THE RATE AND ASSOCIATED FACTORS FOR GFR DECLINE AMONG CHRONIC KIDNEY DISEASE STAGE 3 PATIENTS IN HUSM: A RETROSPECTIVE STUDY

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LIST OF ABBREVIATIONS

ACEI	Angiotensin-converting-enzyme inhibitor
ARB	Angiotensin receptor blockers
CKD	Chronic Kidney disease
CI	Confidence Interval
CPG	Clinical Practice Guideline
DM	Diabetes Mellitus
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
HbA1c	Haemoglobin A1c
HUSM	Hospital Universiti Sains Malaysia
KDIGO	Kidney Disease: Improving Global Outcomes
NKF	National Kidney Foundation
NSAIDs	Nonsteroidal anti-inflammatory agents
MDRD	Modification of Diet in Renal Disease
MOH	Ministry of Health
SD	Standard Deviation
USRDS	United States Renal Data System

LIST OF SYMBOLS

%	percentage
/	or
:	Ratio
<	less than
=	equal to
>	more than
®	trademark registered
µl	Mikrolitre
µm	Micrometre
1-β	statistical power
G	Gram
kg/m2	Kilogramme per metre squared
M	ratio of control / cases
mg/Dl	milligram per decilitre
Min	Minute
Ml	Millilitre
Mm	Millimetre

mM	Milimolar
mmol/L	milimole per litre
N	number of subjects
ng/µL	nanogram per microlitre
ºC	degree celcius
P	short arm of chromosome
pstat	p value
Pa	probability of exposure in cases
Po	probability of exposure in controls
Q	long arm of chromosome
qstat	1-prevalence
T	Translocation
™	Trademark unregistered
Vs	Versus
A	type 1 error
Δ	Precision
Λ	lambda
K	Kappa

ABSTRAK

Kadar penurunan dan faktor risiko berkaitan untuk penurunan GFR dalam kalangan pesakit Buah Pinggang Kronik Tahap 3 di HUSM: Kajian Retrospektif

Pengenalan: Penambahan pesakit yang dikesan menghidap CKD semakin meningkat, selain memberi kesan terhadap kesihatan individu, kesan ke atas penyakit juga boleh dilihat kepada ekonomi nasional apabila kos pengurusan dan rawatan CKD progresif, terutamanya kegagalan tahap akhir buah pinggang (ESRD) sangat tidak seimbang dengan populasi pesakit yang terjejas. Sifat penyakit ini menyebabkan terdapatnya peningkatan keperluan untuk mengesan dan menguruskan CKD pada tahap awal penyakit seperti CKD tahap 3. Oleh sebab itu, pengesanan faktor risiko berkaitan untuk Kadar Filtrasi Glomerular (GFR) yang menurun dalam kalangan pesakit CKD tahap 3 telah menjadi objektif penting dalam perjalanan objektif kajian ini. **Metodologi:** Ini merupakan kajian kumpulan retrospektif yang melibatkan tinjauan rekod perubatan dan kajian darah 142 pesakit buah pinggang kronik di Hospital USM (HUSM) yang telah dikesan dengan CKD tahap 3 daripada 1 Januari 2008 sehingga 31 Disember 2016. Lain-lain butiran berkaitan adalah umur, jantina, etiologi CKD, kadar HbA1c, tekanan darah Sistolik, tahap albumin Serum, kehadiran proteinuria dan penggunaan enzim perencat penukaran-angiotensin (ACEI)/pemblok reseptor angiotensin (ARB) juga dikumpulkan. Faktor berkaitan dengan perubahan kadar GF dianalisis menggunakan regresi logistik linear dan pelbagai. Tahap signifikan ditentukan pada 0.05. **Keputusan**: Kadar penurunan GFR mengikut tahun dalam kalangan CKD tahap 3 adalah 2.77 mL/min/1.73m2/tahun. Faktor berkaitan dengan perubahan GFR dianalisis menggunakan regresi linear dan logistik pelbagai. Dalam tinjauan selama 3 tahun, 66.19%

peserta adalah penyakit stabil (sama atau kurang daripada 24.5% penurunan GFR) dan 33.81% adalah penyakit progresif (daripada 25% penurunan GFR). Secara predominan, kebanyakan pesakit CKD tahap 3 terus berada di tahap 3 (80.3%) selepas 3 tahun, manakala sedikit sahaja jumlah yang meningkat ke tahap 4 (18.3%) dan tahap 5 (1.4%). Terdapat empat faktor yang dikenalpasti daripada analisis regresis linear pelbagai yang membantu meramalkan perubahan GFR dalam CKD tahap 3; umur (0.33 {95% CI:0.17, 0.49], nilai p = 0.49], nilai p = = <0.001), jantina (-4.48[95% CI: -7.43,-1.52], nilai p = 0.003), tahun albumin serum 3(0.53 [95% CI: 015, 0.90] nilai p 0.006), penggunaan ACEI/ARB (-4.51[95% CI: -8.00, -1.03], nilai p 0.012). **Kesimpulan:** Penurunan GFR setiap tahun dalam CKD tahap 3 boleh dibandingkan dengan kajian lain dan kebanyakannya peserta kekal dalam tahap 3 CKD dan lebih daripada separuh mempunyai penyakit yang stabil. Umur yang lebih tua merupakan faktor predominan dalam penurunan GFR yang perlahan dalam CKD tahap 3, manakala serum albumin normal dikaitkan dengan penurunan GFR yang lebih baik berbanding dengan serum albumin yang rendah. Apa yang menarik adalah, jantina perempuan dalam kajian kami dikaitkan dengan penurunan GFR yang lebih cepat berbanding dengan jantina lelaki. Statistik penggunaan ACEI/ARB telah menunjukkan negatif terhadap GFR di kalangan peserta namun ianya mungkin disebabkan kerana terdapat pelbagai faktor tidak terkira yang memberi kesan terhadap keputusan. Maka, ia perlu diterima dengan waspada.

ABSTRACT

The rate and association factors for GFR decline among Chronic Kidney Disease Stage 3 Patients in HUSM: A Retrospective Study

Introduction: The number of patients diagnosed with Chronic Kidney Disease (CKD) has steadily; other than affecting the health of the individuals, the impact of the disease can also be seen in the national economy as the cost for management and treatment of progressive CKD, in particular end stage renal failure (ESRD) is highly disproportionate to the population of affected patients. Due to the nature of the illness, there is an increased need to detect and manage the CKD at earlier stage of the disease such as CKD stage 3. Hence, identifications of relevant risk factors for Glomerular Filtration Rate (GFR) decline among CKD stage 3 has become the paramount objective of this research endeavour. **Methodology**: This is a retrospective cohort study involving a review of the medical records and blood investigation result of 142 chronic kidney disease patients in Hospital USM (HUSM) that was diagnosed with CKD stage 3 from 1st January 2008 to 31st December 2016. Other relevant details such as age, gender, aetiology of CKD, HbA1c level, Systolic blood pressure, Serum albumin level, presence of proteinuria and usage of angiotensin-converting enzyme inhibitors (ACEI)/ angiotensin receptor blockers (ARB) were also collected. The association factors with GFR rate changes were analysed using linear and multiple linear regressions. Level of significance was fixed at 0.05. Results: The rate of GFR decline per year among CKD stage 3 is 2.77 mL/min/1.73m^2/year. Within 3 year observation, 66.19% of the participants were stable disease ($\leq$ 24.9% GFR reduction) and 33.81% were progressive disease ($\geq$ 25% GFR reduction). Predominantly most CKD stage 3 patient remained in

stage 3 (80.3%) after 3 year, while small numbers progressed to stage 4 (18.3%) and stage 5 (1.4%). There are four factors that were identified from the multiple linear regression analysis that help predicted GFR changes in CKD stage 3; age (0.33 [95% CI: 0.17, 0.49], p value = <0.001), gender (-4.48[95% CI: -7.43,-1.52], p value = 0.003), serum albumin year 3(0.53 [95% CI: 015, 0.90] p value 0.006), usage of ACEI/ARB (-4.51[95% CI: -8.00, -1.03], p value 0.012). **Conclusion**: The rate GFR decline per year in CKD stage 3 are comparable with other studies and predominantly the participant remained in CKD stage 3 and more than half have stable disease. Older age is the predominant factor in slower GFR rate decline in CKD stage 3, while normal serum albumin associated with better GFR rate decline compared to low serum albumin. Interestingly, female gender in our study however, was associated with faster GFR rate decline compared to male gender. The usage of ACEI/ARB statistically had shown to have a negative effect on GFR among our participant but there are possible uncountable factors affecting this result, thus need to treat it with caution.

CHAPTER ONE

INTRODUCTION

1.1 EPIDEMIOLOGY, AETIOLOGY AND THE IMPACT OF CHRONIC KIDNEY DISEASE

Chronic Kidney Disease (CKD) has progressively emerged as one of the significant illnesses that contributed to the increase rate of morbidity and mortality among the worldwide population (Rhee and Kovesdy, 2015). Furthermore, Global Burden of Disease Study has ranked CKD at 18th among the other illnesses in the total number of death in 2010 (NKF, 2017). It has been estimated that approximately 10% of the world population are currently affected by CKD (NKF, 2002). Statistically, based on the meta-analysis study, the global CKD prevalence (Stages 1 to 5) was 13·4% and as for the local population-based study among adult West Malaysia, the prevalence of CKD was 9.07% (Hooi et al., 2013). The detection of CKD among general population also has increased as the surveillance of renal function among patients with chronic illnesses within general practitioner setting has becomes more common.

The definition by The Kidney Disease: Improving Global Outcomes (KDIGO); CKD define as any abnormalities of kidney structure or function that presented more than three months with implications for health (Obrador, 2017, KDIGO, 2013). The abnormalities of kidney function and structure is described as having glomerular filtration rate (GFR) less than 60mL/min/1.73m^2 or having other abnormality such as urine albumin, abnormality of histology and radiology finding or history of renal

transplant (KDIGO, 2013). The symptoms of the CKD can be non-specific and variable; from asymptomatic or mild lethargic to a very severe illness requiring urgent intervention, which depends on the level of GFR itself. The early stage of CKD (stage 1-3) however, mostly have no to very minimal symptoms which resulted very few patients aware of their conditions or undermine their condition. The symptoms manifested in CKD are the result of a complex pathophysiological process due to compromising of overall kidney physiology function in filtering the blood and waste removal, acid-based homeostasis, osmolality regulation, blood pressure regulation and hormonal secretion. Thus, the long term manifestations of the disease can also raise complication in other systems such as cardiovascular disease and mineral-bone disorder.

The major contributors for CKD worldwide are diabetic nephropathy and hypertensive nephropathy, which counted for two third of CKD aetiology overall (NKF, 2017). The other one third mainly contributed by Glomerulonephritis disease, Polycystic Kidney Disease, Obstructive Nephropathy and autoimmune disease such as Systemic Lupus Erythematous(BetterHealthChannel, 2014, Obrador, 2017, NKF, 2017). It has been estimated that 20% to 40% of diabetic patient will develop renal impairment (Diabetic.co.uk, 2018, BetterHealthChannel, 2014) and, uncontrolled of blood pressure has been long recognized as an independent factor for further deterioration of GFR in CKD patients of any aetiology (Ravera et al., 2006). Thus, diabetes and hypertension control have been a major focus in efforts to control the CKD progression as presented in few clinical studies (Mann, 2018). For other causes of CKD such as Glomerulonephritis or Autoimmune disease such as Lupus Nephritis, the degree of renal

impairment are dependent of multiple factorial such the subtype of the disease, timing of the diagnosis and treatment and also controlled of the other risk factors (Jaipaul, 2018).

While at the early stage of CKD most patients remained asymptomatic, the impact of developing CKD to patients' general health per se has been an interesting subject to study. CKD itself is an independent risk factor for Cardiovascular Disease in addition to other traditional factors such as hypertension, hyperlipidaemia or diabetes mellitus, and thus not surprisingly cardiovascular disease is still the leading cause of mortality in CKD patients (Turin et al., 2012a, Coresh et al., 2014). Additionally, the progression of CKD to ESRD has been shown to add significant morbidity and mortality burden to the affected patients (Noordzij and Jager, 2014, Al Wakeel et al., 2002). Even without reaching ESRD, there is a considerable increased mortality risk among CKD patient when there are ≥ 25% reductions of GFR over in 1 year period (Turin et al., 2012a). The impact of the disease can also be seen to the national economy as the cost for management and treatment of progressive CKD, in particular end stage renal failure (ESRD) is normally highly disproportionate to the population of affected patients (Nugent et al., 2011).

1.2 CALCULATING GLOMERULAR FILTRATION RATE AND THE STAGING OF CHRONIC KIDNEY DISEASE

Glomerular Filtration Rate (GFR) is one of the methods used to estimate the overall index of renal function. By definition, GFR is the volume of fluid filtered from the renal glomerular capillaries into the Bowman's capsule per unit time. While there are few methods has been established in measuring GFR and creatinine clearance in estimating renal function; which included methods using substances such as inulin or radioactive tracer, the most convenient ways in clinical setting to estimate overall renal function is to calculate estimated GFR based on serum creatinine.

A number of studies and formulae have been produced to devise the estimated GFR or Creatinine Clearance, and these formulae are using the values of serum creatinine level that are mostly included in the routine blood test for patients with renal impairment. The most commonly used formulae are:

- Cockcroft-Gault formula
- Modification of Diet in Renal Disease (MDRD)
- CKD-EPI
- Mayo Quadratic
- Schwartz formula

Each formula has its own advantages and disadvantages, depending on the patient's factor or clinical setting (NKF, Stevens et al., 2010).

Modification of Diet in Renal Disease (MDRD) formula was an equation developed in 1999 and re-expressed in 2005, using four-variables to estimate the GFR – serum creatinine, age, and ethnicity and gender (Levey et al., 1999a). MDRD Study equation is shown to have reasonable accuracy in non-hospitalized patients that have CKD regardless of diagnosis. This equation however has less accuracy in measuring GFR in group of patient that don't have CKD, and it also has not been validated in young patient, very old patient, pregnant patient and small group of racial ethnicity like Hispanics. It also tends to underestimate the estimated GFR in heavy patients and underestimated the calculated GFR in underweight people due to the formula do not included body mass values.

In the study that observing patient with established CKD (particularly stage 3 and above) with variable aetiology, the usage of MDRD Study equation for GFR is acceptable as this formula correlated well with creatinine clearance in the ranged of 30 – 60mL/min, producing reasonable estimated calculated GFR (Haas, 2006).

Finally, CKD can be classified according to causes, GFR or albuminuria (KDIGO, 2013). From the calculated estimated GFR, CKD can be further classified into five stages; chronic kidney disease stage 1 to chronic kidney disease stage 5.

- Stage 1 : Normal GFR (>90 mL/min/1.73m2) and persistent albuminuria
- Stage 2: GFR 60 to 89.9 mL/min/1.73m2 and persistent albuminuria
- Stage 3a: GFR 45-59.9 mL/min/1.73m2
- Stage 3b: GFR 30-44.9 mL/min/1.73m2
- Stage 4: GFR 15 to 29.9 mL/min/1.73m2
- Stage 5: GFR <15 mL/min/1.73m2

Staging the CKD helping to standardize the condition and assisting specialist referral, general medical management, and indications for investigation and therapeutic interventions (KDIGO, 2013).

1.3 MANAGEMENT OF CHRONIC KIDNEY DISEASE

The principles of management of CKD can be simplified into i) to delay and retard the GFR deterioration ii) to have appropriate diagnosis and treatment to the pathological process of the CKD and lastly iii) to have appropriate and timely planning for the long-term renal replacement therapy (Arora, 2018). The care of patient with CKD should include early referral to nephrologist and also multidisciplinary involvement, depending on the aetiology of the renal disease; such as urologist for obstructive nephropathy and endocrinologist for diabetes mellitus with diabetic nephropathy.

The effort to delay and retard the disease progression in CKD is essential in managing this condition. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has recommended three majors interventions or strategies in slowing the progression of the GFR decline in CKD and also reducing the cardiovascular risk that associated with the disease. NIDDK's strategies included nutritional intervention, lifestyle intervention and medical intervention(NIDDK, 2018). The primary intervention in nutritional intervention is to limit the sodium intake to 2300mg/day and the protein intake to 0.8g/kg body weight/day. Patient should also be advised to limit the intake of dietary phosphorus to maximum 0.8 to 1 g/day and potassium to less than 2400mg/day

if there is present of hyperkalaemia (Monique E Cho, 2018, NKDEP, 2015). A consultation with dietician can help the patient in managing their diet and even individualized the medical nutrition therapy. Lifestyle intervention is focusing on encouraging health-promoting behaviours involving smoking cessation and also appropriate physical activity. Smoking may exaggerate the progression of CKD by its relation to associate with proteinuria (Briganti et al., 2002). Both smoking cessation and regular exercise can also help prevent cardiovascular disease, diabetes control and maintain muscle mass.

The key strategy in retarding the CKD progression from medical intervention is by aggressive controlling and stabilizing the blood pressure, achieving targeted HbA1C as per latest diabetic association recommendation, usage of either Angiotensin-Renin Blocker (ARB) or Angiotensin-converting enzyme inhibitor (ACEI) and also avoidance of nephrotoxic drug or substance such as intravenous (IV) radiocontrast media, nonsteroidal anti-inflammatory agents (NSAIDs), and aminoglycosides(Arora, 2018). There is evidence that even in advance CKD the prospect of long term dialysis can be reduced if patient has good controlled of hypertension. A prospective cohort study by Hsu et al indicated that in patients with advanced CKD and stable hypertension, antihypertensive treatment with ACEIs or ARBs reduces the likelihood of long-term dialysis and lowers the mortality risk as well (Hsu et al., 2014). The usage of ACE Inhibitor in Diabetes Mellitus type 1 and Angiotensin-Renin Inhibitor in Diabetes Mellitus type 2 have shown benefit in reducing proteinuria in such patients and indirectly helped in slowing down the degree of GFR deterioration (Bakris, 2008).

CHAPTER TWO

LITERATURE REVIEW

2.1 THE NATURAL PROGRESSION OF GFR DECLINE OVER TIME AMONG HEALTHY INDIVIDUAL AND CKD PATIENT

There are few published literatures have shown that there are progressive decline and deterioration of the GFR among the CKD patient over time. For example, MDRD Study, a cross-sectional study in 1999 has observed 1628 CKD patients' renal function on average of two years follow-up and the data from the study show that the average rate of GFR decline was approximately 4mL/min/1.73m2 (Levey et al., 1999b). Study by Turin TC et al however show that only 7% has either drop or rise in kidney function while the majority of the participant have stable renal function (74.8%) over one year observational period (Turin et al., 2012a).

Interestingly, this process also shown to occur even among healthy individual where even among carefully screened healthy kidney donor, GFR is shown to decline over time; although at a rate that much slower compared to CKD patient (Denic et al., 2016). Denic et al study further estimated the GFR decline among his study samples was approximately 0.63 mL/min/1.73 m^2 per year. Hommos et al also has looked at the structural and functional changes in human kidneys with healthy aging, and the study indicated that there are macro and micro pathological structural changes in the kidney even in the absence of age-related comorbidities (Hommos et al., 2017). Linderman et al similarly found that two third of older adult with non-significant medical health

problems will have some degree of GFR decline based of creatinine calculation but only less than 2% of these elderly population will developed ESRD requiring renal replacement therapy (Lindeman et al., 1985, Anderson et al., 2009).

Consequently, it is not surprizing that some experts have question the role of screening for CKD stage 3 with using estimated GFR without taking into account the normal age- and gender- associated decline in GFR, as this may leads to an erroneous categorization of large numbers of mostly elderly and female subjects as having an intermediate stage of chronic kidney disease (Glassock and Winearls, 2008). KDIQO has since tried to address this issue through updating on the definition of CKD since 2009 in the KDIQO CKD Guideline by modified the classification definition to include the cause of disease and albuminuria staging(KDIGO, 2013). In summary, we do recognize from all these previous literature reviews that GFR deterioration over time can occurred in healthy individual and CKD patients, but the difference between them is the rate of GFR decline over time.

2.2 THE INCIDENCE AND PREVALENCE OF CHRONIC KIDNEY DISEASE STAGE 3

There are few studies that have been published on the estimated prevalence of CKD, either global or within the Malaysia's population. The prevalence of CKD stage 3 globally was estimated approximately at 7.6% (6.8 – 8.9%) (Hill et al., 2016). However, the true prevalence varies between different countries. For example, the data from the survey of US population by National Health and Nutritional Examination Survey (NHANES) from 2013 to 2014 estimated the prevalence of chronic kidney disease stage 3 in US population is around 7.1% (6.4 – 7.8%) (NHANES, 2016).

On the other hand, the prevalence of CKD in Malaysia from literature is higher; it is estimated at 9% of the general population have some renal impairment, with CKD stage 3 represent 2.26% of the normal population (Hooi et al., 2013). Furthermore, 30.6% of the CKD patients in Malaysia estimated to be represented by CKD stage 3 (CKD stage 3b 21.9% and CKD stage 3a 8.7%) (Salman et al., 2015). The prevalence of CKD manifestation among Diabetes Mellitus (DM) type 2 patients required special attention as it has been recognized as the major aetiology for chronic kidney disease. The study of prevalence of CKD in type 2 DM has been explored by Wu et al based on US National Health and Nutrition Examination Survey (NHANES) datasets developed during 2007–2012 (Wu et al., 2016). This cross-sectional study show that 38.7% patient with DM type 2 has developed chronic renal impairment. MADIABETES study, a prospective cohort study which analysed five-year incidence of CKD (Stage 3-5) among type 2 DM Population in Madrid, Spain also concluded that the cumulative incidence of CKD stage

3-5 at five years was 10.23% (Salinero-Fort et al., 2015). Both studies however didn't highlight the specific incidence of CKD stage 3 among the diabetic population.

2.3 RATE OF GFR DECLINE AND CKD STAGING CHANGES AMONG CKD STAGE 3 OVER TIME

While there are multiple studies have published on the rate of GFR decline among overall CKD patients, only a few mentioned rate of GFR decline specifically among CKD stage 3. There were two studies in Taiwan among CKD stage 3 in single centre reported annual decline rate stated as 2.24 mL/min/1.73m^2/year and a median GFR decline per year of 2.11 mL/min/1.73m^2/year among CKD in general (Tsai et al., 2017, Chiu et al., 2008a). This result is lower than the estimated rate of GFR decline per year reported by MDRD study which was 4.0 mL/min/1.73m^2/year that included all level of CKD into their study (Levey et al., 1999b). Likewise, another study among CKD stage 3b has published rate of GFR decline of 0.47 ± 0.42 mL/min/1.73m^2/year and again the result is lower compared to MDRD (Lin et al., 2013).

In regard to CKD staging changes among CKD stage 3 patients, it was addressed in study by Baek et al; upon reviewing CKD stage 3 patients for 10 years, it has concluded that 48.1% of the studied patient will remained in CKD stage 3 while the other 51.9% of the patient will progressed to higher stage (CKD stage 4 – 17.3%, CKD stage 5 – 34.6%) (Baek et al., 2012). 91 out 196 patients within the study have required

dialysis throughout the 10 years follow-up period. On the other hand, the study by Lin et al among the CKD stage 3b that received follow-up more than 12 weeks reported more higher percentage (54.1%) of patient CKD stage 3b remained in similar staging over time (Lin et al., 2013). Interestingly, Lin et al also reported there were significant proportions of stage reversal (stage 3b to stage 3a) can be observed among CKD stage 3b (19.3%). Tsai et al also reported that CKD stage 3 has lower risk for rapid GFR deterioration in comparison to CKD stage 4 and 5 (Tsai et al., 2017).

2.4 FACTORS CONTRIBUTING TO PROGRESSION OF CHRONIC KIDNEY DISEASE

The factors that can affect rate of GFR decline can be divided into non-modifiable factors (example - gender, age, ethnicity and aetiology); and modifiable patient's factor (example - level of proteinuria, serum albumin, blood pressure level, glycaemic control and smoking). For our study, we have decided to study the influence of gender, age, aetiology, HbA1c, systolic blood pressure, serum albumin, haemoglobin level, proteinuria and usage of ACEI/ARB to our selected study population due to their availability and convenience for access within our database and medical record.

2.4.1 Age

Age-associated loss of kidney function has been well accepted for decades and it is likely due to the anatomical and physiological changes occur in concert with structural changes, including loss of renal mass; hyalinization of afferent arterioles and in some cases, development of aglomerular arterioles; an increase in the percentage of sclerotic glomeruli; and tubulointerstitial fibrosis that lead to reductions in the glomerular capillary plasma flow rate and the glomerular capillary ultrafiltration coefficient (Weinstein and Anderson, 2010). Interestingly though, Linderman et al. found that two third of older adult with non-significant medical health problems will have some degree of GFR decline based of creatinine calculation but only less than 2% of these elderly population will developed ESRD requiring renal replacement therapy (Lindeman et al., 1985, Anderson et al., 2009).

Among CKD patient in general, older age is associated with faster decline of GFR compared to younger patient according to multiple studies (NKF, 2002, Shlipak et al., 2009, Abdulkader et al., 2017). On the other hand, the study by Tsai et al found that GFR decline rate was slower in individuals with CKD diagnosed over the age of 60 years than those with onset at a younger age (Tsai et al., 2017). The opposite however was seen in the diabetic population, where younger age actually associated with faster GFR decline compared to older age (NKF, 2002).

2.4.2 Gender

The evidence of gender effect in rate of GFR decline among CKD is still inconclusive. In Xu R et al study, there were no differences in GFR decline rate between men and women among CKD group (Xu et al., 2010). The same conclusion also founded in Tsai et al study where gender did not associated with GFR decline rate (Tsai et al., 2017). KDIQO guideline however found that among eighteen studies that addressed the gender relationship with GFR rate, the evidences are more suggestive a faster rate of progression in male gender compared to female counterpart (NKF, 2002). In contrary, Turin et al found in their study that the female gender was shown to impose more risk for unstable renal function (Turin et al., 2012a). There were no however, direct study on the influence of gender on rate of GFR decline among CKD stage 3 specifically.

2.4.3 Aetiology of the disease

The rates of GFR decline in chronic kidney disease patients were vary according to the aetiology the disease. KDOQI has summarized the previous studies that has looking into the rate of GFR decline according the aetiology of chronic kidney disease in the Clinical Practice Guidelines for Chronic Kidney Disease; Diabetes: 0 – 12.6mL/min/1.73m^2/year, Glomerular Disease: 1.4 – 9.5mL/min/1.73m^2/year, Hypertension: 2 – 10.4mL/min/1.73m^2/year, Tubolointerstitial disease: 2 – 5.4mL/min/1.73m^2/year, Polycystic Kidney Disease: 3.8 – 5.4mL/min/1.73m^2/year(NKF, 2002). In the disease such as idiopathic membranous nephropathy, Pei Y et al reported that only approximately 35% of the patients will

undergo remission of the disease instead of progressed into CKD (Pei et al., 1992). Almost similar finding also was reported by Chitalia VC et al where only 30% of patients with primary focal glomerulosclerosis went into remission (Chitalia et al., 1999). Specific for diabetic population, MADIABETES study concluded that the cumulative incidence of CKD stage 3-5 at five years was 10.23%.

2.4.4 Level of HbA1c in diabetic nephropathy

One way of monitoring diabetic controlled is by observing the trend of HbA1c. Multiple studies involving large sample of patients, and high methodological quality and applicability support that elevated HbA1c associated with faster rate of GFR decline (NKF, 2002). The study by Rigalleau et al even showed that for each gained 1% HbA1 were associated with 6.0 ml/min per 1.73 m^2 in GFR reduction (Rigalleau et al., 2006).

The appropriate level for HbA1c among CKD patient however may be different from non-CKD diabetic patient. Intensive glucose control compared to conventional glucose control for type 1 diabetes mellitus show reduced risk of developing microvascular diabetes complications including diabetic nephropathy but the opposite consequences was seen in diabetes mellitus type 2 where intensive glycaemic control has an effect on death from kidney failure compared to standard glycaemic control (Fullerton et al., 2014) (Herrera-Gomez et al., 2017). We recognized that there's still some knowledge gap in what is the best HbA1c level specifically for CKD stage 3 without causing too much adverse effects such as hypoglycaemia attack.

2.4.5 Blood pressure controlled

The controlled of blood pressure is well established as part of major treatment in managing CKD and it shown to have effect in retarding GFR decline (Saweirs and Goddard, 2007). Study by Maki et al concluded that for each 10 mmHg drop in mean arterial pressure (MAP) there was an improvement in rate of loss of GFR of 0.18 ml/min/1.73 m^2 /month(Maki et al., 1995). Study by Jafar et al had explored further in term of the ideal blood pressure for CKD patient, and has found that while there were benefit in keeping systolic blood pressure 110 to 129mmHg, systolic blood pressure less than 110 mm Hg may be associated with a higher risk for kidney disease progression instead. Thus, it is crucial to study the control of systolic blood pressure among CKD stage 3 to achieve the optimum benefit of blood pressure control without causing possible adverse effect to the patient.

2.4.6 Serum albumin level

KDIQO guideline summarized based on eight studies that the low serum albumin level associated with a faster rate of GFR decline, in particularly among diabetic patient. There was no study that suggested a lower albumin level may slow the rate of GFR decline (NKF, 2002). One study found that in elderly patients (mean age 74 years) with CKD (mean GFR 73 mL/min/1.73 m^2 at baseline) low serum albumin was an independent factor for GFR decline (Lang et al., 2018). We could not found any specific study on association between serum albumin and rate of disease progression among CKD stage 3 only.

2.4.7 Haemoglobin level

Panjeta et al has found that the erythropoietin levels among CKD patients were already reduced as early as in CKD stage 3 (Panjeta et al., 2017). This reduction of the erythropoietin production contributed to part of the causes of anaemia in CKD patients. There were studies on the usages of erythropoietin to correct anaemia in selected patient at early stage of CKD, that shown to retard the rate of GFR decline (Kuriyama et al., 1997, Kuriyama, 2018). However, the evidence for the direct association between haemoglobin level and the rate of GFR decline is still inconclusive as most of CKD studies on haemoglobin level were related to the effect of the erythropoietin's usage in CKD instead (NKF, 2002, Covic et al., 2014). Nonetheless, there is not enough date to suggest that anaemia is associated with faster rate of GFR progression especially among CKD stage 3.

2.4.8 Presence of proteinuria

Presence of proteinuria in CKD patient is usually reflecting the glomerular damage and can be the first sign of manifestation of renal disease. One study found that the prevalence of proteinuria among CKD stage 3 was found to be approximately 16% (Fraser et al., 2014). Obi Y et al study revealed that overt proteinuria (urine dipstick protein $\geq$ 2+) in older population (mean age 65 years old) have higher incidence of end up with renal replacement therapy compared group without overt proteinuria (Obi et al., 2010). Tsai et al also found that in comparison to CKD patient without proteinuria, presence of proteinuria have significantly associated with an increased annual decline rate at the rate 2.38ml/min/1.73m^2/year (Tsai et al., 2017).

2.4.9 Usage of ACEI and ARB

Multiple established studies and guidelines has recommended the usage of ACEI/ARB in chronic kidney disease and its effect in slowing down the progression of proteinuria and CKD (Maschio et al., 1996, Baltatzi et al., 2011, Jafar et al., 2001, MOH, 2011). The usage of ACEI/ARB however may predispose the CKD patient to worsening of GFR progression if there are underlying renal artery stenosis or fibromuscular dysplasias.

2.5 THE IMPACT GFR DETERIORATION AMONG CKD STAGE 3 PATIENT

Previous literature reviews noted that progressive CKD has significant impact to individual patient's health and also to national economy.

2.51 Impact to individual patient's health

In general, CKD patients are known to have eight to ten time higher risks for cardiovascular mortality, and the risk is even higher if there is presence of diabetes or hypertension (Couser et al., 2011). Turin TC et al found that while only 7% of the CKD patient has either drop or rise in kidney function over one year observation period, these affected patients with reduced kidney function has double the mortality risk compared to patients with stable renal function (Turin et al., 2012a). In his study, *"Short-term change in kidney function and risk of end-stage renal disease"*, Turin et al have categorized his subject into grouping of i) Certain drop [drop in CKD category with >/=25% decrease in

the eGFR]; ii) Uncertain drop [drop in CKD category with <25% decrease in the eGFR]; iii) Stable [no change in CKD category]; iv) Uncertain rise [rise in CKD category with <25% rise in the eGFR]; v) Certain rise [rise in CKD category with >/=25% increase in the eGFR] (Turin et al., 2012b). From the basis of this study, we have further decided to group our end result GFR changes into stable (Reduction GFR ≤ 24.9%) or progressive (Reduction GFR ≥25%).

2.52 Impact to national economy

While the overall screening and monitoring early chronic kidney disease can be readily accessible in most places and inexpensive, progressive CKD and ESRD is an economically costly condition to manage. The cost of management and treatment of ESRD may involve up to 2-3% of annual health care budget for a disease that only affecting 0.02% to 0.03% of its population (Couser et al., 2011, Wang et al., 2016). The similar report has been released by University of Virginia's Department of Public Health Sciences in 2017 United State Renal Data System Annual Data Report shown that CKD and ESRD are disproportionately imposed significant burden to the economy in relative to its patient's population compared to other chronic illnesses (USRDS, 2017).

2.6 THE LOCAL RECOMMENDED MANAGEMENT OF CHRONIC KIDNEY DISEASE

Malaysia Clinical Practice Guideline (CPG) has been published since 2011 and has highlighted recommendation in the management of CKD. At the level of screening for CKD, all patients with underlying diabetes mellitus or hypertension were recommended to be screened at least yearly for CKD using urine dipstick for protein and also blood test for renal function. Screening also recommended in non-diabetic or non-hypertensive patient with high risk factor for chronic kidney disease.

The aim in management of CKD by Malaysia CPG is to retard the progression of renal disease while managing the renal related complication and also reduce cardiovascular disease risk. The main focus of the treatment is to hypertension and proteinuria. The usage of Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) should have been first line-agent in patient that has evidence of proteinuria. In a non-proteinuria patient, any class of antihypertensive is suitable although the grade of recommendation is lower. The targeted blood pressure level for CKD patient are less than 140/90 but Malaysia CPG recommended lower blood pressure target (<130/80) in patient with proteinuria and diabetic kidney disease.

In regards of diabetes control, Malaysia CPG recommended for HbA1C to be less than 7% in diabetes patient with CKD but the target HbA1C should also consider other co-morbidities as strict HbA1C can lead to recurrent hypoglycaemia and increased cardiovascular mortality in some cases (W Arnold and Wang, 2014). One of the leading causes of death in CKD is cardiovascular disease (Thompson et al., 2015). Malaysia

CPG has recommended that lipid lowering agent such as Statin should be offered to CKD patients as primary or secondary prevention of cardiovascular disease. Aspirin has been suggested to be used as secondary prevention of cardiovascular disease as per clinical guideline.

Another recommendation in retarding the progression of CKD is by dietary intervention in particularly by restricting the dietary protein intake which shown to slow down the progression to ESRD (Robertson et al., 2007, Metzger et al., 2018). Malaysia CPG has recommend low protein diet (0.6 – 0.8 g/kg/day) with adequate energy intake (30 – 35 kcal/kg/day) for all stage 3 to 5 CKD patients. In some stage 3 to 5 CKD patients, very low protein diet (0.3 g/kg/day) with keto-acid supplementation can be considered to retard the GFR decline (MOH, 2011, Garneata et al., 2016). Other than restricting protein intake, the clinical guideline also has highlighted on Sodium intake restriction to total intake less than 2400mg/day in all CKD patients.

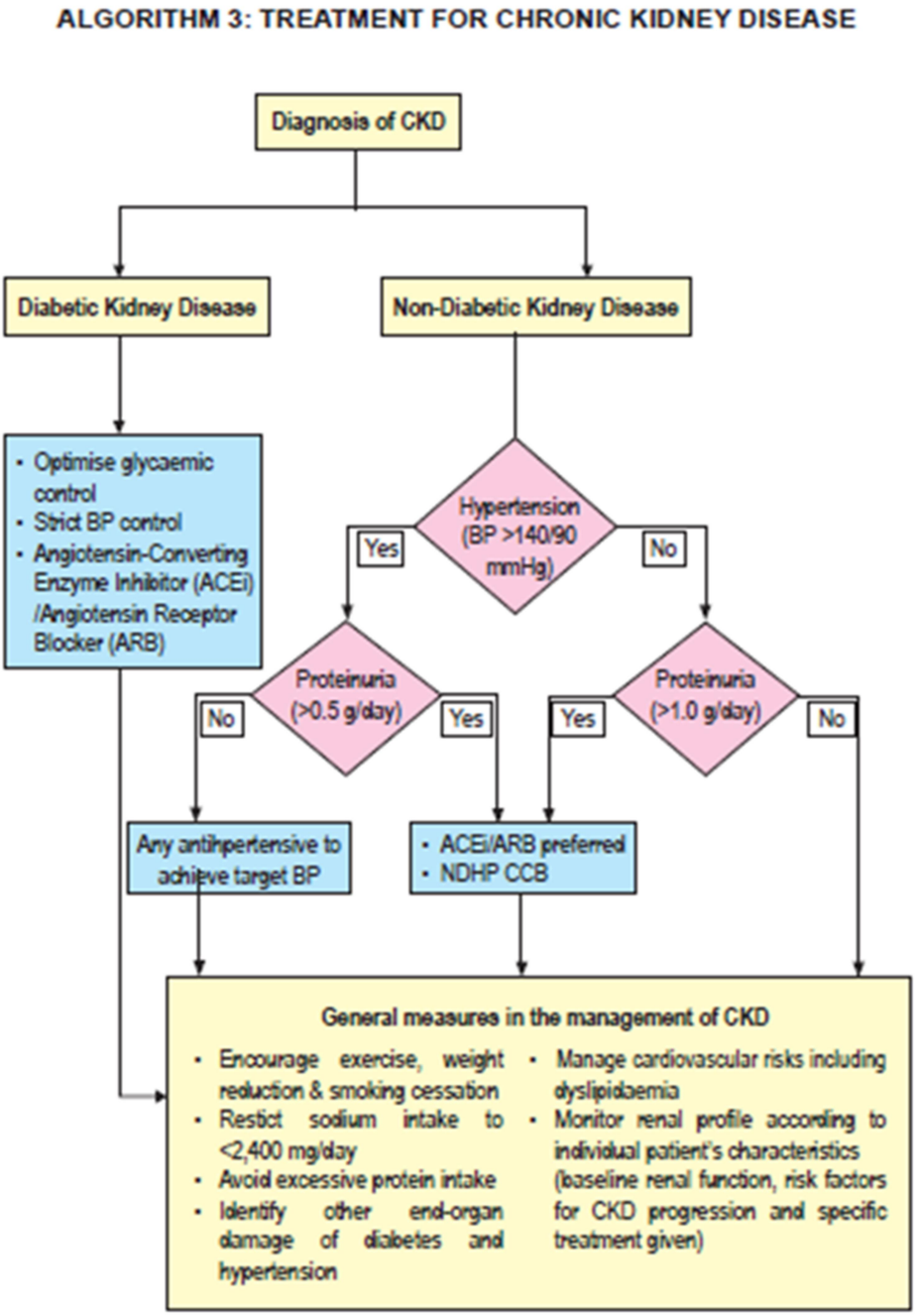

FIGURE 1: *Diagram from Malaysia Clincal Practice Guideline 2011 Management of Chronic Kidney Disease in Adult – page X*

2.7 RATIONALE OF THE STUDY

Based on the data from Malaysia National Renal Registry 2014, the number of patient subjected to haemodialysis has increased from 6702 in year 2000 to 31 637 in years 2013 (Begum et al., 2016). The surge of patients' requiring dialysis indicated that the incidence and diagnosis of CKD has increased in the last few years. Despite there is a wide variation in the disease presentation, the prevalence of earlier stages of CKD is far more prevalent than ESRD and therefore, it is extremely crucial to retard or slow the progression of disease in its earlier stage (NHANES, 2016). The rate of GFR decline however may differs between CKD patients, reflecting individual aetiology of the renal impairment and also the effect of controlling the risk factors related to CKD. Furthermore, we have not yet to determine how comparable our rate of GFR decline is, in particularly among CKD stage 3, when comparing to other centre or country. By obtaining an approximate rate of GFR decline, it can help us to objectively assess our ability in retarding the disease progression.

While there were prior studies looking into the rate of CKD progression, there is scarcity of published information about the rate and factors associated with the progression of chronic kidney disease in regard to our own patient in our country or state. In clinical practice also, it's still difficult to determine which patient with impaired GFR will progressed to ESRD, or how fast the disease will progresses, especially in the patient with early stage of CKD. Evaluation the rate and association of risk factors for progression of CKD in local CKD stage 3 patients could aid individualized decision making, thus enabling early and suitable patient care and retarding the rate of CKD progression in hospital based settings.

Our study also would like to assess the management of the selected associated factors for disease progression among the CKD patient in our centre. As an example, a proper control of factor like HbA1C, blood pressure, proteinuria and usage of ACEI/ARB in diabetic nephropathy has proven benefit in retarding GFR decline in diabetic patient for example (Obrador, 2017). Effort to control these factors are important as the major contributor towards renal impairment in Malaysia are still diabetic nephropathy; which responsible for 58% of the aetiology of CKD in Malaysia population (Begum et al., 2016). By collecting and assessing the rate of GFR decline, and identifying the possible co-contributors for the disease progression in our centre, it would help us to prepare our patient or estimate their need for dialysis later in future.