ANEMIA AS RISK FACTOR FOR MORTALITY IN PATIENTS WITH END STAGE RENAL DISEASE (ESRD)

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THIS DISSERTATION IS SUBMITTED AS PART OF THE PRE-REQUIREMENT TO BE CONFERRED THE DEGREE IN BACHELOR OF SCIENCE IN MATHEMATICS WITH ECONOMICS

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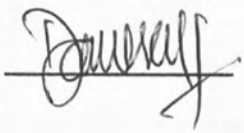
   (PN. DARMESAH BT GABDA) 

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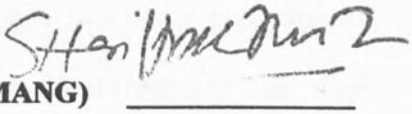
   (ASSOCIATE PROF. DR. SHARIFF A.K. OMANG) 

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ABSTRACT

This study sought to determine the survival rate of End Stage Renal Disease (ESRD) patients in Kota Kinabalu Queen Elizabeth Hospital and to evaluate the relationship between anemia, hypertension and diabetes with survival rate. Anemia, hypertension and diabetes occur frequently in ESRD patients. Sample data for this study is obtained from KKQEH pool of kidney disease patients of year 2005. A total of 248 patients from various age groups and ethnicity were included in the study. Life Table method is used to find the survival rate of ESRD patients and Kaplan Meier Survival Analysis is used to determine the survival rate of patients who are anemic, diabetic or had hypertension. Log-Rank Test is used to compare survival rates between groups. Survival time is associated with age groups and ethnicity. The result of the study shows that older patients have lower survival rate. Chinese and Kadazan Dusun patients have higher survival rate compared to other ethnicity. Anemia and diabetes were found to be risk factors of mortality (90% CI: $p<0.051$ and $p<0.037$). The risk was higher for interaction between anemia and diabetes ($p<0.007$), diabetes and hypertension ($p<0.086$) and all three factors ($p<0.018$) than that predicted by these three factors independently. Anemia and diabetes are risk factors for mortality in patients with End Stage Renal Disease, especially when both are present along with hypertension.

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ABSTRAK

Kajian ini bertujuan untuk mendapatkan kadar mandiri bagi pesakit *End Stage Renal Disease* (ESRD) di Hospital Queen Elizabeth Kota Kinabalu dan menentukan hubungan antara anemia, hipertensi dan diabetis dengan kadar mandiri. Anemia, hipertensi dan diabetis kerap kali dihidapi pesakit ESRD. Sampel data untuk kajian ini didapatkan dari kalangan pesakit penyakit ginjal QEHKK bagi tahun 2005. Seramai 248 orang pesakit dari pelbagai peringkat umur dan bangsa disertakan dalam kajian ini. Kaedah Sifir Umur diguna untuk mendapatkan kadar mandiri pesakit ESRD dan Analisis Kaplan Meier digunakan untuk memperoleh kadar mandiri pesakit yang menghidap anemia, hipertensi dan diabetis. Ujian Log-Rank digunakan untuk membandingkan kadar mandiri antara kumpulan. Hasil kajian mendapati kadar mandiri adalah lebih rendah bagi pesakit yang berusia. Pesakit berbangsa Cina dan Kadazan Dusun mempunyai kadar mandiri yang lebih tinggi berbanding pesakit dari bangsa lain. Anemia dan diabetis didapati merupakan faktor risiko kepada kadar kemortalan (SK 90%: $p<0.051$ dan $p<0.037$). Risiko adalah lebih tinggi bagi interaksi antara anemia dan diabetis ($p<0.007$), diabetis dan hipertensi ($p<0.086$) dan ketiga-tiga faktor ($p<0.018$) berbanding yang dijangkakan oleh tiga faktor ini secara berasingan. Anemia dan diabetis merupakan faktor risiko untuk kemortalan dalam pesakit *End Stage Renal Disease*, terutamanya jika kedua-dua faktor ini hadir bersama hipertensi.

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LIST OF SYMBOLS

%	percentage
±	plus and minus
/	over or divide
>	more than
<	less than
≥	more than or equal to
≤	less than or equal to
=	equals
≠	not equals to
Δt	delta t
$\Delta t \rightarrow 0$	delta t approaches 0
$\sum$	summation
∞	infinity
H_0	null hypothesis
H_1	alternative hypothesis
λ	lambda
$\overline{X}$	sample mean
χ^2	Chi-Square
$\lim_{\Delta t \rightarrow 0}$	limit as delta t approaches 0

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LIST OF ABBREVIATIONS

ABSC	Absconded
AOR	Against Order/ Restriction
CHI	Chinese
CI	Confidence Interval
CKD	Chronic Kidney Disease
ESRD	End Stage Renal Disease
EXP	Expired
Hb	Haemoglobin
HF	Heart Failure
K/D	Kadazan Dusun
KD	Kidney Disease
KKQEH	Kota Kinabalu Queen Elizabeth Hospital
OSB	Other Sabah Bumi
SK	Selang Keyakinan
SR	Survival Rate

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CHAPTER 1

INTRODUCTION

Statistic shows that kidney disease is on the rise. According to a report from Nephrology Unit of Hospital UKM (Kong, 2001), about 2200 new cases of ESRD are recorded in Malaysia each year. Few studies and researches had been carried out on kidney disease; mostly by university hospitals. However, the majority was on the management of the disease and very few evaluated survival rate of ESRD patients with survival analysis. Even though ESRD is not a curable disease without dialysis or transplant, with the advance technology, people with End Stage Renal Disease (ESRD) are living longer than ever. Dialysis treatments (both hemodialysis and peritoneal dialysis) though do not cure ESRD, helps patients to feel better and live longer. Over the years, ESRD can cause other problems such as bone disease, high blood pressure, nerve damage, and anemia (having too few red blood cells).

Anemia is a well known complication in renal failure (Al-Ahmad *et. al*, 2001). Anemia is defined by hemoglobin <13g/dl in men and <12g/dl in women. Test and studies has been conducted to test the relationship between the two. However, testing the survival rate of the ESRD patients in Sabah, Malaysia has never been conducted for year 2005. As almost all ESRD patients are also battling anemia (interview, Dg Aishah, 2007) it is important to determine the survival rate and the risk

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factor for mortality in the patients. This will be evaluated using survival analysis tests on data collected from Queen Elizabeth Hospital, Kota Kinabalu, Sabah.

1.1 Renal Failure

Renal failure refers to temporary or permanent damage to the kidneys that result in loss of normal kidney function. The kidneys function includes removing waste products and excess fluids from the body via the urine, and also maintain a critical balance of salt, potassium and acid (Woo, 1988). The kidneys produce a hormone called erythropoietin or EPO that stimulates the production of red blood cells. Other kidney hormones help regulate blood pressure and calcium metabolism. The kidneys even synthesize the hormones that control tissue growth (PDR,2004). Thus when the kidneys' ability to remove and regulate water and chemicals is impaired by disease or blockage, fluids and waste products accumulate, ultimately resulting in extreme swelling and symptoms of uremia (an overload of toxic by products) or renal failure.

Renal failure can be put into two groups which is acute and chronic. Chronic renal failure can be categorized into five stages (Kodner, 2003). Stage one is the earliest stage of kidney damage, signify by normal or elevated Glomerular Filtration Rate or GFR. As the stages increases, the GFR decreases and damage to the kidney heightens. In stage five, which we also recognize as ESRD, the GFR is <15ml per minute per $1.17m^2$ which is too low for the patients to survive without dialysis or transplant.

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Conditions like Diabetic Nephropathy, Hypertension, Lupus (SLE) and prolonged urinary tract obstruction or blockage causes Acquired Kidney Disorders (Agha, 2003). While Congenital Kidney Diseases typically involves malformation of the genitourinary tract that can lead to blockages that injures the kidney tissues which in turn causes permanent kidney damages. Polycystic Kidney Disease is a kind of inherited disorder that commonly causes the patients to develop ESRD between ages of 40 to 60. The rarer form (autosomal recessive PKD) causes kidney failure in early childhood (Agha, 2003).

Some of the more apparent symptoms of ESRD are unintentional weight loss, nausea or vomiting, frequent hiccups, greatly decreased or no urine output and some may experience blood in the vomit or stools. As ESRD patients usually progressed from chronic kidney failure (CKD), lab test are usually carried out to determine the stages of the disease. These include blood test (to determine blood cells counts, electrolyte levels, and kidney function), urine test, chest x-ray, bone scan, renal ultrasound (also called sonography), electrocardiogram (ECG or EKG) and kidney biopsy. Other signs of complications commonly present are chronically high levels of Creatinine and Blood Urea Nitrogen (BUN) which both can be determined by their respective test (Mushnick, 2005).

Some of the complications causes by ESRD are congestive heart failure, hypertension, platelet dysfunction, anemia, decreased functioning white blood cells and immune system and permanent skin pigmentation changes (Mushnick, 2005). Glomerulonephritis, urinary tract infection and kidney stones are the milder complications but none the less, must be treated. Female patients run the possibilities

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of miscarriage, menstrual irregularities and infertility while male patients might experience decreased libido or becomes impotent.

ESRD are fatal unless treated with dialysis or transplantation. Both of these treatments can have serious risk and consequences. The outcome varies and is unique to each individual. The methods of treatments currently available in well-equipped hospitals are hemodialysis and peritoneal dialysis (NKUDIC,2005). In hemodialysis an artificial kidney machine carries out the vital functions the kidneys can no longer perform. In this procedure, a person is connected to the machine by plastic tubing that attaches to special blood vessels in the arm or leg. The treatment can be done at home or at a dialysis unit. In peritoneal dialysis, waste products from the blood are flushed from the body with fluid instilled and drained through a catheter that has been surgically placed in the abdomen (Interview, Dg Aishah, 2007). Once the catheter is in place, this technique is usually done at home.

1.2 Anemia

Anemia, one of the more common blood disorders, occurs when the level of healthy red blood cells (RBCs) in the body becomes too low. This can lead to health problems because RBCs contain hemoglobin, which carries oxygen to the body's tissues (NKUDIC, 2005). Anemia can cause a variety of complications, including fatigue and stress on bodily organs. Anemia can be temporary or it can be a long-term disease/illness. One is considered anemic if they have hemoglobin <13g/dl in men and <12g/dl in women or hematocrit <40% (Sarnak, *et. al*, 2002). Hematocrit is the percentage of blood volume that is occupied by red blood cells.

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There are a few types of common anemia; differs in their causes. The type of anemia associated with kidney disease is usually anemia of chronic diseases. The chance of developing anemia increases as kidney disease gets worse. However, anemia can occur in the earliest stages of the disease. A study has shown anemia affected 28% of people with mild kidney disease and 87% of people with severe kidney disease (Al Ahmad *et. al*, 2001). A kidney performing at its normal level sends a hormone called erythropoietin (EPO) to the bone marrow which then produces the RBCs. The RBCs circulate in the blood and carry oxygen and carbon dioxide to and from every cell in the body. However, when kidney disease or renal failure sets in, the kidney is unable to send as much EPO to the bone marrow. This resulting in fewer RBCs produced which is the condition we call anemia. Fewer RBCs cells to carry oxygen through the bloodstream means less oxygen gets to the organs, which leads to other complications (NKUDIC, 2005).

Anemic patients are given EPO to correct anemia where synthesized EPO is injected into the body of the patients. Before EPO was synthesized and made available for injection, many patients with kidney disease had to receive blood transfusions to treat anemia. The injectable form is called recombinant human erythropoietin and is almost identical to what a normal kidney makes (PDR, 2004). It may be injected directly into a vein (intravenous) during dialysis or under the skin (subcutaneous) Patients would probably have to rely on EPO as long as they are on dialysis. EPO will be given regularly to maintain the red blood cell count (hematocrit) at a stable level, usually between 30 and 36 percent. When a patient have a successful kidney transplant, the new kidney will produce EPO and they will no longer need recombinant human erythropoietin.

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Another common form of anemia is iron deficiency anemia that affects about one in five women and half of pregnant women (McClellan *et. al*, 2004). Bone marrow needs iron to make haemoglobin. When there is a shortage of iron, the body can't produce enough haemoglobin for red blood cells thus causing iron deficiency anemia. Iron from dead blood cells can be recycled. However, if there is blood loss, such as heavy menstruation or chronic blood loss within the body (ulcer, colon polyp or colon cancer) the iron is loss in the process. In pregnant women, a growing fetus can deplete the mother's store of iron, leading to iron deficiency anemia. This is more so if the mother's diet does not contain enough iron.

The amount of iron absorbed and loss in healthy individuals matches. About 1 to 2 mg of iron is absorbed through diet and 1 or 2 mg is loss a day. In kidney patients, there is less iron absorption; only about 0.5 mg per day and yet still losses the 1 to 2 mg in the normal way (Mushnick, 2005). Furthermore, patients are losing 3 to 9 mg of iron a day during their dialysis. These amplified the lack of iron in the patients and thus even less hemoglobin as produced. As anemia worsen, so do the complications it brings and chances of the patient surviving get dimmer.

People who have both kidney disease and anemia have an increased risk of death, stroke, or heart failure. The chance of early death is even higher in people with anemic kidney disease and who also have heart failure and/or diabetes. Lack of oxygen makes a heart work harder, so the muscles in its left lower chamber may get too thick. This condition is called left ventricular hypertrophy (LVH), and can even occur in people with early kidney disease, and increases the risk of people having a heart attack or dying. Studies done so far do not guarantee a patient will live longer if

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the anemia is corrected, but it shows how important it is to treat anemia (Al-Ahmad *et. al*, 2001).

1.3 Survival Analysis

Survival analysis is concerned with studying the time between entry to a study and a subsequent event (Johnson & Johnson, 1999). Survival analysis is applicable to many areas as well as mortality even though originally the analysis was concerned with the time from treatment until death. Survival analysis takes the survival times of a group of subject (usually with a kind of medical condition) and generates a survival curve, which shows how many of the members remain alive over time. Survival time is usually defined as the length of the interval between diagnosis and death. However, the definition of survival time is dependent on the analysis involved.

Survival analysis will be conducted to find the survival rates of ESRD patients who also suffered from anemia. The reason to use survival analysis for this study is to get a more accurate result. This is because when the outcome of a study is the time between an event and another, a number of problems can occur. First of all, the times are most unlikely to be normally distributed and secondly it is not economical to wait until event happens to all the subjects, for example until all are dead. The expenses to maintain the study till that time would be too high and it might take too long. The non-normality of data violates the normality assumption of other statistical test like ANOVA and multiple regressions. Furthermore, the usual statistical test does not take into account the censored and truncated observations.

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There are three basic forms of censoring, right-censoring, left censoring and interval censoring. Some patients might have left the study early before the event occurs (shifted to another hospital or moved to another area) they are lost to follow up (Lee & Wang, 2003). Thus the only information we have about some patients would be they are still alive at the last follow up. Yet, we do not know how much longer they might ultimately have survived. These are termed right-censored observations. Left-censoring is much more rarely encountered where some subjects experienced the event before the detailed observations commences. Interval censoring happens where observations are infrequent that we do not know the time where the event occurs (Lee & Wang, 2003). All is known is that the time the event occurred between two observation times. Several methods have been developed for using this information to preparing unbiased survival curve estimates, the most common being the Life Table method and the method of Kaplan and Meier.

Truncated observation is always confused with censored observations, but it is a distinct mechanism. In truncation, only individuals for whom the event occurs after or before a specific time are observed. In left truncation, subjects enter the study at times other than the origins for the event of interest and are followed up until the event of interest occurs or they are lost to follow up (Johnson & Johnson, 1999). If they experience the event before their observation period starts they will not appear in the study. For example, in this study, truncation can happen between the time patient has been diagnosed with the ESRD and anemia before the date of 1st January 2005 the commencement date of the study. The survival time is measured from the date of diagnosis to death and the delayed entry is different for each patient. One situation that often occurs in clinical trials is where patients move from one treatment group to

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another when some event occurs, such as receiving a transplant. They must survive long enough to receive the transplant before they can be considered part of this treatment group. Where else, in censoring, the survival time is from the commencement time or the time they joined the study. Right truncation refers to the study where the subject is only observed if they had an event; studies based on death records are an example of this (Johnson & Johnson, 1999).

Another important concept in survival analysis is the hazard rate. Hazard rate is used to determine a reasonable model for the survival data. From looking at the data with discrete time, we can get an intuitive idea of hazard rate. For discrete time hazard rate is the probability that an individual will experience an event at time t while that individual is at risk for having an event. In other words, our knowledge relates the rate of failure at some times, conditional on the subject surviving to that time. For example, if all the subjects in a study, considering their conditions are likely to have an event within a period of three months, there is no point in doing a study for two years at observation intervals of four months. The hazard rate is an un-observed variable yet it controls both the occurrence and timing of the events (Johnson & Johnson, 1999. It is the fundamental dependent variable in survival analysis.

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