PREDICTIVE FACTORS OF FIRST-YEAR MORTALITY IN NEWLY DIAGNOSED END-STAGE RENAL DISEASE PATIENTS COMMENCING ON HEMODIALYSIS IN KELANTAN.

DR. INGRID TING PAO LIN

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ABBREVIATION

ESRD	End Stage Renal Disease
RRT	Renal Replacement Therapy
GFR	Glomerular Filtration Rate
pmp	Per million population
HD	Hemodialysis
DM	Diabetes mellitus
HPT	Hypertension
ADNAN	Advanced Dialysis Nephrology Application Network
HDU	Hemodialysis Unit
ALP	Alkaline phosphatase
iPTH	intact parathyroid hormone

FAKTOR-FAKTOR RAMALAN UNTUK MORTALITI BAGI TAHUN PERTAMA PADA PESAKIT KEGAGALAN BUAH PINGGANG PERINGKAT AKHIR YANG BARU MENJALANI RAWATAN HEMODIALISIS DI KELANTAN

ABSTRAK

LATARBELAKANG:

Secara global, bilangan pesakit buah pinggang tahap akhir (ESRD) telah menunjukkan trend peningkatan di kedua-dua sudah negara membangun di seluruh dunia. Kematian tahunan kerana ESRD di peringkat hemodialisis (HD) di Malaysia pada tahun 2015 adalah 13.8%. Kemandirian/Survival menyeluruh selama 5 hingga 10 tahun pada dialisis adalah 52% dan 27%. Trend kematian dalam kalangan pesakit HD beransur menurun sejak 2 abad kebelakangan. Dialisis mempunyai kesan yang berat ke atas sumber kewangan dan penggunaannya. Kematian paling tinggi dicatatkan ketika tahun pertama permulaan hemodialisis. Analisa komprehensif yang telah dilaksanakan secara menyeluruh oleh beberapa penyelidikan terhadap pelbagai faktor risiko yang wujud semasa tahap pra-dialisis bagi kematian tahun pertama selepas bermulanya HD; menunjukkan keputusan yang tidak konsisten disebabkan kekurangan data tempatan. Kajian ini dilaksanakan bertujuan untuk mengenalpasti faktor prognostik yang menyumbang kepada kematian tahun pertama rawatan hemodialisis di kalangan pesakit baru di negeri Kelantan, Malaysia.

KAEDAH:

Kajian prospektif kohort dijalankan melibatkan 373 pesakit ESRD yang baru memulakan hemodialisis daripada 28 pusat hemodialisis di Kelantan daripada 1 Januari 2016 sehingga 31 Disember 2016. Temujanji susulan subjek selepas satu tahun direkrut dilakukan sehingga 31 Disember 2017. Kesemua pesakit yang memenuhi kriteria dimasukkan ke dalam kajian. Maklumat yang diperlukan ke atas pembolehubah yang terpilih diambil setiap 3 bulan semasa pengambilan darah dan direkodkan dalam sistem ADNAN ("Advanced Dialysis Nephrology Application"). Status kemandirian/survival sehingga 31 Disember 2017 direkodkan ke dalam borang pengumpulan data.

KEPUTUSAN:

Kemandirian/Survival terkumpul menyeluruh ESRD semasa tahun pertama memulakan HD di Kelantan adalah 89.5 (95% CI 86.5, 92.7) peratus.

Berdasarkan analisis multipembolehubah Cox Proportional Hazards Regression selepas melaraskan beberapa pembolehubah, faktor prognostik signifikan yang memberi kesan ke atas risiko kematian pesakit ESRD semasa tahun pertama permulaan hemodialisis adalah jantina wanita (HR=2.40, 95% CI: 1.23, 4.69) and serum albumin less than 30 g/l (HR=0.93, 95% CI: 0.89, 0.98) dan serum albumin kurang daripada 30 g/l (HR=0.93, 95% CI: 0.89, 0.98).

KESIMPULAN:

Tahap kemandirian/survival pesakit ESRD semasa tahun pertama permulaan HD di Kelantan boleh dibandingkan dengan negara membangun yang lain. Faktor-faktor prognostik bebas yang signifikan yang dikenalpasti adalah lebih kurang sama dengan negara-negara lain.

Kata kunci: Penyakit buah pinggang tahap akhir, hemodialisis, tahun pertama, insiden hemodialisis, kemandirian/survival, faktor prognostik.

ABSTRACT

BACKGROUND:

Globally the number of End-stage renal disease (ESRD) patients has been increasing in trend both developed and developing countries, worldwide. The annual death rate for ESRD on hemodialysis (HD) in Malaysia 2015 was 13.8%. The overall 5 years and 10 years survival on dialysis were 52% and 27% respectively. The trend for death rate among HD patients had gradually increased over the past 2 decades. Dialysis has a massive impact on financial resources and utilization. The highest incidence of mortality is found to be during the first year of initiation of hemodialysis. Several studies have comprehensively analyzed various existing risk factors during the pre-dialysis stage associated with first-year mortality after commencing HD; however, the results were inconsistent due to lack of local data. This study was carried out to identify prognostic factors that contribute to the first-year mortality in newly diagnosed ESRD patients in the state of Kelantan, Malaysia.

METHOD:

A prospective cohort study was conducted involving 373 ESRD patients newly initiated hemodialysis from 28 hemodialysis center in Kelantan from 1st January 2016 to 31st December 2016. Follow up of one year after recruitment of the subjects was done until 31st December 2017. All patients who fulfilled the criteria were included in the study. The required information on variables of interest was taken every 3 months during blood taking and recorded in ADNAN (Advanced Dialysis Nephrology Application) system. The survival status until 31st December 2017 was recorded into a data collection form.

RESULTS:

The overall cumulative survival of ESRD during the first-year initiation on HD in Kelantan was 89.5 (95% CI 86.5, 92.7) percent.

Based on Cox Proportional Hazards Regression multivariable analysis after adjusting other variables, the significant prognostic factors that influenced the risk of mortality in ESRD patients during first-year of initiation of hemodialysis were female gender (HR=2.40, 95% CI: 1.23, 4.69) and serum albumin less than 30 g/l (HR=0.93, 95% CI: 0.89, 0.98).

CONCLUSION:

The survival rate of ESRD patients during the first-year initiation of HD in Kelantan was comparable with other developed countries. Significant independent prognostic factors identified were considered similar to other countries.

Keyword: End-stage renal disease, hemodialysis, first-year, incident hemodialysis, survival, prognostic factor

CHAPTER 1: INTRODUCTION

1.1 OVERVIEW OF END STAGE RENAL DISEASE

1.1.1 Definition

End Stage Renal Disease

Definition of ESRD based on KDIGO Guideline on CKD. It is GFR category G5 with eGFR less than 15 mL/min/1.73 m^2 and described as kidney failure.

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Source: (KDIGO Guideline on Chronic Kidney Disease, 2014)

Figure 1.0: Stages of Chronic Kidney Disease

1.1.2 Pathophysiology

Approximately 1 million nephrons are present in each kidney, each contributing to the total GFR (Jacobson, 1991). Regardless of the etiology of renal injury, with progressive destruction of nephrons, the kidney has an innate ability to maintain GFR by hyperfiltration and compensatory hypertrophy of the remaining healthy nephrons. This nephron adaptability allows for continued normal clearance of plasma solutes. The urea and creatinine start to

show significant increases in plasma levels only after total GFR has decreased to 50% when the renal reserve has been exhausted. The plasma creatinine from a baseline value of 0.6 mg/dL (53µmol/L) to 1.2 mg/dL (106µmol/L) in a patient, although still within the reference range, actually represents a loss of 50% of functioning nephron mass. The residual nephron hyperfiltration and hypertrophy although beneficial for the reasons noted, has been hypothesized to represent a major cause of progressive renal dysfunction. This is believed to occur because of increased glomerular capillary pressure, which damages the capillaries and leads initially to focal and segmental glomerulosclerosis and eventually global glomerulosclerosis.

1.1.3 Treatment of End Stage Renal Disease

Early nephrology referral is of extreme importance as this would significantly decrease morbidity and mortality (Innes *et al.*, 1992). Timely initiation of chronic renal replacement therapy is imperative to prevent the uremic complications of CKD that can lead to significant morbidity and death.

In general, renal replacement therapy is required when the kidneys are functioning at less than 10% to 15%. Renal replacement therapy is accomplished in one of the following ways:

1. Dialysis either Hemodialysis or Peritoneal dialysis
2. Kidney transplant either Cadaver donated or Living-relative donated

At least 1 year is required for a renal care team to prepare patients adequately for dialysis. These include educating patients and their families about the different treatment

modalities (transplantation, hemodialysis or peritoneal dialysis), and either planning for noncadaveric renal transplantation or creating peritoneal or vascular access (Mendelssohn *et al.*, 1999). Dialysis preferably should be initiated when the creatinine clearance falls to 5-10 ml/min (0.08-0.17 ml/s) in asymptomatic patients or 15-20 ml/min (0.25-0.33 ml/s) in symptomatic patients (Churchill, 1999).

Renal transplantation is the treatment of choice for patients with end-stage renal disease (Suthanthiran and Strom, 1994). Improvement in quality of life, as well as the reduction in mortality risk, are observed in patients with successful kidney transplantation (Schnuelle *et al.*, 1998). However, renal transplantation is limited due to the shortage of suitable donors, the incidence of organ transplant rejection and the age and health of many ESRD patients. The vast majority of patients, therefore, must rely on dialysis for the remainder of their lives.

Choice of dialysis depends on various factors namely social and family support, comorbid conditions, home surrounding, patient's independence and motivation.

Hemodialysis removes uremia solutes and excess fluid from the blood when the kidneys cannot do sufficiently. The blood is drawn intravenously, sent through a dialyzer, and returned to the body via patient's arterio-venous fistula. Inside the dialyzer, the blood is passed over an artificial membrane that filters waste and fluid into a dialysate solution. A dialysate is then pumped out to a disposal tank and new dialysate is pumped in. The process of removing excess fluid is known as ultrafiltration. A machine is required for the purpose.

The blood is circulated and diffused numerous times during a dialysis session; each circulation through the machine removes more waste and excess fluid. Hemodialysis is usually performed three or more times a week for 4 hours or more.

There are three methods of accessing the bloodstream for hemodialysis:

1. Arteriovenous fistula (AVF)
2. Arteriovenous graft (AVG)
3. Temporary venous dialysis catheter

1.2 RESEARCH BACKGROUND

Globally the number of ESRD patients has been increasing in trend both developed and developing countries, worldwide. The incidence of ESRD in Malaysia has been an increase in trend for the past 10 years. In 2001 there were 88 per million populations (pmp) and this had doubled to 170 pmp in 2010. Meanwhile, the prevalence of patients with ESRD on dialysis had doubled from 562 pmp in 2006 to 1220 pmp in 2015 (*23rd Report of the Malaysian Dialysis and Transplant Registry*, 2015). Current projections indicate that, by 2030, the global population of ESRD patients living on dialysis may exceed 2 million (Szczech and Lazar, 2004). Dialysis has a massive impact on financial resources and utilization.

The annual death rate for ESRD on hemodialysis (HD) in 2015 was 13.8%. The overall 5 years and 10 years survival on dialysis were 52% and 27% respectively (*23rd Report of the Malaysian Dialysis and Transplant Registry*, 2015). The trend for death rate among HD patients had gradually increased over the past 2 decades.

The prognosis of the patient with ESRD remains poor even though there had been many advances in the treatment; therefore identification of risk factors which predispose to mortality is important. With early identification of the risk factors, the morbidity and mortality of these patients going for HD will be reduced in the future.

One of the risk factors associated with deterioration of renal function is cardiovascular disease. This factor is more predominant in the patient when they were initiated on dialysis. Based on National Registry 2015, cardiovascular disease accounted for

34% of all death. Death at home accounted for another 18% and the majority of this death was attributed to probably cardiovascular events (*23rd Report of the Malaysian Dialysis and Transplant Registry*, 2015).

Therefore, besides treating the modifiable risk factors namely; smoking, diabetes mellitus (DM), hypertension (HPT), and hyperlipidemia, it is also important to treat the non-modifiable risk factors namely iron deficiency, anemia, insulin resistance and also vitamin D deficiency (Wheeler *et al.*, 2003; Wolf *et al.*, 2007; Zoccali *et al.*, 2003). Preventive measures should not only focus on disease prevention, but also in modifying disease outcomes. To improve patient's survival and quality of life on dialysis therapy, it is important to modify these risk factors (Anand *et al.*, 2011; Mapes *et al.*, 2003; Richards *et al.*, 2007).

1.3 RATIONALE OF THE STUDY

The risk of mortality among patients on HD is high and it varies among patients. There is no tool that is widely available for use to predict the mortality. Availability of a tool or predictive model which is able to stratify risk of mortality would be helpful for HD centers. This model will be able to classify patients into high, moderate and low risk. With this, dialysis providers can have an overview of types of patients that they are dealing with. This tool can also be used in the future study and help to identify suitable dialysis prescriptions or medications. This will help in providing clinical evidence in our clinical practice. This 'risk-stratification-tool' could either be used as a clinical score or embedded in computer-based management systems.

Data in South East Asia population is also lacking with the nearest data available being Singapore.

Patient variables that have a significant impact on mortality were age, gender, primary renal disease, dialysis modality, body mass index (BMI), diastolic blood pressure and the presence of cardiovascular disease. The biochemical variables associated with a significant risk factor for mortality were serum albumin, serum cholesterol, hemoglobin, calcium, calcium phosphate product, phosphate and hepatitis B status (*23rd Report of the Malaysian Dialysis and Transplant Registry*, 2015).

This study intends to describe the demographic profile of newly diagnosed HD patients within their first year of treatment focusing on mortality among them. It will determine the risk factors associated with early death among the Kelantan population during

the first year of dialysis. Risk factors assessed include patient's demography, co-morbidities, and several laboratory parameters. This study will then further analyze the significance of each parameter in relation to one-year mortality.

Determination of these key predictors of early mortality will enable formulation of an effective risk prediction scoring system for clinical use in improving and reducing mortality of ESRD initiated on HD. Careful selection of patients for HD based on a predictive scoring system can improve the mortality rate of HD patients and ensure optimal utilization of public resources.

Besides, this will create an opportunity for intervention for those modifiable risk factors such as HPT, DM, and renal bone chemistry.

CHAPTER 2: LITERATURE REVIEW

2.1 REGIONAL PREVALENCE AND PREVIOUS LOCAL STUDIES

The equivalent incidence and prevalence of patients on dialysis were 249 and 1,220 pmp in 2015. 6479 new HD cases were reported. The total number of HD patients increased to 33,456 giving a prevalence rate of 1097 pmp. The dialysis treatment rate exceeded 200 pmp for all states in Malaysia in 2015, 207 pmp for Kelantan.

Data were based on Malaysian Dialysis and Transplant Registry 2015 and there were no previous local studies done.

2.2 INCIDENCE OF FIRST YEAR MORTALITY AND CAUSE OF DEATH

The highest incidence of mortality is found to be during the first year of initiation of HD. This is proven by few studies which were conducted throughout various countries around the world over the period of 2001 to 2010 (Bradbury *et al.*, 2007; Cherukuri and Bhandari, 2009; Chua *et al.*, 2014; Lukowsky *et al.*, 2012; Wagner *et al.*, 2011).

Based on Malaysian Dialysis and Transplant Registry 2015, patient survival by year of starting dialysis remained unchanged over the last 10 years with a 1 year and 5 years patient survival 86-88% and 50-53% respectively. Cardiovascular events remained the main cause of death accounted 34% for all death. The mean patient survival at 1 year (adjusted for age and diabetes) among HD centers for the 2006-2014 cohort was 91.4%. There was

marked center variation (*23rd Report of the Malaysian Dialysis and Transplant Registry*, 2015).

In 2002, a study was carried out in the UK and it was found that 56% of patient passed away during the first year of initiation of HD. Death was attributed to either vascular disease or infection accounted for the majority of them (Cherukuri and Bhandari, 2009). This was supported by another earlier study conducted in the same hospital in the year 2001 to 2002. The mortality rate was 60% and this was made up of vascular disease and sepsis (Browne *et al.*, 2014).

Subsequently, a study conducted in Europe, Japan, United States, Australia, New Zealand, and Canada, and other European countries from 2002 to 2004. From this study, there were 4802 newly diagnosed ESRD initiated on HD patients, and risk for death was elevated during the first 120 days compared with 121 to 365 days (27.5 versus 21.9 deaths per 100 person-years; P=0.002). The main cause of death was cardiovascular-related deaths (Bradbury *et al.*, 2007).

Another study also had a similar finding where mortality was high in the first 6 months, especially during 1st 2 months. This study was conducted in the United States from 2001 to 2006 (Lukowsky *et al.*, 2012).

Singapore had conducted a study from 2005 to 2010, and of 983 patients, 66 (6.7%) died within 90 days, and a further 103 (10.5%) died after 90 days to within one year from dialysis initiation. The incidence of first-year mortality was 17.2%. The majority of known causes of death in the first year were attributed to major adverse cardiac events and pneumonia which accounted for >30% of deaths (Chua *et al.*, 2014).

2.3 FACTORS THAT CONTRIBUTE TO FIRST YEAR MORTALITY

Several studies have comprehensively analyzed various existing risk factors during the pre-dialysis stage associated with first-year mortality after commencing HD; however, the results were inconsistent.

Patient variables that had a significant impact on mortality were age, gender, primary renal disease, dialysis modality, BMI, diastolic blood pressure and the presence cardiovascular disease. The biochemical variables associated with a significant risk factor for mortality were serum albumin, serum cholesterol, hemoglobin, calcium, calcium phosphate product, phosphate and hepatitis B status (*23rd Report of the Malaysian Dialysis and Transplant Registry*, 2015).

From 2002 to 2004, several studies were conducted in UK and US to study different factors attribute to mortality during the first year of initiation of HD.

A significant proportion of mortality occurred in the first year (56%). The patients who died in the first year had lower eGFR and hemoglobin levels. This group was also older with higher calcium phosphate products. Patients who had a significantly worse mean of survival periods while on dialysis are patients who had vascular disease, DM and in the highest quartile of calcium phosphate product (Cherukuri and Bhandari, 2009).

Bradbury et al. identified older age, catheter vascular access, albumin <35, phosphorus <1.0, cancer and congestive heart failure as mortality risk factors (Bradbury *et al.*, 2007).

Older age, white race, diabetes as a cause of ESRD and HD treatment were independently associated with an increased risk of all-cause mortality in a study done in the UK. Laboratory variables (hemoglobin, serum albumin, creatinine, calcium) and more specific factors, for example, cardiac function or biomarkers, such as C-reactive protein (CRP), adiponectin or N-terminal pro b-type natriuretic peptide (NT-proBNP) have found to be associated with mortality in ESRD patients (Wagner *et al.*, 2011).

A study was conducted in Singapore to examine patient comorbidities and biochemistry prior to dialysis initiation and its relationship to mortality. Older age, DM, IHD, cerebral vascular accident (CVA), peripheral vascular diseases (PVD) were significantly associated with mortality during the first year. These patients also had a low left ventricular ejection fraction (LVEF), low serum albumin, high eGFR, serum urea, alkaline phosphatase (ALP), and uric acid (Chua *et al.*, 2014).

Stevens et al. found that serum phosphate, after adjusting for demographic, dialysis type and adequacy, hemoglobin, albumin, independently predicted mortality. When combinations of parameters were modeled, the combinations of high serum phosphate and calcium with high intact parathyroid hormone (iPTH) and low iPTH had highest risks for mortality as compared with the combination of high iPTH with normal serum calcium and phosphate that had the lowest mortality.

An analysis done in East Yorkshire showed that high calcium phosphate product, DM, vascular disease (such as peripheral vascular disease), older age, low hemoglobin and lower eGFR at initiation of dialysis are predictive of mortality (Browne *et al.*, 2014).

Lukowsky et al. examined mortality patterns and predictors during the first several months of hemodialysis treatment in 18,707 incident patients since the first week of HD therapy and estimated the population attributable fractions for selected time periods in the first 24 months from 2001 to 2006. Highest mortality occurred during months 1 and 2, and mortality rates decreased over periods of 7 months. Early death was associated with more advanced age, a higher proportion of central venous catheters (CVC), and higher prevalence of cardiovascular diseases. Among laboratory parameters, serum levels of albumin, hemoglobin, and calcium were also predictors of 2-year mortality.

2.3.1 PATIENTS VARIABLES

2.3.1.1 Age

Age at initiation of dialysis had a significant impact on early mortality. Patients who died within 90 days of initiation of dialysis were significantly older p<0.001(Chua *et al.*, 2014). A study from UK Renal National Registry cohort also support these findings (Wagner *et al.*, 2011). In another separate study conducted in United Kingdom, those aged greater than 65 years had a mean survival time of 51 months compared to those less than 65 years who had a mean survival of 85 months (p=0.001)(Browne *et al.*, 2014) In United States, age >75 years was found to be significantly associated with high risk of mortality during first 120 days (Bradbury *et al.*, 2007).

2.3.1.2 Co-morbid

Prevalence of diabetes mellitus is increasing among the patients with chronic kidney disease (CKD) (Whaley-Connell *et al.*, 2008). It represents a strong cardiovascular risk factor and a risk factor for mortality in both the general population and patients with ESRD (Brunner *et al.*, 1988; Chantrel *et al.*, 1999). Diabetic patients had a high risk of mortality compared to non-diabetics (Brunner *et al.*, 1988). The 5-year survival rate for patients with DM is 47% vs. 63% without DM (p=0.03) (Cherukuri and Bhandari, 2009). A study conducted in Singapore also showed similar result p=0.04 (Chua *et al.*, 2014). Another study conducted in the UK showed that patients with DM had a cumulative survival of 22% compared to 31% without DM (p=0.03) (Browne *et al.*, 2014).

2.3.2 BIOCHEMICAL VARIABLES

2.3.2.1 Haemoglobin

Anemia is an important complication of chronic kidney disease (CKD) and it contributes significantly to symptoms burden of CKD.

Hemoglobin levels vary substantially over time in hemodialysis patients, and this variability may portend poor outcomes. For a given patient, hemoglobin concentration over time can be described by absolute levels, rate of change, or by the difference between observed level and expected level based on the preceding trend (*i.e.*, seemingly random variability). Survival analyses indicated that each 1g/dl increase in the residual standard deviation was associated with a 33% increase in rate of death. It was concluded that greater hemoglobin variability is independently associated with higher mortality (Yang *et al.*, 2007). This was supported by another study where they found that mortality was greatest in patients who had experienced low hemoglobin levels for ≥3 months. The authors suggest that the number of months that the patient's hemoglobin is below the target level might be a better predictor of mortality than variability itself (Gilbertson *et al.*, 2008).

There were controversies regarding the optimal hemoglobin target in the patient undergoing hemodialysis. Low hemoglobin was associated with high mortality (Messana *et al.*, 2009; Servilla *et al.*, 2009). Based on UK Renal registry data from 2007, 58% of patients started dialysis with a hemoglobin level of <10g/dl (Richardson *et al.*, 2009). Cherukuri et al found a similar finding where 68% of patients started on dialysis with hemoglobin concentration <10g/dl. Early mortality was increased in patients with this hemoglobin level, however, in the longer term; there was no significant effect on mortality. It was proposed

that this may possibly due to anemia management improving on dialysis (Cherukuri and Bhandari, 2009).

2.3.2.2 Alkaline phosphatase (ALP)

Raised ALP is associated with poor survival in HD patients, and such associations persist across different PTH strata (Kalantar-Zadeh *et al.*, 2006). An ALP >80 U/l predicted early mortality, and it remained significant even after adjustment for iPTH (Chua *et al.*, 2014). Raised ALP is linked to vascular health. The raised ALP caused vascular calcification by an increase in the hydrolysis of pyrophosphate, which is a potent inhibitor of vascular calcification (Lomashvili *et al.*, 2008).

2.3.2.3 Albumin

Low albumin has been consistently shown to be associated with death in ESRD (Chua *et al.*, 2014). 33% of death in the first 90 days was associated with hypoalbuminemia in the United States. Reduction of serum albumin per 2 g/L associated with 21% increase in mortality in first 90 days and 12% during the 12-24 month period. There were 5-fold higher infection-related mortality and 2-fold higher cardiovascular mortality in patients with low serum albumin (Lukowsky *et al.*, 2012).

In an earlier similar study in 2007, albumin levels <35 g/L was associated with increased risk of mortality during the first 120 days (Bradbury *et al.*, 2007). Low albumin level is frequently related to anorexia and malnutrition. However, CKD studies suggested

different and more complex etiologies such as acidosis and chronic inflammation (Eustace *et al.*, 2004). The relationship between raised inflammatory markers, low albumin, and cardiovascular events in CKD patients has recently been described (Soriano *et al.*, 2007). Low albumin levels also represent the severity of acute illnesses during the dialysis initiation as it is a negative acute-phase reactant and this usually implies poorer prognosis.

2.3.2.4 Calcium, phosphate and calcium-phosphate products

It is a recognized risk factor in the literature that calcium phosphate product had a significant association with the vascular burden. High calcium phosphate product adversely affects mortality. This association is present even before initiation of dialysis (Cherukuri and Bhandari, 2009).

The changes in biochemical markers of CKD–MBD contribute to the high mortality in patients with CKD. A study conducted in the Europe country had shown that among patients whose mineral bone disorder markers were within The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) target range had lowest risk of mortality (Floege *et al.*, 2010). This was also supported by another study in South America where they confirmed that patients are best maintained at the target ranges as defined by both KDOQI and KDIGO and levels too low or too high are associated with an increased mortality. The comfort of having these serum parameters maintained in the trough of this U-shaped biochemical mortality relationship is shown figuratively in the model (Kalantar-Zadeh *et al.*, 2006).

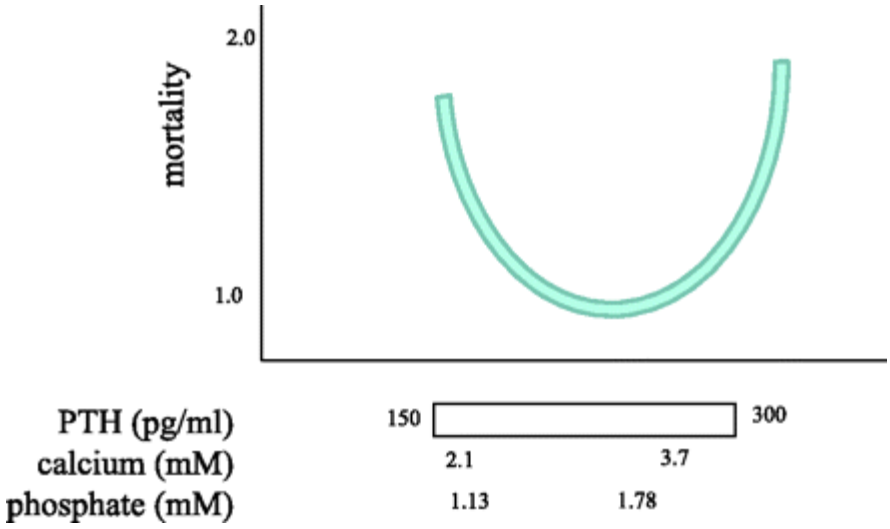

Figure 2.0: U-shaped biochemical mortality relationship

Source: CKD–MBD: comfort in the trough of the U
Nephrology Dialysis Transplantation, Volume 26, Issue 6, 1 June 2011, Pages 1764–1766,https://doi.org/10.1093/ndt/gfr205

A high calcium level have strong prognostic value for long-term mortality base on baseline analysis, whereas a low calcium level has little prognostic value despite its positive association with mortality, when all values of calcium are updated over time (Floege *et al.*, 2010).

The evidence for serum phosphate seems to suggest that either a low or a high level is a risk factor for mortality (Floege *et al.*, 2010). With respect to low phosphate levels, this seems clinically plausible since a low serum phosphate is a marker for malnutrition, a known predictor of mortality (Qureshi *et al.*, 2002). This relation persisted even after adjustment for serum albumin (de Mutsert *et al.*, 2009), which suggests the possibility that the effect of serum phosphate on mortality is acting through another biological mechanism besides nutritional status.

Usually, serum phosphate is elevated in patients with CKD especially when GFR less than 30 ml/min. High phosphate may cause development and progression of secondary hyperparathyroidism. When the product of serum calcium and phosphorus is elevated this predisposes to metastatic calcification. Patients are prescribed with phosphate binders with the advice of restriction of dietary phosphate to reduce serum phosphate. All these conditions lead to morbidity and mortality in ESRD patients (Block *et al.*, 1998; Melamed *et al.*, 2006; Noordzij *et al.*, 2005).

The relationship between bone mineral parameters and mortality was explained in few laboratory and clinical studies through a biological mechanism. The high levels of serum phosphate activate the osteoblastic activity of the smooth muscle cells in the vessels which subsequently promote mineralization of the vascular system (Jono *et al.*, 2000; Moe and Chen, 2004).

There a high rate of coronary calcification among the young hemodialysis patients. This is associated with high calcium intake (Goodman *et al.*, 2000). This might be one of the explanations of mortality in patients with high serum calcium. This is shown by Raggi *et al.* where higher serum calcium and phosphate levels are associated with coronary calcification, in addition to a cross-sectional association of calcification with myocardial infarction (MI), angina and claudication (Raggi *et al.*, 2002).

During the first 120 days of hemodialysis, a phosphate level of <1.13 mmol/L were significantly associated with mortality. Between 121 and 365 days, calcium level >2.37 mmol/L were associated with high mortality risk. A calcium level <2.1 mmol/L was associated with lower risk for mortality.

2.3.2.5 Serum intact parathyroid hormone (iPTH)

Some studies showed that high levels of serum phosphate, calcium-phosphate product, or intact parathyroid hormone (iPTH) are associated with mortality or cardiovascular disease (Block *et al.*, 1998; Ganesh *et al.*, 2001; Stack and Bloembergen, 2001). while others showed implication with low iPTH levels (Avram *et al.*, 2001; Guh *et al.*, 2002). These have led to confusions.

Recently, there a description of the association between high ALP with poor survival in HD patients and this association persist across different PTH strata. PTH levels above 300 pg/ml were associated with high mortality risk among maintenance HD patients. Compared to the iPTH levels 150 to 300 pg/ml (reference) group, iPTH 300 to 600 pg/ml group were incrementally associated with higher mortality risk. However, PTH levels above 600 pg/ml, did not show an increase in mortality but still associated with high death risk. This can be explained as most dialysis patients with very high PTH levels usually received higher than usual doses of the active vitamin D analogs (Kalantar-Zadeh *et al.*, 2006). This was also supported by Floege *et al*., 2010 where they found U-shaped association between iPTH and mortality where low iPTH levels <75 pg/mL are a potential risk factor for mortality.

Those with lowest iPTH levels at the start of dialysis are most likely to die (Avram *et al.*, 2001; Guh *et al.*, 2002), and high serum iPTH levels have an adverse impact (Block *et al.*, 1998; Ganesh *et al.*, 2001).

Higher values of serum phosphate and the highest categorical level of calcium-phosphate product as well as the constellation of the three parameters calcium, phosphate, and iPTH, were a statistically significant predictor of mortality. Patients on dialysis for <6

months seem to have a worse outcome when their phosphate is high, irrespective of whether the calcium and iPTH are high or low, with the highest risk being identified in those with low iPTH, high calcium, and high phosphate. The lowest risk is associated with higher iPTH levels, with normal serum calcium and phosphate levels. Therefore, it is important to maintain some iPTH activity to enable buffering of calcium salts and this reflects an active bone turnover (Stevens *et al.,* 2004). A lower value of iPTH indicates low bone turnover (adynamic bone disease) however, not all patients with low iPTH have low bone turnover, it was patients with low iPTH with raised serum calcium and phosphate levels who had the highest risk of mortality. The constellation of this parameters are better markers for adverse outcomes and low bone turnover compare to iPTH alone.

Thus the interpretation of serum iPTH is important within the context of the duration of dialysis and levels of calcium and phosphate.

2.4 INTRODUCTION TO STUDY AREA

Kelantan is one of the thirteen states in Malaysia. It consists of ten districts including its capital, Kota Bharu. The district of Kota Bharu covers an area of about 410 square kilometers and has a population of about 1.83 million. The majority (95%) is Malay with a small percentage of Chinese and Indian. Two tertiary hospitals namely Hospital Raja Perempuan Zainab II (HRPZ II) and Hospital Universiti Sains Malaysia (HUSM) are located in this district. HRPZ II is a government general hospital while HUSM is a teaching hospital. Apart from receiving patients from Kota Bharu area itself, these two tertiary hospitals also receive patients referred from other district hospitals.

In relation to hemodialysis, Kelantan has 31 hemodialysis centers. Besides the two tertiary hospitals, eight districts hospitals also have hemodialysis facility which includes Hospital Kuala Krai, Hospital Tanah Merah, Hospital Pasir Mas, Hospital Machang, Hospital Tumpat, Hospital Tengku Anis, Hospital Jeli, and Hospital Gua Musang. Another two clinics which also has hemodialysis facilities are Mahligai and Chiku 3. These 10 are all government-sponsored hemodialysis facilities.

There were 20 private or NGO sponsored hemodialysis fascilities. A total of 640 patients currently undergoing hemodialysis in the government sponsored hemodialysis unit in Kelantan for the year of 2016 while another 185 patients awaiting for hemodialysis placement.

CHAPTER 3

OBJECTIVES, RESEARCH QUESTIONS & HYPOTHESIS

3.1 OBJECTIVES

3.1.1 General Objective

To identify prognostic factors affecting 1-year mortality after initiating hemodialysis in newly diagnosed End Stage Renal Disease (ESRD) patients in the state of Kelantan, Malaysia.

3.1.2 Specific Objectives

1. To describe demographic profile of incident patients initiated on hemodialysis.

2. To estimate survival probability within one year in End Stage Renal Disease patients initiated on hemodialysis in Kelantan.

3. To identify prognostic variables for mortality during 1 year follow up of a patient with End Stage Renal Disease initiated on hemodialysis in Kelantan.

3.2 RESEARCH QUESTIONS

1. What are the demographic profiles of End Stage Renal Disease patients in Kelantan?

2. What are the overall survival probabilities of ESRD patients during the first-year initiation of hemodialysis?

3. What are the risk factors that contribute to the first year mortality in incident patients initiated on hemodialysis?

4. How significant is the above risk factors in contributing mortality in incident patients initiated on hemodialysis?