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A COMPETING RISKMODELFOR THE RECURRENCETIMEOFKIDENY STONEPATIENTS AFTER SURGERY AT FELEGE HIWOT REFERALHOSPITAL.

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DEPARTMENT OF STATISTICS

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A COMPETING RISKMODELFOR THE RECURRENCETIMEOFKIDENY STONEPATIENTS AFTER SURGERY AT FELEGE HIWOT REFERALHOSPITAL.

BY

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A THESIS SUBMITED TO THE DEPARTMENT OF STATISTICS, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN STATISTICS

Advisor: -Dr. EsseyKebede (Associate professor)

June, 2017

BAHIR DAR

ETHIOPIA

Declaration

I hereby declare that the research work presented in this thesis entitled **"A Competing Risk Model for the Recurrence Time of Kidney Stone Patients after Surgery at FelegeHiwotReferal Hospital"** has been carried out by me and this work, or part thereof, has I, the undersigned, declare that the thesis is my original work, has not been presented for a degree in any other university and that all sources of material used for the thesis have been duly acknowledged.

Derebe KelkaySignature: _____

College of Science

Place of submission: Depatement of Statistics,Bahir Dar University .

Date of Submission: 15/06/2017

CERTIFICATE

I hereby certify that the thesis entitled **"A Competing Risk Model for the Recurrence Time of Kidney Stone Patients after Surgery at FelegeHiwotReferal Hospital"** is a bonafide record of research work done by Mr.DerebeKelkay under my guidance in Bahir Dar University, Ethiopia.I recommend that the hesis be submitted to the department of Statistics.

_____

EsseyKebede (PhD)

Associate Professor,

Department of Statistics,

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Date _____

As a member of the Examining Board of the MSc Thesis Open Defence Examination, I certify that I have read and evaluated the Thesis prepared by and examined the candidate. I recommend that the thesis be accepted as fulfilling the thesis requirement for the degree of Master of Science in Statistics (bio statistics).

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ChairpersonSignatureDate

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External Examiner Signature Date

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Acronyms

AIC	Akaki Information criterion
BIC	Bayesian Information Criterion
CIF	Cumulative Incidence Function
CKD	Chronic Kidney Disease
CRF	Chronic Renal Failure
CS	Case- specific
ER	Emergency Room
ESRD	End Stage Renal Disease
ESWL	Extracorporeal shock wave lithotripsy
GFR	Glomerular Filtration Rate
GP	General Practitioner
LR	likelihood ratio
Min	Minimum
PH	Proportional Hazard
PL	Partial Likely Hood
RAT	Renal Tubular Acidosis

Abstract

*Kidneys are among our most vital organs as they filter toxins and produce essential chemicals in our bodies. Kidney stones are often very painful, and can keep happening in some people. When the kidneys stop functioning properly our body becomes toxic and we cannot survive. Chronic Kidney Disease is a dangerous medical condition characterized by a gradual loss of kidney function over time, which if left untreated can then lead to Chronic Renal Failure (CRF). Once you have reached end-stage chronic renal failure you have two options dialysis for the rest of your life, or a kidney transplant.The objective of this study is to investigate a competing risk model of recurrence time for kidney stone disease after surgery with the consideration of various factors.The study analyzed a competing risk model for recurrence of kidney stone disease after surgery competed by death. A total of 193 patients were taken for this study, which had removal of the disease by surgical. Sub hazard plots of the events and competing risk models of each event separately used to explore the major risk factors and covariates for the recurrence and death rates of a patient in Bahir Dar FelegeHiwotsurgical ward.Based on median time of each even type,the median death time was 6days, the median recurrence and median censor time was 6days. According to sub hazardratiosfor recurrence event hazard the hazard for urban residentswas about 72% higher than rural residents with 95% confidence interval (1.640, 3.058), the hazard of recurrence for out of office workers was around two times than the hazard of unemployed patients with 95% confidence interval (1.960, 4.258**)** and also the hazard of recurrence for in office (civil servants) was around 63% less than the hazard of unemployed patientswith confidence interval (.117, .441), the hazard of recurrence for patients who smoked cigarette was about 6.7% higher than nonsmokers with confidence interval (1.032, 3.563).According to our findings, place of residence had been found a significant effect on the recurrence of kidney stone disease after it removed by surgery on kidney stone patients. Our finding shown that the urban residents had higher hazard of recurrence the disease compared with rural resident patients.According to patient's history of diabetes, diabetic patients had higher hazard of recurrence than non-diabetic patients.*

Key words*:*competing risk model, kidney stone disease, case specific hazards, sub hazard plot, sub hazard model.

CHAPTRE ONE

1.Introduction

1.1. Background

Kidneys are among our most vital organs as they filter toxins and produce essential chemicals in our bodies. The kidneys are fist-size organs that handle the body's fluidand chemical levels. Most people have two kidneys, one oneach side of the spine behind the liver, stomach, pancreasand intestines. Healthy kidneys clean waste from theblood and remove it in the urine. They control the levels ofsodium, potassium and calcium in the blood.The kidneys, ureters and bladder are part of urinarytract. The urinary tract makes, transports, and storesurine in the body. The kidneys make urine from water andbody's waste. The urine then travels down the uretersinto the bladder, where it is stored. Urine leaves the bodythrough the urethra.Kidney stones form in the kidney. Some stones move fromthe kidney into the ureter. The ureters are tubes leadingfrom the kidneys to the bladder. If a stone leaves the kidneyand gets stuck in the ureter, it is called a ureteral stone.Stones in the kidney often do not cause any symptoms andcan go undiagnosed. When a stone leaves the kidney, it travels to the bladder through the ureter, often the stonecan become lodged in the ureter. When the stone blocks theflow of urine out of the kidney, it can cause the kidney toswell (hydronephrosis), often causing a lot of pain.Common symptoms of kidney stones are:

• A sharp, cramping pain in the back and side, oftenmoving to the lower abdomen or groin. Some womensay the pain is worse than childbirth labor pains. The pain often starts suddenly and comes in waves. It can comeand go as the body tries to get rid of the stone.

• A feeling of intense need to urinate.

• Urinating more often or a burning feeling duringurination.

• Urine that is dark or red due to blood. Sometimes urinehas only small amounts of red blood cells that can't beseen with the naked eye.

• Nausea and vomiting.

• Men may feel pain at the tip of their penis.Kidney stones come in many different types and colors.

Calcium stones (80 percent of stones): Calcium stones are the most common type of kidney stone.There are two types of calcium stones: calcium oxalateand calcium phosphate. It has been estimated that 10% of the world's population had some degree of CKD3. It is estimated that 5 million South Africans over the age of 20 years of age have CKD3. Kidney failure in South African adults is mainly due to inherited Hypertension (60-65%) or Type 2 Diabetes (another 20-25%)(Eknoyan et al., 2004). High risk groups include those with diabetes, hypertension and family history of kidney failure (Eknoyan et al., 2004). Kidney failure in the black population is 4 times higher than other groups – due to the high incidence of Hypertension.

- Hypertension causes CKD and CKD causes hypertension (Eknoyan et al., 2004).
- Two simple tests can detect CKD: blood pressure, urine albumin and serum creatinine(Eknoyan et al., 2004).
- Early detection can help prevent the progression of kidney disease to kidney

When the kidneys stop functioning properly our body becomes toxic and we cannot survive. The difficulty lies in the fact that Chronic Kidney Disease is an insidious disease - it often goes undetected as many people whose kidneys are dysfunctional do not develop symptoms until their kidneys are close to failing(Fiseha. et al., 2014). Kidney disease can be check by Glomerular Filtration Rate (GFR)with the measure ofserum creatnine.

A more precise measure of the kidney function can be estimated, how much creatinine is cleared from the body by the kidneys. This is referred to as creatinine clearance and it estimates the rate of filtration by kidneys (glomerular filtration rate, or GFR). The creatinine clearance can be measured in two ways. It can be estimated by using serum (blood) creatinine level, patient's weight, and age. The formula is 140 minus the patient's age in years times their weight in kilograms (times 0.85 for women), divided by 72 times the serum creatinine level in mg/dL. Creatinine clearance can also be more directly measured by collecting a 24-hour urine sample and then drawing a blood sample. The creatinine levels in both urine and blood are determined and compared. Normal creatinine clearance for healthy women is 88-

128 mL/min. and 97 to 137 mL/min. in males (normal levels may vary slightly between labs). Blood urea nitrogen (BUN) level is another indicator of kidney function.

Urea is also a metabolic byproduct which can build up if kidney function is impaired. The BUN-to-creatinine ratio generally provides more precise information about kidney function and its possible underlying cause compared with creatinine level alone. BUN also increases with dehydration(Abdel et al., 2003).

Chronic Kidney Disease is a dangerous medical condition characterized by a gradual loss of kidney function over time, which if left untreated can then lead to Chronic Renal Failure (CRF). Once it reached end-stage chronic renal failure there are two options – dialysis for the rest of the life, or a kidney transplant. Life Renal Dialysis, part of the Life Healthcare Group, is a specialized healthcare service dedicated to treating patients on acute and chronic renal dialysis. These specialized services assist patients in chronic renal failure requiring out-patient chronic services; or requiring peritoneal dialysis at home; or in acute renal failure in an acute hospital facility.

There are most horrific diseases in the world today, it must be very few that outweigh the tight grip of the chronic Kidney Disease. The gravity of the disease is not confined to its being naturally painful. The majority of the people in the world do not have a ready access to the treatment when they are affected by it. The problem of access to treatment is both in terms of people's inability to cross a continent to have medical services such as surgery or dialyses and affordability of the service.

According to the Global Reports on Kidney Decease, people that comprise ten percent of the world population are affected by the disease and millions breathe their last each year. The chronic disease is dominantly prevalent in developing countries. Of more than 2 million people in the world who receive treatment the majority reside in five developed countries like United States, Japan, Germany, Brazil and Germany, according to 2010 Global Burden of Disease Study.Surprisingly, these countries represent only 12 percent of the population. And, only 20 percent are treated in about 100 developing countries that make up over 50 percent of the world population. Renal disease is a major problem in sub-Saharan Africa. Fifty million people suffer from pre-dialysis chronic kidney disease and more than 500,000 individuals are estimated to die annually from renal disease.

Research done with non-Africa populations has identified several genes associated with kidney disease in adults and children. This grant, led by Dr. DwomoaAdufrom the University of Ghana Medical School, studied 8,000 kidney disease patients and unaffected controls using genomic technologies to find whether those genes are also associated with kidney disorders in Africans and whether there were genes that are uniquely associated with kidney disorders in Africans(Yirsaw, 2012).Being part of the developing world, Ethiopia has been a victim of the disease since few years. Fund raising for patients of kidney that need go abroad for treatment was not an uncommon thing in streets of Addis Ababa till recently.To respond to the call for dealing with this harrowing disease here in the country, two- years of efforts were made by Ethiopian born doctors and renowned surgeons from University of Michigan to establish a kidney transplantation center in Ethiopia.

The use of medications to speed the spontaneous passage of stones in the ureter is referred to as medical expulsive therapy. Several agents, including alpha adrenergic blockers (such as tamsulosin) and calcium channel blockers (such as nifedipine),have been found to be effective. Alpha blockers appear to lead to both higher and faster stone clearance rates.Alpha blockers; however, only appear to be effective for stones over 4 mm but less than 10 mm in size. A combination of tamsulosin and a corticosteroid may be better than tamsulosin alone. These treatments also appear to be a useful adjunct to lithotripsy(Morgan and Pearle, 14 March 2016).

Extracorporeal shock wave lithotripsy (ESWL) is a noninvasive technique for the removal of kidney stones. Most ESWL is carried out when the stone is present near the renal pelvis. ESWL involves the use of a lithotripter machine to deliver externally applied, focused, high-intensity pulses of ultrasonic energy to cause fragmentation of a stone over a period of around 30–60 minutes. Following its introduction in the United States in February 1984, ESWL was rapidly and widely accepted as a treatment alternative for renal and ureteral stones(Wang et al., September 2016). It is currently used in the treatment of uncomplicated stones located in the kidney and upper ureter, provided the aggregate stone burden (stone size and number) is less than 20 mm (0.8 in) and the anatomy of the involved kidney is normal.For a stone greater than 10 mm (0.4 in), ESWL may not help break the stone in one treatment; instead, two or three treatments may be needed. Some 80 to 85% of simple renal calculi can be effectively treated with ESWL(Morgan and Pearle, 14 March 2016). Beginning in the mid-1980s, less

invasive treatments such as extracorporeal shock wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy began to replace open surgery as the modalities of choice for the surgical management of urolithiasis(Miller and Lingeman, 2007).

Kidney stonepatients after surgery were follow treatment for some period of time depend on level of disease, each person attained the treatment and their serum creatinine was measured until it became normal but there would death before becoming normal so the data for kidney stone after surgery are survival data with competing risk .In case of that the researcher useda Cox like regression with competing risk (Fine and Gray model) a non-parametric method of survival analysis were apply.

1.2. Statement of the problem

Kidney stones are often very painful, and can keep happening in some people. Kidney stone attacks lead to more than 2 million health care provider visits and 600,000 Emergency Room (ER)visits each year. People tend to get stones in midlife. During midlife, family and work commitments are at their highest, which make kidney stones costly. The diagnosis, treatment and prevention of kidney stones, as well as the lost time from work because of stones, cost almost $5.3 billion each year. Imaging tests to diagnose stones and minimally invasive procedures to treat stones are improving.

Changing diet and using medications can be good ways to stop stones from forming(Anand et al., 2014). This guide will go over how stones are diagnosed and treated, and how they can be prevented. Urine contains many dissolved minerals and salts. When urine has high levels of these minerals and salts, stonescan be formed. Kidney stones can start small but can grow larger in size, even filling the inner hollow structures of the kidney. Some stones stay in the kidney, and do not cause any problems. Sometimes, the kidney stone can travel down the ureter, the tube between the kidney and the bladder. If the stone reaches the bladder, it can be passed out of the body in urine. If the stone becomes lodged in the ureter, it blocks the urine flow from that kidney and causes pain.

Historical evidence has shown a significant increase in kidney stones during the past 100 years, with the exception of the two World Wars. Bladder stone disease still remains a significant medical problem in the developing world(VanDervoort et al., 2007).The world’s

disease profile is changing and chronic diseases are now considerably the leading causes of morbidity and mortality in the world, accounting for 60% of all deaths. One of the chronic diseases of worldwide public health problem is chronic kidney disease (CKD), which recently had an increased prevalence in sub-Saharan Africa. In Ethiopia, kidney stone becomes a leading chronic disease killing at all age levels. Especially at middle age,it is estimated that 6.1% of annual deaths in Ethiopia(Fiseha. et al., 2014). This problem also occurs in Ethiopia and also in Amhara region.Thisresearch paper wasaddressing the following questions.

- What are the factors that affect the recurrencetime of kidney stone patients after surgery?
- Is there recovery difference between categories, like sex, history of diabetes, hypertension, smoking status and alcohol use?
- Is there a competing risk effect on recurrence time?

1.3. Objectives of the study

1.3.1. General objective

- To identify demographic, socio-economic and environmental factors determining the time to recurrence of kidney stone patients after surgery.

1.3.2. Specific objectives

- To identify significant factors affecting time to recurrence after surgery of kidney stone patients.
- To assess recurrencedifferences among categories.
- To assess the influence of competing risk over the event of interest(recurrence).
- Suggest valuable strategies to reduce the progression of kidney stone disease.

1.4. Significance of the study

The following will be few points that can be taken as significance of this study to the users:

- It identifies the effect of the risk factors the available treatments that patients were treated.
- The outcome of the research helps to indicate the recurrence rate and competing risk effect of the patients after surgery in the area.
- It reduces the ambiguities& confusions on comparison of competing risk models specifically in fitting data with two events.
- It helps the government &nongovernmental institution to take evidence based interventions to give aware about factors and covariates that affect kidney stone patients' recurrencetime after surgery.
- It recommendsdifferent methods to control the disease progression.
- It will give clear difference between survival analysis and competing risk model.
- Additionally the study used as a start point for further studies.

CHAPTER TWO

2. Literature review

The literature selected and discussed were related and relevant to this study. Studies related to competing risk analysis on the kidney stone patients recurrence variation after surgery in kidney stone patients was scarce; however the explanatory variables are studied in different studies of kidney stone patients. The literature review given below had several parts; reviewed on the over view, clinical feature and management of the disease, review on determinant factors and review on the study model.

2.1. General overview of kidney stone disease

Kidney stone disease has been a well-known entity for centuries. This has been markedly established by different archeological findings, as well as by writings about painful stone colic and therapeutic trials for stone removal(Eknoyan et al., 2004). In ancient centuries urolithiasis was often a disastrous disease, with a catastrophic outcome all too often leading to the patient's death.

Since the early days, people have wanted to treat kidney stone disease by conservative measures. In this respect a variety of plant ingredients were used, which, according to our experiences today, would lead to an increase in urine volume or reduced pain, or had anti-inflammatory components. Hence, today's (pediatric) nephrologists' approach to stone prevention instead of repeated—although now easy—stone removal is based on historical grounds. Nevertheless, stone disease differed, and still differs, through geographic, socio-economic and even religious boundaries.

2.2. Differences in epidemiology

2.2.1. Geographical distribution

The overall probability that an individual will form stones varies in different parts of the world. The risk of developing urolithiasis in adults appears to be higher in the western hemisphere (5–9% in Europe, 12% in Canada, 13–15% in the USA) than in the eastern hemisphere (1–5%), although the highest risks have been reported in some Asian countries

such as Saudi Arabia (20.1%)(Robertson and Hughes, 1994, Ramello et al., 2000). The incidence of urolithiasis in a given population is dependent on the geographic area, racial distribution, and socio-economic status of the community. Changes in socio-economic conditions over time, and the subsequent changes in dietary habits, have affected not only the incidence but also the site and chemical composition of calculi.

Stone composition has changed substantially over the past decades, with a progressive increase in frequency of calcium oxalate and calcium phosphate stones, even in the eastern hemisphere, where these stones have been traditionally less frequent than uric acid and infection stones.

Recent epidemiology studies from different continents and countries report that calcium oxalate accounts for 60% to 90% of stones in children, followed by calcium phosphate (10–20%), struvite (1–14%), uric acid (5–10%), cystine (1–5%), and mixed or miscellaneous(Al-Eisa, 2002, Perrone et al., 1992, Rizvi et al., 2002, Sarkissian, 2001).Hypercalciuria is recognized worldwide as the most frequent underlying factor in calcium oxalate stones, although, in some countries of the eastern hemisphere, hypocitraturia has been reported as the leading cause (Tekin et al., 2000, Stitchantrakul et al., 2007).

Other less frequent metabolic risk factors reported in that studies are hyperuricosuria and hyperoxaluria. However, increased urinary oxalate excretion might be underestimated and might even be a more prevalent risk factor than hypercalciuria for stone disease in some populations.Struvite or infection-related stones, very common in children until the last century, are rarely seen today in industrialized countries, possibly due to improved management of both pediatric obstructive uropathy and urinary tract infections. Nevertheless, epidemiological studies from various countries continue to report a frequency of struvite stones of between 25% and 38% (Cachat et al., 2004,Djelloul et al.,2006, Daudon et al., Desrez G 2004).

Bladder stones based on malnutrition during the first years of life are currently a frequent finding in various areas of Turkey, Iran, India, China, Indochina and Indonesia, although the incidence is proportionally decreasing as social conditions improve. The incidence of bladder stones has been gradually decreasing during the past 100 years in Europe, with a steeper slope in some Asian countries where this tendency has changed quite significantly since the

1980. This trend defined, as “stone wave”, has been explained in terms of changing social conditions and the consequent changes in eating habits. In Europe, Northern America, Australia, Japan, and, more recently, Saudi Arabia, affluence has spread to all social classes and with it the tendency for individuals to increase protein intake and to eat rich food in large quantities(Trinchieri 1996).

The Afro-Asian stone-forming belt stretches from Sudan, the Arab Republic of Egypt, Saudi Arabia, the United Arab Emirates, the Islamic Republic of Iran, Pakistan, India, Myanmar, Thailand, and Indonesia to the Philippines. In this area of the world, the disease affects all age groups, from less than 1 year old to more than 70 years old, with a male-to-female ratio of 2 to 1. The prevalence of calculi ranges from 4% to 20%(Robertson 2003). The higher prevalence of urolithiasis in many of those countries is possibly determined by the high consanguinity that prevails among ethnic groups that live in those geographical areas and which may reach 72% according to recent studies (Sarkissian, 2001). Several studies from northeast Thailand have confirmed the high prevalence of endemic metabolic disorders such as Renal Tubular Acidosis (RTA) as well as a high prevalence of renal stone and hypocitraturia in the same population.(Sarkissian, 2001). There are few pediatric epidemiologic studies from other countries of the American continent. A study from Venezuela reported that urolithiasis was responsible for 7% of general outpatient consultations in all national children’s hospitals during 1998. In Chile, the reported rate of pediatric urolithiasis was 1.6 in 1,000 pediatric admissions and 4.3% of pediatric nephrology admissions during 2003 (Lagomarsino et al., 2003).In summary, the epidemiology of renal stones with regard to stone composition is continuing to change all over the world towards a predominance of calciumoxalate stones. Major differences in the frequency of the other constituents, particularly uric acid and struvite, reflect particular eating habits and infection risk factors specific to certain population.

2.2.2.Race and gender

Idiopathic stone disease occurs more frequently in white Caucasians than in Blacks, irrespective of the geographic area concerned. In the USA and Brazil, the same 4 to 1 Caucasian-to-Blackratio between stone formers was reported(Robertson and Hughes, 1994). Probably, these differences cannot simply be accounted for by inborn racial factors. Indeed, there was a significant increase in the prevalence of urolithiasis in Black Americans once

they had adopted Caucasian dietary habits (Robertson and Hughes, 1994). With regard to gender distribution, the male-to-female ratio appears to be higher in White populations than in Black Americans and Hispa.

2.2.4. Climate and season

It has been well documented that the incidence of urinary stones is higher in countries with warm or hot climates, probably due to low urinary output and scant fluid intake. Also, in a given population, stone recurrence is higher in summer and fall than in winter and spring. In a North American study the prevalence of stones tended to increase as the average annual temperature (5.2°C in North Dakota to 22°C in Florida) and sunlight index (14.6 in Washington state to 39.7 in Florida) increased (Soucie et al., 1996).

2.2.5. Dietary habits

Epidemiologic observations leave no doubt that diet plays a major, if not the most important, role in the pathogenesis of urolithiasis. Much evidence has been put forward that the consumption of animal protein is closely related to the prevalence of stone disease in a given populationcomposition of urinary calculi.Recent studies report that actual protein consumption in children in Europe and North America is three-time to five-times higher than recommended(Prentice et al., 2004).

A meta-analysis of the data from a variety of studies in children has been used to derive values for the average protein requirements and for a safe level of protein intake. Protein requirements range from 1.12 g/kg per day at age 6 months to 0.74 g/kg per day at 10 years, followed by a small decline towards the adult value in adolescence. Safe values of protein intake are said to range from 1.43 g/kg per day at 6 months to 0.91 g/kg per day at 10 years(Prentice et al., 2004).The higher prevalence of urolithiasis in Saudi Arabia than in the USA and Europe has been ascribed to a high intake of animal protein, which was 10% and 50% higher than in the USA and Europe, respectively. The prevalence of uric acid and calcium oxalate stones also appeared to be influenced by animal protein in the diet.

Kidneys make 150 liters of urine a day, but keep back (reabsorb) 149 liters of useful substances, like protein, and excrete two litters of waste. They can be likened to a huge swimming pool filter which never needs backwashing, and will rarely need an overhaul if

you look after your health. Epidemiological and clinical evidences have shown an increased risk for CKD among individuals with diabetes, hypertension, obesity and infections. Owing to limited publishedreports available so far on the prevalence of CKDpatients in the region, this review suggested a research need for CKD screening.

The world's disease profile is changing and chronic diseases are now considerably the leading cause of morbidity and mortality in the world, accounts for 60% of all deaths. This imperceptible epidemic is an underrated cause of poverty and hampers the economic growth of many countries. Contrary to the common perception, 80% of chronic disease deaths occur in low- and middle-income countries(Bitsori et al., 2004, Eknoyan et al., 2004).One of the chronic disease of a worldwide publichealth problem is chronic kidney disease (CKD),(Bitsori et al., 2004)which recently has an increased prevalence in sub- Saharan Africa(Dardioti et al., 1997).CKD is defined according to the presence or absence of kidney damage and level of kidney function—irrespective of the type of kidney disease (diagnosis).

The disease is now recognized as a global publichealth problem. While the disease magnitude has been better characterized in developed countries; increasing evidence shows developing countries to receive even the greater burden. CKD and, to a greater extent, end-stage renal disease (ESRD),contribute substantially to the disparate burden of illness, disability and premature death across sex, age, race/ethnicity, socioeconomic status, and geographic boundaries(Sachs, 2003).Epidemiological and clinical evidences haveshown an increased risk for CKD among individuals with certain clinical and socio-demographic characteristics(Bitsori et al., 2004).Cohort studies identified hypertension, diabetes, hyperlipidemia, obesity, and smoking as risk factors or markers in the general population for the development of CKD(Abdel et al., 2003, Sachs, 2003). However, in some places in Sri Lanka and Nicaragua, the conventional risk factors were not associated with the disease prevalence(Ganem and Carson, 1999, Riethe, 2005).

According to an extensive review made by Barsoum2006,(Antonello et al., 2002)chronic glomerulonephritis and interstitial nephritis are currently the principal causes of CKD in developing countries, reflecting the high prevalence of bacterial, viral, and parasitic infections that affect the kidneys(Haddad et al., 1994).

The risk for clinical CKD remainedincreased in stone formers (HR 1.50; 95% CI 1.32 to 1.70). Theincreased risk for clinical CKD among the stone formersremained statistically significant and did not change substantivelyafter adjustment for age, gender, and co morbidities.Diabetic nephropathy is estimated to be prevalentin South Africa (14.5–16.7%), Zambia (23.8%),Egypt (12.4%), Sudan (8.9–9.2%), and Ethiopia (6.1%)(Vandenbroucke and 2001) In addition, it was estimated that by the year 2030, more than 70% of patients withESRD will be residents of developing countriesdemanding organizational and financial resourcesfor the prevention and early detection of CKD(Haddad et al., 1994).This substantial burden on healthcare resources isas a result of the progressive nature of CKD and the ensuing ESRD.

A research identifying the featureof this rapidly increasing disease in a particulargeography has fundamental academic, clinical andepidemiological importance, which helps in therecognition of specific risk factors and subsequentplanning for adequate prevention. Within 120 days of the initial procedure, approximately 1 in 5 individuals (10 038 of 47 851 [21.0%]) underwent an additional procedure to fragment or remove urinary stones. (Antonello et al., 2002, Abdel et al., 2003).

Several studies was presented about kidney stone disease with cross-sectional method whether they survive or not, survival analysis under standard product-limit method and also based on both non-parametric and parametric survival regression models.It has frequently been pointed out that in presence of competing risks, the standard product-limit method of describing the distribution of time-to-event yields biased results.

The main assumption of this method is that any subject whose survival time is censored would experience the event of interest if followed up long enough this assumption is not only for product-limit method but also for Cox regression and parametric survival models. This does not hold if competing risks are present, as the occurrence of the event of interest is made impossible by an antecedent competing event. As a remedy, the cumulative incidence estimatesemi parametric survival models with competing risk eventproposed by (Kalbeisch. and . 1980) was apply to estimate case specific cumulative incidences.

CHAPTER THREE

3. Methodology

3.1.Study area and design

3.1.1.Study area

The study was conducted atFelegeHiwot referral hospital, which is found in Bahir Dar city. The hospital is located in Bahir Dar city, in Northwest of AmharaRegion, at a distance of 565 kilometres from Addis Ababa, the capital city of Ethiopia.

3.2. Data type

The data was retrospective survival data and it is secondary data that were found at FelegeHiwot referral Hospital which was followed up by physicians from September 01, 2014 to March 8, 2017 to know the recent problem of kidney stone recurrence after it removed by surgery.

3.3. Study design

There are many techniques of study design in statistical methods. Among those, this study was apply retrospective survival data analyses with competing risk study design used to assess the recurrence and death time that were treated under kidney stone. In this study kidney stone patients who had surgical treatment were included. We used all patients' id that was admitted in kidney stone case and we included patients who have kidney stone surgery from the sampling frame of kidney stone patients who are hospitalized from September 01, 2014 to March 8, 2017 which is found at FelegeHiwot Referral Hospital.

3.4. Variables included in the model

3.4.1. Response variable

- The response or outcome variable for this study is Recurrence time records of hospitalized kidney stone cases for consecutive day visits by the professionals (doctors, nurses or care givers etc).

3.4.2. Explanatory variables

The explanatory variables for this study are:-

- Age:- continuous
- Sex:- male or female (female=0, male=1)
- marital status:-single, married, , divorced, widowed(0,1,2 &3 respectively)
- Education:- illiterate, literate(0 &1)
- Residence:- Rural or urban (0 &1)
- Type of work:- unemployed, office or outside office(0,1&2)
- history of diabetes mellitus:- yes or no (1&0)
- hypertension:-yes or no (1 &0)
- smoking status:- yes or no (1 &0)
- Alcohol use:- yes or no(1& 0)
- Weight:- continuous

3.5 Eligibility criteria

- Kidney stone patients who have surgery are included, because kidney disease has no any symptom until the stage of removal by this method. But in some case the stone removed without surgery.
- Patients follow up by physicians until they complete their surgical time in the hospital are included, but exclude patients who gave referral after surgery and who are followed back.

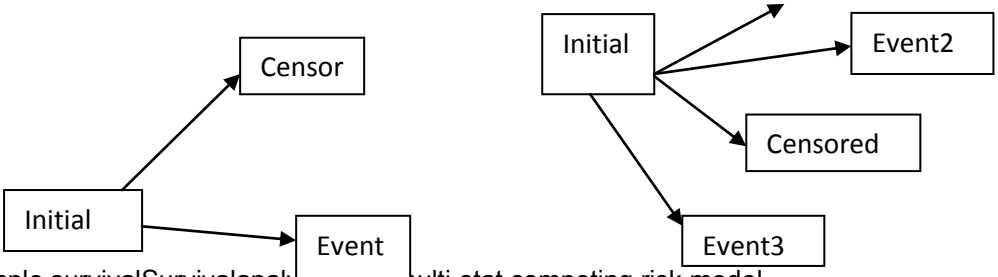
3.6 Data processing and analysis

The collected data was entered and analyzed usingSTATA version 12. Basic descriptive statistics and a profile plot of the median survival timeover the period of the study were used to explore the data.Univar able and multivariable analysis was included.

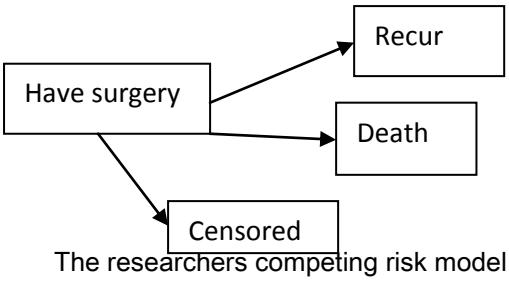
3.6.1. Competing risk Model

Competing risks arise in the analysis of time-to-event data, if the event of interest is impossible to observe due to a different type of event occurring before. Competing risks may be encountered, e.g., if interest focuses on a specific cause of death, or if time to a non-

fatalevent such as stroke or myocardial infarction is studied. In both situations, death from a non-disease-related cause would constitute the competing risk. Competing risks arise when individuals can experience any one of J distinct event types and the occurrence ofone type of event prevents the occurrence of other types of events or alters the probability of occurrence of the other event. For the analysis of competing risks data, standard survival analysis should not be applied. Parallel to the standard survival analysis, competing risks data analysis includes estimation of the cumulative incidence of an event of interest in the presence of competing risks, comparison of cumulative incidence curves in the presence of competing risks, and competing risks regression analysis applied(Gray, 1988). The assumption of independence is untestable and unjustifiable in the competing risks setting in which the biological mechanisms among risks of events may be either unknown or likely interdependent.



Simple survivalSurvivalanaly ulti-stat competing risk model



The researchers competing risk model

3.6.1.1 Approaches

Failure time in the competing risks setting can be described univariately or multivariate.

3.6.1.1.1. Traditional (latent failure times) Approach

$(T_1,\cdots,T_k)$:k latent failure times, where T_i is the time to failure of cause i, $(i = 1,\cdots,k)$

$T = \min(T_1,\cdots,T_k)$ since only one of the failures can occur.

Accounting for censoring, the observable quantities are (Y, I), where Y = C if I = 0, and Y = T andI = i if an event occurs with a failure type i, ($i = 1, 2, \cdots, k$).

- Focused on cause-specific hazard

Because the latent approach is based on multivariate failure times, the cause-specific hazard for anevent of interest is derived from a joint and marginal survivor functions.The joint distribution of competing risks failure times is unidentifiable unless failure times areindependent (Gray, 1988).Even though competing risks are observable, observations of (Y, I) give no information on whetherfailure times are independent or not andthe assumption of independence is untestable and unjustifiable in the competing risks setting in whichthe biological mechanisms among risks of events may be either unknown or likely interdependent.

3.6.1.1.2. Modern Approach based on sub-distribution function

T: denote time to an event

C: censoring time

$Y = \min(T, C)$: observed failure time

$I = i$ ($i = 1, 2, \cdots, k$) for failure type i

(Y, I): observable quantities

• Focus on cumulative incidence function of cause i directly

• No independence assumptiondefinitions:-

Suppose there are k distinct types of failure.

• Overall hazard function at time t

$\lambda(t) = \lim_{u \to 0} \frac{1}{u} prob(t \leq T < t | T \geq T)$

Cause-specific (CS) hazard

$\lambda i(t)=\lim_{u\to 0}\frac{1}{u}prob(\ t \le T < t+u, I=i|T \ge t) i=1,2,\dots,k$

$\lambda_i(t)$ represents the instantaneous rate for failure of type i at time t in the presence of other failuretypes.

CS Cumulative hazard function

$\Lambda_i(t) = \int_0^t \lambda_i(u)du$ andCS Survival function is $S_i(t) = \exp[-\Lambda_i(t)]$

If only one of the failure types can occur for each individual, then $\lambda(t) = \sum_{i=1}^{k} \lambda_I(t)$and

$S(t) = P(T > t) = exp[-\sum_{i=1}^{k} \Lambda_i(t)]$.

Sub-density function for failure i

$f_i(t) = \lim_{u\to 0}\frac{1}{u}prob(\ t \le T < t+u, I=i) = \lambda_i(t)S(t)$, i = 1, … , k. Thus $\lambda_i(t) = \frac{f_i(t)}{S(t)}$

Cumulative incidence function (CIF) of case $i, F_i(t) = prob(T \le t, I=i) = \int_0^t f_i(u)du =$ $0t\lambda iuSudu$fori = 1, ⋯ , k. This is also called sub-distribution function.

As t →∞,$F_i(\infty) = prob(I=i) = p_i < 1\ where\ \sum_o^k p_i = 1$

CIF for cause i ignoring other causes

$F_i^*(t) = \int_0^t \lambda_i(u)S_i^*(u)du$, Where $S_i^*(t)$ is a cause-specific survival function for cause i censoring competing risks.$F_i^*(t) + S_i^*(t) = 1$.Because events from causes other than i are treated as censored in $S_i^*(t)$, $S(t) \le S_i^*(t)$, and thus$F_i(t) \le F_i^*(t)$.$S_i^*(t)$ is used in the standard survival analysis and it is biased if there are competing risks.Since no one-to-one relationship exists between the cause-specific hazard and the CIF for failure i, thecomparison of cause specific hazards of failure i between different groups can be quite different fromthe comparison of the cumulative incidence of failure i.To be able to directly compare sub distributionfunctions, (Gray, 1988)further defined ahazard function that corresponds to the sub distribution. Sub distribution hazard for failure i is

$$\gamma_i(t) = \lim_{u\to 0}\frac{1}{u}\Pr\{t \le T < t+u, I=i|T \ge t \cup (T \le t \cap I \ne i)\} = \frac{f_i(t)}{1-F_i(t)}$$

Sub distribution hazard: probability of observing an event of interest in the next time interval giventhat either the event did not occur until that time or that the competing risks eventoccurred.

3.6.2. Estimation of Cumulative Incidence Function

If t is discrete, the hazard of failing from cause i is$\lambda_i(t_j) = \frac{prob\ (T=t_j, I=i)}{prob\ (T>t_j-1)}, j = 1, \dots, t-1$ and the estimate is $\hat{\lambda}_i(tj) = \frac{d_{ij}}{n_j}$ whered_{ij} is the number of failures of cause i at time t_j and n_j is the number of subjects at risk justprior to t_j.

Let $d_i = \sum_{i=1}^{k} d_{ij}$ and $\hat{\lambda}(t_j) = \sum_{i=1}^{k} \hat{\lambda}_i(t_j)$.

Then the KM estimate of the overall survival functionis $\hat{S}(t) = \prod_{j:tj<t}(1 - \hat{\lambda}(t_j)) = \prod_{j:t_j<t}(1 - \frac{d_j}{n_j})$.Thus, the estimate of the CIF is$\hat{F}_i(t) = \sum_{j:t_j<t} \frac{d_j}{n_j} \hat{S}(t_j - 1)$.

3.6.3. Fine and Gray model

Analysis of competing risks data based on the cause-specific hazard using Coxregression can be conducted in statistical standard software packages by implementingclassical Cox regression treating failures from the cause of interest as events andfailures from other causes as censored observations. A Cox PH like model for the sub distribution hazard(Fine and Gray, 1999). The model uses the partial likelihood principle and weighted estimated equations to obtain consistent estimators of the covariate effects.Let $\gamma_1(t; X)$ be the sub-distribution hazard for failure 1, conditional on the covariates, X. In this model the base line hazard ratio is assumption free.

$\gamma_1(t;X) = \lim_{u\to 0} \frac{1}{u} \text{Prob}\{t \le T < t+u, I = 1 | T \ge t \cup (T \le t \cap I \neq 1), X\} = \frac{f_1(t,X)}{1-F_1(t,X)} = \gamma_{10}(t) \exp(X'\beta)$. Where $\gamma_{10}(t)$ is the baseline hazard of the sub-distribution, F_1, X is the vector of covariates, and β is the vector of coefficients. The risk set is$R_i = j : \{(\min(Cj, Tj) \ge Ti) \cup (Tj \le Ti \cap I \neq 1 \cap Cj \ge Ti)\}$

{Those who have no failed from any case}{Those who have failed from another cause}

The cause-specific hazards "completely determinethe competing risks process", so cumulative incidence functions can be estimated from Separate cause-specific hazard regression models for all types of event.

3.7. Parameter Estimation technique

In order to estimate the coefficients of both the event of interest and competing risk we will use partial likelihood estimation techniques since partial likelihood estimates the parameters without concerning the values of censored observations, so it is better than maximum likelihood method. The risk set is improper and unnatural since in reality those individuals who failed from causes otherthan failure 1 prior to time $t_i$cannot be "at risk" at t_i.Although the risk set is unnatural, it leads to a proper PL for the improper $F_1(t;X)$.The partial likelihood function is

$PL(\beta) = \prod_j \sum_{i\epsilon R_j} \frac{exp(X_i\beta)}{w_{ij}(t)\exp(X_i\beta)}$,a choice of weight is$w_{ij}(t) = \frac{\hat{G}(t_i)}{\hat{G}(t_i \cap t_j)}$where$\hat{G}$ is theKaplan-Meier estimate of the survivor function of the censoring distribution. The weight is 1 for those who did not experience any event by time t_i and ≤ 1 for those who experienced a Competing risk event before time t_i. i.e., individuals experiencing a competing risk event are not fullycounted in the PL.As in the Cox partial likelihood function, taking derivatives with respect to β to the log partial likelihood function gives the score statistic(Han and Hausman, 1990)

$U(\beta) = \{\sum_j^l \{X_j - \frac{\sum_{r\epsilon R_{J-1}} w_{ij}(t)X_r\ exp(X_r\beta)}{\sum_{r\epsilon R_j} w_{ij}(t)X_r\ exp(X_r\beta)}\}$ $\widehat{B}$ is then the value which maximizes the score function.

3.8. Parameter interpretation

Parameter interpretation is giving credits for the effects of the determinant covariates and factors. Our model contains categorical and continues variables. Independent variables wereinterpret as the hazard rate of that categorycompare with the baseline(reference) category by considering one category as reference category and the rest variables are ignored. In continues variable thecase specific hazard shows us the hazard rate per aunit change of the explanatory variable by considering the rest variables constant.

3.9. Model Building

Model selection approaches with special emphasis on information-theoretic criteria (i.e. AIC, BIC and −2Logˆ L). Selection among a suite of models has become a common approach to interpretation of complex biological systems. If one chooses a model selection approach, be reminded that "Although selection procedures are helpful exploratory tools, the model-building process should utilize theory and common sense"(Burnham and Anderson, 2004). Beware of model dredging with too many a priorimodels; i.e. going on a fishing trip with model selection procedures). An important point to remember concerning model selection is that all of the procedures select the 'best' fit models from theprioriopti ons in a relative framework.

Information-theory developed in the 1950s and was quantified in statistics with Akaike Information Criterion in the 1970s. No attempt will be make to detail the theory or procedures here. An extensive summary of information theoretic criteria involving model parsimony and the practical use of model inference can be found in (Kuha, 2004) and (Burnham and Anderson, 2004) respectively. AIC is a valid procedure to compare non-nested models. AIC is a better estimator of predictive accuracy, whereas BIC is a better criterion for determining process.Accepting partial likelihood as method for measuring how well a model fits data, i.e., Accuracy Measure = E[log likelihood of the fitted], AIC is an unbiased estimator of −2LogL.

AIC = −2Logˆ L+ 2 * p where ˆ L is the maximized likelihood function, p is the number of parameters in the model.Since Log (L) increases as the number of parameters increases, 2*p serves as a penalty term.Bayesian Information Criterion (BIC): Tends to smaller models than AIC (due to an extra penalty for parameters when n<7.4)(Akaike, 1998), proponents of BIC state, "In general, models chosen by BIC will be more parsimonious than those chosen by AIC." While detractors contend that BIC under fits the data and introduces bias in the form of overestimating precision. Both AIC and BIC the smaller value is the best.

3.10. Model diagnostics

The process of model checking for competing model is same to survival with a separate diagnose the event of interest and competing event. The Martingale or Deviance residual is used to assess adequacy of the regression assumptions of predictors and functional forms of

predictors.The martingal residual is the difference between the observed and expected number of deaths in the time interval $(0,t_i)$ for the i^{th} individual. The deviance residuals are similar to martingal residuals but more symmetrically distributed than martingal residual. An index plot of both deviance and martngal residuals highlight individuals whose survival time not well fited by the model and its out of line.And also, influantial observations over estimated parameters are tested by DFBETA.

3.11. Model Adequacy checking

Tests for the significance of the effects in the model can be performed via the Wald statistic, the likelihood ratio (LR), or score statistic. Detailed descriptions of these tests can be found in (Thomas, 1981). The Wald statistic which is computed as the generalized inner product of the parameter estimates with the respective variance-covariance matrix is an easily computed, efficient statistic for testing the significance of effects.

To test the null hypothesis of no effect ($H_0: \hat{B} = 0$), one can use

$$w^2 = (\frac{\hat{\beta}}{se(\hat{\beta})})^2$$

Where, $\hat{\beta}$ is the corresponding estimated regression coefficient and $se(\hat{\beta})$ is estimate of the standard error of$\hat{\beta}$. This test statistics has the chi-square distribution with one degree of freedom.The score statistic is obtained from the generalized inner product of the score vector with the Hessian matrix (the matrix of the second-order partial derivatives of the maximum likelihood parameter estimates). The likelihood ratio (LR) test requires the greatest computational effort (another iterative estimation procedure) and is thus not as fast as the first two methods; however, the LR test provides the most asymptotically efficient test known. For details concerning these different test statistics,see(Thomas, 1981). LR is the ratio of two likelihoods. This means likelihood of the null (likelihood without effect) and the alternative (likelihood with effect).

3.12. Ethical considerations

Ethical clearance and approval to conduct the research obtained from Bihar Dar University College of Science, College of science research and Ethical committee. Official letter from

department of Statistics was written to Felege-Hiwote Referral Hospital. Then, informed verbal consent was obtained from Felege-Hiwote referral hospital manager, after explained the objective of the study. Privacy of the patients maintained, and cultural norms respected properly. Other responsible authorities were also informed to contribute their support and commitment to the study.

3.13. Dissemination of the results

The final report has been disseminated to the Department of Statistics, Bihar Dar University. Also the study findings will be disseminated to the, regional health bureau, respectivehealth facility. Attempts will be made to publish the findings in scientific journal.

CHAPTER FOUR

ANALYSIS ANDRESULTS

4. Introduction

The results of the study are discussed in this chapter. The response variable, Recurrence time of Kidney stone patients after surgery is recorded until one event occurred, survive and not recurrence (censored), death or recurrence. The glomular filtration rate of patients is measured based on their weight, sex and serum creatinine.In this study competing risk model is used to see the progression effect magnitude between the proposed independent variables and the response variable.

4.1. DESCRIPTIVE STATISTICS

4.1.1. Summary Statistics for categorical variables

The medical cards of 193 kidney stone patients have been reviewed and all of these 193 patients stayed until one event occurred on them (i.e censored, death or recurrence). Among 193 cases, 72 (37.31%) were females and 121(62.69%) were males. The status category proportion showed 106(54.92%) of them were censored, 38(19.69%) of them died, and the rest 49(25.39%) of them had recurrence. Among 193 cases, 74(38.34%)came from rural area and 119(61.66%) of them came from urban area and 116(60.1%) were educated(from literate up to higher levels) and the rest 77(39.9%) of them were uneducated(illiterate).

Among 193 cases, 55(28.5%) patients were unemployed, 92(46.67%) patients worked out of office and the rest 46(23.83%) patients worked in office. Among 193 cases, 55(28.5%) were single, 129(66.84%) were married, 4(2.07%) were divorced and the rest 5(2.59%) were widowed and 178(92.23%) were nonsmoker and the rest 15(7.77%) were smoker. Based on alcohol use history 159(82.38%) patients had no alcohol use history and the rest 34(17.62%) patients had alcohol use history. Among 193 cases, 173(89.64%) were have no history of diabetes and the rest 20(10.36%) had history of diabetes and 160(82.9%) had no history of hypertension and the rest 33(17.1%) hadhypertension history. All the results have been summarized in Table 4.1.

Table 4.1;descriptive statistics summary of categorical variables

Categorical variable	Level	No of observation(N)	Percent (%)	Cumulative %
Sex	Male	121	62.69	62.69
	Female	72	37.31	100.00
Status	Censored	106	54.92	54.92
	Death	38	19.69	74.61
	Recur	49	25.39	100.00
Residence	Rural	74	38.34	38.34
	Urban	119	61.66	100.00
Education level	Educated	116	60.10	60.10
	Uneducated	77	39.90	100.00
Type of work	No work	55	28.50	28.50
	Out of office	92	47.67	76.17
	In office	46	23.83	100.00
Smoking history	Yes	15	7.77	7.77
	No	178	92.23	100.00
Alcohol use history	Yes	34	17.62	17.62
	No	159	82.38	100.00
History of diabetes	Yes	20	10.36	10.36
	No	173	89.64	100.00
Marital status	Single	55	28.50	25.50
	Married	129	66.84	95.34
	Divorced	4	2.07	97.41
	Widowed	5	2.59	100.00
History of hypertension	Yes	33	17.10	17.10
	No	160	82.90	100.00

4.1.2. Summary statistics for categorical variables based on each type of event withcorresponding median time

The total medical cards of 193 kidney stone patients have been reviewed and among these 38 weredie, the kidney stone was recur on 49 patients and the rest 106 patients were censored The gender category proportion based on event death showed 25(65.79%) of them were males with median death time of 6 days and 12(34.21%) of them are females out of 38 died patients with median death time of 5 days. Among 49 recurrence event 32(65.31%) were males with median recurrence time of 6 days and the rest 17(34.69%) were females with median recur time of 7 days. On the other hand, among 106 censored events 64(60.38%) were males with median censor time of 6 days and 42(39.62%)were females with median censor time of 6 days. From 38 death events 17(44.74%)were educated with median death time of 8 days and 21(55.26%) are uneducated with median death time of 5.5 days. Among 49 recurrence events 28(57.14%) were educated with median time 6 days and the rest 21(42.86%) were uneducated with median recur time of 7 days. Among 106 censor events 71(66.98%) are educated with median censor time of 5 days, 35(33.02%) were uneducated with mediancensor time of 6 days.

Among 38 death events 16(42.11%) lived in rural area with median death time of 5.5 days and 22(57.89%) lived in urban areas with median death time of 5.5 days. Based on recur event from 49 patients 16(32.65%) lived in rural areas with media recur time 6 days and 33(67.35%) lived in urban areas with median recur time of 7.5 days. From 106 censor event 42(39.62%) lived in rural areas with median censor time of 6days and 64(60.38%) lived in urban areas with median survival time of 6 days. Among 38 death event 11(28.95%)had no work, 23(60.53%) worked out of office and 4(0.53%) worked in office with median death time of 5days, 5 days and 10.5 days respectively. Based on recur event 11(22.45%) had no work, 26(53.06%) worked out of office and 12(24.49%) worked in office with their corresponding median recur time of 9 days, 6.5 days and 5 days respectively. On the other hand from 106 censored event 33(31.13%) were have no work with median censored time of 6 days, 43(40.57%) were work out of office with median censored time of 6 days and the rest 30(28.30%) were work in office with median censor time of 6 days. From 38 death event 3(7.89%) were smokers with median death time of 2 days and 35(92.11%) werenon-smokers with median death time of 6 days. Continue this from 49 recurrence event 4(8.16%) were smokers with median recur time of 5 days and 45(91.84%) were non-smokers with median

recur time of 6 days. For censored event among 106, 8(7.55%) were smokers with median censor time of 7 days and 98(98.45%) were non-smokers with median censor time of 6 days.

According to history of alcohol use from 38 death event 13(34.21%) were use alcohol with median death time of 5.5 days and 25(65.79) were not use alcohol with median death time of 5.5 days. Continue to this from 49 recur event 4(8.16%) were alcohol user and 45(91.84%) were non-user with their median recurrence time of 5.5days and 6 days respectively. Among 106 censor event 17(16.04%) were alcohol user and 89(83.96%) were non-user with corresponding median censor time of equal 6 days. Based on history of diabetes from 38 death event 9(23.68%) were diabetic with median death time of 5 days and 29(76.32%) were non-diabetic with median death time of 6days. Continue to this from 49 recur event 4(8.16%) were diabetic and 45(91.84%) were non-diabetic with their corresponding median recur time of 5.5 days and 7 days respectively and also from 106 censor event 7(6.60%) were diabetic and 99(93.40%) were non-diabetic with their median censor time of 7 days and 6 days respectively.

According to marital status, among 38 death event 8(21.05%) were single, 25(65.79%) were married, 2(5.26%) were divorced and 3(7.89%) were widowed with median death time of 6 days 5 days, 5.5 days and 10 days respectively and also among 49 recur event 14(28.57%) were single, 31(63.27%) were married, 2(4.08%) were divorced and 2(4.08%) were widowed with median recur time of 9 days, 6days, 6.5 days and 9 days respectively. In addition to this among 106 censor event 33(31.13%) were single and 73(68.87%) were married with median censor time of equal 6 days. According to hypertension history from 38 death event 11(28.95%) had hypertension with median death time of5days and 27(71.05%) had no hypertension with median death time of 7 days. Among 49 recurrence event 8(16.33%) had hypertension and 41(83.67%) had no hypertension with corresponding median recur time of 6days and 7days. In addition among 106 censor event 14(13.21%) had hypertension with median censor time of 7days and 92(86.79%) had no hypertension with median censor time of 6 days. Lastly the median death time is 6days, the median recurrence and median censor times were 6days.All the results have been summarized in table 4.2.

Table 4.2;cross tabulation of categorical variables by event type with their corresponding median time.

Variables		Events								
		Death			Recur			Censor		
		N	%	Med time(days)	N	%	Med time(days)	N	%	Med time(days)
Sex	Male	25	65.79	6	32	65.31	6	64	60.38	6
	Female	13	34.21	5	17	34.69	7	42	39.62	6
	Total	38	100	5.5	49	100	6	106	100	6
Education level	Educated	17	44.74	8	28	57.14	6	71	66.98	5
	Uneducated	21	55.26	5.5	21	42.86	7	35	33.02	6
	Total	38	100	5.5	49	100	6	106	100	6
Residence	Rural	16	42.11	5.5	16	32.65	6	42	39.62	6
	Urban	22	57.89	5.5	33	67.35	7.5	64	60.38	6
	Total	38	100	5.5	49	100	6	106	100	6
Type of work	No work	11	28.95	5	11	22.45	9	33	31.13	6
	Out of office	23	60.53	5	26	53.06	6.5	43	40.57	6
	In office	4	10.53	10.5	12	24.49	5	30	28.30	6
	Total	38	100	5.5	49	100	6	106	100	6
Smoking history	Yes	3	7.89	2	4	8.16	5	8	7.55	7
	No	35	92.11	6	45	91.84	6	98	98.45	6
	Total	38	100	5.5	49	100	6	106	100	6
History of alcohol use	Yes	13	34.21	5.5	4	8.16	5.5	17	16.04	6
	No	25	65.79	5.5	45	91.84	6	89	83.96	6
	Total	38	100	5.5	49	100	5.75	106	100	6
History of diabetes	Yes	9	23.68	5	4	8.16	5.5	7	6.60	7
	No	29	76.32	6	45	91.84	7	99	93.40	6
	Total	38	100	5.5	49	100	6	106	100	6
History of hypertension	Yes	11	28.95	5	8	16.33	6	14	13.21	7
	No	27	71.05	7	41	83.67	7	92	86.79	6
	Total	38	100	5.5	49	100	6	106	100	6
Marital status	Single	8	21.05	6	14	28.57	9	33	31.13	6
	Married	25	65.79	5	31	63.27	6	73	68.87	6
	Divorced	2	5.26	5.5	2	4.08	6.5	0	0	__
	Widowed	3	7.89	10	2	4.08	9	0	0	___
	Total	38	100	5.5	49	100	6	106	100	6

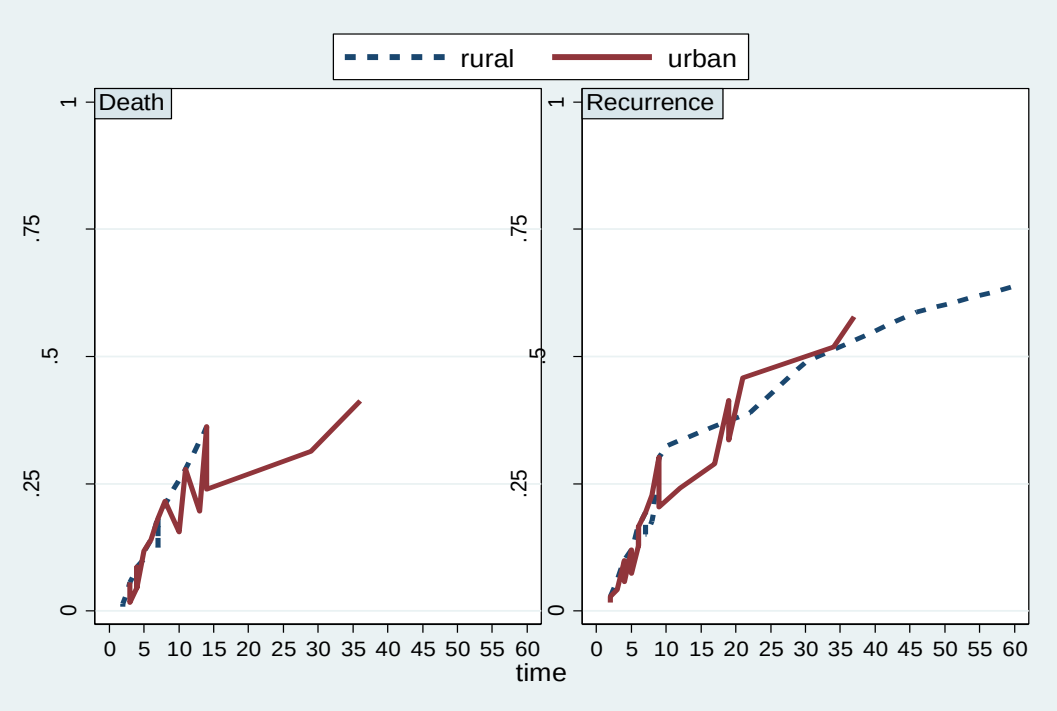
4.1.3. Summary statistics for continuous factors

The descriptive statistics for continuous variables indicated that the average age in years for kidney stone patients who had surgery included in the study is 36.72 with standard deviation 15.72, minimum age of 12 years and maximum age of 82 years. The weight of kidney stone patients who had surgical removal of the disease included in the study had 58.81 average kilogram with standard deviation 10.18, minimum weight of 5 kilograms and maximum weight of 86 kilograms. The variable stay time in the hospital had mean 8.33 dayswith standard deviation 7.90, minimum stayed time 1 day and maximum stayed time 60 days.All the results had been summarized in table 4.3 below.

Table 4.3; summary statistics of continuous variables

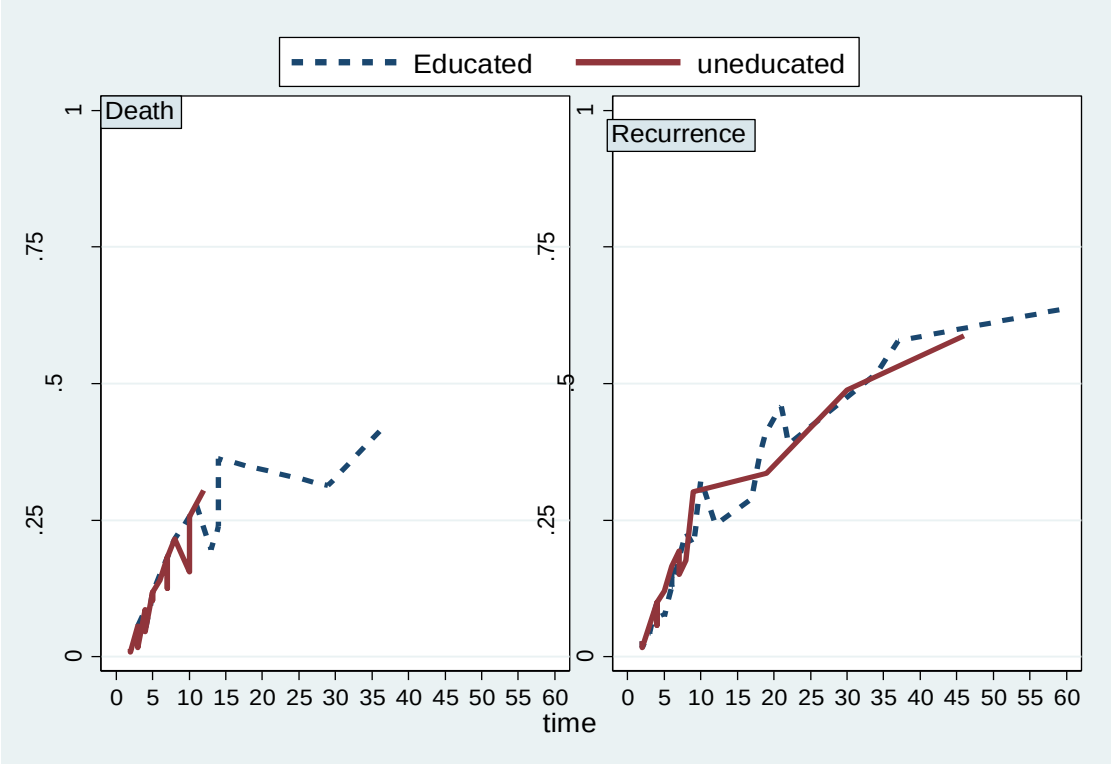
Variable	N	Min	Max	Range	Mean	Std.	Variance
Weight	193	5	86	81	58.81	10.18	103.6324
Age	193	12	82	70	36.72	15.72	247.1184
Time	193	1	60	59	8.33	7.90	62.41

4.2. Graphical descriptions of categorical variables by two competent events(profile plots)



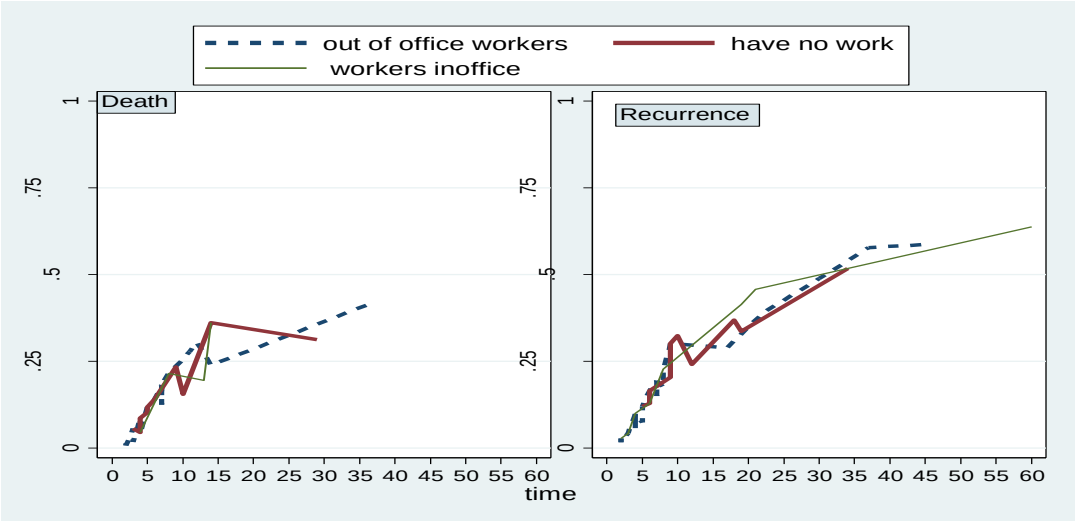
Graph 4.1; cumulative incidence graph of residence category

Graph 4.1;indicated that after removed kidney stone by surgery the hazard of death was similar on both rural and urban resident patients around up to nine days. But from ten days up to fifteen days the hazard of death for rural resident patients was higher than urban resident patients. On the other hand after removed the kidney stone by surgery, there was no recurrence hazard difference between urban and rural resident patients around ten days. But from day ten up to twenty days rural resident patients had higher hazard of recurrence. In addition to that between days twenty and thirty five urban resident patients had higher risk of recurrence and as a conclusion urban resident patients had recurrence risk in short period.



Graph 4.2; cumulative incidence graph of education category

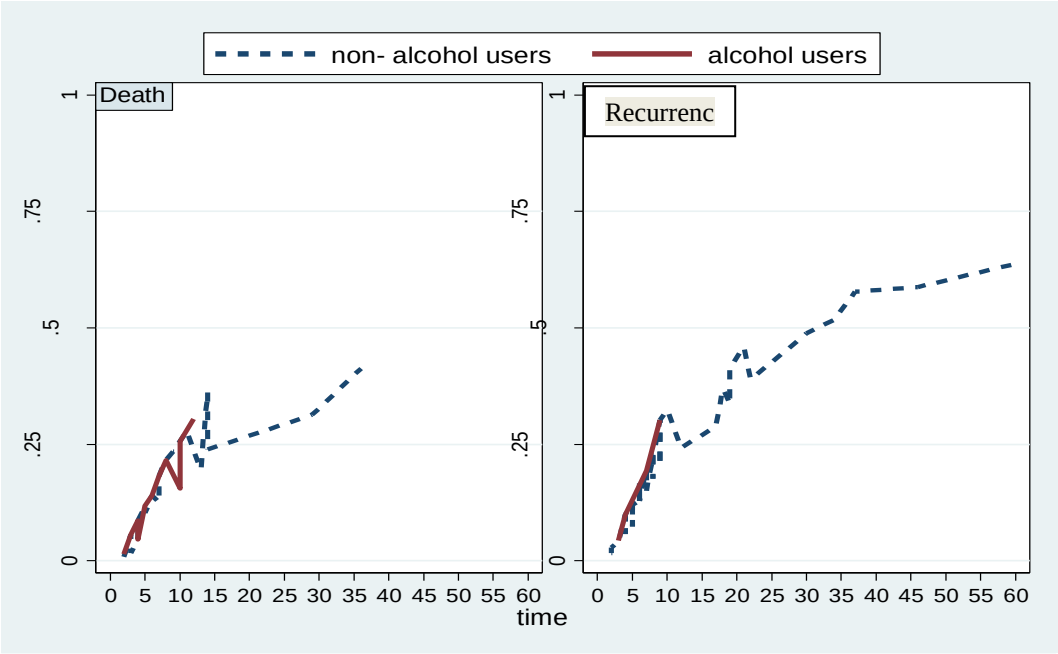
As we seen on the above graphs after kidney stone removed by surgery from them, uneducated patients had a risk of death in short days. On the other hand most of the time educated patients had higher risk to recur the disease after it removed from them.



Graph 4.3cumulative incidence graph of work type category

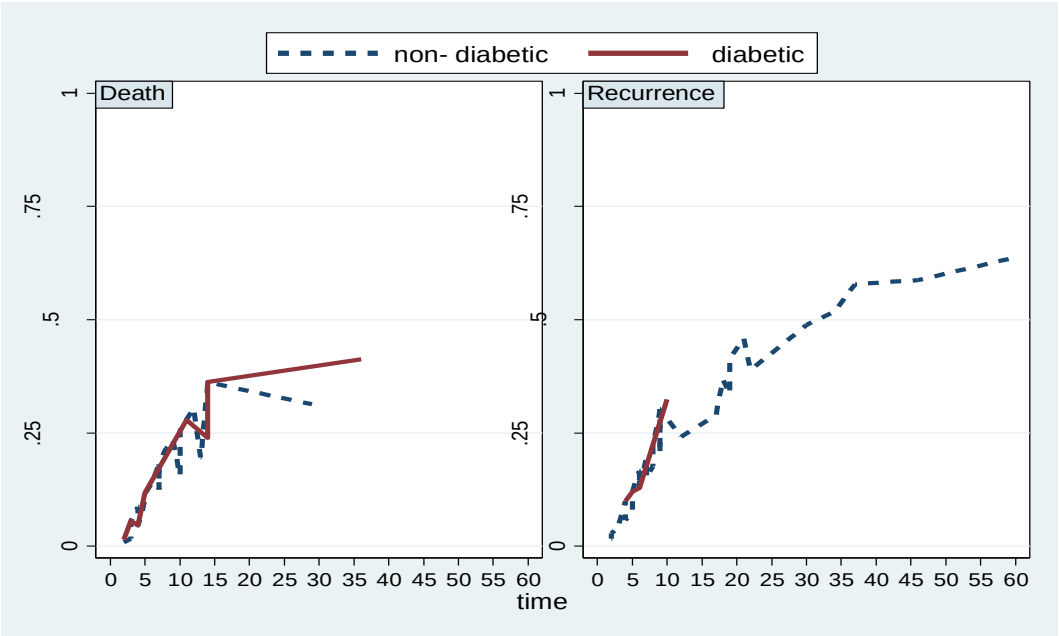
As indicated on the above graphs, in short period of time there were no the hazard of death difference among work type categories. But Most of the time the hazard of death for patients who worked in office was lowest than the hazard of out of office workers and non workers. In addition to that after removed the kidney stone by surgery, patients who have no work had high hazard of death in a short period.

On the other hand after removed kidney stone by surgery,the hazard of recurrence was approximately similar for three type work workers around up to tendays. But from day ten up to around day thirty five the hazard of recurrence for in office workers was the highest than other work type workers.



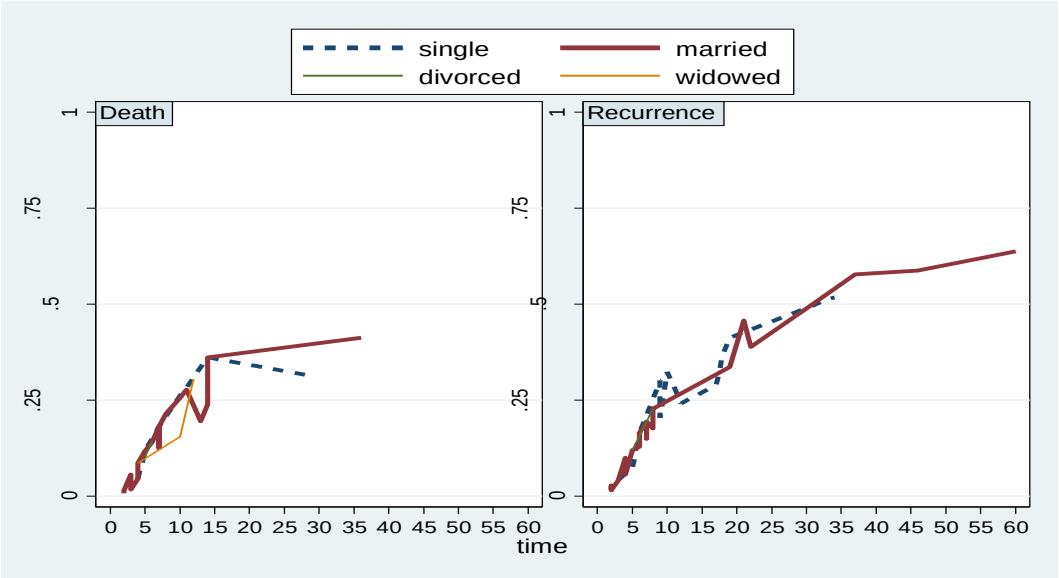
Graph 4.4; cumulative incidence graph of alcohol use category

As we seen the above graphs, after the kidney stone removed by surgery alcohol addicted patients died in short period .And also the disease was recur in short period on alcohol user patients.



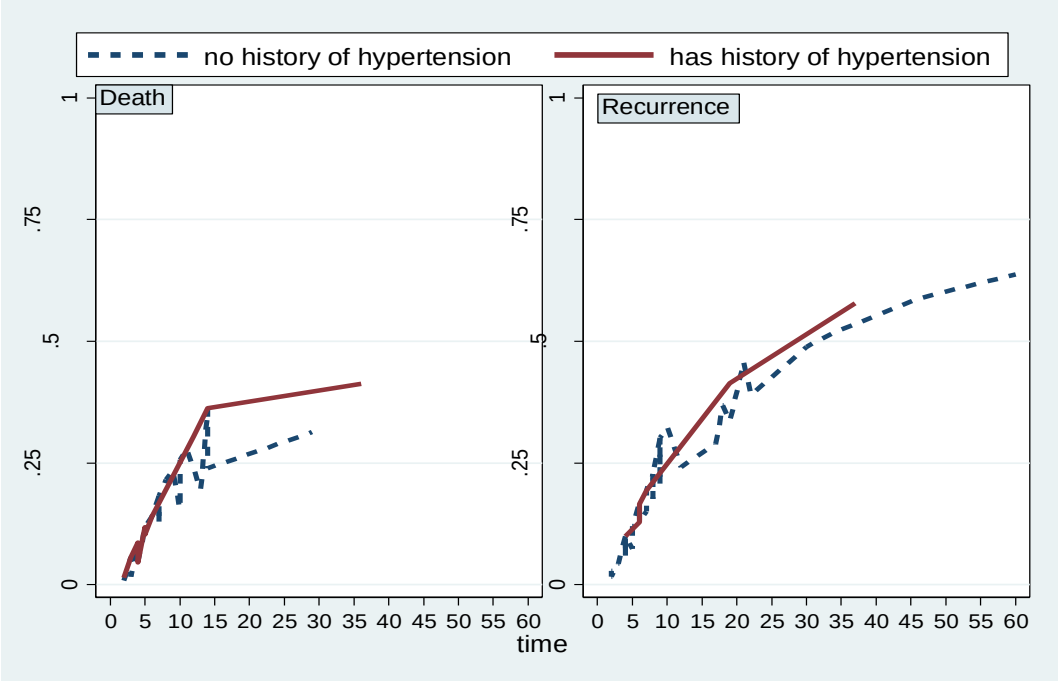
Graph 4.5; cumulative incidence graph of diabetic history

Graph 4.5 indicated that after kidney stone removed by surgery; in short days there was no death hazard difference between diabetic and non-diabetic patients. But most of the time diabetic patients had higher risk of death than non-diabetic patients. On the other side patients with diabetic disease whose kidney stone was removing from them had a risk of recurrence the disease in a short period.



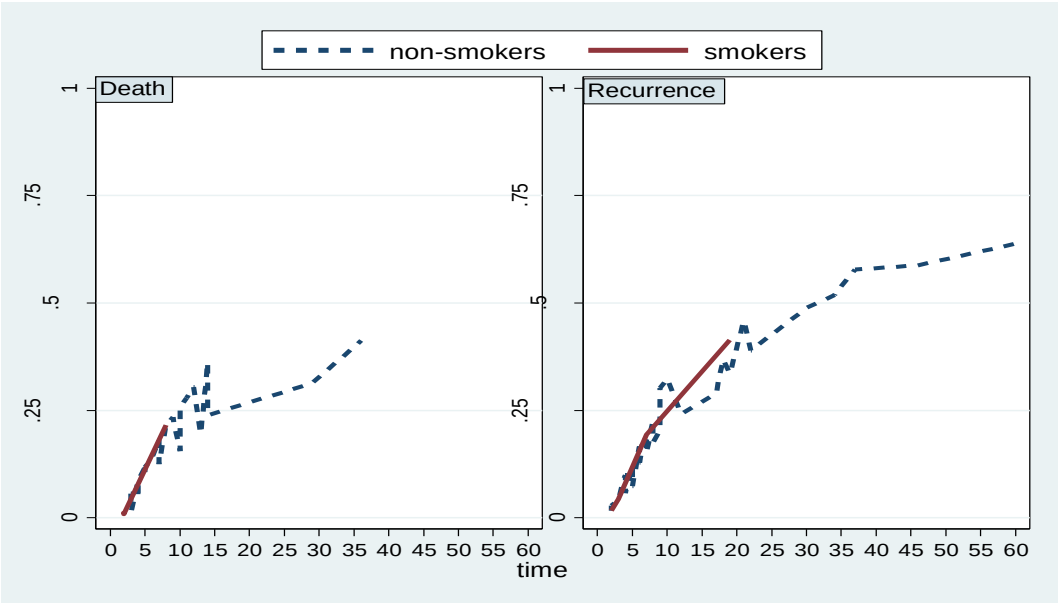
Graph 4.6; cumulative incidence graph of marital status category

The above graph 4.6 indicated that after kidney stone removed from the patients, the hazard of death for widowed patients was least around day four up to around twelve, but they died earlier. On the other hand the right side of the graph indicated that approximately there was no recurrence risk difference between single and married patients. We also saw that there were no divorced and widowed patients that recurred the disease, and no died divorced patients.



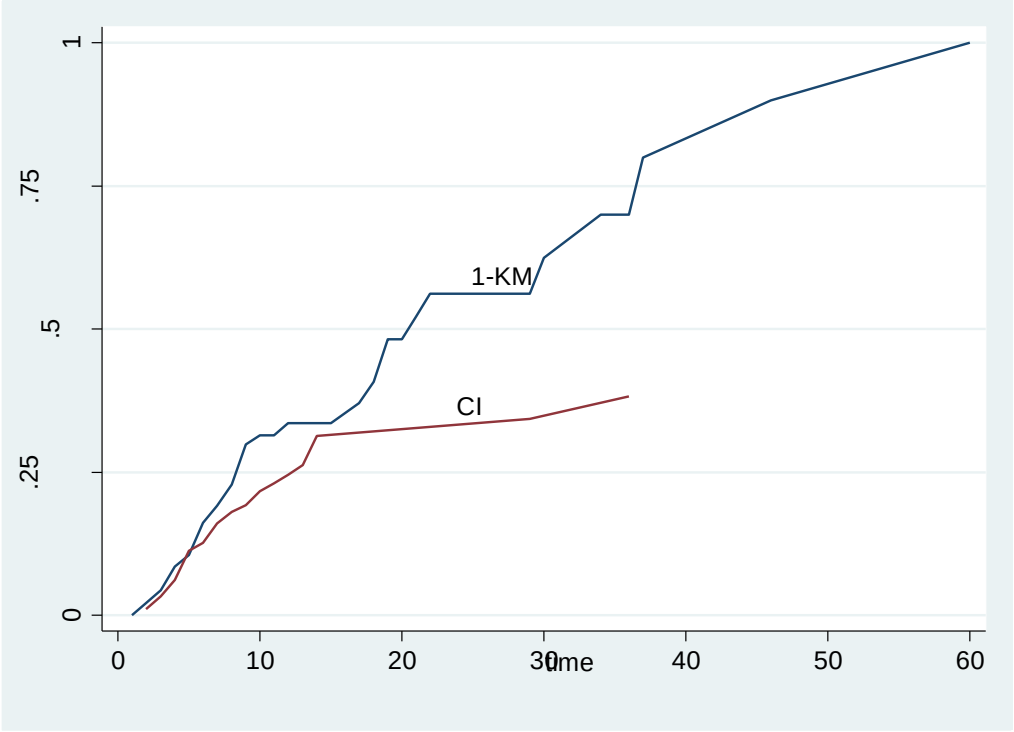
Graph 4.7;Cumulative incidence graph of hypertension history

Graph 4.7 indicated that after removed kidney stone by surgery, the death for patients who had hypertension was higher than the hazard of patients who had no hypertension. In addition to this the risk of recurrence for patients who had hypertension was higher than the recurrence risk of patients who had no hypertension.



Graph 4.8; cumulative incidence graph of smoking status

Based on the above graph after removed kidney stone by surgery from the patients, smoker patients died earlier than nonsmokers.In addition to this the disease recurred earlier for smoker patients.



Graph 4.9; comparisons of KM and CI

Graph 4.9 indicated that the comparison of Kaplan Meir hazard function and Cumulative Incidence function. As we seen from the graph Kaplan Meir hazard graph is above the cumulative hazard graph of competing risk model, because Kaplan Meir takes one event as the interest and takes others as censored and its cumulative ends at one but not in cumulative incidence. Cumulative incidence is the partition of case specific hazards.

4.3. Model Building

Model fit is tested using Log pseudo likelihood, AIC or BIC that are used to compare the null model and the full model. The model which had smaller Log pseudo likelihood, AIC or BIC is selected as fitted model.

4.3.1. Fitted model selection

Table 4.4; fitted model selection summary of competing risk model

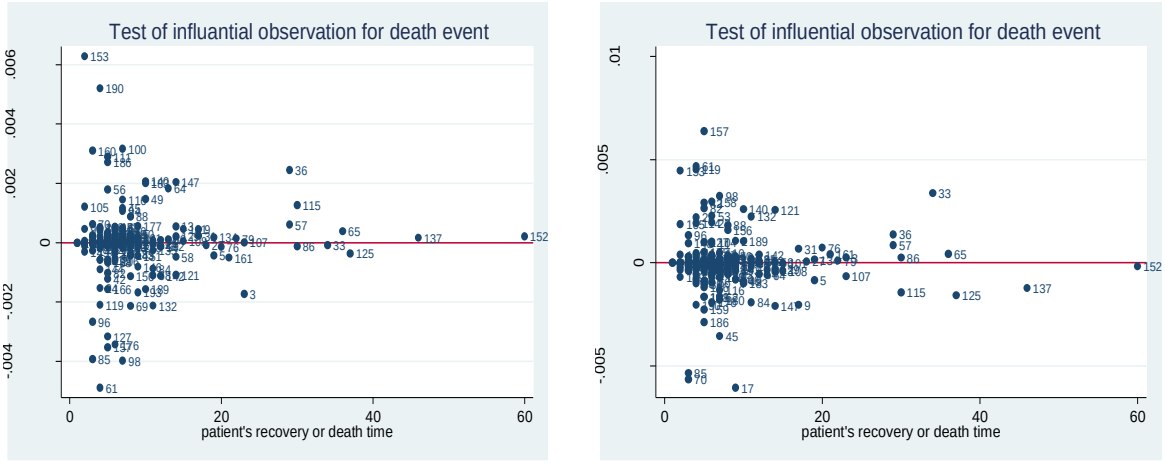
Model	Observation	Df	Log pseudo likelihood	AIC	BIC
Null model	193	1	-218.2486	432.7388	432.7388
Full model	193	14	-216.39938	404.4971	409.1708

As we see in the above table log pseudo likelihood values, AIC and BIC of the full model is lower than the values of null model, this shows that the structural (full) model is better.

The effect of covariates and factor explanatory's on the response for survival analysis with competing risk model were test to check whether the variables had effect on our interest or to test effect difference between categories on the interest event or not. The effect of the variables tested based on their" p" values or their confidence intervals. If this value is less than 0..05 or if the confidence interval values of βs were not contain zero or if the confidence intervals of exp(β) were not contain one, it shows that there were category effect difference or the variable had its effect on the interest event.

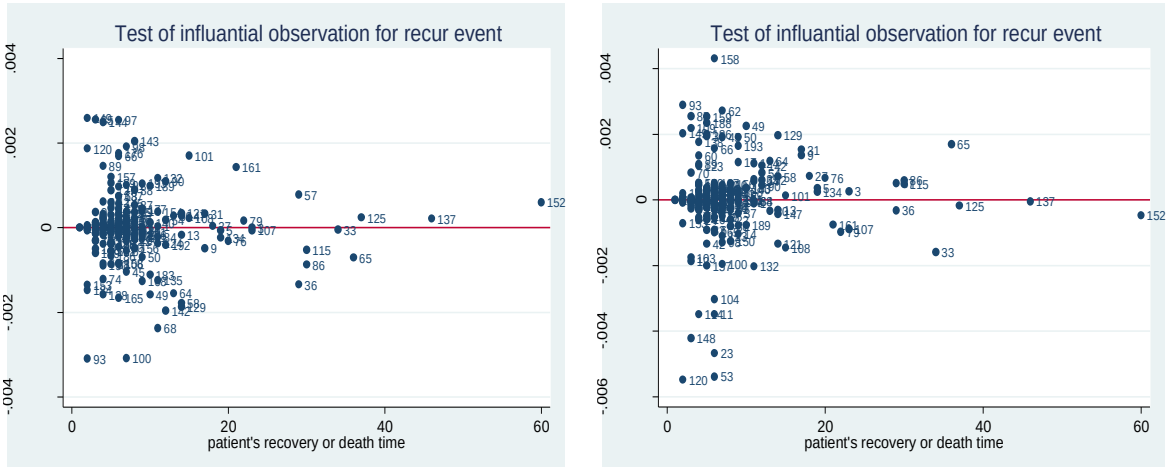
4.4. Model diagnostic

The assesment of influantial observations variables over estimated parameters were tested by DFBETA plots.



Graph 4.9; test of influential observation for continues independents

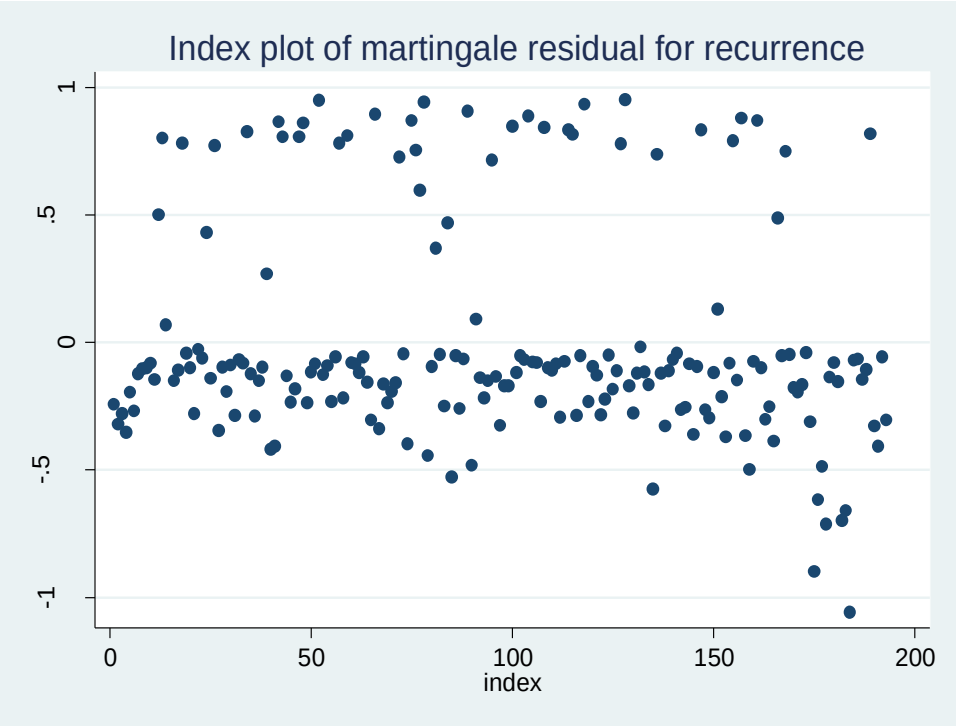
From the above graph, for age variable removed observation 153 increases the estimated βs approximately by 0.006 and remove observation 61 decreases the estimated βs approximately by 0.004. For weight variable remove observations 6, 19, 133 and 157 are increase the estimated βs around by 0.005 and remove observations 17, 70 and 85 decrease the estimated βs around 0.005.This indicates the removal of listed observations do not make that much variation over the estimated parameters. That gave a conclusion of no influential observation.



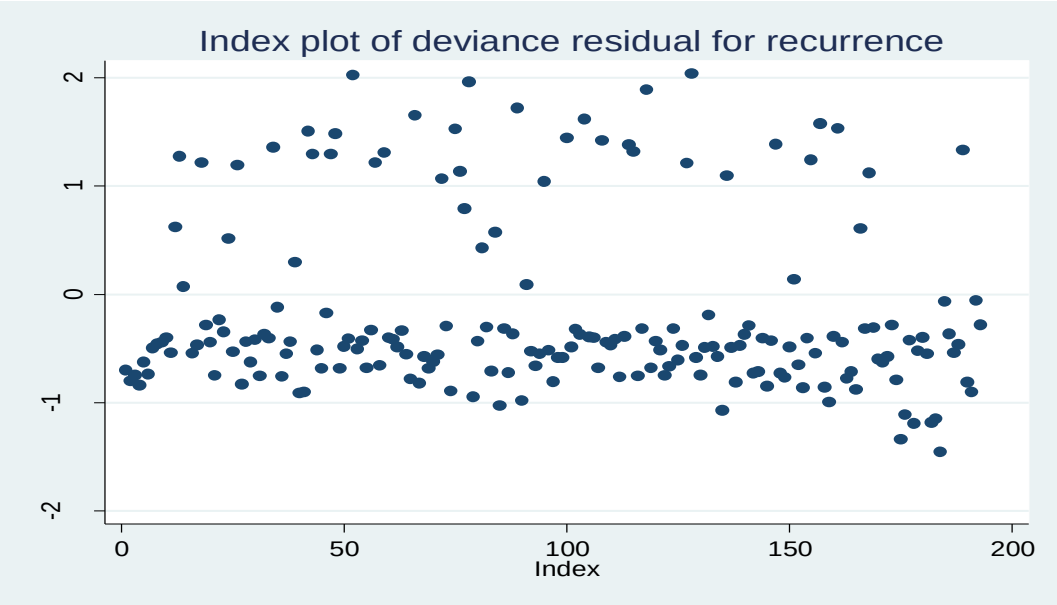
Graph 4.10; Influential observation test graphs for recurrence event

The above graph indicated that the removal of any observation do not give that much change of the estimated parameters. So we Saied there were no influential observation in the independent variables.

Regression assumptions of predictors and functional forms of predictors were assessed by index plots of martingale and deviance residuals.



Graph 4.11; Index plot of martingale residual



Graph 4.12; Index plot of deviance residual

The index plot of martingale and deviance residuals indicated that no any residual value were found to be outside the "box" [-1, 1] from index plot of martingale residual and no residual values were found to be outside the "box" [-2, 2] from index plot of deviance residual.

4.5. Results of competing risk model

The competing survival model analysis was used to identify the basic determinant factors and their progression effect on the recurrence of kidney stone disease and also the effect of these factors on the competing event(death) on kidney stone patients after surgery at Bahir Dar Felegehiwot referral hospital. The study data is taken for a period of days until one event or censor is occurred, so survival analysis with competing risk model was used.

4.5.1. Univar ate analysis of competing risk Model

By using survival model with competing risk analysis, the study fits the individual variables with the response variable to select potentially relevant variables that should be included in the general competing riskmodel. By considering survival analysis with competing risk result of the fitted model p-value, the study selected statistically significant variables for the effect of recurrence time. Since sex, weight and marital status of a patient had no significance effect

on the recurrence time because their p-value were greater than 0.25(level of significance); but the rest variables had statistical significance effect on the recurrence time of a patient because their p-value were greater than 0.25(level of significance). The study use STATA software and stset time, stcrregsoftware command procedure to generate the Univar ate output.

Table 4.5; Results of univariablecompeting risk model

Variables	Coefficients	Z	p>|z|
Sex	.2124	.85	.397
Age	-0.0061	-.75	.045
Residence	.3326	1.17	.024
Work type	.5191	1.33	.195
Education level	-.1206	-1.43	.066
Smoking status	.7513	2.15	.008
History of alcohol use	.9964	-1.89	.005
History of diabetes	-.6157	-2.12	.026
Weight	.0006	.04	.970
Marital status	.5196	.69	.809
History of hypertension	.2471	-2.66	.124

4.5.2. Results of multivariablecompeting risk model

We fitted Fine and Gray case specific regression model to analyze the determinant factors for the progression of kidney stone disease recurrence on kidney stone patients after surgery. To seehow the different variables of interest operate to affect recurrence, the variables were regressed univariabley in the competing risk regression model.Variables that had more than .25 p_ value were excluding in the multivariable competing risk model analysis. The multi variable analysis was done with 5%level of significance. After adjusting other variables,the hazard of recurrence for urban residents was around 72% higher than rural residentswith 95% confidence interval (1.640, 3.058). The hazard of recurrencefor out of office workers was around two times higher than the hazard of unemployed patients with 95% confidence

interval (1.960, 4.258**)**and also the hazard of recurrencefor in office workers(civil servants) was around 63% less than unemployed oncewith confidence interval (.117, .441)keeping other variables at the reference.After adjusting other variables the hazard of recurrence for patients who smoke cigarette was around 6.7% higher than nonsmokers with confidence interval (1.032, 3.563). The hazard of recurrence for alcohol users is around 31% higher than non-alcohol users with confidence interval (1.106**,** 2.919) keeping other variables at the reference. The incidence of recurrencefor diabetic patients is around 51% higher than non-diabetics with confidence interval (1.155**,** 1.646), and also the incidence of recurrence for patients who had hypertension is around 15% lower than patients who had no hypertension with confidence interval (.781, .976) by considering the remaining variables at the reference. But the variables age and education level were statistically insignificant in the multivariable competing risk regression. The results are given in table 4.6 and table 4.7 accordingly with sub hazard ratio and sub hazard coefficients.

Table 4.6;the effect of explanatory variables with sub hazard ratio at multivariable competing risk analysis

Variables		SHR	Robust std. error	Z	P >|z|	95% conf. interval	
						Lower	Upper
Residence	Rural	1	____	__	__	___	____
	Urban	1.723	.504	1.86	.045	1.640	3.058
Work type	Unemployed	1	_____	___	___	____	__
	Out of office	2.022	.768	1.85	.044	1.960	4.258
	In office	.372	1.103	-1.43	.015	.117	.441
Smoking status	No	1	___	____	_____	_____	____
	Yes	1.067	.637	.11	.019	1.032	3.563
History of alcohol use	No	1	_____	_____	_____	____	___
	Yes	1.313	.172	2.11	.035	1.106	2.919
History of diabetes	No	1	____	_____	___	_____	____
	Yes	1.505	.304	1.13	.025	1.155	1.646
History of hypertension	No	1	____	____	____	_____	____
	Yes	.848	.325	-.43	.007	.781	.976

Table 4.7; the effect of explanatory variables with sub hazard coefficients at multivariate competing risk analysis

Variables		Coefficients(βs)	Robust std. error	Z	P >|z|	95% conf. interval	
						Lower	Upper
Residence	Urban	.544	.012	1.16	0.04	.004	.909
Work type	Out of office	.704	.380	1.85	.044	.041	1.449
	In office	-.990	.497	-1.43	.015	-1.527	-.263
Smoking status	Yes	.065	.615	0.11	.019	.040	1.271
History of alcohol use	Yes	.272	.550	2.11	.035	.240	2.084
History of diabetes	Yes	.409	.602	1.13	.025	.386	1.498
History of hypertension	Yes	-.165	.383	-0.43	.007	-.558	-. 022
Constant	-	.000	.671	-.29	.583	-..641	1.67

Case specific hazard competing risk model for the above summary is:-

$\lambda r(X,\beta) = \exp\{0.5440\text{residence(urban)} + 0.704\text{worktype(outofoffice)} - 0.990\text{worktypeinoffice} + 0.065\text{smoking historyyes} + 0.272 \text{ history of alcohol useyes} + 0.409\text{history of diabetesyes} - 0.165 \text{ history of hypertensionyes}, \lambda 0r = 1.$

Because β_0=0, this implies e^{β}=1.

Chapter five

5. Discussions, Conclusion and recommendations

5. 1. Discussion and Conclusion

The purpose of this paper was to determine factors and covariates for the hazard of recurrence rate of kidney stone disease patients who had surgery in Bahir Dar FelegeHiwot referral hospital by using a competing risk model for survival data procedure. The study used the hospital chart to collect data from September 01/ 2014 up to march 08/ 2017 identified some of the factors that were responsible for the hazard of interest event and competing event.

Before the analysis of competing risk model, graphical comparison of Kaplan Meier hazard function and cumulative incidence were done. Based on the result Kaplan Meier graph was over the cumulative incidence graph, that indicated survival analysis was over estimated.

According to our findings, residence had been found a significant effect on the recurrence of kidney stone disease after it removed by surgery on kidney stone patients.Our finding shown that the urban residents hadhigher hazard of recurrence the disease compared with rural resident patients.Category work type had significant effect on the recurrence event. Out office workers had higher hazard of recurrence the disease than non-workers. On the other hand civil servants (in office workers) have lower hazard of recur the disease compared with patients who have no work.Regarding smoking status, the finding indicated that the patient's smoking status had significant effect on the hazard of recur. Patients who smoked hadgreater hazard of recur than Patients who are not smoked.History of alcohol use had significant effect on recur event with a greater hazard of recur of alcohol users than non-users.

According to patient's history of diabetes, diabetic patients had higher hazard of recurrence than non-diabetic patients. Lastly the category hypertension history has significant effect on the interest event. The result indicated that patients with hypertension had greater hazard of recur than patients who had not hypertension.According to(Mollerup et al., 2002)stonedisease recurrence were more likely on hypertension, diabetes and alcohol dependence patients.

5.2. Recommendations

On the basis of our findings, we recommend the following.

- More attentionshould be given to patients who live in urban area and the risk of smoking for the recurrence of kidney stone disease after it removed by surgery.
- Special attention should be given to out of office worker patients. The respected should be crate safe work atmospheres for such type of workers.
- Lastly the researcher recommended that clinical trial study should do to include the effect of unregistered explanatory variables.

REFERENCES

ABDEL, H., RE., ALTWAIJIRI , A., ELFAQIH, S., MITWALLI, A. & SAUDI, M., J. 2003. Extraction of urinary bladder stone as described by Abul-Qasim Khalaf Ibn Abbas Alzahrawi (Albucasis) . *A translation of original text and a commentary.,* 24**,** :1283–1291

AKAIKE, H. 1998. A Bayesian analysis of the minimum AIC procedure. *Selected Papers of Hirotugu Akaike.* Springer.

AL-EISA, A. 2002. Pediatric urolithiasis in Kuwait. *Int Urol Nephrol* 33**,** 3–6.

ANAND, S., KHANAM, M. A. & FINKELSTEIN, F. O. 2014. Global Perspective of Kidney Disease. 11-23.

ANTONELLO, A., BONFANTE, L., FAVARO, S., GAMBARO, G., D'ANGELO , A., MENNELLA, G., CALO, L. & 2002. Hermann Boerhaave and lithotomy: what he thought about it. *Am J Nephrol* 22**,** 290–294

BITSORI, M., GALANAKIS, E. & WORLD, J., UROL . 2004. Epicurus' death. 22**,** 466–469

BURNHAM, K. P. & ANDERSON, D. R. 2004. Multimodel inference understanding AIC and BIC in model selection. *Sociological methods & research,* 33**,** 261-304.

CACHAT, F., BARBEY, F., GUIGNARD, J. & 2004. Urinary calculi epidemiology in children. . *Rev Med Suisse Romande,* 124**,** 433–437.

DARDIOTI , V., ANGELOPOULOS, N., HADJICONSTANTINOU, V. & AM, J., NEPHROL. 1997. Renal diseases in the Hippocratic era. 17**,** 214–216.

DAUDON, M., BOUNXOUEI, B., SANTA CRUZ, F., LEITE DA SILVA, S., DIOUF , B., ANGWAFOO, F. & TALATI, J. Desrez G 2004. of renal stones currently observed) Composition in non-industrialized countries. . *Prog Urol* 14**,** 1151–1156

DJELLOUL, Z., DJELLOUL , A., BEDJAOUI , A., KAID-OMAR, Z., ATTAR, A., DAUDON, M., ADDOU, A. & 2006. Urinary stones in Western Algeria: study of the composition of 1,354 urinary stones in relation to their anatomical site and the age and gender of the patients. *Prog Urol* 16**,** 328–335,.

EKNOYAN, G., CLIN., REV, B. & MIN, M. 2004. History of urolithiasis. 2**,** 177–185

FINE, J. P. & GRAY, R. J. 1999. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American statistical association,* 94**,** 496-509.

FISEHA., T., KASSIM., M. & YEMANE., T. 2014. Prevalence of chronic kidney disease and associated risk

factors among diabetic patients in southern Ethiopia. *American Journal of Health Research*.

GANEM, J. & CARSON, C. 1999. Frère Jacques Beaulieu: from rogue lithotomist to nursery rhyme character. . *J Urol* 161**,** 1067–1069.

GRAY, R. J. 1988. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *The Annals of statistics***,** 1141-1154.

HADDAD, F., FLAMANT, S., HADDAD, L. & 1994. Marin Marais and his "Le tableau de l'operation de la taille" (1725). *Acta Belg Hist Med* 7**,** 66–70

HAN, A. & HAUSMAN, J. A. 1990. Flexible parametric estimation of duration and competing risk models. *Journal of applied Econometrics,* 5**,** 1-28.

KALBEISCH. & ., P. 1980.

KUHA, J. 2004. AIC and BIC comparisons of assumptions and performance. *Sociological Methods & Research,* 33**,** 188-229.

LAGOMARSINO, E., AVILA, D., BAQUEDANO, P., CAVAGNARO , F. & CÉSPEDES, P. 2003. Litiasis urinaria en pediatría. *Rev Chil Pediatr* 74**,** 381–388

MILLER, N. & LINGEMAN, J. 2007. "Management of kidney stones".

MOLLERUP, C. L., VESTERGAARD, P., FRØKJÆR, V. G., MOSEKILDE, L., CHRISTIANSEN, P. & BLICHERTTOFT, M. 2002. Risk of renal stone events in primary hyperparathyroidism before and after parathyroid surgery: controlled retrospective follow up study. *Sørensen*.

MORGAN, M. & PEARLE, M. 14 March 2016. "Medical management of renal stones.". *BMJ (Clinical research ed.)*, PMID 26977089.

PERRONE, H., DOS-SANTOS, D., SANTOS, M., PINHEIRA, M. & TOPOROVSKI J, R. O. 1992. Urolithiasis in childhood: metabolic evaluation. *Pediatr Nephrol,* 6**,** 54–56.

PRENTICE, A., BRANCA, F., DECSI, T., MICHAELSEN, K., FLETCHER, R., GUESRY, P., MANZ, F., VIDAILHET, M., PANNEMANS, D. & SAMARTÍN, S. 2004. Energy and nutrient dietary reference values for children in Europe: methodological approaches and current nutritional recommendations. . *Br J Nutr 92,* Suppl 2**,** S83–S146.

RAMELLO, A., VITALE C & MARANGELLA, M. 2000. Epidemiology of nephrolithiasis. . *J Nephrol,* 13**,** S65–S70

RIETHE, P. 2005. Hildegards von Bingen 'Liber simplicis medicinae' in the Mainz 'Garden of Health'.

RIZVI, S., NAQVI, A., HUSSAIN, Z., HASHMI, A., HUSSAIN, M., ZAFAR, M., SULTAN, S. & MEHDI , H. 2002. Pediatric urolithiasis: developing nation perspectives. . *J Urol* 168**,** 1522–1525

ROBERTSON , W. 2003. Renal stones in the tropics. . *Semin Nephrol* 23**,** 77–87

ROBERTSON, W. & HUGHES, H. 1994. Epidemiology of urinary stone disease in Saudi Arabia. In: Ryall R, Bais R, Marshall VR, Rofe AM, Smith LH, Walker VR (eds) Urolithiasis 2. Plenum Press, New York London,. pp 453–455

SACHS, M. 2003. The prohibition of lithotomy within the Hippocratic Oath: historical and ethical considerations on the history of surgery. . *Zentralbl Chir,* 128**,** 341–347

SARKISSIAN, A. 2001. Pediatric urolithiasis in Armenia: a study of 198 patients observed from 1991 to 1999. *Pediatr Nephrol* 16**,** 728–732.

SOUCIE , J., COATES, R., MCCLELLAN, W., AUSTIN, W. & THUN, M. 1996. Relation between geographic variability in kidney stones prevalence and risk factors for stones. . *Am J Epidemiol* 143**,** 487–495

STITCHANTRAKUL, W., KOCHAKARN, W., RUANGRAKSA, C. & DOMRONGKITCHAIPORN, S. 2007. Urinary risk factors for recurrent calcium stone formation in Thai stone formers. . *J Med Assoc Thai,* 90**,** 688–698.

TEKIN, A., TEKGUL, S., ATSU, N., SAHIN, A., OZEN, H. & BAKKALOGLU, M. 2000. A study of the etiology of idiopathic calcium urolithiasis in children: hypocitruria is the most important risk factor. . *J Uol,* 164**,** 62–65

THOMAS, D. C. 1981. General relative-risk models for survival time and matched case-control analysis. *Biometrics***,** 673-686.

TRINCHIERI , A. 1996. Epidemiology of urolithiasis. *Arch Ital Urol Androl* 68**,** 203–249.

VANDENBROUCKE, J. & 2001. Commentary: treatment of bladder stones and probabilistic reasoning in medicine: an 1835 account and its lessons for the present. *Int J Epidemiol*

30**,** 1253–1258.

VANDERVOORT, K., WIESEN, J., FRANK, R., VENTO, S., CROSBY, V., CHANDRA, M. & TRACHTMAN , H. 2007. Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome. *J Urol* 177**,** 2300–2305.

WANG, C., R., SMITH-BINDMAN, REBECCA, WHITAKER, EVANS, NEILSON, JERSEY, ALLEN, ELAINE, I., STOLLER, L., M., FAHIMI & JAHAN September 2016. "Effect of Tamsulosin on Stone Passage for Ureteral ".

YIRSAW, B. D. 2012. Chronic kidney disease in sub-Saharan Africa: hypothesis for research demand. *Ann Afr Med,* 11**,** 119-20.

Appendix

Appendix1

Cross tabulation of each factor with the events

```
tab Sex  status, column row

+-------------------+
| Key               |
|-------------------|
|     Frequency     |
| Row percentage    |
| Column percentage |
+-------------------+

    Sex of |          patient status
a patient |     censored     death    recur |   Total
-----------+---------------------------------+----------
    Female |        42         13         17 |     72
           |     58.33      18.06      23.61 |    100.00
           |     39.62      34.21      34.69 |     37.31
-----------+---------------------------------+----------
Male |        64         25        32 |      121
           |     52.89      20.66      26.45 |    100.00
           |     60.38      65.79      65.31 |     62.69
-----------+---------------------------------+----------
     Total |       106         38         49 |     193
           |     54.92      19.69      25.39 |    100.00
           |    100.00     100.00     100.00 |    100.00
```

Table1 Cross tabulation of patient status and sex

```
tab   residence  status, column row

+-------------------+
| Key               |
|-------------------|
|     Frequency     |
| Row percentage    |
| Column percentage |
+-------------------+

 Patient's |          patient status
residence |    censored      death    Recur |    Total
-----------+---------------------------------+----------
     Rural |        42         16         16 |    74
           |     56.76      21.62      21.62 |    100.00
           |     39.62      42.11      32.65 |     38.34
-----------+---------------------------------+----------
Urban |        64         22         33 |       119
           |     53.78      18.49      27.73 |    100.00
           |     60.38      57.89      67.35 |     61.66
-----------+---------------------------------+----------
     Total |       106         38         49 |     193
           |     54.92      19.69      25.39 |    100.00
           |    100.00     100.00     100.00 |    100.00
```

Table2 cross tabulation of patient status and residence

```
tabEdu_level  status, column row

+-------------------+
| Key               |
|-------------------|
|     Frequency     |
| Row percentage    |
| Column percentage |
+-------------------+

Patient's_education_
Level|          patient status
                   | Censored       death      recur | Total
+---------------------------------+----------
Uneducated  | 35         21         21 |    77
                   | 45.45      27.27    27.27 |    100.00
                   | 33.02      55.26      42.86 |     39.90
+---------------------------------+----------
Educated| 71         17         28 |       116
                  | 61.21         14.66    24.14 |    100.00
                  | 66.98          44.74    57.14 |     60.10
+---------------------------------+----------
Total |       106         38       49 |       193
|     54.92      19.69      25.39 |    100.00
|    100.00     100.00     100.00 |    100.00
```

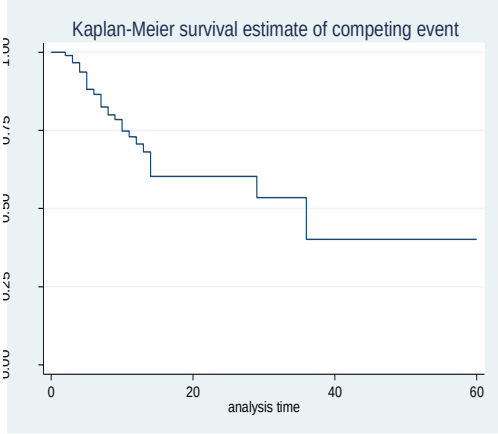
Table3 cross tabulation of patient status and education level

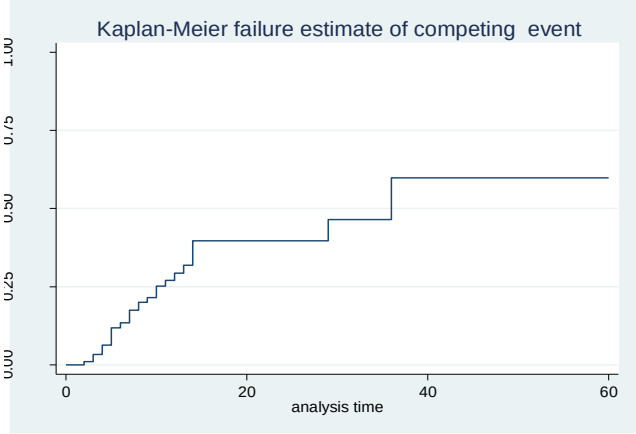
```
tabWorktypestatus, column row

+-------------------+

| Key               |

|-------------------|

|     Frequency     |

| Row percentage    |

| Column percentage |

+-------------------+

   Patient's |          patient status

work type |    censored     death     recur |     Total

-----------+---------------------------------+----------

 No work   |        33         11         11 |        55

           |     60.00      20.00      20.00 |    100.00

           |     31.13      28.95      22.45 |     28.50

-----------+---------------------------------+----------

Out office |        43         23         26 |        92

           |     46.74      25.00      28.26 |    100.00

           |     40.57      60.53      53.06 |     47.67

-----------+---------------------------------+----------

 In office |        30          4         12 |        46

           |     65.22       8.70      26.09 |    100.00

           |     28.30      10.53      24.49 |     23.83

-----------+---------------------------------+----------

     Total |       106         38         49 |       193

           |     54.92      19.69      25.39 |    100.00

           |    100.00     100.00     100.00 |    100.00
```

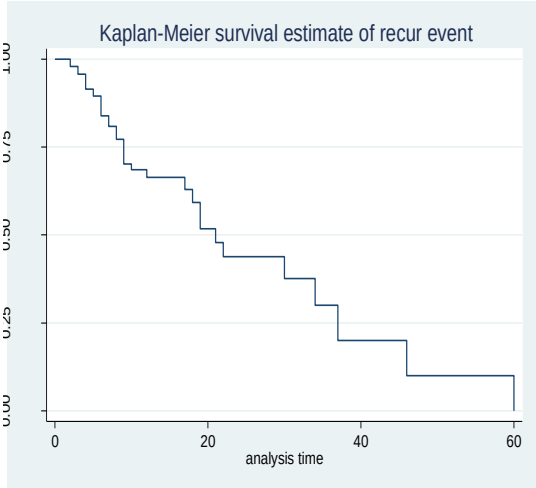
Table4 cross tabulation of patient status and work type

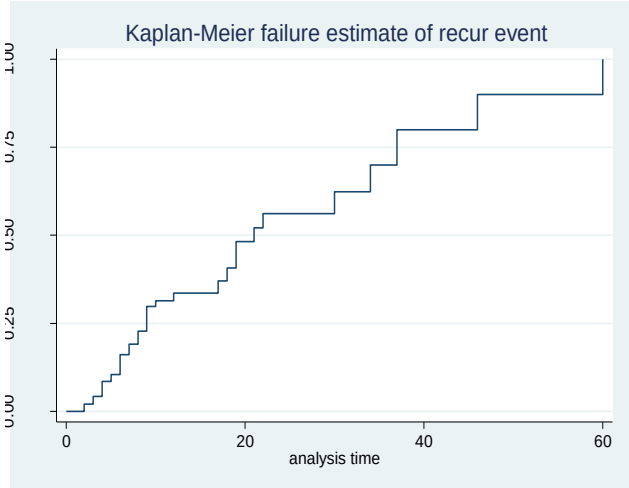
Appendix 2

Survival and hazard graph of each event take as normal survival



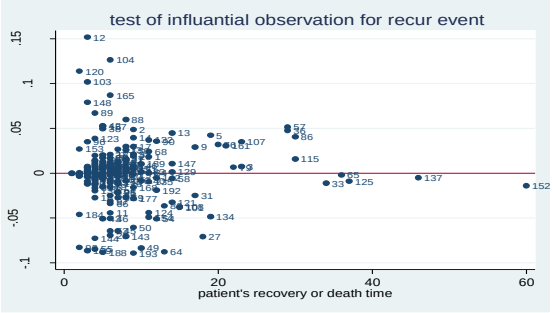


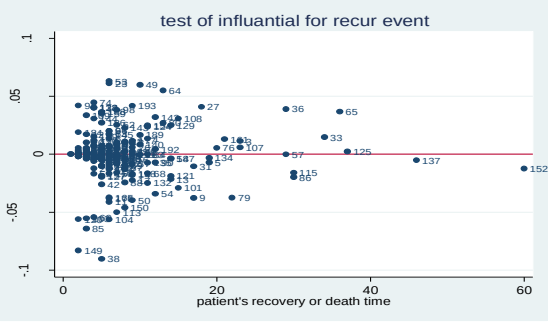


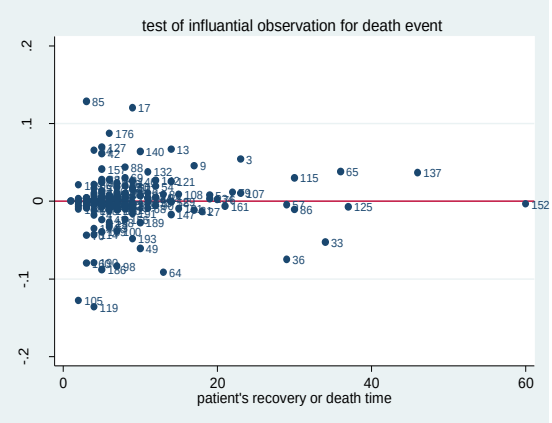


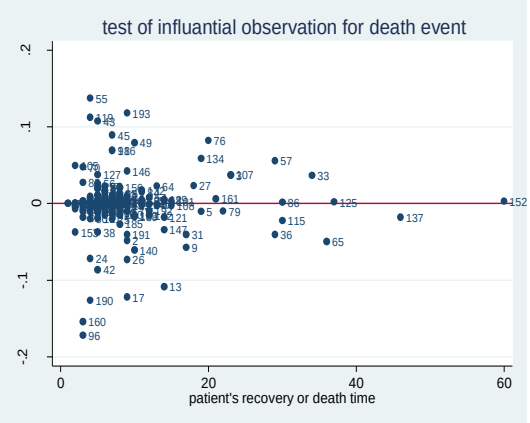
Appendix 3

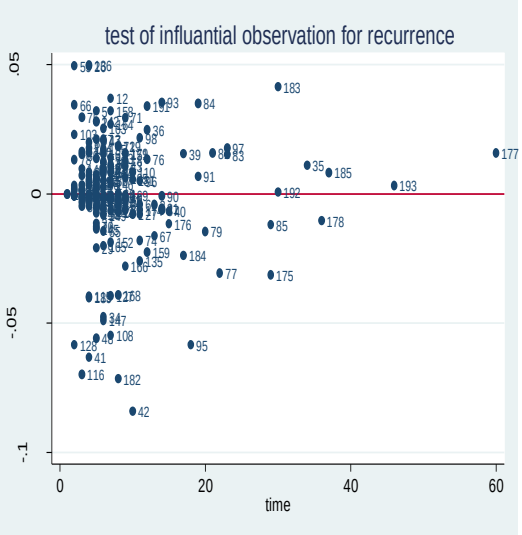
Test of influential observation for some categorical variables

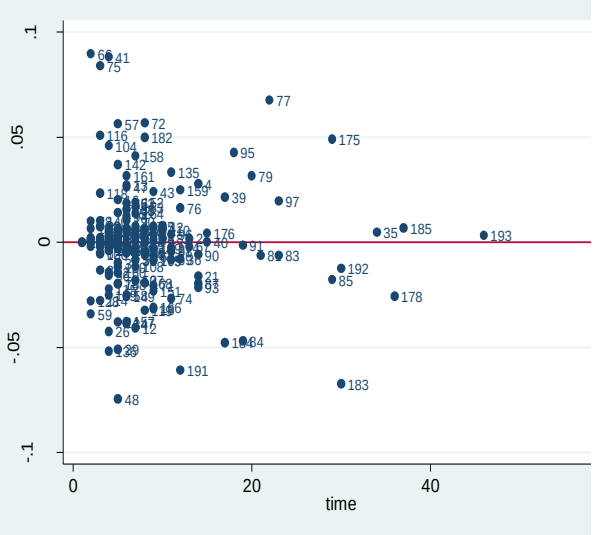


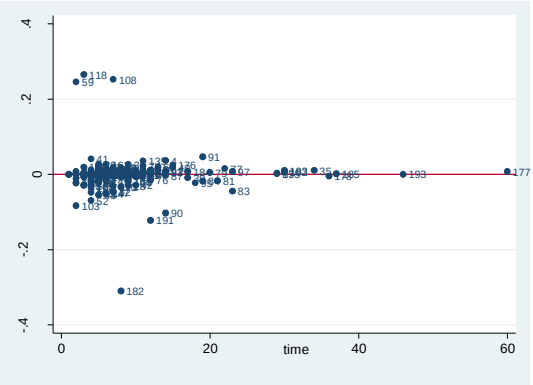


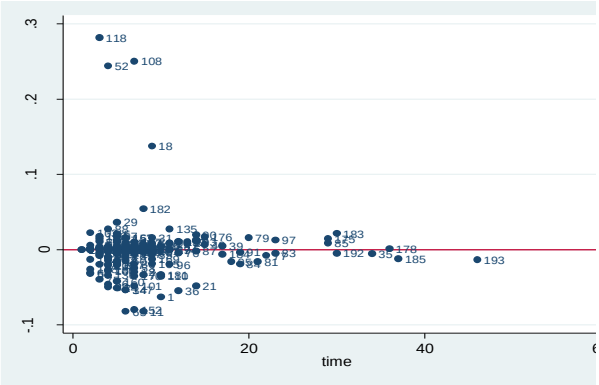


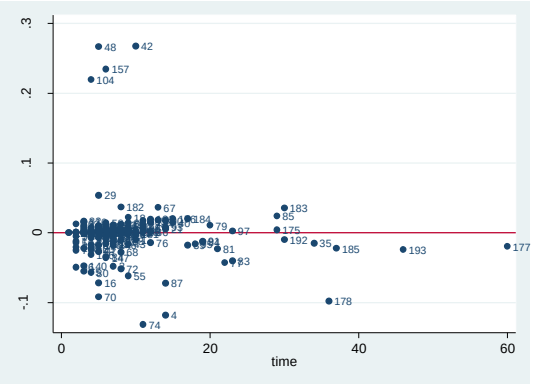


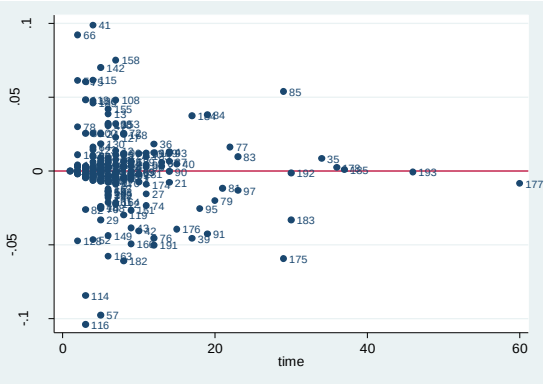


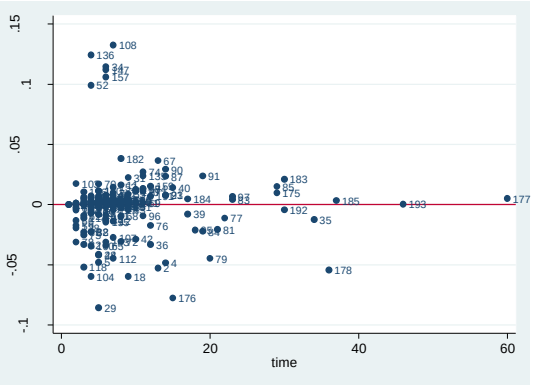



time


time


time


time


time

Appendex4

Competing risk regression STATA commands

.stset time, failure(status==1)

.stset time, failure(status==2)

. xi:stcrregi.Sex Age i.residencei.Edu_leveli.Worktypei.smok_statui.his_alco_use

>i.his_diabetes weight i.marit_stati.hypertension, compete(status==1)