國立臺灣大學公共衛生學院

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博士論文

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National Taiwan University

Doctoral Dissertation

慢性腎臟病進展的定量化流行病學模型

Quantitative Epidemiological Models for Chronic Kidney Disease Progression

蔡明憲

Ming-Hsien Tsai

指導教授：陳秀熙 博士

Advisor: Hsiu-His Chen, Ph.D.

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中文摘要

研究背景和目的

慢性腎臟病是一種具有世界性，和非傳染性特色的疾病，它的盛行率有越來越高的趨勢。而且，慢性腎臟病會導致較高的死亡率和失能率，所以照顧慢性腎臟病變成是世界政府的財政負擔和嚴重的健康照護問題。台灣在 2014 年時，有著有著全世界最高的透析盛行率和發生率。慢性腎臟病的高盛行率可能是主要的原因。然而，關於台灣慢性腎臟病相關的流行病學統計資料是有所不足的。因此，我門設計此研究來探討台灣慢性腎臟病的樣貌，慢性腎臟病進展的危險因子和轉移機率預測方程式。最後，我們還試著去估算慢性腎臟病在不同期別之間的年度轉移機率，也就是慢性腎臟病的自然病史。

材料與方法

本論文所研究的資料來自參與基隆闔家歡篩檢計劃的民眾。首先，描述台灣慢性腎臟病的盛行率與發生率。之後，利用加速失效模式(Accelerated failure time model)來評估影響慢性腎臟病狀況轉換的危險因子。影響腎絲球過濾率從≥60到59-30 mL/min/1.73m^2 為起動因子，而影響eGFR 59-30到<30 mL/min/1.73m^{2}是為促進因子。同時建立慢性腎臟病進展的預測方程式。最後，還利用五階段馬爾可夫模式來描述慢性腎臟病的自然病史（第一階段：腎絲球過濾率從≥60 mL/min/1.73m^2，第二階段：腎絲球過濾率從59-30 mL/min/1.73m^2，第三階段：腎絲球過濾率從<30 mL/min/1.73m^2，第四階段：接受透析，第五階段：全因死亡）。

結果

第一部分：慢性腎臟病的盛行率與發生率

預估所有慢性腎臟病(1-5 期)的盛行率是 15.46%，而慢性腎臟病 3-5 期盛行率是 9.06%。預估所有慢性腎臟病的發生率是 27.21/每 1000 人年，而慢性腎臟病 3-5 期的發生率是 16.89/每 1000 人年。在次族群分析中，老年人，男生，高血壓，糖尿病，代謝代謝症候群，和蛋白尿者，有較高的慢性腎臟病盛行率和發生率。此外，慢性腎臟病 3-5 期盛行率與發生率的比值顯示為 5.37 (代表平均處於這個時期的時

doi:10.6342/NTU201900529

間為 5.37 年)。男生，年紀較輕，和代謝代謝症候群者，有較低的盛行率與發生率比值（與他們相對的族群比較）。

第二部分：慢性腎臟病的啟動因子和促進因子。

慢性腎臟病的獨立啟動因子為年紀大(風險比率: 1.08；95%信賴區間: 1.07-1.09)，糖尿病(風險比率: 1.49；95%信賴區間: 1.23-1.81)，代謝症候群分數 (風險比率: 1.13；95%信賴區間: 1.0-1.19),，蛋白尿 (風險比率: 1.16；95%信賴區間: 1.10-1.22),，高尿酸血症 (HR: 1.12；95%CI: 1.08-1.17)，與較高的低密度膽固醇(風險比率: 1.15；95%CI: 1.02-1.30) ，和腎絲球過濾率 (風險比率: 0.94；95%CI: 0.93-0.95)。慢性腎臟病的獨促進因子為冠狀動脈疾病(風險比率: 1.57；95%CI: 1.04-2.36)，代謝症候群分數(風險比率: 1.31；95%CI: 1.12-1.53),，蛋白尿(風險比率: 1.48；95%CI: 1.31-1.67，高尿酸血症(風險比率: 1.11 ; 95%CI: 1.02-1.22),，與貧血(風險比率: 0.84；95%CI: 0.75-0.95), 和腎絲球過濾率(風險比率: 0.89；95%CI: 0.87-0.91)。此外，我們針對慢性腎臟病的發生與慢性腎臟病的進展，發展出兩套預測方程式，可以估算出慢性腎臟病狀態轉移的絕對發生機率。

第三部分：慢性腎臟病的隨機過程馬可夫鍊模式

我們成功地估計出慢性腎臟病的自然病史。每年腎絲球過濾率從≥60 到 59－30 mL/min/1.73m^{2}的進展機率是 0.0169。 從 eGFR 59－30 到<30 mL/min/1.73m^{2}的進展機率是 0.0259。從 eGFR <30 mL/min/1.73m^2 到需要接受透析的進展機率是 0.0988。男性相對約女性，有較有較高的慢性腎臟病進展機率和死亡率。整體而言，平均停留在腎絲球過濾率從 59－30 mL/min/1.73m^2（慢性腎臟病第三期）的時間是 5.84 年，平均停留在腎絲球過濾率從<30 mL/min/1.73m^2（慢性腎臟病第 4－5 期）的時間是 2.99 年。不同性別，糖尿病，和蛋白尿會表現出不同的平均停留時間。

結論

台灣有高的慢性腎臟病盛行率與發生率。我們的研究找出了慢性腎臟病進展的相關獨立因子，同時並建立慢性腎臟病進展的預測方程式。這些結果可以讓我們對慢性腎臟病的進展能有更加的瞭解，有助於在慢性腎臟病的照護中，針對危險族

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群發展出特異化醫療。而發展出的危險預估方程式也可以輕易地被整合入報告系統，可以早期警示醫師，將高危險群病患轉介至腎臟科，接受多學科的全人照護。此外，慢性腎臟病的平均停留時間可以被當成慢性腎臟病介入政策的評量指標。最後，我們還利用隨機馬可夫模式，發展出慢性腎臟病的進展病史（近似自然病史），這讓我們對慢性腎臟病的進展有更近一步的了解。也有利於未來慢性腎臟病介入計畫的成本效益的分析。

關鍵字： 慢性腎臟病，盛行率，發生率，存活分析，平均存續時間，多階段馬可夫模式，隨機過程，自然病史。

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Abstract

Background and objectives

Chronic kidney disease (CKD) is a major noncommunicable disease and has become a global public health problem with an increasing prevalence. Caring for patients with CKD has been shown to present financial and medical burdens owing to high mortality and morbidity. In 2014, Taiwan has the highest incidence and prevalence of end-stage renal disease, requiring renal replacement therapy. CKD may contribute to this burden. However, the current data on the epidemiologic features of CKD in Taiwan are incomplete. Therefore, we designed this study to elucidate the epidemiologic pictures of CKD, the risk factors for CKD progression and the annual transition rate between CKD stages.

Materials and Methods

Subjects from Keelung Community-based Integrated Screening (KCIS) Program were enrolled since 1999 to 2009. We reported prevalence and incidence rate of CKD stages and tried to estimate the risk factors for CKD state transition using accelerated failure time model. The initiator and progressor were defined as the factor affecting the eGFR from eGFR ≥60 to 59–30 and from eGFR 59–30 to <30 mL/min/1 respectively. Moreover, a five-state Markov process was used to describe the Clinical history of CKD stages (state 1: eGFR ≥60 mL/min/1.73 m^2, state 2: eGFR 59–30 mL/min/1.73 m^2, state 3: eGFR <30 mL/min/1.73 m^2, state 4; Receiving dialysis, and state 5: all-cause death).

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Results

Part I: The prevalence and incidence of CKD stages

The participants' mean age was 47.7 ± 15.4 years. The estimated prevalence was 15.46% for total CKD and 9.06% for CKD stages 3–5. The incidence was 27.21/1000 person-years (PY) for total CKD and 16.89/1000-PY for CKD stages 3–5. Older patients, males, and those patients with comorbidities of diabetes mellitus (DM), hypertension, and metabolic syndrome (MetS) exhibited higher prevalence and incidence rates than their opposing counterparts. Moreover, the average dwelling time (ADT) of CKD stages 3–5 was 5.37 years (95% confidence interval (CI): 5.17–5.57). Males and those with comorbidities of DM or MetS had shorter ADTs in CKD stages 3–5 than their opposing counterparts.

Part II: The independent initiators and progressors of CKD

The independent initiators of CKD were old age (HR, 1.08; 95% CI, 1.07–1.09), diabetes (HR, 1.49; 95%CI, 1.23–1.81), metabolic syndrome scores (HR, 1.13; 95%CI, 1.08–1.19), proteinuria (HR, 1.16; 95%CI, 1.10–1.22), hyperuricemia (HR, 1.12; 95%CI, 1.08–1.17), higher low-density lipoprotein level (HR, 1.15; 95%CI, 1.02–1.30), and low eGFR level (HR, 0.94; 95%CI, 0.93–0.95). The independent progressors of CKD were coronary artery disease (HR, 1.57; 95%CI, 1.04–2.36), metabolic syndrome scores (HR, 1.31; 95%CI, 1.12–1.53), proteinuria (HR, 1.48; 95%CI, 1.31–1.67), hyperuricemia (HR, 1.11; 95%CI, 1.02–1.22), low hemoglobin level (HR, 0.84; 95%CI, 0.75–0.95), and low eGFR level (HR, 0.89; 95%CI, 0.87–0.91). Furthermore, two risk prediction functions were also built for the absolute risk prediction of CKD state transition.

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Part III: The stochastic Markov model of CKD

The annual progression rate was 0.0169 (95% CI, 0.0164–0.0173) from eGFR ≥60 to 59-30 mL/min/1.73m^2, was 0.0259 (95%CI, 0.0240–0.0278) form eGFR 59-30 to <30 mL/min/1.73m^2, was 0.0988 (95% CI, 0.0902–0.1075) from eGFR <30 mL/min/1.73m^2 to dialysis. The man had higher progression rate for the movement from eGFR ≥60 to eGFR 59–30 mL/min/1.73m^2 than the woman. The ADT of eGFR 59–30 mL/min/1.73m^2 (CKD stage 3)was 5.48 years (95%CI, 5.62–6.07) and was 2.99 years (95%CI, 2.77–3.25) for eGFR <30 mL/min/1.73m^2 (CKD stages 4–5). The ADT varied by age, gender and comorbidities.

Conclusion

The prevalence and incidence of CKD in Taiwan are high. We ascertained the independent initiators and progressors of CKD in our study. The results are useful to understand the association between factors and the state transition of CKD, which can be beneficial for developing specialized CKD care programs for the risky population. Also, these two prediction functions can be easily integrated into the reporting system to early alert the physicians to transfer the risky patients to receive a nephrologist-based multidisciplinary care. Moreover, the ADT in CKD can be used as an indicator for evaluating the CKD policy. Finally, a stochastic mode of CKD was successfully established to elucidate the approximated natural history of CKD in Taiwan, which this can offer an updated understanding of the CKD progression and also can be applied to the cost-effectiveness analysis of CKD intervention.

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Keywords: chronic kidney disease, prevalence, incidence, survival analysis, average dwelling time, multi-state Markov model, stochastic process, natural history.

doi:10.6342/NTU201900529

CONTENTS

doi:10.6342/NTU201900529

doi:10.6342/NTU201900529

doi:10.6342/NTU201900529

LIST OF FIGURES

doi:10.6342/NTU201900529

LIST OF TABLES

doi:10.6342/NTU201900529

Chapter 1 Introduction

1.1 Background

Chronic kidney disease (CKD) is a major noncommunicable disease and has become increasingly prevalent and has emerged as a global public health problem with a high prevalence ranging from 10% to 15%. Caring for patients with CKD presents a financial and medical burden due to their higher risks of morbidity and mortality [1-4], and CKD can also progress to end-stage renal disease (ESRD) with requiring renal replacement therapy (RRT) to sustain life. In 2014, Taiwan had the highest incidence (0.455/1000 person-year) and prevalence (0.32%) of ESRD with RRT based on an international comparison of data from the US Renal Data system [5]. Therefore, a better understanding in the epidemiologic features of CKD is necessary for arranging the healthy policy to impede its progression to ESRD. CKD is thought to be a progressive disease, and the early identification of risk factors for progression is the primary focus of current guidelines [6, 7].

Late referral to nephrologists is associated with poor outcomes and increased mortality and morbidity [8-10], whereas early referral to nephrology departments allows sufficient pre-dialysis education, which can delay the initiation of dialysis and improve mortality rates [11, 12]. A cooperative intervention with nephrologist-based multidisciplinary care (MDC) was developed to improve positive attitudes toward disease management among patients with CKD. This level of care has a substantial influence on mortality and morbidity and delays entry into hemodialysis [13-15]. Accordingly, a unique protocol to standardize and regulate pre-ESRD care has been established as a part of the medical system in Taiwan, and all medical costs are covered by the National Health Insurance (NHI). Specifically, Chen et al. showed improved

doi:10.6342/NTU201900529

survival rates, control of mineral bone disease, and slower declines of renal function in patients with CKD receiving MDC in Taiwan [13]. Therefore, early identifying the risky population to CKD is beneficent for CKD management.

The prevalence of CKD stages 1–5 is 11.9%, 11.3%–13%, 11%, 12.9%, and 10.2% in Taiwan [16], China [17, 18], the USA [19], Japan [20], and Europe [21], respectively. The medical burden of CKD has been addressed by collaborative intervention using nephrologist-based multidisciplinary care to facilitate positive attitudes toward disease management and improve the clinical outcomes of patients with CKD [15]. CKD stages 3–5, which is defined as moderate to advanced CKD, represents the major clinical burden of CKD [16], occurring in 6.9%–9.8%, 3.2%, 4.4%, 10.6%–15%, and 11.2% of all individuals in Taiwan [1, 16, 22], China [23], the USA [19], Japan [20, 24], and Australia [25], respectively.

However, the current data on the epidemiologic features of CKD in Taiwan, including the prevalence, incidence, and transition rate between CKD stages (natural history of CKD progression), are incomplete.

1.2 Study Aims

The prevalence, incidence, and averaged time dwelling in CKD

Because of the incomplete data of epidemiologic CKD, the aim of part I study was to use a large population-based screening sample to estimate the prevalence and incidence of CKD at stages 3–5 in Taiwan using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Based on the estimated prevalence and incidence, we further derived the average dwelling time (ADT) in main clinical burden of CKD (stages 3–5) by using the ratio of the two estimates to elucidate the disease course by

doi:10.6342/NTU201900529

the demographic characteristics of Taiwan community population. The results can add to the literature concerning the prevalence and incidence of CKD stages in Taiwan, providing a reference for policymakers when establishing medical programs for CKD management.

The risk factors associated with the evolution of CKD

Knowing the information about the factors associated with the multi-state transition of CKD is important for individually tailored care programs. Therefore, in the part II study, we aimed to use longitudinal follow-up data from a large population-based screening program to elucidate the influencing clinical factors in a three-state transition model of CKD, which included initiators and progressors. We used two accelerated failure time regression models with interval censoring to elucidate the influencing clinical determinants associated with the progression from those with eGFR ≥60 to eGFR 59–30 mL/min/1.73 m^2 (initiation of CKD) and from those with eGFR 59–30 to eGFR <30 mL/min/1.73 m^2 (progression of CKD) based on the Keelung Community-based cohort study. The results gives the clues on the initiators and progressors through the course of CKD evolution. Moreover, two risk prediction functions were also developed for predicting the probability of CKD state transition in order to identify the risky person and early transfer them to receive the nephrologist-based MDC.

doi:10.6342/NTU201900529

Stochastic multi-state Markov transition model of CKD

After taking into consideration the continuous process of CKD evolution through the stages of eGFR change, a stochastic model that describes the process of CKD including the states of eGFR ≥60 mL/min/1.73 m^2, eGFR 59–30 mL/min/1.73 m^2, eGFR <30 mL/min/1.73 m^2, dialysis, and death was proposed. Based on the proposed five-state Markov model, the state-specific dwelling time and the effect of clinical determinant associated with the initiation and the progression of CKD was assessed. The dynamic change on the risk of CKD states for the study population was further developed.

doi:10.6342/NTU201900529

Chapter 2 Literature Review

2.1 The epidemiologic features of CKD in Taiwan

The prevalence of CKD in stages 1–5 is reported as 9.8–11.9% in Taiwan [3]. The participants (n= 6001) over 20 years-old were recruited in a nationwide, randomized, stratified survey for hypertension, hyperglycemia and hyperlipidemia by Hsu *et al*., which reported a prevalence rate of 9.8% for CKD stage 1–5 and 6.9% for CKD stage 3–5 [26]. A large database (n=462293) from a cohort of commercial health examination reported an overall prevalence of 11.9% of CKD stage 1–5 of which the prevalence was 1.0% for stage 1, 3.8% for stage 2, 6.8% for stage 3, 0.2% for stage 4 and 0.1% for stage 5 by Wen *et al*. [16]. Moreover, another survey from the dataset of National Health Insurance (NHI) using disease code analysis by Kou *et al*. reported the prevalence of clinically recognized CKD as 9.83% [22].

However, only one study, conducted by Kuo et al., has assessed the overall incidence of clinically detectable CKD (approximately equivalent to CKD stages 3–5 [27]), reporting an incidence of 13.5/1000 person-years (PY) from 1997 to 2003 based on data from Taiwan's NHI system [22]. However, assessing clinically detectable CKD only may underestimate the true incidence of CKD because patients with early CKD may not exhibit any clinical symptoms and medical data from the NHI are not classified into CKD stages, which could introduce coding bias.

Moreover, the estimated glomerular filtration rate (eGFR) has become a standard method of evaluating CKD and is assessed using the diagnostic criteria and classifications proposed by the National Kidney Foundation in the US [6]. The modification of Diet in Renal Disease (MDRD) equation has been widely used to

doi:10.6342/NTU201900529

calculate eGFR. All the epidemiologic studies about CKD in Taiwan adopted MDRD to calculate the eGFR. However, the precision of the MDRD decreases when the GFR is >60 or <20 mL/min/1.73 m2 [28, 29]. Accordingly, the CKD-EPI formula was developed to offer a more accurate estimation of eGFR [30, 31].

A lower awareness rate of CKD was reported by Hsu et al., which 8% for CKD stage 3, 25% for CKD stage 4 and 71.4% for CKD stage 5 [1]. Moreover, Wen et al. had reported a 3.5 % of awareness in CKD stages 1-5, of which was 2.66% for stage 1, 2.68% for stage 2, 4.10% for stage 3, 23.67% for stage 4 and 52.40% for stage 5 [16]. These raise the crucial need for the promotion of CKD education for general population. Moreover, continuing medical education is needed for each level of medical physician to learn the new concept of CKD definition and how to provide the ideal care for this rapidly growing population of CKD.

Taiwan has the highest incidence and prevalence of ESRD needing dialysis [5]. Approximately half of the incidence of dialysis cases were the elderly and diabetic cases constitute approximately 40% of the incidence of dialysis cases [32]. There are some possible explanations for this burden. First, the high prevalence and incidence of CKD in Taiwan. Second, the launching of NHI in 1995 covering the dialysis therapy fully. Third, low transplantation rate and low mortality rate in dialysis patients. Those reasons would retain the numbers of the dialysis pool.

doi:10.6342/NTU201900529

2.1.1 The prevalence of CKD in different centuries

CKD is a global problem and its burden is increasing as time goes by. Hill NR et al. [33] has reported a meta-analysis study showing global mean CKD prevalence of 1–5 stages 13.4% (95%CI, 11.7–15.1%), and stages 3–5 was 10.6% (95%CI, 9.2–12.2%). Table 1 shows some import reports of the prevalence of CKD in different countries. The prevalence of CKD in American increased from 10% in 1988-1994 to 13.1% in 1999-2004 [34]. In Europe, the population-based Health Survey (N=92,939) reported a 10.2% prevalence of CKD in Norway [21] and there was a higher prevalence of all CKD (26.7%) had been reported in Germany [35]. Moreover, a 12.7% prevalence of CKD stages 1–4 had been disclosed in Italy [36]. In the Asia, the prevalence of CKD was approximately 12.9–15.1% in Japan (N=154,019–527,594) [20, 24], 7.2–13.7% in Korea (N=2,356–60,921) [37, 38], 3.2–18.6% in Singapore (N=2,783–3,979) [39, 40], and 3.2–11.3% in China (N=13,925–15,540) [17, 41].

doi:10.6342/NTU201900529

Table 1. The prevalence of CKD in different countries.

Area/Authors	Size	Period	Equation of eGFR	Prevalence
Taiwan				
Wen et al.[16]	462,293	1994–2006	MDRD	All CKD: 11.9%
				CKD stages 3–5:7.1%
Hsu et al.[1]	5,409	2002	MDRD	CKD stages:3–5:6.9%
Kuo et al.[22]	176,365	1997–2003	ICD-9	Clinical CKD:9.8%
China				
Zhang et al.[17]	13,925	-	Chinese-MDRD	All CKD: 13.0%
Chen et al.[41]	2,353	-	Chinese-MDRD	CKD stages 3–5:2.5%
Japan				
Ima et al.[20]	527,594	2000–2004	Japan-MDRD	All CKD: 12.9%
				CKD stages 3–5:10.6%
Lseki et al.[24]	154,019	2003	MDRD	CKD stages 3–5:15.1%
Korea				
Kim et al. [37]	2,356	2006	MDRD	All CKD: 13.7%
				CKD stages 3–5: 5.0%
Change et al.[38]	60,921	2001–2007	MDRD	All CKD: 7.2%
Thailand				
Ong A. et al.[42]	3,117	2004	MDRD	CKD stages 3-–5:8.5%
Perkovic et al. [43]	7,909	2000	MDRD	CKD stages 3–5:16.3%
Singapore				
Teo et al.[39]	3,979	2000–2005	Chinese-MDRD	All CKD:75.2%
				CKD stages 3–5:3.2%
Shankar et al.[40]	2,783	-	MDRD	CKD stages 3–5:18.6%
American				
Coresh et al.[34]	13,233	1988–1994	MDRD	CKD stages 1–4:10.0%
		1999–2004		CKD stages 1–4:13.1%

doi:10.6342/NTU201900529

Continuous Table 1

Area/Authors	Size	Period	Equation of eGFR	Prevalence
India				
Singh et al.[44]	5,252	2005–2007	MDRD	CKD stages 3-–5:4.2%
Australia				
Chadban et al.	11,247	1999–2000	CG	CKD stages 3–5:11.2%
Norway				
Hallan et al.[21]	92,939	1995–1997	MDRD	All CKD:10.2%
Canada				
Arora p et al.[45]	3,689	2007–2009	MDRD	All CKD: 12.5% CKD stages 3–5:3.1%
Germany				
Zhang QL et al.[35]	9,953	2000–2002	MDRD	All CKD: 26.7% CKD stages 3–5: 17.4%
Iran				
Najafi I et al.[46]	1,557	2007–2009	MDRD	All CKD: 19.52% CKD stages 3-–5: 8.9%
Italy				
Gambaro, G et al.[36]	3,870	2006	MDRD	CKD stages 1–4: 12.7% CKD stages 3–4: 6.7%
Romania				
Cepoi, V et al.[47]	60,969	2007–2008	MDRD CKD-EPI	CKD stages 3–5: 6.69% CKD stages 3–5: 7.32%

Abbreviation: CKD, chronic kidney disease; MDRD, Modification of Diet in Renal Disease; CG, Cockcroft-Gault.; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation.

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2.2 The risk factors of CKD initiation or progression

CKD is associated with age-related renal function decline , which would be accelerated by comorbidities and primary renal disorders [48]. CKD has the higher risks of dialysis, hospitalization, cardiovascular morbidity and mortality [49, 50]. End-stage renal disease (ESRD) is the final stage for CKD, and with the improvement in dialysis techniques and the quality of medical care, dialysis patients have longer life- spans which in turn leads to the increasing prevalence of ESRD. According to the latest annual report of United States Renal Data System, the average yearly increase of prevalence of ESRD across countries was from 0.1 to 109 (per million population) during the period of 2003 to 2016 [51], thus placing a greater burden on the health insurance system of many countries. Especially, Taiwan has the largest average yearly increase of ESRD prevalence [51]. Therefore, knowing the associated factors for CKD is necessary to delaying its progression to later stage.

The incidence of CKD and the decline rate of eGFR are highly variable among individuals with the same underlying cause of renal injury or degree of functional impairment. Therefore, early identification and treatment of people with CKD are essential worldwide. Many epidemiological studies have examined the risk factors, including Aristolochic acid digestion [52], diabetes [53], hypertension [54], proteinuria [55], hyperlipidemia [56], hyperuricemia[57], smoking habit [58], advanced age [59], male sex [60], race [60], analgesic abuse [61], alcohol consumption [62], low socioeconomic status [63], lower birther weight [64], metabolic syndrome (MetS) [65], and so on for CKD development and progression. Moreover, a lot of CKD progression prediction model have been proposed [66-69], of which the endpoints were estimated glomerular filtration rate (eGFR) lower than 60 mL/min/1.73 m^2, doubling of serum

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creatinine, 20% decrease of eGFR, or ESRD requiring renal replacement therapy. However, information about the factors associated with a state transition in a multi-state CKD model is lacking. The use of state transition as an endpoint can decrease the effect of variability in the eGFR measurement on CKD progression. Furthermore, all of the studies adopted the statistical methods of Cox regression and logistic regression models to estimate the event risk [66-69], which they can provide relative risks but not absolute risks. Principally, the absolute risk model can be realized straightforwardly.

Table 2 shows some important studies about the risk factors on CKD progression worldwide, modified from one previous systemic review report focusing mainly on the cohort studies [70]. In Taiwan, some studies have reported the associated risk for CKD progression. One study had showed that old age, diabetes, hypertension, hyperlipidemia and female sex were associated with a higher risk of developing CKD using NHI dataset [22]. A prospective cohort study demonstrated that hypertension, diabetes, dyslipidemia, smoker, obesity, low socioeconomic state and regular user of Chinese herbal drugs were significant risky for CKD developing [16].

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Table 2.The studies for the risks of CKD initiation or progression

Baseline eGFR /Authors	CKD stage	Years	Country	Design	Size	age	Endpoint of CKD	Duration (months)	Statistic methods	Risk factors for CKD progression
eGFR ≥60 mL/min/1.73 m^2										
Ryu [71]	0	2009	Korea	PC	10685	37	Stages 3-5	46	Cox Time-dependent	Metabolic syndrome, TG and HDL.
O'Seaghdha[72]	0	2011	USA	CC	200	64	Stage 3	-	Logistic reg.	Urinary connective tissue growth factor
Shankar [73]	0-2	2006	USA	PC	3392	62	Stages 3-5	60	Logistic reg.	Current smoker, alcoholism
Bash [74]	0-2	2009	USA	PC	14854	54	Stages 3-5	174	Cox reg.	Leukocyte count, fibrinogen, v-W factor, factor VIIIc, albumin
Chien [75]	0-2	2010	Taiwan	PC	5168	51	Stages 3-5	26	Passion reg.	Age, BMI, DBP , diabetes, stroke, proteinuria, uric acid
Shastri [76]	0-2	2011	USA	PC	5422	61	Stage 3	56	Passion reg.	Microalbuminuria, cystatin C
Shankar [77]	0-2	2011	USA	PC	4926	58	Stages 3-5	180	Cox reg.	Tumor necrosis factor-a receptor 2, leukocyte count, interleukin-6
Regalado [78]	1-2	2000	USA	PC	53	52	Slop of 1/cr	36	Linear reg.	Smoking, proteinuria, black, age, mean blood pressure
Yoshida [79]	1-2	2008	Japan	RC	485	42	eGFR slop	60	Linear reg.	Proteinuria, smoking, hypertension, HDL
Gopinath [80]	1-2	2013	Australia	PC	1952	>50	Stage 3	120	Logistic reg	Poor diet quality
Khatri [81]	0-2	2014	USA	PC	900	64	Stage 3	84	Logistic reg	non Mediterranean diet

doi:10.6342/NTU201900529

Continuous Table 2

Baseline eGFR /Authors	CKD stage	Years	Country	Design	Size	age	Endpoint of CKD	Duration (months)	Statistic methods	Risk factors for CKD progression
Lin[82]	0-2	2015	USA	PC	400	58	eGFR drop	54	linear mixed	Elevated plasma Lp(a)
Bowe[83]	0-2	2017	USA	PC	1594700	-	eGFR drop	110	Cox reg	Monocyte count
Park[84]	0-2	2018	USA	RC	225782	55	Stage 3	30	Cox reg	Chronic HCV infection
JiaHui [85]	0-2	2018	China	PC	469459	51	Stage 3	108	Cox reg	Chronic HBV infection
Michel[86]	1-2	2017	USA	PC	540	37	eGFR drop	65	Cox reg Linear reg	FGF23
eGFR ≥30 mL/min/1.73 m^2										
Baek [87]	3	2012	Korea	RC	347	64	Stages 4-5	142	Cox reg.	Albuminuria, hematuria, eGFR
Cheng [88]	1-3	2012	Taiwan	PC	916	73	eGFR slop	38	Cox reg.	Metabolic syndrome, insulin resistance, TG, glucose
Ishizuke[89]	1-3	2016	Japan	RC	91		ESRD eGFR slop		Linear reg	eGFR, HDL, and total bilirubin
eGFR <60 mL/min/1.73 m^2										
Locatelli [90]	3-5	1996	Italy	PC	456	49	ESRD Double Cr	24	Cox reg.	Creatinine, proteinuria, calcium, underlying nephropathy
Hunsicker [91]	3-4	1997	USA	PC	585	-	eGFR slop	28	Linear reg.	Proteinuria, PKD, transferrin, black, MAP, HDL

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Continuous Table 2

Baseline eGFR /Authors	CKD stage	Years	Country	Design	Size	age	Endpoint of CKD	Duration (months)	Statistic methods	Risk factors for CKD progression
Hunsicker [91]	4-5	1997	USA	PC	255	-	eGFR slop	26	Linear reg.	Proteinuria, PKD, transferrin, eGFR
Boaz [92]	3-5	1998	Israel	PC	104	65	Slop of 1/cr	18	Linear reg.	Dietary pattern, lipid, proteinuria
Evans [93]	4-5	2005	Sweden	PC	920	-	ESRD	24	Cox reg.	Age, male, diabetes, eGFR
Levin [94]	4-5	2008	Canada	RC	4231	67	ESRD	31	Cox reg.	Age, male, eGFR, BP , Hb, phosphate, PTH, proteinuria, use of ACEI/ARB
Hoefield [95]	3-5	2010	UK	PC	1325	65	ESRD	26	Cox reg.	Age, DBP, Hb, phosphate, proteinuria, CKD stage
De Nicola [96]	3-5	2011	Italy	PC	1248	67	ESRD	60	Competing risk reg.	Age, proteinuria, phosphate, BMI, CVD, Hb
Khedr [97]	3-5	2011	Canada	RC	214	68	eGFR drop	54	Linear reg.	eGFR, proteinuria, diabetes, use of ACEI/ARB
Pereira[98]	3-5	2012	Brazil	RC	211	65	ESRD	57	Cox reg.	Diabetes
Obi [99]	3-5	2010	Japan	RC	461	67	ESRD	38	Competing risk reg.	Age, proteinuria

doi:10.6342/NTU201900529

Continuous Table 2

Baseline eGFR /Authors	CKD stage	Years	Country	Design	Size	age	Endpoint of CKD	Duration (months)	Statistic methods	Risk factors for CKD progression
All CKD										
Agarwal [100]	1-5	2009	USA	PC	218	68	ESRD	84	Cox reg.	SBP
Kuo [101]	1-5	2010	Taiwan	RC	19161	52	ESRD	-	Cox reg.	Use of acetaminophen, aspirin, and NSAID
Sugiura [102]	1-5	2011	Japan	PC	281	54	eGFR drop ESRD	48	Cox reg.	Proteinuria, resistive index, GFR, systolic blood pressure
Wu [103]	1-5	2011	Taiwan	PC	268	67	eGFR drop ESRD	21	Cox reg.	P-cresyl sulphate, indoxyl sulphate
Rahman[104]	1-5	2013	USA	PC	3939	-	eGFR drop	72	Cox reg.	heart failure
Yonemoto[105]	1-5	2018	Japan	RC	703	70	eGFR drop ESRD	22	Linear reg. Cox reg.	Higher RDW was independently associated with worse renal outcome in patients with non-DM
Tsai[106]	1-3	2017	Taiwan	PC	4600	70	ESRD	120	Cox reg.	Absolute annual eGFR decline rate
Gooch [107]	0-5	2007	Canada	PC	10184	76	eGFR drop	33	Logistic reg.	Use of NSAID
Hemmelgarn[108]	0-5	2007	Canada	RC	10184	76	eGFR drop	24	Logistic reg.	Age, CVD, diabetes, gout, anti-emetic drugs

doi:10.6342/NTU201900529

Continuous Table 2

Baseline eGFR /Authors	CKD stage	Years	Country	Design	Size	age	Endpoint of CKD	Duration (months)	Statistic methods	Risk factors for CKD progression
Imai [109]	0-5	2008	Japan	RC	120727	-	eGFR drop	120	Linear reg.	Hypertension, proteinuria, eGFR
Bash [74]	0-5	2010	USA	PC	14854	54	ESRD	174	Cox reg.	eGFR, black, age, male, diabetes, SBP, CAD, BMI, smoking, TG
Agarwal [110]	0-5	2011	USA	PC	420	64	ESRD	120	Cox reg.	Granulocyte, monocyte
Other										
Hallan [111]	0-4	2009	Norway	PC	65589	50	ESRD	124	Cox reg.	Age, male, low physical activity, diabetes, SBP, antihypertensive drugs, HDL, eGFR, albuminuria
Ozsoy [112]	1-4	2007	Netherland	PC	169	47	eGFR drop ESRD	49	Logistic reg.	Apolipoprotein B, type of renal disease, MAP, proteinuria
Ravani [113]	2-5	2005	Italy	PC	131	71	ESRD	27	Cox reg.	ADMA, Hb, proteinuria, eGFR
Bolignano [114]	2-4	2009	Italy	PC	96	57	ESRD Double Cr	19	Cox reg.	Urinary NGAL, serum NGAL, eGFR
Yuste[115]	4-5	2013	Spain	PC	400	65	eGFR slop	19	Linear reg.	Serum phosphate and PTH levels and proteinuria.

doi:10.6342/NTU201900529

Continuous Table 2

Baseline eGFR /Authors	CKD stage	Years	Country	Design	Size	age	Endpoint of CKD	Duration (months)	Statistic methods	Risk factors for CKD progression
Tin[4]		2016	USA	PC	622	-	eGFR slop	-	Logistic reg.	APOL1 high–risk genotype
Ricardo [116]	1-4	2017	USA	PC	431	150	ESRD	60	Cox reg.	Short and poor-quality sleep
Wu [117]	1-4	2018	China	RC	295	37	ESRD eGFR drop	45	Logistic reg.	BMI and interstitial fibrosis

Abbreviation: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PC, prospective cohort; RC, retrospective cohort, CC, case control; Cr, creatinine; ESRD, end stage of renal disease; reg., regression; RDW, red cell distribution width; PKD, polycystic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; TG, triglyceride; HDL, high dense lipoprotein; Hb, hemoglobin; PTH, parathyroid hormone; v-W factor, von Willebrand factor; ACEI, angiotensin-converting-enzyme inhibitor; ARB, Angiotensin II Receptor Blocker; NSAID; Non-Steroidal Anti-Inflammatory Drug; CAD, coronary artery disease; CVD, cardiovascular disease; ADMA, Asymmetric dimethylarginine; NGAL, Neutrophil gelatinase-associated lipocalin; APOL1, apolipoprotein L1.

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2.3 CKD transition model

Chronic and noncommunicable diseases have been responsible for the main clinical problems worldwide [118]. One of these diseases is CKD which is defined according to the presence or absence of proteinuria and level of eGFR [6]. It forms a substantial financial and medical burden because of the high mortality and morbidity [1-3]. Early detection with suitable intervention is one of the strategies of defeating the CKD to delay their transition to more severe stages. Therefore, the knowledge about the progression of CKD is necessary because it can help health policy makers to evaluate expected burden of disease in future and to analysis the cost effectiveness of competing interventions.

In longitudinal studies, participants with covariate information are observed over time. The analysis in such studies where individuals may experience several events is often accessed using multistate model, which is a model for a continuous time stochastic process allowing individuals to move among a finite number of states [119]. A change of state status is called transition where state can be transient or absorbing (no change can be observed in this state). This approach has the Markovian assumption that the values in current state are only determined by the values of the previous state before proceeding. These models can be simple as illness-death model [120] or complicated as competing risks model [121]. The transition intensities in the multistate models can be assumed to be constant as function of time or be non-homogenous. Examples include the recent applications in the fields of asthma [122] and human immunodeficiency virus [123]. In addition, Multistate model based on Markov processes are useful for describing the natural history of chronic disease and cancer [124, 125] and for estimating rates of transition between stages of diseases and the

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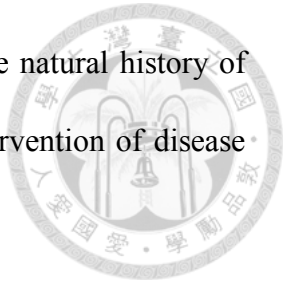

average dwelling time (ADT) of disease [126, 127]. Knowing the natural history of disease can be applied to the cost-effectiveness analysis on the intervention of disease [128, 129].

A nature history of CKD is not available in current literature. Begun et al. has proposed a stochastic model for the progression of CKD using continuous time Markov chain [130]. A six-state model was proposed since eGFR 59–30 mL/min/1.73m^2 to death (state 1:eGFR 59–30, state 2: eGFR 29–15, state 3: eGFR 5, state 4: dialysis, state 5: transplantation, and state 6: death). Mahmoud et al. used the same dataset using a 5-state model without the state of dialysis (state 1:eGFR 60–90, state 2: eGFR59–30, state 3: eGFR 29–15, state 4: eGFR <15, state 5: death). However, the data source was collected from a dialysis center, indicating these CKD patients may have high severity of disease. Therefore, the results may not fit to the general population.

Semi-Markov multistate models has the assumption of making dependence on the time spent in the current state with a fitted probability density function of the duration in each state, which this emphasized the importance of time spent in a state [131, 132]. Foucher et al. had applied a semi-Markov model to the longitudinal follow up of kidney transplantation recipients based on generalized Weibull hazard function with a 5-state model (state 1: proteinuria<0.5g/d, state 2: clearance decreased 20% in 1 year and/or proteinuria 1-0.5 g/d, state 3: clearance decreased 30% in 1 year and/or proteinuria >1 g/d, state 4: definitive rejection, and state 5: death with kidney function) [133].

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Chapter 3 Data Source and Methods

3.1 The data source

A prospective cohort design was adopted for the participants, who were age ≥20 years using a community-based multiple screening program in Keelung, the northernmost county of Taiwan. There was no significant difference in the population distribution of gender and age between Keelung and Taiwan in 2009 (Table 3), meaning that Keelung can act as a representative in assessing the epidemiologic features of Taiwan. This screening program, which is known as the Keelung Community-based Integrated Screening (KCIS), was implemented from 1999 to 2009 (Table 4). Details regarding the study design, implementation and preliminary results of this program have been described elsewhere [134, 135]. Briefly, the KCIS program mainly targets five cancers (breast cancer, cervical cancer, oral neoplasm, colon neoplasm, and liver cancer) and screens for chronic diseases (diabetes, hypertension, dyslipidemia, and impaired kidney function). Adults residing in Keelung and eligible for the KCIS program were invited annually; among those who attended the program, 51,153 (48.2%) attended the program once, 21,993 (20.7%) attended twice, 12,317 (11.6%) attended thrice, 7,647 (7.2%) attended four times, 5,178 (4.8%) attended five times, 3,477 (3.2%) attended six times, 2,231 (2.1%) attended seven times, 1,279 (1.2%) attended eight times, 644 (0.6%) attended nine times, and 175 (0.1%) attended ten times (

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). This program was fully governed by the Health Bureau of Keelung city, Taiwan. This study was approved by the local Ethical Committee of Health Bureau of Keelung city and all procedures followed the ethical standard of the Helsinki Declaration that revised in 2008. The written informed consent was introduced and obtained from all participants in each screening activity.

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Table 3. The distribution of gender and age in the population of Keelung and Taiwan in 2009.

	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years	80–89 years
Taiwan (%)	3,524,602 (20)	3,770,314 (21)	3,756,394 (21)	3,237,696 (18)	1,666,759 (9.5)	1,117,796 (6.4)	506,074 (2.9)
Male	51%	50%	50%	49%	48%	47%	51%
Keelung (%)	57,422 (19)	61,841(21)	66,651 (22)	58,686 (19)	28,130 (9.3)	19,253 (6.4)	9,026 (3.0)
Male	51%	51%	51%	49%	48%	46%	51%

doi:10.6342/NTU201900529

Table 4. The number of attendants of KCIS by year

Years	Number	%	Accumulative %
1999	128	0.12	0.12
2000	19,047	17.95	18.07
2001	21,224	20.00	38.07
2002	13,172	12.42	50.49
2003	10,505	9.90	60.39
2004	8,258	7.78	68.17
2005	9,827	9.26	77.43
2006	8,559	8.07	85.50
2007	5,409	5.10	90.60
2008	4,949	4.67	95.27
2009	5,016	4.73	100

doi:10.6342/NTU201900529

Table 5. The frequency of repeated visit of KCIS participant

Number of repeated visit	Number	%	Accumulative %
1	51,153	48.2	48.2
2	21,993	20.7	68.9
3	12,317	11.6	80.5
4	7,647	7.2	87.7
5	5,178	4.8	92.6
6	3,477	3.2	95.9
7	2,231	2.1	98.0
8	1,279	1.2	99.2
9	644	0.6	99.8
10	175	0.1	100

doi:10.6342/NTU201900529

3.2 Data collection

As the KCIS program screened for neoplastic and non-neoplastic diseases, the information collected at each screening round included

(1) A series of anthropometric measures, such as body mass index (BMI) and waist circumference, and biochemical variables, including blood lipid profile, uric acid, fasting blood sugar, alanine aminotransferase (ALT), aspartate aminotransferase (AST), renal function, hemoglobin, urinary analysis by dipstick, stool occult blood test, and so on;

(2) Lifestyle factors, including smoking, alcohol intake and physical activity. Alcohol drinking status was classified as never, current and former. The smoking and betel-nut chewing habits were defined in the same manner. The frequency of physical activity was defined as low (regular exercise less than twice per week) or high (regular exercise more than twice per week), with a duration of at least 30 min each time;

(3) Individual medical history of chronic diseases and cancer. This included age at onset and type of disease. Family history of chronic disease and cancer: whether parents and other first or second-degree relatives suffered from any chronic diseases, such as type 2 diabetes mellitus (DM), hypertension, cardiovascular disease, and so on.

The data in our study were extracted from this cohort and included anthropometric measures at baseline, such as body mass index (BMI) and waist circumference; biochemical variables, such as spot urine analysis by dipstick and serum

doi:10.6342/NTU201900529

creatinine, blood lipids, fasting blood sugar levels, and lifestyle factors, such as alcohol intake, smoking, betel-nut chewing, and physical activity. Participants were classified according to alcohol intake as never and ever drank alcohol. Participants were classified according to smoking and betel-nut chewing habits in the same manner. Individual medical history included the presence of DM, hypertension, coronary artery disease (CAD) and participants' knowledge of CKD diagnosis, which was determined by affirmative responses to the question, 'Have you ever been informed by a physician that you have chronic kidney disease? The participants reeving dialysis in the first run screening were not chosen into analysis.

Dialysis events were ascertained by linking the participants in first screening run to the database of National Health Insurance (NHI) in Taiwan until December, 2012. In Taiwan, uremic patients who require long-term dialysis therapy qualify to apply to the NHI for a catastrophic illness card [the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 585]. Therefore, among then, there 601 incident dialysis were recorded. Moreover, to ascertain the death evets, the participants in our study were linked to the mortality registry in Taiwan until December, 2010. Among them, there were 6398 all-cause deaths.

doi:10.6342/NTU201900529

3.3 Glossary

1. **Prevalent case**: Those who met the CKD classification at the time of first recruitment.
2. **Incident cases**: New cases diagnosed in the follow-up of subjects free of desired CKD stage at baseline.
3. **Prevalence (%)**: Prevalent cases divided by all participants.
4. **Person-years at risk**: The sum of follow-up times among cases and non-cases with more than two screens.
5. **Incidence rates (%)**: Incident cases divided by the person-years at risk.
6. **Average dwelling time:** The average time spent in a certain state before preceding to

   next state.
7. **Markov process:** The probability of each event depends only on the state attained in the previous event.
8. **Accelerated failure time:** A method for survival analysis using parametric approaching. This approach doesn't need the proportional hazard assumption as the Cox regression model.
9. **Interval censoring:** The event was not observed directly but we know it occurred in a certain interval.
10. **Natural history of disease:** The course a disease takes in individual people from its pathological onset until its eventual resolution through complete recovery or death.

doi:10.6342/NTU201900529

3.4 The definition of chronic kidney disease stages

We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to evaluate the estimated glomerular filtration rate (eGFR), with the following formula: $eGFR = 141 \times min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} \times max\left(\frac{Scr}{\kappa}, 1\right)^{-1.0209} \times 0.993^{Age} \times (1.018\ if\ female) \times (1.159\ if\ black)$(abbreviations and units: eGFR = mL/min/1.73 m^2, Scr (standardized serum creatinine) = mg/dL, κ = 0.7 (females) or 0.9 (males), α = -0.329 (females) or -0.411 (males), min = indicates the minimum of S_{Cr}/κ or 1, max = indicates the maximum of S_{Cr}/κ or 1, age = years) [30]. We also used an abbreviated equation from the Modification of Diet in Renal Disease (MDRD) study [136], which calculated the eGFR as $186.3 \times (Scr)^{-1.154} \times Age^{-0.2.03} \times (0.742\ for\ women)$.

Because of the lack of quantitative data on urine protein, we defined the presence of protein (>1+) in spot urine dipstick analysis as having proteinuria [137]. The following values represent the grades of proteinuria provided by the manufacturers of the urine dipstick test: grade 0, absent; grade 1 (trace), 15–30 mg/dL; grade 2 (1+), 30–100 mg/dL; grade 3 (2+), 100–300 mg/dL; grade 4 (3+), 300–1000 mg/dL; and grade 5 (4+), >1000 mg/dL. *The Kidney Disease Outcomes Quality Initiative* (KDOQI) CKD stages [6] were defined as follows: (1) stage 0, non CKD, (eGFR ≥90 mL/min/1·73 m^2 without proteinuria); non CKD but decreased GFR, (eGFR 89–60 mL/min/1.73 m^2 without proteinuria) (2) Stage 1 (eGFR ≥90 mL/min/1·73 m^2 with proteinuria), (3) Stage 2 (eGFR 89–60 mL/min/1·73 m^2 with proteinuria), (4) Stage 3a (eGFR 59–45 mL/min/1·73 am^2); (5) Stage 3b (eGFR 44–30 mL/min/1·73 am^2); (6) Stage 4, eGFR 29–15 mL/min/1·73 m^2), and (7) Stage 5 (eGFR <15 mL/min/1·73 m^2).

doi:10.6342/NTU201900529

When the data of proteinuria is not available, the patient with an eGFR <60 mL/min/1·73 m^2 for three months was also though as having obvious CKD even [138, 139].

3.5 Metabolic syndrome

The metabolic syndrome (MetS), or syndrome X, was first described in 1988[140] and is a condition associated with metabolic abnormalities (the core value is obesity), which it has a higher risk for the development of CAD, stroke and diabetes [141-143]. It is defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria (Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol In Adults, 2001) [144], which require the presence of at least three of the following criteria: (1) central, visceral, and abdominal obesity (waist circumference ≥80 cm for females, and ≥90 cm for males), (2) elevated blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg), (3) hyperglycemia (fasting blood glucose ≥100 mg/dl), (4) hypertriglyceridemia (triglyceride ≥150 mg/dl) and (5) a low level of high-density lipoprotein cholesterol (HDL-C) (HDL-C <50 mg/dl for females and <40 mg/dl for males).

MetS affects over 20% of adults in Western populations and the burden of its prevalence is increasing worldwide as time [145]. The association of obesity and CKD has been reported extensively [146, 147]. Patients with obesity would develop renal damage due to glomerulomegaly [148], which was evidenced by some studies reporting the positive association of MetS to CKD [149-151]. Moreover, Thomas et al. [152] has been reported a meta-analysis showing a significant association between MetS and the development of an eGFR of less than 60 ml/min/1.73 m^2 (odds ratio (OR) 1.55; 95% CI 1.34–1.80) using all of the major definitions of MetS

doi:10.6342/NTU201900529

3.6 Prevalence and incidence of CKD

The data of first-run screening was used for prevalence calculation. The prevalence was expressed as the percentage of CKD stages among the individuals attending the first screening. We cannot precisely define the CKD stages 1–2 because of many missing values of urine analysis. Therefore, the number of patients with CKD stages 1–2 was estimated as the proportion of proteinuria (protein > 1+ in urine dipstick test) in the population with eGFR ≥ 60 mL/min/1.73 m^2 under the assumption of missing data at random.

Moreover, three cohorts were generated from the first run screen to assess the incidence of CKD, including participants without CKD, participants with non-CKD or CKD stages 1–2, and participants with non-CKD or CKD stages 1–4. The incidence was expressed as the ratio of total events in the following period to the total observational time (PY). The time to event for each participant included in the incidence estimate was calculated as the time from their date of entry into the screening program until the date of the first studied CKD event in subsequent screenings, the date of loss to follow-up or the end of the study (whichever came first).

3.7 Multi-state model of chronic kidney disease

We proposed two multi-state modes of CKD for further evaluation (Fig 1 and Fig 2). The first model was assessed by survival analysis of accelerated failure time model and the second model was evaluated using stochastic process. The details are shown below:

doi:10.6342/NTU201900529

3.7.1 Accelerated failure time mode with interval censoring

A three-state model of CKD (

Fig 1) was adopted to assess the risk determents of state transition among eGFR ≥60 (none to mild CKD), eGFR 59–30 (moderate CKD) and eGFR <30 mL/min/1.73m^2 (advanced CKD). Survival analysis was performed using an accelerated failure time (AFT) model [153] with a Weibull distribution. The AFT model, a parametric approach, can estimate the baseline hazard, which cannot be obtained with Cox proportional hazards regression analysis. In addition, the AFT model does not need the assumption of proportional hazards and provides more precise results in the analysis of censored data when compared with the Cox proportional hazards regression model. Because, the events occurred between the interval of two consequent screening, the interval censoring [154] was adopted to get more precise results.

Furthermore, almost of the previous studies adopted the statistical methods of Cox regression and logistic regression models to estimate the event risk (Table 2), which they can provide relative risks but not absolute risks. Principally, the absolute risk model provided by the accelerated failure time can be realized straightforwardly.

Fig 1 An illustration of 3-state transition model of CKD

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3.7.1.1 Accelerated life models

Consider a regression model for log survival time, of the form

$$Y = log\ T = -x'\beta + \sigma W \qquad \textbf{(3-1)}$$

where the error term W has a suitable distribution, including extreme value, generalized extreme value, normal or logistic. For the elucidation of CKD progression at a given status defined by eGFR value, Weibull distribution (T~Weibull (λ, p), $\boldsymbol{f}(t) = \lambda p t^{p-1} e^{(-\lambda t^p)}$, where p >0 and λ >0) was used for depicting the time to the occurrence of event and a extreme value distribution for W was thus adopted.

Proportional hazards characteristics of AFT model with Weibull distribution for event time

This AFT model has an accelerated life interpretation in that the error term W was viewed as a reference distribution when covariates *x* is 0 (reference case). Then, we can translate the reference distribution to the time scale by defining $T_0 = e^{\sigma W}$. The probability of survival in time t of a reference subject will be denoted **S_0(t)**.

$$S_0(t) = Pr[100] = Pr\{\ e^{\sigma W} > t\ \} = Pr\{\ W > \log\frac{t}{\sigma}\ \} \qquad \textbf{(3-2)}$$

Now the covariates x=1 is considered and then T is set as the distribution of $T_0 e^{-x'\beta}$. Therefore, the covariates act multiplicatively on survival time. The following is the survival function:

$$S(t, x) = Pr\{\ T > t|x\ \} = Pr\{\ T_0 e^{-x'\beta}\ > t\ \} = Pr\{\ T_0 > te^{x'\beta}\} = S_0(te^{x'\beta}) \qquad \textbf{(3-3)}$$

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The factor $e^{x'\beta}$ can be interpreted as an accelerated factor γ (the value >0). If $\gamma > 1$, they exposure benefits survival. If $\gamma < 1$, they exposure harmful to survival. Moreover, if $\gamma = 1$, there is no effect on survival from the exposure. Therefore, we can also write the density and hazard functions for any subject with the baseline or reference density and hazard:

$$f(t) = f_0(\mathrm{te}^{x'\beta})e^{x'\beta} \quad \textbf{(3-4)}$$

$$\lambda(t) = \lambda_0(\mathrm{te}^{x'\beta})e^{x'\beta} \quad \textbf{(3-5)}$$

the likelihood function under general non-informative censoring is

$$L(\Theta) = \prod_{i=1}^{n} \lambda(t_i|x_i)^{d_i} S(t_i|x_i) \quad \textbf{(3-6)}$$

where the t_i is the survival or censoring time, x_i is the parameter and d_i is the indicator of event ($d_i = 1$ means event occurred).

However, the censoring type in our study is interval censoring. The $\lambda(t_{ab}|x_i) = \int_{t_a}^{t_b} \lambda(s|x_i)ds$, where the event ($d_i$) occurred between t_a *to* t_b

Therefore, equation (3-6) can be changed to

$$L(\Theta) = \prod_{i=1}^{n} (\int_{t_a}^{t_b} \lambda(s|x_i)ds)^{d_i} S(t_i|x_i)$$

$$= \prod_{i=1}^{n} (S(t_b|x_i) - S(t_a|x_i))^{d_i} S(t_i|x_i) \quad \textbf{(3-7)}$$

doi:10.6342/NTU201900529

3.7.1.2 Weibull proportional hazard model in AFT model

(1) Assuming AFT model as

$log\ T = \alpha_0 + \alpha_1 X + \sigma W$, W~ Weibull (λ, p) and then

$$log\ T = \alpha_0 + \alpha_1 X + \frac{1}{p} W. \quad \textbf{(3-8)}$$

(2) The survival function with Weibull distribution

S(t)= $e^{(-\lambda t^p)}$ and then -log(S(t)) = λt^p

Finally, t= $(-\log(s(t)))^{1/p} \times \frac{1}{\lambda^{1/p}}$ **(3-9)**

(3) Reparameterizing

$$\frac{1}{\lambda^{1/p}} = exp(\alpha_0 + \alpha_1 X)$$

$$(1/p) log(\lambda) = -(\alpha_0 + \alpha_1 X)$$

$$log(\lambda) = -p(\alpha_0 + \alpha_1 X) \quad \textbf{(3-10)}$$

(4) Hazard ratio (x=1 vs. x=0) in AFT model with Weibull distribution

$$= \frac{exp(-p(\alpha_0 + \alpha_1 X(x=1)))}{exp(-p(\alpha_0 + \alpha_1 X(x=0)))} = exp(-p\alpha_1) \quad \textbf{(3-11)}$$

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3.7.1.3 The prediction function of CKD initiation and progression

To develop the function for absolute risk prediction, we split the sample into two parts, 2/3 trained dataset and 1/3 validated dataset. We used the trained data to estimate the regression coefficients in the AFT model for CKD state transition, including initiation and progression. Concordance statistics (C statistics) were computed as measures of discrimination (CKD state transition vs. non-CKD state transition) using logistic regression [model: logit (event probability) = CKD state transition probability of total follow-up duration, calculated from the trained dataset].

Furthermore, we validated the model with the Hosmer-Lemeshow test by comparing the observed probability from the validated dataset and the predictive probability from the trained dataset.

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3.7.2 A stochastic model for the dynamic changes of CKD

The CKD is known as a progressive disease, of which the disease course could be long. Therefore. The majority of participants will experience death before entering the next CKD state. Therefore, the five-state Markov model was proposed below. Let X(t) denote a random variable for a five-state continuous-time Markov process to describe the disease progression history for CKD stages, dialysis and all-cause death during time t; the state space would be Ω={1, 2, 3, 4, 5}, where the states are defined as follows.

State 1= eGFR ≥60 mL/min/1.73 m^2 (CKD stages 0–2; non to mild CKD)

State 2= eGFR 59–30 mL/min/1.73 m^2 (CKD stage 3; moderate CKD)

State 3= eGFR <30 mL/min/1.73 m^2 (CKD stages 4–5; advanced CKD)

State 4= requiring dialysis (hemodialysis and peritoneal dialysis)

State 5 = all-cause death

The Markov model is shown in Fig 2.

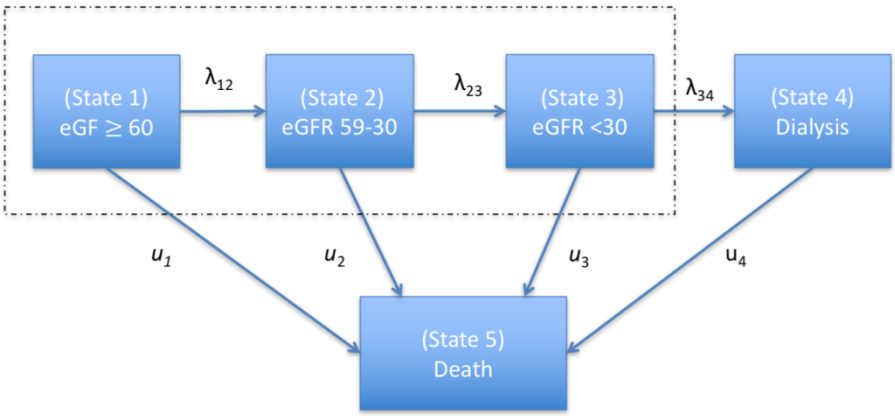

Fig 2. Five-state continuous-time Markov model of CKD.
The dotted line indicated natural history without special intervention.

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The λ_{12}, λ_{23}, and λ_{34} indicate instantaneous transition rates from eGFR ≥60 to eGFR 59–30 mL/min/1.73m^2, eGFR 59–30 to eGFR <30 mL/min/1.73m^2 and eGFR <30 mL/min/1.73m^2 to dialysis, respectively. μ_1 to μ_4 represent the rate of all-cause death form eGFR ≥60, eGFR 59–30, eGFR <30 mL/min/1.73m^2 and dialysis respectively. This model enables the onset of eGFR ≥60 mL/min/1.73m^2, progression to dialysis and all-cause death, to be quantified.

3.7.2.1 Transition intensity matrix

Transition intensity $\lambda_{ij}(t)$, i≠j may be defined when $P_{ij}(s,t)$ is continuous both in s and t, as the following limits

$$\lambda_{ij}(t)=\lim_{\Delta t\to 0} P_{ij}\frac{(t,\ t+\Delta t)}{\Delta t} = \lim_{\Delta t\to 0}\frac{P(X_{t+\Delta t}=j|X_t=i)}{\Delta t} \quad \textbf{(3-12)}$$

The total hazard out of state i, $\sum_{i\neq j}\lambda_{ij}(t)$, is the hazard function associated with the distribution of the sojourn time in state i and $\lambda_{ii} = -\sum_{i\neq j}\lambda_{ij}(t)$. In homogeneous Markov process, the transition intensity does not depend on time, all λs are constant over time, thus $\lambda_{ij}(t) = \lambda_{ij}$. The matrix of transition intensities in our study is expressed as

Fig 3.

$$Q=\begin{array}{c} \\ \text{State 1} \\ \text{State 2} \\ \text{State 3} \\ \text{State 4} \\ \text{State 5} \end{array}\begin{array}{c}\begin{array}{ccccc}\text{State1} & \text{State 2} & \text{State 3} & \text{State 4} & \text{State 5}\end{array}\\ \begin{bmatrix} -(\lambda_{12}+\mu_1) & \lambda_{12} & 0 & 0 & \mu_1 \\ 0 & -(\lambda_{23}+\mu_2) & \lambda_{23} & 0 & \mu_2 \\ 0 & 0 & -(\lambda_{34}+\mu_3) & \lambda_{34} & \mu_3 \\ 0 & 0 & 0 & 0 & \mu_4 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}\end{array}$$

Fig 3. The matrix of transition intensities of 5-state CKD model

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3.7.2.2 The relationship between transition probability and transition intensity

From the total hazard out of a state, it is easy to evaluate the probability of no transition event during a period, but evaluating the precise number and types of transitions to other states is much more complicated. To do so, the derivation of transition probabilities was got by using Spectral Analysis. The transition probabilities must be considered and expressed by transition intensities. For homogeneous processes a simple relationship between P(t) (transition probability matrix) and Q can be deduced from the Kolmogorov equations: P(t)=e^{tQ}.

The exponential of the matrix tQ can easily be computed if it can be diagonalized. Then Q = $V^{-1}DV$, where D is a diagonal matrix, and it can be shown that P(t) = $V^{-1}e^{tD}V$. The exponential of a diagonal matrix can easily be computed by replacing the diagonal elements by their exponentials. The transition probability can be expressed from the specific transition intensity according to the forward Kolmogorov equation[155]. The corresponding matrix form is shown in Fig 4.

$$
\begin{array}{lc}
 & \text{Current} \\
 & \begin{array}{ccccc} \text{State1} & \text{State 2} & \text{State} & \text{State 4} & \text{State 5} \end{array} \\
\text{P(t)=Previous} & \begin{array}{c} \text{State 1} \\ \text{State 2} \\ \text{State 3} \\ \text{State 4} \\ \text{State 5} \end{array}
\begin{bmatrix}
P_{11}(t) & P_{12}(t) & P_{13}(t) & P_{14}(t) & P_{15}(t) \\
P_{21}(t) & P_{22}(t) & P_{23}(t) & P_{24}(t) & P_{25}(t) \\
0 & 0 & P_{33}(t) & P_{34}(t) & P_{35}(t) \\
0 & 0 & 0 & P_{44}(t) & P_{45}(t) \\
0 & 0 & 0 & 0 & 1
\end{bmatrix}
\end{array}
$$

Fig 4. The matrix of transition probability of 5-state CKD model

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3.7.2.3 Likelihood function and Parameter estimation

For estimation of the above model, we first needed to specify the likelihood function. The notations Ja, Ka, La indicated the number in each state of baseline: eGFR ≥60 mL/min/1.73 m^2 (CKD state 1), eGFR 59–30 mL/min/1.73 m^2 (CKD state 2) and eGFR <30 mL/min/1.73 m^2 (CKD state 3) at a given age, a. Moreover, Bt, Ct, Dt, and Et indicated the number of right censoring events. Mt, Nt, Ot, Pt, Qt, Rt, St, Tt, Ut, Vt, Wt, and Yt, and Zt indicated the number of each state transition in our proposed model at a given time period, t. The state space of time was A. Thus,

$$\text{Log-likelihood}= \sum_{a,t\in A}\{[\text{Ja}\times log\pi 1(a)+\text{Ka}\times log\pi 2(a)+\text{La}\times log\pi 3(a)]+ [\text{Mt}\times \text{logP11(t)}+\text{Nt}\times \text{logP12(t)}+\text{Ot}\times \text{logP13(t)}+\text{Pt}\times \text{logP14(t)}+\text{Qt}\times \text{logP15(t)}+\text{Rt}\times \text{logP22(t)}+\text{St}\times \text{logP23(t)}+\text{Tt}\times \text{logP24(t)}+\text{Ut}\times \text{logP25(t)}+\text{Vt}\times \text{logP33(t)}+\text{Wt}\times \text{logP34(t)}+\text{Yt}\times \text{logP35(t)}+\text{Zt}\times \text{logP45(t)}+\text{Bt}\times \log(1-\text{P14(t)})+\text{Ct}\times \log(1-\text{P24(t)})+\text{Dt}\times \log(1-\text{P34(t)})+E\text{t}\times \log(1-\text{P45(t)})]\}$$

(3-13)

Baseline distribution

The baseline distributions are as below

$$(1)\pi 1(a)=\frac{\text{P11(a)}}{[\text{P11(a)+P12(a)+P13(a)}]}$$

$$(2)\pi 2(a)=\frac{\text{P12(a)}}{[\text{P11(a)+P12(a)+P13(a)}]}$$

doi:10.6342/NTU201900529

$$(3)\pi 3(a) = \frac{\mathrm{P13(a)}}{[\mathrm{P11(a)+P12(a)+P13(a)}]}$$

Events with interval censoring

The events of CKD state transition occurred between two consequent screening. Their transition probabilities are shown below:

(1) The probability from state 1 to state 1 in time t=P11(t).

(2) The probability from state 1 to state 2 in time t=P12(t).

(3) The probability from state 1 to state 3 in time t=P13(t).

(4) The probability from state 2 to state 2 in time t=P22(t).

(5) The probability from state 2 to state 3 in time t=P23(t).

(6) The probability from state 3 to state 3 in time t=P24(t).

.

Fully observed events

Moreover, because the dialysis and death events were fully observed due to national Registration System, the following transition rate can be expressed as

(1) P14(t)=P13(t)× λ_{34}

(2) P24(t)= P23(t)× λ_{34}

(3) P34(t)= P33(t)× λ_{34}

(4) P15(t)= P11(t)× μ_1 + P12(t)× μ_2 + P13(t)× μ_3.

(5) P25(t)= P22(t)× μ_2 + P23(t)× μ_3.

(6) P35(t)= P33(t)× μ_3.

(7) P45(t)= P44(t)× μ_4.

Events with right censoring

The probability of dialysis event with right censoring can be expressed as

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(1) The final observation state is 1=1-P14(t)

(2) The final observation state is 2=1-P24(t)

(3) The final observation state is 3=1-P34(t)

(4) The final observation state is 4=1-P45(t)

Thus, the likelihood can be entirely expressed as a function of the parameters. The maximum likelihood estimates (MLE) of the parameters of transition intensities were obtained from the solution of the derivation of log-likelihood function to parameters to be zero. The variance-covariance matrix is derived from the inverse of negative Hessian matrix, evaluated at MLE. The asymptotic 95% confidence intervals (CIs) are obtained accordingly. The model is flexible and can be reformulated according to the possible transitions, but the formulae then become more complex.

In our study, we also noticed some regression events from eGFR 59–30 to ≥60 mL/min/1.73 m^2. However, CKD is well known as a progressive disease, so these regression events were defined as measurement error.

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3.8 Average dwelling time (ADT)

3.8.1 Prevalence and incidence (P/I) ratio

We can use P/I ratio to estimate the ADT. Based on the estimated results on the two epidemiological indicators, prevalence and incidence, the average duration for subjects live with CKD (CKD stages 3–5 can be derived based on the concept of prevalence pool. Considering a steady cohort with CKD stages 3–5, an equilibrium will be attained for the inflow to and the outflow from the pool of CKD, which implies the newly developed subjects with CKD stages 3–5 and those dismissed from this status, either due to recovery or death from the status, will equate each other. The number of subjects evolved with the status of CKD stages 3–5 can be derived by the product of incidence of CKD stages 3–5 (I), the population at risk of developing CKD, and the time unit (Δt), which gives

$$I \times (N - m) \times \Delta t, \quad \textbf{(3-14)}$$

where *N* is the entire population and *m* is the prevalent case of CKD. For the number of subjects dismissed from the pool of CKD stages 3–5, this can be estimated by

$$\mu \times m \times \Delta t, \quad \textbf{(3-15)}$$

where μ is the average rate for those with CKD stages 3–5 to departure from the pool. By equating the two equation, we have

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$$\frac{m}{N-m} = \frac{I}{\mu} \quad , \tag{3-16}$$

which can be simplified to

$$\frac{m}{N} = \frac{I}{\mu} \tag{3-17}$$

given a relative small number of subject with the state of CKD stages 3–5 compared with the entire population. Note that the left hand side of (3-4) is the prevalence of CKD stages 3–5 ($P=m/N$), we thus have

$$\frac{I}{\mu} = \frac{P}{I} = average\ dewelling\ time, \tag{3-18}$$

the average time for subjects live with the state of CKD stages 3–5 (average dwelling time).

For the derivation of the average dwelling of CKD stages 3–5 by demographic characteristics such as age and sex and comorbidity such as metabolic syndrome, diabetes mellitus and hypertension, two regressions can be introduced to the incidence and prevalence of CKD stages 3–5 as follows.

$$log(I_j)=\log(PY_i)+\beta_0+\beta_1\times age_{j1}+\beta_2\times sex_{j2}+\beta_3\times Comorbidity_{j3} \ ,$$

and

$$logit(P_j)=r_0+\ r_1\times age_{j1}+\ r_2\times sex_{j2}+\ r_3\times Comorbidity_{j3.} \tag{3-19}$$

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The demographic characteristics- and comorbidity- specific dwelling time can thus be derived by using the regression formula of (3-19) in conjunction with (3-18).

$$log(I\_all)=\beta_0+\beta_1\times age_{(dist.)}+\beta_2\times sex_{(dist.)}+\beta_3\times Comorbidity_{(dist.)}\ ,$$

and

$$logit(P\_all)=r_0+r_1\times age_{(dist.)}+r_2\times sex_{(dist.)}+r_3\times Comorbidity_{(dist.)}. \quad \textbf{(3-20)}$$

The average dwelling time for subjects live with CKD stages 3–5 taking into account the effect of relevant risk factors can also be derived by integrated out the distribution of these factors among the population with the formula of (3-20) in conjunction with (3-18).

Fig 5 illustrates the derivation of P/I ratio shown as above using a doodle picture in WinBUGs, which included P/I ratio in subgroups and P/I ratio adjusted with age, sex and comorbidities.

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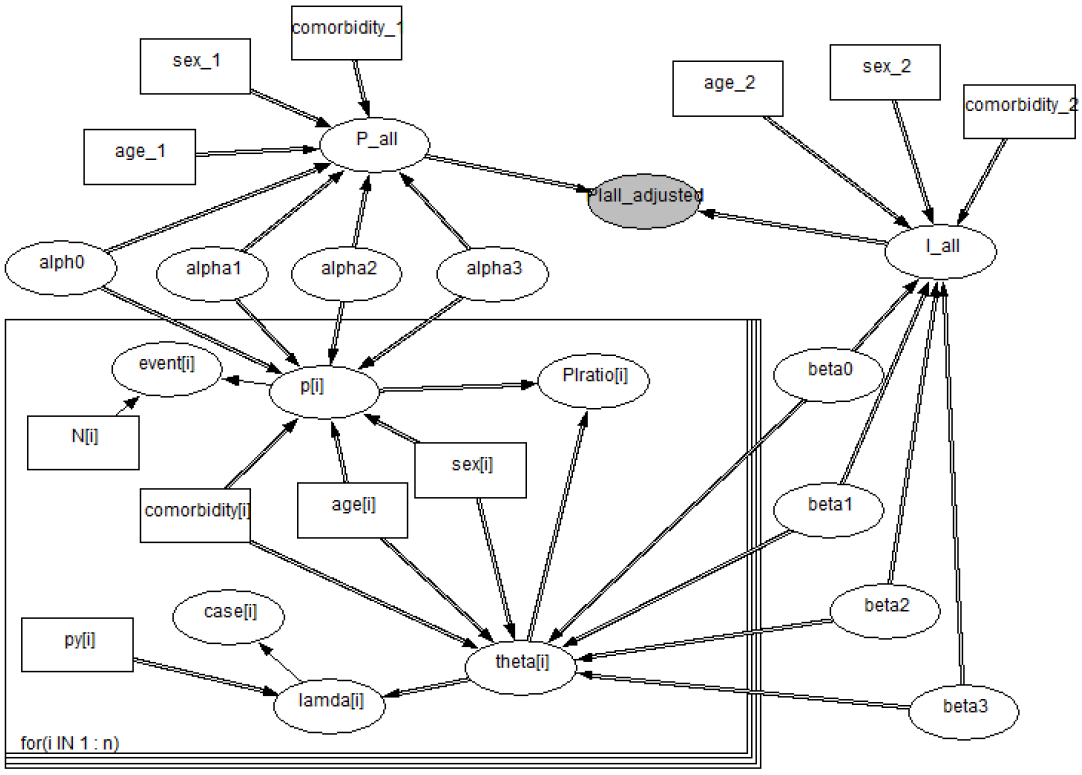

Fig 5. A doodle picture for the illustration of the derivation of P/I ratio.

Event[i] : Prevalence case of certain subgroups.

N[i] : The population size of certain subgroups.

Case[i] : Incidence case of certain subgroups.

Py[i] : Total following person-year of certain subgroups.

PIratio[i] : P/I ratio in certain subgroups.

I_all : The annual incidence in population, adjusted with sex, age, and comorbidity.

P_all : The prevalence in population, adjusted with sex, age, and comorbidity.

Age_1 : The distribution of age in population.

Sex_1 : The distribution of sex in population.

comorbidity_1 : The distribution of comorbidity in population.

Age_2 : The contribution of age in the sum of following person-year.

Sex_2 : The contribution of sex in the sum of following person-year.

Comorbidity_2 : The distribution of comorbidity in the sum of following person-year.

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In sum, the P/I ratio can present the average dwelling time (ADT) in certain CKD state. The lower the P/I ratio is, the sooner the patient return to non-case status, dialysis or death. For malignancy disease, returning to normal is hardly to seen. However, CKD is a progressive disease, returning to prior stage seems have low probability. Therefore, the decomposed the departure rate form CKD stage 3–5 is shown as following (Fig 6).

A short ADT may be the consequence of either a rapid departure from the CKD pool, which implies issues regarding healthcare and case management quality, or an abundant occurrence of CKD, which complicates the etiology findings by affecting the occurrence of renal assaults.

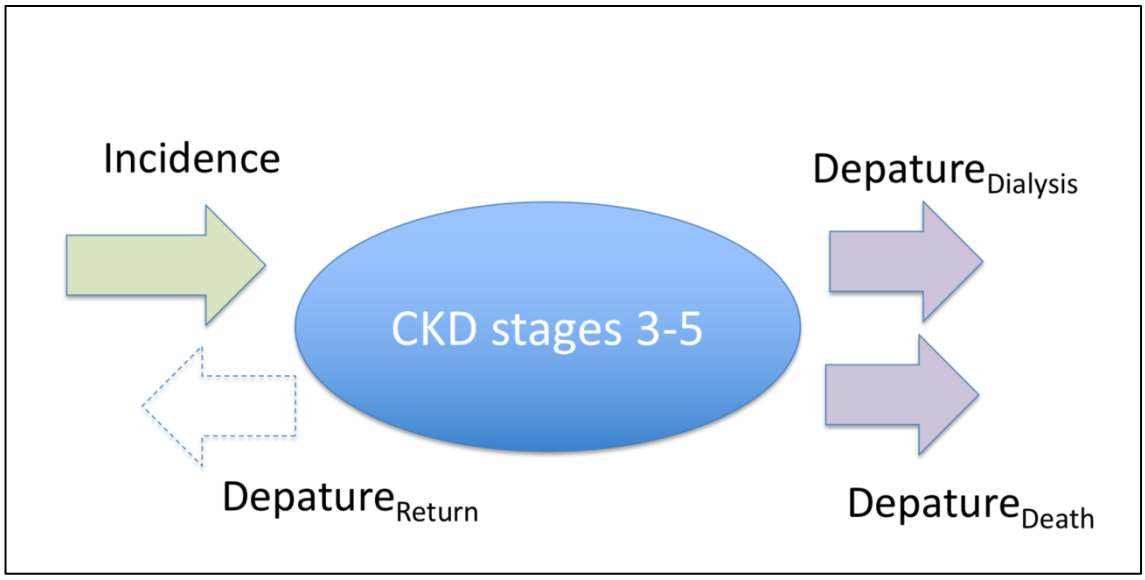

Fig 6. An illustration of the dynamic changes in CKD stages 3-5 over time.
The dotted line indicates that departure from the pool of CKD stages 3–5, return to non-case, is of low possibility.

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3.8.2 Markov process using stochastic process

The ADT taken before developing eGFR <30 mL/min/1.73m^2 and all-cause death is expressed as following

$$MST\ (State\ 2) = \int_0^\infty s \cdot f_2(s)ds = \int_0^\infty s \cdot (\lambda_{23} + u_2) \cdot P_{22}(s)ds \quad \textbf{(3-20)}$$

where $f_2(.)$ are the probability density functions of time to progression for individuals with eGFR 59–30 mL/min/1.73m^2. The corresponding formula for eGFR <30 mL/min/1.73m^2 is expressed as the same way.

$$MST\ (State\ 3) = \int_0^\infty s \cdot f_3(s)ds = \int_0^\infty s \cdot (\lambda_{34} + u_3) \cdot P_{33}(s)ds$$

(3-21)

Owing to the Markov property and the fact that there is no regression in our 5-state CKD transition model, expression (3-20) is simply the reciprocal of $(\lambda_{23} + u_2)$ and expression (3-21) is simply the reciprocal of $(\lambda_{34} + u_3)$.

3.9 Statistical software used in our study

All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA). The software of WinBUGS (Bayesian inference Using Gibbs Sampling) was used to generate the post distribution based on Bayesian theory and the doodle picture.

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Chapter 4 Results

4.1 Part 1 Epidemiologic features of CKD in Taiwan

Fig 7 shows the enrolled participants in part I of this study. The 106,094 participants had a mean age of 47.7 ± 15.4 years, and the median duration of follow-up was 4.4 years (interquartile range 2.6–6.2). In the Table 5, the estimated total CKD (stages 1–5) prevalence was 15.46%. Overall, 9.06% of the participants had CKD stages 3–5, 40% were men, 5% were diabetic, 13% were hypertensive, 8% had proteinuria (≥ 1+ in urine dipstick test), and 22% had MetS. Compared with those with non CKD or CKD stages 1–2, participants with CKD stages 3–5 exhibited a higher BMI (25.4 vs. 24.1 kg/m^2), waist circumstance (84.5 vs. 78.6 cm), and proteinuria (28% vs. 7%) and were more likely to present with DM (16% vs. 4%), hypertension (38% vs.11%), or MetS (42% vs. 20%). Moreover, 32% didn't have the data of proteinuria by dipstick.

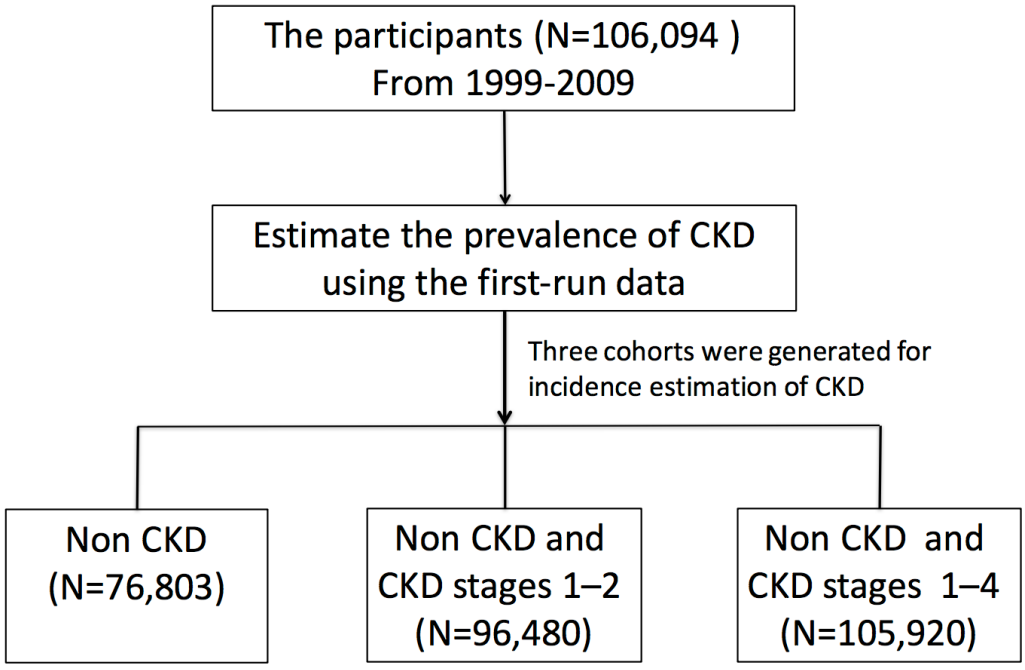

Fig 7. Patient enrollment in the part 1 of study

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4.1.1 Clinical characteristics of CKD stages 3–5

Table 6 also provides the demographic and clinical characteristics of the participants stratified by CKD stages 3–5. The mean age of participants with CKD stages 3–5 was 67.4 ±11.1 years with a female predominance (53%). 16% were diabetic, 38% were hypertensive, and 42% had MetS. The proportion for CKD stages 3–5 was 9.06%, which it is 6.61% for CKD stage 3a, 1.84% for CKD stage 3b, 0.45% for CKD stage 4 and 0.16% for CKD stage 5.

Their knowledge of CKD diagnosis, the awareness of CKD, was 5.1% in the entire CKD stages 3–5 and increased with CKD stages from 2.9% (stage 3a) to 33.3% (stage 5). The average age increased with CKD stages but decreased in CKD stage 4–5 (67.1 years in stage 3a, 72.7 years in stage 3b, 71.5 years in stage 4, and 61.4 years in stage 5) and the average waist circumstance followed with a similar manner (85.4 cm in stage 3a, 85.5 cm in stage 3b, 85.8 cm in stage 4, and 82.8 cm in stage 5). Proteinuria (≥ 1+ in urine dipstick test) increased with CKD stages (28% in stage 3a, 37% in stage 3b, 61% in stage 4, and 81% in stage 5). BMI seems to have no obvious difference across the CKD stages 3–5.

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Table 6. Baseline characteristics of the study population stratified by CKD stages

Parameters	Overall (N=106094)	eGFR ≥60 mL/min/1.73 m^2 (N=96480)		eGFR <60 mL/min/1.73 m^2				
		Non CKD	CKD Stages 1-2	All (N=9614)	CKD stage 3a (N=7013)	CKD stage 3b (N=1951)	CKD stage 4 (N=476)	CKD stage 5 (N=174)
Proportion to overall	-	84.54%	6.40%	9.06%	6.61%	1.84%	0.45%	0.16%
CKD awareness	-	-		5.1%	2.9%	7.4%	18.1%	33.3%
Age (years)	47.7 ± 15.4	45.9 ± 14.4		67.4 ± 11.1	67.1 ± 11.1	72.7 ± 9.4	71.5 ± 11.4	61.4 ± 15.0
Male	42091 (40)	37542 (39)		4549 (47)	3483 (50)	803 (41)	211 (44)	52 (30)
BMI (kg/m^2)	24.3 ± 3.9	24.1 ± 3.9		25.4 ± 3.9	25.3 ± 3.8	25.4 ± 4.0	25.2 ± 4.0	24.9 ± 4.1
Waist circumstance (cm)	79.2 ± 11.0	78.6 ± 10.9		84.5 ± 10.4	84.5 ± 10.3	85.5 ± 10.2	85.8 ± 10.9	82.8 ± 10.8
Diabetes mellitus	5535 (5)	4005 (4)		1530 (16)	969 (14)	385 (20)	137 (29)	39 (23)
Hypertension	13918 (13)	10298 (11)		3620 (38)	2481 (36)	828 (43)	246 (52)	65 (38)
Metabolic syndrome	23709 (22)	19674 (20)		4035 (42)	2726 (39)	959 (49)	270 (57)	80 (46)
Proteinuria by dipstick								
Missing	33774 (32)	31130 (32)		2644 (28)	1894 (27)	533 (27)	129 (27)	88 (51)
Non and trace	65767 (91*)	60752 (93*)		5015 (72*)	3971 (78*)	894 (63*)	134 (39*)	16 (19*)
1+	3325 (5*)	2596 (4*)		729 (10*)	490 (10*)	168 (12*)	58 (17*)	13 (15*)
2+	1863 (3*)	1262 (2*)		601 (9*)	364 (7*)	164 (12*)	60 (17*)	13 (15*)
3+	1162 (2*)	649 (1*)		513 (7*)	253 (5*)	160 (11*)	68 (20*)	32 (37*)
4+	203 (0.2*)	91 (0.1*)		112 (2*)	41 (1*)	32 (2*)	27 (8*)	12 (14*)

Data are mean ± standard deviation (SD) or number (%). *indicates the proportion without considering the missing
Abbreviation: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; BMI, body mass index.

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4.1.2 Prevalence of CKD stages 3-5 in subgroups

Our estimates of the prevalence of CKD stages 3–5 according to the characteristics of the subjects are presented in Table 7. Prevalence increased with age (1.1% and 19.9% for ages 20–49 and ≥50 years, respectively) and severity of proteinuria (from 7.63% to 55.17%). Moreover, compared with their opposing counterparts, higher prevalence was observed in males (men, 10.81%; women, 7.91%) and those who had DM (yes, 26.64%; no, 7.95%), hypertension (yes, 26.01%; no, 6.43%), or MetS (yes, 17.02%; no, 6.77%).

4.1.3 Incidence of CKD

Our estimates of the incidence of progression from the normal cohort to CKD stages 3–5 by age, gender, comorbidity, MetS, and proteinuria are presented in Table 7. The incidence of CKD stages 3–5was 16.89/1000 PY. Incidence increased with age (from 2.74/1000 PY to 38.09/1000 PY) and severity of proteinuria (from 15.34/1000 PY to 64.29/1000 PY) and was higher in males (men, 23.03/1000 PY; women, 13.86/1000 PY) and those who had DM (yes, 55.57/1000 PY; no, 25.35/1000 PY), hypertension (yes, 49.48/1000 PY; no,13.14/1000 PY), or MetS (yes, 37.2/1000 PY; no, 12.69/1000 PY).

Table 8 and Table 9 show that the overall incidence of CKD stages 1–5 and CKD stage 5 are 27.21/1000 PY and 0.43/1000 PY, respectively. The pattern of incidence of CKD stages 1–5 and CKD stage 5 in different groups was similar to that of CKD stages 3–5.

doi:10.6342/NTU201900529

Table 7. The prevalence and incidence of CKD stages 3–5

Characteristics	Prevalence	Incidence of CKD stages 3–5			
	CKD stages 3-5 (%)	Number of participants with CKD stages 0–2	Case progressing to CKD stages 3–5	Follow-up (PY)	Estimate (1000 PY)
Overall	9.06	97332	3888	230163	16.89
Age (years)					
20-49	1.1	60499	384	140221	2.74
≥50	19.9	35981	3504	91982	38.09
Gender					
Male	10.81	37542	1750	75989	23.03
Female	7.91	58938	2138	154174	13.86
Diabetes					
No	7.95	90421	3315	216013	15.35
Yes	26.64	4005	437	7837	55.76
Hypertension					
No	6.43	84364	2650	201669	13.14
Yes	26.01	10298	1134	22918	49.48
Mets					
No	6.77	76806	2421	190759	12.69
Yes (score≥3)	17.02	19674	1467	39404	37.20
Proteinuria					
Non and trace	7.63	60752	1731	112802	15.34
1+	21.92	2596	163	5436	29.98
2+	32.26	1262	133	3160	42.08
3+	44.15	649	89	1439	61.85
4+	55.17	91	9	140	64.29

CKD stage 0 indicates non CKD. Abbreviation: CKD, chronic kidney disease; Mets, metabolic syndrome; PY, person-year.

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Table 8. The incidence of CKD stages 1–5

Characteristics	Number of participants without CKD	Cases progressing to CKD stages 1–5	Follow-up (PY)	Estimate (1000 PY)
Overall	76803	4102	150778	27.21
Age (years)				
20-49	46591	1140	84272	13.53
≥50	30212	2962	67505	43.88
Gender				
Male	30175	1760	52206	33.71
Female	46628	2342	98572	23.76
Diabetes				
No	72522	3622	142079	25.49
Yes	2877	331	4835	68.46
Hypertension				
No	67667	3030	132510	22.87
Yes	7965	981	15114	64.91
Mets				
No	61413	2777	125126	22.19
Yes (score≥3)	15390	1325	25652	51.65

Abbreviation: CKD, chronic kidney disease; Mets, metabolic syndrome; PY, person-year.

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Table 9. The incidence of CKD stage 5

Characteristics	Number of participants with CKD stages 0–4	Cases progressing to CKD stage 5	Follow-up (PY)	Estimate (1000 PY)
Overall	105927	109	258797	0.42
Age (years)				
20-49	61136	12	143195	0.08
≥50	44791	97	115602	0.84
Gender				
Male	42039	49	88636	0.55
Female	63888	60	170161	0.35
Diabetes				
No	98104	76	240750	0.32
Yes	5496	31	10725	2.9
Hypertension				
No	90060	50	220192	0.23
Yes	13856	59	32330	1.8
Mets				
No	82297	52	209316	0.25
Yes (score≥3)	23630	57	49481	1.15
Proteinuria				
Non and trace	65755	11	123614	0.08
1+	3313	4	7049	0.57
2+	1851	18	4475	4.02
3+	1131	25	2303	10.86
4+	191	8	268	29.85

CKD stage 0 indicates non CKD. Abbreviation: CKD, chronic kidney disease; Mets, metabolic syndrome; PY, person-yea.

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4.1.4 ADT in CKD stages 3-5

Table 10 presents the ADT of CKD stages 3–5 stratified by sex, age, and comorbidities. The overall ADT was 5.37 years (95% confidence interval [CI]: 5.17–5.57) for CKD stages 3–5. Differences in ADT according to age, gender, hypertension, and MetS were also observed; specifically, participants who were ≥50 years of age, female, hypertensive, or without MetS demonstrated a higher ADT than their opposing counterparts. Table 6 reveals that elderly women have the longest ADT (5.35 years, 95% CI: 5.06–5.62) while young males have the shortest ADT (2.56 years, 95% CI: 2.05–3.12) among all age and gender groups surveyed.

Moreover, Table 11 shows that elderly women (≥50 years) had the longest ADT (5.35, 95% CI: 5.02-5.62) of all age and gender groups and young male (20–49 years) had the shortest ADT (2.56 95% CI: 2.05-3.12). The ADT in female with age 20–49 years was 5.12 (95%CI, 4.35–5.93), showing less difference to the group of female with age ≥50 years. The ADT in male with age ≥50 years was 4.69 (95%CI, 4.44–5.95), showing obvious different to the group of male with age 20–49 years.

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Table 10. The average dwelling time in CKD stages 3-5

Characteristics	Average dwelling time	
	P/I ratio (95%CI)	aP/I ratio (95%CI)
All	5.37 (5.17–5.57)	3.32 (3.08-3.57)
Age (year)		
20-49	4.02 (3.54–4.53)	-
≥50	5.23 (5.03–5.43)	-
Gender		
Male	4.70 (4.44–4.95)	-
Female	5.62 (5.33–5.88)	-
Diabetes		
No	5.24 (5.03–5.44)	5.04 (4.65-5.44)
Yes	4.97 (4.48–5.47)	4.50 (3.93-5.15)
Hypertension		
No	4.95 (4.74–5.18)	5.36 (4.94-5.78)
Yes	5.27 (4.91–5.61)	6.47 (5.82-6.46)
Metabolic syndrome		
No	5.34 (5.09-5.59)	5.15 (4.78-5.56)
Yes (score>3)	4.57 (4.32-4.83)	4.58 (4.17-5.03)

Abbreviation: CKD, chronic kidney disease, aP/I, adjusted prevalence incidence ratio.

The multivariable model was adjusted by age and sex.

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Table 11. Average dwelling times in CKD stages 3–5, stratified by gender and age

Characteristics	Prevalence of CKD stages 3–5			Incidence of CKD stages 3–5			Average dwelling time
	Cases	Total number	Estimate (%)	Events	Follow-up (PY)	Estimate (1000 PY)	P/I ratio (95%CI)
Sex and age (years)							
Male, age 20–49	204	22660	0.90	150	42452	3.53	2.56 (2.05–3.12)
Male, age ≥50	4345	19431	22.36	1600	33537	47.7	4.69 (4.44–4.95)
Female, age 20–49	469	38512	1.22	234	97768	2.39	5.12 (4.35–5.93)
Female, age ≥50	4596	25491	18.03	1904	56405	32.76	5.35 (5.06–5.62)

Abbreviation: CKD, chronic kidney disease; PY, person years; P/I, prevalence/incidence; CI, confidence interval.

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4.2 Part 2 The initiators and progressors of CKD

Fig 8 shows the enrolled participants in part II of this study. As urinary analyses were not obtained in 1999 and 2000, we included 100,169 participants from 2001 to 2009 in our study. There were 90,713 participants with eGFR ≥60 mL/min/1.73 m^2. The mean age of these participants was 45.8 ± 14.1 years. Overall, 38.7% of these participants were men, 4.3% were diabetic, 11% had hypertension and 4.6% had CAD. Moreover, there were 8871 participants with eGFR 59–30 mL/min/1.73 m^2. The mean age of these participants was 69.2 ± 10.2 years. Overall, 47.7% of these participants were men, 16% were diabetic, 38.4% had hypertension and 19.3% had CAD (Table 12). Other information about these two cohorts is presented in Table 12.

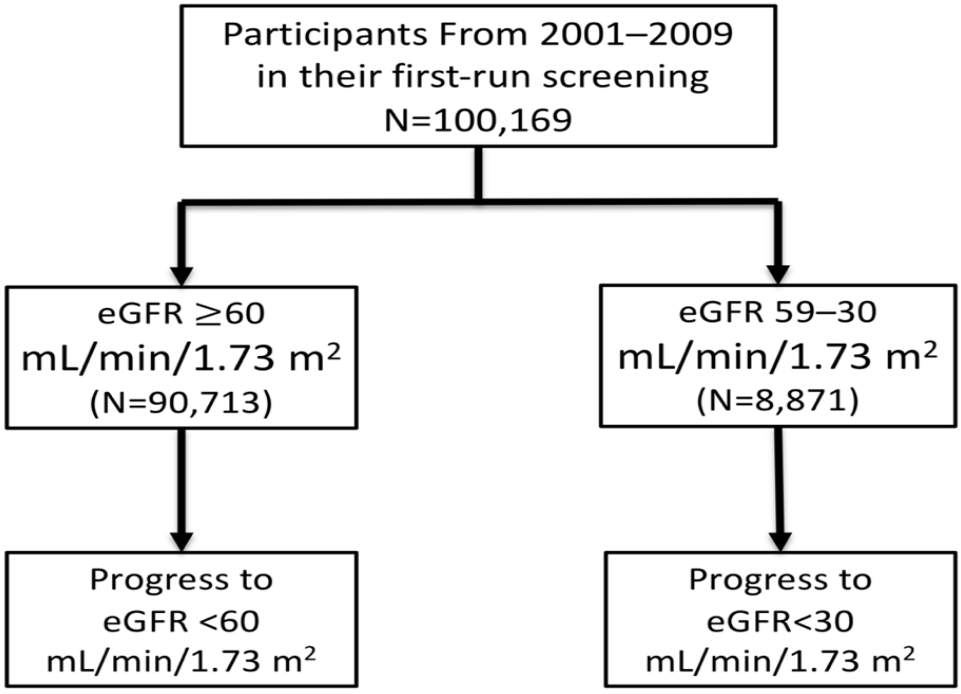

Fig 8. Patient enrollment in the part II of study

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Table 12. Baseline characteristics of the population in study II

Parameter	eGFR ≥60 mL/min/1.73 m^2 (n = 90,713)	eGFR 59–30 mL/min/1.73 m^2 (n = 8,871)
Age (years)	45.9 ± 14.1	69.2 ± 10.2
Male sex	35092 (38.7)	4232 (47.7)
BMI (kg/m^2)	24.2 ± 3.9	25.3 ± 3.8
Diabetes (%)	3847 (4.3)	1384 (16)
Hypertension (%)	9842 (11)	3348 (38.4)
CAD (%)	4134 (4.6)	1665 (19.3)
SBP (mmHg)	123 ± 20	137 ± 22
DBP (mmHg)	77 ± 12	81 ± 13
Waist circumference (cm)	78.4 ± 10.9	85 ± 10
Smoker (%)	25237 (28.0)	2448 (27.7)
Alcohol drinker (%)	21629 (24.1)	1610 (18.3)
Betel quid chewer (%)	6463 (7.2)	197 (2.2)
Regular exerciser (%)	55470 (62.4)	5929 (40.7)
Metabolic syndrome (%)	18294 (20.2)	3613 (40.7)
Total cholesterol (mg/dL)	195 ± 39	208 ± 43
Triglyceride (mg/dL)	127 ± 120	157 ± 114
LDL (mg/dL)	113 ± 33	122 ± 36
HDL (mg/dL)	57 ± 15	56 ± 15
Glucose (mg/dL)	94 ± 28	106 ± 50
Hemoglobin (mg/dL)	14.0 ± 4.3	13.6 ± 1.7
Albumin (mg/dL)	4.5 ± 0.3	4.4 ± 0.4
Uric acid (mg/dL)	5.6 ± 1.6	6.8 ± 1.9
Proteinuria		
Grade 0 (%)	67331 (89.7)	5493 (69.7)
Grade 1 (%)	2258 (3.0)	370 (4.7)
Grade 2 (%)	3087 (4.1)	786 (10.0)
Grade 3 (%)	1497 (2)	634 (8.0)
Grade 4 (%)	783 (1)	505 (6.4)
Grade 5 (%)	100 (0.1)	93 (1.2)
Events of state change (%)	3018 (3.3)	322 (3.6)

Abbreviations: eGFR, estimated glomerular filtration rate; BMI, body mass index; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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4.2.1 Factors associated with the progression of state 1 in the CKD transition model

During a median follow-up of 4.0 years (IQR: 2.4–6.0), 3018 participants showed progression to state 2 (eGFR 59–30 mL/min/1.73 m^2) from state 1 (eGFR ≥60 mL/min/1.73 m^2). In the crude analysis, the significant predictors for CKD initiation included old age [hazard ratio (HR): 1.11; 95%CI, 1.10–1.1], male gender (HR:1.95; 95%CI, 1.76–2.18) , DM (HR:3.66; 95%CI, 3.10–4.32), previous CVD (HR:2.97; 95%CI, 2.51–3.53), components of MetS (HR:1.54; 95%CI, 1.49–1.61), lifestyle including smoking (HR,1.36; 95%CI, 1.06–1.35), alcohol consumption (HR,1.20; 95%CI, 1.06–1.35), and regular exercise (HR,1.40; 95%CI, 1.24–1.58); proteinuria (HR:1.35; 95%CI, 1.28–1.42), uric acid level (HR:3.66; 95%CI, 3.10–4.32), albumin level (HR:0.61; 95%CI, 0.52–0.71), low-density lipoprotein (LDL) level (HR:1.68; 95%CI, 1.51–1.87), and eGFR (HR:0.91; 95%CI, 0.90–0.92), (all $P < 0.05$) (Table 13).

In the multivariable analysis, only older age (HR, 1.08; 95% CI, 1.07–1.09), DM (HR, 1.49; 95%CI, 1.23–1.81), MetS scores (HR, 1.13; 95%CI, 1.08–1.19), proteinuria (HR, 1.16; 95%CI, 1.10–1.22), uric acid level (HR, 1.12; 95%CI, 1.08–1.17), LDL level >130 mg/dL (HR, 1.15; 95%CI, 1.02–1.30), and eGFR (HR, 0.94; 95%CI, 0.93–0.95) remained significant (Table 13).

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Table 13. Progression analysis for participants with eGFR ≥60 mL/min/1.73 m^2

Parameter	Crude		Multivariable	
	HR (95%CI)	*P*	aHR (95%CI)	*P*
Demography				
Age (years) (per 1 year)	1.11 (1.10, 1.12)	<0.001	1.08 (1.07, 1.09)	<0.001
50~69 vs. 20–49	10.4 (8.54, 12.6)	<0.001		
≥70 vs. 20–49	38.7 (30.5, 49.1)	<0.001		
Sex (male vs. female)	1.95 (1.76, 2.18)	<0.001	1.00 (0.85, 1.18)	0.998
Comorbidity				
Diabetes mellitus (yes vs. no)	3.66 (3.10, 4.32)	<0.001	1.49 (1.23, 1.81)	<0.001
CAD (yes vs. no)	2.97 (2.51, 3.53)	<0.001	0.89 (0.73, 1.07)	0.215
MetS scores (per 1 unit)	1.54 (1.49, 1.61)	<0.001	1.13 (1.08, 1.19)	<0.001
Individual components				
Triglyceride (yes vs. no)	1.83 (1.63, 2.04)	<0.001		
HDL (yes vs. no)	1.67 (1.47, 1.88)	<0.001		
Waist (yes vs. no)	2.06 (1.85, 2.30)	<0.001		
Glucose (yes vs. no)	2.47 (2.19, 2.77)	<0.001		
Blood pressure (yes vs. no)	2.82 (2.51, 3.17)	<0.001		
Lifestyle (ever vs. never)				
Smoking	1.36 (1.22, 1.53)	<0.001	1.10 (0.93, 1.28)	0.261
Alcohol drinking	1.20 (1.06, 1.35)	<0.001	1.04 (0.89, 1.22)	0.615
Betel nuts chewing	0.78 (0.59, 1.03)	0.075	1.34 (0.97, 1.84)	0.076
Regular exercise	1.40 (1.24, 1.58)	<0.001	1.04 (0.91, 1.18)	0.556
Laboratory data				
Proteinuria (per 1 degree)	1.35 (1.28, 1.42)	<0.001	1.16 (1.10, 1.22)	<0.001
Uric acid (per 1 mg/dL)	1.27 (1.23, 1.30)	<0.001	1.12 (1.08, 1.17)	<0.001
Albumin (per 1 mg/dL)	0.61 (0.52, 0.71)	<0.001	0.92 (0.77, 1.10)	0.359
Hemoglobin (per 1 g/dL)	1.00 (0.99, 1.01)	0.621	1.01 (0.97, 1.57)	0.669
LDL (>130 mg/dL)	1.68 (1.51, 1.87)	<0001	1.15 (1.02, 1.30)	0.020
eGFR (per 1 unit)	0.91 (0.90, 0.92)	<0.001	0.94 (0.93, 0.95)	<0.001

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CAD, coronary artery disease; MetS, metabolic syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate

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4.2.2 Factors associated with the progression of state 2 in the CKD transition model

322 participants showed progression to state 3 (eGFR <30 mL/min/1.73 m^2) from state 2 (eGFR 59–30 mL/min/1.73 m^2) during a median follow-up of 3.9 years (IQR: 2.1–5.7). In the crude analysis, the significant predictors for CKD progression included older age (HR, 1.04; 95%CI, 1.02–1.06), DM (HR, 3.21; 95%CI, 2.18–4.73), previous CAD (HR, 1.81; 95%CI, 1.25–2.63), components of MetS (HR, 1.52; 95%CI, 1.34–1.73), proteinuria (HR, 1.70; 95%CI,1.50–1.91), uric acid level(HR, 1.21; 95%CI, 1.13–1.31), hemoglobin level (HR, 0.83; 95%CI, 0.75–0.91), and eGFR (HR, 0.86; 95%CI, 0.84–0.88) (all $P < 0.05$) (Table 14). However, life styles had no significant association with the progression of CKD.

In the multivariable analysis, only previous CAD (HR, 1.57; 95%CI, 1.04–2.36), MetS scores (HR, 1.31; 95%CI, 1.12–1.53), proteinuria (HR, 1.48; 95%CI, 1.31–1.67), uric acid (HR, 1.11; 95%CI, 1.02–1.22), hemoglobin level (HR, 0.84; 95%CI, 0.75–0.95), and eGFR (HR, 0.89; 95%CI, 0.87–0.91) remained significant (Table 14).

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Table 14. Progression analysis for participants with eGFR 30–59 mL/min/1.73 m^2

Parameter	Crude		Multivariable	
	HR (95%CI)	*P*	aHR (95%CI)	*P*
Demography				
Age (years) (per 1 year)	1.04 (1.02, 1.06)	<0.001	1.00 (0.98, 1.02)	0.831
50~69 vs. 20–49	3.35 (1.05, 10.8)	0.001		
≥70 vs. 20–49	6.69 (2.09, 21.4)	0.041		
Sex (male vs. female)	1.24 (0.91, 1.68)	0.179	1.56 (0.99, 2.48)	0.057
Comorbidity				
Diabetes mellitus (yes vs. no)	3.21 (2.18, 4.73)	<0.001	1.48 (0.92, 2.34)	0.087
CAD (yes vs. no)	1.81 (1.25, 2.63)	0.001	1.57 (1.04, 2.36)	0.031
MetS scores (per 1 unit)	1.52 (1.34, 1.73)	<0.001	1.31 (1.12, 1.53)	<0.001
Individual components				
Triglyceride (yes vs. no)	2.04 (1.49, 2.82)	<0.001		
HDL (yes vs. no)	1.95 (1.39, 2.75)	<0.001		
Waist (yes vs. no)	1.74 (1.27, 2.41)	<0.001		
Glucose (yes vs. no)	2.02 (1.46, 2.78)	<0.001		
Blood pressure (yes vs. no)	1.61 (1.14, 2.27)	0.007		
Lifestyle (ever vs. never)				
Smoking	1.09 (0.76, 1.60)	0.634	1.01 (0.63, 1.61)	0.978
Alcohol drinking	0.99 (0.66, 1.48)	0.952	0.93 (0.56, 1.54)	0.780
Betel nuts chewing	0.96 (0.31, 1.42)	0.529	—	—
Regular exercise	1.12 (0.78, 1.62)	0.529	1.15 (0.75, 1.77)	0.514
Laboratory data				
Urine protein (per 1 degree)	1.70 (1.50, 1.91)	<0.001	1.48 (1.31, 1.67)	<0.001
Uric acid (per 1 mg/dL)	1.21 (1.13, 1.31)	<0.001	1.11 (1.02, 1.22)	0.022
Albumin (per 1 mg/dL)	0.73 (0.47, 1.12)	0.150	1.02 (0.61, 1.69)	0.949
Hemoglobin (per 1 g/dL)	0.83 (0.75, 0.91)	<0.001	0.84 (0.75, 0.95)	0.005
LDL (>130 mg/dL)	0.83 (0.59, 1.15)	0.261	1.01 (0.69, 1.48)	0.946
eGFR (per 1 unit)	0.86 (0.84, 0.88)	<0.001	0.89 (0.87, 0.91)	<0.001

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CAD, coronary artery disease; MetS, metabolic syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate

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4.2.3 Factors influencing state transition of CKD

A summary of the initiators and progressors of CKD with multivariable adjusting is shown in Fig 9. The elderly had a higher risk for developing, but not for progression of CKD. Gender and smoking seems play no role in the initiation and progression of CKD. CAD just had an effect on CKD progression and DM just had an effect on CKD development. Those with lower proteinuria and higher eGFR had a better outcome in developing and progression of CKD. However, those with more components of MetS and hyperuricemia had hazardous impacts on CKD development and progression. Anemia had a poor outcome in progression but not in the initiation of CKD. LDL (>130 mg/dL) was an independent risk for CKD initiation.

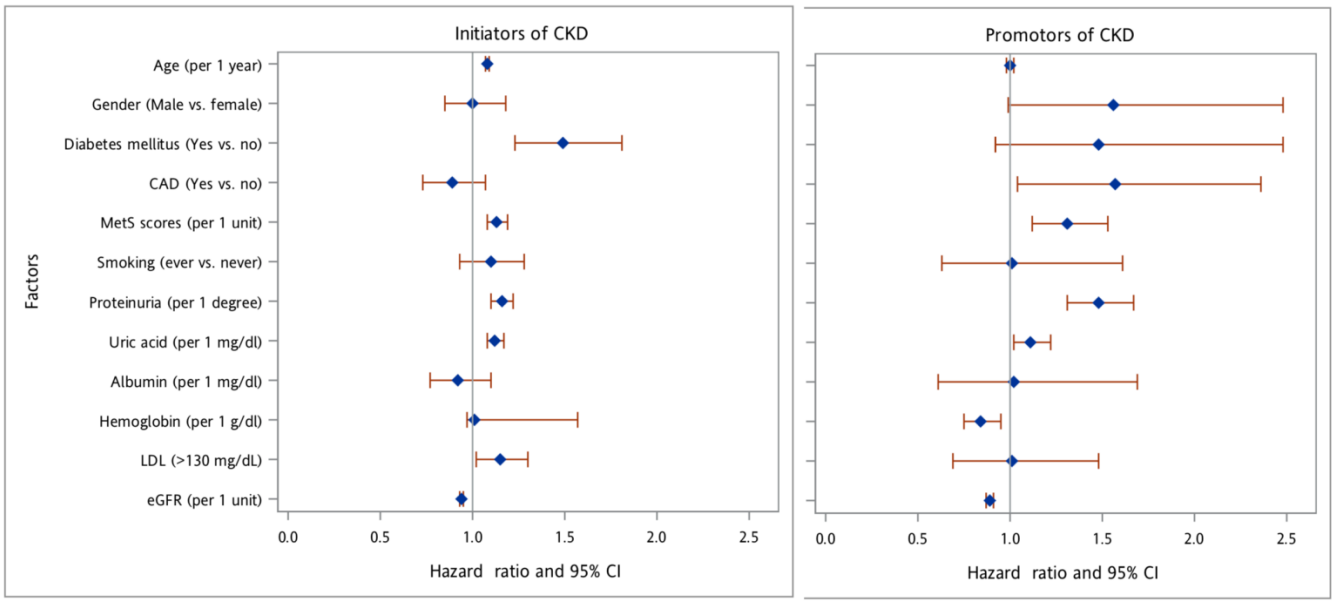


Fig 9. A summary of the influencing factors on the state transition of CKD.

doi:10.6342/NTU201900529

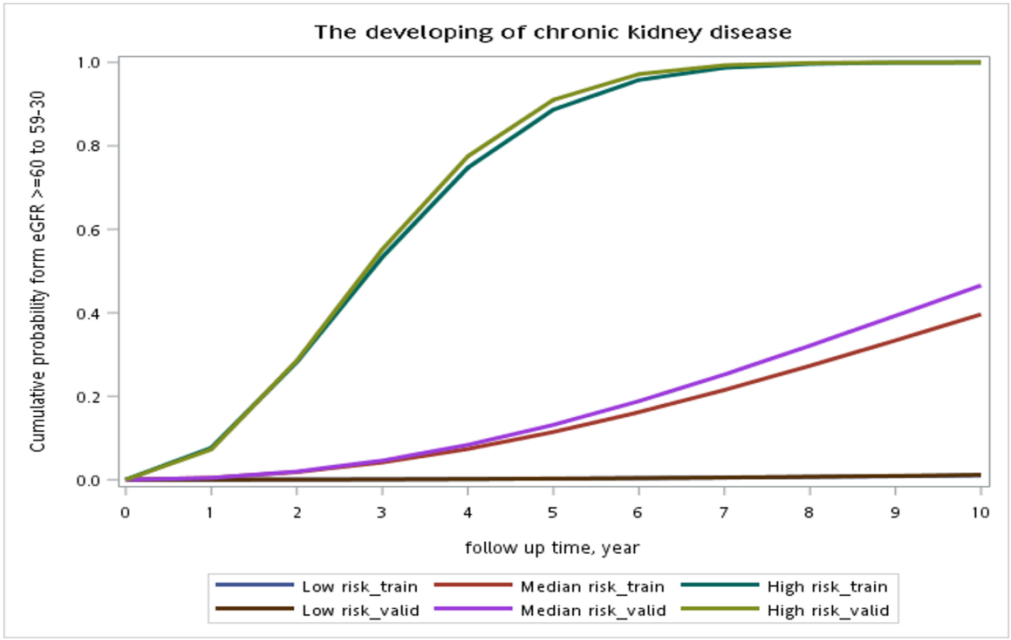
Fig 10 shows the cumulative transition probabilities of the different characteristics of three subjects who each represented different risk groups. The components of risks for CKD initiation included age, gender, DM, MetS scores, proteinuria, Uric acid, LDL and eGFR. Moreover, the components of risks for CKD progression included age, gender, DM, CAD, MetS scores, proteinuria, Uric acid, hemoglobin and eGFR. The subject with high-risk characteristics had a high probability for CKD development and progression in a 10-year follow-up. The subject with low-risk characteristics had very low probability for CKD development and progression.

The probability of CKD initiation in the high-risk group was 7.6% in the first year, 53.3% at 3 years, 88.6% at 6 years, and 99.9% after 10 years. Such probability in the moderate-risk group was 0.4% in the first year, 4.2% at 3 years, 16.2% at 6 years, and 39.% after 10 years. The probability for the low-risk group was <0.1% in the first year, 0.08% at 3 years, 0.36% at 6 years, and 1.03% after 10 years (Fig 10A).

The probability of CKD progression in the high-risk group was 7.2% in the first year, 55.2% at 3 years, 97.2% at 6 years, and 99.9% after 10 years. Such probability of for the moderate-risk group was 0.4% in the first year, 4.6% at 3 years, 18.8% at 6 years, and 46.5% at 10 years. The probability for the low-risk group was <0.1% in the first year, 0.08% at 3 years, 0.37% at 6 years, and 1.13% after 10 years (Fig 10B).

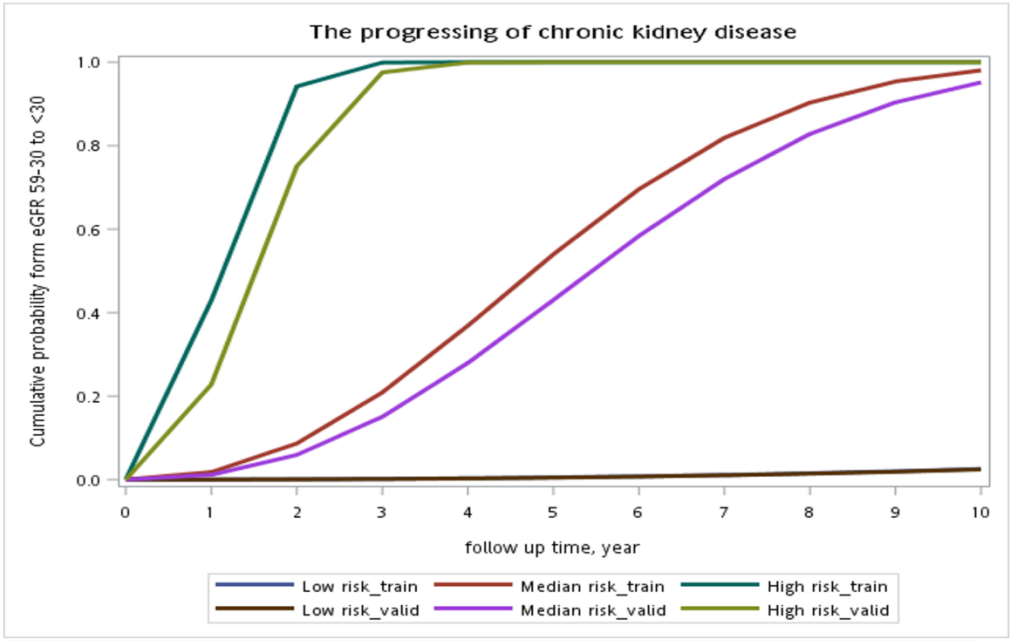
doi:10.6342/NTU201900529

A



	Age	Gender	DM	Mets	Uprotein	UA	LDL	eGFR
Low risk	40	Female	No	0	0	4.0	No	95
Midian risk	60	Male	Yes	3	2	6.0	Yes	80
High risk	80	Male	Yes	5	4	8.0	Yes	70

B



	Age	Gender	DM	CAD	Mets	Uprotein	UA	Hb	eGFR
Low risk	40	Female	No	No	0	0	4.0	12	55
Midian risk	60	Male	Yes	Yes	3	2	6.0	10	45
High risk	80	Male	Yes	Yes	5	4	8.0	8	35

Fig 10. An illustration of the cumulative probabilities by time of three hypothetical conditions in different risk groups. (A) Initiation and (B) Progression of chronic kidney disease.

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4.2.4 Risk prediction functions of CKD state transition

Two risk prediction functions are shown below:

(1) Score I for initiation of CKD =exp[−2.06×(3.21−0.04×(Age)−0.02×(Male) −0.18×(DM)−0.06× (MetS score)−0.07×(Proteinuria) −0.06×(Uric acid) −0.06×(LDL>130 mg/dL) + 003×(eGFR))].

(2) Score P for progression of CKD = exp[− 2.35 × (0.04 − 0.002 × (Age) − 0.17 × (Male) − 0.17 × (DM) − 0.20 × (CAD) − 0.14 × (MetS score) − 0.24 × (Proteinuria) − 0.05 × (Uric acid) + 0.08 × (Hemoglobin) + 0.05 × (eGFR))].

The functions of cumulative probability for state transition are shown below, where T indicates the follow-up duration in years.

(1) Cumulative risk to state 2 from state 1 = $1 - \exp(-Score\ I \times T^{2.06})$.

(2) Cumulative risk to state 3 from state 2 =$1 - \exp(-Score\ P \times T^{2.35})$.

Moreover, Fig 10 shows the cumulative transition probabilities of the different characteristics of three subjects who each represented different risk groups using the above predictive equations in train dataset. The group with high-risk characteristics had a high probability for CKD development and progression with a steeper slope in a 10-year follow-up. Otherwise, the group with low-risk characteristics had a very low chance for CKD development and progression.

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4.2.5 Model discrimination and Validation.

C statistic was 0.79 (95% CI, 0.78–0.80) for the prediction model of CKD initiation and was 0.80 (95% CI, 0.77–0.83) for the prediction model of CKD progression (Fig 11). Moreover, we evaluated the goodness of fit between train dataset and valid dataset by testing the risk probability in three different risk profiles during a 10 years observation, which was shown in Fig 10. The *p* value of Hosmer-Lemeshow test were 0.999 and 0.183 for initiation and progression of CKD respectively, indicating there was lacking statistical difference between the trained and validated dataset.

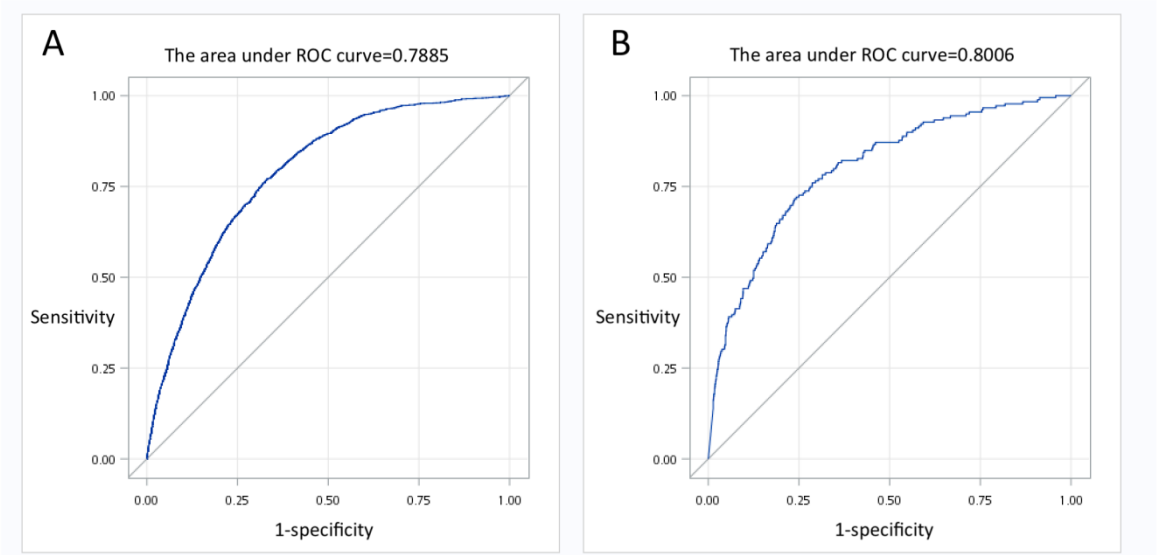

Fig 11. ROC curve for the prediction function.

(A) The initiation of CKD (B) The progression of CKD

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4.3 Part 3 Stochastic Markov model of CKD

4.3.1 Prevalence of CKD in the subgroups

Of 106,094 participants recruited into our study (mean age, 47.7 ± 15.4 years), 39.7% were male, 5.3% had DM, 13.4% had hypertension, and 5.8% had CAD (Table 15). Clinical characteristics are shown in Table 15. Men were older and had higher body mass index values (24.9 vs. 23.9 kg/m^2), more comorbidities [DM (6.1% vs. 4.8%), hypertension (16.1% vs. 11.6%), and CAD (6.2% vs. 5.5%)], more hazardous lifestyles [smoking (56.9% vs. 9.7%), alcohol consumption (45.6% vs. 9.4%), and betel nut chewing (16.1% vs. 0.8%)], and higher prevalence of metabolic syndrome (32.2% vs. 15.9%) than women.

In Table 16, our estimates of the prevalence of States 1– 3 in all population were 90.9%, 8.5%, and 0.7%, respectively. Women (92.1%, 7.3%, and 0.6%, respectively) had less moderate and advanced CKD than men (89.2%, 10.2%, and 0.7%, respectively). Moreover, the prevalence of State 1 (98.9% to 63.5%) decreased with age, and the prevalence of states 2 (1% to 34.9%) and 3 (0.1% to 0.7%) increased with age in the overall population. Men and women also followed this pattern. The distribution of CKD in diabetic participants was 72.4% for state 1, 24.5% for state 2 and 3.2% for state 3. The diabetic participant with more severe proteinuria had a higher prevalence of advanced CKD.

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Table 15. Baseline characteristics of study population, stratified by sex

Characteristics	All (n = 106,094)	Sex		P value
		Women (n = 64,003)	Men (n = 42,091)	
Age (years)	47.7 ± 15.4	46.6 ± 14.8	49.4 ± 16.1	<0.001
BMI (kg/m^2)	24.3 ± 3.9	23.9 ± 4.0	24.9 ± 3.6	<0.001
Waist circumstance (cm)	79.1 ± 11.0	75.2 ± 10.0	85.2 ± 9.7	<0.001
Diabetes mellitus (yes)	5535 (5.3)	3034 (4.8)	2501 (6.1)	<0.001
Hypertension (yes)	13,932 (13.4)	7299 (11.6)	6633 (16.1)	<0.001
CAD (yes)	6009 (5.8)	3448 (5.5)	2561 (6.2)	<0.001
Smoking (ever)	29,901 (28.4)	6132 (9.7)	23,769 (56.9)	<0.001
Alcohol drinking (ever)	24,880 (23.8)	5934 (9.4)	18,946 (45.6)	<0.001
Betel nut chewing (ever)	7215 (6.9)	502 (0.8)	6713 (16.1)	<0.001
Hemoglobin (g/dL)	14.0 ± 4.3	13.2 ± 5.3	15.2 ± 1.6	<0.001
Uric acid (mg/dL)	5.6 ± 1.8	5.0 ± 1.6	6.4 ± 1.8	<0.001
Albumin (g/dL)	4.4 ± 0.7	4.4 ± 0.7	4.5 ± 0.6	<0.001
Mets (yes)	23,709 (22.4)	10,167 (15.9)	13,542 (32.2)	<0.001

Abbreviations: BMI, body mass index; CAD, coronary artery disease; Mets, metabolic syndrome.

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Table 16. The distribution of eGFR among participants

Parameter	Number	State 1	State 2	State 3
		eGFR ≥60 mL/min/1.73 m^2	eGFR 59–30 mL/min/1.73 m^2	eGFR <30 mL/min/1.73 m^2
Overall	106094	96480 (90.9)	8964 (8.5)	650 (0.6)
20–49 years (%)	61172	60499 (98.9)	614 (1.0)	59 (0.1)
50–64 years (%)	27121	24852 (91.6)	2130 (7.9)	139 (0.5)
≥65 years (%)	17801	11129 (62.5)	6220 (34.9)	452 (2.5)
Women (age)	64003	58938 (92.1)	4678 (7.3)	387 (0.6)
20–49 years (%)	38512	38043 (98.8)	433 (1.1)	36 (0.1)
50–64 years (%)	16644	15374 (92.4)	1185 (7.1)	85 (0.5)
≥65 years (%)	8847	5521 (62.4)	3060 (34.6)	266 (3.0)
Men (age)	42091	37542 (89.2)	4286 (10.2)	263 (0.6)
20–49 years (%)	22660	22456 (99.1)	181 (0.8)	23 (0.1)
50–64 years (%)	10477	9478 (90.5)	945 (9.0)	54 (0.5)
≥65 years (%)	8954	5608 (62.6)	3160 (35.3)	186 (2.1)
Diabetes	5535	4005 (72.4)	1354 (24.5)	176 (3.2)
Proteinuria (non to 2+)	4006	2909 (72.6)	988 (24.7)	109 (2.7)
Proteinuria (3+ to 4+)	1529	1096 (71.2)	366 (23.9)	67 (4.2)

Abbreviation: eGFR, estimate glomerular filtration rate

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4.3.2 Annual transition rate in a multi-state model

Our estimates of the annual transition rates between CKD states in a five-state Markov model are presented in Table 17. In all participants, the annual transition rate was 0.0169 (95% CI, 0.0164–0.0173) form eGFR ≥60 to 59–30 mL/min/1.73m^2, was 0.0259 (95%CI, 0.0240–0.0278) form eGFR 59-30 to <30 mL/min/1.73m^2, was 0.0988 (95% CI, 0.0902–0.1075) from eGFR <30 mL/min/1.73m^2 to dialysis. The annual death rate increased with decreased eGFR [0.0082 to 0.2352]. However, the annual death rate became better after receiving dialysis (0.1778).

4.3.2.1 The subgroups by gender and age

In Table 17, men had higher annual incidence of eGFR 59–30 mL/min/1.73m^2 than women [0.0218 (95%CI, 0.0209–0.0228) vs. 0.0138 (95%CI, 0.0133–0.0144)]. The progression rate since the state of eGFR 59–30 mL/min/1.73m^2 was almost the same between genders.

Our estimates of the annual transition rates between states, by gender and age, are presented in Table 18. The younger men (age ≤60 years) have high annual transition rate from eGFR ≥60 to 59-30 mL/min/1.73m^2 [0.0071(95%CI, 0.0064–0.0078) vs. 0.0033(95%CI, 0.0029–0.0036)] and form eGFR <30 mL/min/1.73m^2 to dialysis [0.2760 (95%CI, 0.2143–0.3377) vs. 0.2243 (95%CI, 0.1839–0.2647)] than younger women. The older men (age >60 years) have lower annual transition rate form eGFR <30 mL/min/1.73m^2 to dialysis than older women [0.0799 (95%CI, 0.0660–0.0939) vs. 0.0905 (95%CI, 0.0781–0.1029)]. It is interesting to note that men had poor survival outcome in all states than women even in different age groups.

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Table 17. The estimate of parameters in CKD transition model by gender

Parameters	All	Female	Male
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
λ_{12} (eGFR ≥60 to eGFR 59–30)	0.0169 (0.0164–0.0173)	0.0138 (0.0133–0.0144)	0.0218 (0.0209–0.0228)
λ_{23} (eGFR 59–30 to eGFR <30)	0.0259 (0.0240–0.0278)	0.0275 (0.0248–0.0301)	0.0248 (0.0219–0.0276)
λ_{34} (eGFR <30 to dialysis)	0.0988 (0.0902–0.1075)	0.1004 (0.0891–0.1116)	0.0976 (0.0840–0.1112)
u_1 (eGFR ≥60 to death)	0.0082 (0.0077–0.0087)	0.0043 (0.0038–0.0048)	0.0154 (0.0143–0.0165)
u_2 (eGFR 59–30 to death)	0.1452 (0.1405–0.1499)	0.1308 (0.1245–0.1372)	0.1646 (0.1576–0.1717)
u_3 (eGFR <30 to death)	0.2352 (0.2174–0.2531)	0.2150 (0.3418–0.4234)	0.2691 (0.1391–0.2992)
u_4 (dialysis to death)	0.1778 (0.1575–0.1908)	0.1706 (0.1455–0.1956)	0.1912 (0.1567–0.2257)

Abbreviation: CKD, chronic kidney disease; eGFR, estimated glomerular filtration; CI, confidence interval.

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Table 18. The estimate of parameters in CKD transition model by age and gender

Parameters	Female		Male	
	≤60 years	>60 years	≤60 years	>60 years
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
λ_{12} (eGFR ≥60 to eGFR 59–30)	0.0033 (0.0029–0.0036)	0.0626 (0.0600–0.0653)	0.0071 (0.0064–0.0078)	0.0663 (0.0632–0.0695)
λ_{23} (eGFR 59-30 to eGFR <30)	0.0267 (0.0220–0.0314)	0.0269 (0.0237–0.0300)	0.0293 (0.0229–0.0357)	0.0224 (0.0193–0.0255)
λ_{34} (eGFR <30 to dialysis)	0.2243 (0.1839–0.2647)	0.0905 (0.0781–0.1029)	0.2760 (0.2143–0.3377)	0.0799 (0.0660–0.0939)
u_1 (eGFR ≥60 to death)	0.0029 (0.0025–0.0033)	0.0056 (0.0037–0.0074)	0.0069 (0.0060–0.0078)	0.0257 (0.0228–0.0285)
u_2 (eGFR 59-30 to death)	0.0909 (0.0779–0.1040)	0.1639 (0.1569–0.1708)	0.2025 (0.1809–0.2242)	0.1826 (0.1754–0.1898)
u_3 (eGFR <30 to death)	0.1101 (0.0634–0.1569)	0.2396 (0.2149–0.2642)	0.1316 (0.0620–0.2013)	0.2959 (0.2638–0.3281)
u_4 (dialysis to death)	0.0689 (0.0440–0.0938)	0.2694 (0.2269–0.3111)	0.1224 (0.0779–0.1668)	0.2428 (0.1928–0.2928)

Abbreviation: CKD, chronic kidney disease; eGFR, estimated glomerular filtration; CI, confidence interval.

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4.3.2.2 The subgroups by DM and proteinuria

In Table 19, the participants with higher proteinuria had higher annual incidence of CKD state transition than those with mild proteinuria, showing 0.0753 (95%CI, 0.0658–0.0848) vs. 0.0383 (95%CI, 0.0348–0.0419) from eGFR ≥60 to 59–30 mL/min/1.73m^2, 0.1122 (95%CI, 0.0958–0.1286) vs. 0.0335 (95%CI, 0.0280–0.0390) from eGFR 59–30 to <30 mL/min/1.73m^2, 0.1761(95%CI, 0.1533–0.1989) vs. 0.0894 (95%CI, 0.0733–0.1056) from eGFR <30 mL/min/1.73m^2 to dialysis. The annual death rate in the state of eGFR ≥60 mL/min/1.73m^2 was mildly elevated in the group with high proteinuria but the death rates in other states of CKD were almost the same.

In Table 20, for diabetic participants, the annual transition rate was 0.0576 (95% CI, 0.0531–0.0613) form eGFR ≥60 to 59–30 mL/min/1.73m^2, was 0.0575 (95%CI, 0.0501–0.0649) form eGFR 59-30 to <30 mL/min/1.73m^2, was 0.1585 (95% CI, 0.1383–0.1787) from eGFR <30 mL/min/1.73m^2 to dialysis. The annual death rate increased with CKD states (0.0179 to 0.3147).

Our estimates of the annual transition rates between states, by DM and the level of proteinuria, are presented in Table 20. The diabetic participants with higher proteinuria (3+ to 4+) had high annual transition rate form eGFR ≥60 to 59-30 mL/min/1.73m^2 [0.0986 (95%CI, 0.0830–0.1143) vs. 0.0532 (95%CI, 0.0489–0.0575)], form eGFR 59–30 to <30 mL/min/1.73m^2 [0.1241(95%CI, 0.1009–0.1472) vs. 0.0464 (95%CI, 0.0376–0.0551)] and from eGFR <30 mL/min/1.73m^2 to dialysis [0.2128 (95%CI, 0.1806–0.2450) vs. 0.1080 (95%CI, 0.0840–0.1321)] than those with low proteinuria (1+ to 2+).

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Table 19. The estimate of parameters in CKD transition by proteinuria

Parameters	No proteinuria and trace	1+ and 2+	3+ and 4+
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
λ_{12} (eGFR ≥60 to eGFR 59–30)	0.0155 (0.0150–0.0159)	0.0383 (0.0348–0.0419)	0.0753 (0.0658–0.0848)
λ_{23} (eGFR 59–30 to eGFR <30)	0.0212 (0.0190–0.0235)	0.0335 (0.0280–0.0390)	0.1122 (0.0958–0.1286)
λ_{34} (eGFR <30 to dialysis)	0.0668 (0.0570–0.0766)	0.0894 (0.0733–0.1056)	0.1761 (0.1533–0.1989)
u_1 (eGFR ≥60 to death)	0.0075 (0.0070–0.0080)	0.0168 (0.0131–0.0204)	0.0239 (0.0142–0.0336)
u_2 (eGFR 59–30 to death)	0.1532 (0.1479–0.1586)	0.1312 (0.1186–0.1437)	0.1019 (0.0813–0.1226)
u_3 (eGFR <30 to death)	0.3120 (0.2811–0.3429)	0.1935 (0.1636–0.2233)	0.1954 (0.1649–0.2259)
u_4 (dialysis to death)	0.1333 (0.1080–0.1586)	0.2132 (0.1627–0.2637)	0.2054 (0.1678–0.2429)

Abbreviation: CKD, chronic kidney disease; eGFR, estimated glomerular filtration; CI, confidence interval.

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Table 20. The estimate of parameters in CKD transition by DM and proteinuria

Parameters	Non DM	DM	DM with low proteinuria	DM with high proteinuria
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
λ_{12} (eGFR ≥60 to eGFR 59–30)	0.0148 (0.0144–0.0153)	0.0576 (0.0531–0.0613)	0.0532 (0.0489–0.0575)	0.0986 (0.0830–0.1143)
λ_{23} (eGFR 59–30 to eGFR <30)	0.0202 (0.0184–0.0221)	0.0575 (0.0501–0.0649)	0.0464 (0.0376–0.0551)	0.1241 (0.1009–0.1472)
λ_{34} (eGFR <30 to dialysis)	0.0731 (0.0645–0.0816)	0.1585 (0.1383–0.1787)	0.1080 (0.0840–0.1321)	0.2128 (0.1806–0.2450)
u_1 (eGFR ≥60 to death)	0.0074 (0.0070–0.0079)	0.0179 (0.0140–0.0217)	0.0161 (0.0122–0.0201)	0.0274 (0.0125–0.0423)
u_2 (eGFR 59–30 to death)	0.1449 (0.1398–0.1499)	0.1635 (0.1505–0.1765)	0.1731 (0.1579–0.1882)	0.1233 (0.0942–0.1524)
u_3 (eGFR <30 to death)	0.2391 (0.2176–0.2606)	0.2387 (0.2063–0.2712)	0.3184 (0.2637–0.3731)	0.1939 (0.1544–0.2335)
u_4 (dialysis to death)	0.1171 (0.0967–0.1376)	0.3147 (0.2675–0.3620)	0.3387 (0.2606–0.4167)	0.2733 (0.2170–0.3296)

Abbreviation: CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration; CI, confidence interval.

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4.3.3 Kinetic epidemiological curves of CKD stages

Fig 12 shows the predicted probabilities of progression to eGFR 59–30 mL/min/1.73m^2, eGFR <30 mL/min/1.73m^2, dialysis, and death for a cohort of eGFR ≥ 60 mL/min/1.73m^2 by gender. As time goes by, in all participants, the proportions progressing to eGFR 59–30 mL/min/1.73m^2 is 6.9% at 10 years, and drop to 6.6% at 20 years and 5.4% after 30 years. The proportions progressing to eGFR <30 mL/min/1.73m^2 is 4.5% at 10 years, 5.3% at 20 years and drop to 4.4% after 30 years. The proportion of death increases steadily. The risk of progressing to death increases steadily over time. The kinetic curve for male and female follows a similar shape. However, the absolute risks of all stages are consistently lower in women.

Fig 13 shows the predicted probabilities of progression to eGFR 59–30 mL/min/1.73m^2, eGFR <30 mL/min/1.73m^2, dialysis, and death for a cohort of eGFR ≥60 mL/min/1.73m^2 by DM and proteinuria. As time goes by, in all diabetic participants, the proportions progressing to eGFR 59-30 mL/min/1.73m^2 is 14.3% at 10 years, and drop to 8.3% at 20 years and 4.1% after 30 years. The proportions progressing to eGFR <30 mL/min/1.73m^2 is 2.0% at 10 years, 1.4% at 20 years and drop to 0.7% after 30 years. The proportion of death increases steadily. The risk of progressing to death increases steadily over time. The kinetic curve for DM with low or high proteinuria follows a similar shape. However, the probability from eGFR ≥60 to 59–30 mL/min/1.73m^2 in the DM with high proteinuria elevated higher than those with low proteinuria in the initial 5 years.

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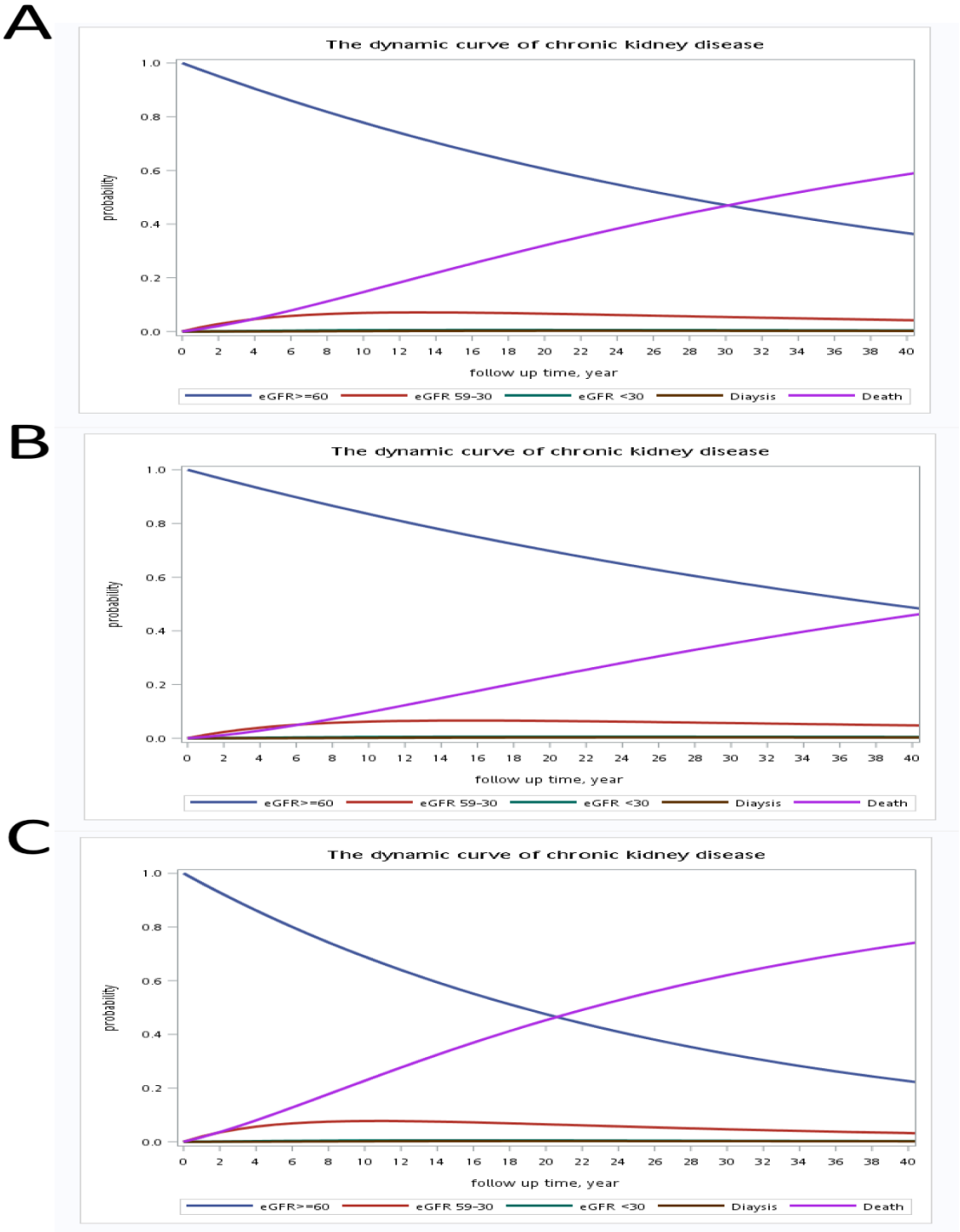

Fig 12. Transition probabilities from a cohort of eGFR ≥60 mL/min/1.73m^2 by gender.

(A) All participants (B) female (C) male

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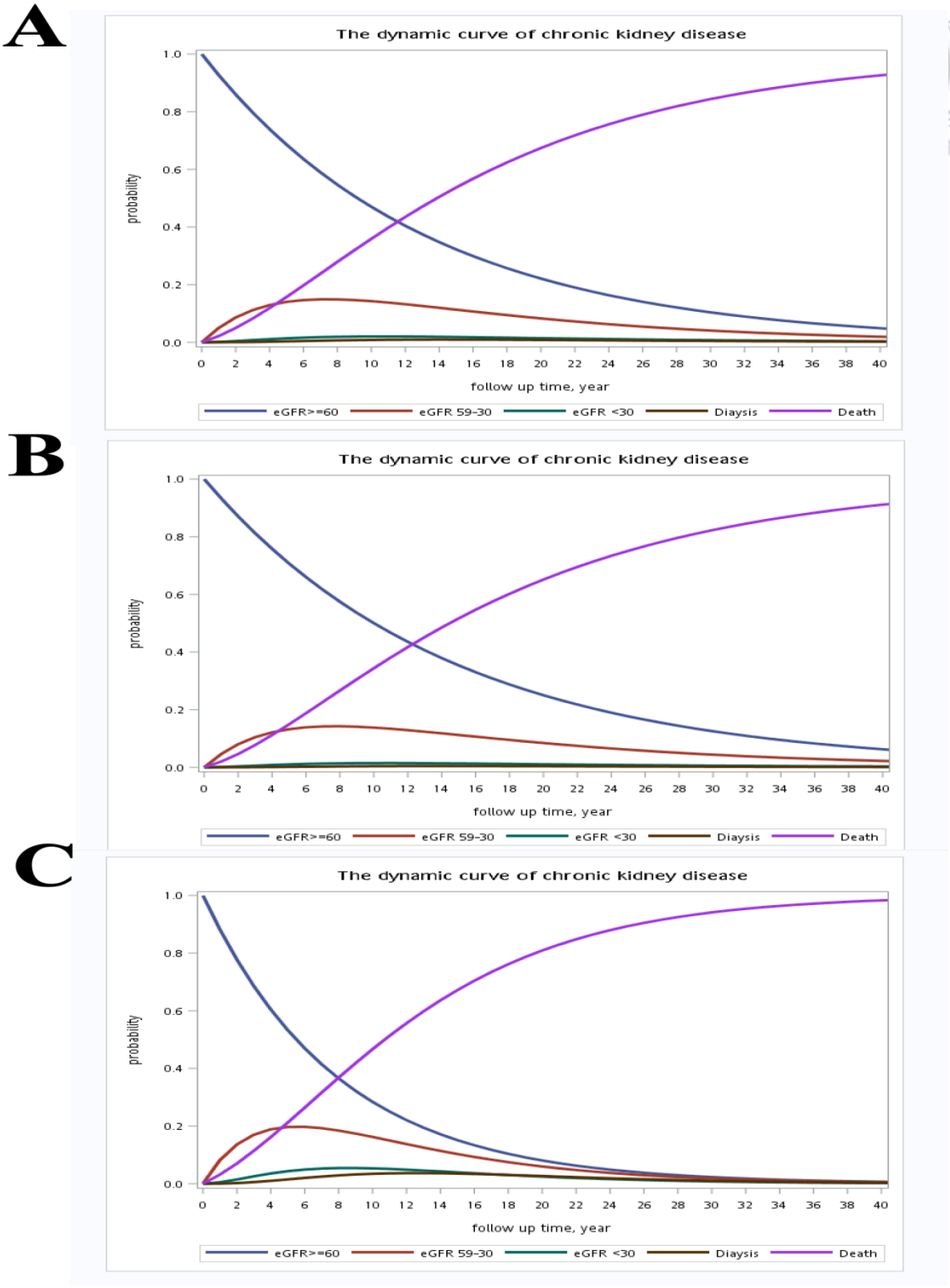

Fig 13. Transition probabilities from a cohort of eGFR ≥60 mL/min/1.73m^2 by DM and proteinuria.

(A) Diabetes (B) Diabetes with low proteinuria (C) Diabetes with high proteinuria

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4.3.4 Average dwelling time (ADT)

Table 21 shows that the ADT of eGFR 59–30 mL/min/1.73m^2 was 5.84 years (95%CI, 5.62–6.07), where 5.27 years (95%CI, 5.01–5.57) in men and 6.31 years (95%CI, 5.97–6.69) in women. Moreover, the ADT of eGFR <30 mL/min/1.73m^2 was 2.99 years (95%CI, 2.77–3.25), were 2.72 years (95%CTable 18I,2.43–4.48) in men and 3.17 years (3.32–1.86) in women. The long ADT in women is mainly a reflection of their lower mortality rate in any stages than men, shown in Table 18.

The ADT of eGFR 59–30 mL/min/1.73m^2 was 4.52 years (95%CI, 4.14–4.98 in DM and 6.05 years (95%CI, 5.81–6.32) in non-DM. Moreover, the ADT of eGFR <30 mL/min/1.73m^2 was 2.52 years (95%CI, 2.22–2.90) in DM and 3.20 years (95%CI, 2.92–3.54) in non-DM. The ADT of eGFR 59–30 mL/min/1.73m^2 decreased as the severity of proteinuria (5.73–4.67 years from non to severe). However, the participant with moderate proteinuria had the longest ADT of eGFR <30 mL/min/1.73m^2 among the three groups of proteinuria.

In Table 22, younger women (age, ≤60 years) had the longest ADT of eGFR 59-30 mL/min/1.73m^2 (8.50 years; 95%CI, 7.38–10.01), where the younger men have the shortest ADT(4.31 years; 95%CI, 3.84–4.09). The ADT of eGFR <30 mL/min/1.73m^2 varied within small range among the groups. DM with low proteinuria had lower ADT of eGFR 59-30 mL/min/1.73m^2 but higher ADT of eGFR <30 mL/min/1.73m^2 than those with low proteinuria.

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Table 21. The average dwelling time using stochastic process

Parameters	Average dwelling time (years, 95%CI)	
	The state of eGFR 59–30 mL/min/1.73m^2	The state of eGFR <30 mL/min/1.73m^2
All	5.84 (5.62–6.07)	2.99 (2.77–3.25)
Women	6.31 (5.97–6.69)	3.17 (2.32–1.86)
Men	5.27 (5.01–5.57)	2.72 (2.43–4.48)
Diabetes		
Yes	4.52 (4.14–4.98)	2.52 (2.22–2.90)
No	6.05 (5.81–6.32)	3.20 (2.92–3.54)
Proteinuria		
No proteinuria (0 to trace)	5.73 (5.49–5.99)	2.63 (2.38–2.95)
Moderate (1+ to 2+)	6.07 (5.47–6.82)	3.53 (3.04–4.22)
Severe (3+ to 4+)	4.67 (3.98–5.64)	2.69 (2.35–2.69)

Abbreviation: eGFR, estimate glomerular filtration rate.

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Table 22. The average dwelling time in different groups

Parameters	Average dwelling time (years, 95%CI)	
	The state of eGFR 59–30 mL/min/1.73m^2	The state of eGFR <30 mL/min/1.73m^2
Gender and age (years)		
Women with age ≤60	8.50 (7.38–10.01)	2.99 (2.71–4.04)
Women with age >60	5.24 (4.98–5.53)	3.02 (2.72–3.41)
Men with age ≤60	4.31 (3.84–4.90)	2.45 (1.85–3.61)
Men with age >60	4.87 (4.64–5.13)	2.66 (2.36–3.03)
DM and proteinuria		
DM with low proteinuria	4.55 (4.11–5.11)	2.34 (1.97–2.87)
DM with high proteinuria	4.04 (3.33–5.12)	2.45 (2.08–2.98)

Abbreviation: eGFR, estimate glomerular filtration rate; DM, diabetes mellitus.

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Chapter 5 Discussion and Future Work

5.1 part I Epidemiologic study

5.1.1 The main finding of part I

This population-based study utilized the CKD-EPI equation to determine the eGFR of patients with the objective of demonstrating the epidemiologic features of CKD in Taiwan. Our analyses indicated that the overall prevalence of CKD stages 1–5 was 15.46% with an incidence of 27.21/1000 PY. Moreover, the prevalence of CKD stages 3–5 was 9.06% with an incidence of 16.89/1000 PY. The estimated ADT in CKD stages 3–5 was 5.37 years, and the ADTs in the subgroups are shown in Tables 5 and 6. This study not only confirmed the high prevalence and incidence of CKD in the Taiwanese population but also quantified the ADT in CKD stages 3–5. Our results add to the literature concerning the prevalence and incidence of CKD stages in Taiwan, thereby providing a reliable reference for policymakers when establishing medical programs for CKD management.

5.1.2 Discussion of part I

The increase in ESRD populations worldwide is concerning for many countries because ESRD expenditures are gradually consuming increasing proportions of the healthcare budget [5, 156]. In Taiwan, although ESRD patients represent only 0.15%

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of the total population, they are responsible for 7% of the total annual budget of Taiwan's NHI Program owing to their use of dialysis. The high incidence of CKD stages 3–5 identified in our study could partly explain this medical burden. Unfortunately, limited data concerning the incidence of new-onset CKD in other countries are available. The Framingham Offspring study, which was conducted in Massachusetts, USA, comprised 2,585 participants with no pre-existing kidney disease. After a mean follow-up of 18.5 years, 244 participants (9.4%) had developed kidney disease [157]. In a retrospective cohort study of 405,000 participants in Southampton, UK, the estimated annual incidence of CKD (serum creatinine $\geq$ 1.7 mg/dL) was 1,700 per million population [158] at a mean follow-up of 5.5 years. An Iranian community-based cohort (3,313 participants with eGFR $\geq$ 60 mL/min/1.73 m^2) with a mean follow-up of 9.9 years reported an incidence of CKD stages 3–5 of 21.5/1000 PY[159]. One study reported that, during a 10-year follow up with 123,764 participants in Japan, 19,411 subjects exhibited CKD stages 3–5 (incidence of about 15.6/ 1000 PY) [160]. Compared with these studies, Taiwan appears to have a higher incidence of CKD stages 3–5.

In the present study, the estimated ADT in CKD stages 3–5 was 5.37 years. Kuo et al. [22] reported that the prevalence and incidence of clinically detectable CKD in Taiwan using NHI claims data are 9.3% and 13.5/1000 PY respectively,

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thereby indicating an estimated ADT (P/I ratio) of 6.89 years. The difference in ADTs between these two studies mainly stems from disparities in incidence because using clinically detectable CKD will underestimate the incidence of CKD. Moreover, in the subgroup analysis, those aged <50 years had a lower ADT in CKD stages 3–5, which indicates that a young age may be a risk factor of CKD progression; this supposition is consistent with previous studies [161, 162]. Interestingly, participants without hypertension exhibited a lower ADT than those with hypertension. We thus hypothesize that extensive use of renin-angiotensin-aldosterone system (RAAS) blockers for hypertension treatment also protects hypertensive patients from CKD because these blockers have been proven to confer renal protective effects [163, 164]. One study has reported the median time spent in different stages of CKD using the data from Chronic Renal Insufficiency Cohort study in the USA [162]. It showed that participants with systolic blood pressure (SBP) ≥140 mmHg was associated with shorter median time than those with SBP <140 mmHg. The discrepancy comparing to our current study may be due to the different populations (hospital-based vs. community-based) or target subgroups (SBP control vs. hypertension history). Therefore, a further study is needed to clarify it.

A sex difference in the epidemiologic features of CKD was observed; specifically, women exhibit a higher proportion of predialysis CKD than men in most

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regions, with the opposite findings in Japan and Singapore [165]. We observed a sex difference in the epidemiology of CKD in our study, with women exhibiting a lower prevalence and incidence than men. This finding is consistent with that in other Asian countries. Moreover, while a higher ADT in CKD stages 3–5 was noted in female participants aged ≥ 50 years, the shortest ADT was observed in male participants aged 20–49 years. Some potential mechanisms of this gender difference have been proposed, including differences in nitroxide (NO) metabolism, sex steroids, and the impact of sex on lifestyle and risk factors. One animal study showed that female rats have higher NO levels than their male counterparts [166], and NO was determined to play an essential role in the regulation of vascular tone and endothelial function [167]. Some animal models also demonstrate that endogenous estrogens exert antifibrotic and antiapoptotic effects on the kidney [168]. Another potential explanation for the broad differences observed between sexes may involve differences in the impact of lifestyle and traditional risk factors on men and women with CKD [169]. Further studies are needed to elucidate the actual mechanisms responsible for these differing relationships.

Few study participants with CKD were aware of their disease, and only 33.3% of the participants were aware of their advanced CKD status. Therefore, education regarding early CKD recognition may aid in delaying disease progression. Moreover,

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those patients with underlying diabetes, hypertension, and MetS revealed a higher prevalence and incidence of CKD stages 3–5 than those without. These associations are clinically relevant because strict glycemic control [170], antihypertensive therapy with the use of RAAS blockers [171], lipid-lowering agents [172], and treatment of MetS [173] have been shown to slow the progression of kidney disease.

5.1.3 the limitation of part I

The present study has several strengths. First, it examined differences in CKD stages in a large cohort of individuals over a relatively long period of 10 years, thereby enabling assessment of a sufficient number of CKD events. Second, we utilized the CKD-EPI formula to calculate eGFRs. This equation provides more accurate estimations of GFR than those generated by the Modification of Diet in Renal Disease equation, which was adopted in previous studies. Third, although an earlier study reported the incidence of clinically detectable CKD (approximately equivalent to CKD stages 3–5) in Taiwan using NHI claims data [22], we examined the incidence of biochemically recognized CKD stages 3–5 in our study. Considering these strengths, we also acknowledge the potential limitations of our work. First, a large proportion of quantitative data regarding proteinuria was missing from the records we collected. Therefore, the prevalence of CKD stages 1–2 may have been overestimated.

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Second, as we used only one laboratory result to define the CKD stage, and measurement errors may introduce bias to the results. However, a large sample size could reduce this limitation under the assumption of random measurement errors. Third, the number of participants lost to follow-up may also induce bias in the estimation of incidence. However, the incidence of CKD stage 5 (0.42/1000 PY) in our study was very similar to the incidence of ESRD requiring RRT (0.45/1000 population-year) reported by the US Renal Data System [5]. This similarity validates our findings because CKD stage 5 is a surrogate for the disease state that requires dialysis.

5.1.4 The conclusion of part I

This study provides an epidemiological description of CKD in Taiwan. Using a large population-based screening program, we documented a high prevalence and incidence of biochemically recognized CKD stages 3–5. Moreover, we estimated ADT in the main CKD burden (stages 3–5) as 5.37 years. Further exploration about the factors associated with the shifting of this ADT will facilitate the CKD management.

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5.2 part II Risk determents of CKD transition

5.2.1 main finding of part II

This population-based study demonstrated the factors influencing state transition in a three-state CKD model. We showed the independent initiators and progressors in CKD transition and consequently provided the risk prediction functions for the initiation and progression of CKD. Those parameters used in our models are checked routinely in the general health examination, of which the calculated risks can be conjoined easily with the information reporting system. Knowledge of the factors influencing the different state transitions of CKD can help clinical physicians arrange for an specialized plan for risky population to prevent CKD and slow the progression of CKD. Moreover, identifying higher-risk patients can provide more efficient management of CKD.

5.2.2 Discussion of part II

It is not surprising that age, DM, and the components of MetS were well known as risk factors for the development of CKD, and the difference in the distribution of these factors can be seen in these two different groups. Some previous studies reported results [65, 67, 70, 174-176] similar to our findings. Proteinuria and eGFR can worsen with an increase in the severity of kidney damage [99, 177], and low proteinuria and high eGFR indicate good preservation of kidney function. Therefore, it is reasonable to consider that individuals with high renal damage may be prone to the development and progression of CKD. Uric acid has been proposed to have a causal role in the development of de novo CKD owing to the possible mechanism of causing endothelial dysfunction in vascular cells [178] and renal damage via fructose [179]. Moreover,

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some studies have mentioned that uric acid is associated with the progression of CKD [180, 181]. In our study, uric acid was not only an initiator but also a progressor of CKD. Finally, lifestyle, including smoking, alcohol consumption, betel-nut chewing and regular exercise appears to not be an independent risk factor for CKD development, indicating that the influence on CKD might be through other consequent factors, such as MetS or proteinuria.

In our study, DM appears to not have an independent effect on the progression of CKD, which is supported by a meta-analysis showing that DM was not a progressor of CKD [70]. One possible explanation for this phenomenon is that DM may affect CKD progression via proteinuria mainly, which is a hallmark of renal damage caused by DM. Age had no independent effect on the progression of CKD. One hypothesis is that the effect of age on CKD progression was modulated by residual renal function, such as eGFR and serum hemoglobin level. It has been shown that anemia occurs when nephron loss develops owing to a decrease in the production of erythropoietin [182]. Thus, a lower serum hemoglobin level without any evidence of blood loss may indicate higher nephron loss, and this will induce a tendency for CKD progression. One recent study reported that poor lifestyle was associated with the progression of CKD (50% eGFR decrease or ESRD) in a 4-year cohort with 3006 CKD participants [183]; however, our study did not identify such an association. This discrepancy may be associated with the difference in endpoints.

Elucidation of the factors that influence the state transition of CKD is valuable for the prevention of CKD. From a practical perspective, the identification of initiators can help in the design of individually tailored prevention programs, and the elucidation of promoters may enable the consideration of individually tailored strategies in multidisciplinary CKD care, which has been shown by a team consisting of

doi:10.6342/NTU201900529

nephrologists, nurses, dietitians, social workers, and surgeons [13]. Moreover, in risk stratification, we found that progression is much quicker in high-risk patients than in low-risk patients. Some studies have reported that late referral to nephrologists is associated with poor prognosis [8-10]. Therefore, higher-risk patients could receive more intensive intervention and early nephrology referral; whereas low-risk patients could be attended by the primary care physician.

5.2.3 The limitation of part II

This study had several strengths. First, it examined the changes in CKD states in a large cohort of individuals over a long period of 8 years, which enabled assessments of a sufficient number of desired events. Second, a multi-state transition model can offer more details about the influence of risk factors on the clinical progression history of CKD. Third, using an AFT model with a Weibull distribution can estimate the absolute risk of CKD state transition, which it can be understood straightforwardly and be interpreted easily. However, there were some potential limitations in our study. First, we used only one laboratory result to define the participant's current eGFR state, which it will lead a bias due to the variability of eGFR measurement. However, under the assumption of random measurement error of eGFR, large sample size can alleviate this bias. Second, the medication history was not available in our study because some medications can affect the decrease in eGFR [184, 185]. However, medical access is unrestricted for Taiwanese individuals owing to the health insurance program, which this can reduce the bias. Finally, the risk prediction functions for CKD transition still need the further external validation to test their generalization.

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5.2.4 The conclusion of part II

We documented the independent initiators and progressors in a three-state CKD transition model to classify the risk for the clinical course of CKD. Moreover, we successfully developed two absolute risk functions for predicting the initiation and progression of CKD. Such information is beneficial for alerting the physicians to early transfer the risky patients to receive the nephrologist based MDC.

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5.3 Part III stochastic Markov model of CKD

5.3.1 Main finding of part III

This large-scale community-based study elucidates a kinetic view of the CKD development process by quantifying transitions between states in a five-state Markov model. It offers the approximated natural history of CKD in Taiwan. In subgroups analysis, it shows that women had a lower incidence of CKD and better survival rate than did men, which can explain the different CKD loading in genders in Taiwan. We also offered a clinical history of DM-related CKD, disclosing that the progression rates of CKD in diabetic participants were faster than those in non-DM participants. Moreover, the ADT for eGFR 59–30 mL/min/1.73m^2 and eGFR <30 mL/min/1.73m^2 in different groups were estimated and are shown in Table 20 and 21, of which the result can support our finding about the ADT in CKD stages 3–5 in the study part I. Finally, such finding can be applied to the cost-effectiveness analysis of CKD intervention.

5.3.2 Discussion of part III

Two studies have proposed a stochastic model for the progression of chronic kidney disease using the same data source [130, 186], which one is 6-state model form eGFR 59–30 mL/min/1.73m^2 to death [130] and another is 5-state model form eGFR 90–60 mL/min/1.73m^2 to death [186]. However, the data source was from dialysis hospital, which may indicate the higher severity of CKD with intervention in this group. The hospital-based disease course is always different to the natural history of the disease. their annual transition rate between CKD states were obviously higher than our study, of which the stochastic model was proposed from eGFR ≥60 mL/min/1.73m^2 to death.

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For example, the annual transition rate from eGFR 59–30 to ≤30 mL/min/1.73m^2 is 0.27 in the 5-state model [186] and 0.149 in the 6-state model [130]. However, it is 0.026 in our 5-state model. Davies et al. had reported the average decline in GFR was 0.96 ml/min/1.73 m^2/ year [187], which the annual transition rate from the CKD state of eGFR 59–30 to ≤30 mL/min/1.73m^2 is about 0.032. Its result is very similar to our estimation. Thereafter, such information can be applied to the general population.

GFR declining with normal aging, perhaps inevitably, usually begins since 30–40 years of age and accelerates in the 50–60 years, which was evidenced by the studies conducted in the 1930's–1950's [188]. Our results also confirmed this finding, which it showed that the participants with age >60 years have the higher annual incidence and progression rate of CKD than those with age ≤60 years in both male and female participants. This decline appears to be a part of the normal physiologic process of cellular in the kidneys. DM with proteinuria has been known as a strong risk factor for CKD [189]. Therefore, our study also provided the clinical history of diabetic nephropathy.

The ADT in CKD stages 3–5 in our previous study is 5.37 years using the formula of prevalence incidence (P/I) ratio of CKD stages 3–5. The departure form CKD stages 3–5 involve regression and progression from CKD stages 3-5 and death. Regression is of less possibility because CKD is thought to cause progressive and irreversible damage to the kidney in the long-run [190]. The estimated ADT in CKD stages 3–5 in our study part III is 5.64 years (5.84×(8.45/9.06)+2.99×(0.61/9.06)), which is consistent with the result via the method of P/I ratio (5.37 years in CKD stages 3–5) in our study part I. Because not all the participants in CKD stage 3 can enter the stage 4–5, actually most participants died before entering the advanced CKD stage, the

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ADT of CKD stages 3–5 is not simple as ADT in stage 3 plus ADT in stages 4–5. Therefore, we should weight their contribution to ADT by their distribution in population. Finally, such finding of ADT can offer a reference to clinical physicians and policymakers.

We can observe the different CKD burden in gender form our data. The kinetic picture of transitions between states by gender in Fig 12 made a significant contribution to explain the obvious gender difference, which men have a higher prevalence of CKD stages 3–5 than women (10.9% VS. 7.9%). High CKD incidence rate in men (two times than women; 0.0218 vs. 0.0138) contributed this gender discrepancy. Moreover, adding the higher mortality to men introduced a lower ADT in CKD stage 3 than women (5.27 vs. 6.31 years). Some potential mechanisms of this gender difference in CKD have been proposed, including differences in nitroxide (NO) metabolism [166], sex steroids [168] and the impact of sex on lifestyle and risk factors [169].

In general, the prevalence of CKD was greater in women than in men, regardless of age. Although the longer life expectancy of women and inappropriate use of the eGFR equation had been proposed, the real explanation remains undetermined. Conversely, population studies in Asian countries showed the reverse finding that men had a higher CKD prevalence than women [191, 192]. Wen et al. [16] reported a higher CKD prevalence in men than in women in Taiwan (7.6% vs. 6.7% eGFR <60 mL/min/1.73 m^2), which was comparable with our findings. In our data, it is reasonable that women had a lower CKD prevalence than men because women had a lower incidence of CKD. Longer life expectancy of women contributed to the longer ADT of CKD, but not the lower prevalence of CKD.

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5.3.3 The limitation of part III

This study had several strengths. First, it examined the changes in CKD stage in a large cohort of individuals over a long period of 10 years, which enabled assessments of a sufficient number of CKD transitions. Second, we used the CKD-EPI formula to calculate eGFR; this equation provided more accurate estimations of GFR than those generated by the MDRD equation, which has been adopted in previous studies. However, there are several potential limitations to our study. First, we used only one laboratory result to define the CKD stage, which it needed sustained renal impairment for three months to be defined. However, large sample size can alleviate this bias [193]. Second, a natural history of disease represents the progression course without any medical intervention for the disease. Therefore, it is hard to estimate the natural history of CKD because of its long disease course and the convenient medical access in Taiwan. However, using community-based data may approximate the natural history of CKD. Furthermore, our estimation of the natural history of CKD was validated by our Part I study because of the similar estimation of ADT in CKD stages 3–5. Third, the annual death rate in dialysis state may be overestimated in the subgroup analysis due to the insufficient case numbers.

5.3.4 The conclusion of part III

We developed a 5-state stochastic Markov model of CKD and the results we found sounds reasonable. This modeling may help to quantify disease progression and the estimates can be used to predict incidences and prevalence over some time horizon. Moreover, the approximated natural history of CKD in our Markov model can be used to compare the economic and health outcomes of public health interventions (Fig 14).

doi:10.6342/NTU201900529

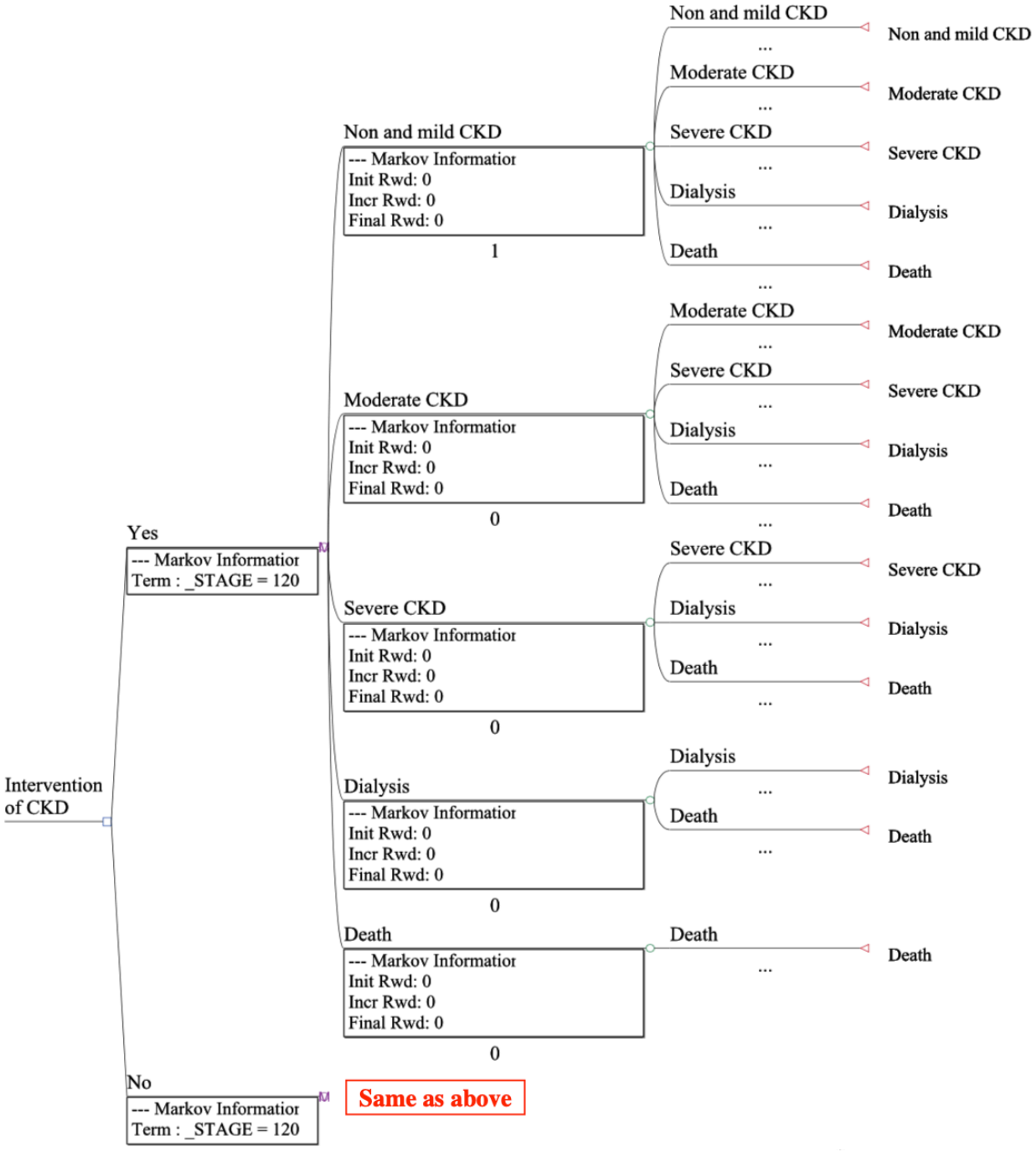

Fig 14. A decision tree for the CKD intervention based on Markov model.

The five-state Markov model is based on the result from our study. The intervention can be the public policy for CKD management. Non to mild CKD: stages 0–2; moderate CKD, stage 3; severe CKD, stages 4–5.

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5.4 Further work

In the future, we can extend our current study into the following topics, including Bayesian clinical reasoning prediction model and semi-Markov analysis. The preliminary ideas are shown below.

5.4.1 Prediction model for dialysis using Bayesian clinical reasoning

Aside from our study Part II, a prediction model of CKD progression using accelerated failure time model, I would like to establish another prediction function for incident dialysis using Bayesian clinical reasoning model in the further work. The Bayesian clinical reasoning model had been used in developing the prediction function of hypertension in the general population [194]. Such a method can offer a quick reference for the physicians and it also allows us to update the risk as the same manner when a new risk factor is applied.

Step 1: Specify baseline age-sex-specific risk (prior information)

We will use the logistic regression model with the parameters of sex and age to estimate the baseline risk for incident dialysis from CKD stage 3. This baseline risk will be considered as a prior of risk for dialysis.

$$Logit\ P(D; X_1, X_2, X_3) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3$$

where $X_1 = observation\ perion.$

$X_2 = Sex$

$X_3 = Age$

$$P_{prior} = \frac{\exp(\alpha+\beta_1 X_1+\beta_2 X_2+\beta_3 X_3)}{1+\exp(\alpha+\beta_1 X_1+\beta_2 X_2+\beta_3 X_3)} \quad (5\text{-}1$$

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Step 2: Establish metabolic score

We will collect the laboratory parameters related to CKD progression according to our prior analysis of risk for CKD progression. We will standardize the values of each parameters and then do the summation with natural log transformation.

$$\text{Score}=\log\left(\frac{Z1-mean_{Z1}}{SD_{Z1}}+\frac{Z2-mean_{Z2}}{SD_{Z2}}+\frac{Z3-mean_{Z3}}{SD_{Z3}}+\frac{Z4-mean_{Z4}}{SD_{Z4}}+\cdots\right) \quad (5\text{-}2)$$

Step 3: Formulate the likelihood ratio (LR) by progression score of CKD

Let $f_1(Y;\mu_D,\sigma_D)$ and $f_2(Y;\mu_{\bar{D}},\sigma_{\bar{D}})$ be the probability density function for subjects diagnosed as ESRD and those in the absence of ESRD, where Y represents a random variable of metabolic score (MS) of CKD, μ_D and $\mu_{\bar{D}}$ the mean of MS for ESRD and non-ESRD, respectively, σ_D and $\sigma_{\bar{D}}$ are two corresponding parameters of standard deviation. Given Y=y

$$LR_{MS}=\frac{f_1(Y=y;\mu_D,\sigma_D)}{f_2(Y=y;\mu_{\bar{D}},\sigma_{\bar{D}})}=\frac{\frac{1}{\sqrt{2\pi(\sigma_D)^2}}\exp\{-\frac{1}{2}(\frac{y-\mu_D}{\sigma_D})^2\}}{\frac{1}{\sqrt{2\pi(\sigma_{\bar{D}})^2}}\exp\{-\frac{1}{2}(\frac{y-\mu_{\bar{D}}}{\sigma_{\bar{D}}})^2\}}=\exp\{-\frac{1}{2\sigma^2}[(y-\mu_D)^2-(y-\mu_{\bar{D}})^2]\} \quad (5\text{-}3)$$

doi:10.6342/NTU201900529

Step 4: Formulate the likelihood ratio by other bivariate risk factors

For other risk factors, X, with binary property, the likelihood ratios follows two binomial distributions for D with $Bin(P_{X|D}, n_D)$ and $\overline{\mathrm{D}}$ with $Bin(P_{X|\overline{D}}, n_{\overline{D}})$.

$$LR_x = \frac{P(X \mid D)}{P(X \mid \overline{D})} = \frac{(P_{X|D})^{m_D}(1-P_{X|D})^{n_D-m_D}}{(P_{X|\overline{D}})^{m_{\overline{D}}}(1-P_{X|\overline{D}})^{n_{\overline{D}}-m_{\overline{D}}}} \quad (5\text{-}4)$$

Step 5: Posterior probability model

X: is a vector of gender, age, and period

Y: Metabolic score

Z: other risk factors

$$\frac{P(D \mid X,Y,Z)}{P(\overline{D} \mid X,Y,Z)} = \frac{P(D \mid X)}{P(\overline{D} \mid X)} \times LR(\cdot) \quad = \text{Prior Odds} \times \text{LR} \quad (5\text{-}5)$$

Step 6: Predictive distribution with Monte Carlo Markov Chain (MCMC) simulation

We will derive the predictive distribution for an unobserved event ($\boldsymbol{y_{pred}}$) of developing ESRD in 10-year conditional on the observed data ($\boldsymbol{y_{obs}}$), with the following formula,

doi:10.6342/NTU201900529

$$P(y_{pred}) = \int p(y_{pred}, \theta | y_{obs}) d\theta = \int p(y_{pred} | \theta, y_{obs}) p(\theta | y_{obs}) d\theta$$

$$= \int p(y_{pred} | \theta) p(\theta | y_{obs}) d\theta \text{ , where } \theta \text{ is a vector for parameters} \quad (5\text{-}6)$$

Step 7: Internal validation and external validation

I will separate our dataset into 2/3 and 1/3. The 2/3 dataset will be used as the training dataset and the other 1/3 dataset will be used for the internal validation. I will also try to find a dataset from another place for the external validation.

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5.4.2 Semi-Markov application to CKD transition

It is reasonable that the time spent in the current state will have an impact on the transition to the next state in our CKD multistate transition model. The related analysis is called semi-Markov, which emphasized the importance of staying time in a particular state. Foucher et al. had applied the semi-Markov model in the following-up after renal transplantation [133]. Therefore, I will try to use the semi-Markov model to our CKD data.

Step 1: The hazard function in the semi-Markov process

Let S={1,2,3,4,5} be a finite state space representing the possible states of the evolution of a patient. Suppose that the sample is constituted of n subjects, denoted by k (k=1,2,...,n), r=0,...,Z_k. Z_k represents the number of transitions for the subject k. We also consider the observed durations $d_{k,r}$ in the state $X_{k,r}$, before the transition to the state $X_{k,r+1}$. The probabilities of jumping from state i to state j, associated with this chain, can be expressed as

$$P_{ij} = P(X_{k,r+1} = j | X_{k,r} = i) \quad \text{for r=0,1,2….}Z_k\text{-1} \tag{5-6}$$

$\sum_j P_{ij} = 1$ if state i is not absorbing. $P_{ij} = 0$ is state i is absorbing.

Formally, the time scale of interest is $d_{k,rr} = t_{k,r+1} - t_{k,r}$. Thus, the probability density function (PDF) of the time spent in state i, before passing to state j, is given by

doi:10.6342/NTU201900529

$$f_{ij}(d_{k,r}) = \lim_{\Delta d \to 0^+} \frac{P(d_{k,r} \le D_{k,r} < d_{k,r+\Delta d} | X_{k,r+1} = j, X_{k,r} = i)}{\Delta d} \quad (5\text{-}7)$$

and the hazard function is as

$$\lambda_{ij}(d_{k,r}) = \lim_{\Delta d \to 0^+} \frac{P\left(d_{k,r} \le D_{k,r} < d_{k,r+\Delta d} \middle| D_{k,r} > d_{k,r},\ X_{k,r+1} = j, X_{k,r} = i\right)}{\Delta d}$$

$$= f_{ij}(d_{k,r}) / S_{ij}(d_{k,r}) \quad (5\text{-}8)$$

the hazard function of the semi-Markovian process, a_{ij}, can be defined

$$\alpha_{ij} = \lim_{\Delta d \to 0^+} \frac{P\left(d_{k,r} \le D_{k,r} < d_{k,r+\Delta d},\ X_{k,r+1} = j \ \middle| D_{k,r} > d_{k,r},\ X_{k,r} = i\right)}{\Delta d}$$

$$= P_{ij} f_{ij}(d_{k,r}) / S_{i.}(d_{k,r}) \quad (5\text{-}9)$$

Step 2: Distribution of duration

We assume the distribution of duration is Weibull distribution. Therefore, the hazard function is

$$\lambda_{ij} = \gamma_{ij} X^{(\gamma_{ij}-1)}$$

when in the consideration with parameters ($\boldsymbol{COVA_{ij}}$)

$$\lambda_{ij} = \lambda_{0,ij}(x) exp\left(\beta_{ij}^T \times COVA_{ij}\right) \quad (5\text{-}10)$$

doi:10.6342/NTU201900529

Step 3: Probabilities of initial state

We define that the $\pi_{k,i}$ is the probability of initial state and P_i is the distribution of state in our CKD cohort.

$\pi_{k,i} = P_i/(\sum_{i=1}^{h} P_i)$ (where h is total number of state we can observe in our cohort; h is 3 (state 1, state2, and state 3 in our CKD model)) (5-11)

Step 4: Probabilities of different event types

Fig 15 shows the possible event types when a transition occurs in our model. Three types will be observed in our multistate CKD model, shown below.

(1) Right censoring

No transition event was detected during two consequent screening, belongs to right censoring. For example, one participant stayed in state 1 in the time of screening 1 and still stay in state 1 in the time of screening 2.

$$C_{k,r}^{R} = P\left(D_{k,r} > d_{k,r}^{0} \middle| X_{k,r} = i\right) = \sum_{j \neq i} P(X_{k,r+1} = j | X_{k,r} = i) \int_{d_{k,r}^{0}}^{\infty} f_{ij}(u) du$$

$$= \sum_{j \neq i} P_{ij} S_{ij}\left(d_{k,r}^{0}\right)$$

$$= S_{i.}\left(d_{k,r}^{0}\right) \quad (5\text{-}12)$$

(2) Interval censoring

The transition event is detected during two consequent screening, which this is called interval censoring. For example, one participant stayed in state 2 in

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the time of screening 1 and then was detected as state 3 in the time of screening 2. We know this participant had the transition event from state 2 to state 3 between the time of two consequent screening. However, we don't know the exact time of state transition.

$$C_{k,r}^{I} = P(d_{k,r}^{0} < D_{k,r} < d_{k,r}^{1}, X_{k,r+1} = j | X_{k,r} = i)$$

$$= P(X_{k,r+1} = j | X_{k,r} = i) \int_{d_{k,r}^{0}}^{d_{k,r}^{1}} f_{ij}(u)du$$

$$= P_{ij}(\int_{0}^{d_{k,r}^{1}} f_{ij}(u)du - \int_{0}^{d_{k,r}^{0}} f_{ij}(u)du)$$

$$= P_{ij}(S_{ij}(d_{k,r}^{0}) - S_{ij}(d_{k,r}^{1})) \quad (5\text{-}13)$$

(3) Exact observation of event

The dialysis and death events were fully observed due to national Registration System, meaning that we know the definite occurrence date of dialysis or death.

$$C_{k,r}^{E} = \lim_{\Delta d \to 0^{+}} P(d_{k,r} < D_{,r} < d_{k,r+\Delta d}, X_{k,r+1} = j | X_{k,r} = i) / \Delta d$$

$$= P_{ij} f_{ij}(d_{k,r}) \quad (5\text{-}14)$$

doi:10.6342/NTU201900529

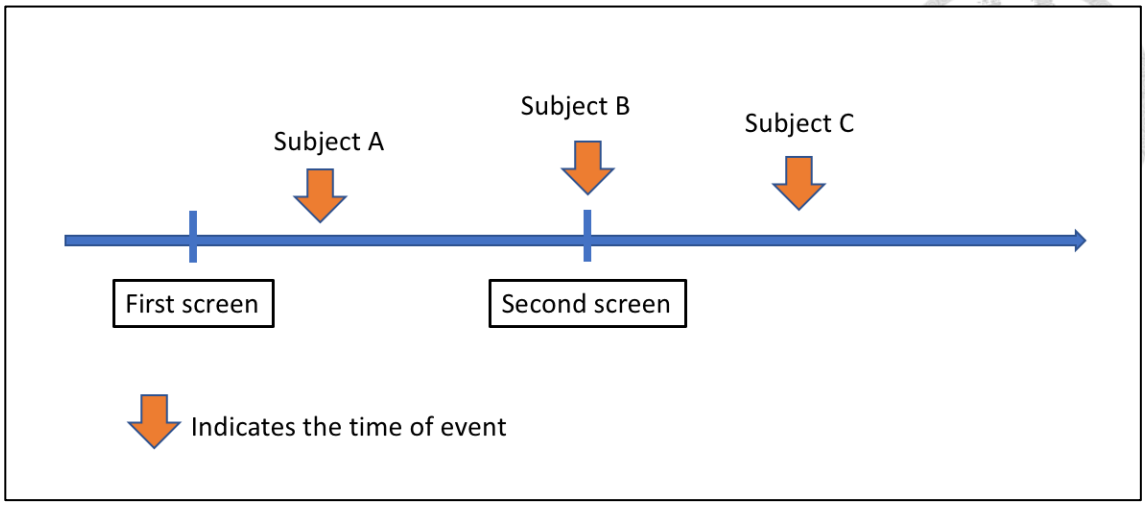

Fig 15. The illustration of event types.

Subject A is the type of interval censoring; subject B is the type of event with exact observation time; and subject C is the type of right censoring

Step 5: Likelihood function of semi-Markov

$$likelihood =$$

$$\prod_{k=1}^{n}\{\pi_{k,i}\prod_{ij}\prod_{X_{k,r}=i,X_{k,r+1}=j}(C_{k,r}^{E\ \delta_{k,r}^{E}}\ C_{k,r}^{I\ \delta_{k,r}^{I}})\prod_{ij}\prod_{X_{k,r}=i}(C_{k,r}^{R\ \delta_{k,r}^{R}})\} \qquad (5\text{-}14)$$

Where $\delta_{k,r}^{z}$ (Z=E, I, and R) is an indicator for event types

doi:10.6342/NTU201900529

Reference

1. Hsu, C.C., et al., *High prevalence and low awareness of CKD in Taiwan: a study on the relationship between serum creatinine and awareness from a nationally representative survey.* Am J Kidney Dis, 2006. **48**(5): p. 727-38.
2. Centers for Disease, C. and Prevention, *Prevalence of chronic kidney disease and associated risk factors--United States, 1999-2004.* MMWR Morb Mortal Wkly Rep, 2007. **56**(8): p. 161-5.
3. Hwang, S.J., J.C. Tsai, and H.C. Chen, *Epidemiology, impact and preventive care of chronic kidney disease in Taiwan.* Nephrology (Carlton), 2010. **15 Suppl 2**: p. 3-9.
4. Tin, A., et al., *Patterns of Kidney Function Decline Associated with APOL1 Genotypes: Results from AASK.* Clin J Am Soc Nephrol, 2016. **11**(8): p. 1353-9.
5. Saran, R., et al., *US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States.* Am J Kidney Dis, 2017. **69**(3 Suppl 1): p. A7-A8.
6. National Kidney, F., *K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification.* Am J Kidney Dis, 2002. **39**(2 Suppl 1): p. S1-266.
7. Stevens, P.E., A. Levin, and M. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group, *Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline.* Ann Intern Med, 2013. **158**(11): p. 825-30.
8. Kessler, M., et al., *Impact of nephrology referral on early and midterm outcomes in ESRD: EPidemiologie de l'Insuffisance REnale chronique terminale en Lorraine (EPIREL): results of a 2-year, prospective, community-based study.* Am J Kidney Dis, 2003. **42**(3): p. 474-85.
9. Huisman, R.M., *The deadly risk of late referral.* Nephrol Dial Transplant, 2004. **19**(9): p. 2175-80.
10. Israni, R.K., et al., *Physician characteristics and knowledge of CKD management.* Am J Kidney Dis, 2009. **54**(2): p. 238-47.
11. Smart, N.A. and T.T. Titus, *Outcomes of early versus late nephrology referral in chronic kidney disease: a systematic review.* Am J Med, 2011. **124**(11): p. 1073-80 e2.
12. Mason, J., et al., *Educational interventions in kidney disease care: a systematic review of randomized trials.* Am J Kidney Dis, 2008. **51**(6): p. 933-51.
13. Chen, Y.R., et al., *Effectiveness of multidisciplinary care for chronic kidney disease in Taiwan: a 3-year prospective cohort study.* Nephrol Dial Transplant, 2013. **28**(3): p. 671-82.
14. Hemmelgarn, B.R., et al., *Association between multidisciplinary care and survival for elderly patients with chronic kidney disease.* J Am Soc Nephrol, 2007. **18**(3): p. 993-9.
15. Curtis, B.M., et al., *The short- and long-term impact of multi-disciplinary clinics in addition to standard nephrology care on patient outcomes.* Nephrol Dial Transplant, 2005. **20**(1): p. 147-54.
16. Wen, C.P., et al., *All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan.* Lancet, 2008.

doi:10.6342/NTU201900529

371(9631): p. 2173-82.
17. Zhang, L., et al., *Prevalence and factors associated with CKD: a population study from Beijing.* Am J Kidney Dis, 2008. **51**(3): p. 373-84.
18. Zhang, L., et al., *Community-based screening for chronic kidney disease among populations older than 40 years in Beijing.* Nephrol Dial Transplant, 2007. **22**(4): p. 1093-9.
19. Coresh, J., et al., *Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey.* Am J Kidney Dis, 2003. **41**(1): p. 1-12.
20. Imai, E., et al., *Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient.* Clin Exp Nephrol, 2007. **11**(2): p. 156-63.
21. Hallan, S.I., et al., *International comparison of the relationship of chronic kidney disease prevalence and ESRD risk.* J Am Soc Nephrol, 2006. **17**(8): p. 2275-84.
22. Kuo, H.W., et al., *Epidemiological features of CKD in Taiwan.* Am J Kidney Dis, 2007. **49**(1): p. 46-55.
23. Chen, W., et al., *Prevalence and risk factors associated with chronic kidney disease in an adult population from southern China.* Nephrol Dial Transplant, 2009. **24**(4): p. 1205-12.
24. Iseki, K., *Chronic kidney disease in Japan.* Intern Med, 2008. **47**(8): p. 681-9.
25. Chadban, S.J., et al., *Prevalence of kidney damage in Australian adults: The AusDiab kidney study.* J Am Soc Nephrol, 2003. **14**(7 Suppl 2): p. S131-8.
26. Baghestani, A.R., E. Hajizadeh, and S.R. Fatemi, *Parametric model to analyse the survival of gastric cancer in the presence of interval censoring.* Tumori, 2010. **96**(3): p. 433-7.
27. Foley, R.N., et al., *Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999.* J Am Soc Nephrol, 2005. **16**(2): p. 489-95.
28. Poggio, E.D., et al., *Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease.* J Am Soc Nephrol, 2005. **16**(2): p. 459-66.
29. Rule, A.D., et al., *Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease.* Ann Intern Med, 2004. **141**(12): p. 929-37.
30. Levey, A.S., et al., *A new equation to estimate glomerular filtration rate.* Ann Intern Med, 2009. **150**(9): p. 604-12.
31. Pugliese, G., et al., *The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation provides a better definition of cardiovascular burden associated with CKD than the Modification of Diet in Renal Disease (MDRD) Study formula in subjects with type 2 diabetes.* Atherosclerosis, 2011. **218**(1): p. 194-9.
32. Yang, W.C., S.J. Hwang, and N. Taiwan Society of, *Incidence, prevalence and mortality trends of dialysis end-stage renal disease in Taiwan from 1990 to 2001: the impact of national health insurance.* Nephrol Dial Transplant, 2008. **23**(12): p. 3977-82.
33. Hill, N.R., et al., *Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis.* PLoS One, 2016. **11**(7): p. e0158765.
34. Coresh, J., et al., *Prevalence of chronic kidney disease in the United States.*

doi:10.6342/NTU201900529

JAMA, 2007. **298**(17): p. 2038-47.
35. Zhang, Q.L., et al., *Epidemiology of chronic kidney disease: results from a population of older adults in Germany.* Prev Med, 2009. **48**(2): p. 122-7.
36. Gambaro, G., et al., *Prevalence of CKD in northeastern Italy: results of the INCIPE study and comparison with NHANES.* Clin J Am Soc Nephrol, 2010. **5**(11): p. 1946-53.
37. Kim, S., et al., *The prevalence of chronic kidney disease (CKD) and the associated factors to CKD in urban Korea: a population-based cross-sectional epidemiologic study.* J Korean Med Sci, 2009. **24 Suppl**: p. S11-21.
38. Chang, I.H., et al., *Association between metabolic syndrome and chronic kidney disease in the Korean population.* Nephrology (Carlton), 2009. **14**(3): p. 321-6.
39. Teo, B.W., et al., *The choice of estimating equations for glomerular filtration rate significantly affects the prevalence of chronic kidney disease in a multi-ethnic population during health screening.* Nephrology (Carlton), 2009. **14**(6): p. 588-96.
40. Shankar, A., et al., *Association between body mass index and chronic kidney disease in men and women: population-based study of Malay adults in Singapore.* Nephrol Dial Transplant, 2008. **23**(6): p. 1910-8.
41. Chen, J., et al., *Prevalence of decreased kidney function in Chinese adults aged 35 to 74 years.* Kidney Int, 2005. **68**(6): p. 2837-45.
42. Ong-Ajyooth, L., et al., *Prevalence of chronic kidney disease in Thai adults: a national health survey.* BMC Nephrol, 2009. **10**: p. 35.
43. Perkovic, V., et al., *High prevalence of chronic kidney disease in Thailand.* Kidney Int, 2008. **73**(4): p. 473-9.
44. Singh, N.P., et al., *Prevalence of low glomerular filtration rate, proteinuria and associated risk factors in North India using Cockcroft-Gault and Modification of Diet in Renal Disease equation: an observational, cross-sectional study.* BMC Nephrol, 2009. **10**: p. 4.
45. Arora, P., et al., *Prevalence estimates of chronic kidney disease in Canada: results of a nationally representative survey.* CMAJ, 2013. **185**(9): p. E417-23.
46. Najafi, I., et al., *Prevalence of chronic kidney disease and its associated risk factors: the first report from Iran using both microalbuminuria and urine sediment.* Arch Iran Med, 2012. **15**(2): p. 70-5.
47. Cepoi, V., et al., *The prevalence of chronic kidney disease in the general population in Romania: a study on 60,000 persons.* Int Urol Nephrol, 2012. **44**(1): p. 213-20.
48. Gansevoort, R.T., et al., *Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention.* Lancet, 2013. **382**(9889): p. 339-52.
49. Go, A.S., et al., *Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization.* N Engl J Med, 2004. **351**(13): p. 1296-305.
50. Foster, M.C., et al., *Cardiovascular risk factor burden, treatment, and control among adults with chronic kidney disease in the United States.* Am Heart J, 2013. **166**(1): p. 150-6.
51. Saran, R., et al., *US Renal Data System 2017 Annual Data Report: Epidemiology of Kidney Disease in the United States.* Am J Kidney Dis, 2018. **71**(3S1): p. A7.
52. Yang, H.Y., P.C. Chen, and J.D. Wang, *Chinese herbs containing aristolochic acid associated with renal failure and urothelial carcinoma: a review from epidemiologic observations to causal inference.* Biomed Res Int, 2014. **2014**: p.

doi:10.6342/NTU201900529

569325.
53. Leehey, D.J., et al., *Progression of kidney disease in type 2 diabetes - beyond blood pressure control: an observational study.* BMC Nephrol, 2005. **6**: p. 8.
54. Zucchelli, P. and A. Zuccala, *The kidney as a victim of essential hypertension.* J Nephrol, 1997. **10**(4): p. 203-6.
55. Jafar, T.H., et al., *Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease.* Kidney Int, 2001. **60**(3): p. 1131-40.
56. Fried, L.F., T.J. Orchard, and B.L. Kasiske, *Effect of lipid reduction on the progression of renal disease: a meta-analysis.* Kidney Int, 2001. **59**(1): p. 260-9.
57. Rodenbach, K.E., et al., *Hyperuricemia and Progression of CKD in Children and Adolescents: The Chronic Kidney Disease in Children (CKiD) Cohort Study.* Am J Kidney Dis, 2015. **66**(6): p. 984-92.
58. Orth, S.R., E. Ritz, and R.W. Schrier, *The renal risks of smoking.* Kidney Int, 1997. **51**(6): p. 1669-77.
59. Goetz, F.C., et al., *Risk factors for kidney damage in the adult population of Wadena, Minnesota. A prospective study.* Am J Epidemiol, 1997. **145**(2): p. 91-102.
60. Pugh, J.A., et al., *Excess incidence of treatment of end-stage renal disease in Mexican Americans.* Am J Epidemiol, 1988. **127**(1): p. 135-44.
61. McLaughlin, J.K., et al., *Analgesic use and chronic renal failure: a critical review of the epidemiologic literature.* Kidney Int, 1998. **54**(3): p. 679-86.
62. Perneger, T.V., et al., *Risk of end-stage renal disease associated with alcohol consumption.* Am J Epidemiol, 1999. **150**(12): p. 1275-81.
63. Perneger, T.V., P.K. Whelton, and M.J. Klag, *Race and end-stage renal disease. Socioeconomic status and access to health care as mediating factors.* Arch Intern Med, 1995. **155**(11): p. 1201-8.
64. Lackland, D.T., et al., *Low birth weights contribute to high rates of early-onset chronic renal failure in the Southeastern United States.* Arch Intern Med, 2000. **160**(10): p. 1472-6.
65. Prasad, G.V., *Metabolic syndrome and chronic kidney disease: Current status and future directions.* World J Nephrol, 2014. **3**(4): p. 210-9.
66. Echouffo-Tcheugui, J.B. and A.P. Kengne, *Risk models to predict chronic kidney disease and its progression: a systematic review.* PLoS Med, 2012. **9**(11): p. e1001344.
67. Taal, M.W. and B.M. Brenner, *Predicting initiation and progression of chronic kidney disease: Developing renal risk scores.* Kidney Int, 2006. **70**(10): p. 1694-705.
68. Tangri, N., et al., *A predictive model for progression of chronic kidney disease to kidney failure.* JAMA, 2011. **305**(15): p. 1553-9.
69. Johnson, E.S., et al., *Predicting the risk of dialysis and transplant among patients with CKD: a retrospective cohort study.* Am J Kidney Dis, 2008. **52**(4): p. 653-60.
70. Tsai, W.C., et al., *Risk Factors for Development and Progression of Chronic Kidney Disease: A Systematic Review and Exploratory Meta-Analysis.* Medicine (Baltimore), 2016. **95**(11): p. e3013.
71. Ryu, S., et al., *Time-dependent association between metabolic syndrome and risk of CKD in Korean men without hypertension or diabetes.* Am J Kidney Dis, 2009. **53**(1): p. 59-69.
72. O'Seaghdha, C.M., et al., *Lower urinary connective tissue growth factor levels*

doi:10.6342/NTU201900529

and incident CKD stage 3 in the general population. Am J Kidney Dis, 2011. **57**(6): p. 841-9.
73. Shankar, A., R. Klein, and B.E. Klein, *The association among smoking, heavy drinking, and chronic kidney disease.* Am J Epidemiol, 2006. **164**(3): p. 263-71.
74. Bash, L.D., et al., *Inflammation, hemostasis, and the risk of kidney function decline in the Atherosclerosis Risk in Communities (ARIC) Study.* Am J Kidney Dis, 2009. **53**(4): p. 596-605.
75. Chien, K.L., et al., *A prediction model for the risk of incident chronic kidney disease.* Am J Med, 2010. **123**(9): p. 836-846 e2.
76. Shastri, S., et al., *Cystatin C and albuminuria as risk factors for development of CKD stage 3: the Multi-Ethnic Study of Atherosclerosis (MESA).* Am J Kidney Dis, 2011. **57**(6): p. 832-40.
77. Shankar, A., et al., *Markers of inflammation predict the long-term risk of developing chronic kidney disease: a population-based cohort study.* Kidney Int, 2011. **80**(11): p. 1231-8.
78. Regalado, M., S. Yang, and D.E. Wesson, *Cigarette smoking is associated with augmented progression of renal insufficiency in severe essential hypertension.* Am J Kidney Dis, 2000. **35**(4): p. 687-94.
79. Yoshida, T., et al., *Risk factors for progression in patients with early-stage chronic kidney disease in the Japanese population.* Intern Med, 2008. **47**(21): p. 1859-64.
80. Gopinath, B., et al., *A better diet quality is associated with a reduced likelihood of CKD in older adults.* Nutr Metab Cardiovasc Dis, 2013. **23**(10): p. 937-43.
81. Khatri, M., et al., *The association between a Mediterranean-style diet and kidney function in the Northern Manhattan Study cohort.* Clin J Am Soc Nephrol, 2014. **9**(11): p. 1868-75.
82. Lin, J., et al., *Relation of atherogenic lipoproteins with estimated glomerular filtration rate decline: a longitudinal study.* BMC Nephrol, 2015. **16**: p. 130.
83. Bowe, B., et al., *Association between Monocyte Count and Risk of Incident CKD and Progression to ESRD.* Clin J Am Soc Nephrol, 2017. **12**(4): p. 603-613.
84. Park, H., et al., *Chronic hepatitis C virus (HCV) increases the risk of chronic kidney disease (CKD) while effective HCV treatment decreases the incidence of CKD.* Hepatology, 2017.
85. Si, J., et al., *Chronic hepatitis B virus infection and risk of chronic kidney disease: a population-based prospective cohort study of 0.5 million Chinese adults.* BMC Med, 2018. **16**(1): p. 93.
86. Chonchol, M., et al., *Fibroblast Growth Factor 23 and Kidney Disease Progression in Autosomal Dominant Polycystic Kidney Disease.* Clin J Am Soc Nephrol, 2017. **12**(9): p. 1461-1469.
87. Baek, S.D., et al., *Does stage III chronic kidney disease always progress to end-stage renal disease? A ten-year follow-up study.* Scand J Urol Nephrol, 2012. **46**(3): p. 232-8.
88. Cheng, H.T., et al., *Metabolic syndrome and insulin resistance as risk factors for development of chronic kidney disease and rapid decline in renal function in elderly.* J Clin Endocrinol Metab, 2012. **97**(4): p. 1268-76.
89. Ishizuka, T., et al., *Relationship between kidney function decline and initial risk factors for the progression of diabetic kidney disease: a retrospective analysis of 91 Japanese patients with type 2 diabetes.* Diabetol Int, 2016. **7**(4): p. 432-439.
90. Locatelli, F., et al., *Proteinuria and blood pressure as causal components of*

doi:10.6342/NTU201900529

progression to end-stage renal failure. Northern Italian Cooperative Study Group. Nephrol Dial Transplant, 1996. **11**(3): p. 461-7.
91. Hunsicker, L.G., et al., *Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study.* Kidney Int, 1997. **51**(6): p. 1908-19.
92. Boaz, M., et al., *Patterns of dietary intake and serum lipids interact with proteinuria as risk factors for progression of chronic renal failure.* Ren Fail, 1998. **20**(2): p. 383-90.
93. Evans, M., et al., *The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden.* Am J Kidney Dis, 2005. **46**(5): p. 863-70.
94. Levin, A., et al., *Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort.* Am J Kidney Dis, 2008. **52**(4): p. 661-71.
95. Hoefield, R.A., et al., *Factors associated with kidney disease progression and mortality in a referred CKD population.* Am J Kidney Dis, 2010. **56**(6): p. 1072-81.
96. De Nicola, L., et al., *Prognosis of CKD patients receiving outpatient nephrology care in Italy.* Clin J Am Soc Nephrol, 2011. **6**(10): p. 2421-8.
97. Khedr, A., E. Khedr, and A.A. House, *Body mass index and the risk of progression of chronic kidney disease.* J Ren Nutr, 2011. **21**(6): p. 455-61.
98. Pereira, A.C., et al., *Association between laboratory and clinical risk factors and progression of the predialytic chronic kidney disease.* J Bras Nefrol, 2012. **34**(1): p. 68-75.
99. Obi, Y., et al., *Impact of age and overt proteinuria on outcomes of stage 3 to 5 chronic kidney disease in a referred cohort.* Clin J Am Soc Nephrol, 2010. **5**(9): p. 1558-65.
100. Agarwal, R., *Blood pressure components and the risk for end-stage renal disease and death in chronic kidney disease.* Clin J Am Soc Nephrol, 2009. **4**(4): p. 830-7.
101. Kuo, H.W., et al., *Analgesic use and the risk for progression of chronic kidney disease.* Pharmacoepidemiol Drug Saf, 2010. **19**(7): p. 745-51.
102. Sugiura, T. and A. Wada, *Resistive index predicts renal prognosis in chronic kidney disease: results of a 4-year follow-up.* Clin Exp Nephrol, 2011. **15**(1): p. 114-20.
103. Wu, I.W., et al., *p-Cresyl sulphate and indoxyl sulphate predict progression of chronic kidney disease.* Nephrol Dial Transplant, 2011. **26**(3): p. 938-47.
104. Rahman, M., et al., *Association between chronic kidney disease progression and cardiovascular disease: results from the CRIC Study.* Am J Nephrol, 2014. **40**(5): p. 399-407.
105. Yonemoto, S., et al., *Red cell distribution width and renal outcome in patients with non-dialysis-dependent chronic kidney disease.* PLoS One, 2018. **13**(6): p. e0198825.
106. Tsai, C.W., et al., *Longitudinal change in estimated GFR among CKD patients: A 10-year follow-up study of an integrated kidney disease care program in Taiwan.* PLoS One, 2017. **12**(4): p. e0173843.
107. Gooch, K., et al., *NSAID use and progression of chronic kidney disease.* Am J Med, 2007. **120**(3): p. 280 e1-7.
108. Hemmelgarn, B.R., B.F. Culleton, and W.A. Ghali, *Derivation and validation of*

doi:10.6342/NTU201900529

a clinical index for prediction of rapid progression of kidney dysfunction. QJM, 2007. **100**(2): p. 87-92.
109. Imai, E., et al., *Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study.* Hypertens Res, 2008. **31**(3): p. 433-41.
110. Agarwal, R. and R.P. Light, *Patterns and prognostic value of total and differential leukocyte count in chronic kidney disease.* Clin J Am Soc Nephrol, 2011. **6**(6): p. 1393-9.
111. Hallan, S.I., et al., *Combining GFR and albuminuria to classify CKD improves prediction of ESRD.* J Am Soc Nephrol, 2009. **20**(5): p. 1069-77.
112. Ozsoy, R.C., et al., *Dyslipidaemia as predictor of progressive renal failure and the impact of treatment with atorvastatin.* Nephrol Dial Transplant, 2007. **22**(6): p. 1578-86.
113. Ravani, P., et al., *Asymmetrical dimethylarginine predicts progression to dialysis and death in patients with chronic kidney disease: a competing risks modeling approach.* J Am Soc Nephrol, 2005. **16**(8): p. 2449-55.
114. Bolignano, D., et al., *Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease.* Clin J Am Soc Nephrol, 2009. **4**(2): p. 337-44.
115. Yuste, C., et al., *Factors related with the progression of chronic kidney disease.* Nefrologia, 2013. **33**(5): p. 685-91.
116. Ricardo, A.C., et al., *The Association of Sleep Duration and Quality with CKD Progression.* J Am Soc Nephrol, 2017. **28**(12): p. 3708-3715.
117. Wu, C., et al., *Association of high body mass index with development of interstitial fibrosis in patients with IgA nephropathy.* BMC Nephrol, 2018. **19**(1): p. 381.
118. Hunter, D.J. and K.S. Reddy, *Noncommunicable diseases.* N Engl J Med, 2013. **369**(14): p. 1336-43.
119. Meira-Machado, L., et al., *Multi-state models for the analysis of time-to-event data.* Stat Methods Med Res, 2009. **18**(2): p. 195-222.
120. Touraine, C., C. Helmer, and P. Joly, *Predictions in an illness-death model.* Stat Methods Med Res, 2016. **25**(4): p. 1452-70.
121. Andersen, P.K., S.Z. Abildstrom, and S. Rosthoj, *Competing risks as a multi-state model.* Stat Methods Med Res, 2002. **11**(2): p. 203-15.
122. Combescure, C., et al., *Assessment of variations in control of asthma over time.* Eur Respir J, 2003. **22**(2): p. 298-304.
123. Alioum, A., et al., *Effect of gender, age, transmission category, and antiretroviral therapy on the progression of human immunodeficiency virus infection using multistate Markov models. Groupe d'Epidemiologie Clinique du SIDA en Aquitaine.* Epidemiology, 1998. **9**(6): p. 605-12.
124. Day, N.E. and S.D. Walter, *Simplified models of screening for chronic disease: estimation procedures from mass screening programmes.* Biometrics, 1984. **40**(1): p. 1-14.
125. Kuo, H.S., et al., *A Markov chain model to assess the efficacy of screening for non-insulin dependent diabetes mellitus (NIDDM).* Int J Epidemiol, 1999. **28**(2): p. 233-40.
126. Hui-Min, W., Y. Ming-Fang, and T.H. Chen, *SAS macro program for non-homogeneous Markov process in modeling multi-state disease progression.* Comput Methods Programs Biomed, 2004. **75**(2): p. 95-105.

doi:10.6342/NTU201900529

127. Duffy, S.W., et al., *Estimation of mean sojourn time in breast cancer screening using a Markov chain model of both entry to and exit from the preclinical detectable phase.* Stat Med, 1995. **14**(14): p. 1531-43.
128. Hung, H.F. and T.H. Chen, *Probabilistic cost-effectiveness analysis of the long-term effect of universal hepatitis B vaccination: an experience from Taiwan with high hepatitis B virus infection and Hepatitis B e Antigen positive prevalence.* Vaccine, 2009. **27**(48): p. 6770-6.
129. Yang, K.C. and H.H. Chen, *Probabilistic Cost-Effectiveness Analysis of Vaccination for Mild or Moderate Alzheimer's Disease.* Curr Alzheimer Res, 2016. **13**(7): p. 809-16.
130. Begun, A., et al., *Identification of a multistate continuous-time nonhomogeneous Markov chain model for patients with decreased renal function.* Med Decis Making, 2013. **33**(2): p. 298-306.
131. Abner, E.L., R.J. Charnigo, and R.J. Kryscio, *Markov chains and semi-Markov models in time-to-event analysis.* J Biom Biostat, 2013. **Suppl 1**(e001): p. 19522.
132. Chen, X., J. Ding, and L. Sun, *A semiparametric additive rate model for a modulated renewal process.* Lifetime Data Anal, 2017.
133. Foucher, Y., et al., *A semi-Markov model for multistate and interval-censored data with multiple terminal events. Application in renal transplantation.* Stat Med, 2007. **26**(30): p. 5381-93.
134. Chen, T.H., et al., *Community-based multiple screening model: design, implementation, and analysis of 42,387 participants.* Cancer, 2004. **100**(8): p. 1734-43.
135. Chiu, Y.H., et al., *Progression of pre-hypertension, stage 1 and 2 hypertension (JNC 7): a population-based study in Keelung, Taiwan (Keelung Community-based Integrated Screening No. 9).* J Hypertens, 2006. **24**(5): p. 821-8.
136. Levey, A.S., et al., *A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group.* Ann Intern Med, 1999. **130**(6): p. 461-70.
137. Agarwal, I., et al., *Quantitation of proteinuria by spot urine sampling.* Indian J Clin Biochem, 2004. **19**(2): p. 45-7.
138. Levey, A.S., et al., *Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO).* Kidney Int, 2005. **67**(6): p. 2089-100.
139. Levey, A.S., et al., *National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification.* Ann Intern Med, 2003. **139**(2): p. 137-47.
140. Reaven, G.M., *Banting lecture 1988. Role of insulin resistance in human disease.* Diabetes, 1988. **37**(12): p. 1595-607.
141. Eckel, R.H., S.M. Grundy, and P.Z. Zimmet, *The metabolic syndrome.* Lancet, 2005. **365**(9468): p. 1415-28.
142. Expert Panel on Detection, E. and A. Treatment of High Blood Cholesterol in, *Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III).* JAMA, 2001. **285**(19): p. 2486-97.
143. Arenillas, J.F., M.A. Moro, and A. Davalos, *The metabolic syndrome and stroke:*

doi:10.6342/NTU201900529

potential treatment approaches. Stroke, 2007. **38**(7): p. 2196-203.
144. Kassi, E., et al., *Metabolic syndrome: definitions and controversies.* BMC Med, 2011. **9**: p. 48.
145. Cameron, A.J., J.E. Shaw, and P.Z. Zimmet, *The metabolic syndrome: prevalence in worldwide populations.* Endocrinol Metab Clin North Am, 2004. **33**(2): p. 351-75, table of contents.
146. Kaneko, K., et al., *Obesity and the kidney.* J Pediatr, 2010. **156**(2): p. 342-3.
147. Axelsson, J., *Obesity in chronic kidney disease: good or bad?* Blood Purif, 2008. **26**(1): p. 23-9.
148. Rea, D.J., et al., *Glomerular volume and renal histology in obese and non-obese living kidney donors.* Kidney Int, 2006. **70**(9): p. 1636-41.
149. Kurella, M., J.C. Lo, and G.M. Chertow, *Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults.* J Am Soc Nephrol, 2005. **16**(7): p. 2134-40.
150. Kanauchi, M., et al., *Associations of chronic kidney disease with the metabolic syndrome in non-diabetic elderly.* Nephrol Dial Transplant, 2006. **21**(12): p. 3608-9.
151. Ding, C., et al., *The associations of metabolic syndrome with incident hypertension, type 2 diabetes mellitus and chronic kidney disease: a cohort study.* Endocrine, 2018. **60**(2): p. 282-291.
152. Thomas, G., et al., *Metabolic syndrome and kidney disease: a systematic review and meta-analysis.* Clin J Am Soc Nephrol, 2011. **6**(10): p. 2364-73.
153. Wang, S.J., et al., *Parametric survival models for predicting the benefit of adjuvant chemoradiotherapy in gallbladder cancer.* AMIA Annu Symp Proc, 2010. **2010**: p. 847-51.
154. Zhang, Z. and J. Sun, *Interval censoring.* Stat Methods Med Res, 2010. **19**(1): p. 53-70.
155. Cox, D.M., HD, *The theory of stochastic processes.* Chapman & Hall, 1965.
156. Eknoyan, G., et al., *The burden of kidney disease: improving global outcomes.* Kidney Int, 2004. **66**(4): p. 1310-4.
157. Fox, C.S., et al., *Predictors of new-onset kidney disease in a community-based population.* JAMA, 2004. **291**(7): p. 844-50.
158. Drey, N., et al., *A population-based study of the incidence and outcomes of diagnosed chronic kidney disease.* Am J Kidney Dis, 2003. **42**(4): p. 677-84.
159. Tohidi, M., et al., *Incidence of chronic kidney disease and its risk factors, results of over 10 year follow up in an Iranian cohort.* PLoS One, 2012. **7**(9): p. e45304.
160. Yamagata, K., et al., *Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study.* Kidney Int, 2007. **71**(2): p. 159-66.
161. Johnson, E.S., et al., *Predicting renal replacement therapy and mortality in CKD.* Am J Kidney Dis, 2007. **50**(4): p. 559-65.
162. Ku, E., K.L. Johansen, and C.E. McCulloch, *Time-Centered Approach to Understanding Risk Factors for the Progression of CKD.* Clin J Am Soc Nephrol, 2018. **13**(5): p. 693-701.
163. Kelly, T.N., et al., *The role of renin-angiotensin-aldosterone system genes in the progression of chronic kidney disease: findings from the Chronic Renal Insufficiency Cohort (CRIC) study.* Nephrol Dial Transplant, 2015. **30**(10): p. 1711-8.

doi:10.6342/NTU201900529

164. Siragy, H.M. and R.M. Carey, *Role of the intrarenal renin-angiotensin-aldosterone system in chronic kidney disease.* Am J Nephrol, 2010. **31**(6): p. 541-50.
165. Carrero, J.J., et al., *Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease.* Nat Rev Nephrol, 2018. **14**(3): p. 151-164.
166. Ji, H., et al., *Sex differences in renal injury and nitric oxide production in renal wrap hypertension.* Am J Physiol Heart Circ Physiol, 2005. **288**(1): p. H43-7.
167. Luksha, L., et al., *Mechanisms of endothelial dysfunction in resistance arteries from patients with end-stage renal disease.* PLoS One, 2012. **7**(4): p. e36056.
168. Elliot, S.J., et al., *Gender-specific effects of endogenous testosterone: female alpha-estrogen receptor-deficient C57Bl/6J mice develop glomerulosclerosis.* Kidney Int, 2007. **72**(4): p. 464-72.
169. Pscheidt, C., et al., *Sex- and Time-Dependent Patterns in Risk Factors of End-Stage Renal Disease: A Large Austrian Cohort with up to 20 Years of Follow-Up.* PLoS One, 2015. **10**(8): p. e0135052.
170. Fioretto, P., et al., *Renal protection in diabetes: role of glycemic control.* J Am Soc Nephrol, 2006. **17**(4 Suppl 2): p. S86-9.
171. Ruster, C. and G. Wolf, *Renin-angiotensin-aldosterone system and progression of renal disease.* J Am Soc Nephrol, 2006. **17**(11): p. 2985-91.
172. Harper, C.R. and T.A. Jacobson, *Managing dyslipidemia in chronic kidney disease.* J Am Coll Cardiol, 2008. **51**(25): p. 2375-84.
173. Lucove, J., et al., *Metabolic syndrome and the development of CKD in American Indians: the Strong Heart Study.* Am J Kidney Dis, 2008. **51**(1): p. 21-8.
174. Iseki, K., *The okinawa screening program.* J Am Soc Nephrol, 2003. **14**(7 Suppl 2): p. S127-30.
175. Uc, A., et al., *Chronic Pancreatitis in the 21st Century - Research Challenges and Opportunities: Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop.* Pancreas, 2016. **45**(10): p. 1365-1375.
176. Garg, A.X., et al., *Estimating the prevalence of renal insufficiency in seniors requiring long-term care.* Kidney Int, 2004. **65**(2): p. 649-53.
177. Wu, H.Y., et al., *Diagnostic performance of random urine samples using albumin concentration vs ratio of albumin to creatinine for microalbuminuria screening in patients with diabetes mellitus: a systematic review and meta-analysis.* JAMA Intern Med, 2014. **174**(7): p. 1108-15.
178. Siu, Y.P., et al., *Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level.* Am J Kidney Dis, 2006. **47**(1): p. 51-9.
179. Lanaspa, M.A., et al., *Endogenous fructose production and fructokinase activation mediate renal injury in diabetic nephropathy.* J Am Soc Nephrol, 2014. **25**(11): p. 2526-38.
180. Iseki, K., et al., *Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects.* Hypertens Res, 2001. **24**(6): p. 691-7.
181. Weiner, D.E., et al., *Uric acid and incident kidney disease in the community.* J Am Soc Nephrol, 2008. **19**(6): p. 1204-11.
182. Babitt, J.L. and H.Y. Lin, *Mechanisms of anemia in CKD.* J Am Soc Nephrol, 2012. **23**(10): p. 1631-4.
183. Ricardo, A.C., et al., *Healthy lifestyle and risk of kidney disease progression, atherosclerotic events, and death in CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study.* Am J Kidney Dis, 2015. **65**(3): p. 412-24.

doi:10.6342/NTU201900529

184. Hsu, T.W., et al., *Renoprotective effect of renin-angiotensin-aldosterone system blockade in patients with predialysis advanced chronic kidney disease, hypertension, and anemia.* JAMA Intern Med, 2014. **174**(3): p. 347-54.
185. Leporini, C., et al., *Effect of pentoxifylline on renal outcomes in chronic kidney disease patients: A systematic review and meta-analysis.* Pharmacol Res, 2016. **107**: p. 315-332.
186. Mahmoud, N.A.M.R., *A Stochastic Model for the Progression of Chronic Kidney Disease.* Journal of Engineering Research and Applications, 2014. **vol. 4**(11): p. 08-19.
187. Davies, D.F. and N.W. Shock, *Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males.* J Clin Invest, 1950. **29**(5): p. 496-507.
188. Glassock, R.J. and C. Winearls, *Ageing and the glomerular filtration rate: truths and consequences.* Trans Am Clin Climatol Assoc, 2009. **120**: p. 419-28.
189. Hahr, A.J. and M.E. Molitch, *Management of diabetes mellitus in patients with chronic kidney disease.* Clin Diabetes Endocrinol, 2015. **1**: p. 2.
190. Olson, J.L. and R.H. Heptinstall, *Nonimmunologic mechanisms of glomerular injury.* Lab Invest, 1988. **59**(5): p. 564-78.
191. Epidemiology & Disease Control Division, M.o.H., Singapore., *National Health Survey 2010.* MOH Singapore, 2011), 2011.
192. Nagata, M., et al., *Trends in the prevalence of chronic kidney disease and its risk factors in a general Japanese population: the Hisayama Study.* Nephrol Dial Transplant, 2010. **25**(8): p. 2557-64.
193. Kaplan, R.M., D.A. Chambers, and R.E. Glasgow, *Big data and large sample size: a cautionary note on the potential for bias.* Clin Transl Sci, 2014. **7**(4): p. 342-6.
194. Liu, Y.M., et al., *Individual risk prediction model for incident cardiovascular disease: a Bayesian clinical reasoning approach.* Int J Cardiol, 2013. **167**(5): p. 2008-12.

doi:10.6342/NTU201900529

Appendix

The SAS code for the estimation of parameters in the 5–state CKD Markov model.

```
/*Markov estimate*/

data markov;
      set CKDdata;
      where transition in (10, 20, 30, 11, 12, 13, 14, 15, 21, 22, 23, 24, 25, 33, 34, 35,
      45,140, 240, 340, 450);
run;

data a1;
      set markov;
      tt=round(tratime);
      if tt=0 then tt=0.5;
run;

proc freq data=a1;
      table tt*transition/out=model noprint;
run;


proc iml;
      use model;
      read all var{transition} into mode;
      read all var{count} into num;
      read all var{tt} into tt;
      m=nrow(mode);

      start pmtrx(h,t);
      Q=J(5,5,0);
      Q[1,1]=-(h[1]+h[4]);
      Q[1,2]=h[1];
      Q[1,5]=h[4];
      Q[2,2]=-(h[2]+h[5]);
      Q[2,3]=h[2];
      Q[2,5]=h[5];
      Q[3,4]=h[3];
      Q[3,5]=h[6];
      Q[3,3]=-(h[3]+h[6]);
      Q[4,4]=-h[7];
      Q[4,5]=h[7];


      A=teigvec(Q);
      v=teigval(Q);
      D=diag(exp(v[,1]#t));
```


doi:10.6342/NTU201900529

```
PP=A*D*inv(A);
return(PP);
finish pmtrx;


start f_logL(h) global(mode, m, num, tt);
sum=0;
do i=1 to m;

P=pmtrx(h,tt[i]);
value=0;

if mode[i]=10 then    value=P[1,1]/(P[1,1]+P[1,2]+P[1,3]);
if mode[i]=20 then    value=P[1,2]/(P[1,1]+P[1,2]+P[1,3]);
if mode[i]=30 then    value=P[1,3]/(P[1,1]+P[1,2]+P[1,3]);
if mode[i]=11 then    value=P[1,1];
if mode[i]=12      then value= P[1,2];
if mode[i]=13      then value= P[1,3];
if mode[i]=14      then value= P[1,3]*h[3];
if mode[i]=15      then value= P[1,1]*h[4]+P[1,2]*h[5]+P[1,3]*h[6];
if mode[i]=22      then value= P[2,2];
if mode[i]=21      then value= P[2,2];
if mode[i]=23      then value= P[2,3];
if mode[i]=24      then value= P[2,3]*h[3];
if mode[i]=25      then value= P[2,2]*h[5]+P[2,3]*h[6];
if mode[i]=32      then value= P[3,3];
if mode[i]=33      then value= P[3,3];
if mode[i]=34      then value= P[3,3]*h[3];
if mode[i]=35      then value= P[3,3]*h[6];
if mode[i]=45      then value= P[4,4]*h[7];
if mode[i]=140     then value= 1-P[1,4];
if mode[i]=240     then value= 1-P[2,4];
if mode[i]=340     then value= 1-P[3,4];
if mode[i]=450     then value= 1-P[4,5];


if value>0 then sum=sum+ num[i]*log(value);
else return(.);
end;
return (sum);
finish f_logL;

h0 ={ 0.012   0.002   0.001   0.001   0.001   0.001   0.001 };
con={ 1.e-5   1.e-5   1.e-5    1.e-5    1.e-5   1.e-5   1.e-5 ,
          .     .     .     .     .     .     . };
test=f_logL(h0);
print test;

optn={1 2};
```


doi:10.6342/NTU201900529

```
        call nlpnra(rc,xres,"f_logL",h0,optn,con);
        estimate=xres`;
        call nlpfdd(f,g,hes2,"f_logL",estimate);
        cov=-inv(hes2);
        print "Variance-Covariance Matrix";
        print cov;
        prob=.05;
        norqua=probit(1-prob/2);
        stderr=sqrt(vecdiag(cov));
        lowbound=estimate-norqua*stderr;
        upbound=estimate+norqua*stderr;
        print "Asymptotic 95% Confidence Interval";
        print lowbound estimate upbound stderr;
        print rc;
quit;
run;
```


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