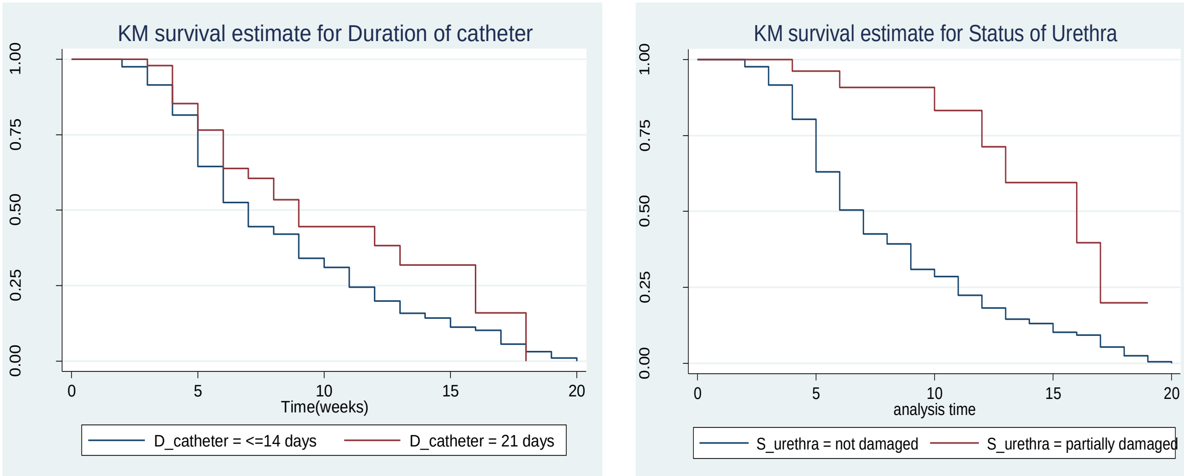


Figure 4.8: K-M plot of survival of time-to-recovery by Duration of catheter and status of Urethra.

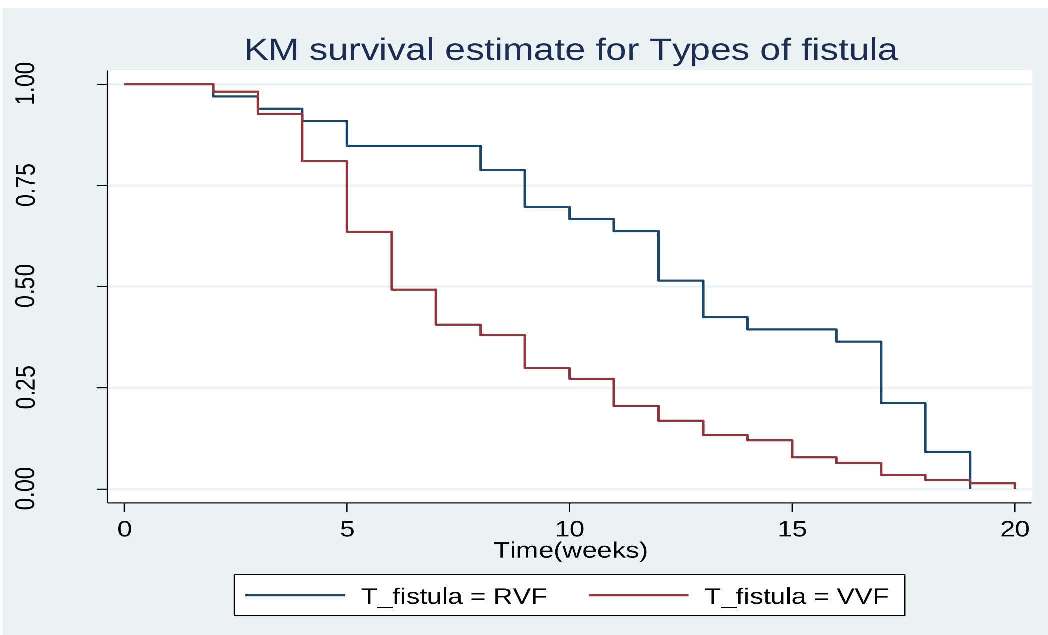
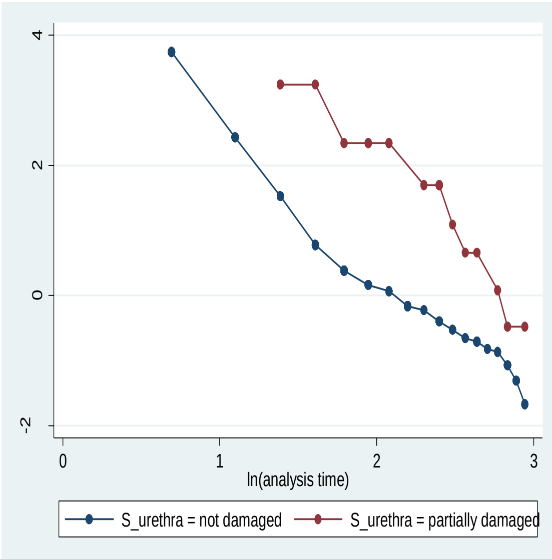


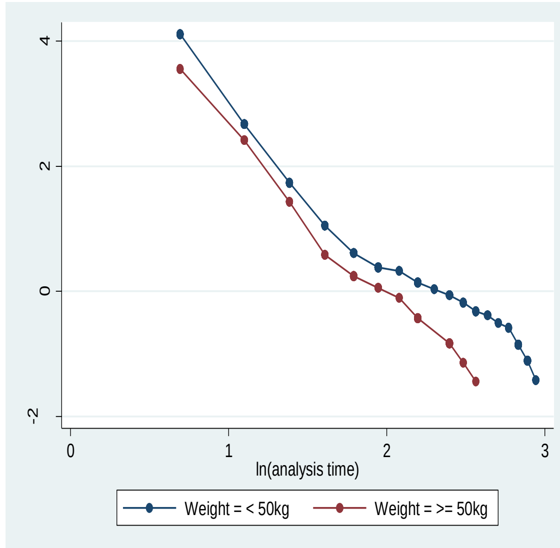
Figure 4.9: K-M plot of survival of time-to-recovery by Types of fistula

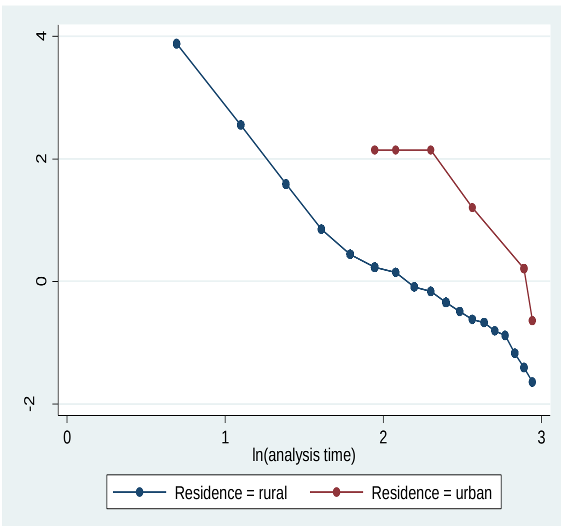
Table 4.3: Univariable Analysis of Cox PHfor time-to-recovery from OBF in JUMC

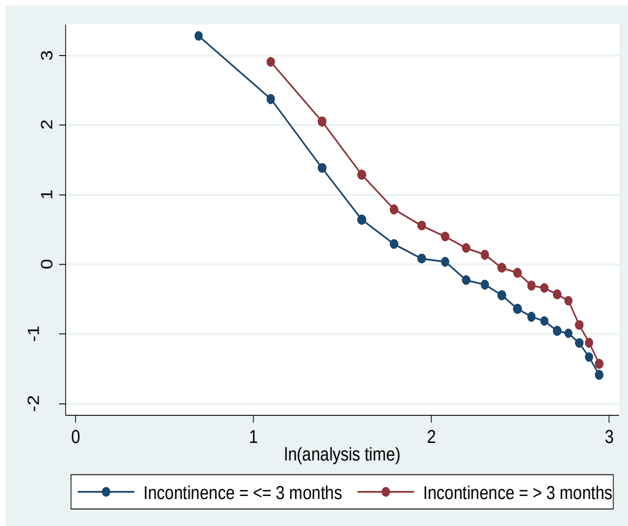
Covariates	Categories	$\hat{\beta}$	SE	Wald	P-value	HR	95% CI HR
Age	<20®						
	21-30	0.045	0.165	0.27	0.786	1.05	[0.757, 1.45]
	>30	0.028	0.193	0.146	0.884	1.03	[0.705, 1.5]
Weight	< 50kg®						
	≥50kg	0.595	0.152	3.91	9.19e-05	1.81	[1.35, 2.44]
Marital status	Married®						
	Divorced	-0.607	0.166	-3.67	0.000	0.55	[0.39, 0.75]
	Others	0.378	0.344	1.1	0.271	1.46	[0.74, 2.86]
Parity	1 child®						
	2-4 children	0.389	0.192	2.02	0.043	1.5	[1.01, 2.15]
	>5 children	0.47	0.196	2.4	0.016	1.6	[1.09, 2.35]
Place of Residence	Rural®						
	Urban	-1.42	0.423	-3.4	0.000	0.24	[0.11, 0.554]
Education Level	Illiterate(R)						
	Literate	0.018	0.172	0.103	0.918	1.02	[0.73, 1.43]
Incontinence of urine	≤3 months®						
	>3 months	-0.384	0.139	-2.76	0.006	0.68	[0.52, 0.89]
Antenatal care	Yes®						
	No	-0.683	0.164	-4.16	3.2e-05	0.51	[0.366, 0.697]
Duration of labor	≥ 2days®						
	<2days	0.182	0.141	1.29	0.199	1.199	[0.91, 1.58]
Place of delivery	Home®						
	Health center	0.32	0.169	1.87	0.062	0.73	[0.524, 1.02]
Mode of delivery	CS®						
	Vaginal	-0.48	0.174	-2.76	0.006	0.619	[0.44, 0.87]
Surgery Approach	Abdominal®						
	Vaginal	-0.41	0.179	-2.265	0.024	0.67	[0.469, 0.947]
Duration of Catheter	≤14 days®						
	>21 days	-0.391	0.226	-1.73	0.084	0.68	[0.435, 1.054]
Status of Urethra	not damaged®						
	P. damaged	-1.444	0.236	-3.757	0.0002	0.24	[0.11, 0.501]
Types of Fistula	VVF®						
	RVF	0.73	0.1958	3.72	0.0002	2.072	[1.41, 3.04]

$\hat{\beta}$: *Regression coefficient, HR: hazard ratio, SE: Standard Error*


4
2
0
-2
0
1
2
3
ln(analysis time)
S_urethra = not damaged
S_urethra = partially damaged


4
2
0
-2
0
1
2
3
ln(analysis time)
Weight = < 50kg
Weight = >= 50kg


4
2
0
-2
0
1
2
3
ln(analysis time)
Residence = rural
Residence = urban


3
2
1
0
-1
-2
0
1
2
3
ln(analysis time)
Incontinence = <= 3 months
Incontinence = > 3 months

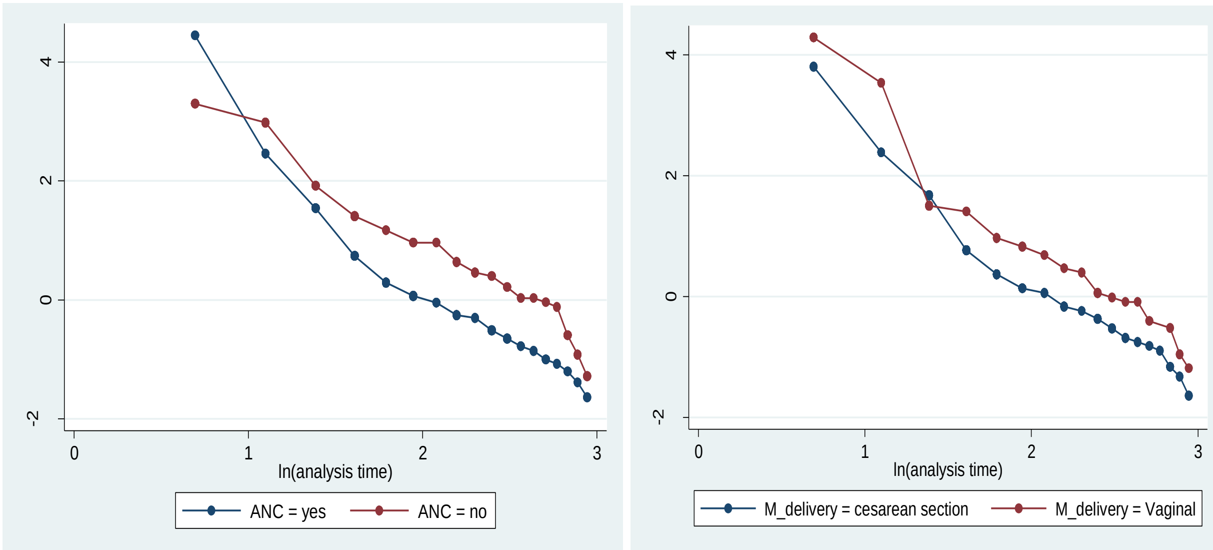


Figure 4.10: Plot of log (-log (survival)) versus log survival time for categorical covariates in the fitted model

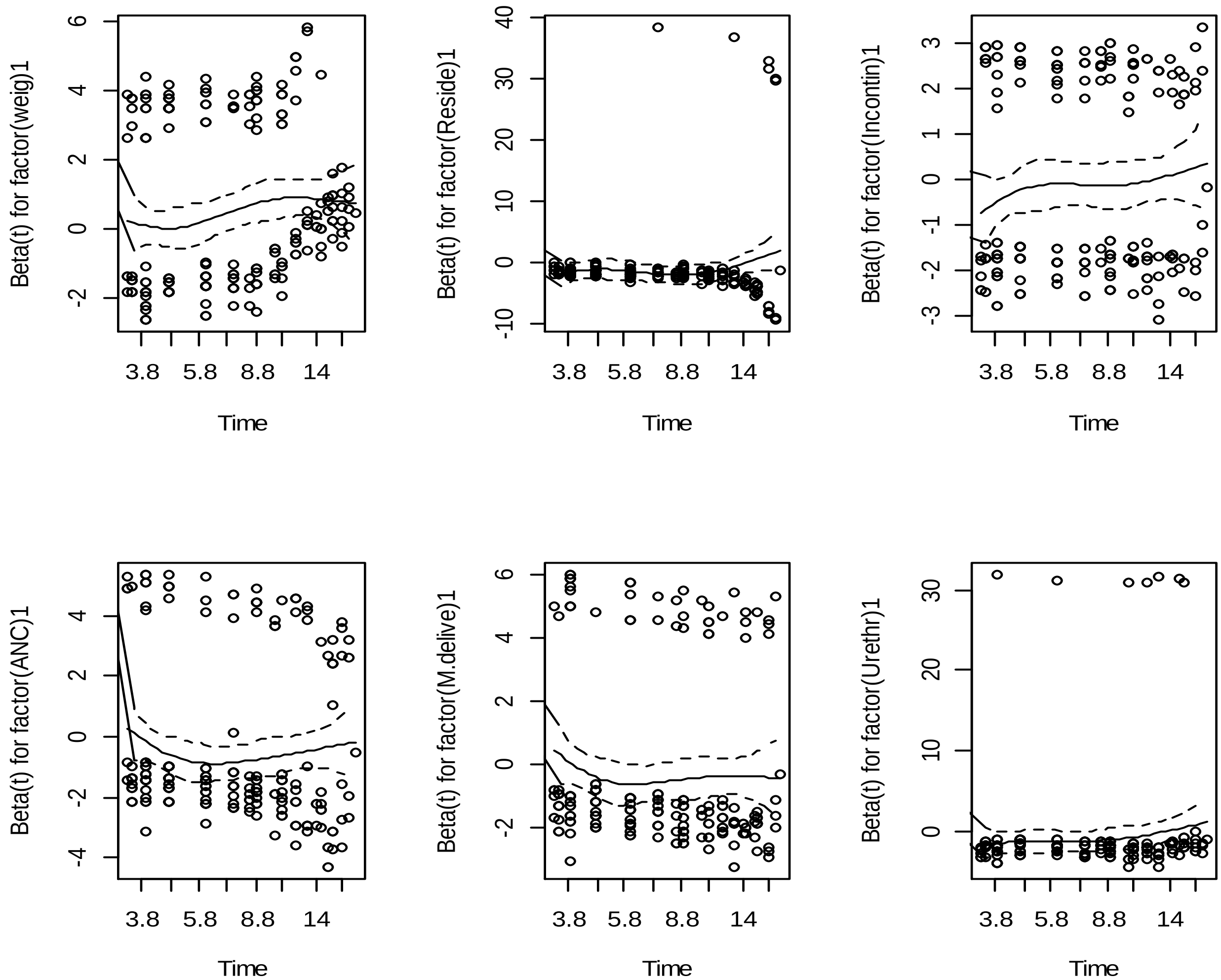


Figure: 4.11:The Plot of Schoenfeld residuals for to check thePH assumptionfor categorical covariates in the fitted model

Table 4.6: Univariable Analysis of AFT model for modeling-time-to-recovery from OBF in JUMC

Covariates	Weibull		Log-logistic		Log-normal	
	$\hat{\beta}$(95% CI β)	P-value	$\hat{\beta}$ (95% CIβ)	P-value	$\hat{\beta}$ (95% CI β)	p-value
Age						
<20 ®						
21-30	-0.029(-0.19, 0.13)	0.72	-0.04(-0.23, 0.14)	0.65	-0.04(-0.22, 0.13)	0.61
>30	-0.033(-0.22, 0.155)	0.73	-0.08(-0.29, 0.13)	0.44	-0.08(-0.28 0.13)	0.47
Weight						
< 50kg®						
≥50kg	-0.34(-0.47, 0.2)	1.1e-06	-0.23(-0.38, -0.073)	.0004	-0.24(-0.39, -0.08)	0.003
Marital status						
Married®						
Divorced	0.31(0.15, 0.47)	0.0001	0.36(0.195, 0.54)	2.6e-05	0.32(0.16 0.48)	9.3e-05
Others	-0.21(-0.54, -0.12)	0.21	-0.21(-0.6, 0.17)	2.8e-01	-0.23(-0.6 0.13)	0.2
Parity®						
1 child						
2-4 children	-0.19(-0.375, 0.002)	0.05	-0.23(-0.43, -0.03)	0.02	-0.22(-0.4 -0.03)	0.025
>5 children	-0.22(-0.42,-0.03)	0.024	-0.22(-0.432, -0.02)	0.03	-0.21(-0.41 -0.02)	0.03
Residence						
Rural®						
Urban	0.68(0.28, 1.07)	7.6e-04	0.86(0.49, 1.24)	4.9e-06	0.84(0.44, 1.24)	3.1e-05
Education Level						
Illiterate®						
Literate	-0.04(-0.21, 0.125)	0.62	-0.06(-0.24, 0.11)	0.48	-0.05(-0.21, 0.122)	0.59
Antenatal care						
Yes®						
No	0.37(0.22, 0.53)	3e-06	0.41(0.24, 0.58)	2.6e-06	0.33(0.17, 0.49)	5.4e-05
Duration of incontinence urine						
≤3 months®						
>3 months	0.21(0.078, 0.349)	0.002	0.25(0.098, 0.4)	0.0012	0.24(0.094, 0.38)	0.0012
Duration of labor						
≥ 2days®						
<2days	-0.105(-0.24, 0.03)	0.13	-0.13(-0.29, 0.02)	0.009	-0.12(-0.265, 0.03)	0.12
Place of delivery						
Home®						
Health center	-0.16(-0.0056, 0.33)	0.06	-0.14(-0.035, 0.32)	0.11	-0.12(-0.048, 0.29)	0.16
Mode of delivery						
Cesarean section®						
Vaginal	0.26(0.09 0.43)	0.003	0.29(0.1097 0.47)	0.002	0.25(0.08 0.42)	0.004
Surgery Approach						
Abdominal®						
Vaginal	0.19(0.016, 0.37)	0.03	0.18 (-0.0037, 0.37)	0.05	0.17(-0.003, 0.347)	0.05

Duration of Catheter			
≤14 days®			
>21 days	0.192(-0.034, 0.42)0.09	0.19(-0.025, 0.42) 0.08	0.198(-0.011, 0.41) 0.063
Status of Urethra			
Not damaged®			
P. damaged	0.75(0.36, 1.14)1.4e-04	0.8(0.49, 1.12) 4.5e-07	0.76(0.46, 1.076) 1.3e-06
Types of Fistula			
VVF®			
RVF	-0.4 (-0.57, -0.22) 8.6e-06	-0.56(-0.75, -0.37) 1.1e-08	-0.46(-0.66, -0.27) 3.5e-06

***$\widehat{\beta}$**:Estimated regression coefficients, **95% CI ϕ:** 95% confidence interval for acceleration factor, **®**= reference*

Table 4.11: Results of multivariable lognormal Gamma frailty model for time-to-recovery from OBF in JUMC

Covariate	Coef.	SE	Wald	P-value	Φ	95% CI for Φ
Weight						
<50kg®						
≥50kg	-0.1639	0.0715	-2.293	0.022	0.85	[0.738, 0.976]
Marital status						
Married®						
Divorced	0.1855	0.0806	2.301	0.021	1.2	[1.028, 1.41]
Others	-0.1921	0.1622	-1.184	0.24	0.82	[0.601, 1.134]
Place of Residence						
Rural ®						
Urban	0.4045	0.2022	2.001	0.045	1.5	[1.008, 2.227]
Urine incontinence						
≤3 months®						
>3 months	0.2202	0.0679	3.244	0.0012	1.25	[1.091, 1.42]
Antenatal care						
Yes®						
No	0.1686	0.0762	2.211	0.027	1.18	[1.019, 1.37]
Duration of labor						
≥2 days®						
<2days	-0.1528	0.0670	-2.278	0.023	0.86	[0.753, 0.979]
Place of delivery						
Home®						

Health center	-0.2884	0.1368	-2.108	0.035	0.75	[0.573, 0.98]
Mode of delivery						
Cesarean section®						
Vaginal	0.4051	0.1465	2.765	0.0057	1.5	[1.125, 1.998]
Status of urethra						
Not damaged®						
Partially damaged	0.4330	0.1578	2.744	0.006	1.54	[1.13, 2.101]
Types of Fistula						
VVF®						
RVF	-0.2999	0.0992	-3.024	0.0025	0.74	[0.61, 0.8998]
θ =0.363 AIC = 1204.017						
τ = 0.154				ρ = 1.675		
Likelihood-ratio test of θ= 0: Chi-square = 99.8 P = 3.21e-12						

***SE** =standard error; ϕ=acceleration factor; **95% CI ϕ:** 95% confidence interval for acceleration factor, θ=Variance of the random effect, τ= Kendall's tau, AIC=Akaike's information criteria,ρ= shape, **®**= Reference*

Table 4.12: Results of multivariable Weibull inverse Gaussian frailty model for time-to-recovery from OBF in JUMC

Covariate	Coef.	SE	Wald	P-value	Φ	95% CI for Φ
Weight						
<50kg®						
≥50kg	-0.1968	0.0670	-2.939	0.0033	0.82	[0.72 , 0.937]
Urine incontinence						
≤3 months®						
>3 months	0.1545	0.0643	2.402	0.016	1.17	[1.029, 1.32]
Antenatal care						
Yes®						
No	0.1617	0.0762	2.121	0.034	1.18	[1.012, 1.365]
Mode of delivery						
Cesarean section®						
Vaginal	0.3248	0.1198	2.712	0.0067	1.4	[1.094, 1.75]
Status of urethra						
Not damaged®						
Partially damaged	0.4667	0.1777	2.627	0.0086	1.59	[1.126, 2.259]

Types of Fistula						
VVF®						
RVF	-0.2268	0.0948	-2.393	0.017	0.797	[0.662, 0.9598]

θ =1.00	AIC = 1212.534	λ=0.004
τ = 0.223	ρ = 2.28	

Likelihood-ratio test of θ= 0: Chisq= 95.11 on 15.6 degrees of freedom, p= 2e-13

SE *=standard error; ϕ=acceleration factor;* ***95% CI ϕ:*** *95% confidence interval for acceleration factor, θ=Variance of the random effect, τ= Kendall's tau, AIC=Akaike's Information Criteria, ρ = shape,* ***®*** *= Reference*

Table 4.13: Results of multivariable log-logistic inverse Gaussian frailty model for time-to-recovery from OBF in JUMC

Covariate	Coef.	SE	Wald	P-value	Φ	95% CI for Φ
Marital status						
Married®						
Divorced	0.1877	0.0802	2.341	0.019	1.2	[1.03, 1.41]
Others	-0.2034	0.1850	-1.100	0.27	0.82	[0.5678, 1.17]
Place of Residence						
Rural ®						
Urban	0.3958	0.1835	2.157	0.031	1.5	[1.037, 2.128]
Urine incontinence						
≤3 months®						
>3 months	0.1917	0.0676	2.837	0.0069	1.2	[1.06, 1.383]
Antenatal care						
Yes®						
No	0.2096	0.0776	2.7	0.0069	1.23	[1.059, 1.436]
Duration of labor						
≥2 days®						
<2days	-0.1467	0.0674	-2.176	0.03	0.86	[0.7566, 0.986]
Mode of delivery						
Cesarean section®						
Vaginal	0.3965	0.1458	2.719	0.0065	1.49	[1.117, 1.9786]
Status of urethra						
Not damaged®						
Partially damaged	0.4750	0.1551	3.063	0.0022	1.6	[1.1866, 2.179]

Types of Fistula						
VVF®						
RVF	-0.3781	0.0982	-3.851	0.0001	0.685	[0.565, 0.83]

θ =0.217 AIC = 1205.697
τ = 0.1078ρ = 3.69
Likelihood-ratio test of θ= 0: Chisq= 101.68 on 15.6 degrees of freedom, p= 1.1e-14

***SE** =standard error; ϕ=acceleration factor; **95% CI ϕ:** 95% confidence interval for acceleration factor, θ=Variance of the random effect, τ= Kendall's tau, AIC=Akaike's Information Criteria, ρ = shape, ® = Reference*

Table 4.14: Comparison of Lognormal AFT and Lognormal Inverse-Gaussian Frailty Model

Covariates	Lognormal AFT			Lognormal inverse-Gaussian Frailty		
	$\hat{\beta}$	**Φ**	**95% CI Φ**	$\hat{\beta}$	**Φ**	**95% CI Φ**
Weight						
<50kg®						
≥50kg	-0.1496	0.86	[0.748, 0.992]	-0.1505	0.86	[0.747, 0.99]
Marital status						
Married®						
Divorce	0.1868	1.2	[1.03, 1.413]	0.1867	1.2	[1.028, 1.413]
Others	-0.187	0.83	[0.601, 1.145]	-0.187	0.83	[0.601, 1.14]
Place of residence						
Rural ®						
Urban	0.446	1.56	[1.049, 2.325]	0.4428	1.56	[1.046, 2.317]
Dur. of incontinence urine						
≤3 months®						
>3 months	0.182	1.2	[1.053, 1.367]	0.1848	1.2	[1.056, 1.371]
Antenatal care						
Yes®						
No	0.1736	1.19	[1.023, 1.383]	0.1732	1.189	[1.023, 1.382]
Duration of labor						
≥2days®						
<2days	-0.1449	0.865	[0.758, 0.987]	-0.1456	0.86	[0.758, 0.986]
Place of delivery						
Home®						
Health center	-0.2803	0.76	[0.576, 0.9897]	-0.2809	0.76	[0.576, 0.989]
Mode of delivery						
Cesarean section®						
Vaginal	0.4043	1.5	[1.125, 1.996]	0.4044	1.5	[1.125, 1.996]

Status of urethra						
Not damaged®						
Partial damaged	0.4671	1.6	[1.171, 2.174]	0.4639	1.59	[1.168, 2.166]
Types of Fistula						
VVF®						
RVF	-0.3083	0.735	[0.604, 0.894]	-0.3077	0.735	[0.6045, 0.894]
AIC=1206				AIC = 1199.655		

***$\hat{\beta}$**, regression coefficient**,** ϕ=acceleration factor; **95% CI ϕ:** 95% confidence interval for acceleration factor, AIC=Akaike's Information Criteria,**®** = Reference*