RENAL SURVIVAL AND ITS PROGNOSTIC FACTORS IN CHRONIC KIDNEY DISEASE PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA, KELANTAN

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by

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LIST OF ABBREVIATIONS

A	Accrual time
ABG	Arterial blood gas
ACEi	Angiotensin-converting enzyme inhibitors
ACR	Albumin to creatinine ratio
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ARBs	Angiotensin receptor blockers
AST	Aspartate aminotransferase
BE	Bases excess
CAKUT	Congenital Anomalies of the Kidney and the Urinary Tract
CGN	Chronic glomerulonephritis
CI	Confidence interval
CKD	Chronic Kidney Disease
CO_2	Carbon dioxide
CPN	Chronic pyelonephritis
CVD	Cardiovascular disease
df	Degree of freedom
DM	Diabetic mellitus
DN	Diabetic nephropathy
eGFR	Estimated-Glomerular filtration rate
ESR	Erythrocyte sedimentation rate
ESRD	End stage renal disease
F	Additional follow up
FSGS	Focal segmental glomerulonephritis
GFR	Glomerular filtration
Hb	Hemoglobin
HCO3	Bicarbonate
HCT	Hematocrit test
Hospital USM	Hospital Universiti Sains Malaysia
HPT	Hypertension
HR	Hazard ratio
HTN	Hypertensive nephrosclerosis
IRD	Ischemic renal disease
K	Potassium
KDIGO	Kidney Disease Improving Global Outcome
LR	Likelihood ratio
m	Ratio of two group independent variables
m_1	The median survival time on control
MCH	Mean cell hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modified Diet in Renal Disease
Na	Sodium
NKF-KDOQI	National Kidney Foundation-Kidney Disease Quality Initiatives
NSAIDs	Non-steroidal anti-inflammatory drugs
P04	Phosphate
pCO2	Partial pressure of carbon dioxide
pH	Acidity
pmp	Per million population
pO2	Partial pressure of oxygen
RBC	Red blood cell

RLC	Relative lymphocyte count
RPGN	Rapidly progressive glomerulonephritis
RRT	Renal replacement therapy
SD	Standard deviation
SLE	Systemic lupus erythematous
SPSS	Statistical package for the social sciences
UA	Uric acid
WBC	White blood cell

LIST OF SYMBOLS

n	Sample size
%	Percentage
<	Less than
≤	Less than or equal
>	More than
≥	More than or equal
=	Equal
b	Regression coefficient
β	Beta
r	Pearson coefficient
| |	Modulus
^	Hat
^{2}	Hat square

KADAR JANGKA HAJAT BUAH PINGGANG DAN FAKTOR-FAKTOR PROGNOSTIK DALAM KALANGAN PESAKIT BUAH PINGGANG KRONIK DI HOSPITAL UNIVERSITI SAINS MALAYSIA.

ABSTRAK

Pengenalan: Penyakit buah pinggang tahap terakhir dalam kalangan pesakit buah pinggang kronik merupakan satu beban yang berat kepada pesakit, keluarga, dan sistem penjagaan kesihatan. **Objektif:** Objektif kajian adalah untuk mengetahui tempoh hayat buah pinggang dalam kalangan pesakit buah pinggang kronik di Hospital USM serta mengenalpasti factor-faktor prognostik yang mempengaruhi jangka hayat buah pinggang. **Kaedah:** Kajian kohort retrospektif dijalankan melibatkan 247 orang pesakit buah pinggang kronik di Hospital USM Kelantan bermula pada Januari 2005 hingga Disember 2015. Semua pesakit yang memenuhi kriteria yang perlu telah dimasukkan ke dalam kajian ini. Data pesakit diperolehi melalui rekod perubatan dan tempoh jangka hayat buah pinggang berdasarkan tempoh pesakit disahkan menghidapi penyakit buah pinggang kronik sehingga buah pinggang tahap terakhir. Analisis 'Kaplan-Meier' dan 'Cox proportional hazard regression' telah digunakan dalam analisis statistik. **Keputusan:** Secara kesuluruhan, kadar jangka hayat buah pinggang dari tempoh disahkan sehinnga tahap akhir buah pinggang adalah 26 bulan. Factor-faktor prognostik yang mempegaruhi jangka hayat buah pinggang dalam kalangan pesakit buah pinggang kronik adalah GFR (Nisbah bahaya selaras (HR)= 0.96, 95% Selang keyakinan: 0.98,0.99; nilai p<0.001), status merokok (Nisbah bahaya selaras= 2.19, 95% Selang keyakinan: 1.53, 3.13; nilai p=0.042), comorbid penyakit kolestrol (Nisbah bahaya selaras=1.87, 95% Selang keyakinan: 1.34,2.60; nilai p = 0.005), analgesik (Nisbah bahaya selaras= 1.87, 95% Selang keyakinan: 1.21,2.88; nilai p = 0.015), gangguan GI berfungsi (Nisbah bahaya selaras=1.42, 95 % Selang keyakinan: 1.07,2.01; nilai p = 0.016), ejen merendahkan lipid (Nisbah bahaya selaras= 1.41, 95% Selang keyakinan: 1.02,1.97; nilai p = 0.039), kortikosteroid (Nisbah bahaya

selaras= 2.10, 95% Selang keyakinan: 1.25,3.55; nilai p = 0.005), urea (Nisbah bahaya selaras= 1.03, 95% Selang keyakinan: 1.01,1.05; nilai p <0.001), dan kreatinina (Nisbah bahaya selaras= 0.98, 95% Selang keyakinan: 0.97,0.99; nilai p = 0.005). **Kesimpulan**: Jangka hayat bauh pinggang dalam kalangan pesakit buah pinggang kronik dalam kajian ini sangat cepat iaitu dalam masa 26 bulan. Factor-faktor prognostik seperti takat GFR, status merokok, comorbid penyakit kolestrol, analgesic, gangguan GI berfungsi, ejen merendahkan lipid, kortikosteroid, urea dan kreatinina mempengaruhi buah pinggang dalam kalangan pesakit buah pinggang kronik.

RENAL SURVIVAL AND ITS PROGNOSTIC FACTORS IN CHRONIC KIDNEY DISEASE (CKD) PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA, KELANTAN

ABSTRACT

Introduction: End Stage of Renal Disease (ESRD) in Chronic Kidney Disease (CKD) patients represents a heavy burden for patients, families, and health care systems. **Objectives:** The objectives of this study were to determine the renal survival time of CKD patients at Hospital USM and to identify the prognostic factors that influence the renal survival of patients. **Methodology:** A retrospective cohort study was conducted involving 247 CKD patients at Hospital USM, Kelantan from January 2005 until December 2015. All patients who fulfilled the criteria were included in the study. The medical record were reviewed and the renal survival time based on the time of the first date of diagnosis with CKD until the the first date of diagnosis with ESRD or received dialysis. The Kaplan-Meier and Cox proportional hazard regression analyses were used in the statistical analysis. **Results:** Overall renal survival time of CKD patients was 26 months. The significant prognostic factors that influence the renal survival of CKD patients were GFR (adjusted hazard ratio (HR)=0.96, 95% confidence interval (CI): 0.98,0.99; p value <0.001), smoking status (adjusted HR=2.19, 95% CI: 1.53, 3.13; p value=0.042), comorbid hyperlipidemia (adjusted HR=1.87, 95% CI: 1.34,2.60; p value =0.005), analgesics (adjusted HR=1.87, 95% CI: 1.21,2.88; p value =0.015), functional GI disorder (adjusted HR=1.42, 95% CI:1.07,2.01; p value =0.016), lipid lowering agents (adjusted HR=1.41, 95% CI: 1.02,1.97; p value=0.039), corticosteroid (adjusted HR=2.10, 95% CI: 1.25,3.55; p value =0.005), urea (adjusted HR=1.03, 95% CI: 1.01,1.05; p value <0.001), and creatinine (adjusted HR=0.99, 95% CI: 0.98,1.00; p value =0.005). **Conclusion:** The medium renal survival time of CKD patients in this

study very fast within 26 month. The prognostic factors of renal survival identified were GFR level, smoking status, comorbid hyperlipidemia, analgesics, lipid lowering agents, functional GI disorder, corticosteroid drugs, urea and creatinine are significant to renal survival among CKD patients in Hospital USM. Thus, the clinician can change the clinical management by focus on the factors and slow the progression to ESRD.

CHAPTER 1

INTRODUCTION

1.1 Epidemiology of CKD

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than three months, with the implications for health. CKD is classified based on its cause, GFR category and albuminuria category (Levin and Stevens, 2013)

The incidence and prevalence of CKD were increasing (Rowa Al-Ramahi, 2012). The estimated prevalence of CKD in the US was 16.8% (CPG Secretariat, 2011). CKD is one of the most diseases, leading to death among adults in Malaysia (CPG Secretariat, 2011)

According to Li *et al.* (2001), the global epidemic of CKD has posed a main public health problem, not only in high-income countries but also in Asia. In Asia, the prevalence ranged from 12.1% to 17.5% (CPG Secretariat, 2011). The estimated prevalence of CKD was 13% in a large sample of 13 295 adults in China, a cohort of 574 024 adults in Japan showed the same prevalence of CKD was as reported in China (Li *et al.*, 2001). The overall prevalence of CKD in West Malaysia was 9.07% (Hooi *et al.*, 2013)

According to Wulandari *et al.* (2013), CKD patients diagnosed in Hospital Universiti Sains Malaysia were the end-stage renal failure which was the most frequency disease diagnosed (36.8%), and the second frequency was CKD stage IV (18.4%). With 18 million populations in Malaysia, the number cases of kidney failure case per year were 1800 and 100 cases in 2010 were ESRD (Wulandari *et al.*, 2013). In Scotland, the

increasing of the prevalence of diabetes is the most cause probable to a significant increase in patients with end-stage renal disease (ESRD) requiring renal replacement therapy (RRT). The incidence of new patients on RRT in 2011 was 96 per million population (pmp) with 24% of patients with diabetes as their primary renal diagnosis between 2007 and 2011 (S. Bell *et al.*, 2014).

1.2 Burden of CKD

CKD contribute to a major challenge for the healthcare systems around the world. Patients with kidney disease have implications for their individual health which can occur abruptly, and either resolved or became more chronic. The growing number of ESRD places an enormous human, economic and social burden on the healthcare system (Kerr *et al.*, 2012). The prevalence of CKD by stages 1, 2, 3, 4, and 5 were 4.16%, 2.05%, 2.26%, 0.24%, and 0.36%, respectively (Hooi *et al.*, 2013). The prevalence of stages 3 and 4 CKD at baseline was 4.4% and 0.1% of patients who progress to ESRD (Stein I. Hallan *et al.*, 2009). Furthermore, according to management CKD in adults books reported the incidence and prevalence of patients with ESRD on dialysis had increased from 88 and 325 per million population (pmp) respectively in 2001 to 170 and 762 pmp respectively in 2009 in Malaysia (CPG Secretariat, 2011).

Kerr *et al.* (2012) also reported the definition of direct costs were from health care provided explicitly for or because of CKD while indirect costs are defined as those rising from non-renal conditions for which CKD carries increased hazard. For non-renal conditions, costs were estimated only for 'excess' events, above the level probable for a matched population without CKD. In the year 2009 to 2010, the estimated expenditure on CKD spending on renal problems at £1.64 based on NHS Programmed Budgeting data (Kerr *et al.*, 2012). Primary concern of ESRD among the elderly and

diabetics is the increasing the cost of care in a treatment modality that already consumes a disproportionate share of the health care budget (White *et al.*, 2008). In Malaysia, accordingly to CPG Secretariat (2011), in an economic evaluation of Ministry of Health dialysis centers in Malaysia, the cost of dialysis and erythropoietin was RM2,500 per month.

Adult patients who experienced episodes of AKI were leading to more rapid progression of CKD (Stuart *et al.*, 2010). In 2009, the United States Renal Data System Report revealed that adults patient with an acute kidney injury (AKI) episode during hospitalization have about ten times greater risk of progressing to ESRD by twelve months than patients who did not experience with AKI (Stuart *et al.*, 2010). Social burden reported by CKD patients were cognitive impairment, dementia, sleep disturbance, pain, and emotional and physical dysfunction (Braun *et al.*, 2012).

In Malaysia, there were 27,572 patients on RRT by the end of 2011, which places a large burden on the health-care budget and the prevalence rate of 966 per million population (Nagata *et al.*, 2010). There has been increasing trend in dialysis provision for ESRD in Malaysia from 96 per million population in 2002 to 182 per million population in 2011(Hooi *et al.*, 2013). The donation of RRT in developing economies was limited by lack of financial and other resources. Thus, there are no national reimbursement policies for RRT in many countries in Southeast Asia of Singapore, Malaysia, Thailand, and Indonesia where have accepted a plan of encouraging public-private partnerships to increase the RRT rates in their respective countries (Morad *et al.*, 2015)

1.3 Problem Statement

CKD and ESRD are currently considered as major health burdens. The Kidney Disease Improving Global Outcome (KDIGO) stated that the complications of CKD affect all organ systems. Kidney failure leads to the commonly recognized symptoms of uremia (Levin and Stevens, 2013)

According to last decades, therapeutic advances to slow down the progression of CKD have largely unsuccessful due to several possible reasons such as the lack of profound understanding of the pathophysiology of chronic renal damage, an inadequate characterization of molecular mechanisms of currently approved therapies such as renin angiotensin aldosterone-system (RAAS) blockade, the unclear biochemical property needs required for novel therapeutic approaches, the missing quantity and quality of clinical trials in the nephrology field and the main reasons is the absence of prognostic renal biomarkers that reflect the severity of the structural organ damage and predict ESRD. Currently, CKD remains without approved treatment underlying the need for new treatment to successfully address this high unmet medical need. (Formentini *et al.*, 2012)

1.4 Justification of Study

Many studies have been done in other countries include Malaysia to determine the survival of CKD, but only a few studies had been published from Malaysia. Although many studies had been done about CKD, there is no well-documented study on renal survival in different CKD staging, from diagnosis with CKD at different stages to the ESRD. A study about the prognostic factors of kidney disorders at the Hospital Universiti Sains Malaysia had been conducted by Wulandari *et al.* (2013). However, this study did not investigate the renal survival of CKD patients.

The majority of studies explored the risk factors or prognostic factors among CKD patients. However, there is not much information on the associated of factors of renal survival of CKD patients in Malaysia. Thus, this study will provide some beneficial information regarding renal survival and prognostic factors prognostic factors in CKD in Hospital USM, Kubang Kerian, Kelantan. The research findings of this study highlighted the importance of knowing the time progression of CKD staging.

This study had come up with renal survival which more prognostic factors had been considered. The results of this study were expected to give some positive impact to know the time progression of CKD staging from stage to stage. Early recognition and intervention are essential to slowing disease progression, maintaining the quality of life, and improving outcomes. Physicians have the opportunity to screen the time progression of CKD patient from diagnosis to ESRD, identify the factors that are influencing the CKD progression. This study can help alert physicians to need interventions, and help slow disease progression.

1.5 Research Questions

1. What are the profiles of renal survival of chronic kidney disease (CKD) patients in Hospital Universiti Sains Malaysia?
2. What is the renal survival time of chronic kidney disease (CKD) patients in Hospital Universiti Sains Malaysia?
3. What are the prognostic factors of renal survival of chronic kidney disease (CKD) patients in Hospital Universiti Sains Malaysia?

1.6 General Objective

To determine renal survival time and its prognostic factors in CKD patients in Hospital Universiti Sains Malaysia.

1.6.1 Specific Objectives

1. To determine socio demographics and premobid conditions of chronic kidney disease (CKD) patients in Hospital Universiti Sains Malaysia.
2. To determine the renal survival time of chronic kidney disease (CKD) patients in Hospital Universiti Sains Malaysia
3. To identify the prognostic factors of renal survival of chronic kidney disease (CKD) patients in Hospital Universiti Sains Malaysia

1.7 Hypothesis

1. The prognostic factors of renal survival of chronic kidney disease (CKD) patients in Hospital Universiti Sains Malaysia are socio-demographic characteristics, clinical characteristics, laboratory parameters and treatment characteristics.

CHAPTER 2

LITERATURE REVIEW

Literature search strategies were used to identify the relevant information and articles of the area of interest. The literature searches were used by using phrase searching such as citation search and Boolean operators. Several phases had been used in phase searching include “renal survival among CKD”, “prognostic factors with renal survival”, and “progression of CKD in Malaysia”. For keywords used were “prognostic factors AND renal survival” and “renal survival AND progression of CKD AND chronic kidney disease”. For citation search, author’s name and title of article were used. The search engines used were PubMed, Google Scholar and Science Direct. Related articles needed were imported to Endnote library.

2.1 Progression of CKD patients

2.1.1 Staging of CKD

Renal survival time was calculated from the time to progression from onset of the date of diagnosed of CKD to the date of confirmed end stage of renal disease (ESRD) (Tsai *et al.*, 2014). If all patients who were found to have CKD stages 1 through 4 were referred to nephrologists, then it would place under specialist care 50.2% of all patients in the general population and would progress to ESRD within the next 10.3 year (Hallan *et al.*, 2009). Moreover, the prevalence of CKD stages 3 and 4 at baseline characteristics was 4.4% and 0.1% and prevalence of patients who did not progress to ESRD 46.0% whereas patients who did progress to ESRD was 23.4% (Hallan *et al.*, 2009).

Differences in CKD stages also raise important questions concerning the identification of risk factors associated with progression of CKD to ESRD. Among these is the observation that prevalence rates of stage 3 CKD are now 10 to 20 times more than prevalence rates of stages 4 and 5 CKD (Winearls and Glassock, 2009).

Table 2.1 shows the description of CKD staging based on (National Kidney Foundation-Kidney Disease Outcomes Quality Initiatives) NKF-KDOQI classification. The classification based on GFR (level of kidney function) factor, pathological changes (kidney damage) factor and the presence of the abnormality for at least three months. From KDOQI, the kidney damage was defined when persistent microalbuminuria, persistent proteinuria, persistent hematuria, radiological evidence of structural abnormalities of the kidneys and biopsy-proven glomerulonephritis (CPG Secretariat, 2011).

Table 2.1 Staging of Chronic Kidney Disease

Stage	**GFR (ml/min/1.73m²)**	**Description**
1	≥90	Normal or increased GFR, with other evidence of kidney damage
2	60-89	Slight decrease in GFR, with other evidence of kidney damage
3A	45-59	Moderate decrease in GFR, with other evidence of kidney damage
3B	30-44	
4	15-29	Severe decrease in GFR, with other evidence of kidney damage
5	<15	Establish renal failure

(CPG Secretariat, 2011)

2.1.2 GFR level

In multivariable survival analysis, estimated GFR (eGFR) was independently and strongly associated with progression to ESRD with hazard ratios for eGFR 45-59, 30-44, and 15-29 ml/min per 1.73 m^2 were 6.7, 18.8, and 65.7, respectively and $P < 0.001$ for all category of eGFR (Hallan *et al.*, 2009). Furthermore, time-dependent receiver operating characteristic analyses showed that considering for both urinary albumin/creatinine ratio and eGFR substantially improved diagnostic accuracy. Referral based on current stages 3 to 4 CKD (eGFR 15 to 59 ml/min per 1.73 m^2) would include 4.7% of the general population and recognize 69.4% of all individuals progressing to ESRD. (Hallan *et al.*, 2009).

Currently, Formentini *et al.* (2012) reported accepted end points for ESRD among CKD patients were defined as GFR <15 mL/min per 1.73 m2 or initiation of RRT were impractical for clinical development. The reason is most of CKD patients progress relatively slowly, and long follow-up would be needed for a CKD study before reaching ESRD and second reasons based on renal patients who start RRT with a much lower progress compare to patients who postpone their starting appointment of RRT (Formentini *et al.*, 2012)

According to Cox regression analysis by Hallan *et al.* (2009), showed that within each albumin to creatinine ratio (ACR) category, lower eGFR categories were associated with a higher risk. Similarly with progressively higher ACR categories were associated with a progressively higher risk within each eGFR category. Steadily, results of the Modified Diet in Renal Disease (MDRD) study from Peterson *et al.* (1995) showed that reduction of proteinuria achieved by intensified BP control was associated with lower GFR decline.

Among multiethnic Asian population, there is a consensus on the accuracy in assessing the CKD by using the MDRD and C-G formula (Chin and Mooi, 2012). According to Carroll (2006), stated that the best available method to estimate GFR is the equation from the Modification of Diet in Renal Disease (MDRD) study. In clinical practice, the MDRD equation has several advantages where the formula was accurate when compared to GFRs measured with nuclear medicine techniques, which are considered the gold standard for measuring kidney function, though they are rarely available, and are difficult to perform (Carroll, 2006). The formula for MDRD eGFR is calculated in ml/mim/1.73m^2 : 175 x (Serum Creatinine/ 88.4)$^{1.154}$ x (Age) $^{-0.203}$ x (0.742 if female) (CPG Secretariat, 2011).

2.1.3 NSAID Usage as Progression of CKD

Consumption of non-steroidal anti-inflammatory drugs (NSAIDs) is well-known, and they are frequently prescribed and can be easily obtained over the counter as analgesics. The examples of NSAIDs are diclofenac, ibuprofen, and indomethacin, and selective COX-2 inhibitors. The previous study showed that use of NSAIDs has to have adverse effects on renal function and prior studies have associated both NSAIDs and a subclass, cyclooxygenase-2 (COX-2) inhibitors, to an increased risk of kidney disease (Patel *et al.*, 2012).

High-cumulative NSAID exposure was significantly associated with an increased risk of the faster of CKD progression (Gooch *et al.*, 2007).The previous study also found that those on regular aspirin with stage 4–5 CKD had a slower rate of disease progression per year (Nderitu *et al.*, 2013). Nderitu *et al.* (2013) found that those with stage 3B CKD was significantly associated with NSAID use in both gender. The incidence rate of stage 3B CKD was 58.46 and 42.02 per 10 000 person years for

women and men (Nderitu *et al.*, 2013). NSAIDs and selective COX-2 inhibitors, only be given with monitoring of the serum creatinine level as the drugs can lead to further of permanent renal damage (Dtsch Arztebl, 2010)

High dose NSAID used may significantly increase the risk of accelerated renal function decline by 26% (Nderitu *et al.*, 2013). Whereas, a study from Yarger *et al.* (2011) reported the high-dose NSAID users made up just 4.2% of the total sample population and only 13.4% of these patients had accelerated CKD progression.

2.1.4 CKD progression by Socio-demographic Characteristics

According to Tsai *et al.* (2014), from 2831 patients with ESRD, the younger age below than 30 years were initially identified. The incidence rates of ESRD progressively increased with age, except for a small peak in infants (Tsai *et al.*, 2014).

According to multivariate analysis, variables younger age, male gender, higher blood pressure, not on ACEIs or ARBs, lower haemoglobin, higher proteinuria and lower relative lymphocyte count (RLC) were give significant results with associated with progression to ESRD after adjustment (Mi and Woo, 2014).

The survival time were divided into early and late start groups by the median estimated creatinine clearance (eCCr) for all patients at initiation of dialysis, which was 8.3 ml/min. Patients who started dialysis shows a lower estimated creatinine clearance tended to survive longer. The model retained significance when gender, age, weight, presence of diabetes, mode of first dialysis, initial dialysis access, hemoglobin, serum albumin, blood leukocyte count, and eCCr at the start of dialysis was controlled (Traynor *et al.*, 2002).

In previous studies, smoking had previously been associated with progression of CKD. The prevalence of diabetic nephropathy was highly significantly among heavy smokers which defined as more than ten cigarettes a day for more than one year compared than among non-heavy smokers (Telmer *et al.*, 1984). Smoking also reported a significant associated with progression of ESRD by hazard ratio 1.56 and 95% CI 0.84 to 2.87 compared for those non-smoker (Kim and Kim, 2014). Among diabetic patients smoking has been repeatedly confirmed as an independent risk factor for onset and progression of diabetic nephropathy. Moreover, insulin are dependent and independent diabetes mellitus the risk to develop microalbuminuria or proteinuria that substantially higher in smokers, and smoking also accelerates the rate of progression of diabetic nephropathy to end-stage renal failure (ESRF) (El Nahas and Bello, 2005).

2.2 Median Survival of CKD patients

Causes of ESRD from Tsai *et al.* (2014) study reported the most common causes of ESRD in the young population were glomerulonephropathy, followed by hypertension and genetic and metabolic diseases. The median time of overall renal survival was 0.8 year (interquartile range, 0.7–3.5 years). Congenital anomalies of the kidney and urinary tract (CAKUT) had the longest progression time with median renal survival was 16.0 years to ESRD, while glomerulonephropathy progressed more rapidly than in patients whose ESRD was due to diabetic nephropathy (median renal survival, 0.5 versus 3.2 years). Among the glomerulonephropathy related cases of ESRD, HSP and SLE had longer renal survival time compared with other glomerulonephropathies with median renal survival time for HSP (3.1 years) compared than for SLE (2.7 years) and other glomerulonephropathies was 0.3 year (Tsai *et al.*, 2014)

The probability of reaching CKD stage 5 was estimated as 52% for ten years, where the most accurate model included eGFR, proteinuria at admission, and primary renal

disease. The probability of renal survival was estimated about 63% for patients in the low-risk group and 43% for the medium-risk group and all patients assigned to the high-risk group had CKD stage 5 with a p-value less than 0.001.The median renal survival was only 23 months with 95% CI, 13 to 45 months for patients with glomerular disease versus 122 months with 95% CI, 91.2 to 152.3 months for children with other primary diseases (Cerqueira *et al.*, 2014).

The median survival time in patients with aged <75 years was 69.6 months in RRT group with p-value <0.001, in the absence of high comorbidity and non-diabetics CKD patients. While, the medium survival time for older patients was 28.5 months with P-value < 0.001.(Chandna *et al.*, 2010).

Among a total of 500 patients who had IgA-N therapy, based on time follow up, the renal survival from the time of apparent disease onset was 96.4% at 10 years, 84.5% at 15 years and 73.9% at 20 years (Yata *et al.*, 2008). According to Kukla *et al.* (2008) that conducted a study about stage-to-stage progression based on baseline two group of CCR and eGFR, the median time of stage half-life according to CCR was 5.4 years whereas according to eGFR was 6 years. Study from Traynor *et al.* (2002), patients who started dialysis shows a lower estimated creatinine clearance (eCCr) tended to survive longer. A Cox proportional hazards model reported a significant inverse relationship between eCCr at start of dialysis and survival with hazard ratio 1.1 and p-value 0.02 (Traynor *et al.*, 2002)

2.3 Prognostic Factors of Renal Survival of CKD patients

2.3.1 Socio-demographic factors

2.3.1.1 Age

A study from Eriksen and Ingebretsen (2006), Cox proportional hazards regression analyses were found age, gender, and GFR significant result toward competing for renal failure and death. Furthermore, the interactions between these three variables were tested in the analyses, but none was found significant. Older people with increased one year of aged were increased hazard risk in renal progression with two group of eGFR (eGFR ≥ 45 ml/min/1.73 m2 ; HR:1.11) and (eGFR < 45 ml/min/1.73 m2; HR: 1.06) (Wu *et al.*, 2013).

According to study by Kim *et al.* (2014) with mean age at enrollment was 59 ± 12 years, and 191 (66 %) patients were male with mean eGFR was 37 ± 11 ml/(min 1.73 m2). The factor associated with increased progression to ESRD was younger age, with HR 0.96 and 95 % CI 0.94 to 0.98. However, study from Eriksen and Ingebretsen (2006), showing that older patients are more likely to die than to develop ESRD in contrast to younger patients.

2.3.1.2 Smoking Status

Former and current-smokers less than 70 years of age at inclusion had significant multi-adjusted hazard ratios of 3.32 and 4.01 for kidney failure compared to those who never smoked (Hallan and Orth, 2011).

Hallan and Orth (2011) reported that the prevalence of current smoking did not differ between genders, females (10.2 pack-years) had smoked less than men (15.8 pack-years), and the number of kidney failure cases was lower in females than in men. The

effect of smoking on the risk of kidney failure was similar between women (HR=2.94) and men (HR=4.30), but did not reach statistical significance in women. Thus, this large population-based sample, this study found that smoking is a significant risk factor for future kidney failure (Hallan and Orth, 2011).

Cigarette smoking has been known as a risk factor for the development and progression of chronic kidney disease (CKD) in community-based longitudinal cohort studies. Hazard ratio of Multivariate Cox proportional hazards models identified current smokers was HR, 2.03 (95% CI, 1.33-3.10) as the primary outcome and number of cigarettes at kidney biopsy as significant predictors of the outcomes (Yamamoto *et al.*, 2010).

2.3.2 Comorbidities

One of the prognostic factors for CKD is hypertension that had been shown worldwide. In hypertension, glomerular filtration had been reported to decline more rapidly at a rate of 1.5 mL/ min per 1.73 m2 every year compared to those without hypertension whose decline at 0.75–1.00 mL/ min per 1.73 m2 every year with age of 40 years and above (Hanratty R *et al.*, 2010).

According to Meng and Ahmad (2011) , large studies showed that patients with hypertension had a significantly higher risk of developing CKD compared with normotensive patients. Besides that, hypertension may be a cause or consequence of renal failure. It accelerates the progression of renal disease and may lead to ESRD.

High systolic blood pressure was shown to be significantly correlated to low GFR, which indirectly depicts the importance of optimising blood pressure control in CKD patients (p=0.001; r =-0.229). This result was supported by Marc A. Pohl et al. in

Irbesartan Diabetic Nephropathy Trial (IDNT), which also showed the presence of a direct relationship between control of systolic BP and adverse renal outcomes among type 2 diabetic nephropathy patients, independent of baseline renal function (Hamid *et al.*, 2011).

The major underlying disease of end-stage kidney failure throughout the world in both developed and developing nations is diabetes. It is the primary diagnosis causing kidney disease in 20-40 % of people starting treatment for ESRD (Atkins and Zimmet, 2010). Diabetes is a common disease of CKD patients that requires aggressive management. HbA1C should be reduced to less than 7%, higher levels of HbA1C are associated with CKD progression (Carroll, 2006).

In Malaysia, the number of diabetics has increased by almost 80 percent in the last ten year (Hamid *et al.*, 2011). Furthermore, DM is a major cause contributed to CKD, which is contributing to 58% of new patients requiring dialysis in 2009 (Ong Loke Meng and Ghazali Ahmad, 2011). Commonly, Chronic kidney disease (CKD) can be found in up to 23% of patients with diabetes (Kerri L. Cavanaugh, 2007).

According to Thomas *et al.* (2008), anaemia may be diagnosed in patients at different stage of CKD, and there is a strong correlation between the prevalence of anaemia and the severity of CKD. Therefore, primary care providers play an important role in diagnosing and managing anaemia in CKD patients (Thomas *et al.*, 2008). A study from Levin and Rocco (2006), defined CKD patient were related to anaemia when result of haemoglobin levels less than 13.5 g/dL in men or 12 g/dL in women.

The majority of enroled patients were in CKD stage 3 (65%), in stage 4 (31%) and in stage 5 (4%). The results from Cox Regression analyses, patients with persisting mild

anaemia and those with progressing anemia had a risk of ESRD that was about 80% higher than that of the patients with no anaemia (De Nicola *et al.*, 2010)

2.3.3 Biochemical parameters

2.3.3.1 Proteinuria

Trace amounts of protein in the urine are normal among CKD patients. However, persistently high levels of proteinuria are associated with progressive CKD. Patients with type 2 diabetes and hypertension were had a small amounts microalbuminuria are widely appreciated as a marker of “endothelial mischief”. In addition, all patients with even trace amounts of proteinuria should be considered candidates for cardiac stress testing, and further workup (Carroll, 2006).

The prognostic factor of progression to ESRD among patients who had proteinuria during the first 6 months of follow-up was 3.7 fold times than that among patients who did not have proteinuria during the study period with significant p-value was 0.007, hazard ratio was 3.685 and 95 % confidence interval was 1.437–9.499 (Kim and Kim, 2014).

Proteinuria is an important risk factor for kidney failure and provides a means to identify patients at greatest risk. Halving proteinuria halves the kidney risk. Angiotensin receptor-blocking agent, such as irbesartan, should be regarded as an important therapeutic goal in renoprotective strategies since can reduced proteinuria. For each halving of proteinuria level between baseline and 12 months with treatment, risk for kidney failure was reduced by more than half (HR: 0.44; 95% CI: 0.40, 0.49; $P < 0.001$) (Atkins *et al.*, 2005)

2.3.3.2 Uric Acid

Both correlation results between serum uric acid level and level of GFR was inverse, significant for women (r=0.17; P=0.02) and men (r=0.22; P=.001). Whereas, the unadjusted HR results for uric acid level of Cox Regression analysis was 1.15 (95% CI: 1.04-1.27; P-value: 0.009), and after adjustment for potential confounders, the HR was 1.23 (95% CI, 1.09-1.39; P-value: 0.001). The only factors significantly associated with GFR decrease were uric acid level (Bellomo *et al.*, 2010). Thus, according to Bellomo *et al.* (2010) study, the findings contributed to the demonstration of uric acid as an important risk factor for loss of kidney function.

Greater uric acid levels were associated with older age, male, smoking status, greater BMI, greater prevalence of hypertension, diabetes, use of blood pressure medications, including diuretics, and ECG abnormalities according to Chonchol *et al.* (2007). Patients with an estimated GFR less than 60 mL/min/1.73 m2 increased more than 5 times across uric acid quintiles .The multivariate adjustment, the odds of an estimated GFR less than 60 mL/min/ 1.73 m2 remained linearly associated with increasing quintiles of uric acid concentration . The model was repeated evaluating uric acid as a continuous variable after multivariate adjustment, 1 mg/dL (59 mol/L) increased in uric acid level, the odds of CKD increased by 1.71 (95% CI, 1.61 to 1.81) (Chonchol *et al.*, 2007)

2.3.3.3 Blood Pressure

There is a longitudinal association between achieved blood pressure (BP) and end-stage renal disease (ESRD) among patients with chronic kidney disease (CKD) have not incorporated time-updated BP with appropriate covariate adjustment. The finding

indicated the time-updated SBP greater than 130 mm Hg was more strongly associated with CKD progression than analyses based on baseline SBP (Anderson *et al.*, 2015).

2.3.3.4 Relative Lymphocyte Count

According to Kim *et al.* (2014), 105 of 288 patients (37 %) progressed to ESRD. Decreased absolute lymphocyte counts were associated with the accelerated rate of GFR decline in simple correlation analysis ($r = 0.133$; $p = 0.024$), indicating that lymphocyte count may be reflected CKD progression. When progression to ESRD was compared between patients with low or high RLC (Relative Lymphocyte Count), the low RLC group showed significantly greater progression to ESRD than the high RLC group (Kim and Kim, 2014)

There is no association between high serum calcium (>9.8 mg/dL) and renal outcome since low serum calcium (<9.0 mg/dL) is an independent prognostic factors of rapid renal function progression in CKD stages 3–4 patients (Lim *et al.*, 2014)

2.3.3.5 Blood Urea Nitrogen (BUN)

Increased blood urea nitrogen (BUN) is a helpful clinical clue for the diagnosis of prerenal azotemia, but other causes of unbalanced increment of BUN should be considered including high protein intake. Especially important in the elderly patients with underlying CKD and CHF (Shavit *et al.*, 2012) . Among 260 of patients (17.3%), an increase in BUN 50% occurred in during hospital course, and was associated with increased risk of mortality after adjustments of clinical variables, eGFR and BUN on admission (HR, 1.7 95% CI 1.3–2.2; $P < 0.0001$) (Aronson *et al.*, 2008).

2.3.4 Drug development in CKD

Medications used are important among CKD patients which require consideration. Many drugs such as cimetidine and trimethoprim interfere with creatinine tubular secretion and thus raise serum creatinine levels. The result is a decrease in estimated GFR even though there has been no real effect on renal function. Likewise, unstable kidney function was leading to produce unreliable estimated GFRs, since a steady state must be achieved before the GFR can be estimated (Stevens *et al.*, 2006).

According to Hartmann *et al.* (2010), if the patient is in CKD stage 3 or higher with GFR is below 60 mL/min, certain drugs should no longer be given, either because they tend to damage the kidneys or because they are insufficiently eliminated by poorly functioning kidneys and will therefore accumulate in the body and cause toxic side effects on other organs. Three of the drugs were ACE inhibitors, AT1 blockers, and the renin inhibitor have renal dependent pharmacokinetics, so that it suffices to give these drugs in half the normal dose to patients with renal insufficiency, hence for this situation, special attention must be paid to the risk of hyperkalemia. (Hartmann *et al.*, 2010). Spironolactone should be given only in a low dose no or not at all, to patients with renal insufficiency to avoid hyperkalemia. A patient with renal insufficiency is given, then only in combination with a thiazide diuretic, furosemide, or both (Hartmann *et al.*, 2010).

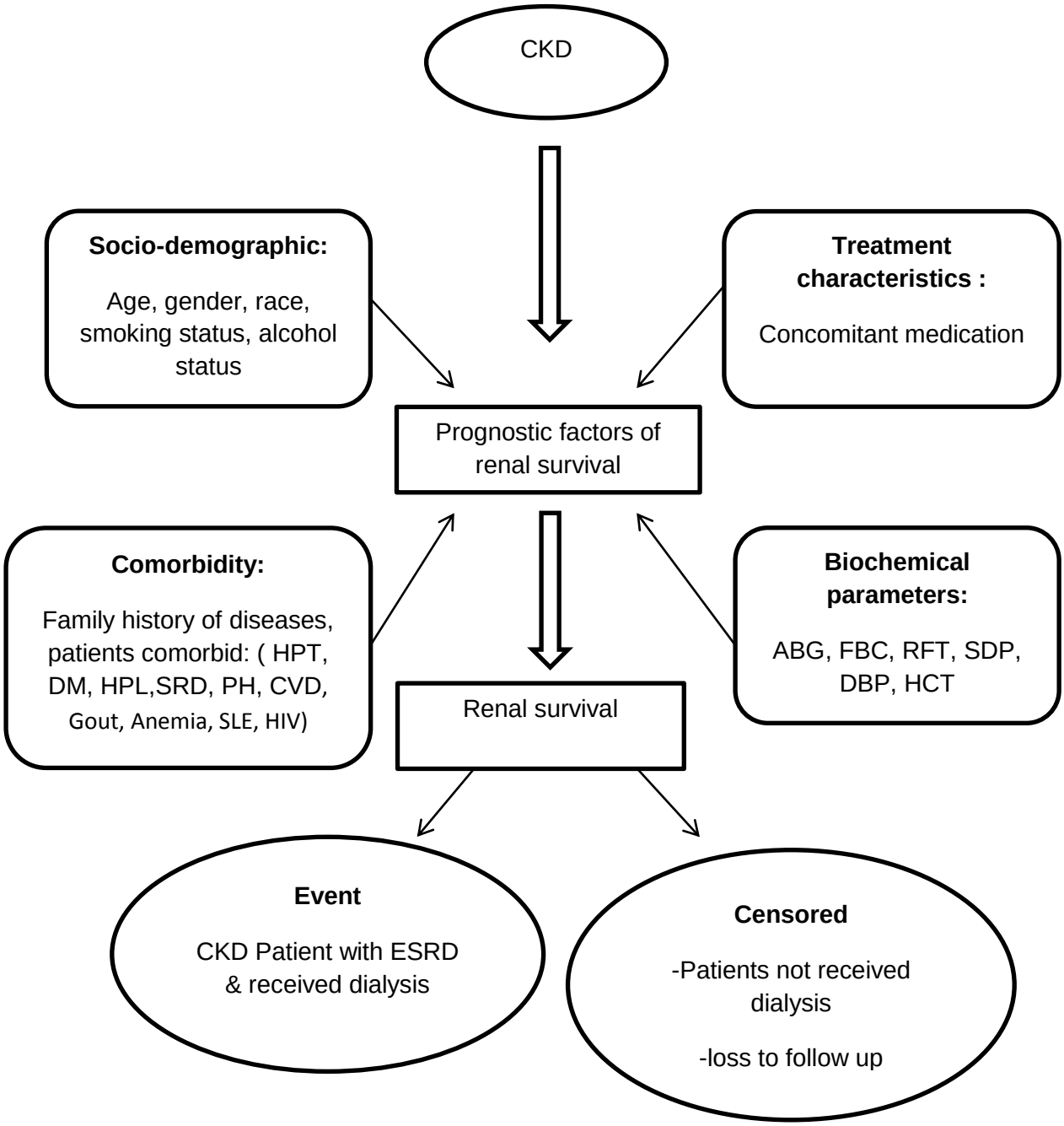
Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) are probably the first-choice antihypertensive, particularly if proteinuria is present as they are effective in delaying progression of diabetic and non-diabetic proteinuric nephropathy. Although ACEi and ARB therapy reduce proteinuria by reducing angiotensin II, this dilates the efferent arteriole and reduces intraglomerular pressure and GFR (Haynes and Winearls, 2010).

Moreover, a study from Haynes and Winearls (2010) stated that the anti-proteinuric effect of ACEi or ARB therapy is improved by sodium restriction and/or diuretic therapy. In the advanced stages of CKD, sodium retention contributes to hypertension and hence diuretic therapy when relatively with high doses can reduce blood pressure successfully. Patients with CKD frequently need multiple agents to control blood pressure.

Systolic blood pressure was slightly higher in patients with CKD than in patients with normal eGFR. There was little change in systolic and diastolic blood pressure. There was a greater used of inhibitors of the renin-angiotensin system during the trial in patients with CKD where, 64.8% of patients receiving atorvastatin 80 mg and 66.0% of patients receiving atorvastatin 10 mg compared than in patients with normal eGFR with 56.5% receiving atorvastatin 80 mg and 59.4% receiving atorvastatin 10 mg (Shepherd *et al.*, 2008).

Lipid-lowering therapy is not widely used in persons with chronic kidney disease (CKD) regardless of a high burden of dyslipidemia and cardiovascular disease. This therapy decreased cardiac death and atherosclerosis-mediated cardiovascular events in persons with CKD (Upadhyay *et al.*, 2012). Furthermore, the lowering LDL cholesterol with the combination of simvastatin and ezetimibe safely reduces the risk of major atherosclerotic events in a wide range of patients with chronic kidney disease. Among the 6247 patients not on dialysis at randomisation, simvastatin plus ezetimibe did not produce significant reductions in any of the prespecified measures of renal disease progression: ESRD defined as commencement of maintenance dialysis or transplantation (RR 0·97, 95% CI 0·89–1·05, p=0·41); ESRD or death (RR 0·97, 0·90–1·04, p=0·34); and ESRD or doubling of baseline creatinine (RR 0·93, 0·86–1·01; p=0·09) (Baigent *et al.*, 2011)

2.4 Conceptual framework



CHAPTER 3

METHODOLOGY

3.1 Study Design

The study design applied in this study was a retrospective cohort study. Patients' medical records were reviewed from Medical Record Unit, Hospital USM. The advantage of this study design included typically requiring less time and these studies tend to be less expensive because the outcome and exposure had already occurred.

3.2 Study Period

The recruitment phase of the subjects began from year 1st January 2005 until 31st December 2015. The period of study was from September 2015 until April 2016. The data collection period was from February 2016 until April 2016.

3.3 Study Location

The study was conducted in the Hospital USM which is an urban, academic hospital and tertiary care center with specialist in nephrology. CKD Resource Centre HUSM have nephrology clinic, CKD research unit (Renal Lab), CKD Interventional Nephrology Unit, CKD education and training Unit and Hemodialysis Unit.

3.4 Study Population

3.4.1 Reference Population

The reference population was all CKD patients in Kelantan

3.4.2 Source Population

The source population was all CKD patients registered in Hospital USM, Kubang Kerian, Kelantan during the study period from 1st January 2005 until 31st December 2015.

3.4.3 Sampling Frame

The sampling frame was a list of all CKD patients registered in Hospital USM from 1st January 2005 until 31st December 2015 that fulfill inclusion and exclusion criteria.

3.4.3 (a) Inclusion Criteria

The inclusion criteria are all CKD patients who received dialysis registered in Hospital USM from 1st January 2005 until 31st December 2015.

3.4.3 (b) Exclusion Criteria

The exclusion criteria CKD patients with more than 30% of missing data and patients who were transferred out from Hospital USM.