DEVELOPING THE PROGNOSTIC MODEL OF CHRONIC KIDNEY DISEASE PROGRESSION AND ELUCIDATING THE GLOBAL PREVALENCE OF CHRONIC KIDNEY DISEASE DEPRESSION AMONG ELDERLY

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by

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Dedicated to

My Parents

For simply being my parents

And to my brother Shaheed Arif Ullah Khan

For always believing in me

And to the rest of my family.

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All praise to Almighty ALLAH(SWT), the Lord of this world and hereafter, the absolute source of knowledge of every type. Nothing can happen without the will of ALLAH (SWT). I thank you, Allah, for all the favors you have bestowed upon me throughout my existence and my Ph.D. journey. This achievement would not have materialized without your generosity. الحمد لله. And all peace be upon Prophet Muhammad (صلى الله عليه وسلم), a beacon of knowledge for the mankind.

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LIST OF ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitor
AdaBoost	Adaptive Boosting
ANN	Artificial Neural Network
ARB	Angiotensin Receptor Blocker
BDI	Beck Depression Inventory
BMI	Body Mass Indices
CAPD	Continuous Ambulatory Peritoneal Dialysis
CART	Classification and Regression Tree
CKD	Chronic kidney disease
D2D	Disease2disease
ESRD	End-Stage Renal Disease
GFR	Glomerular Filtration Rate
GUI	Graphical User Interface
Hb	Haemoglobin
HbA1c	Haemoglobin, Calcium, Phosphorus, Glycated Haemoglobin
HUSM	Hospital Universiti Sains Malaysia
K/DOQI	Kidney Disease Outcomes Quality Initiative clinical practice guidelines
KDIGO	Kidney Disease Global Outcome
LDL	Low-Density Lipoprotein
MAD	Mean absolute deviance
MDTR	Malaysian Dialysis and Transplant Registry
mhGAP	Mental Health Gap Action Programme
MLP	Multilayer Perceptron
MLR	Multiple Logistic Regression
NHANES	National Health and Nutrition Examination Survey

PLS	Partial Linear Square
PLS-SEM	Partial Least Square Structural Equation Modelling
TA	Temporal Abstraction
UPCR	Urinary Protein-to-Creatinine Ratio
WHO	World Health Organization

LIST OF APPENDICES

MEMBANGUNKAN PROGNOSTIK MODEL UNTUK PERKEMBANGAN PENYAKIT BUAH PINGGANG KRONIK DAN MENJELASKAN KELAZIMAN GLOBAL KEMURUNGAN PENYAKIT BUAH PINGGANG KRONIK DALAM KALANGAN ORANG TUA

ABSTRAK

Penyakit buah pinggang kronik (CKD) merupakan masalah kesihatan awam yang signifikan dengan kejadian dan prevalen yang meningkat di seluruh dunia. Pola ini juga diperhatikan di Malaysia, di mana prevalens CKD adalah 9.07% pada tahun 2011. Perkembangan CKD dikaitkan dengan parameter metabolik dan diagnostik tertentu yang penting dalam perkembangan penyakit ini. Pesakit CKD sering mengalami kemurungan, yang boleh memberi kesan terhadap kebajikan mereka. Satu model perkembangan penyakit prognosis telah dibangunkan bagi pesakit CKD untuk memahami variasi antara individu mengenai parameter metabolik dan diagnostik, yang meliputi semua faktor yang relevan. Kajian ini terdiri daripada analisis retrospektif terhadap 470 pesakit CKD yang dipilih dari klinik Hospital Universiti Sains Malaysia (USM) dan penilaian keratan rentas terhadap 300 pesakit dari klinik pesakit luar menggunakan soal selidik Beck Depression Inventory untuk menilai tahap kemurungan. Pendekatan pemodelan statistik komputasi digunakan untuk menilai ciri-ciri sosiodemografi, metabolik, dan diagnostik pesakit CKD. Nisbah bahaya telah diuji dan dilaksanakan menggunakan perisian dan sintaks R-Studio, yang juga digunakan untuk merancang dan membangunkan pendekatan biometri hibrid. Kaedah termaju tersebut telah dilakukan dalam tiga peringkat: membangunkan sintaks untuk R bagi kaedah biometri hibrid yang terdiri daripada perceptron lapisan pelbagai (MLP), regresi logistik, dan tarikan rawak bergantian data. Kajian soal selidik keratan-rentas

dianalisis menggunakan Permodelan Persamaan Struktur Kuasa Kekurangan Sebahagian (PLS-SEM). Selanjutnya, prevalens global kemurungan dikenalpasti melalui penyemakan sistematik dan meta-analisis. Artikel yang relevan yang terindeks dalam pangkalan data PubMed, Web of Science, Scopus, ScienceDirect, dan Google Scholar, yang diterbitkan sehingga 4 Oktober 2022, dikaji semula. Berkenaan dengan jantina, pesakit CKD lelaki mengambil purata 72 bulan untuk mencapai peringkat CKD 5, manakala pesakit CKD perempuan mengambil masa 54 bulan, diikuti oleh pesakit CKD yang hanya menghidap hipertensi, yang mengambil masa 72 bulan, manakala pesakit CKD yang menghidap hipertensi dan diabetes mellitus mengambil masa 42 bulan. Jantina, hipertensi, rematik gout, diabetes mellitus, dan diabetes mellitus dengan hipertensi dikenalpasti sebagai faktor-faktor yang signifikan berkaitan dengan perkembangan penyakit dalam pesakit CKD (nilai-p <0.05). Selain itu, parameter diagnostik (eGFR, proteinuria, dan albuminuria) dan parameter metabolik (hemoglobin, kalsium, fosforus, hemoglobin terglikasi (HbA1c), trigliserida, dan lipoprotein berketumpatan rendah (LDL)) berkait rapat dengan perkembangan penyakit CKD (nilai-p <0.05). Kajian rentas-seksyen ini menyimpulkan bahawa prevalens kemurungan dalam pesakit CKD adalah 30%. Umur, jantina, status ekonomi, dan status perkahwinan dikenalpasti sebagai faktor-faktor yang signifikan berkaitan dengan kemurungan dalam pesakit CKD berdasarkan pembangunan model (nilai-p <0.05). Sejumlah 66 kajian yang melibatkan 1,296,290 peserta telah dimasukkan dalam analisis, menunjukkan prevalens global kemurungan sebanyak 32.9% di kalangan pesakit CKD. Penemuan ini menyumbang kepada pemahaman punca-punca asas CKD, yang berpotensi meningkatkan ramalan, dan membimbing keputusan klinikal berkenaan ujian, rawatan, dan rujukan. Selain itu, kajian ini mengenalpasti faktor risiko potensi bagi CKD dalam populasi Kelantan. Prevalens

global kemurungan telah menekankan beban keseluruhan kemurungan dalam populasi CKD. Faktor-faktor yang dikenalpasti dalam kajian rentas-seksyen akan membantu para doktor dalam mengurangkan risiko kemurungan dalam pesakit CKD.

DEVELOPING THE PROGNOSTIC MODEL OF CHRONIC KIDNEY DISEASE PROGRESSION AND ELUCIDATING THE GLOBAL PREVALENCE OF CHRONIC KIDNEY DISEASE DEPRESSION AMONG ELDERLY

ABSTRACT

Chronic kidney disease (CKD) is a significant public health problem with increasing incidence and prevalence worldwide. This trend is also observed in Malaysia, where the prevalence of CKD was 9.07% in 2011. CKD progression is associated with specific metabolic and diagnostic parameters important in the disease's progression. CKD patients frequently experience depression, which can further impact their well-being. A prognostic disease progression model was developed for CKD patients to understand the variations among individuals about metabolic and diagnostic parameters, encompassing all relevant factors. The study consisted of a retrospective analysis of 470 CKD patients selected from the Hospital Universiti Sains Malaysia (USM) clinic and a cross-sectional evaluation of 300 patients from outpatient department clinics using the Beck Depression Inventory questionnaire to assess depression. Computational statistical modeling approaches were utilized to evaluate CKD patients' sociodemographic, metabolic, and diagnostic characteristics. The hazard ratio was tested and implemented using the R-Studio software and syntax, which was also used to design and develop the hybrid biometry approach. The advanced methodology was carried out in three stages: developing syntax for R for the hybrid biometry method, which consists of multiple layer perceptrons (MLP), logistic regression, and data bootstrapping. The cross-sectional questionnaire study was analyzed using Partial Least Squares Structural Equation Modeling (PLS-SEM)

software. Furthermore, the global prevalence of depression was identified by conducting a systematic review and meta-analysis. Relevant articles indexed in PubMed, Web of Science, Scopus, ScienceDirect, and Google Scholar databases, published until October 4th, 2022, were reviewed. Regarding gender, male CKD patients take an average of 72 months to reach CKD stage 5, while female CKD patients take 54 months, followed by CKD patients suffering from only hypertension, who concede 72 months, while CKD patients suffering from hypertension and diabetes mellitus take 42 months. Gender, hypertension, gouty arthritis, diabetes mellitus, and diabetes mellitus with hypertension were identified as significant factors associated with disease progression in CKD patients (p-value<0.05). Moreover, the diagnostic parameters (eGFR, proteinuria, and albuminuria) and metabolic parameters (hemoglobin, calcium, phosphorus, glycated hemoglobin (HbA1c), triglyceride, and low-density lipoprotein (LDL)) were significantly associated with CKD disease progression (p-value<0.05). The cross-sectional study concluded that the prevalence of depression in CKD patients was 30%. Age, gender, economic status, and marital status were identified as significant factors associated with depression in CKD patients based on the development of a model (p-value <0.05). A total of 66 studies involving 1,296,290 participants were included in the analysis, revealing a global prevalence of depression of 32.9% among CKD patients. These findings contribute to understanding the underlying causes of CKD, potentially improving the prognosis, and guiding clinical decisions regarding testing, treatment, and referral. Additionally, the study identified potential risk factors for CKD in the Kelantan population. The global prevalence of depression underscores the overall burden of depression in the CKD population. The factors identified in the cross-sectional study will assist clinicians in mitigating the risk of depression in CKD patients.

CHAPTER 1

INTRODUCTION

1.1 Introduction of chronic kidney disease

Kidney disease can be either chronic or acute. In contrast to chronic kidney disease (CKD), which progressively destroys kidney mass involving nephron loss and permanent sclerosis with time, either in months or years, acute kidney injury results in a faster decline in kidney function that is reversible [1].

The term "CKD" refers to a pathological condition in which both the appearance and functionality of the kidneys are affected [2]. Various factors, including the cause, the pathology, the severity, and the rate of progression, are somehow connected to the variability in disease expression. CKD is frequently linked to an increased risk of hospitalization, morbidity, and death from cardiovascular problems, reported as a major global health problem [3, 4]. A global initiative to address such issues would not only be considered as rational but rather "a must-be-done activity" given the alarmingly high number of patients suffering from kidney-cum-cardiovascular diseases, which undoubtedly contribute to in increasing number of premature deaths even before reaching the condition of kidney failure [5]. CKD can potentially result in end-stage renal disease (ESRD), which necessitates dialysis and, in some cases, kidney transplantation for patients [6]. Numerous initiatives have been made in this direction to improve the relevant results and CKD patient treatment to stop them from developing the serious health issue of renal failure [7].

In the past ten years, CKD has evolved from a life-threatening condition to a common manageable disease. The development of the CKD model and improved guidelines for defining and staging the disease have helped in early detection and CKD

prevention [2, 8]. It is necessary to correctly characterize the disease severity of CKD patients and categorize various risk levels honestly to decide on the best treatment plan for such patients and help to avoid the progression of the illness toward renal failure.

1.2 Definition and classification of chronic kidney disease

1.2.1 Definition and criteria for chronic kidney disease

The Kidney Disease Outcomes Quality Initiative clinical practice guidelines (K/DOQI) of the United States (US) National Kidney Foundation provided the initial definition of CKD in 2002. Kidney Disease Global Outcome (KDIGO) recommendations published in 2013 define CKD as "abnormalities of kidney structure or function, present for ≥ three months, with health implications" [9].

1.2.2 Classification of chronic kidney disease

The 2013 KDIGO recommendations state that CKD should be categorized in accordance with glomerular filtration. The location of the observed or suspected pathological-anatomic abnormalities inside the kidney and the absence or presence of systemic disease are used to determine the etiology of CKD. GFR in young, healthy individuals varies between 120 and 130 ml/min/1.73 m^2, and it declines with aging [10]. According to KDIGO recommendations and guidelines, CKD is divided into five stages depending on the estimated glomerular filtration rate (eGFR) [11]. Table 1.1 describes renal function gradually and continuously decreased from stage 1 to stage 5.

Table 1.1 Stages of chronic kidney disease based on GFR (Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group, 2013)

Stages of CKD	GFR (ml/min/1.73m^2)	Description
Stage 1	≥90	Kidney damage and normal or increased kidney function
Stage 2	60–89	Kidney damage with mild decrease in kidney function
Stage 3a	45–59	Mildly to moderate decreased in kidney function
Stage 3b	30–44	Moderate to severe decline in kidney function
Stage 4	15–29	Severe decline in kidney function
Stage 5	<15	Kidney failure

The remaining nephrons can perform a process known as hyper-filtration in the early stages of CKD, which increases intraglomerular pressure and filtration rate, allowing the kidneys to compensate for the impairment and maintain the GFR consistently. This process makes it challenging to diagnose CKD in its early stages. However, over time, persistently high intraglomerular pressure damages the remaining nephrons and causes kidney failure, characterized by albuminuria [12]. The albuminuria categories according to KDIGO are shown in Table 1.2.

Table 1.2 Albuminuria categories in chronic kidney disease (kidney disease: Improving Global outcomes (KDIGO) CKD Work Group, 2013)

Category	Description	Albumin excretion rate	Albumin to creatinine ratio
A1	Normal to mild increase	<30 mg/24 hours	< 30mg/g
A2	Moderate increase	30-300 mg/24 hours	30-300 mg/g
A3	Severe increase	> 300 mg/24hours	> 300mg/g

1.3 Chronic kidney disease overview

The term "chronic kidney disease" (CKD) refers to a wide range of diseases that affect the structure and function of the kidney. Since the disease progresses too slowly, symptoms don't show up until kidney function is only a tenth of normal and kidney failure is imminent. The only way to identify the disease in its early stages is to evaluate renal function [13]. Rapidly progressing illness can cause renal failure in months if left untreated. The gold standard for assessing kidney function is the glomerular filtration rate (GFR). In practical practice, it is unfortunately not possible to compute GFR directly. Estimated GFR, or eGFR, is calculated in clinical settings to help patients deal with their condition [14].

The prevalence of the disease is rising annually despite rising mortality, morbidity, and productivity losses. The asymptomatic character of the illness, which makes it challenging to evaluate kidney function, is the cause of the rise in prevalence [15]. Currently, 10–16% of adults worldwide suffer from CKD. Globally, disease prevalence is increasing, with kidney disorders ranking as the 9th leading cause of death in the United States in 2010, accounting for more than 47.5 billion dollars in total costs. Over 100 million people die yearly from end-stage renal failure because of the lack of access to renal replacement medication. Asia has a similar prevalence of CKD to the rest of the world, which ranges between 10 and 18 percent. The precise burden and expense of disease are still unknown, though, as there is an absence of data in most Asian nations [16, 17]. Malaysia's CKD incidence rate was 9.01% in 2011[18].

1.4 Chronic kidney disease in elderly patients

There is an inclining trend of CKD observed, particularly among the elderly population [19]. GFR is estimated to decline at an average rate of 8mL/min/1.73

m^2/decade after age 30. This ageing-related reduction in renal function is considerably debated [20]. The incidence of co-morbidities and risk factors such as hypertension, diabetes, and atherosclerosis are rising along with life expectancy, which increases the CKD load in the elderly population. Approximately half of individuals over 70 years have an estimated GFR (eGFR) of less than 60 mL/min/1.73 m^2. Elderly CKD patients may have numerous additional renal comorbidities, including hypertension and diabetes mellitus. Such individuals typically have minimal chances for rehabilitation and a poor prognosis [21].

1.5 Chronic kidney disease progression

The prevalence of chronic kidney disease, which is indicated by proteinuria, structural renal disease, or lower glomerular filtration rate (GFR), is rising in the elderly population [22]. Although ESRD, which is kidney failure treated with dialysis or transplantation, is less common than previous CKD stages, the number of ESRD patients older than 65 years has nearly doubled over the past 25 years, and the fastest rising age group in this population over the past ten years is older than 75 years. Race, ethnicity, diabetes, hypertension, and proteinuria are significant risk factors for the progression of CKD to ESRD [23-30]. Even though only one to two percent of older individuals with CKD develop end-stage renal disease (ESRD) [22], death rates are high among these patients [31]. About two-thirds of older adults have a decline in renal function with time, as indicated by creatinine clearance [32].

1.6 Epidemiology of chronic kidney disease

1.6.1 Global prevalence of chronic kidney disease

Patients with CKD were found to be on the rise worldwide [33, 34]. The prevalence of CKD is high worldwide, with an estimated global prevalence of 13.4% and a preponderance of stage 3 cases.

Table 1.3 Global CKD stage-wise prevalence

CKD Stage	Prevalence (eGFR range)
Stage 1	3.5% (>90 ml/min/m^2)
Stage 2	3.9% (60–89 ml/min/m^2)
Stage 3	7.6% (30–59 ml/min/m^2)
Stage 4	0.4% (29–15 ml/min/m^2)
Stage 5	0.1% (<15 ml/min/m^2)

Globally, the prevalence of CKD across all five stages was 13.4% (11.7-15.1%). However, from stages 3-5, it was 10.6% (9.2-12.2%) [35].

The CKD prevalence was 8.5% and 13.1% in Mexico and US [17, 36]. In another study from the US, it was found that among the general population who were not institutionalized, the MDRD equation forecasted a 4.5% prevalence of CKD, the CG equation predicted a 7.0% [37], whereas 12.5% of Canadians expected to have CKD [38].

Among European nations, there are also regional variations in the prevalence of CKD. In contrast to Australia and England, where the prevalence of CKD was 11.5% and 11.9%, Italy had a prevalence of CKD of 7.1%, 10.3% in Norway, 5.8% in Poland, 10.0% in Switzerland, 10.4% in the Netherlands, and 9.1% in Spain respectively [39-46]. The prevalence of CKD was 10.8%,6.6%, and 17.5% in China,

Singapore, and Thailand [47-49]. While the prevalence of CKD was 7.5% in India, it was only 0.6%, 1.7%, 10.4%, and 0.2% for CKD stages 1,2,3,4 and 5 in Japan in 2005 [50, 51].

1.6.2 Prevalence of chronic kidney disease in Malaysia

The CKD prevalence has been rising in Malaysia. Likewise, elsewhere [52], CKD staging in Malaysia is based on eGFR utilizing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation and serum creatinine (Scr) as a marker [53]. A population-based research study conducted in West Malaysia found that the prevalence of CKD was 11.09%, and almost 3.3 million Malaysians were at risk of developing ESRD [18]. The most common potential risk for ESRD is rising diabetes prevalence, which accounts for 58% of all new occurrences of the disease. The majority of diabetic patients eventually develop ESRD [54]. Based on the 22nd report from the Malaysian Dialysis and Transplant Registry (MDTR), the number of CKD patients who switched to renal replacement treatment increased rapidly from 6702 in 2000 to 31,637 in 2013, having a substantial cost effect on the healthcare system [55].

1.7 Detection and assessment of chronic kidney disease

Determining renal function is a common and necessary approach for identifying clinical findings. Chronic kidney disease is rising globally because of an aging population and an increase in type 2 diabetes mellitus, which is reflected in the usage of renal function measurements [33]. Glomerular filtration rate (GFR) is an essential metric for evaluating kidney function [56]. Glomerular filtration is computed as a mean of Scr since it is challenging to assess the glomerular filtration rate directly without doing so. Serum creatinine is typically used to calculate eGFR, and because

of eGFR, individuals have been identified as having chronic kidney disease, which is further explored by concerned nephrologists [57, 58]. However, eGFR can also be regarded as one of the crucial tools in clinical management of CKD patients, together with other tests for CKD confirmation.

1.8 Glomerular filtration rate

The most accepted method to assess kidney function is the GFR, defined as "GFR (glomerular filtration rate) is equal to the total of the filtration rates of the functioning nephrons in the kidney." GFR relies on both systemic blood pressure and blood pressure in afferent and efferent arterioles because it depends on the overall pressure on the glomeruli membrane. The overall number of glomeruli also influences GFR. GFR is often expressed as ml/min/m^2 and calibrated for body size (relative GFR).

GFR similarly declines with age, achieving its peak throughout childhood while beginning to fall in later life around middle age [59]. The best approach for assessing renal function is still the GFR [59-62].

1.8.1 Commonly used estimated GFR equations

The GFR of kidney patients can be estimated using several different equations. Efferose reportedly devised the first eGFR equation based on creatinine in 1957 [63]. The details of the eGFR equations are provided below.

1.8.2 Cockroft Gault equation

The CG equation was created in 1973 to predict creatinine clearance (Ccr) using Scr, age, and body weight [64]. The CG formula is written as follows:

$$Ccr = (140\text{-age}) \times \text{weight (Kg)} / 72 \times Scr \; [\times 0.85 \text{ if female}]$$

1.8.3 Modification of Diet in Renal Disease (MDRD) study equation

The MDRD study equation was created in 1999 utilizing data from CKD patients who were Caucasian and African American and had GFR between 5 to 90 ml/min/1.73 m^2 of body surface area.

$$\text{MDRD eGFR} = 186 \times (Scr)^{-1.154} \times (age)^{-0.023} \; [\times 0.742 \text{ if female}] \; [\times 1.21 \text{ if black}]$$

The aforementioned calculation requires data of gender, serum creatinine (Scr), and age [65]

1.8.4 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation

The MDRD research equation was created in a group of people with chronic kidney disease, and its main drawbacks were its ambiguity and consistent underestimating of GFR at levels below 60 ml/min/1.73 m^2 [66]. As a result, the CKD-EPI creatinine equation, which is more accurate, was created in 2009 [67].

The CKD-EPI equation is given below:

$$eGFR = 141 \times \min (S_{cr}/k, 1)^{\alpha} \times \max (S_{cr}/k, 1)^{-1.209} \times 0.0993^{Age} \; [\times 1.018 \text{ if female}]$$

$$[\times 1.159 \text{ if black}]$$

Whereas Scr stands for serum creatinine (mg/dl), k is equal to 0.7 for women and 0.9 for men, is equal to 0.329 for women and -0.411 for men, min is equal to the minimum of Scr/k or 1, and max is equal to the maximal Scr/k or 1.

Overall, the CKD-EPI creatinine formula (CKD-EPIcr), which was tested in comparison with the MDRD formula, performed better [68]

1.8.5 CKD-EPI cystatin C equation

Serum cystatin C (ScysC) level alone produced GFR estimations that were more accurate than Scr when used as a substitute for Scr in the evaluation of renal function [69]. The following is the CKD-EPI cystatin C equation (CKD-EPIcys):

$$eGFR = 133 \times \min(ScysC/0.8,1)^{-0.499} \times \max(ScysC/0.8, 1)^{-1.328} \times 0.996^{Age}$$

$$[\times 0.932 \text{ if female}]$$

Where ScysC stands for serum cystatin C, min is the smallest ScysC/0.8 or 1 value, while the max is the highest ScysC/0.8 or 1.

1.8.6 CKD-EPI creatinine-cystatin C equation

The most precise estimations of GFR were obtained using an equation that used race, age, sex, Scr level, and Scys C level [69]. The following is the CKD-EPI creatinine-cystatin C equation (CKD-EPIcr-cys):

$$eGFR = 135 \times \min(Scr/k, 1)^{\alpha} \times \max(Scr/k, 1)^{-0.601} \times \min(ScysC/0.8,1)^{-0.375} \times$$

$$\max(ScysC/0.8, 1)^{-0.711} \times 0.995^{Age} [\times 0.969 \text{ if female}] [\times 1.08 \text{ if black}]$$

Whereby Scr is serum creatinine (mg/dl); ScysC is serum cystatin C (mg/l); k is o.7 for females and 0.9 for males; α is -0.248 for females and -0.207 for males; min (Scr/k,

1) is minimum of Scr/k or 1; max (Scr/k, 1) is maximum of Scr/k or 1; min (ScysC/0.8, 1) is minimum of ScysC/0.8 0r 1 max (ScysC/0.8, 1) is maximum of ScysC/0.8 or 1.

1.9 Mortality of chronic kidney disease

One in 50 people will have chronic renal failure in their lifetime by the time they are 40 years old [70]. According to the 2010 Global Burden of Disease survey, CKD was ranked 27th globally among all causes of mortality in 1990 (age-standardized annual death rate: 157 per 100 000) but rose to 18th in 2010 (annual death rate: 163 per 100 000) [71]. In numerous poor countries, especially South America (Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, and Venezuela), chronic renal failure is rated as the fifth (5th) most prevalent cause of death, the Andean region (Bolivia, Ecuador, and Peru), and Latin America [72]. Based on a research study by Rao and colleagues on the causes of death in the USA and Australia, the projected multiple-cause mortality rates from diabetic renal illness were four to nine times higher than the rates for "diabetes with renal complications" in both countries and were on the rise. These results suggested that the death rate from diabetic renal illness is significantly underestimated in regular mortality cause statistics for the USA and Australia [73].

1.10 Economic burden of chronic kidney disease

CKD is a devastating socioeconomic health-related problem worldwide [74]. Socioeconomic factors including finances, literacy, and the environment influence the prevalence, incidence, and development of CKD. These aspects might be changed. Nearly half of the participants in the western Malaysian study (41.8%) were middle-income earners, while low- and high-income earners were represented by 35.7% and

22.5%, respectively [18]. The prevalence of CKD has grown by 40% in the UK population, which is also affected by the aforementioned socioeconomic factors [75]. Like Sweden, households without a job have a 110% higher chance of developing chronic kidney disease than families with at least one employee [76]. In contrast to financially stable people, white Americans (USA) have an 86% increased risk of developing CKD due to possible financial problems [77].

Compared to healthy individuals, the cost of medical treatment in the USA was 2.6 times higher for patients with CKD stage 4 and 1.7 times higher for those in stage 3 [78]. Hemodialysis treatments cost [79] between RM79.61 to RM475.99 in Malaysia (a mean price of RM169 per HD), in contrast to the average monthly cost of RM2186 for continuous ambulatory peritoneal dialysis (CAPD) [80]. Additionally, the annual cost of CAPD and erythropoietin for HD is RM4500 and RM2500 annually, respectively. The findings mentioned above make it evident that CKD significantly strains the healthcare system financially.

1.11 Depression

"According to the guidelines of the World Health Organization (WHO), depression is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration " [81]. It could have a negative impact on a person capacity to manage everyday life issues or function at work effectively. It can result in suicidal attempts when it reaches its worst state. When it is in its early stages, it can be managed without medication. Still, when it is in its middle or severe stages, patients may need a proper combination of pertinent pharmaceuticals and a type of psychotherapy that includes expert talking treatments. Additionally, it can afflict

women more frequently than men. In addition to this, depression is often prevalent among unemployed people. No one is immune to depression, which can strike anyone everywhere. Over 300 million people suffer from depression globally, claims research. Because of this, the WHO has given depression "priority status" under its unique program known as the "mental health Gap Action Programme (mhGAP)" [81]. The majority of patients with this type of depression may also experience other medically significant complications, such as anxiety symptoms, sleep problems, appetite loss, moderate to severe levels of lower self-worth and/or guilt, poor concentration on other important tasks, and various types of medically complex signs and symptoms [82].

1.11.1 Depression in elderly chronic kidney disease patients

Depression has been identified as the most prevalent psychological issue in patients with CKD [83, 84]. The most pervasive psychological problem in CKD patients is depression, which has a prevalence range of 7% to 42% and is higher than other chronic diseases [85, 86]. Depression may have a negative impact on functional ability and quality of life, make it more challenging to comply with medical therapy, and affect nutritional status [87, 88]. Accumulating evidence of research has revealed that subthreshold depressed symptoms and clinical depression are longitudinally linked to an elevated risk of unfavorable clinical outcomes in individuals with chronic renal disease [89-92]. Globally, the elderly population is gradually increasing due to an increase in life expectancy [93]. At the same time, the elderly population mental health of society issues have grown to be a serious public policy concern [94]. Depression more easily affects older people’s life than it does younger people, in addition to the fact that it is becoming more common in this age group. Elderly people with other disabilities and illnesses are more prone to depression, which lasts longer.

Elderly persons are typically less active, and family members and medical practitioners may sometimes fail to recognize depressive symptoms [95, 96]. As a result, prompt psychological treatment is frequently delayed, leaving many older people to battle depression unnecessarily [94].

ESRD or CKD, has been the subject of numerous studies in Western countries that have examined its implications on depression. These studies have discovered that ESRD and CKD are independently linked to a significant rise in morbidity and mortality [90]. Furthermore, patients with a clinical diagnosis of depression receiving treatment for chronic kidney disease are twice as likely to pass away or need hospitalization within a year as those without depression [97, 98]. The duration of hospitalizations and cumulative hospital days are independently linked with 30% increases in patients with ESRD who had a diagnosis of depression, which contribute to elevated Medicare costs [99].

1.12 Problem statement

KDIGO guidelines stated that creatinine had been used in the stratification of CKD using the eGFR equation. A Proteinuria test is done among elderly individuals with CKD to monitor the progression of the disease. The albumin excretion rate for CKD patients ranges from 30 mg/24 hours to more than 300 mg/24 hours [100]. eGFR varies with the stages of CKD and proteinuria. By creating a predictive disease progression model in CKD patients to characterize both components, it is possibly better to understand the variances in individuals' eGFR and proteinuria levels. Several metabolic variables, including low-density lipoprotein (LDL), triglycerides, glycated haemoglobin (HbA1c), calcium, phosphorus, and haemoglobin (Hb), are also linked to the progression of CKD [101, 102], which play essential roles in the disease

progression of CKD. The geriatric population, which generally includes people with CKD, is growing globally with time. The prevalence of depression has been reported in the CKD population [103]. Based on published literature following factors, including Age, gender, marital and economic status, can all have an impact on CKD patient likelihood of developing depression. Depression has a direct effect on the patient's health outcomes. Therefore, there is a need to identify not only the prevalence of depression but also the associated factors which are responsible for depression in CKD patients.

By 2020, it is predicted that there will be more than 51,000 patients receiving hemodialysis in this nation using a variety of modeling and prediction formulas based on the rise of ESRD patients as reported by the Malaysia Dialysis and Transplant Registry (MDTR). Malaysia can anticipate that by 2040, more than 106,000 patients will be dependent on dialysis [104] if significant successful efforts are not made to slow this growth. Extrapolating the total cost estimates to the 38,000 dialysis patients in Malaysia in 2015 yields RM1.5 billion; without considering inflation, the figures rise to RM2 billion in 2020 and RM4 billion in 2040. The rise in EERD would place a strain on the health sectors in addition to being financially burdensome [105].

Apart from the financial burden, there are additional co-morbid illnesses, such as the main risk factors of diabetes and hypertension, that are contributing to the greater proportion of older CKD patients. Diabetes is currently the main contributor to ESRD, accounting for 65% of all new cases in 2016, and its prevalence is rising. Additionally, before starting dialysis, 58% of new cases of ESRD were older than 55, demonstrating the increasing persistence of elderly patients [106]. Developing a CKD disease progression model that considers changes in both diagnostic (eGFR, proteinuria) and metabolic disease progression parameters is still needed. The machine

learning-based prognostic disease progression model will offer a platform for quantifying the changes in diagnostic and metabolic components among Malaysia's geriatric population with CKD.

1.13 Justification of the study

Worldwide, there is a need for early detection and treatment strategies for CKD patients. Particularly in situations where renal replacement therapy is not easily accessible, the utilization of complicated and potentially costly detection procedures may make it impossible for those at risk to benefit from preventative interventions. The prognostic disease progression model in patients already diagnosed with CKD has been updated to include several risk factors that are independently related to the development of CKD and conveniently assessable in everyday clinical settings. It is also considered essential to identify depression prevalence and the variables that contribute to it in CKD patients. It will result in more precise management of the CKD patient treatment.

Hybrid biometry techniques and machine learning algorithms are increasingly applied in medical diagnosis and prognosis. Clinicians frequently rely on their assessments of prognosis on clinicopathologic characteristics. It may be difficult for even the most experienced doctor to accurately predict based only on these qualities. Therefore, to improve prognosis accuracy, cutting-edge statistical techniques are required. The main goal of this work is to predict the prognosis of CKD based on the association of sociodemographic, comorbid, metabolic, and diagnostic characteristics using a combination of feature selection and machine learning methodologies.

To date, only a small number of modeling studies give decision-makers and healthcare professionals a balanced picture of the performance of existing CKD risk models in Malaysia. A predictive model based on diagnostic parameters (eGFR and proteinuria) and metabolic factors (haemoglobin, calcium, phosphorus, glycated haemoglobin (HbA1c), triglyceride, and low-density lipoprotein (LDL)) associated with CKD progression in Malaysia is urgently needed. For several reasons, modelling is helpful for managing CKD patients and treatment outcomes. The estimated model can point targeted therapy in the right direction to delay the disease onset. However, there isn't enough data in Malaysia to prove that CKD patients' management protocols should include prediction models. Considering this, we would like to present more data on this subject that is now available and that pertains more to the local people than the data found in existing international databases. It is important because it might act as a standard for creating management methods at community hospitals that are more centred on treatment plans and patient education.

1.14 Objectives

1.14.1 General objective

To develop a prognostic disease progression model based on socio-demographical, metabolic, and diagnostic parameters of CKD patients and the prevalence of depression among CKD patients.

1.14.2 Specific objectives

1. To develop a prognostic disease progression model of stage 5 CKD from stage 3, based on socio-demographic and comorbid factors using Kaplan Meier analysis.

2. To develop and validate the predictive disease progression model of CKD based on metabolic parameters (i.e., haemoglobin, calcium, phosphorus, glycated haemoglobin (HbA1c), triglyceride, and low-density lipoprotein (LDL) by using hybrid biometry method.
3. To develop and validate the predictive disease progression model of CKD based on diagnostic parameters (i.e., estimated glomerular filtration (eGFR), proteinuria, albuminuria) among geriatric patients by using a hybrid biometry method.
4. To determine the depression level among geriatric CKD patients by using Beck Depression Inventory (BDI) questionnaire.

CHAPTER 2

LITERATURE REVIEW

2.1 Preview of the chapter

This chapter aims to shed light on previously conducted studies on kidney disease progression based on socio-demographical, metabolic, and diagnostic parameters among CKD patients. Moreover, it will also elaborate on the prevalence and factors associated with depression among CKD patients.

2.2 Prognostic disease progression model of chronic kidney disease

Predictive modeling techniques applied to the growing number of clinical datasets have shown promise in accurately predicting the progression of chronic disease in the population [107-109]. Previous attempts have employed various prediction models, from well-established generalized linear models to more recent Machine Learning (ML) techniques [110]. Renal clinicians and researchers recognize the significant potential in developing risk prediction models that can improve our ability to identify individuals at risk and potentially improve our understanding of the natural history of disease progression and contribute to the clinical management of CKD [111-113]. The application of ML models provides the capacity to tap into the information contained in large and complex datasets and exploit the complex non-linear dependencies [108, 110, 112, 114]. Applying these analytical techniques promises to improve our understanding of CKD progression and inform critical interventions to help slow progression and reduce the burden of CKD [115].

Table 2.1 Prognostic Models of Chronic Kidney Disease

Study, Year (Reference)	Country	Study duration	Model development technique
Cheng et al (2007) [116]	Taiwan	10 years	Temporal Abstraction (TA) technique with data mining methods (classification and regression tree (CART), support vector machine, and adaptive boosting (AdaBoost)
Makino et al (2019) [117]	Japan	12 years	AI constructed the predictive model (time series data using logistic regression analysis)
Zhao et al (2019) [118]	United States	9 years	Random Forest regression
Zhou et al (2020) [119]	United States	11 years	Low-dimensional embedding model disease2disease (D2D)

The use of machine learning, a branch of artificial intelligence, in medical applications has increased widely in recent years, driven by the rapidly accumulating volume of medical data. Similarly, artificial neural networks (ANNs) are an integral part and a subfield of machine learning [120]. An ANN is an innovative software model that functions in a way inspired by the human brain. In addition, ANN seems effective since the complex relationship between input and output can be accurately modeled with a relatively simple computer programming code. Structurally, ANN comprises input, hidden, and output layers [121].

The global nephrology community recognizes that current models of care are insufficient to curb the growing CKD burden and that new care models are required to improve patient outcomes [122, 123]. It has been suggested that the management framework for CKD needs to consider the disease across the entire life course of each individual. New care models also need to consider improvements in areas such as disease surveillance, mitigation of risk factors, expanding research knowledge, and developing novel clinical interventions to slow the progression of CKD [123]. Despite having identified several risk factors associated with the onset of CKD, gaps remain

in the methods for predicting the risk of CKD progression and interventions to slow CKD progression [124, 125]. In addition, many patients with CKD remain undetected through health systems, and clinicians have the challenge of managing the growing number of cases with limited tools for triaging patients [125].

Based on the published literature, there is a dire need for prognostic disease modeling in CKD patients. We presume that our developed prognostic disease progression models based on diagnostic and metabolic parameters by using the hybrid biometry method would help to understand the trend of the associated risk factors but also can predict the risk of end-stage renal disease, i.e., CKD stage 5 (non-dialysis) in an appropriate way. Model development will further decrease the CKD burden.

2.3 CKD disease progression

CKD stages change with time in patients due to disease progression. A research study by Baek et al, who followed patients with stage 3 CKD for ten years, reported that among patients, 48.1% would remain in stage 3 while the other 51.9% would advance to higher stages (17.3% for CKD stage 4 and 34.6% for stage 5 of CKD) [126]. Throughout the research study's 10-year follow-up period, 12 dialysis treatments were necessary for 91 out of 196 participants due to declined renal indicators, including eGFR and proteinuria. On the other hand, Lin et al study found that more patients in terms percentage (54.1%) with CKD stage 3b remained in the same stage throughout the study duration among those who were followed up for more than 12 weeks [127]. Interestingly, Lin et al also addressed that 19.3% of people with CKD stage 3b experienced stage reversal (going from stage 3b to stage 3a). Additionally, Tsai et al observed that compared to CKD stages 4 and 5, a decreased

probability of rapid GFR degradation was observed in CKD patients with stage 3 [128].

2.4 Role of sociodemographic and Co-morbid factors in CKD progression

2.4.1 Gender

Gender as a risk factor has reportedly produced contrasting results. The incidence of CKD and ESKD is higher in males than women, according to several research investigations, while a few other studies have made conflicting findings [129]. Men are more likely than women to develop various renal illnesses. Women with postmenopausal status are at risk for CKD, but this needs to be proven through relevant research findings. According to Suzuki et al study, estrogen has been demonstrated to (a) diminish the expression of angiotensin type 1 receptor in the kidneys and vasculature; (b) decrease the expression and activity of angiotensin-converting enzyme; and (c) induce the liver to release angiotensinogen substrate. However, estrogen is unclear to what extent to which it activates or suppresses the renin-angiotensin-aldosterone pathway [130, 131]. eGFR is based on sex and other factors when referring to the disparities in gender-related CKD between men and women. The two eGFR equations that use gender as a variable are MDRD and CKD-EPIcr. Both calculations are predicated on men having higher eGFR than women for a given creatinine concentration because they have more muscle mass and better renal function [132].

One of the clinical research studies reported the prevalence of CKD in elderly patients. The study findings reported that 1066 females (19.8%) had a higher prevalence of CKD [133]. Yu et al study described in their findings that diabetic female patients are more likely to develop CKD than diabetic male patients [134].

Variability in terms of gender was observed in the Malaysian prevalence-based study on CKD. According to the study demographic information, based on gender, male and female CKD prevalence was reported as 12.6 % and 17.3 % [18]. The prevalence of chronic renal failure was recently shown to be greater in women (15.1%) than in males (12.1%) between 2007 and 2012, according to the United States Renal Data System (USRDS) annual data report [135]. A French epidemiological study found that the incidence of renal failure was higher in men than in females [136]. In contrast, a Chinese cross-sectional survey found that men and women had the exact prevalence of chronic kidney disease (CKD) [137].

In a prospective multicenter study, Martinez-Castelao et al examined 1129 patients with CKD stages 3 (n = 434) and 4 (n = 695) from Spanish government hospitals with nephrology outpatient clinics. The mean cohort age was 68±13 years, and there was no noticeable age difference among the several stages of CKD. They also noted that the cohort was predominately male. There were 64% men and 36% women. Those with CKD stages 3 and 4 (91.2% and 94.1%, respectively) almost had hypertension [138]. A prospective study was conducted by Bailie et al. at four US nephrology clinics. The study had 619 participants, 150 for CKD stages 2 and 3, 350 for CKD stage 4, and 119 for CKD stage 5. The cohort average age was 60.6 ±16.0. Men were more likely than women to develop CKD in the study population (66% vs. 44%). CKD stages 2 and 3, 4 and 5, and their prevalence were 24.2%, 56.5%, and 18.7% respectively. Diabetes (37%) and hypertension (90%) were the two co-morbid conditions that were most prevalent [139]. Al-Rahami et al carried out a prospective study on 600 CKD patients in Malaysia. Most of the CKD patients were male Chinese in terms of racial origin, and the study participants mean age was 55.56±14.15 years. Based on gender, males made up 321 (53.5%) and females 279 (46.5%), respectively.

CKD Stages 3, 4, and 5 were the most common, with a prevalence of 3.7%, 7.7%, and 8.8%, respectively. Diabetes mellitus (62.3%), hypertension (80.0%), and anemia (87.3%) were the most prevalent co-morbid conditions among study participants [140].

2.4.2 Diabetes mellitus

Diabetes mellitus is the most prevalent primary cause of CKD in developed and developing nations. Furthermore, as nearly 40% of diabetic individuals progress to CKD, all diabetic patients should receive a routine annual diagnosis. The progression of CKD can be slowed when hypertension is treated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in the presence of microalbuminuria or proteinuria [141].

Since type 2 diabetes mellitus (DM) has been identified as the primary etiology risk factor for chronic renal disease, CKD development incidence among type 2 diabetes mellitus patients requires further attention. Wu et al studied the occurrence of CKD in type 2 DM, which was conducted from 2007 to 2012 using data from the US National Health and Nutrition Examination Survey (NHANES) [142]. According to the cross-sectional investigation, 38.7% of type 2 DM patients have developed chronic renal impairment. The MADIABETES research was a prospective study that examined the five-year incidence of CKD (Stage 3-5) and concluded that the cumulative incidence of CKD stage 3-5 during follow-up duration was 10.23% among type 2 diabetic patients in Madrid, Spain [143].