STATISTICAL ANALYSIS OF TIME TO RECOVERY FROM VESICO-VAGINAL OBSTETRIC FISTULA: A CASE STUDY AT METU HAMLIN FISTULA CENTER, METU, SOUTH WEST ETHIOPIA

By

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MSc Thesis

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As thesis research advisors, we herby certify that we have read the thesis prepared by FEYSAL KEMAL under our guidance, which is entitled "**STATISTICAL ANALYSIS OF TIME TO RECOVERY FROM VESICO-VAGINAL OBSTETRIC FISTULA: A CASE STUDY AT METU HAMLIN FISTULA CENTER,SOUTH WEST ETHIOPIA**", in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including tables and figures are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the university library.

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ACRONYMS

AIC	Akakie Information Criteria.
CPD	Cephalo Pelvic disproportion
LASSO	Least Absolute Shrinkage and Selection Operator
MHFC	Mettu Hamlin Fistula Centre
MOH**:**	Ministry of Health
NCTPE	National Committee on Harmful Traditional Practices of Ethiopia.
OF	Obstetric Fistula
PH	Proportional Hazard
RVF	Recto-Vaginal Fistula
VVF	Vesico-Vaginal Fistula
VVOF	Vesico-Vaginal Obstetric Fistula
WHO	World Health Organization

ABSTRACT

Introduction: This study was done to identify factors affecting recovery time of vesico-vaginal obstetric fistula patients. A sample of 206 patients was taken from a hospital records at Metu Hamlin Fistula Center enrolled from November 2010 to June 2014 G.C.

Objective: The objective of this paper is to model time to recovery from VVOF at Metu Hamlin Fistula Center and to compare the performance of LASSO method of variable selection with step wise selection methods.

Methods: Least Absolute Shrinkage and Selection Operator (LASSO) method of variable selection and stepwise variable selection method, Kaplan-Meier estimation method, Cox proportional hazard model and parametric regression model were applied.

Results: The Cox PH analysis using LASSO variable selection method identified that survival of the patients was significantly related with age at first marriage, weight, antenatal care ,educational status, marital status, duration of labor, duration of incontinence, place of delivery, mode of delivery, width of fistula and status of urethra. But the covariate like current age of a patient, height, parity, accompanying person, fetal outcome, and bladder size were not statistically significant at 5% significance level. The result from Weibull regression analysis showed that recovery of VVOF patients was significantly related with age at first marriage, duration of incontinence, duration of labor, place of delivery, mode of delivery, fetal outcome, width of fistula, and status of urethra.

Conclusion: The finding of this study showed that out of 206 VVOF patients 76.2% of them were physically cured while the rest 23.8% were censored. The Cox PH model provides better predictions to the survival probability of VVOF patients. It is advisable to make an intervention on the identified risk factors.

CHAPTER ONE

1. INTRODUCTION

1.1 BACK GROUND INFORMATION

Fistula is a relatively hidden problem, largely because it affects the most marginalized members of society: young, poor, illiterate women in remote areas. Many never present themselves for treatment. Because they often suffer alone, their terrible injuries may be ignored or misunderstood. (WHO, 1998). 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. (Arshad et.al,2009)

Women affected by VVF have to suffer not only the consequence of losing their children, physical, psychological and but also subjected to social humiliation, shame and embracement. They become outcasts due to pungent smell and wetness from urinary incontinence (Wall, L.L., et al., 2004). VVF is considered to be still a major gynecological problem in many developing countries, yet an indicator of poor obstetric services and low socio-economic status of the community they represent are only the tip of the ice berg (UNFPA, 2003).

RVF occurs in a similar way to VVF however, holes form between the tissues of the vagina and rectum, leading to uncontrollable leakage of faeces. RVF is also sometimes referred to as Recto-vaginal Fistula or Recto Vaginal Fistula. Vaginal fistulas can also result from violent rape. This injury has become common in some war zones, where rape is used as a weapon against female civilians. As a result, some health centers in countries such as the

Democratic Republic of Congo have begun to specialize in the surgical repair of vaginal fistulas. (Hafeez et.al.,2005)

Genital tract fistula is an international public health problem afflicting millions of women, mostly young, in the poor countries of Africa and south Asia. It is an injury often caused by obstructed labor due to poor access to adequate obstetric care. The condition has devastating physical consequences, such as uncontrolled leakage of urine and sometimes faeces if the rectum is involved. Many women are abandoned by their communities and often also by their own families, making them extremely vulnerable. Fetal outcome is usually stillbirth. (Wall LL, 2006)

Inequality that exists between men and women in the social, political, and economic arenas is also manifested in the health status of men and women. Although both men and women are equally exposed to a number of health problems, women are vulnerable to 108 certain health hazards due to their role in child bearing and rearing and their lower status in the society. Women are particularly exposed to many health problems associated with early marriage, pregnancy, childbirth, rape, abduction, other traditional harmful practices and violence against women (Ruth, A., 2007). Considered one of the most severe maternal morbidities, obstetric fistula represents both a medical and a social crisis for the women affected and their communities. Obstetric fistula is a hole in the birth canal usually caused by obstructed labor without prompt medical intervention, usually a caesarean section. The woman is left with chronic incontinence and in most cases, a still born baby. (UNFPA, 2006)

Throughout the world, but mainly in parts of sub Saharan Africa and Asia, it is conservatively estimated that more than two million young women live with untreated obstetric fistula. It has also been estimated that between 5,000 and 10,000 new women are affected each year. It is probable that these figures are under estimate but it has been impossible to determine the true burden of suffering to date. Not only has there been generally a lack of commitment in addressing and solving this problem, but also these young girls or women tend to live with their fear and stigmatization in silence and isolation, unknown to the health care system.

Some in depth studies serve to support the widely held belief that the true number of women living with untreated fistula and suffering the consequent pain and degradation may have been under estimated, suggesting that there may be between 100,000 and one million women living with fistula in Nigeria alone and over 70, 000 in Bangladesh. Other studies in Ethiopia, Nigeria and other parts of West Africa estimate the incidence of fistula to be 1-10 per 1000 birth. In Ethiopia it is estimated that 9,000 women annually develop a fistula, of which only 1,200 are treated (WHO, 1998).

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 obstetric fistula. Obstetric fistulas mostly appear in one of the two most common types, vesico-vaginal (VVF) or recto-vaginal fistula (RVF) and sometimes both VVF and RVF can occur together. VVF is an abnormal communication between the bladder and the vaginal. (Anple Thomson Bramley. D, 1999)

In Ethiopia 95% of VVF is obstetric. The main cause in over 85%of OF is obstructed labor that is not relieved in time by performing the caesarian section. In addition, insufficient access to emergency obstetric care, coupled with the desire to delivery at home, (which often occurs without skilled attendance) result in situation where women, especially young women, at high risk Other less common causes of VVF are injury to bladder, caesarian section, elective gynecological operations, destructive and instrumental deliveries, radiation therapy, trauma, serious infection and advanced carcinoma of the cervix. (Anple Thomson Bramley. D, 1999)

1.2 STATEMENT OF THE PROBLEM

An objective of survival analysis is to identify the risk factors and their risk contributions. Often, many covariates are collected (as it is the case in our study) and to reduce possible modeling bias, a large number of semi parametric/parametric models are built. An important and the first challenging task are to efficiently select a subset of significant variables upon which the hazard function depends. There are many variable selection techniques in linear regression models. Some of them have been extended to the context of censored survival data analysis, such as the step wise selection and stepwise deletion. Despite their popularity, the sampling properties of the aforementioned selection methods are largely unknown and confidence intervals derived from the selected variables may not have right coverage probabilities. Fan and Li(2001) proposed a family of new variable selection methods based on a non concave penalized likelihood approach. The proposed methods are different from traditional approaches of variable selection in that they delete insignificant variables by estimating their coefficients as 0. Thus their approaches simultaneously select significant variables and estimate regression coefficients. LASSO, proposed by Tibshirani (1996, 1997), is a member of this family with the $L1$- penalty. In this research we will use LASSO method of variable selection and compare with that of step wise selection and stepwise deletion in terms of performance and model stability. The second challenge in survival analysis is the choice between semi parametric (Cox) and parametric modeling. The interesting feature of Cox model is its applicability to a wider class of distributions. For instance, when parametric models such as exponential/Weibull model are applicable then Cox model is also applicable, but not the other way around. Thus in this study we fit both Cox and parametric models to VVOF and compare their performance.

Generally, the motivation behind this study is to address the following research questions:

- what are the covariates significantly affecting the time to recovery for VVOF at the center?
- which variable selection method performs well when we have more predictors' variable?
- which type of survival models, Cox-PH or Parametric models, predicts well the recovery time of VVOF patients.

After doing this research it is expected that the above research questions will be answered and adds some information in VVOF.

1.3 SIGNIFICANCE OF THE STUDY

The results of this study is expected to create awareness to public health policy makers, researchers, and the public at large that VVOF must come to public agenda and help policy makers to implement appropriate treatment and control strategies along with a population wide surveillance intervention. Also the findings` of this study help health care workers to inform patients about the possible related risk factors of recovery they might encounter and it gives a clue for clinicians in minimizing the recovery time from VVOF by implementing early diagnosis and appropriate intervention. The outcome of the study also helps non-governmental and governmental organization to understand risk factors for VVOF and act accordingly. Furthermore, the result of this study could provide base line information for detailed and further studies in the future.

1.4 OBJECTIVES OF THE STUDY

1.4.1 GENERAL OBJECTIVE

The general objective of this study is to model time to recovery from VVOF at MHFC Hamlin Fistula Center using semi-parametric and parametric survival models.

1.4.2 SPECIFIC OBJECTIVES

- ✓ To develop a statistical model that predicts the time-to-recovery of VVOF patients adjusting for significant risk factors.
- ✓ To compare the performance of LASSO method of variable selection with step wise selection and stepwise deletion method.
- ✓ To compare the efficiency of Cox and parametric survival models.
- ✓ To assess risk factors for time to recovery from VVOF during the treatment period at the center.

CHAPTER TWO

2. LITERATURE REVIEW

2.1 INTRODUCTION

VVOF is an abnormal fistulous tract extending between the bladder (or vesico) and the vagina that allows the continuous involuntary discharge of urine into the vaginal vault. VVOF has been a social and surgical problem for centuries. VVOF leads to devastating effects on physical, social and mental health of women. VVOF is a condition that has been known since ancient times being recognized in mummified remains of Egyptian Queen Henheit back in 2000 BC (Riley VJ. ,2001.) VVOF are mostly seen in young women of child bearing age. (Ghumro AA. 1993; Sobia Mazhar, 2013)

Major cause in developing countries is obstetrical trauma (Hafeez M, et al. 2005; Goh JT. 1998; Moudini S, et al. 2001; Amr MF. 1998). A recent study showed that out of VVOF patients, 79% was caused by obstetrical trauma and 66.6% are due to obstructed labor (Sobia Mazhar, et al. 2013). It is often caused by childbirth (in which case it is known as an obstetric fistula), when a prolonged labor presses the unborn child tightly against the pelvis, cutting off blood flow to the vesico-vaginal wall. The affected tissue may necrotize (die), leaving a hole.

An obstetric fistula is a hole between a woman's birth passage and one or more internal organs that typically develops as a result of obstetrical trauma (Wall, L.L. 1996). It is also a chronic condition usually caused by prolonged, obstructed labor without timely, appropriate and quality medical intervention. Labor is considered obstructed when the presenting part of the fetus cannot progress into the birth canal, despite strong uterine contraction (Kelly, J. 1998). During prolonged labor, the pressure of the baby's head against the mother's pelvis can cut off the flow of blood to the soft tissues of the bladder, vagina, and rectum. The mother's injured pelvic tissue soon sloughs away, leaving a fistula between adjacent organs. It could be between the vagina and the bladder or the vagina and the rectum or both, resulting in permanent incontinence of urine or faeces or both. (Ramsey, K. et al. 2005)

Obstetric fistula is a devastating child birth injury. Women with a fistula have not only suffered the pain and the constant leaking urine and feces but they also suffer extreme social isolation. Abandonment by partners, families and communities, living in isolation, feelings of humiliation, pain, loneliness, shame and mourning for the loss of their lives and the child they lost during delivery. Fistula can be surgically repaired where trained surgeons and good post operative care are available and accessible. (Ramsey, K. et al. 2005)

Surgical repair for VVF can be performed through vaginal or abdominal route. The choice of procedure in a particular patient depends upon location of fistula, presence or absence of vaginal steno sis and experience of surgeon. To increase vascularity and provide support to the repaired tissue synthetic and tissue graft interposition in between bladder and vaginal mucosa is done.

Surgeons can repair fistulas successfully in 80% to 90% of cases (AMR, M.F., 1998; Goh JT. 1998; WAALDIJK, K., 1989). There are internationally recognized techniques for fistula repair (WAALDIJK, K. 1994). The specific method used usually depends on the surgeon's preferences and the nature of the fistula. Most surgical experts recommend waiting two to three months after the fistula has occurred before attempting repair in order to avoid operating on dying tissues (KELLY, J., 1996). If a fistula is suspected immediately following an obstructed labor, the patient may initially receive continuous bladder drainage to avoid stretching the injured tissues, which would impede healing. Prompt catheterization increases the likelihood of spontaneous closure of some fistulas (HILTON, P., 2003; WAALDIJK, K. 1997). The patient may also receive treatment for anemia and malnutrition and antibiotics to prevent infection. (HILTON, P., 2003)

Repair often is more difficult on patients with extensive scarring from prolonged obstructed labor. Successful repair can depend on both the initial state of the fistula and the skill of the surgeon (WALL, L.L., et al., 2001) as well as on the quality of post-operative care (KIIRU, J.M., 2004). Especially in difficult and complex cases, even after a fistula is repaired, the patient may continue to suffer from involuntary loss of urine (stress incontinence) because the urethral sphincter may be permanently damaged (GOH, J.T. 1998). This post-surgical problem occurs in an estimated 10% to 12% of patients (HAMLIN, C. and KENNEDY, R. 2001). In the worst cases the patient may need a permanent urinary diversion operation (WALL, L.L., et al., 2001; HAMLIN, C. et al., R. 2001).

Recovery after surgery generally takes two weeks, during which the patient needs to drain her bladder through a catheter. Most patients can leave the hospital after 14 to 21 days. Women with successfully repaired fistulas are advised not to resume sexual relations for three or four months to give tissues time to heal fully. The length of recovery varies with the extent of the damage repaired (HILTON, P., 2003; KIIRU, J.M., 2004).

The success of VVOF has been regarded as closure of fistula and patient became continent. From previous study, success rate is 83.3% which is comparable with the studies presented world wide (Garthwaite M, et al., 2005; Begum A., 1989), but studies conducted by Nargis et al (2007) and Memon GU et al (2005) showed success rate of 67% and 69% respectively. Rasool M et al (2006) reported success rate of 100% with vaginal repair.

Predisposing risk factors for VVOF include a history of pelvic irradiation, cesarean section, endometriosis, prior pelvic surgery or pelvic inflammatory disease, diabetes mellitus, concurrent infection, vasculopathies, and tobacco abuse. In developing countries, obstetric trauma remains the leading cause of VVOFs. In some countries in Africa, it is customary for early marriages involving adolescent girls to be contracted prior to the commencement of their menses. In sub-Saharan Africa, nearly 50% of the women are married by age 18, some by age 15 or younger. A recent study from Katsina, Nigeria, found that primiparous girls who married during early adolescence were more likely to experience VVOF than those who married at an older age. Women without formal education and those married to men with unskilled jobs were 14 times more likely to sustain a VVOF than their cohorts (Ojanuga D et al., 1999).

2.2 EPIDEMIOLOGY OF VESICO VAGINAL OBSTETRIC FISTULA

Worldwide, it is estimated that approximately two million women suffer from OF; of these, between 26 000 and 40 000 live in Ethiopia (WHO, 2006). 100,000 to 1,000,000 live in Northern Nigeria, and over 70 000 live in Bangladesh (UNFPA, 2006; WHO, 1998). Reports from Kenya and Nigeria also show that about one delivery per 1000 results in OF. (Cook RJ, et al ; HILTON, P. 2003). The most commonly quoted estimates are 2 million prevalent cases of obstetric fistula worldwide, with 50,000 to 100,000 incident cases annually (Bangser M., 2002; Donnay F, et al, 2004). The 2-million prevalence, however, has been reported as a global total as well as the estimate for Africa (Browning A., 2004) or for Africa and Asia (Kelly J., 2004). Worldwide, obstructed labor occurs in an estimated 5% of live births and accounts for 8% of maternal deaths. Adolescent girls are particularly susceptible to obstructed labor, because their pelvises are not fully developed. (WHO, 2006)

In developing countries the commonest cause of VVF is obstetrical and constitutes about 80%-90% cases, as opposed to only 5-15% in developed countries. The patients are usually young primiparous with a history of difficult labor or instrumental delivery in recent past. (D.C Dutta; 2007)

The major cause of VVF in West Africa is pressure necrosis due to prolonged labor. In Nigeria VVF as social, economical and religious implications many women with VVF are regarded as social out casts and marriage have dissolved. In the northern Nigeria, study done on 241 cases of VVF, prolonged labor constituted 75.9% of the total cases. “Gushier cut” an incision commonly done is the second common cause (6.2%), there causes included cervical carcinoma (1.7%), surgical trauma (31%) and infection was 2.1.%. more than 26.9% of fistula occurred in women less than 15 years, and 58.8% of them were less than 8yrs, as well as 51.9% of them had a height of below 150cm.(OF awareness,2010)

Ethiopia is one of the countries with the highest rates of early marriage in sub-Saharan Africa. Rates of marriage during early adolescence, by age 15, are among the highest on the continent (Population Council, 2007). A study conducted by the National Committee on Harmful Traditional Practices of Ethiopia estimated the proportion married before the age 18 was 57%. (NCTPE, 2003) . Early marriages lead to early childbirth, which increases the risk of obstructed labor, since young mothers who are poor and malnourished may have under-developed pelvises.

The great majority of fistulas are, however vesico-vaginal. Estimates of the extent of recto-vaginal fistulas are few including 7% in a case series of patients in Ethiopia and 4% in a series of patients in Nigeria. An estimated 6% to 24% of obstetric fistula cases are combined VVF and RVF. (Hinrichsen, D. 2004)

Only about 50% of the general population in Ethiopia has access to primary health care services, and only about 7% to 10% of all births are attended by skilled personnel. The median age at first marriage in Ethiopia is 16 years, and 31% of women are married by age 15.9 about 12% of the total fertility rate in Ethiopia derives from births to women aged between 15 and 19 years. (Abou-Zahr, C. 2003)

A study conducted in Africa reported that immediately after the fistula occurred 42 % of the chronic fistula patients were divorced by their husbands. According to Smith (1996) unpublished data from Ethiopia suggest that almost 50 % of VVF victims are divorced or separated. (Ahmed, S. 2007)

Immediate causes for fistula may be obstructed labor, pelvic surgery, sexual abuse before reaching physical maturity, malignancy, radiotherapy or a combination of these. In most third world countries, however, over 90% of fistulas are of obstetric nature and usually caused by obstructed labor. (Hilton, P. 2001)

Studies conducted at Addis Ababa Fistula Hospital revealed that a total of 19 153 houses were surveyed, and 55 women with fistulae were identified, of whom 52 were interviewed. Thirty-six of the interviewed women (69.2%) were divorced, 10 (19.2%) were not allowed to eat with family members, and 23 (44.2%) were not members of any community associations. Of the 48 women with feelings of depression, 28 (54.2%) had suicidal ideation. Twenty-four women attributed their development of a fistula to evil spirits, to a curse, or to sin. Treatment improved family and social life; however, some health, social, and sexual problems remained. (Muleta M. et al, 2008)

2.3 LITERATURE RELATED TO THE VARIABLES USED IN THE STUDY

Most studies reported that the demographic factors such as age, height, weight, small pelvic size are known to be associated with obstetric fistula and any others factors associated with obstetric fistula can be socio-cultural, economic, and health services. The review of some relevant papers are presented below. A study on Socio-Demographic Problem and Obstetric Experience of Fistula Patients using logistic regression and cross tabulation 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 M., 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.,et al.. 1990)

According to studies (Jonas et al., 1984; Symonds, 1984; Lee et al.' 1988 and Tancer, 1992) the most common cause of VVF in most industrial countries is routine abdominal or vaginal hysterectomies. All major studies have shown that 75-90% of VVF 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 etiology and duration of fistula, quality of tissues available for repair and probably most importantly the experience and training of the surgeon.

Fouzia Parveen et al. (1998) reported that with an increase in parity, there is an increase in birth weight, mal presentations and mal positioning and these result in more case of obstetric injuries. Wall LL et al, (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).

Several prospective studies reported those women with a height less than 146cm and weight 50 or less than are more likely to experience fistula (Hamlin et al., 1996; Ahmed et al., 2007).Similar results were reported by Wall et al. (2004) based on retrospective study using medical records of all women who had obstetric fistula at the local hospital in Jos (Nigeria) between January 1992 and June 1999.

In Sub-Saharan Africa countries, 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 disproportion (CPD) was the most common indication for cesarean delivery in sub-Saharan Africa. Studies have found CPD 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)

Similarly: 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).

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.

A study carried out by Tesfaye G., (2013) concluded that, among the patients of obstetric fistula considered, 81.7% of them were physically cured while the rest 18.3% were censored. The average mean of a patient stay in the hospital to treated and physically cured is 4.64 weeks.

Using Cox's PH model fitted using complete case analysis, the paper done by Tesfaye G. (2013) has identified eleven variables that can serve as predictive factors on the recovery of obstetric fistula patients. These are age at first marriage, weight, height, follow up of antenatal care, duration of labor, place of delivery, mode of delivery, duration of incontinence urine, length, width of fistula and status urethra. With regard to the parametric regression models this paper also included hazard which do not assume constant baseline hazards except for exponential regression models.

One of the factors that affect recovery from obstetric fistula is the patient's age at first marriage. The hazard of a patient who had married early before fifteen years was higher as compared to patient who had married after twenty years. This result is in accordance with the study in Ethiopia by Muleta (2004). Weight of a patient is an important predictor for the recovery of obstetric fistula patient. Tesfaye G.,(2013) also showed that the hazard rate of a patient with weight < 50kg is higher as compared to those whose weight ≥ 50kg. This results indicates that smaller weight increases the chance of recovery as compared to higher weight. Height of a patient is also a prognostic factor that significantly predicts the recovery time of obstetric fistula patient. In the same manner he had also showed that the hazard rate of a patient with height < 150cm were much higher. That is, taller patient is more likely to recover than shorter one. The result is comparable with earlier study (Hamlin et al., 1996; Ahmed et al., 2007; Wall and Karshima, 2004).

For antenatal care use, Tesfaye G.,(2013) findings revealed that the hazard rate of a patient who had no follow up of antenatal care is higher than those who had antenatal care service. Use of antenatal care service improves the chance of recovery. These results confirm the result obtained from the previous studies in Ethiopia (Gessessew et al., 2003). Tesfaye's findings (2013) also showed duration of labor and place of delivery as an important predictor for the recovery of obstetric fistula patient. This study shows that the hazard rate of a patient who had labored for > 4 days is higher than those who labored for < 2 days. That is, a shorter time of obstructed labor is more likely to recover than long time labored patient. The result is comparable with the earlier study (Cisse et al., 1998; Van Dillen et. al., 2007; Tebeu et al., 2008).

Similarly, place of delivery is also found as the stronger predictor for recovery time of obstetric fistula patient. The hazard rate of home delivery is 1.481 and 1.339 times greater than those who delivered at institutions in Cox and Weibull regression model, respectively. This means that a patient who delivered at health center has more chance to recover than a patient who delivered at home. This result is in accordance with the studies from Niger by Haroun et al.(2001).

Another variable which Tesfaye's G.(2013) findings found is that, the mode of delivery is prognostic factor that significantly predicts the recovery time of obstetric fistula patient. The result obtained from this study indicates the hazard rate of non-vaginal delivery (like assisted vaginal and abdominal) is about 45.1% and 75.9% higher than those who delivered vaginally using both methods. This shows that the recovery time for vaginal delivery of a patient is shorter than non-vaginal delivery. These results confirm the result obtained from some previous studies (Jonas et al.(1984); Symonds(1984); lee et al.(1988)).

The length and width of fistula were also been found to be significant predictors for recovery of obstetric fistula patient Tesfaye G.(2013).This result indicates that smaller size of length and width of fistula increases the chance of recovery as compared to large size of length and width of fistula hole. The result is comparable with earlier study (Jeremy et al.(2008)). In addition to those factors, status of urethra also had a significant effect on the recovery time of obstetric fistula patient. The finding has also illustrated that the hazard of recovery due to obstetric fistula patient is higher for patients who had complete destructed of urethra than those who had intact and partially damaged of urethra.

2.4 REVIEW OF SURVIVAL [TIME TO EVENT] MODELS

The origin of survival analysis goes back to the time when life tables were introduced. Life tables are one of the oldest statistical techniques and are extensively used by medical statisticians and by actuaries. Yet relatively little has been written about their formal statistical theory. Kaplan and Meier (1958) gave a comprehensive review of earlier work and many new results. Cox (1972) was largely concerned with the extension of the results of Kaplan and Meier to the comparison of life tables and more generally to the incorporation of regression like arguments into life table analysis. Survival models have the capability of handling censored data. Cox (1972) and Cox and Oakes (1984) used survival analysis in modeling human lifetimes. Fergusson, 1984 used hazard functions to study the time to marital breakdown after the birth of child. Hazard functions had been also used in studies of time to shift in attentions in classroom Felmlee (1983); in study of relapse of mental illness (Lavori, 1984), marital dissolutions Morgan (1988) and human lifetimes (Gross et al., 1975).

PH modeling is the most frequently use type of survival analysis modeling in many research areas, having been applied to topics such as smoking relapse (StevensandHollis, 1989) and employee turnover (Morita, et al., 1989), and in medical areas for identification of important covariates that have as significant impact on the response of the interested variables. Ayalnesh (2011) used proportional hazards model to examine risk factors for time to recovery and determinants of obstetric fistula patients. Zelalem (2010) also use proportional hazards Modeling of HIV/AIDS Evolution and Survival of AIDS Patients. And Derbachew (2012) used PH modeling and parametric models to examine causes of Survival of Patients with Diabetes Mellitus. Tesfaye (2013) used Kaplan-Meier estimation method, Cox PH model and parametric regression to model Survival Analysis of Time to Recovery from Obstetric Fistula.

CHAPTER THREE

3. DATA AND METHODOLOGY

3.1 DATA SOURCE

This study was conducted in Mettu Hamlin fistula center which is found in south western part of the country, in Oromia regional state in Illuabbaora zonal administration, Mettu town 620k/m away from Addis Ababa and around 265km from Jimma town.

The center focuses on the treatment of patients and prevention of new VVF cases by raising awareness of the health professional and the community. The center also distributes birth kits for health extension workers and trained traditional birth attendants to facilitate clean delivery. (MHFC report, 2011)

3.2. STUDY DESIGN AND PERIOD

A retrospective institutional based study will be conducted on mothers who came for fistula repair in MHFC from November 2010 to June 2014 G.C.
The study is a retrospective study (i.e. all the events-exposure had already occurred in the past), which reviews the patient cards and patent's information sheet.

3.3. STUDY POPULATION

In determining our sample, first we have to know our source population (in this case all women who visited MHFC) and the study sample includes all women who visited MHFC having VVOF case only during the study period. Our inclusion criterion is to include all women who are admitted in MHFC from the year November 2010 to June 2014 G.C having VVOF with complete information. Therefore, among the total of 585 OF patients registered in the given year, only 246 VVOF patients satisfy the inclusion criteria and hence are included in this study.

3.4. STUDY VARIABLES

3.4.1 DEPENDENT VARIABLE

The response variable for the i^{th} individual is represented by Y_i and it measures the duration to the event, which is indicated by physically cured. A patient is said to be recovered if she physically cured from her sickness and no requirement for intervention of health care professionals. We say a patient is physically cured if there is no urine incontinence or drop out. If no recovery in the study period, censoring is taken as an outcome. We say it is censored when referred to Addis Ababa hospital and when they have given appointment for some another time.

3.4.2 INDEPENDENT VARIABLES

The predictor variables in this survival analysis are either categorical or continuous. The Predictor variables which are assumed to influence the recovery of VVOF patients included are:

Covariates	***Categories and their codes***
Age at first marriage	0=≤15, 1=16-19, 2=≥ 20 years
Age at occ. of VVOF	0= ≤20, 1=21-29, 2=≥ 30 years
Height of patient at arrival in MHFC	0=< 150,1= ≥150cm
Weight of patient at arrival in MHFC	0=< 50,1= ≥50kg
Parity	0=primipara,1=multipara,2=Grandmultipara,3=Nuli para
Educational status	0=illitrate, 1=litrate
Marital status	0=single,1=married,2=divorced,3=widowed, 4=separated
Accompanying person	0=self,1=husband,2=relatives,3=hus+relatives, 4=others
Antenatal care	0=yes, 1=no

Place of delivery	0=home, 1=health institution,2=other
Mode of delivery	0=vaginal, 1=others
Duration of incontinence	0=≤ 3, 1=4-6, 2=≥ 7 month
Duration of labor	0=≤ 2, 1=3,2= ≥ 4 day
Fetal outcome	0=still birth, 1=alive,2= early neonatal, 3=1 dead+1 alive
Width of fistula hole	0=≤2, 1=3-5, 2=> 5cm
Length of fistula hole	0=≤2,1= 3-5,2= > 5cm
Status of urethra	0=intact, 1=partially damaged, 2=complete destructed)
Bladder size	0=none, 1=small, 2=fair, 3=good, 4=no information)

3.5 BASIC SURVIVAL ANALYSIS

3.5.1 CENSORING

Survival analysis is the phrase used to describe the analysis of data in the form of times from a well defined time origin until the occurrence of some particular event or end-points. In medical research, the time origin will often correspond to the recruitment of an individual into an experimental study, such as a clinical trial to compare two or more treatments. If the end-points is the death of a patient, the resulting data are literally survival times. However, data of similar form can be obtained when the end-points is not fatal, such as the relief of a pain, or the recurrence of symptoms .In this case the observations are often referred to as time to event data. The reasons why survival data are not amendable to the standard statistical procedures used in data analysis are given as follows. The main feature of survival data that renders standard methods inappropriate is that survival times are frequently censored. The survival time of an individual is said to be censored when the end-point of interest has not been observed for that individual. The second reason is that survival data are generally not symmetrically distributed, this implies it will not be reasonable to assume that data of this type have normal distribution. (David Collet, 2003)

Censoring may occur in one of the following forms:

– Termination of the study before the event occurs (administrative censoring);

– Death due to a cause not considered to be the event of interest (in cause-specific Survival analyses); and

– Loss to follow-up, for example, if the patient emigrates.

To study, we must introduce some notation and concepts for describing the distribution of “time to event" for a population of individuals. Let the random variable *T* denote time to the event of our interest. Of course, *T* is a positive random variable which has to be unambiguously defined; that is, we must be very specific about the start and end with the length of the time period in-between corresponding to *T*.

The most common encountered form of a censored observation is one in which observation begins at the defined time, say T = 0 and terminates before the outcome of interest is observed. Since the incomplete nature of the observation occurs in the right tail of the time axis, such observations are said to be right censoring.

3.5.2 NON PARAMETRIC SURVIVAL APPROCH

This approach obtains the Kaplan-Meier estimate of the survivor function. To obtain the Kaplan-Meier estimate, a series of time intervals is constructed, as for the life-table. This estimate is actually the probability of surviving through the interval from $t_{(k)}$ to $t_{(k+1)}$, and all preceding intervals, and leads to the Kaplan-Meier estimate of the survivor function, which is given by

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

In this study we use the log rank test and generalized Wilcoxon test which are special cases of Q. Where Q is given by: $Q = \frac{\left[\sum_{i=1}^{m} w_i (r_{1i} - \hat{e}_{1i}) \right]^2}{\sum_{i=1}^{m} w_i^2 \hat{V}_{1i}}$ (2)

And $\hat{e}_{1i} = \frac{n_{1i} r_i}{n_i}$ is the expected number of events (recovery) corresponding to r_{1i}.

$\hat{V}_{1i} = \frac{n_{1i} n_{0i} r_i (n_i - r_i)}{n_i^2 (n_i - 1)}$ is the variance of the number of events r_{1i} 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 1, r_{0i} is the number of observed recovery in group 0, r_{1i} 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.

3.5.3 SEMI-PARAMETRIC SURVIVAL MODELS

Now-a-days, the identification of the most important risk factors is becoming the important task for handling the disease. Regression analysis is generally used for identifying the risk factors. But due to the presence of censoring in survival data, ordinary regression models are not used on survival data. For this purpose, in survival analysis, Cox's regression model/ Cox PH model is widely used. The PH regression model is very popular due to the easy concept and accessibility of software.

The Hazard Function

The Cox PH Model is usually written in terms of the hazard model formula.

$$h_i(t_i, \mathbf{X_i}) = h_0(t) \exp(\boldsymbol{\beta}' \mathbf{X}_i) \qquad (3)$$

where $h_0(t)$ is the baseline hazard function that characterizes how the hazard function changes as a function of survival time, $\mathbf{X}_i$ is the vector values of nx1 explanatory variables for the i^{th} individual at time t and, $\boldsymbol{\beta}$ is the vector of $(k+1)\times 1$ unknown regression parameters that are assumed to be the same for all individuals in the study, which measures the influence of the covariate on the survival experience.

The baseline hazard describes the shape of the distribution while exp ($\boldsymbol{\beta} \mathbf{X}_i$) gives the level of each individual's hazard. The model based on the assumption that independent covariates affect the hazard in a multiplicative way.

The Cox model formula has the property that if the $\mathbf{X}_i$'s are entirely zero, the formula reduces to the baseline hazard function. This property of the Cox model is the reason why $h_0(t)$ is called baseline function. Another appealing property of the Cox model is that, even though the baseline hazard part of the model is unspecified, it is still possible to estimate the **β**'s in the exponential parts of the model. So, it can equally be regarded as linear model which is a linear combination of the covariates of the logarithm transformation of the hazard ratio. It is given as:

$$\log\left(\frac{h_i(t, \mathbf{X}_i)}{h_0(t)}\right) = \boldsymbol{\beta}' \mathbf{X}_i\,, \qquad (4)$$

The cumulative hazard function is given by:

$$H_i(t) = H_0(t)\exp(\boldsymbol{\beta}'\mathbf{X}_i), \qquad (5)$$

Consequently, conditioning from the proportional hazard function, we obtain the survivor function given by: $S_i(t,\mathbf{X}_i) = S_0(t)\exp(\boldsymbol{\beta}\mathbf{X}_i)$ (6)

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

3.5.3.1 FITTING COX PROPORTIONAL HAZARD MODEL

Fitting the PH model given in equation (3) to an observed set of survival data entails estimating the unknown coefficients of the explanatory variables, $X_{I,}\ X_{2\ldots}\ X_{K,}$ in the linear component of the model, $\beta_{I,}\ \beta_2 \ldots \beta_{K..}$ The baseline hazard function, $h_0(t)$, may also need to be estimated. It turns out that these two components of the model can be estimated separately. The β's are estimated first and these estimates are then used to construct an estimate of the baseline hazard function. This is an important result, since it means that an in order to make inferences about the effects of k explanatory variables $X_{I,}\ X_{2,} \ldots X_K$, on the relative hazard, $h_i(t)/h_0(t)$.We don't need an estimate of $h_0(t)$.

The β- coefficients in the PH model, which are the unknown parameters in the model, can be estimated using the method of maximum likelihood. To operate this method, we first obtain the likelihood of the sample data. This is the joint probability of the observed data, regarded as a function of the unknown parameters in the assumed model. For the proportional hazards model, this is a function of the observed survival times and the unknown β- parameters in the linear component of the model. Estimates of the β's are then those values that are the most likely on the basis of the observed data. These maximum likelihood estimates are therefore the values that maximize the likelihood function. From computational viewpoint; it is more convenient to maximize the logarithm of the likelihood function. Furthermore, approximations to the variance of maximum likelihood estimates can be obtained from the second derivatives of the log-likelihood function.

The formula for Cox model likelihood function is actually called a partial likelihood function rather than a (complete) likelihood function, as it considers only for those subjects who recover, and not for those subjects censored. Suppose the survival data is represented by (t_i, δ_i, **X**i) for i= 1, 2... n where t_i the length of time a subject is observed (survival time), δ_i an indicator of censoring for i^{th} individual and X_i a vector of covariates for the i^{th} individual.

The likelihood for right censored data includes both survival and hazard functions and is given by:

$$L(\beta/\text{data}) = \prod_{i=1}^{n} h_i\left(t, \mathbf{X_i}\right)^{\delta_i} S\left(t, \mathbf{X_i}\right) \qquad (7)$$

The proposed partial likelihood function suggested by Cox, 1972 avoids specification of the baseline hazard function, treating it as a nuisance parameter and removing it from the estimating equation. It assumes that there were no tied values among the observed survival times.

Suppose we have m distinct recovery time and let X_i be the vector of expected variables at ordered recovery time t_i. Partial Likelihood is defined as:

$$L_p(\beta\ /\text{data}) = \prod_{i=1}^{m} \left(\frac{e^{\beta' X_i}}{\sum_{j \in R(t_i)} e^{\beta' X_j}} \right)^{r_i} \qquad (8)$$

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. And the summation in the denominator is over all subjects at risk at time t_i, R(t_i). The maximization of L_p(β /data) is carried out by taking partial derivatives of the log of L_p(β /data) with respect to each parameter in the model. This can be carried out using the statistical packages SAS and R.

The PH model for survival assumes that the hazard function is continuous, and under this assumption, the tied survival times are not possible. Of course, survival times are usually recorded to the nearest day, month or year, and so tied survival times can arise as a result of this rounding process.

The partial likelihood derived above is valid when there are no ties in the data set. But in most real situations tied survival times are more likely to occur. In addition to the possibility of more than one physically cured at a time, there might also be more than one censored observations at a time of physically cured.

In order to accommodate tied observations, the likelihood function in equation (8) has to be modified in some way. The appropriate likelihood function in the presence of tied observations has been given by Kalbfleish and Prentice, 2002 but the computation of this likelihood function can be very time consuming ,particularly when there are a relatively large number of tied at one or more death times. Fortunately, there are a number of approximations to the likelihood function that have computational advantages over the exact method. There are three approaches in common to estimate regression parameters when there are ties such as Breslow, Efron and Exact. The most popular and easy approach is Breslow's approximation.

Assumption of Cox proportional hazard model

1. The baseline hazard h_o (t) depends on t, but not on covariates $x_1 \dots x_p$.
2. The hazard ratio, i.e. exp (β'X) depends on the covariates $X = (x_{1,..,} x_p)'$, but not on time t.
3. The covariates x_i doesn't depend on time t.

Assumption (2) is what led us to call this a proportional hazards model. To express this mathematically, consider two distinct values of the covariate X, say, x_1 and x_2.

$$\lambda(t, \mathbf{X}) = \lambda_o(t) \exp(\beta' X) \qquad (9)$$

Then, the hazard ratio becomes:

$$\frac{\lambda(t, x_1, \beta)}{\lambda(t, x_2, \beta)} = \frac{\lambda_o(t)\exp(\beta' x_1)}{\lambda_o(t)\exp(\beta' x_2)}$$

$$= \frac{\exp(\beta' x_1)}{\exp(\beta' x_2)} \qquad (10)$$

$$HR = e^{\beta'(x_1 - x_2)}$$

This shows that ratio of the hazard functions for two individuals with different covariate values do not vary with time.

Interpretation of the coefficients of the Cox-regression model

The estimated coefficients for continuous predictor variables represent the slope or rate of change of a function of the outcome variable per unit of change in the predictor variable by keeping the remaining predictor variables fixed (Hosmer-Lemeshow(1989)). Thus interpretation involves two issues, determining the functional relationship between the outcome variable and the covariate and appropriately defining the unit of change for the predictor variable (Hosmer- Lemeshow(1989)).

When the proportional hazards model is used in the analysis of survival data, the coefficients of the explanatory variables in the model can be interpreted as logarithms of the ratio of the hazard of death to the baseline hazard. This means that estimates of this hazard ratio, and corresponding confidence intervals, can be found from the fitted model.

The estimated regression coefficients $\hat{\beta}'s$ reflect linear for continuous variables and they will be interpreted as the change in the log-hazards ratio for every unit increase/decrease, depending on the variable change in x_i, holding other predictors constant.

For example, for a dichotomous covariate with value 1 and 0, the hazard ratios of being in the category of interest for the j^{th} subject, becomes,

$\frac{\lambda_O(t)\exp(\hat{\beta}_i*1)}{\lambda_O(t)\exp(\hat{\beta}_i*0)} = \exp(\hat{\beta}_i)$, fixing other covariates constant. This is interpreted as the hazard rate among subjects with i^{th} covariate value equals 1 is $\exp(\hat{\beta}_i)$ time higher than subjects with i^{th} covariate equals zero, i=1,2,3,…,n. For covariates having L levels (L>2), similar interpretation can be made by taking one of the L-levels as a reference group.

Hazard Ratio (HR)

Hazard ratio (HR) is defined as the hazard for one individual divided by the hazard for a different individual. The two individuals being compared can be distinguished by their values for the set of predictors, that is, the **X**'s. We can write the hazard ratio as the estimate of h(t, $\mathbf{X}^*$) divided by the estimate of h(t, **X**), where $\mathbf{X}^*$ denotes a set of predictors for one individual, and X denotes the set of predictors for the other individual.

$$\hat{HR} = \frac{\hat{h}(t, \mathbf{X}^*)}{\hat{h}(t, \mathbf{X})} \tag{11}$$

In this study, single covariate analysis may be used for investigating the relationships between the outcome and each of the potential independent variables and for selecting the set of variables to include in the multi covariate analysis. Multiple covariate analysis may be used for investigating the relationship between the dependent variable and a series of other variables simultaneously.

3.5.3.2 EXTENSIONS OF THE PH MODEL

We have used a PH model with a common unspecified baseline hazard function where all the study covariates have values that remained fixed over the follow-up period. Additionally, we assumed that the observations of the time variable were continuous. In some settings one or more of these assumptions may not be appropriate.

Now to accommodate non-proportionality assumption one can apply stratified proportional hazards model in which the stratification in most cases is done by using a covariate fixed by design. Suppose we have s = 1, 2,...,S strata, and then allow the baseline unspecified hazard function to vary among the strata.

The hazard function for stratum, s is

$$h_s(t,\mathbf{X})=\lambda_{so} exp\,(\boldsymbol{\beta}'\boldsymbol{X}) \tag{12}$$

The form of the partial likelihood for the s^{th} stratum is identical to the partial likelihood used in proportional hazards model, but it includes an additional subscript, s, indicating the stratum. The contribution to the partial likelihood for the s^{th} stratum is

$$L_{SP}(\boldsymbol{\beta}) = \prod_{i=1}^{n} h_s(t_{si}, x_{si})^{\delta_{si}} S(t_{si}, x_{si}) \tag{13}$$

Where n_{si} is the number of observations in the s^{t}h stratum, t_{si} is the i^{t}h observed value of time in s^{t}h stratum, δ_{si} is the value of the censoring indicator associated with t_{si}, R (t_{si}) : the risk set for subjects in stratum s at time t_{si} , X_{si} is the vector of p -covariates for subject i in stratum s .

The full stratified partial likelihood is obtained by multiplying the contributions to the likelihood, namely (β) = $\prod_{s=1}^{s} L_{sp}(\beta)$

The maximum stratified partial likelihood estimator of the parameter vector, β, is obtained by solving the p equations obtained by differentiating the (β) with respect to the p unknown parameters and setting the derivatives equal to zero. Finally model building and model assessment is the same as that of proportional hazards model

3.5.4 PARAMETRIC SURVIVAL MODELS

The previous topics were focused entirely on the use of semi-parametric model and proportional hazards Cox regression model. But there are parametric survival model that assume that the survival time follows a know distribution. Many models using different distribution have been developed.

The commonly applied models are exponential, weibull, log-logistic and log normal models.

3.5.4.1 EXPONENTIAL SURVIVAL MODEL

For skewed to the right time data with exponential distribution, the time of survival for covariates matrix X, which is called, accelerated failure time, expressed as:

$$T=exp\ (\beta'X+\varepsilon) \tag{14}$$

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

$$\ln T=\beta'X+\varepsilon \tag{15}$$

where ε is the error component and β'=(β_o,β_1,…,β_k).

The exponential model (t~exp(α)) is the simplest parametric model and assumes a constant risk or hazard over time, which reflects the property of the distribution appropriately called "lack of memory". The survivorship function may be obtained by expressing in terms of time as:

$$S\ (t,\boldsymbol{X}) = exp\ (-te^{-\beta' X}) \qquad (16)$$

The hazard function of the exponential regression model is:

$$h(t,\mathbf{X})=\exp(-(\beta' X)) \qquad (17)$$

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

$$h_i(t,\mathbf{X}_i)=h_o exp(\beta_o+\beta_1 x_{i1}+\cdots+\beta_k x_{ik}) \qquad (18)$$

For exponential regression survival models, the hazard ratio is interpreted as , with one unit increase in covariate $\boldsymbol{X}_i$ while other covariates being held fixed, at a time t is $HR(\boldsymbol{X}_i) = e^{-\beta i}$.

3.5.4.2 WEIBULL SURVIVAL MODEL

Suppose that survival times are assumed to have a Weibull distribution with scale parameter μ and shape parameter λ, the Weibull density function can be expressed as:

$$f(\ t,\mu,\alpha) = \mu\alpha t^{\alpha-1} \exp\left(-\mu t^{\alpha}\right), \text{ where } \mu > 0 \text{ and } \alpha > 0 \qquad (19)$$

And the baseline hazard of this model for the i^{th} subject is

$$h_o\ (t_i; \mathbf{X}) = \mu\alpha t^{\alpha-1} \qquad (20)$$

Independent observation (t_i,δ_i), i=1,2,...,n with survival time t_i, and censoring indicator δ_i which has value of one if i^{th} observation is not censored and zero when the i^{th} observation is censored and let β be the unknown parameter. The likelihood function is

$$L(\beta) = \prod_{i=1}^{n} \left\{ f(t_i)^{\delta_i} \left(s(t_i)\right)^{1-\delta_i} \right\} = \prod_{i=1}^{n} \left\{ \left(\frac{f(t_i)}{s(t_i)} \right)^{\delta_i} s(t_i) \right\} \qquad (21)$$

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

$$h(\ t;\boldsymbol{X}) = \lambda\alpha t^{\alpha-1} exp\ (\boldsymbol{X\beta}) \qquad (22)$$

The model assumes that individuals' i and j with covariates X_i *and* X_j have proportional hazard functions of the form:

$$\frac{h(t;X_i)}{h(t;X_j)} = \frac{\exp(X_i\beta)}{\exp(X_j\beta)} = \exp((X_i - X_j)\beta) \quad (23)$$

The quantities *exp* (β) can be interpreted as hazard ratios.

3.5.4.3 LOG-LOGISTIC SURVIVAL MODEL

A lifetime T has a log-logistic distribution when for k > 0, $\theta \in \Re$

$$f(t) = \frac{e^{\theta}kt^{k-1}}{(1+e^{\theta}t^k)^2} \quad (26)$$

$$S(t) = \left[1+e^{\theta}t^k\right]^{-1} \quad (27)$$

$$\lambda(t) = \frac{e^{\theta}kt^{k-1}}{1+e^{\theta}t^k} \quad (27)$$

Since (t,z) is the probability of surviving to time t for any given time t, the ratio $\frac{S(t,\mathbf{X},\sigma)}{(1 - S(t,\mathbf{X},\sigma))} = \exp(-\theta)$ is often called the *odds* of surviving to time *t*.

Therefore, with one unit increase in covariate X_i while other covariates being held fixed, the odds ratio at a time t is given by

$$O(X_i) = \frac{\exp\left(\frac{-(y-\beta_i(X_i+1))}{\sigma}\right)}{\exp\left(\frac{-(y-\beta_i X_i)}{\sigma}\right)} = \exp\left(\frac{\beta_i}{\sigma}\right) \quad (24)$$

which is independent of time.

3.5.5 MODEL BUILDING

3.5.5.1 VARIABLE SELECTION

In fitting a model, an initial step is to identify a set of explanatory variables that have the potential for being included in the linear combination of proportional hazards model. The idea behind this point is to select those variables that result in the "best" model within the scientific context of the problem.

A traditional variable selection method is known as the best subset selection. The procedure first determines a criterion of model goodness, for example, residual sum of squares, adjusted R^2, Mallow's *Cp*, the Akaike information criterion (AIC), or the Bayesian information criterion (BIC). Then all possible subsets of variables are evaluated by the criterion and the subset that optimizes the criterion is selected. However, when the number of variables p is large, the best subset selection is computationally intensive. Huo and Ni (1996) prove that the best subset selection is an NP-hard (nondeterministic polynomial-time hard) problem. That is, the best subset solution cannot be obtained in computation times as a polynomial of the number of variables. Alternatively, sequential approaches can be used, including forward selection, backward elimination, and stepwise regression. The sequential approaches are computationally less demanding than the best subset selection. However, their heuristic searches of variables cannot guarantee an optimal solution to the regression model.

Collett (1994) recommended the approach of first doing a single covariate analysis to "screen" out potentially significant variables for consideration in the multi covariate model in order to identify the importance of each predictor. All variables that will be significant at 25% level, the modest level of significance, from single covariate regression model will be taken into multi covariate model. In step wise selection procedure, variables are added to the model one at a time and the variable that has been included in the model can be considered for exclusion at a later stage. Thus after adding a variable to the model ,the procedure then checks whether any previously included variable can now be significant reduction in the value of $-2\log\hat{L}$,that term would be included in the model.(David collet,2003).

More recently, penalized least squares methods have been used for variable selection. A promising technique called the lasso was proposed by Tibshirani(1996). The lasso is a penalized least squares method imposing an L1-penalty on the regression coefficients. Owing to the nature of the L1-penalty, the lasso does both continuous shrinkage and automatic variable selection simultaneously. Tibshirani(1996) and Fu(1998) compared the prediction performance of the lasso, ridge and bridge regression (Frank and Friedman, 1993) and found that none of them uniformly dominates the other two. However, as variable selection becomes increasingly important in modern data analysis, the lasso is much more appealing owing to its sparse representation.

The most popular one is Lasso (Least absolute shrinkage and selection operator) proposed by Tibshirani(1996) .The Lasso estimators are defined by

$$\hat{\beta}_{Lasso} = \arg\min_{\beta} \left\| Y - X\beta \right\|^2 + \lambda \sum_{j=1}^{p} \left| \beta_j \right| \qquad (25)$$

Where λ is a non negative regularization parameter. The second term of the sum of the absolute regression coefficients is usually called L1 penalty. Equivalently, Lasso is a constrained ordinary least squares that minimizes

$$\left\| Y - X\beta \right\|^2 \quad \textit{subject to} \sum_{j} \left| \beta_j \right| \le s \qquad (26)$$

Where s is a corresponding regularization parameter. Due to the nature of L_1 penality, Lasso shrinks the regression coefficients towards zero and produces some coefficients that are exactly 0, and implements variable selection.

Finally, the importance of each variable included in the multi covariate model should be verified by different model assessment.

3.5.5.2. MODEL COMPARISION

To select the model that can predict the survival time of VVOF patients, we will use Akaikie information criterion (AIC). Akaikie, 1974 proposed an informative criterion (AIC) statistic to compare different models and/or models with different numbers. For each model the value is computed as:

$$AIC = -2\log(likelihood) + 2(p + c + 1) \qquad (27)$$

where p denotes the number of covariates in the model without including the constant term and c is the number of anarchy parameter in specified model. According to the criterion, a model with small AIC value will be considered as it fits for the data.

3.6 MODEL ADEQUACY ASSESSESMENT

Once the model has been developed through the various steps indicated in the above section, then we need to assess the goodness of fit of the model (Agrest, 1996). Some of the methods for the assessment of a fitted proportional hazard can be equally used for parameter regression models. Some of them are:

Checking for Proportionality Assumption for Cox proportional hazard model

In order to use the Cox model, we must check the assumption of whether the effects of covariates on hazard ratio remain constant over time. This is a critical assumption of proportional hazards model and must be checked for each covariate.

Different studies suggest that several tests and graphical techniques can be used to assess proportionality assumptions in fitting the Cox model.

- The Grambsch-Therneau, 1994 test of non proportionality uses partial residuals for the test of proportional hazards assumption proposing a time varying coefficient.

$$\beta_i(t) = \beta_i + \gamma_i g(t) \qquad (28)$$

Where $\beta_i(t)$ is time varying coefficient, β_i is constant, $g_i(t)$ is some specified function of time, usually $g_i(t) = \ln(t)$.

- The Scaled Schoenfeld residuals graphical techniques can be used to assess Cox model assumption.

Goodness-of-Fit

Like that of regression analysis, some measure analogous to R^2 may be of interest as a measure of model performance. In proportional hazards regression model as in all regression analyses there is no single, simple method of calculating and interpreting R^2, because in this model, R^2 depends on the proportion of the censored observations in the data. A perfectly adequate model may have what, at face value, seems like a terribly low R^2 due to high percent of censored data (Hosmer and Lemeshow, 1989). Cox and Snell (1989) proposed model assessment using R^2 similar to the one used in linear regression which is given by:

$$R^2 = 1 - exp\left[\frac{2}{\mathrm{n}}(\mathrm{LL}_0 - \mathrm{LL}_\beta)\right] \quad (29)$$

Where LLo is the log likelihood for zero models or without covariates, LL_β is the log likelihood including covariates, n is the number of subjects included in the study.

To check the measure of goodness of fit for the final model in addition to R^2 we use tests like: the partial likelihood ratio, Wald and Score tests.

The Partial Likelihood Ratio (LR) Test: To use this we need to fit both the unrestricted and the restricted models. We shall obtain the value of the log-partial likelihood function (in the unrestricted model and $LLp\ \beta = 0$ when the model imposes the restrictions under H_o. The test statistic for H_o is based on the difference of the log-likelihood values. Under H_o, the statistic is asymptotically distributed as $\chi 2$ with P degrees of freedom.

$$Q_{LR} = 2\,[LL_{\mathrm{p}}(\hat{\beta}) - LL(\hat{\beta} = 0)] \sim \chi^2(\mathrm{P}) \quad (30)$$

The Wald and Score Test: To test the significance of predictors in the model, other two common approaches are the Wald (Q_W) and Score (Q_S) tests. Under H_O, the statistic is asymptotically distributed as $\chi 2$ with P degrees of freedom. If chi-square is significant, the variable is considered to be a significant predictor in the equation.

The test statistics are:

$$Q_W = \hat{\beta}' I_{PXP}^{-1} \hat{\beta} \sim \chi^2(P) \tag{31}$$

$$Q_S = U'_{Ho} I_{PXP}^{-1} (\hat{\beta} = 0) U_{H_O} \sim \chi^2(P) \tag{32}$$

where $I_{PXP}^{-1} \hat{\beta}$ and $I_{PXP}^{-1} (\hat{\beta} = 0)$ are indicate the matrix of dimension $p \times p$, extracted from the inverse of the observed information matrix evaluated at $\hat{\beta}$ and $\hat{\beta} = 0$ respectively and U_{HO} is the score function under H_O. Both Q_W and Q_S have approximately χ^2 distribution with P degrees of freedom.

Identification of Influential and poorly fit Covariates

Another important aspect of model evaluation is a thorough examination of regression diagnostic statistic to identify, if any, subjects: (1) have unusual configuration of covariates or (2) have an undue influence on the fit of the model.

Leverage is a diagnostic statistic that measures how "unusual" the values of the covariates are for an individual. In linear and logistic regression leverage is the distance of the value of the covariates for a subject to the overall mean of the covariates. Leverage is not easily defined nor does it have the same nice properties in proportional hazards regression. This is due to the fact that subjects may appear in multiple risk sets and thus may be present in multiple terms in the partial likelihood.

The score process residual for the i^{th} subject on the k^{th} covariate may be expressed as

$$L_{ik} = \sum_{j=1}^{n} \left(X_{ik} - \bar{X}_{wjk} \right) dM_i(t_j) \tag{33}$$

It is a weighted average of the distance of the value, X_{ik}, to the risk set means, where the weights are the change in martingale residual ($dM_i(t_j)$) defined as

$$dM_i(t_j) = dN_i(t_i) - Y_i(t_j) \exp(\beta' x_i) \lambda o (t_j) \quad (34)$$

where $dN_i(t_i)$ is the change in the count function for the i^{th} subject at time t_j , always equal to zero for censored subjects and one for non-censored subjects, at actual observed survival time. The function $Y_i(t_j)$ is called the at risk process and defined as zero if $t_i \leq t_j$ and one if $t_i \geq t_j$, λ_o (t_j) is the value of $\frac{\delta_i}{\sum_{j \in R(t)} \exp(x'_j \beta)}$ evaluated at t_j .

The net effect is that, for continuous covariates, the score residuals have the linear regression leverage property that the further the value is from the mean the larger the score residual is, but large may be either positive or negative. Thus, the score residuals are sometimes referred to as the leverage or partial leverage residuals. We plot score residuals against each continuous covariates to observe if there is individuals far away from the mean.

Generalized (Cox-Snell) Residuals:

The estimated cumulative hazard for each individual at the time of their death or censoring should be like a censored sample from a unit exponential. This quantity is called the generalized or Cox-Snell residual. Here is how the generalized residual might be used. Suppose we fit a PH model:

$$S(t;Z) = [S_0(t)]\exp(\beta Z) \quad (35)$$

or, in terms of hazards:

$$\lambda(t;Z) = \lambda_o(t) \exp(\beta Z)$$

$$= \lambda_0(t) \exp(\beta_1 Z_1 + \beta_2 Z_2 + \ldots + \beta_k Z_k) \quad (36)$$

So, for each person with covariates Z_i, we can get

$$\hat{S}(t;)\,(t;Zi) = \left[\hat{S_0}(t) \right]^{\exp(\beta Z_i)} \tag{37}$$

This gives a predicted survival probability at each time t in the dataset. Then we can calculate

$$\hat{\Lambda}_i = -\log\left[\hat{S}(T_{i,} Z_i) \right] \tag{38}$$

In other words, first we find the predicted survival probability at the actual survival time for an individual, then log-transform it.

CHAPTER FOUR

4. RESULTS AND DISCUSSION

4.1. DESCRIPTIVE ANALYSIS OF VVOF PATIENTS

In this retrospective institutional based study, medical data of 206 registered VVOF patients from November 2010 to June 2014 G.C were considered. The average mean recovery time of a VVOF patient stay in the hospital to be physically cured is 39.448 days (5.635 weeks) and the standard error is 1.961 days. Among the patients of VVOF considered, 76.2% of them were physically cured while the rest 23.8% were censored. Out of the patients 40.8%, 35.9% and 23.3%, were in age groups ≤ 20, 21-30 and > 30, respectively. The proportion of the patients who were physically cured among these age groups was 75%, 75.7%, and 79.2% respectively. For age at first marriage there was 47.6% early marriage before fifteen years, out of which 73.5% were physically cured. In the same manner, among 22.8% first marriage between 16 to 20 patients, 74.5% were physically cured. And patients age at first marriage > 20 year were 29.6%, out of which 81.9% are physically cured.

VVOF patients with height < 150cm hold 83.9 % and patient with height ≥150cm are 16% in the sample. The proportion of the patients who were physically cured among the height groups < 150cm and ≥150cm were 73.1% and 86.9%, respectively. There were 77.7% and 22.3% patients their weight are < 50kg and ≥50kg, respectively. The physically cured proportion among this weight groups of < 50kg and ≥50kg were 73.1% and 86.9%, respectively.

In parity case, there are 12.1% with one child, out of which 84% were physically cured. Similarly, among 50.4% of mother having 2 to 5 children, 73.1% were physically cured. And mother having more than 5 children were 37.4%, out of which 77.9% are physically cured.

When we see their educational backgrounds of the patients, 29.1% were literate, out of the literate group, 83.3 % of the patients were physically cured where as 70.8% of the patients were illiterate. Physically cured proportion among the illiterate group was 73.3%. With regard to the marital status of VVOF patients, there were 4.8%, 64.1%, 24.3% and 6.8% patients who had not married, married divorced and widowed, respectively. The proportion of the patients who were physically cured among the marital status groups of not married, married, divorced and widowed were 60%, 78.8%, 78% and 57.1 %, respectively.

When you see who brings the patients for surgery, among all the patients 3.9% of them avail for surgery by themselves, 30.1% by their husbands, 23.8% by their relatives, 4.9% by their husbands and relatives and the rest 37.4% were brought by the organization. The proportion of the patients who were physically cured for those avail themselves for surgery was 75%, by their husbands was 75.8%, by their relatives was 79.6%,by both their husbands and their relatives was 60% and the rest are 76.6%.

The result also identified that patients who have antenatal care follow up hold 59.7% and those who have no antenatal care follow up are 40.3%. The proportion of the patients who were physically cured among those with antenatal follow up care and those with no antenatal care follow up were 75.6% and 77.1%, respectively.

Another factor considered under this study was duration of incontinence. Under these 14.1%, 56.8% and 29.1% of the patients came to the heath center after urine incontinence of ≤ 3, 4-7 and > 7 month, respectively. The proportion of the patients who were physically cured among this duration of incontinence urine groups ≤ 3, 4-7 and > 7 month were 75.9%, 75.2% and 78.3%, respectively.

Among duration of labor, 32%, 14.1%, 53.9% patients gave birth after a labor of < 2 day, 2-4 day and > 4 day, respectively. The physically cured proportion among this duration of labor groups < 2, 2-4 and > 4 day were 78.8%, 82.8% and 83% respectively. Only 36.9% of the women give birth at health center assisted by skilled birth attendants and 63.1% were delivered at home. The physically cured proportion was 69.7% among patients who delivered at health center and 80% for those who gave birth at home.

More than half (59.2%) of VVOF patients gave birth by assisted vaginal delivery and 40.8% patients delivered normal vaginal. The physically cured proportion among this mode of delivery groups of vaginal and non-vaginal delivery were 80.9% and 72.9%, respectively. With regard to the fetal outcome, 87.4% of fetal outcome were still birth and 12.6% of fetal outcome are alive. The physically cured proportion among this fetal outcome of those still birth and alive were 76.1% and 76.9% respectively.

The proportion of VVOF patients with length of fistula ≤ 2cm and 3-5 cm were 82.5% and 17.5%. and the proportion of physically cured among the length of fistula hole ≤ 2 cm and 3-5 groups were 81.2%and 52.8%, respectively. Regarding with width of fistula of patients, 69.4% and 30.6% patients had width of fistula ≤ 2cm and > 5cm, respectively. Proportion of physically cured among the width of fistula groups ≤ 2cm and > 5cm were 82.5% and 61.9 %, respectively. Patients with large length and width of fistula size were more likely to have unsuccessful repair than those with small fistula size.

Patients with bladder size of small, fair and good was found to be 61.2%, 34% and 4.8% respectively out of the total patients. The physically cured proportion among the bladder size of small, fair and good bladder size were 80.2%, 74.3% and 40%, respectively. Finally, when we see the status of urethra, patients with intact urethra were 58.7% and those partially damaged of urethra was 41.3%. The proportion of physically cured among status of urethra groups intact, and partially damaged were 80.2% and 70.6%, respectively. Similarly, patients with partially damaged urethra were more likely to take more recovery time than those with good status of urethra fistula.

Table 1: Summary Results of Socio-Demographic and Health Variables Associated with VVOF Patients at MHFC.

Variables	***Status***		***Number out of 206(%)***
	Censored	**Phy.cured(%)**	
Current age			
≤ 20	21(25%)	63(75%)	84(40.8%)
21-30	18(24.32%)	56(75.7%)	74(35.9%)
>30	10(20.83%)	38(79.2%)	48(23.3%)
Ageatfirst marriage			
≤ 15	26(26.5%)	72(73.5%)	98(47.6%)
16-20	12(25.5%)	35(74.5%)	47(22.8%)
>20	11(18.0%)	50(81.9%)	61(29.6%)
Height(kg)			
<50	44(25.4%)	129(74.6%)	173(83.9%)
≥50	5(15.2%)	28(84.8%)	33(16%)
Weight(kg)			
<50	43(26.9%)	117(73.1%)	160(77.7%)
≥50	6(13.04%)	40(86.9%)	46(22.3%)
Parity			
Primi para	4(16%)	21(84%)	25(12.1%)
Multi para	28(26.9%)	76(73.1%)	104(50.4%)
Grand multi para	17(22.1%)	60(77.9%)	77(37.4%)
Educational status			
Literate	10(16.7%)	50(83.3%)	60(29.1%)
Illiterate	39(26.7%)	107(73.3%)	146(70.8%)

Marital status			
Not married	4(40%)	6(60%)	10(4.8%)
Married	28(21.2%)	104(78.8%)	132(64.1%)
Divorced	11(22%)	39(78.0%)	50(24.3%)
Widowed	6(42.9%)	8(57.1%)	14(6.8%)
Accompanying person			
Self	2(25%)	6(75%)	8(3.9%)
Husband	15(24.1%)	47(75.8%)	62(30.1%)
Relatives	10(20.4%)	39(79.6%)	49(23.8%)
Husb and relatives	4(40%)	6(60%)	10(4.9%)
Organization	18(23.4%)	59(76.6%)	77(37.4%)
Antenatal care			
Yes	30(24.4%)	93(75.6%)	123(59.7%)
No	19(22.9%)	64(77.1%)	83(40.3%)
Dur. of Incontinence			
≤ 3	7(24.1%)	22(75.9%)	29(14.1%)
4-7	29(24.8%)	88(75.2%)	117(56.8%)
>7	13(21.7%)	47(78.3%)	60(29.1%)
Duration of labor			
≤2	14(21.2%)	52(78.8%)	66(32.0%)
2-4	5(17.2%)	24(82.8%)	29(14.1%)
>4	30(27.0%)	81(83%)	111(53.9%)
Place of delivery			
Home	26(20%)	104(80%)	130(63.1%)
Health center	23(30.3%)	53(69.7%)	76(36.9%)

Mode of delivery			
Vaginal	16(19.1%)	68(80.9%)	84(40.8%)
Others	33(27.1%)	89(72.9%)	122(59.2%)
Fetal outcome			
Still birth	43(23.9%)	137(76.1%)	180(87.4%)
Alive	6(23.1%)	20(76.9%)	26(12.6%)
Length of fistula			
≤ 2 cm	32(18.8%)	138(81.2%)	170(82.5%)
3-5 cm	17(47.2%)	19(52.8%)	36(17.5%)
Width of fistula			
≤ 2 cm	25(17.5%)	118(82.5%)	143(69.4%)
3-5 cm	24(38.1%)	39(61.9%)	63(30.6%)
Bladder size			
Small	25(19.8%)	101(80.2%)	126(61.2%)
Fair	18(25.7%)	52(74.3%)	70(34%)
Good	6(60.0%)	4(40%)	10(4.8%)
Status of urethra			
Intact	24(19.8%)	97(80.2%)	121(58.7%)
Partially damaged	25(29.4%)	60(70.59%)	85(41.3%)

4.1.1 COMPARISON OF SURVIVAL EXPERIENCES OF VVOF PATIENTS

The Kaplan-Meier survivor estimator is used to investigate the significant differences between the survival probabilities of different variables. In this case, the Kaplan-Meier survivor estimators for the three categories of current age of patients which is plotted in Figure 3 in Appendix A show that those patients whose current age is above thirty years had taken more time to get physically cured than those whose current age is between twenty one to thirty years and below twenty years. But the Log-Rank and Wilcoxon test shows that there was no statistically significant difference in the survival probability of a patient by current age of a patient. Again, in order to investigate if there is significant difference between the survivals of a patient by age at first marriage, Kaplan-Meier survivor estimates for three age groups were plotted in Figure 3 in appendix A. This figure shows that the age at first marriage below fifteen years had taken more time to physically cured than those who married between sixty to twenty years and above twenty years. This conclusion was also confirmed using formal hypothesis tests of log-rank and wilcoxon which is given in Table 2. Here both log-rank and wilcoxon tests identify significant difference with patients whose age at first marriage below 15 years, 16 to 20 years and above 20 years with respect to recovery time.

The other variable included in the study was weight of a patient. A Kaplan-Meier survivor estimates for the two groups of weight of a patient were plotted in Figure 3 in appendix A. The curves shows us patients whose weight below fifty kg had taken more time to physically cured than those patients whose weight is greater than or equal to fifty kg and Wilcoxon test also confirms that there is significant difference with patients whose weight below fifty kg and above fifty kg with respect to recovery time. The KM curves for height given in figure 4 Appendix A shows us patients whose height below one hundred fifty cm had taken more time to physically cured than those patients whose height is above one hundred fifty cm. But the Log-Rank and Wilcoxon test shows that there was no statistically significant difference in the survival probability of a patient by height with respect to recovery time.

With regard to the number of children a family has, educational status and marital status of patients , the KM curves are given in figure 5 and 6 in Appendix A. The curves overlap each other indicating that the recovery time may be identical for these groups. Log-rank and Wilcoxon test also showed that there was no statistically significant difference in the physically cured of patients. For variable called accompanying person, the curves overlap each other for these groups, but both Log-rank and wilcoxon test confirm that there is significant difference between the groups by accompanying person with respect to recovery time.

Comparing the survivor functions between follow up of antenatal care and no follow up of antenatal care of patients, Kaplan-Meier survivor estimates for the two groups were plotted in Figure 7 Appendix A. The figure shows that patients who have follow up of antenatal care had slightly shorter recovery time compared with patients who have no follow up of antenatal care service. This impression was confirmed using formal hypothesis tests. Both log-rank and Wilcoxon tests have also identified significant (P < 001) diff erence in recovery time as it is shown Table 2.

Among different categories of duration of labor, place of delivery, and mode of delivery of patients who had a labor below two days, those delivered at health center and those whose mode of delivery was vaginal had lower recovery time than those who had a labor above two days, those delivered at home and those whose mode of delivery was other than vaginal. This impression was confirmed using formal hypothesis tests. Both log-rank and Wilcoxon tests identify significant difference among duration of labor, place of delivery and mode of delivery. The Kaplan-Meier survivor estimates for duration of labor, place of delivery and mode of delivery were given in Figure 8 and 9 in Appendix A. Patients who had urine incontinence below three months, those whose fetal outcome was alive and those whose bladder size was small had lower recovery time than those had duration of urine incontinence above three months, those having fetal outcome of still birth and those whose bladder size was not small. But both log-rank and Wilcoxon tests identify that there is no significant difference among duration of incontinence, fetal outcome and bladder size. The Kaplan-Meier survivor estimates for incontinence, fetal outcome and bladder size were given in Figure 7 and 11 in Appendix A. When we compare different categories of variables like length of fistula and width of fistula, the figure shows that patients who have had length and width of fistula below 2 cm had shorter recovery time compared with patient who had length and width of fistula between 3-5cm. Kaplan-Meier survivor estimates for the two groups were plotted in Figure 10 Appendix A. This conclusion was confirmed using log rank test but Wilcoxon test only identifies width of fistula as significant factor in determining recovery time.

Among different categories of urethra status, there is significant difference in determining recovery time. This aspect is also confirmed using formal log rank and Wilcoxon test. Here patients with intact urethra status had shorter recovery status than those patients with partially damaged urethra status. The information is also supported by Kaplan-Meier survivor estimates for the two groups which is given in Figure 10 Appendix A.

Table2: Comparison of Survival Experience of VVOF Patients at MHFC Using Socio-Demographic and Health Variables.

Test of equality of over strata				
Variables	category	Median recovery time	Chi-square LR(WL)*	P-value LR(WL)*
Current Age	≤ 20	35	1.05(2.340)	0.59(0.31)
	21-30	31		
	>30	36		
Age at first marriage	≤ 15	44	133.5(136.6)	<0.0001 (<0.0001)
	16-20	30		
	>20	19		
Height(cm)	<150	35	2.24(3.74)	0.13(0.05)
	≥150	28		

Weight(Kg)	<50	35	2.45(4.77)	0.117(0.028)
	≥50	28.5		
Parity	Primi para	28	2.54(0.74)	0.28(0.69)
	Multi para	35		
	Grandmulti para	35		
Educational status	literate	30	2.76(2.75)	0.096(0.097)
	Illiterate	35		
Marital status	Not married	21	3.117(2.425)	0.374 (0.489)
	married	35		
	divorced	33		
	widowed	39		
Accompanying person	Self	35	7.92(18.55)	0.095 (0.001)
	Husband	31		
	Relatives	25		
	Husb and relat	38		
	Organization	39		
Antenatal care	Yes	28	6.99(12.41)	0.008 (0.0004)
	No	39		

Duration of in continence	≤ 3	34	1.311(0.649)	0.519 (0.723)
	4-7	35		
	>7	34		
Duration of labor	≤2	18	30.62(56.83)	<0.0001 (<0.0001)
	2-4	35		
	>4	39		
Place of delivery	Home	37	9.203(11.597)	0.002 (0.0007)
	Health center	29		
Mode of delivery	Vaginal	28	11.489(11.81)	0.0007(0.0006)
	others	37		
Fetal outcome	Still birth	35	4.86(3.01)	0.0275(0.0827)
	alive	30		
Length of fistula	≤ 2 cm	32	3.76(4.77)	0.052(0.028)
	3-5 cm	39		
Width of fistula	≤ 2 cm	31	7.91(10.95)	0.0049(0.0009)
	3-5 cm	39		
Bladder size	small	34	0.439(0.497)	0.803(0.779)
	fair	35		

	good	42		
Status of urethra	intact	32	5.076(9.508)	0.024(0.002)
	Partially damaged	39		

4.2: UNIVARIABLE ANALYSIS OF COX PH REGRESSIONMODEL

The relationship between each predictor and recovery probability of VVOF patients after doing single covariate Cox proportional hazards model analysis is given in Table 3.Single covariate Cox proportional hazard model is an appropriate analysis that is used to identify out potentially important variables before directly including in the multi variable model. As can be seen from this Table, survival of the patients was significantly related with age at first marriage, height, antenatal care, duration of labor, place of delivery, mode of delivery, length of fistula, width of fistula and status of urethra. But the covariates like current age of a patient, weight, parity, educational status, marital status, accompanying person, duration of incontinence urine, fetal outcome, and bladder size were not statistically significant at 5% significance level.

Table 3: Single Covariate Analysis of Cox Proportional Hazards Regression Model on the Time to recovery of VVOF Patients at MHFC.

Variables	**Wald**	**Df**	**Sig.**
Current age	1.03	2	0.5915
Age at first marriage	112.8	2	0.0001
Height(cm)	4.12	1	0.0423
Weight(kg)	1.79	1	0.1806
Parity	2.62	2	0.2694

Educ. Status	2.38	1	0.1226
Marital status	3.14	3	0.3712
Accompanying person	8.06	4	0.0893
Antenatal care	6.34	1	0.01178
Duration of in continence	1.48	2	0.477
Duration of labor	22.66	2	1.199e-6
Place of delivery	9.19	1	0.00243
Mode of delivery	12.3	1	0.00045
Fetal outcome	3.58	1	0.0586
Length of fistula	4.18	1	0.0408
Width of fistula	7.23	1	0.00716
Bladder size	0.41	2	0.8136
Status of urethra	4.47	1	0.0344

4.3 MULTI VARIABLE ANALYSIS OF COX PROPORTIONAL HAZARD REGRESSION

One problem of single covariate analysis is it ignores the possibility that a collection of variables, each of which is weakly associated with the outcome, may become important predictors when considered together. From the p values of the output of single covariate analysis at 5% significance level some important predictor variables were ignored and excluded from the model. So multiple covariates analysis must be done to check whether the excluded variables in single covariate analysis are significant in the inclusion of collection of variables.

4.3.1 VARIABLE SELECTION

In cases where the number of independent variables are large enough to allow for some model reduction for easier practical application, one approach was to apply a step wise selection procedure but a promising alternative is to apply the Lasso method, which achieves selection of predictors by shrinking some coefficients to zero by setting a constraint on the sum of the absolute standardized coefficients. The Lasso model was found to be optimal with 13 predictors. In the case of step wise selection procedure with AIC, predictor like accompanying person was also dropped and 12 predictors were selected. In the lasso selection method with more shrinkage, it is expected that some predictor like accompanying person having regression coefficients shrinking to zero may also be dropped and the same set of 12 predictors may be selected as in the stepwise selection procedure (Table 4).

Table 4: Cox regression coefficients in the full model, a stepwise selected model (using Akaike's Information Criterion), and in the Lasso model.

Predictor	Full	Step AIC	Lasso
Current age	-0.0145	Not selected	Not selected
	-0.1326	Not selected	
Age at marriage	-1.3639	-1.4333	-1.2037
	-2.714	-2.8210	
Height(cm)	0.00042	Not selected	Not selected
Weight(kg)	-0.4837	-0.5949	-0.4178
Parity	0.1411	Not selected	Not selected
	0.6258	Not selected	
Educational status	0.4574	0.4671	0.2276

Marital status	-0.4474	-0.4691	-0.0926
	-0.5287	-0.6341	
	-0.7106	-0.5462	
Accompanying person	-0.4267	Not selected	-0.0032
	0.1200	Not selected	
	-0.6261	Not selected	
	-0.7055	Not selected	
Antenatal care	-0.5044	-0.5360	-0.3375
Duration of in continence	0.0344	0.0723	0.1692
	0.6199	0.6185	
Duration of labor	0.5426	0.5146	0.4308
	1.1312	1.2026	
Place of delivery	-0.8213	-0.7736	-0.5575
Mode of delivery	0.9499	1.0036	0.8448
Fetal outcome	0.4913	0.4350	0.2492
Length of fistula	0.1331	Not selected	Not selected
Width of fistula	0.3669	0.4387	0.3459
Bladder size	0.6097	Not selected	Not selected
	0.4502	Not selected	
Status of urethra	0.4007	0.5146	0.3144

4.3.2. MODEL ESTIMATION

Regression coefficients were first estimated as default with Cox regression analysis, i.e. by maximizing the log-likelihood of the fit of the model to the data. The coefficients of the 12 predictors in the stepwise backward selected model were rather similar to their corresponding coefficients in the full model (Table 4). In contrast, the Lasso model shrunk coefficients of weaker predictors such as accompanying person considerably towards zero. The effects of strong predictors, such as age at marriage, weight, antenatal care, place of delivery, mode of delivery, and width of fistula were comparable with the maximum likelihood estimates, but effects of weaker predictors are shrunk considerably.(Figure 1).

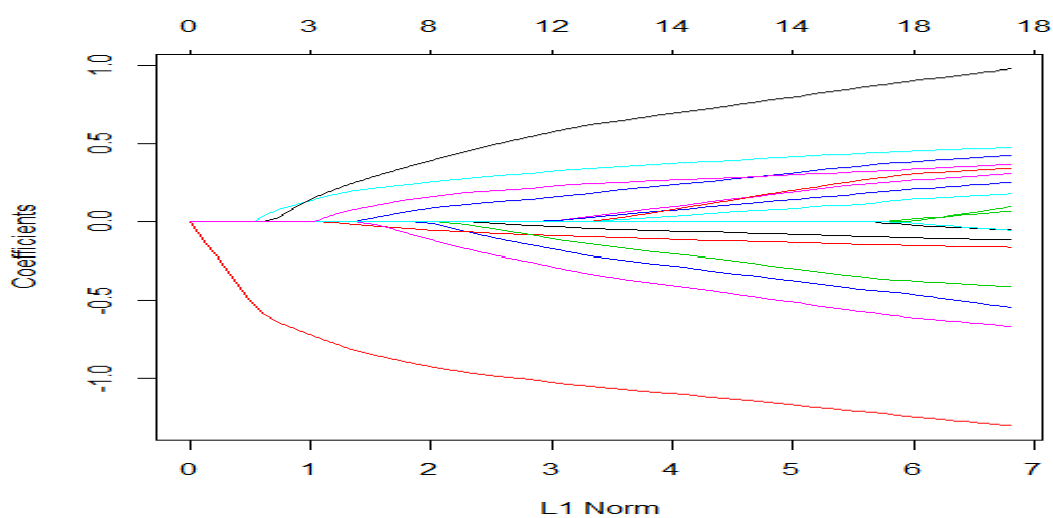

Figure 1: Lasso path with increasing sum of the absolute standardized coefficients (|beta|).

The coefficient path shows that predictors have effects other than zero with higher |beta|.

4.3.3 RESULTS OF THE FINAL MODEL USING LASSO VARIABLE SELECTION METHOD.

The Cox regression coefficients in the final model are interpreted as follows. After adjusting other covariates, the hazard rate for being physically cured of a patient with age at first marriage between 16 to 20 is 76.2% lower than patients whose age at first marriage was < 15 years (adjusted HR=0.238, CI: 0.133, 0.427). The hazard rate for those patients with age at first marriage above > 20 years was 94.1% lower than patients whose age at first marriage was < 15 years (adjusted HR=0.059, CI: 0.034, 0.105).

Looking at the effect of weight of a patients with ≥50kg after adjusting other confounding variables, the hazard rate for being physically cured of patients with weight ≥50kg was 44.8% lower than patients with weight < 50kg (adjusted HR=0.552, CI: 0.367, 0.828) .The hazard rate of the patients who are literate was 59.5% higher than those patients who are illiterate (adjusted HR=1.595, CI: 1.085, 2.345) which means that the recovery time of patients with who were literate was extended by 59.5% when compared with patients who were illiterate. After adjusting other covariates, the hazard rate for getting physically cured of patients who married was 39.1% lower than patients who were single. The hazard rate of patients who are divorced and widowed were 47% and 42.1% lower than patients who were not married. After adjusting other covariates, the hazard rate for getting physically cured of patients having no follow up of antenatal care was 71.9% higher than those who have follow up of the service (adjusted HR=1.709, CI: 1.163, 2.512). For duration of incontinence, the hazard rate of patients with duration of incontinence in between four to seven months was 7.4% higher than those patients whose duration of incontinence was ≤ 3 months (adjusted HR=1.074, CI: 0.687, 1.681). The hazard rate of patients with duration of incontinence above seven months was 85.6% higher than those patients whose duration of incontinence was ≤3 months (adjusted HR=1.856, CI: 1.062, 3.243).

Looking at duration of labor, after adjusting other covariates, the hazard rate of patients who had labored from 2 -4 days was 67.3% higher than those patients who labored below 2 days (adjusted HR=1.673, CI: 1.001,2.797).Similarly, the hazard rate of patients who labored for above 4 days was 232.8% higher than those patients who labored below 2 days.

Place of delivery is the other covariate which has a significant impact on getting physically cured. The hazard rate of patients who delivered at health center was 53.9% higher than those who delivered at home (adjusted HR=0.461, CI: 0.304, 0.698). Similarly, the hazard rate for getting physically cured of patients whose mode of delivery was other than vaginal was 172.8% higher than those patients whose mode of delivery was vaginal (adjusted HR=2.728, CI: 1.849, 4.025).

The hazard rate of patients who gave an alive fetal outcome was 64% lower than those patients who gave still birth fetal outcome (adjusted HR=0.640, CI: 0.501, 0.982). Length of fistula hole is another covariate which has a significant impact on the recovery of patients. The hazard rate of a patient's whose fistula width 3-5 cm was 55% higher than those patients whose fistula width was <2 cm (adjusted HR=1.550, CI: 1.042, 2.308), which means as the width of fistula hole increases the hazard rate also increase.

Lastly, the status of urethra has also a significant effect on getting physically cured of vesico vaginal obstetric fistula patient. The hazard rate for being physically cured of obstetric fistula patient with partially damaged urethra was 67.3% higher than those patients with intact urethra (adjusted HR=1.673, CI: 1.137, 2.462). This indicates that intact urethra have shorter recovery time compared to partially damaged urethra (Table 5).

Table 5: The Parameter Estimates, Standard Errors and the Hazard Ratios of the Cox Proportional Hazards Regression Model Analysis at MHFC.

Predictors	β	SE	HR(95% CI for HR)	p-value
Age at marriage				
≤ 15(R)	0.000		1	
16-20	-1.433	0.297	0.238(0.133,0.427)	1.46e-6
>20	-2.821	0.287	0.059(0.034,0.105)	<2e-16
Weight(kg)				
<50(R)	0.000		1	
≥50	-0.594	0.207	0.552(0.367,0.828)	0.0041
Educ. Status				
literate(R)	0.000		1	
Illiterate	0.467	0.197	1.595(1.085,2.345)	0.0175
Marital status				
Not married(R)	0.000		1	
Married	-0.496	0.432	0.609(0.261,1.421)	0.2513
Divorced	-0.634	0.246	0.530(0.327,0.859)	0.0099
Widowed	-0.546	0.420	0.579(0.254,1.320)	0.1938

Antenatal care				
yes(R)	0.000		1	
No	0.536	0.196	1.709(1.163,2.512)	0.0064
Dur. of incont.				
≤ 3(R)	0.000		1	
4-7	0.073	0.228	1.074(0.687,1.681)	0.7514
>7	0.618	0.285	1.856(1.062,3.243)	0.0297
Dur. of labor				
≤2 (R)	0.000		1	
2-4	0.515	0.262	1.673(1.001,2.797)	0.0497
>4	1.203	0.234	3.328(2.103,5.267)	2.82e-7
Place of delivery				
Home(R)	0.000		1	
Health center	-0.774	0.212	0.461(0.304,0.698)	0.00026
Mode of delivery				
vaginal(R)	0.000		1	
Other	1.004	0.198	2.728(1.849,4.025)	4.22e-7

Width of fistula				
≤ 2 cm(R)	0.000		1	
3-5 cm	0.439	0.202	1.550(1.042,2.308)	0.0306
Status of urethra				
Intact(R)	0.000		1	
Partially damaged	0.515	0.197	1.673(1.137,2.462)	0.0091

4.3.4 ASSESSMENT OF MODEL ADEQUACY

Table 6 given below shows that the time-dependent covariates (interaction of covariates with logarithm of time) were not significant, which justifies that the proportional hazard assumption holds at 5% level of significance. The plot of the scaled Schoenfeld in Figure 12-17 in Appendix B also shows that the residuals looks like random without systematic pattern. This implies that there is no reason for violation of proportional hazards assumption. In the same manner the smoothed plot for figure 12 -17 shows nearly straight line without any departure from the horizontal line. These figures also support that the PH assumption is satisfied for all the covariates in the model.

Table 6: Statistical test for proportional hazards assumption of the covariates and their interaction with log of time for MHFC.

Variables	**chisq**	**Sig**
Age at marriage	0.0074	0.931
Weight(kg)	0.883	0.347
Educ. status	1.460	0.227
Marital status	0.122	0.727
Antenatal care	0.015	0.904
Duration of in continence	2.09	0.149
Duration of labour	0.489	0.484
Place of delivery	0.138	0.710
Mode of delivery	0.0068	0.934
Fetal outcome	0.400	0.527
Width of fistula	0.099	0.753
Status of urethra	0.0027	0.958
Age at marriage*ln(t)	0.00069	0.979
Weight(kg)*ln(t)	0.752	0.386
Educ. Status*ln(t)	1.381	0.240
Marital status*ln(t)	0.105	0.745
Antenatal care*ln(t)	0.021	0.884
Duration of in continence*ln(t)	2.33	0.127
Duration of labour*ln(t)	0.453	0.501
Place of delivery*ln(t)	0.233	0.629

Mode of delivery*ln(t)	0.035	0.851
Fetal outcome*ln(t)	0.141	0.707
Width of fistula*ln(t)	0.1176	0.732
Status of urethra*ln(t)	0.0049	0.944

4.3.4.1 GOODNESS OF FIT

In the final Cox PH regression model with enter method the initial Log Likelihood function was log-likelihood=-2 Log likelihood = 1376.308 and after the covariates were incorporated the Log Likelihood function becomes -2 Log likelihood=1196.622. Furthermore, the results of the likelihood ratio test (chi-square = 179.6865, p < .0001), Score test (chi-square = 198.47, p <.0001) and Wald test (chi-square =155.849, p < .0001) suggest that model is a good fit. It was found that twelve covariates contribute significantly in explaining the variability in the recovery of VVOF patients. Graphically, from cox-snell residuals we can see that most of the residuals fall on a straight line and there are no large departures from the straight line tail. Thus, generally speaking, we can say that our model fits the data very well.

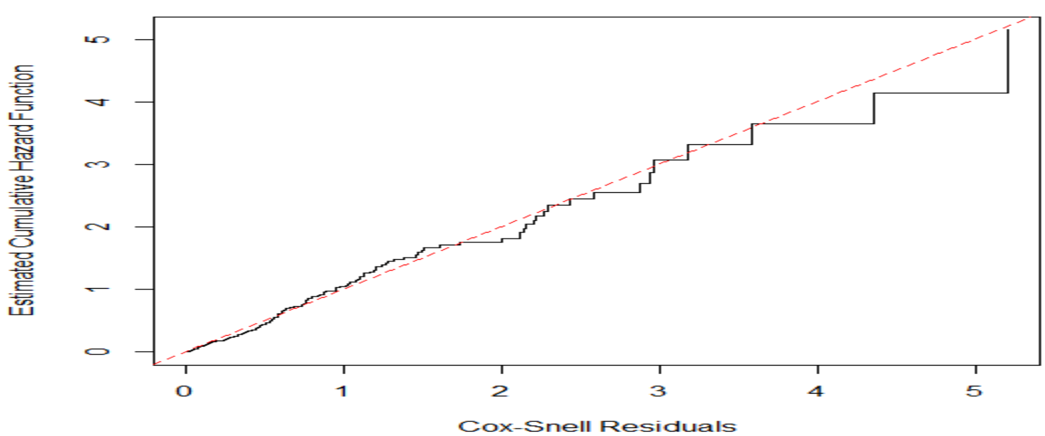

Figure 2: Cox-Snell residual plot for checking model adequacy

4.3.5 PARAMETRIC MODELS

4.3.5.1 MODEL SELECTION AND POTENTIAL SURVIVAL DISTRIBUTION FOR THE DATA

To determine the variables to be included in the parametric survival model, an automatic variable selection method (step AIC) in R is used. Regardless of the survival time distributions, with the exception of the current age of a patient, height, marital status, accompanying person, length of fistula and bladder size, all other variables are extracted to be included in the model.

In order to select the appropriate survival time distribution, the most commonly used parametric models; the Weibull, Exponential and Log logistic models are examined using common applicable criterion called Akaikie information criterion (AIC).

Table 7: Selection of Survival Time Distribution using Log likelihood and AIC Criteria Survival Time Distribution

Model	***log-likelihood***	***AIC***
Weibull	Full -613.8	1262.3
Exponential	Full -728.7	1493.4
Log logistic	Full -610.9	1256.2

Here, since the models are not nested, it is not possible to compare the models using logliklihood values. When the models were compared using AIC, among the parametric models, the Loglogistic model has the smallest AIC. But, there is no much substantial difference among the AIC scores among the two parametric models; the Weibull, and Lognormal models. As a result, it is better to use the Weibull model because of two reasons; firstly, it is the most commonly used and secondly, it is the only model having both a PH and accelerated failure time properties. Hence, weibull model is the appropriate parametric survival model for the data on time to recovery from VVOF.

4.3.5.2. MULTIVARIABLE ANALYSIS OF WEIBULL REGRESSION MODEL

The relationship between covariates and recovery probability of VVOF patients modeled by Weibull regression model are presented in Table 8. As can be seen from this Table, recovery of VVOF patients was significantly related with age at first marriage, duration of incontinence, duration of labor, place of delivery, mode of delivery, fetal outcome, width of fistula, and status of urethra. The Wald test for the parameter estimates indicates that at least one of the parameters in each covariate is significantly different from zero at 0.05 level of significance. The formal tests were applied to the model adequacy and the results are displayed in section 4.3.5.3.

Table 8: The Parameter Estimates, Standard Errors and the Hazard Ratios of the weibull Model Analysis for MHFC.

Predictors	$\hat{\beta}$	***SE***	***Chi square***	***Sig.***	***exp(*** $\hat{\beta}$ ***)***
Age at first marriage					
≤ 15	0.8359	0.0697	143.94	<0.0001	2.307
16-20	0.4223	0.0858	24.2	<0.0001	1.525
>20(R)	0.0000				1
Duration of labor					
≤2	-0.2334	0.0680	11.79	0.0006	0.792
2-4	-0.2268	0.0836	7.36	0.0067	0.797
>4 (R)	0.0000				1
Dur. of incontinence					

≤ 3	-0.2191	0.0936	5.47	0.0193	0.803
4-7	-0.0084	0.0684	0.02	0.9020	0.992
>7(R)	0.0000				1
Place of delivery					
Home	0.2129	0.0658	10.46	0.0012	1.237
Health center(R)	0.0000				1
Mode of delivery					
Vaginal	-0.2883	0.0618	21.78	<0.0001	0.749
others(R)	0.0000				1
Fetal outcome					
Still birth	0.1758	0.0875	4.04	0.0445	1.192
alive(R)	0.0000				1
Width of fistula					
≤ 2 cm	-0.1414	0.0680	4.32	0.0377	0.868
3-5 cm(R)	0.0000				1
Status of urethra					
Intact	-0.1464	0.0617	5.62	0.0177	0.864
Partially damaged(R)	0.0000				1

Now using the link to the accelerated failure model to get the estimates of the different parameters we can fit a Weibull proportional hazard model to study the recovery probability of VVOF patients using the links

$$\lambda = \exp\left(\frac{-\mu}{\delta}\right) \qquad ,\alpha = \frac{1}{\delta} \quad \text{and} \quad \beta = \frac{-\beta_{aft}}{\delta}$$

Implementing the Weibull regression model of equation (22) and with the parameters found in Table 8, the recovery probability of VVOF patients with Weibull distribution can be expressed as t ∼ Weibull(α, λ), with parameters λ =exp(-3.433/0.35) = 5.497e-5 and α = $\frac{1}{\delta}$ = 2.8571, as, time ~ Weibull (2.8571, 5.497e-5).

By substituting the parameters in the final Weibull model , the Weibull hazard regression model that predicts the recovery probability of patients with identical data settings is:

$$h(t;X,\beta) = \lambda\alpha t^{\alpha-1} exp\ (X\beta) = 5.497e\text{-}5 * 2.8571 * t^{1.8571}\ exp\ X\beta \qquad (39)$$

In parametric settings, except for exponential regression models, the baseline hazard function may not be proportional for all subjects as a case of Cox regression model. For the Weibull regression model the baseline hazard vary with $h(t) = \lambda\alpha\, t^{\alpha-1}$; so the base line hazard function of VVOF patients for Metu Hamlin fistula center is given with formula of (40) in every increase in time measured in days:

$$h(t) = 0.000157 * t^{1.8571} \qquad (40)$$

4.3.5.3. ASSESSMENT OF ADEQUACY AND INTERPRETATION OF WEIBULL SURVIVAL MODEL

The likelihood ratio test presented in Table 9 illustrates that the model was good-fit to the data of VVOF patients. And in using the log likelihood, the model has a significant improvement after the covariates are incorporated in the model.

Table 9: The Likelihood Ratio Test of the Final Weibull Regression Model for Recovery Time of VVOF Patients at MHFC.

Loglikelihood(Intercept only)	*Loglikelihood(full model)*	*Chi-square*	*Df*	*P-value*
-703.4	-619.85	160.81	9	<0.0001

Adjusting the other covariates, the hazard rate of VVOF patients whose age at first marriage was below fifteen years was 2.307 times of those patients whose age at first marriage were above twenty years. And hazard rate of patients whose age at first marriage was between 16-20 years was 1.525 times of those patients whose age at first marriage was above twenty years. In another way, this means the hazard rate for those patients with age at first marriage below fifteen years and between 16-20 were 130.7% and 52.5% higher than patients whose age at first marriage was greater than twenty years. Similarly, keeping other covariates constant, the hazard rate of patients whose duration of labor was below two days was 20.8% lower than those patients whose duration of labor was greater than four days. Considering duration of incontinence of patients, the hazard rate of a patients with duration of incontinence of below 3 months were 19.7% lower than those patients with duration of incontinence of greater than 7 months. In the same manner, the hazard rates of patients with duration of incontinence of between 4-7 months were 0.8% lower than those patients with duration of incontinence of greater than 7 months.

For place of delivery, after fixing other covariates constant, the hazard rate of patients who gave birth at home was 1.237 times of those patients who gave birth at health center. In another speaking, patients who gave delivery at home had a hazard rate 23.7% higher than those patients who gave delivery at health center. With regard to mode of delivery, by letting other covariates constant, the hazard rate of patients who delivered with vaginal were 25.1% lower than those who delivered non-vaginal. Similarly, the hazard rate of patients who gave still birth fetal outcome was 19.2% higher than those patients who gave an alive fetal outcome. The other important variable is width of fistula. The hazard rate of patients with fistula width of less than 2 cm was 13.2% lower than those with fistula width between 3-5cm. Finally keeping other covariates constant, the hazard rate of patients with intact urethra were 13.6% larger than those with partially damaged urethra.

4.4 DISCUSSION

VVOF is a health condition caused by the interplay of numerous physical factors and the social, cultural, political and economic situation of women. This study tries to estimate and compare the survival time to recovery probability with a given time of VVOF patients and to determine major predictive factors on the recovery time of VVOF patients. From the study using both model, we found that the factors that significantly affects the recovery status of a patient are age at first marriage, weight, educational status, marital status, antenatal care, duration of labor, duration of incontinence, duration of labor, place of delivery , mode of delivery, fetal outcome, width of fistula hole, and status of urethra.

The Cox's PH model fitted using complete case analysis found twelve variables that can serve as predictive factors on the recovery of VVOF patients. These are age at first marriage, weight, educational status, marital status, antenatal care, duration of incontinence, duration of labor, place of delivery, mode of delivery, fetal outcome, width of fistula hole, and status of urethra.

With regard to the parametric regression models, eight variables were found to be significant to be included in the model .This were age at first marriage, duration of incontinence, duration of labor, place of delivery, mode of delivery, fetal outcome, width of fistula hole, and status of urethra.

Among the above mentioned predictors, age at first marriage was found to be an important factor that affects recovery from VVOF patients. The hazard rate of a patient who had married early before 15 years and married between 16 and 20 is higher than those married after twenty. This result is in line with the study in Ethiopia by Hilton(2003); Muleta(2004) and Tesfaye, 2013. Weight of a patient is also a predisposing factor for the recovery of VVOF patient. This study shows that the hazard rate of a patient with weight < 50kg is higher as compared to those whose weight ≥ 50kg. The finding is in accordance with the study done by (Ahmed et al., 2007); Wall, Karshima, 2004 and Tesfaye, 2013). Educational status is also a prognostic factor that significantly predicts the recovery time of obstetric fistula patient. The hazard rate of a patient who is illiterate was higher than those who are literate. The result is comparable with earlier study (Femi Tinuola and Ada Okau; 2009).

The findings in this study reveal that marriage status is predetermining factor for the recovery of VVOF patients .The hazard rate of a patient were married ,divorced, widowed were higher than those not married but this result doesn't show being married has an advantage in reducing the recovery time than not married. This result is in line with the study by (Femi Tinuola and Ada Okau; 2009) which says even when a woman is not separated from the husband, she could still experience fistula and that whether a woman is separated or divorced from the husband is not a criterion for determining her social and psychological support.

With regard to antenatal care follow up, the study revealed that the hazard rate of a patient who had no follow up of antenatal care is higher than those who had antenatal care follow up. Use of antenatal care follow up improves the chance of recovery. These results confirm the result obtained from the previous studies in Ethiopia (Gessessew et al., 2003 and Tesfaye, 2013). Duration of incontinence is an important predictor for the recovery of obstetric fistula patient. This study shows that the hazard rate of a patient whose duration of incontinence is between 4-7 days and above 7 days is higher than those patients whose duration of incontinence is below 3 days. Duration of labor is also an important predictor for the recovery of obstetric fistula patient. This study shows that the hazard rate of a patient who had labored between 2-4 days and > 4 day is higher than those who labored for < 2 day using both Cox and parametric models. That is, a shorter time of duration of incontinence and obstructed labor is more likely to recover than long time duration of incontinence and labored patient. The result is comparable with the earlier studies (Holme A, Breen M, MacArthur C; 2007; Tebeu et al., 2008' Tesfaye; 2013). Similarly, place of delivery and mode of delivery are significant predictors for recovery time of obstetric fistula patient. The hazard rate of home delivery and non vaginal delivery are higher than those who delivered at health center and those gave delivery vaginally. This result is in accordance with the studies from Niger by (Jonas et al., 1984 ; symmonds, 1984 ; Haroun et al., 2001; Tesfaye, 2013).

However, few results from this study differed from those reported in other studies, especially those from Ampofo et al.(1990) and Tesfaye(2013) which identified height of a patient and length of fistula as significant factor for the recovery time from VVOF. But in this study, height of a patient and length of fistula were not identified as a significant factors for the recovery of VVOF, instead weight of a patient and width of fistula have been found to be significant predictors for recovery of VVOF patient .In other word, smaller size of width of fistula increases the chance of recovery as compared to large size of width of fistula hole.

Among the assumed predictors, status of urethra also had a significant effect on the recovery time of obstetric fistula patient in line with the result by Tesfaye(2013). The finding illustrate that the hazard of recovery from obstetric fistula patient is higher for patients who had complete destructed of urethra than those who had intact and partially damaged of urethra.

Using the same type of variables model comparison between semi-parametric and parametric is carried out using AIC. Cox proportional hazard model was found to be better model than Weibull regression model in fitting to the data on recovery time of VVOF patients considering in this study.

CHAPTER FIVE

5 CONCLUSIONS AND RECOMMENDATIONS

5.1 CONCLUSIONS

Out of 206 patients, 76.2% of them were physically cured while the rest 23.8% were censored. Reports by previous studies conducted on VVOF are in line with some of the characteristics observed in the findings of this study. While it is difficult to attribute VVOF to a particular factor, findings in this study which have been obtained through two different methods reported nearly similar factors as possible causes. In the variable selection procedure with more covariates, when we use LASSO selection procedure, predictors like parity, marital status and accompanying person were also included but the step wise variable selection procedure excluded the above significant predictors which is expected to be predetermining factor.

The Cox regression analysis showed that the major factors that affect the recovery of VVOF patients are age at first marriage, weight, follow up of antenatal care, place of delivery, mode of delivery, duration of labor, duration of incontinence urine, width of fistula hole and status of urethra.

Among the stated factors, group of patients with early age at marriage ,weight below 50kg, illiterate, no follow up of antenatal care, more than four days urine incontinence, labored for more than two days , at home delivery, non-vaginal delivery, still birth fetal outcome, width of fistula greater than 5cm and partially damaged urethra, were less likely to be physically cured. In another aspect, this study also indicated that recovery time of a patient is not statistically different among groups classified current age, height, marital status, accompanying person, length of fistula and bladder size.

For modeling the recovery time of VVOF patients Exponential, Weibull and log logistic parametric regression models were applied. AIC value for log-logistic parametric model is small compared with Weibull regression survival model but the difference is insignificant. Since weibull distiribution is the most commonly used and has wider applicability, it is better to use weibull survival model for recovery time of VVOF patients at Metu Hamlin Fistula Center than the remaining parametric models. By means of step AIC selection the covariates that are selected by the model are age at first marriage, duration of incontinence, duration of labor, place of delivery, mode of delivery, fetal outcome, width of fistula and status of urethra. The Cox proportional regression model provides better predictions to the survival probability of VVOF patients.

5.2 RECOMMENDATIONS

Based on the findings of our study different factors were identified for getting physically cured by VVOF patients. In summary the key recommendations emerging from this study for policy makers, clinicians and the public at large are presented as follows:

- Updating midwifery in health centers with regard to skills including prevention, treatment and care of VVOF; train more community midwives; increase community awareness;
- Serious work must be done on the society on informing and educating the consequence of early marriage before fifteen years. Antenatal care must be given before delivery time especially for those mothers whose weight < 50kg.
- Prolonged labors for more than two day, prolonged urine incontinence and at home delivery with unskilled person have high risk on recovery of VVOF. So proper facilities must be available for pregnant women to come on time to health center before prolonged labour takes place.
- This study shows that main predictive factors for the recovery time of obstetric fistula patients are more health variables. So health workers should be cautious when patient are with partially damaged urethra, large width of fistula, no follow up of antenatal care, prolonged labor and non-vaginal delivery.

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7. APENDICES

Appendix A: The Kaplan-Meier Survival Function Estimates

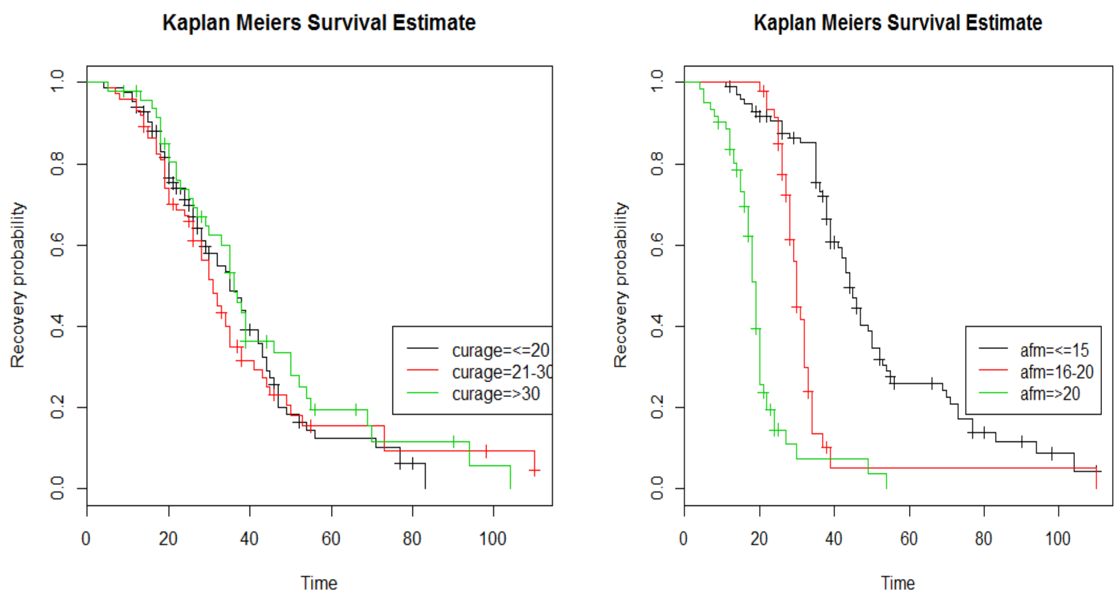

Figure 3: KM estimates of survival for the variable current Age and Age at first marriage

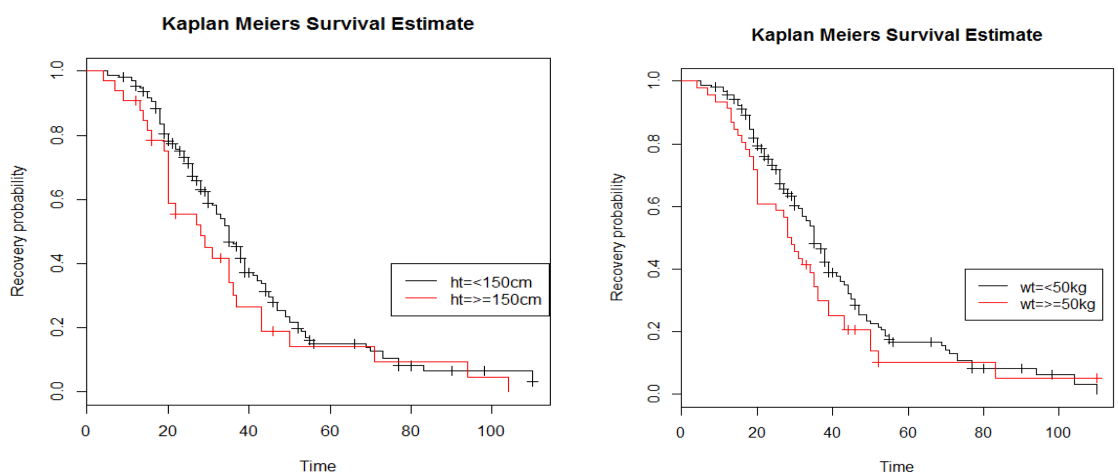

Figure 4: KM estimates of survival for the variable height and weight.

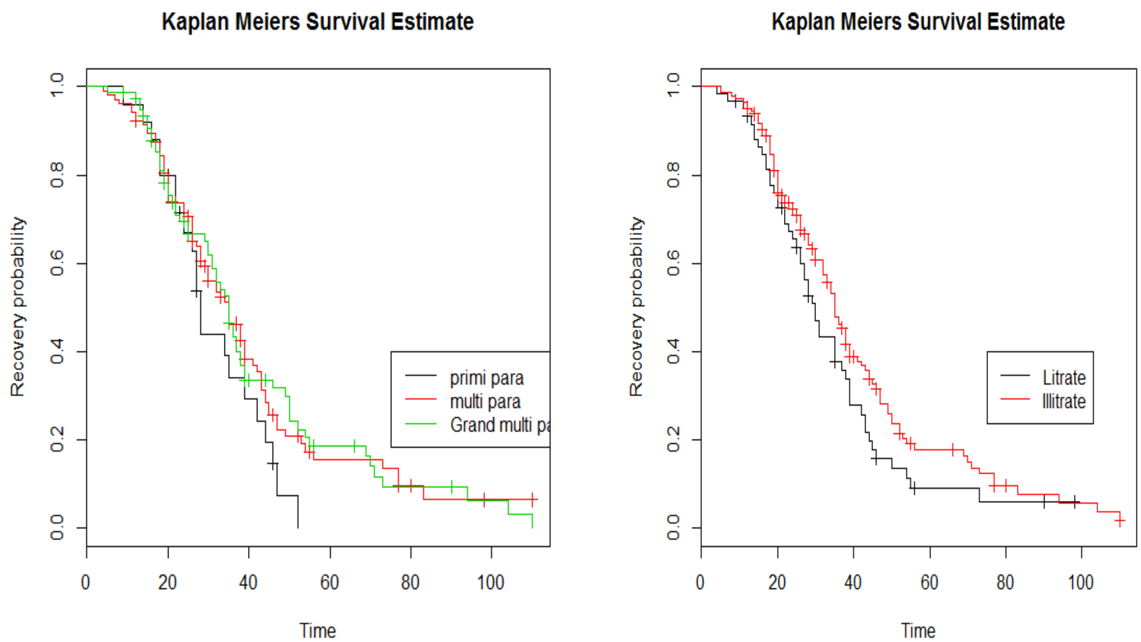

Figure 5: KM estimates of survival for the variable parity and Educational status.

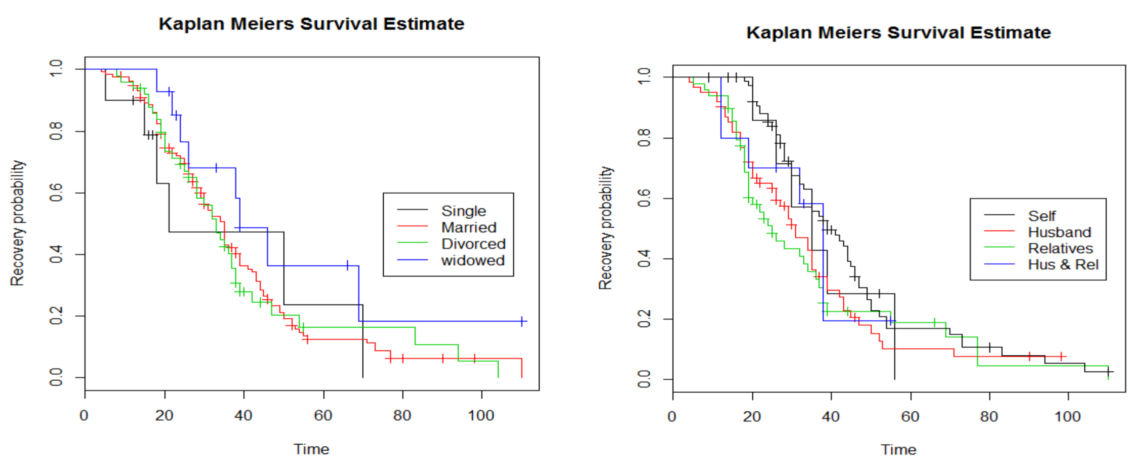

Figure 6: KM estimates of survival for the variable Maritial status and Accompanying person.

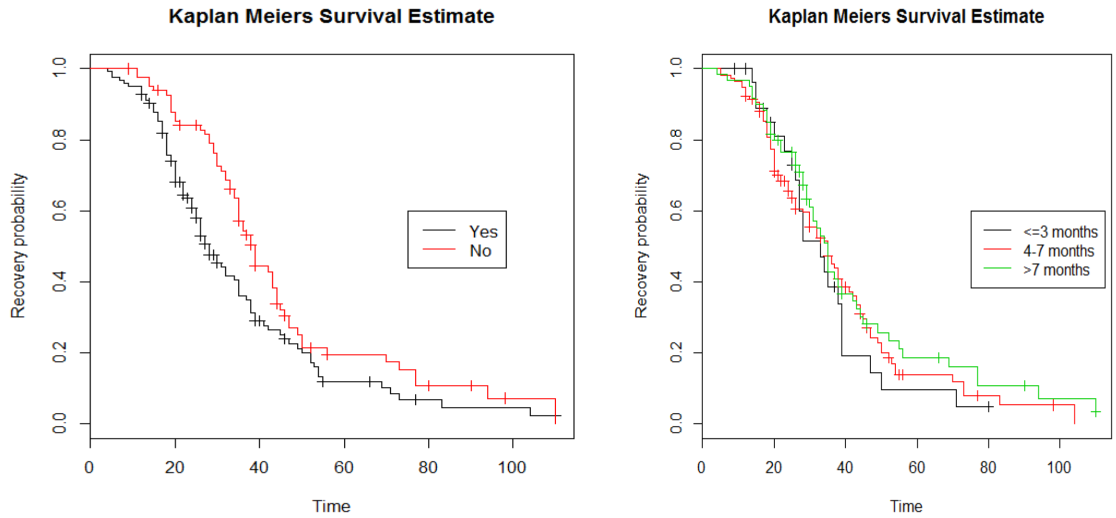

Figure 7: KM estimates of survival for the variable antenatal care and duration of incontinence.

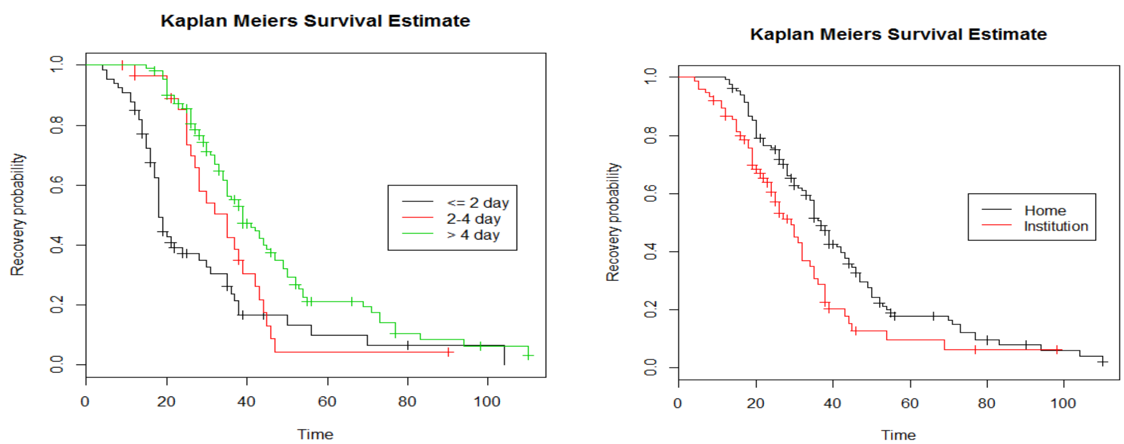

Figure 8: KM estimates of survival for the variable duration of labor and place of delivery

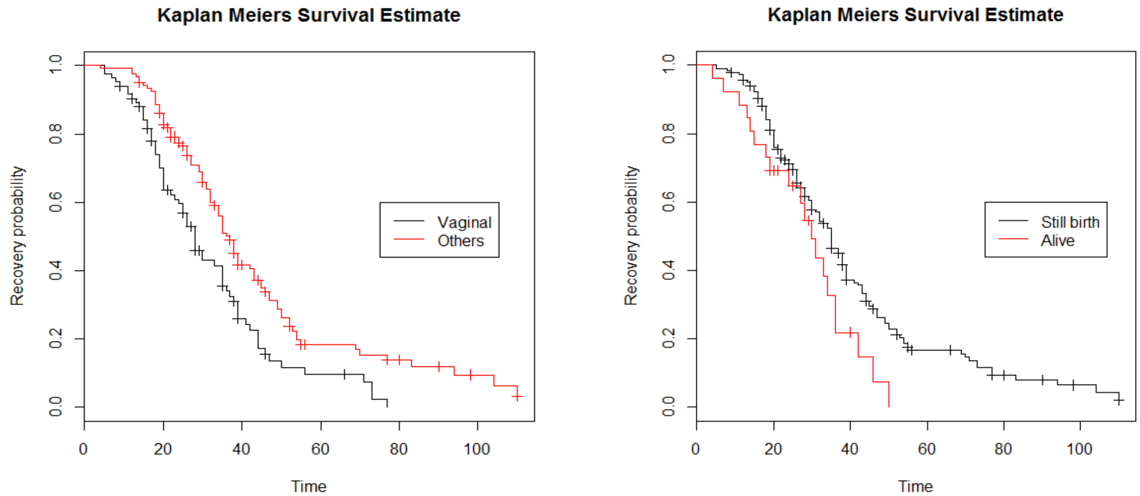

Figure 9: KM estimates of survival for the variable mode of delivery and fetal outcome

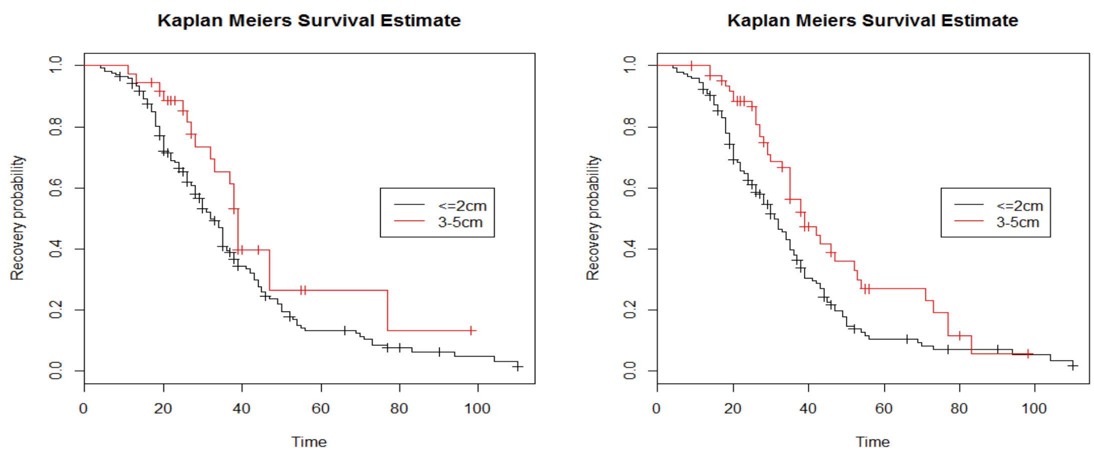

Figure 10: KM estimates of survival for the variable length of fistula and width of fistula

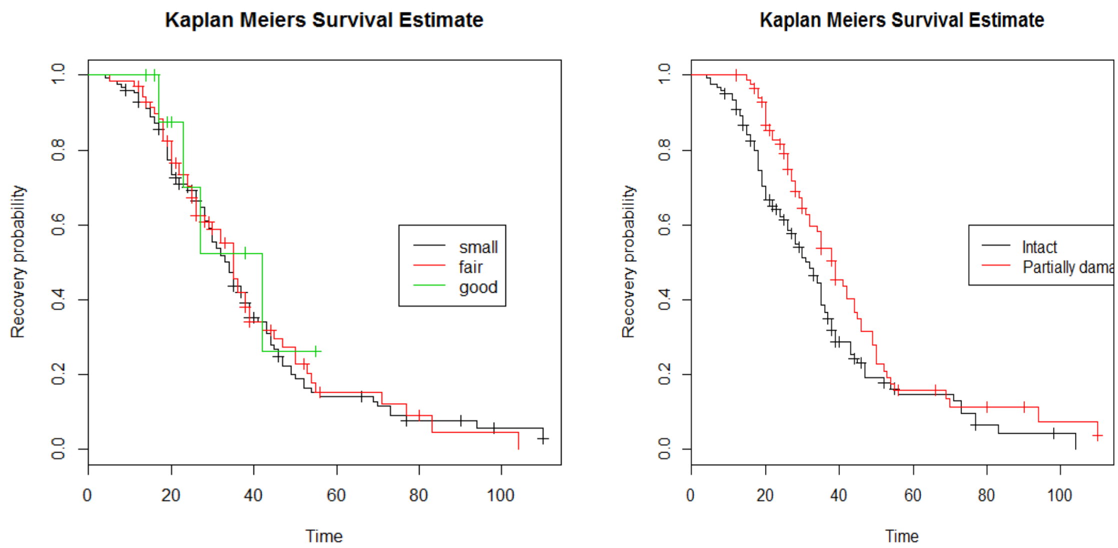

Figure 11: KM estimates of survival for the variable bladder size and status of urethra

Appendix B: Residual plots for model assessment

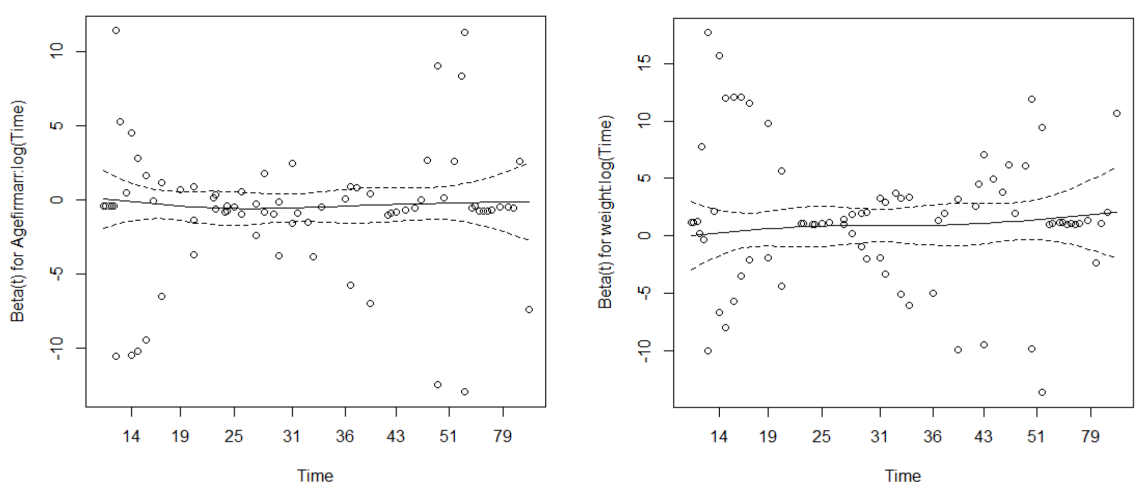

Figure 12: The plot of Scaled Schoenfeld residual for age at first marriage and weight respectively, to check the validity of the PH assumption.

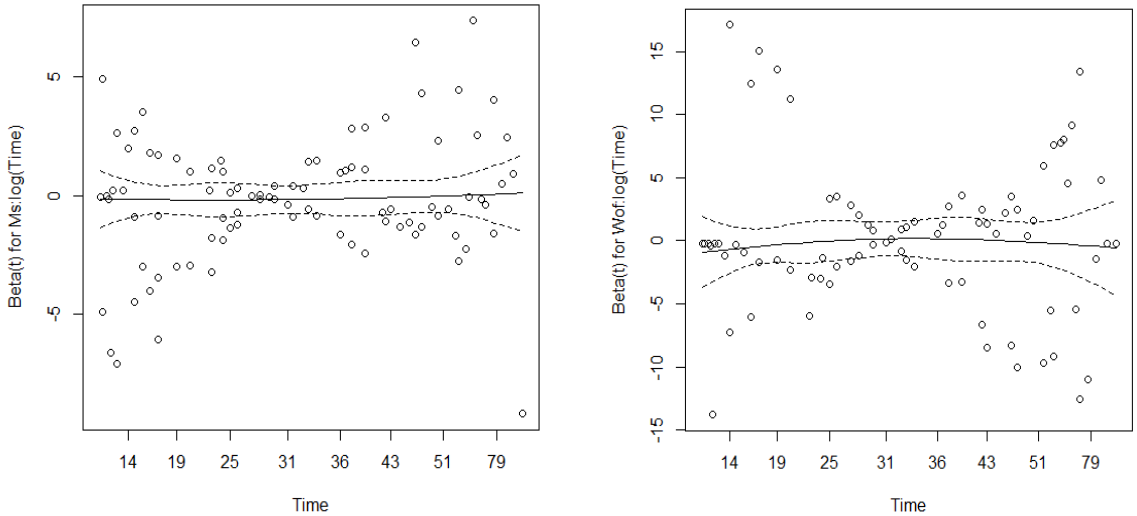

Figure 13: The plot of Scaled Schoenfeld residual for marital status and width of fistula and respectively, to check the validity of the PH assumption

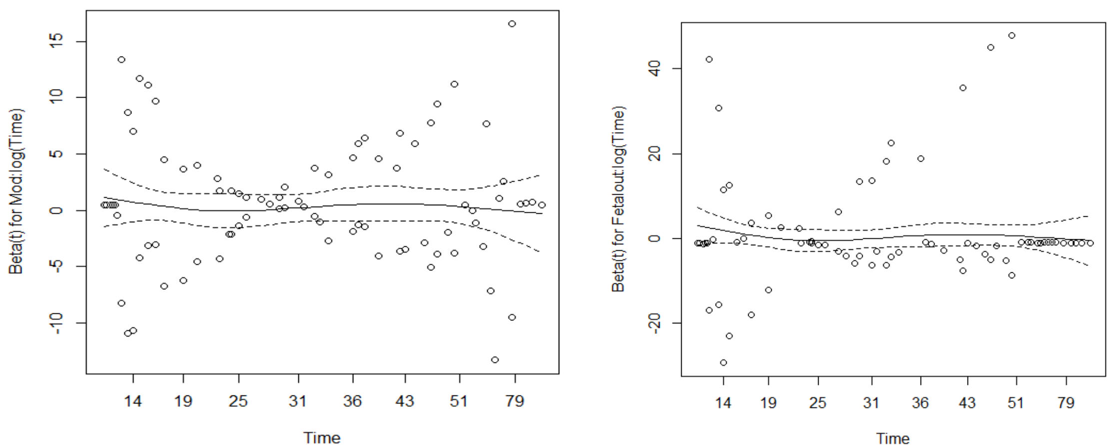

Figure 14: The plot of Scaled Schoenfeld residual for mode of delivery and fetal outcome respectively, to check the validity of the PH assumption

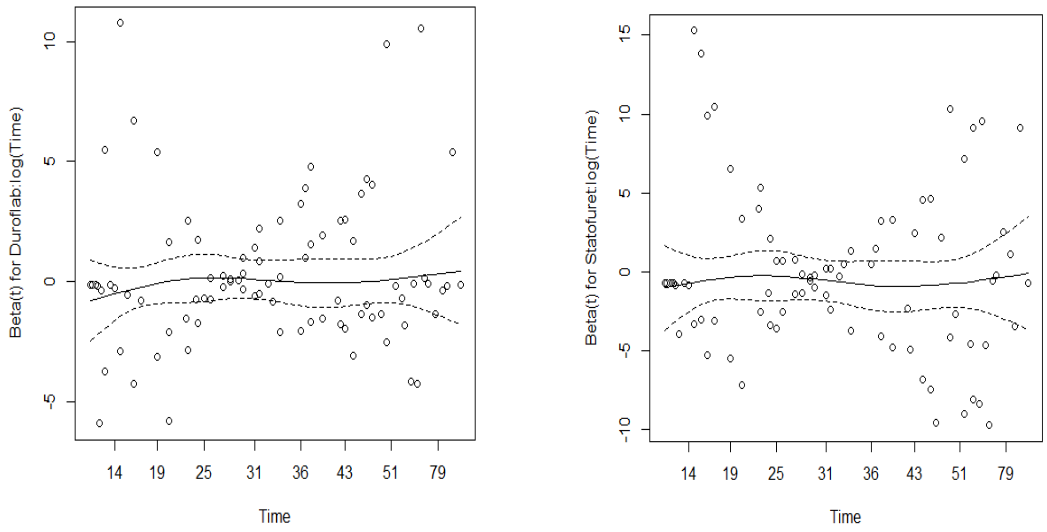

Figure 15: The plot of Scaled Schoenfeld residual for duration of labour and status of urethra respectively, to check the validity of the PH assumption

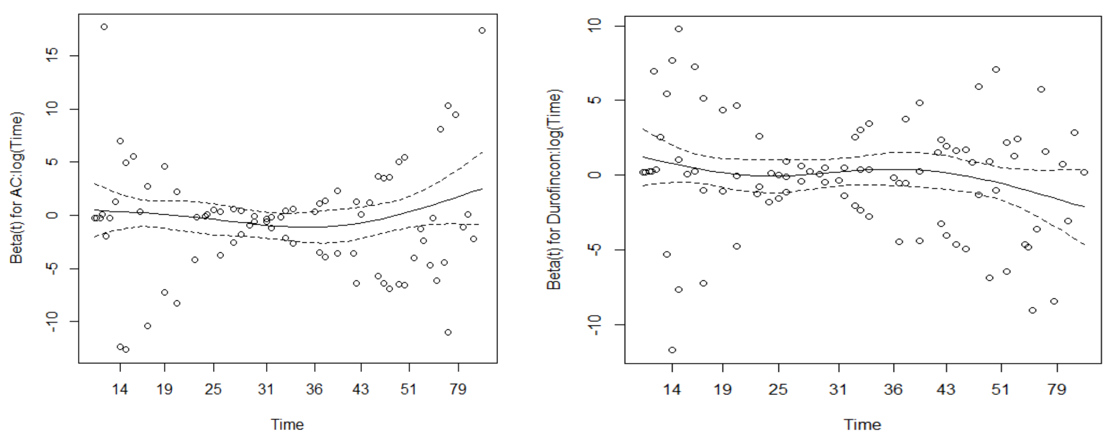

Figure 16: The plot of Scaled Schoenfeld residual for Antenatal care and duration of incontinence respectively, to check the validity of the PH assumption

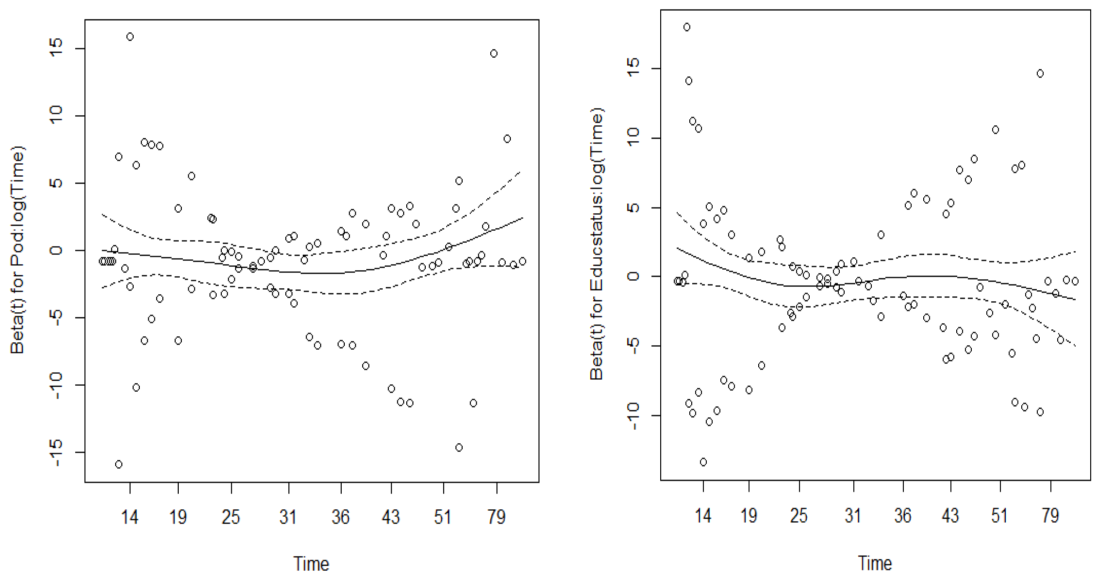

Figure 17: The plot of Scaled Schoenfeld residual for place of delivery and educational status respectively, to check the validity of the PH assumption

Appendix D: Table

Table 10: AIC values for Cox proportional model and weibull survival models

Model	***AIC***
Cox proportional hazard model	1214.71
Weibull	1262.30