BMJ Open

Effect of Early Chronic Kidney Disease Care Program on Kidney Function Deterioration in Patients With Stage I–IIIa Chronic Kidney Disease

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-041210
Article Type:	Original research
Date Submitted by the Author:	06-Jun-2020
Complete List of Authors:	Niu, Shu-Fen; Shin Kong Wu Ho Su Memorial Hospital, Department of Nursing Wu, Chung-Kuan; Shin-Kong Wu Ho-Su Memorial Hospital, Division of Nephrology,Department of Internal Medicine Chuang, Nai-Chen; Taipei Medical University, Clinical Data Center, Office of Data Science Yang, Ya-Bei; Shin Kong Wu Ho Su Memorial Hospital, Division of Cardiovascular Surgery Chang, Tzu-Hao; Taipei Medical University Hospital, Clinical Big Data Research Center
Keywords:	Chronic renal failure < NEPHROLOGY, Nephrology < INTERNAL MEDICINE, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Effect of Early Chronic Kidney Disease Care Program on Kidney Function Deterioration in Patients With Stage I–IIIa Chronic Kidney Disease

Shu-Fen Niu[1,2,3], Chung-Kuan Wu[4,5], Nai-Chen Chuang[6], Ya-Bei Yang[7], Tzu-Hao Chang[8,9]

Reprints and correspondence:

Address to Chung-Kuan Wu, MD, PhD

Division of Nephrology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

No.95, Wenchang Rd., Shilin Dist., Taipei City 11101, Taiwan

Tel: +886-2-2833-2211 ext. 2385 Fax: +886-28389491

E-mail: m008533@ms.skh.org.tw

Or

Tzu-Hao Chang, PhD

Clinical Big Data Research Center, Taipei Medical University Hospital, Taipei, Taiwan

No.250, Wu-Hsing st., Xinyi Dist., Taipei City 11031, Taiwan

Tel: 886-2-6638-2736 #1508 Fax: +886-2-66380233

E-mail: kevinchang@tmu.edu.tw

ABSTRACT

Objectives: To investigate the effect of the Early CKD Care Program on CKD progression in patients with CKD stage I–IIIa

Design: Observational cohort study

Setting: The institutional and clinical research database of Taipei Medical University from three affiliated hospitals.

Participants: Adult nonpregnant patients with CKD stage I–IIIa from the institutional and clinical research database of Taipei Medical University between January 1, 2012 and August 31, 2017 were recruited. These patients were divided into Early CKD Care Program participants (case) and nonparticipants (control). 1:2 propensity score matching for age, sex, estimated glomerular filtration rate, and CKD stage was performed to reduce bias between two groups.

Outcome measures: The risks of CKD stage I–IIIa progression to IIIb between Early CKD Care Program participants and nonparticipants.

Results: Compared with the control group, the case group demonstrated more comorbidities and higher proportions of hypertension, diabetes mellitus, gout, dyslipidemia, heart disease, and cerebrovascular disease, but had lower risk of progression to CKD stage IIIb before and (HR, 0.72; 95% CI, 0.61–0.85) and after (aHR, 0.67; 95% CI, 0.55–0.81) adjustments. Moreover, Kaplan–Meier analysis

revealed the cumulative incidence of CKD stage IIIb was significantly lower in the case group than in the control group. Finally, the program was an independent protective factor against progression to stage IIIb, especially in patients with CKD stage IIIa before (HR, 0.72; 95% CI, 0.61–0.85) and after (aHR, 0.67; 95% CI, 0.55–0.81) adjustments.

Conclusions: The Early CKD Care Program is an independent protective factor against progression of early CKD.

Strengths and limitations of this study

- The study provides the information on the preventive effect of the Early CKD Care Program on CKD progression
- The patients in our study were recruited from the greater Taipei area, which might not be representative of all clinical situations in Taiwan because of the urban–rural medical disparity
- Selection bias should be considered for participants owing to their motivation and role of medical personnel
- The clinical outcome focus on the progression of early CKD, rather than major adverse cardiac events or mortality

Introduction

Chronic kidney disease (CKD) is recognized as a global health concern[1] because its overall prevalence in the general population is more than 10%. CKD prevalence ranged from 11.7% to 15.1%, with stages I-V accounting for 2.8%–4.2%, 2.7%–5.3%, 6.4%–8.9%, 0.3%–0.5%, and 0.1%, respectively. Therefore, most patients with CKD are in the early stages,[2] in which they may have no symptoms or signs.[3] Such early disease stages are not easily discovered and diagnosed by primary care physicians; therefore, most patients had not consulted a nephrologist, with fewer than 6% of the patients had consulting a nephrologist even for stage III CKD.[4] Without appropriate response or management of early CKD, it progresses to advanced CKD and finally to end-stage renal disease (ESRD), which usually requires management with dialysis. Therefore, exponential growth in medical costs[5] is expected. Despite treatment, patients with ESRD have poor quality of life and high mortality risk.[6]

In CKD stages I-II, an optimal outcome can be achieved with adequate assessment, diagnosis, and treatment.[4] The US Centers for Disease Control and Prevention recommends that early CKD progression prevention should include testing for and controlling CKD risk factors as well as maintaining a healthy weight through a balanced diet and physical exercise.[7] Moreover, early monitoring and treatment in conjunction with lifestyle adjustments can improve the revisit rate of patients with

CKD and delay renal function reduction.[8]

In Taiwan, more than 85,000 patients require dialysis and the related National Health Insurance (NHI) expenditure reached NT$44.9 billion in 2017. To reduce kidney function deterioration, improve the quality of life, reduce the burden on the NHI program, and achieve the goal of prioritizing prevention over management, Taiwan's Ministry of Health and Welfare launched the Early CKD Care Program aimed at active management of stage I–IIIa CKD.[9,10] However, the effectiveness of intervention in delaying kidney function deterioration warrants exploration. Therefore, this study explored the effects of an intervention-based Early CKD Care Program in reducing kidney function deterioration in patients with stage I–IIIa CKD.

Materials and Methods

Data Source.

This cohort study obtained information on patients with CKD stages I-IIIa in the institutional and clinical research database of Taipei Medical University (CRDB). This database contains the electronic health and medical records of more than 3 million patients from three affiliated hospitals, namely Taipei Medical University Hospital (TMUH), Wan Fang Hospital (WFH), and Shuang Ho Hospital (SHH). This study was exempted from a full review and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB-201803022).

Study Design and Cohort.

Figure 1 illustrates the patient selection process for the study cohort. From the CRDB, we identified patients with CKD who had more than two medical return visits between January 1, 2012, and August 31, 2017. We enrolled those who met the following criteria of CKD stages I-IIIa: patients with normal renal function but who present signs of kidney damage such as proteinuria, hematuria, and other conditions with eGFR ≥ 90 mL/min/1.73 m2; patients with kidney damage with eGFR 60–89.9 mL/min/1.73 m2; and patients with eGFR 45–59.9 mL/min/1.73 m2, respectively. We excluded patients aged < 18 years and those who were pregnant. The remaining patients were divided into the case group, those who participated in the Early CKD Care Program with P4301C, P4302C, or P403603C treatment codes, and the control group, consisting of those who did not participate in the Early CKD Care Program.

Outcome Measures and Comorbidity.

Major comorbidities diagnosed before the index date, according to claims data, were defined as baseline comorbidities. The comorbidities were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for hypertension, DM, gout, hyperlipidemia, heart disease, and cerebrovascular disease, as shown in Supplementary Table S1. Other baseline demographic data included age, sex, eGFR, CKD stage, and number of comorbidities.

Here, the eGFR was calculated as 186 × creatinine−1.154 × age−0.203 (× 0.742 for female), and the number of comorbidities was defined as the sum of the aforementioned comorbidities in the year prior to the enrollment date. The outcome of the study was patient progression to CKD stage IIIb during the study period.

The Early CKD Care Program.

The Bureau of NHI in Taiwan launched the Early CKD Care Program in 2011. Patients who participated in the program constitute this study's case group. The program involved (i) referral to a nephrologist and provision of medication for hypertension, diabetes, and hyperlipidemia to delay kidney function deterioration, avoid damage caused by improper medication, and prevent complications; (ii) CKD case managers enrolled these patients and provided nursing education and lifestyle consultations and routinely monitored disease progress and conducted renal function tests, urinalysis, and urine albumin–creatinine or protein–creatinine ratio evaluations. The CKD case managers informed the doctors and patients' families regarding medical practice and care-giving. The nursing education provided during the enrollment period included the following: (i) teaching the basic structure and functions of kidneys; (ii) introducing the common symptoms of kidney conditions as well as the examination values; (iii) explaining daily care and prevention of kidney conditions; (iv) communicating the importance of routine monitoring; (v)

communicating the importance of consulting a doctor before using medication; (vi) introducing kidney needle biopsy; (vii) introducing hyperlipidemia, hypertension, DM, kidney conditions, and their complications; and (viii) explaining dietary instructions. Lifestyle recommendations included the following: smoking cessation; weight loss, particularly for those with BMI > 25 kg/m2 or men and women with a waist circumference of >90 and >80 cm, respectively; daily protein intake < 1.5 gm/kg; prevention of routine or excessive alcohol consumption; adequate exercise; and daily salt intake < 100 mEq. Routine physical examinations were conducted at least once every 6 months for CKD stages I-IIIa, and urine protein, urine creatinine, serum creatinine, LDL, and HbA1c were tested. The control group received routine care and was not enrolled or monitored by CKD case managers.

Statistical Analysis.

Descriptive statistics were used to summarize the demographic data. Continuous variables are presented as mean and standard deviation, and categorical variables are presented as the number of enrollees and percentage (%). Propensity score matching (PSM) was used to reduce bias from age, sex, eGFR, and CKD stage. Before PSM, we used Student's t test to assess age and eGFR; and the chi-squared test or Fisher's exact test were used for sex, CKD stage, number of comorbidities, hypertension, DM, gout, heart disease, hyperlipidemia, and cerebrovascular disease. After PSM, we

evaluated the differences between matched pairs using the signed rank test for continuous data and McNemar's test for binary data. Cox proportional hazards regression was used to determine the risk factors for patients progressing to CKD stage IIIb by including all the candidate variables in the model. Subgroup analysis was used to determine the risk factors for patients progressing to CKD stage IIIb from baseline CKD stage IIIa or the stages before it. A two-sided statistical test at 5% significance was used. Analyses were performed using SAS (version 7.11; SAS Institute, Cary, NC, USA).

Patient and public involvement.

The study used de-identified data from the institutional and clinical research database of Taipei Medical University (CRDB). No patients were involved in developing the research question or in determining the outcome measures. Patients were not involved in designing the study. There are no plans to disseminate the results of this study to any participants.

Results

Study Population Characteristics

Table 1 presents the characteristics of the study population. Before PSM, a total of 159,774 patients with stage I–IIIa CKD were enrolled from the participating hospitals, including 1,038 in the case group and 158,736 in the control group. All the variables

were significantly different between the two groups (all $P < 0.001$). Age was significantly higher in the case group than in the control group. By contrast, eGFR was significantly lower in the case group than that in the control group. The proportions of sex, CKD stage IIIa, hypertension, DM, gout, hyperlipidemia, heart disease, cerebrovascular disease, and proportion of number of comorbidity were significantly higher in the case group than in the control group. To reduce bias, 1:2 PSM was used to match the age, sex, eGFR, and CKD stage. After PSM, 3,114 patients with stage I–IIIa CKD from the participating hospitals during the study period were finally enrolled in the study, including 1,038 in the case group and 2,076 in the control group. The proportion of hypertension, DM, gout, heart disease, hyperlipidemia, cerebrovascular disease, and proportion of number of comorbidity remained significantly higher in the case group than in the control group (all $P <$ 0.001)

Association of Early CKD Care Program and Risk Factors with Early CKD Progression

Table 2 lists the crude hazard ratios (HRs) and adjusted HRs (aHRs) of all variables for stage I–IIIa CKD that progressed to CKD stage IIIb during the study period. Compared with patients in the control group, the HR for progression to CKD stage IIIb was 0.72 (95% confidence interval [CI], 0.61–0.85; $P< 0.001$) for those

participating in the Early CKD Care Program. After adjustments for the variables listed in Table 1, those in the control group still exhibited significant risk for progression to CKD stage IIIb (aHR, 0.67; 95% CI, 0.55–0.51; $P< 0.001$). In addition, DM, heart disease, or cerebrovascular disease in patients with stage I–IIIa CKD were significant risk factors for progression to CKD stage IIIb (HR, 1.30; 95% CI, 1.07–1.58; $P= 0.0075$ and aHR, 1.72; 95% CI, 1.23–2.41; $P= 0.0015$ for DM; HR, 1.29; 95% CI, 1.06–1.58; $P= 0.0132$ and aHR, 1.70; 95% CI, 1.20–2.40; $P= 0.0027$ for heart disease; and HR, 1.36; 95% CI, 1.04–1.78; $P= 0.0270$ and aHR, 1.59; 95% CI, 1.12–2.27; $P= 0.0104$ for cerebrovascular disease). The Kaplan–Meier curves for the cumulative incidence of progression to CKD stage IIIb was significantly higher in patients with stage I–IIIa CKD who did not participate in the Early CKD Care Program (control group) than the curves in those who participated in the program (case group) during the follow-up period (log-rank test, $P= 0.0025$; Figure 2). The median follow-up duration was 3.0 (1.0–4.7) years. Deterioration to CKD stage IIIb within 1, 3, and 5 years was respectively noted 374, 563, and 644 patients in the control group and 140, 217, and 234 patients in the case group.

Effect of Early CKD Care Program and Risk Factors on Different Early CKD Stages.

Of the 3114 patients with stage I–IIIa CKD in this study, 1,382 patients with CKD stages I–II and the remaining 1,732 patients were in stage IIIa. Table 3 lists the crude

HRs and aHRs of all variables for the progression of CKD from stage I–IIIa to IIIb during the study period. In the CKD stages I-II subgroup, the Early CKD Care Program, the number of comorbidities, and comorbid hypertension, DM, gout, heart disease, hyperlipidemia, and cerebrovascular disease had no significant influence on the progression of CKD from stage I-II to IIIb even after adjustment for the variables. However, in the stage IIIa CKD subgroup, compared with those in the control group, the HR for progression to CKD stage IIIb in those with participated in the Early CKD Care Program was 0.72 (95% CI, 0.60–0.87; P= 0.005). After adjustments for the variables listed in Table 1, participation in the program remained a significant protective factor against progression to CKD stage IIIb (aHR, 0.67; 95% CI, 0.55–0.81; P< 0.001). In addition, compared with patients with stage IIIa CKD but without DM, those with DM were at a greater risk of progression to CKD stage IIIb (HR, 1.26; 95% CI, 1.01–1.57 and aHR, 1.69; 95% CI, 1.16–2.47; all P< 0.05). Compared with patients without heart disease with CKD stage IIIa, those with heart disease with CKD stage IIIa were at a greater risk for progression to CKD stage IIIb after adjustment for the variables (aHR, 1.65; 95% CI, 1.12–2.45; P= 0.0124).

Discussion

In this clinical observational study, we demonstrated that patients with stage I–IIIa CKD who participated in the Early CKD Care Program exhibited significantly

delayed deterioration of renal function to CKD stage IIIb compared with nonparticipants. Participation in the program significantly delayed the progression of CKD from stage IIIa to IIIb. In addition, we observed that DM, heart disease, and cerebrovascular disease are risk factors for deterioration of renal function among patients with stage I–IIIa CKD.

Compared with the control group, the case group had a higher mean age, a lower eGFR, a higher proportion of CKD stage IIIa, and more comorbidities before PSM. In real-life clinical scenarios, these disparities are reasonable. First, patients with stage I and II CKD typically have no noticeable symptom;[4] hence, they are typically not referred to a nephrologist. Second, patients with CKD stage IIIa are more likely to have clinical symptoms and therefore consult a nephrologist or seek medical attention. Third, patients with CKD IIIa with more comorbidities are more likely to be referred to a nephrologist than are those with fewer comorbidities. Fourth, older patients with more comorbidities are also likely to be referred to specialists. The CKD managers frequently encouraged those with clinical symptoms who consulted nephrologist, those with more comorbidities, or older patients to participate in the Early CKD Care Program. However, each patient's will and motivation also played a role. Therefore, to reduce the bias of basic characteristics between the two groups, PSM was used to match variables such as age, sex, eGFR, and CKD stage for further analysis.

After PSM, we observed that the case group still had more comorbidities such as hypertension, DM, gout, dyslipidemia, heart disease, and cerebrovascular disease than did the control group. Hypertension and CKD are closely interlinked. Uncontrolled hypertension can cause significant cardiovascular morbidity and mortality and accelerate CKD progression.[11] Blood pressure control is essential to preventing CKD progression and cardiovascular disease development.[12] DM is also a major cause of CKD and a risk factor for CKD and cardiovascular disease progression.[13-15] Patients with DM have a 3.8 times higher risk of CKD than do those without DM.[15] Of patients with type 2 DM, 42.3% have kidney injury.[2] Compared with patients with CKD without DM, those with DM developed earlier and more severe CKD complications,[16] because intracellular hyperglycemia leads to endothelial dysfunction, increased oxidative stress, and protein accumulation on the vascular wall, which cause microvascular and macrovascular complications,[17] including atherosclerotic renovascular disease, cardiovascular disease, and cerebrovascular disease.

In addition to hypertension and DM, gout is independently associated with CKD.[18] Patients with hyperuricemia are particularly susceptible to gout development. Hyperuricemia is an independent risk factor for CKD, and hyperuricemia treatment may delay CKD progression.[19, 20] Chronic hyperuricemia is associated with the development of hypertension, metabolic syndrome, CKD, and cardiovascular

disease.[21] Dyslipidemia is a risk factor for CKD, and CKD causes alterations in the lipoprotein profile. Therefore, the dyslipidemia–CKD relationship is reciprocal.[22] In addition to hypertension and DM, dyslipidemia is a major cause of cardiovascular and cerebrovascular disease in patients with CKD. Dyslipidemia treatment in patients with early CKD can reduce the occurrence of cardiovascular events and improve associated outcomes.[23] According to the aforementioned discussion, the high proportion of heart and cerebrovascular disease in the case group is to be expected because these risk factors contribute to heart and cerebrovascular disease. In theory, CKD in patients with more comorbidities should more rapidly progress from stage I–IIIa to IIIb than do those with fewer comorbidities. However, in our study, despite having more comorbidities, the case group had better renal outcomes than did the control group. Therefore, the Early CKD Care Program was instrumental in delaying renal function deterioration.

In addition, the effect of the Early CKD Care Program on the progression of CKD from early stages to stage IIIb was analyzed. We found that participation in the program significantly delayed the progression of CKD from stage IIIa to IIIb, but we observed no significant results for the progression of CKD from stages I-II to IIIb. Although the case group had low HRs for CKD stage IIIb compared with the control group, the difference remained nonsignificant. CKD progression from stage I-II to

IIIb might require more time; hence, few patients in the control group with stage I-II CKD progressed to CKD stage IIIb during the follow-up period. Although some studies have developed clinical predication models for CKD, their study groups had stages III- IV CKD and ESRD was defined as the outcome.[24,25] No available clinical predication model was designed for CKD stages I-II or IIIa-IIIb. Further investigation employing clinical predication models for early to advanced CKD is warranted.

In our clinical study, patients with stage I–IIIa CKD with DM, heart disease, or cerebrovascular disease exhibited considerable risk of progression to CKD stage IIIb. The results are similar to those of the KEEP[4] and a population-level cohort study by Tonelli.[26] DM and heart disease are also significant risk factor for progression of CKD from stage IIIa to IIIb. Therefore, in addition to the Early CKD Care Program, the Diabetes Shared Care Program (DSCP) must be implemented because the DSCP reduces cardiovascular and cerebrovascular event and mortality risks.[27]

The current study had some limitations. First, the CRDB only included data from three educational medical institutions located in New Taipei City and Taipei City in Taiwan. The greater Taipei area has adequate medical resources, which might not be representative of all clinical situations in Taiwan because of the urban–rural medical disparity. Second, participation in the care program was voluntary; therefore, patients' motivation and the encouragement of medical personnel possibly played a role, and

thus, selection bias should be considered. Third, the clinical outcome of our study was limited to the progression of early CKD, rather than being a comprehensive assessment of cardiovascular events and mortality. Finally, the ethnicity of most of Taiwan's population is Chinese; thus, the results might not be generalizable to populations of other ethnic backgrounds.

In conclusion, this study revealed that patients with stage I–IIIa CKD who participated in the Early CKD Care Program benefited from a reduction in renal function deterioration. This program should be promoted and implemented particularly for those with stage IIIa CKD.

Author affiliations

[1]Department of Nursing, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

[2]Department of Nursing, Fu Jen Catholic University, New Taipei, Taiwan

[3]College of Nursing, Taipei Medical University, Taipei, Taiwan

[4]Division of Nephrology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

[5]School of Medicine, Fu-Jen Catholic University, New Taipei, Taiwan

[6]Clinical Data Center, Office of Data Science, Taipei Medical University, Taipei, Taiwan

[7]Division of Cardiovascular Surgery, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

[8]Graduate Institute of Biomedical Informatics, Taipei Medical University, Taipei, Taiwan

[9]Clinical Big Data Research Center, Taipei Medical University Hospital, Taipei, Taiwan

Acknowledgments None

Contributors All authors reviewed the manuscript. S.-F.N. collected and interpreted the data and wrote the manuscript. N.-C.C. and T.-H.C. ran the data and performed statistical analyses. S.-F.N. and C.-K.W. determined the concept and design of this study. Y.-B.Y. contributed to the manuscript revision. T.-H.C. and C.-K.W. helped to write the manuscript and conceived the study.

Funding None

Competing interests None declared

Ethics approval The study was approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB-201803022).

Provenance and peer review Not commissioned; externally peer reviewed

Data availability statement No additional data are available.

References

1. Bello AK, Levin A, Tonelli M *et al*. Assessment of Global Kidney Health Care Status. JAMA 2017; 317(18):1864-81

2. Hill NR, Fatoba ST, Oke JL *et al*. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One 2016;11(7):e0158765

3. Stenvinkel P. Chronic kidney disease: a public health priority and harbinger of premature cardiovascular disease. J Intern Med 2010; 268(5):456-67

4. Agrawal V, Jaar BG, Frisby XY *et al.* Access to health care among adults evaluated for CKD: findings from the Kidney Early Evaluation Program (KEEP). American journal of kidney diseases : the official journal of the National Kidney Foundation 2012; 59(3 Suppl 2):S5-15

5. Mills KT, Xu Y, Zhang W *et al.* A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int 2015; 88(5):950-7

6. Webster AC, Nagler EV, Morton RL *et al.* Chronic Kidney Disease. The Lancet 2017; 389(10075):1238-52

7. Saran R, Robinson B, Abbott KC *et al.* US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States. American journal of kidney diseases : the official journal of the National Kidney Foundation 2019; 73(3S1):A7-A8

8. Yamagata K, Makino H, Iseki K *et al.* Effect of Behavior Modification on Outcome in Early- to Moderate-Stage Chronic Kidney Disease: A Cluster-Randomized Trial. PLoS One 2016; 11(3):e0151422

9. Stack AG. Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. American journal of kidney diseases : the official journal of the National Kidney Foundation 2003; 41(2):310-8

10. Lin MY, Cheng LJ, Chiu YW *et al.* Effect of national pre-ESRD care program on expenditures and mortality in incident dialysis patients: A population-based study. PLoS One 2018; 13(6):e0198387

11. Ku E, Lee BJ, Wei J *et al.* Hypertension in CKD: Core Curriculum 2019. American journal of kidney diseases : the official journal of the National Kidney Foundation 2019; 74(1):120-31

12. Kusaba T, Kimura K. [Management of hypertension in CKD patients]. Nihon Rinsho 2008; 66(9):1747-52

13. Dare AJ, Fu SH, Patra J *et al.*Renal failure deaths and their risk factors in India 2001–13: nationally representative estimates from the Million Death Study. The Lancet Global Health 2017; 5(1):e89-e95

14. Wen CP, Cheng TYD, Tsai MK *et al.* All-cause mortality attributable to chronic

kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. The Lancet 2008; 371(9631):2173-82

15. McCullough PA, Steigerwalt S, Tolia K *et al.* Cardiovascular disease in chronic kidney disease: data from the Kidney Early Evaluation Program (KEEP). Curr Diab Rep 2011; 11(1):47-55

16. Winocour PH. Diabetes and chronic kidney disease: an increasingly common multi-morbid disease in need of a paradigm shift in care. Diabet Med 2018; 35(3):300-5

17. Peters E, van Elsas A, Heemskerk S *et al.* Alkaline phosphatase as a treatment of sepsis-associated acute kidney injury. J Pharmacol Exp Ther 2013; 344(1):2-7

18. Roughley MJ, Belcher J, Mallen CD *et al.* Gout and risk of chronic kidney disease and nephrolithiasis: meta-analysis of observational studies. Arthritis Res Ther 2015; 17:90

19. Zhao G, Huang L, Song M *et al.* Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies. Atherosclerosis 2013; 231(1):61-8

20. Ishihara M, Urushido M, Hamada K *et al.* Sestrin-2 and BNIP3 regulate autophagy and mitophagy in renal tubular cells in acute kidney injury. Am J Physiol Renal Physiol 2013; 305(4):F495-509

21. Borghi C, Rosei EA, Bardin T *et al.* Serum uric acid and the risk of cardiovascular and renal disease. J Hypertens 2015; 33(9):1729-41

22. Bermudez-Lopez M, Arroyo D, Betriu A *et al.* New perspectives on CKD-induced dyslipidemia. Expert opinion on therapeutic targets 2017; 21(10):967-76

23. Galvao TF, Araujo ME, Penha AP *et al.* Statins for early stage chronic kidney disease: an overview of reviews. Cardiovascular & hematological disorders drug targets 2014; 14(3):205-11

24. Tangri N, Stevens LA, Griffith J *et al.* A predictive model for progression of chronic kidney disease to kidney failure. JAMA 2011; 305(15):1553-9

25. Hasegawa T, Sakamaki K, Koiwa F *et al.* Clinical prediction models for progression of chronic kidney disease to end-stage kidney failure under pre-dialysis nephrology care: results from the Chronic Kidney Disease Japan Cohort Study. Clin Exp Nephrol 2019; 23(2):189-98

26. Tonelli M, Muntner P, Lloyd A *et al.* Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. The Lancet 2012; 380(9844):807-14

27. Kornelius E, Chiou JY, Yang YS *et al.* The Diabetes Shared Care Program and Risks of Cardiovascular Events in Type 2 Diabetes. The American journal of medicine 2015; 128(9):977-85

Figure 1. Flow of patient selection for the study cohort.

From January 2012 to August 2017, 307,762 patients with chronic kidney disease (CKD) with more than two visits to the participating hospitals were identified in the institutional and clinical research database of Taipei Medical University. Adult nonpregnant patients with CKD who met the specific criteria of stage I–IIIa CKD were regarded as patients with early CKD. Those who participated in the Early CKD Care Program comprised the case group, and those not participating in the program served as the control group. We conducted 1:2 propensity score matching with age, sex, estimated glomerular filtration rate, and CKD stage to reduce selection bias in the control group.

Figure 2. Cumulative incidence of progression to chronic kidney disease (CKD) stage IIIb in patients with stage I–IIIa CKD in case and control groups.

Kaplan–Meier analysis revealed that the cumulative incidence of progression to CKD stage IIIb was significantly higher in patients with stage I–IIIa CKD who did not participate in the Early CKD Care Program compared with that of those who participated in the program, during the follow-up period (log-rank test, $P = 0.02$

Table 1. Baseline characteristics of enrollees

	Before propensity score matching				After propensity score matching			
	Total n = 159,774 N (%)	Case group n = 1,038 N (%)	Control group n = 158,736 N (%)	*P* value	Total n = 3,114 N (%)	Case group n = 1,038 N (%)	Control group n = 2,076 N (%)	*P* value
Age	59.1 ± 16.1	66.4 ± 12.8	59.1 ± 16.1	< 0.0001	66.6 ± 14.4	66.4 ± 12.8	66.7 ± 15.2	0.5917
Sex, male	89933 (56.3)	697 (67.2)	89236 (56.2)	< 0.0001	2054 (66.0)	697 (67.2)	1357 (65.7)	0.3358
eGFR	79.2 ± 14.0	62.2 ± 12.9	79.3 ± 13.9	< 0.0001	62.2 ± 13.2	62.2 ± 12.9	62.2 ± 13.3	0.8842
CKD Stage				< 0.0001				0.6009
1	44066 (27.6)	53 (5.1)	44013 (27.7)		166 (5.3)	53 (5.1)	113 (5.4)	
2	96435 (60.4)	418 (40.3)	96017 (60.5)		1216 (39.1)	418 (40.3)	798 (38.4)	
3a	19273 (12.1)	567 (54.6)	18706 (11.8)		1732 (55.6)	567 (54.6)	1165 (56.1)	
Comorbidity number				< 0.0001				< 0.0001
0	81576 (51.1)	66 (6.4)	81510 (51.4)		977 (31.4)	66 (6.4)	911 (43.9)	
1	33519 (21.0)	221 (21.3)	33298 (21.0)		698 (22.4)	221 (21.3)	477 (23.0)	
2	25865 (16.2)	303 (29.2)	25562 (16.1)		712 (22.9)	303 (29.2)	409 (19.7)	
3+	18814 (11.8)	448 (43.2)	18366 (11.6)		727 (23.4)	448 (43.2)	279 (13.4)	
Hypertension	44998 (28.2)	755 (72.7)	44243 (27.9)	< 0.0001	1448 (46.5)	755 (72.7)	693 (33.4)	< 0.0001
DM	22601 (14.2)	399 (38.4)	22202 (14.0)	< 0.0001	780 (25.1)	399 (38.4)	381 (18.4)	< 0.0001
Gout	7563 (4.73)	257 (24.8)	7306 (4.6)	< 0.0001	374 (12.0)	257 (24.8)	117 (5.6)	< 0.0001
Hyperlipidemia	28629 (17.9)	549 (52.9)	28080 (17.7)	< 0.0001	882 (28.3)	549 (52.9)	333 (16.0)	< 0.0001

Heart disease	30692 (19.2)	318 (30.6)	30374 (19.1)	< 0.0001	779 (25.0)	318 (30.6)	461 (22.2)	< 0.0001
Cerebrovascular disease	12143 (7.6)	132 (12.7)	12011 (7.6)	< 0.0001	356 (11.4)	132 (12.7)	224 (10.8)	< 0.0001

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; DM, diabetes mellitus.

Matched variables were age, sex, eGFR, and CKD stage.

Table 2. Univariate and multivariate Cox regression analysis of study population (n = 3,114)

	Univariate		Multivariate*	
	HR (95%CI)	*P* value	aHR (95%CI)	*P* value
Group				
Control	ref		ref	
Case	0.72 (0.61, 0.85)	< 0.0001	0.67 (0.55, 0.81)	< 0.0001
Comorbidity number				
0	ref		ref	
1	0.99 (0.77, 1.29)	0.9687	0.80 (0.54, 1.17)	0.2438
2	0.94 (0.73, 1.21)	0.6374	0.54 (0.29, 1.02)	0.0592
3+	1.16 (0.93, 1.46)	0.1931	0.46 (0.17, 1.23)	0.1195
Hypertension				
No	ref		ref	
Yes	0.98 (0.82, 1.16)	0.7803	1.24 (0.85, 1.81)	0.2654
DM				
No	ref		ref	
Yes	1.30 (1.07, 1.58)	0.0075	1.72 (1.23, 2.41)	0.0015
Gout				
No	ref		ref	
Yes	0.86 (0.67, 1.11)	0.2577	1.25 (0.87, 1.77)	0.2241
Hyperlipidemia				
No	ref		ref	
Yes	0.98 (0.81, 1.19)	0.8467	1.26 (0.88, 1.80)	0.2152
Heart disease				
No	ref		ref	
Yes	1.29 (1.06, 1.58)	0.0132	1.70 (1.20, 2.40)	0.0027
Cerebrovascular disease				
No	ref		ref	
Yes	1.36 (1.04, 1.78)	0.0270	1.59 (1.12, 2.27)	0.0104

DM, diabetes mellitus; aHR, adjusted hazard ratio; CI, confidence interval.

*The multivariable model was adjusted for all variables.

Table 3. Univariate and multivariate Cox regression analysis of subgroups

	Baseline Stage < 3a n = 1,382				Baseline Stage = 3a n = 1,732			
	Univariate		Multivariate*		Univariate		Multivariate*	
	HR (95%CI)	*P* value	aHR (95%CI)	*P* value	HR (95%CI)	*P* value	aHR (95%CI)	*P* value
Group								
Control	ref		ref		ref		ref	
Case	0.75 (0.52, 1.08)	0.1244	0.75 (0.48, 1.17)	0.2059	0.72 (0.60, 0.87)	0.0005	0.34 (0.51, 0.80)	< 0.0001
Comorbidity number								
0	ref		ref		ref		ref	
1	0.61 (0.33, 1.12)	0.1090	0.50 (0.20, 1.26)	0.1420	1.09 (0.82, 1.46)	0.5593	0.87 (0.56, 1.35)	0.5345
2	0.82 (0.49, 1.38)	0.4528	0.59 (0.14, 2.48)	0.4753	0.95 (0.71, 1.27)	0.7322	0.51 (0.25, 1.05)	0.0664
3+	0.99 (0.57, 1.72)	0.9617	0.64 (0.06, 6.54)	0.7025	1.18 (0.91, 1.52)	0.2062	0.39 (0.13, 1.20)	0.1013
Hypertension								
No	ref		ref		ref		ref	
Yes	0.93 (0.63, 1.36)	0.6964	1.10 (0.45, 2.66)	0.7025	0.99 (0.81, 1.20)	0.8805	1.32 (0.86, 2.03)	0.2019
DM								
No	ref		ref		ref		ref	
Yes	1.48 (0.94, 2.34)	0.0932	1.99 (0.87, 4.54)	0.1032	1.26 (1.01, 1.57)	0.0385	1.69 (1.16, 2.47)	0.0065
Gout								
No	ref		ref		ref		ref	

Yes	0.79 (0.43, 1.46)	0.4536	1.05 (0.45, 2.43)	0.9181	0.89 (0.67, 1.19)	0.4329	1.34 (0.90, 1.99)	0.1525
Hyperlipidemia								
No	ref		ref		ref		ref	
Yes	0.73 (0.48, 1.11)	0.1404	0.76 (0.34, 1.70)	0.5014	1.07 (0.87, 1.33)	0.5204	1.52 (0.99, 2.30)	0.0507
Heart disease								
No	ref		ref		ref		ref	
Yes	1.20 (0.74, 1.93)	0.4599	1.47 (0.70, 3.12)	0.3093	1.24 (0.99, 1.56)	0.0618	1.65 (1.12, 2.45)	0.0124
Cerebrovascular disease								
No	ref		ref		ref		ref	
Yes	1.78 (0.97, 3.28)	0.0644	1.89 (0.84, 4.26)	0.1247	1.25 (0.92, 1.70)	0.1602	1.48 (0.99, 2.21)	0.0576

DM, diabetes mellitus; HR, hazard ratio; aHR, adjusted HR.

*The multivariable model was adjusted for all variables.

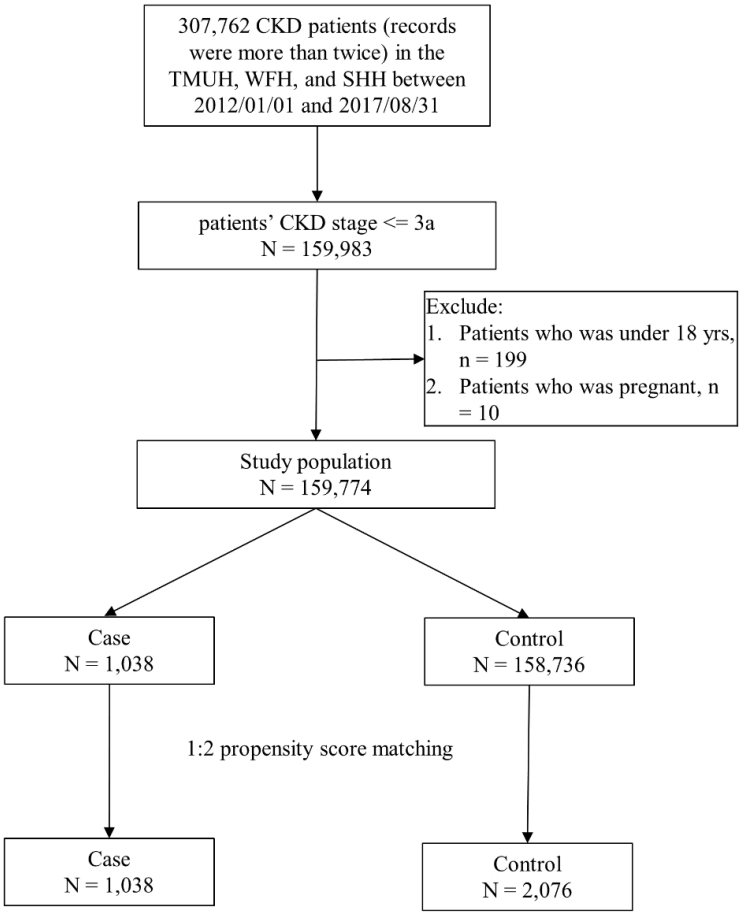

Figure 1. Flow chart of study population.

Figure 1. Flow of patient selection for the study cohort.
From January 2012 to August 2017, 307,762 patients with chronic kidney disease (CKD) with more than two visits to the participating hospitals were identified in the institutional and clinical research database of Taipei Medical University. Adult nonpregnant patients with CKD who met the specific criteria of stage I–IIIa CKD were regarded as patients with early CKD. Those who participated in the Early CKD Care Program comprised the case group, and those not participating in the program served as the control group. We conducted 1:2 propensity score matching with age, sex, estimated glomerular filtration rate, and CKD stage to reduce selection bias in the control group.

107x109mm (300 x 300 DPI)

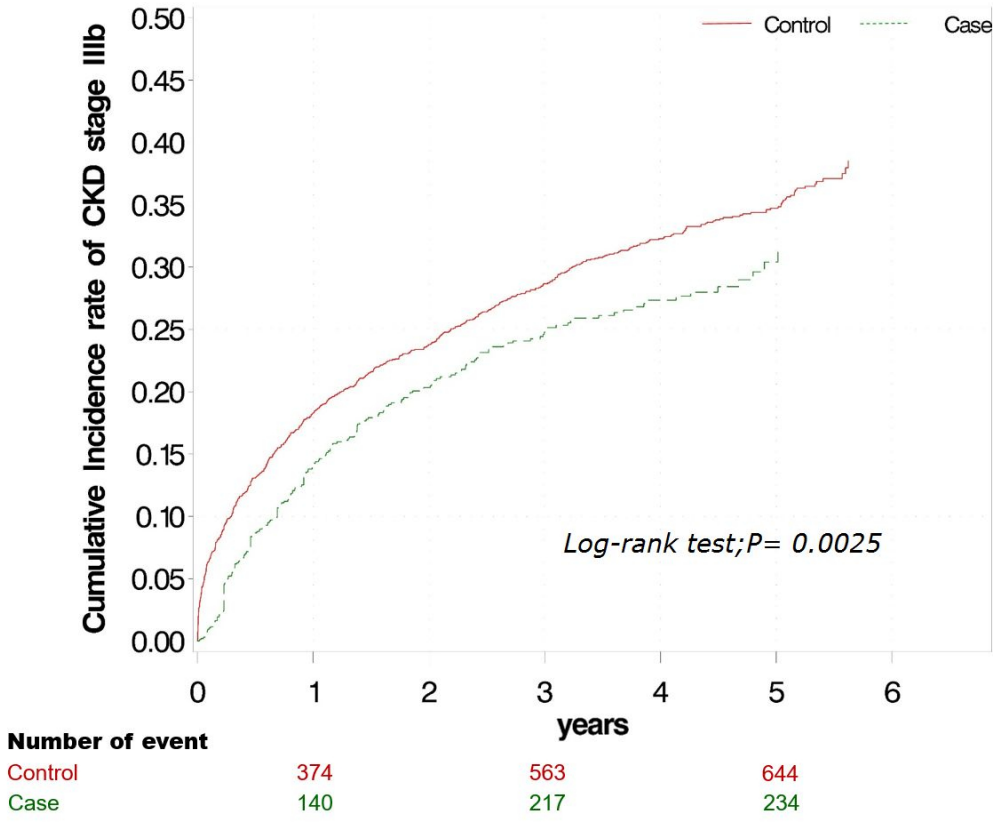

Figure 2. Cumulative incidence of progression to chronic kidney disease (CKD) stage IIIb in patients with stage I–IIIa CKD in case and control groups.
Kaplan–Meier analysis revealed that the cumulative incidence of progression to CKD stage IIIb was significantly higher in patients with stage I–IIIa CKD who did not participate in the Early CKD Care Program compared with that of those who participated in the program, during the follow-up period (log-rank test, P = 0.025)

95x80mm (300 x 300 DPI)

Effect of Early Chronic Kidney Disease Care Program on Kidney Function Deterioration in Patients With Stage I–IIIa Chronic Kidney Disease

Shu-Fen Niu, Chung-Kuan Wu, Nai-Chen Chuang, Ya-Bei Yang, Tzu-Hao Chang

Supplementary material

Table S1. International Classification of Diseases, ninth Revision, Clinical Modification codes used to identify comorbid conditions in this study.

Table S1. International Classification of Diseases, ninth Revision, Clinical Modification codes used to identify comorbid conditions in this study.

Co-morbid diseases	Corresponding ICD-9-CM codes
Hypertension	401.x–405.x
Diabetes mellitus	250.x
Gout	274.x
Hyperlipidemia	272.x
Heart disease	410.x–414.x; 420.x–429.x
Cerebrovascular disease	430.x–438.x

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,6,7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6,7,8.9
Bias	9	Describe any efforts to address potential sources of bias	8,9,16
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	8,9
		(*d*) If applicable, explain how loss to follow-up was addressed	8,9
		(*e*) Describe any sensitivity analyses	8,9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,10
		(b) Give reasons for non-participation at each stage	9,10
		(c) Consider use of a flow diagram	23
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10,24,25
		(b) Indicate number of participants with missing data for each variable of interest	9,10,23
		(c) Summarise follow-up time (eg, average and total amount)	10,11,12,23
Outcome data	15*	Report numbers of outcome events or summary measures over time	11,12,23,26,27
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11,12,23,24,25,26,27,28
		(*b*) Report category boundaries when continuous variables were categorized	11,12,23,24,25,26,27,28
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11,12,27,28
Discussion			
Key results	18	Summarise key results with reference to study objectives	12,13,14,15,16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13,14,1,16,17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Early Chronic Kidney Disease Care Program delay kidney function deterioration in patients with Stage I–IIIa chronic kidney disease: an observational cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-041210.R1
Article Type:	Original research
Date Submitted by the Author:	30-Sep-2020
Complete List of Authors:	Niu, Shu-Fen; Shin Kong Wu Ho Su Memorial Hospital, Department of Nursing Wu, Chung-Kuan; Shin Kong Wu Ho Su Memorial Hospital, Division of Nephrology,Department of Internal Medicine Chuang, Nai-Chen; Taipei Medical University, Clinical Data Center, Office of Data Science Yang, Ya-Bei; Shin Kong Wu Ho Su Memorial Hospital, Division of Cardiovascular Surgery Chang, Tzu-Hao; Taipei Medical University Hospital, Clinical Big Data Research Center
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Public health
Keywords:	Chronic renal failure < NEPHROLOGY, Nephrology < INTERNAL MEDICINE, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Early Chronic Kidney Disease Care Program delay kidney function deterioration in patients with Stage I–IIIa chronic kidney disease: an observational cohort study

Shu-Fen Niu[1,2,3], Chung-Kuan Wu[4,5], Nai-Chen Chuang[6], Ya-Bei Yang[7], Tzu-Hao Chang[8,9]

Reprints and correspondence:

Address to Chung-Kuan Wu, MD, PhD

Division of Nephrology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

No.95, Wenchang Rd., Shilin Dist., Taipei City 11101, Taiwan

Tel: +886-2-2833-2211 ext. 2385 Fax: +886-28389491

E-mail: m008533@ms.skh.org.tw

Or

Tzu-Hao Chang, PhD

Clinical Big Data Research Center, Taipei Medical University Hospital, Taipei, Taiwan

No.250, Wu-Hsing st., Xinyi Dist., Taipei City 11031, Taiwan

Tel: 886-2-6638-2736 #1508 Fax: +886-2-66380233

E-mail: kevinchang@tmu.edu.tw

ABSTRACT

Objectives: To investigate the effect of the Early CKD Care Program on CKD progression in patients with CKD stage I–IIIa

Design: Observational cohort study

Setting: Taipei Medical University Research Database from three affiliated hospitals.

Participants: Adult nonpregnant patients with CKD stage I–IIIa from Taipei Medical University Research Database between January 1, 2012 and August 31, 2017 were recruited. These patients were divided into Early CKD Care Program participants (case) and nonparticipants (control). The models were adjusted by age, sex, estimated glomerular filtration rate, and CKD stage with 1:2 propensity score to reduce bias between two groups.

Outcome measures: The risks of CKD stage I–IIIa progression to IIIb between Early CKD Care Program participants and nonparticipants.

Results: Compared with the control group, the case group demonstrated more comorbidities and higher proportions of hypertension, diabetes mellitus, gout, dyslipidemia, heart disease, and cerebrovascular disease, but had lower risk of progression to CKD stage IIIb before and (HR, 0.72; 95% CI, 0.61–0.85) and after (aHR, 0.67; 95% CI, 0.55–0.81) adjustments. Moreover, Kaplan–Meier analysis revealed the cumulative incidence of CKD stage IIIb was significantly lower in the

case group than in the control group. Finally, the program was an independent protective factor against progression to stage IIIb, especially in patients with CKD stage IIIa before (HR, 0.72; 95% CI, 0.61–0.85) and after (aHR, 0.67; 95% CI, 0.55–0.81) adjustments.

Conclusions: The Early CKD Care Program is an independent protective factor against progression of early CKD.

Strengths and limitations of this study

- The study provides the information on the preventive effect of the Early CKD Care Program on CKD progression
- The patients in our study were recruited from the greater Taipei area, which might not be representative of all clinical situations in Taiwan because of the urban–rural medical disparity
- Selection bias should be considered for participants owing to their motivation and role of medical personnel
- The clinical outcome focuses on the progression of early CKD, rather than major adverse cardiac events or mortality

Introduction

Chronic kidney disease (CKD) is recognized as a global health concern[1] because its overall prevalence in the general population is more than 10%. CKD prevalence ranged from 11.7% to 15.1%, with stages I-V accounting for 2.8%–4.2%, 2.7%–5.3%, 6.4%–8.9%, 0.3%–0.5%, and 0.1%, respectively. Therefore, most patients with CKD are in the early stages,[2] in which they may have no symptoms or signs.[3] Such early disease stages are not easily discovered and diagnosed by primary care physicians; therefore, most patients had not consulted a nephrologist, with fewer than 6% of the patients had consulting a nephrologist even for stage III CKD.[4] Without appropriate response or management of early CKD, it progresses to advanced CKD and finally to end-stage renal disease (ESRD), which usually requires management with dialysis. Therefore, exponential growth in medical costs[5] is expected. Despite treatment, patients with ESRD have poor quality of life and high mortality risk.[6]

In CKD stages I-II, an optimal outcome can be achieved with adequate assessment, diagnosis, and treatment.[4] The US Centers for Disease Control and Prevention recommends that early CKD progression prevention should include testing for and controlling CKD risk factors as well as maintaining a healthy weight through a balanced diet and physical exercise.[7] Moreover, early monitoring and treatment in conjunction with lifestyle adjustments can improve the revisit rate of patients with

CKD and delay renal function reduction.[8]

In Taiwan, more than 85,000 patients require dialysis and the related National Health Insurance (NHI) expenditure reached NT$44.9 billion in 2017. To reduce kidney function deterioration, improve the quality of life, reduce the burden on the NHI program, and achieve the goal of prioritizing prevention over management, Taiwan's Ministry of Health and Welfare launched the Early CKD Care Program aimed at active management of stage I–IIIa CKD.[9,10] However, the effectiveness of intervention in delaying kidney function deterioration warrants exploration. Therefore, this study explored the effects of an intervention-based Early CKD Care Program in reducing kidney function deterioration in patients with stage I–IIIa CKD.

Materials and Methods

Data Source.

This cohort study obtained information on patients with CKD stages I-IIIa in the institutional and clinical research database of Taipei Medical University (CRDB). This database contains the electronic health and medical records of more than 3 million patients from three affiliated hospitals, namely Taipei Medical University Hospital (TMUH), Wan Fang Hospital (WFH), and Shuang Ho Hospital (SHH). This study was exempted from a full review and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB-201803022).

Study Design and Cohort.

Figure 1 illustrates the patient selection process for the study cohort. From the CRDB, we identified patients with CKD who had more than two medical return visits between January 1, 2012, and August 31, 2017. We enrolled those who met the following criteria of CKD stages I-IIIa: patients with normal renal function but who present signs of kidney damage such as proteinuria, hematuria, and other conditions with eGFR ≥ 90 mL/min/1.73 m2; patients with kidney damage with eGFR 60–89.9 mL/min/1.73 m2; and patients with eGFR 45–59.9 mL/min/1.73 m2, respectively. We excluded patients aged < 18 years and those who were pregnant. The remaining patients were divided into the case group, those who participated in the Early CKD Care Program with P4301C, P4302C, or P403603C treatment codes, and the control group, consisting of those who did not participate in the Early CKD Care Program.

Outcome Measures and Comorbidity.

Major comorbidities diagnosed before the index date, according to claims data, were defined as baseline comorbidities. The comorbidities were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for hypertension, DM, gout, hyperlipidemia, heart disease, and cerebrovascular disease, as shown in Supplementary Table S1. Other baseline demographic data included age, sex, eGFR, CKD stage, and number of comorbidities.

Here, the eGFR was calculated as 186 × creatinine−1.154 × age−0.203 (× 0.742 for female), and the number of comorbidities was defined as the sum of the aforementioned comorbidities in the year prior to the enrollment date. The outcome of the study was patient progression to CKD stage IIIb during the study period.

The Early CKD Care Program.

The Bureau of NHI in Taiwan launched the Early CKD Care Program in 2011. Patients who participated in the program constitute this study's case group. The program involved (i) referral to a nephrologist and provision of medication for hypertension, diabetes, and hyperlipidemia to delay kidney function deterioration, avoid damage caused by improper medication, and prevent complications; (ii) CKD case managers enrolled these patients and provided nursing education and lifestyle consultations and routinely monitored disease progress and conducted renal function tests, urinalysis, and urine albumin–creatinine or protein–creatinine ratio evaluations. The CKD case managers informed the doctors and patients' families regarding medical practice and care-giving. The nursing education provided during the enrollment period included the following: (i) teaching the basic structure and functions of kidneys; (ii) introducing the common symptoms of kidney conditions as well as the examination values; (iii) explaining daily care and prevention of kidney conditions; (iv) communicating the importance of routine monitoring; (v)

communicating the importance of consulting a doctor before using medication; (vi) introducing kidney needle biopsy; (vii) introducing hyperlipidemia, hypertension, DM, kidney conditions, and their complications; and (viii) explaining dietary instructions. Lifestyle recommendations included the following: smoking cessation; weight loss, particularly for those with BMI > 25 kg/m2 or men and women with a waist circumference of >90 and >80 cm, respectively; daily protein intake < 1.5 gm/kg; prevention of routine or excessive alcohol consumption; adequate exercise; and daily salt intake < 100 mEq. Routine physical examinations were conducted at least once every 6 months for CKD stages I-IIIa, and urine protein, urine creatinine, serum creatinine, LDL, and HbA1c were tested. The control group received routine care and was not enrolled or monitored by CKD case managers.

Statistical Analysis.

Descriptive statistics were used to summarize the demographic data. Continuous variables are presented as mean and standard deviation, and categorical variables are presented as the number of enrollees and percentage (%). The models were adjusted by age, sex, estimated glomerular filtration rate, and CKD stage with 1:2 propensity score to reduce bias between the case group and the control group. Before PSM, we used Student's t test to assess age and eGFR; and the chi-squared test or Fisher's exact test were used for sex, CKD stage, number of comorbidities, hypertension, DM,

gout, heart disease, hyperlipidemia, and cerebrovascular disease. After PSM, we evaluated the differences between matched pairs using the signed rank test for continuous data and McNemar's test for binary data. Cox proportional hazards regression was used to determine the risk factors for patients progressing to CKD stage IIIb by including all the candidate variables in the model. Subgroup analysis was used to determine the risk factors for patients progressing to CKD stage IIIb from baseline CKD stage IIIa or the stages before it. A two-sided statistical test at 5% significance was used. Analyses were performed using SAS (version 7.11; SAS Institute, Cary, NC, USA).

Patient and public involvement.

The study used de-identified data from the institutional and Taipei Medical University Research Database (TMURD). No patients were involved in developing the research question or in determining the outcome measures. Patients were not involved in designing the study. There are no plans to disseminate the results of this study to any participants.

Results

Study Population Characteristics

Table 1 presents the characteristics of the study population. Before PSM, a total of 159,774 patients with stage I–IIIa CKD were enrolled from the participating hospitals,

including 1,038 in the case group and 158,736 in the control group. All the variables were significantly different between the two groups (all $P < 0.001$). Age was significantly higher in the case group than in the control group. By contrast, eGFR was significantly lower in the case group than that in the control group. The proportions of sex, CKD stage IIIa, hypertension, DM, gout, hyperlipidemia, heart disease, cerebrovascular disease, and proportion of number of comorbidity were significantly higher in the case group than in the control group. To reduce bias, 1:2 PSM was used to match the age, sex, eGFR, and CKD stage. After PSM, 3,114 patients with stage I–IIIa CKD from the participating hospitals during the study period were finally enrolled in the study, including 1,038 in the case group and 2,076 in the control group. The proportion of hypertension, DM, gout, heart disease, hyperlipidemia, cerebrovascular disease, and proportion of number of comorbidity remained significantly higher in the case group than in the control group (all $P <$ 0.001)

Association of Early CKD Care Program and Risk Factors with Early CKD Progression

Table 2 lists the crude hazard ratios (HRs) and adjusted HRs (aHRs) of all variables for stage I–IIIa CKD that progressed to CKD stage IIIb during the study period. Compared with patients in the control group, the HR for progression to CKD stage

IIIb was 0.72 (95% confidence interval [CI], 0.61–0.85) for those participating in the Early CKD Care Program. After adjustments for the variables listed in Table 1, those in the control group still exhibited significant risk for progression to CKD stage IIIb (aHR, 0.67; 95% CI, 0.55–0.51). In addition, DM, heart disease, or cerebrovascular disease in patients with stage I–IIIa CKD were significant risk factors for progression to CKD stage IIIb. The Kaplan–Meier curves for the cumulative incidence of progression to CKD stage IIIb was significantly higher in patients with stage I–IIIa CKD who did not participate in the Early CKD Care Program (control group) than the curves in those who participated in the program (case group) during the follow-up period (log-rank test, P= 0.0025; Figure 2). The median follow-up duration was 3.0 (1.0–4.7) years. Deterioration to CKD stage IIIb within 1, 3, and 5 years was respectively noted 374, 563, and 644 patients in the control group and 140, 217, and 234 patients in the case group.

Association of Early CKD Care Program and risk factors between CKD stage I-II and CKD stage IIIa with Early CKD Progression

Of the 3114 patients with stage I–IIIa CKD in this study, 1,382 patients with CKD stages I–II and the remaining 1,732 patients were in stage IIIa. Table 3 lists the crude HRs and aHRs of all variables for the progression of CKD from stage I–IIIa to IIIb during the study period. In the CKD stages I-II subgroup, the Early CKD Care

Program, the number of comorbidities, and comorbid hypertension, DM, gout, heart disease, hyperlipidemia, and cerebrovascular disease had no significant influence on the progression of CKD from stage I-II to IIIb even after adjustment for the variables. However, in the stage IIIa CKD subgroup, compared with those in the control group, the HR for progression to CKD stage IIIb in those with participated in the Early CKD Care Program was 0.72 (95% CI, 0.60–0.87). After adjustments for the variables listed in Table 1, participation in the program remained a significant protective factor against progression to CKD stage IIIb (aHR, 0.67; 95% CI, 0.55–0.81). In addition, compared with patients with stage IIIa CKD but without DM, those with DM were at a greater risk of progression to CKD stage IIIb (HR, 1.26; 95% CI, 1.01–1.57 and aHR, 1.69; 95% CI, 1.16–2.47). Compared with patients without heart disease with CKD stage IIIa, those with heart disease with CKD stage IIIa were at a greater risk for progression to CKD stage IIIb after adjustment for the variables (aHR, 1.65; 95% CI, 1.12–2.45).

Discussion

In this clinical observational study, we demonstrated that patients with stage I–IIIa CKD who participated in the Early CKD Care Program exhibited significantly delayed deterioration of renal function to CKD stage IIIb compared with nonparticipants. Participation in the program significantly delayed the progression of

CKD from stage IIIa to IIIb. In addition, we observed that DM, heart disease, and cerebrovascular disease are risk factors for deterioration of renal function among patients with stage I–IIIa CKD.

Compared with the control group, the case group had a higher mean age, a lower eGFR, a higher proportion of CKD stage IIIa, and more comorbidities before PSM. In real-life clinical scenarios, these disparities are reasonable. First, patients with stage I and II CKD typically have no noticeable symptom;[4] hence, they are typically not referred to a nephrologist. Second, patients with CKD stage IIIa are more likely to have clinical symptoms and therefore consult a nephrologist or seek medical attention. Third, patients with CKD IIIa with more comorbidities are more likely to be referred to a nephrologist than are those with fewer comorbidities. Fourth, older patients with more comorbidities are also likely to be referred to specialists. The CKD managers frequently encouraged those with clinical symptoms who consulted nephrologist, those with more comorbidities, or older patients to participate in the Early CKD Care Program. However, each patient's will and motivation also played a role. Therefore, to reduce the bias of basic characteristics between the two groups, PSM was used to match variables such as age, sex, eGFR, and CKD stage for further analysis.

After PSM, we observed that the case group still had more comorbidities such as hypertension, DM, gout, dyslipidemia, heart disease, and cerebrovascular disease than

did the control group. Hypertension and CKD are closely interlinked. Uncontrolled hypertension can cause accelerate CKD progression.[11] Blood pressure control is essential to preventing CKD progression.[12] DM is also a major cause of CKD and a risk factor for CKD progression.[13-15] Patients with DM have a 3.8 times higher risk of CKD than do those without DM.[15] Of patients with type 2 DM, 42.3% have kidney injury.[2] Compared with CKD patients without DM, those with DM developed earlier and more severe CKD complications.[16] Intracellular hyperglycemia leads to endothelial dysfunction, increased oxidative stress, and protein accumulation on the vascular wall, which cause microvascular and macrovascular complications.[17]

In addition to hypertension and DM, gout is independently associated with CKD.[18] Patients with hyperuricemia are particularly susceptible to gout development. Hyperuricemia is an independent risk factor for CKD, and hyperuricemia treatment may delay CKD progression.[19, 20] Chronic hyperuricemia is associated with the hypertension, metabolic syndrome, CKD, and cardiovascular disease.[21] Dyslipidemia is a risk factor for CKD, and CKD causes alterations in the lipoprotein profile. Therefore, the dyslipidemia–CKD relationship is reciprocal. [22] Hypertension, DM, and dyslipidemia are major causes of cardiovascular and cerebrovascular disease in patients with CKD. Treatment of hypertension, DM, and dyslipidemia in CKD patients can reduce the occurrence of cardiovascular events and improve associated

outcomes.[23] According to the aforementioned discussion, the high proportion of heart and cerebrovascular disease in the case group is to be expected. In theory, CKD in patients with more comorbidities should more rapidly progress from stage I–IIIa to IIIb than do those with fewer comorbidities. However, in our study, despite having more comorbidities, the case group had better renal outcomes than did the control group. Therefore, the Early CKD Care Program was instrumental in delaying renal function deterioration.

In addition, the effect of the Early CKD Care Program on the progression of CKD from early stages to stage IIIb was analyzed. We found that participation in the program significantly delayed the progression of CKD from stage IIIa to IIIb, but we observed no significant results for the progression of CKD from stages I-II to IIIb. Although the case group had low HRs for CKD stage IIIb compared with the control group, the difference remained nonsignificant. CKD progression from stage I-II to IIIb might require more time; hence, few patients in the control group with stage I-II CKD progressed to CKD stage IIIb during the follow-up period. Although some studies have developed clinical predication models for CKD, their study groups had stages III- IV CKD and ESRD was defined as the outcome.[24,25] No available clinical predication model was designed for CKD stages I-II or IIIa-IIIb. Further investigation employing clinical predication models for early to advanced CKD is warranted.

In our clinical study, patients with stage I–IIIa CKD with DM, heart disease, or cerebrovascular disease exhibited considerable risk of progression to CKD stage IIIb. The results are similar to those of the KEEP[4] and a population-level cohort study by Tonelli.[26] DM and heart disease are also significant risk factor for progression of CKD from stage IIIa to IIIb. Therefore, in addition to the Early CKD Care Program, the Diabetes Shared Care Program (DSCP) must be implemented because the DSCP reduces cardiovascular and cerebrovascular event and mortality risks.[27]

The current study had some limitations. First, the CRDB only included data from three educational medical institutions located in New Taipei City and Taipei City in Taiwan. The greater Taipei area has adequate medical resources, which might not be representative of all clinical situations in Taiwan because of the urban–rural medical disparity. Second, participation in the care program was voluntary; therefore, patients' motivation and the encouragement of medical personnel possibly played a role, and thus, selection bias should be considered. Third, the clinical outcome of our study was limited to the progression of early CKD, rather than being a comprehensive assessment of cardiovascular events and mortality. Fourth, the study did not take reversible acute kidney injury into account. Finally, the ethnicity of most of Taiwan's population is Chinese; thus, the results might not be generalizable to populations of other ethnic backgrounds.

In conclusion, this study revealed that patients with stage I–IIIa CKD who participated in the Early CKD Care Program benefited from a reduction in renal function deterioration. This program should be promoted and implemented particularly for those with stage IIIa CKD.

Author affiliations

[1]Department of Nursing, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

[2]Department of Nursing, Fu Jen Catholic University, New Taipei, Taiwan

[3]College of Nursing, Taipei Medical University, Taipei, Taiwan

[4]Division of Nephrology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

[5]School of Medicine, Fu-Jen Catholic University, New Taipei, Taiwan

[6]Clinical Data Center, Office of Data Science, Taipei Medical University, Taipei, Taiwan

[7]Division of Cardiovascular Surgery, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

[8]Graduate Institute of Biomedical Informatics, Taipei Medical University, Taipei, Taiwan

[9]Clinical Big Data Research Center, Taipei Medical University Hospital, Taipei,

Taiwan

Acknowledgments None

Contributors All authors reviewed the manuscript. S.-F.N. collected and interpreted the data and wrote the manuscript. N.-C.C. and T.-H.C. ran the data and performed statistical analyses. S.-F.N. and C.-K.W. determined the concept and design of this study. Y.-B.Y. contributed to the manuscript revision. T.-H.C. and C.-K.W. helped to write the manuscript and conceived the study.

Funding This study was supported by grant from the Ministry of Science and Technology, Taiwan (MOST 109-2314-B-341-003-MY3).

Competing interests None declared

Ethics approval The study was approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB-201803022).

Provenance and peer review Not commissioned; externally peer reviewed

Data availability statement No additional data are available.

References

1. Bello AK, Levin A, Tonelli M *et al*. Assessment of Global Kidney Health Care Status. JAMA 2017; 317(18):1864-81

2. Hill NR, Fatoba ST, Oke JL *et al*. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One 2016;11(7):e0158765

3. Stenvinkel P. Chronic kidney disease: a public health priority and harbinger of premature cardiovascular disease. J Intern Med 2010; 268(5):456-67

4. Agrawal V, Jaar BG, Frisby XY *et al.* Access to health care among adults evaluated for CKD: findings from the Kidney Early Evaluation Program (KEEP). American journal of kidney diseases : the official journal of the National Kidney Foundation 2012; 59(3 Suppl 2):S5-15

5. Mills KT, Xu Y, Zhang W *et al.* A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int 2015; 88(5):950-7

6. Webster AC, Nagler EV, Morton RL *et al.* Chronic Kidney Disease. The Lancet 2017; 389(10075):1238-52

7. Saran R, Robinson B, Abbott KC *et al.* US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States. American journal of kidney diseases : the official journal of the National Kidney Foundation 2019; 73(3S1):A7-A8

8. Yamagata K, Makino H, Iseki K *et al.* Effect of Behavior Modification on Outcome in Early- to Moderate-Stage Chronic Kidney Disease: A Cluster-Randomized Trial. PLoS One 2016; 11(3):e0151422

9. Stack AG. Impact of timing of nephrology referral and pre-ESRD care on

mortality risk among new ESRD patients in the United States. American journal of kidney diseases : the official journal of the National Kidney Foundation 2003; 41(2):310-8

10. Lin MY, Cheng LJ, Chiu YW *et al.* Effect of national pre-ESRD care program on expenditures and mortality in incident dialysis patients: A population-based study. PLoS One 2018; 13(6):e0198387

11. Ku E, Lee BJ, Wei J *et al.* Hypertension in CKD: Core Curriculum 2019. American journal of kidney diseases : the official journal of the National Kidney Foundation 2019; 74(1):120-31

12. Kusaba T, Kimura K. [Management of hypertension in CKD patients]. Nihon Rinsho 2008; 66(9):1747-52

13. Dare AJ, Fu SH, Patra J *et al.*Renal failure deaths and their risk factors in India 2001–13: nationally representative estimates from the Million Death Study. The Lancet Global Health 2017; 5(1):e89-e95

14. Wen CP, Cheng TYD, Tsai MK *et al.* All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. The Lancet 2008; 371(9631):2173-82

15. McCullough PA, Steigerwalt S, Tolia K *et al.* Cardiovascular disease in chronic kidney disease: data from the Kidney Early Evaluation Program (KEEP). Curr Diab

Rep 2011; 11(1):47-55

16. Winocour PH. Diabetes and chronic kidney disease: an increasingly common multi-morbid disease in need of a paradigm shift in care. Diabet Med 2018; 35(3):300-5

17. Peters E, van Elsas A, Heemskerk S *et al.* Alkaline phosphatase as a treatment of sepsis-associated acute kidney injury. J Pharmacol Exp Ther 2013; 344(1):2-7

18. Roughley MJ, Belcher J, Mallen CD *et al.*Gout and risk of chronic kidney disease and nephrolithiasis: meta-analysis of observational studies. Arthritis Res Ther 2015; 17:90

19. Zhao G, Huang L, Song M *et al.*Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies. Atherosclerosis 2013; 231(1):61-8

20. Ishihara M, Urushido M, Hamada K *et al.* Sestrin-2 and BNIP3 regulate autophagy and mitophagy in renal tubular cells in acute kidney injury. Am J Physiol Renal Physiol 2013; 305(4):F495-509

21. Borghi C, Rosei EA, Bardin T *et al.* Serum uric acid and the risk of cardiovascular and renal disease. J Hypertens 2015; 33(9):1729-41

22. Bermudez-Lopez M, Arroyo D, Betriu A *et al.* New perspectives on CKD-induced dyslipidemia. Expert opinion on therapeutic targets 2017; 21(10):967-76

23. Galvao TF, Araujo ME, Penha AP *et al.* Statins for early stage chronic kidney disease: an overview of reviews. Cardiovascular & hematological disorders drug targets 2014; 14(3):205-11

24. Tangri N, Stevens LA, Griffith J *et al.* A predictive model for progression of chronic kidney disease to kidney failure. JAMA 2011; 305(15):1553-9

25. Hasegawa T, Sakamaki K, Koiwa F *et al.* Clinical prediction models for progression of chronic kidney disease to end-stage kidney failure under pre-dialysis nephrology care: results from the Chronic Kidney Disease Japan Cohort Study. Clin Exp Nephrol 2019; 23(2):189-98

26. Tonelli M, Muntner P, Lloyd A *et al.* Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. The Lancet 2012; 380(9844):807-14

27. Kornelius E, Chiou JY, Yang YS *et al.* The Diabetes Shared Care Program and Risks of Cardiovascular Events in Type 2 Diabetes. The American journal of medicine 2015; 128(9):977-85

Figure 1. Flow of patient selection for the study cohort.

From January 2012 to August 2017, 307,762 patients with chronic kidney disease (CKD) with more than two visits to the participating hospitals were identified in-Taipei Medical University Research Database (TMURD). Adult nonpregnant patients with CKD who met the specific criteria of stage I–IIIa CKD were regarded as patients with early CKD. Those who participated in the Early CKD Care Program comprised the case group, and those not participating in the program served as the control group. We conducted 1:2 propensity score matching with age, sex, estimated glomerular filtration rate, and CKD stage to reduce selection bias in the control group.

Figure 2. Cumulative incidence of progression to chronic kidney disease (CKD) stage IIIb in patients with stage I–IIIa CKD in case and control groups.

Kaplan–Meier analysis revealed that the cumulative incidence of progression to CKD stage IIIb was significantly higher in patients with stage I–IIIa CKD who did not participate in the Early CKD Care Program compared with that of those who participated in the program, during the follow-up period (log-rank test, $P = 0.02$)

Table 1. Baseline characteristics of enrollees

	Before propensity score matching				After propensity score matching			
	Total n = 159,774 N (%)	Case group n = 1,038 N (%)	Control group n = 158,736 N (%)	*P* value	Total n = 3,114 N (%)	Case group n = 1,038 N (%)	Control group n = 2,076 N (%)	*P* value
Age	59.1 ± 16.1	66.4 ± 12.8	59.1 ± 16.1	< 0.0001	66.6 ± 14.4	66.4 ± 12.8	66.7 ± 15.2	0.5917
Sex, male	89933 (56.3)	697 (67.2)	89236 (56.2)	< 0.0001	2054 (66.0)	697 (67.2)	1357 (65.7)	0.3358
eGFR	79.2 ± 14.0	62.2 ± 12.9	79.3 ± 13.9	< 0.0001	62.2 ± 13.2	62.2 ± 12.9	62.2 ± 13.3	0.8842
CKD Stage				< 0.0001				0.6009
1	44066 (27.6)	53 (5.1)	44013 (27.7)		166 (5.3)	53 (5.1)	113 (5.4)	
2	96435 (60.4)	418 (40.3)	96017 (60.5)		1216 (39.1)	418 (40.3)	798 (38.4)	
3a	19273 (12.1)	567 (54.6)	18706 (11.8)		1732 (55.6)	567 (54.6)	1165 (56.1)	
Comorbidity number				< 0.0001				< 0.0001
0	81576 (51.1)	66 (6.4)	81510 (51.4)		977 (31.4)	66 (6.4)	911 (43.9)	
1	33519 (21.0)	221 (21.3)	33298 (21.0)		698 (22.4)	221 (21.3)	477 (23.0)	
2	25865 (16.2)	303 (29.2)	25562 (16.1)		712 (22.9)	303 (29.2)	409 (19.7)	
3+	18814 (11.8)	448 (43.2)	18366 (11.6)		727 (23.4)	448 (43.2)	279 (13.4)	
Hypertension	44998 (28.2)	755 (72.7)	44243 (27.9)	< 0.0001	1448 (46.5)	755 (72.7)	693 (33.4)	< 0.0001
DM	22601 (14.2)	399 (38.4)	22202 (14.0)	< 0.0001	780 (25.1)	399 (38.4)	381 (18.4)	< 0.0001
Gout	7563 (4.73)	257 (24.8)	7306 (4.6)	< 0.0001	374 (12.0)	257 (24.8)	117 (5.6)	< 0.0001
Hyperlipidemia	28629 (17.9)	549 (52.9)	28080 (17.7)	< 0.0001	882 (28.3)	549 (52.9)	333 (16.0)	< 0.0001

Heart disease	30692 (19.2)	318 (30.6)	30374 (19.1)	< 0.0001	779 (25.0)	318 (30.6)	461 (22.2)	< 0.0001
Cerebrovascular disease	12143 (7.6)	132 (12.7)	12011 (7.6)	< 0.0001	356 (11.4)	132 (12.7)	224 (10.8)	< 0.0001

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; DM, diabetes mellitus.

Matched variables were age, sex, eGFR, and CKD stage.

Table 2. Univariate and multivariate Cox regression analysis for the risk of CKD I-IIIa progression to CKD IIIb among the Early Chronic Kidney Disease Care Program and other risk factors (n = 3,114)

	Univariate		Multivariate*	
	HR (95%CI)	*P* value	aHR (95%CI)	*P* value
Group				
Control	ref		ref	
Case	0.72 (0.61, 0.85)	< 0.0001	0.67 (0.55, 0.81)	< 0.0001
Comorbidity number				
0	ref		ref	
1	0.99 (0.77, 1.29)	0.9687	0.80 (0.54, 1.17)	0.2438
2	0.94 (0.73, 1.21)	0.6374	0.54 (0.29, 1.02)	0.0592
3+	1.16 (0.93, 1.46)	0.1931	0.46 (0.17, 1.23)	0.1195
Hypertension				
No	ref		ref	
Yes	0.98 (0.82, 1.16)	0.7803	1.24 (0.85, 1.81)	0.2654
DM				
No	ref		ref	
Yes	1.30 (1.07, 1.58)	0.0075	1.72 (1.23, 2.41)	0.0015
Gout				
No	ref		ref	
Yes	0.86 (0.67, 1.11)	0.2577	1.25 (0.87, 1.77)	0.2241
Hyperlipidemia				
No	ref		ref	
Yes	0.98 (0.81, 1.19)	0.8467	1.26 (0.88, 1.80)	0.2152
Heart disease				
No	ref		ref	
Yes	1.29 (1.06, 1.58)	0.0132	1.70 (1.20, 2.40)	0.0027
Cerebrovascular disease				
No	ref		ref	
Yes	1.36 (1.04, 1.78)	0.0270	1.59 (1.12, 2.27)	0.0104

DM, diabetes mellitus; aHR, adjusted hazard ratio; CI, confidence interval.

*The multivariable model was adjusted for all variables.

Table 3. Univariate and multivariate Cox regression analysis for the risk of baseline stage < 3a progression to stage 3b and stage 3a progression to stage 3b among the Early Chronic Kidney Disease Care Program and other risk factors

	Baseline Stage < 3a n = 1,382				Baseline Stage = 3a n = 1,732			
	Univariate		Multivariate*		Univariate		Multivariate*	
	HR (95%CI)	*P* value	aHR (95%CI)	*P* value	HR (95%CI)	*P* value	aHR (95%CI)	*P* value
Group								
Control	ref		ref		ref		ref	
Case	0.75 (0.52, 1.08)	0.1244	0.75 (0.48, 1.17)	0.2059	0.72 (0.60, 0.87)	0.0005	0.34 (0.51, 0.80)	< 0.0001
Comorbidity number								
0	ref		ref		ref		ref	
1	0.61 (0.33, 1.12)	0.1090	0.50 (0.20, 1.26)	0.1420	1.09 (0.82, 1.46)	0.5593	0.87 (0.56, 1.35)	0.5345
2	0.82 (0.49, 1.38)	0.4528	0.59 (0.14, 2.48)	0.4753	0.95 (0.71, 1.27)	0.7322	0.51 (0.25, 1.05)	0.0664
3+	0.99 (0.57, 1.72)	0.9617	0.64 (0.06, 6.54)	0.7025	1.18 (0.91, 1.52)	0.2062	0.39 (0.13, 1.20)	0.1013
Hypertension								
No	ref		ref		ref		ref	
Yes	0.93 (0.63, 1.36)	0.6964	1.10 (0.45, 2.66)	0.7025	0.99 (0.81, 1.20)	0.8805	1.32 (0.86, 2.03)	0.2019
DM								
No	ref		ref		ref		ref	
Yes	1.48 (0.94, 2.34)	0.0932	1.99 (0.87, 4.54)	0.1032	1.26 (1.01, 1.57)	0.0385	1.69 (1.16, 2.47)	0.0065
Gout								

No	ref		ref		ref		ref	
Yes	0.79 (0.43, 1.46)	0.4536	1.05 (0.45, 2.43)	0.9181	0.89 (0.67, 1.19)	0.4329	1.34 (0.90, 1.99)	0.1525
Hyperlipidemia								
No	ref		ref		ref		ref	
Yes	0.73 (0.48, 1.11)	0.1404	0.76 (0.34, 1.70)	0.5014	1.07 (0.87, 1.33)	0.5204	1.52 (0.99, 2.30)	0.0507
Heart disease								
No	ref		ref		ref		ref	
Yes	1.20 (0.74, 1.93)	0.4599	1.47 (0.70, 3.12)	0.3093	1.24 (0.99, 1.56)	0.0618	1.65 (1.12, 2.45)	0.0124
Cerebrovascular disease								
No	ref		ref		ref		ref	
Yes	1.78 (0.97, 3.28)	0.0644	1.89 (0.84, 4.26)	0.1247	1.25 (0.92, 1.70)	0.1602	1.48 (0.99, 2.21)	0.0576

DM, diabetes mellitus; HR, hazard ratio; aHR, adjusted HR.

*The multivariable model was adjusted for all variables.

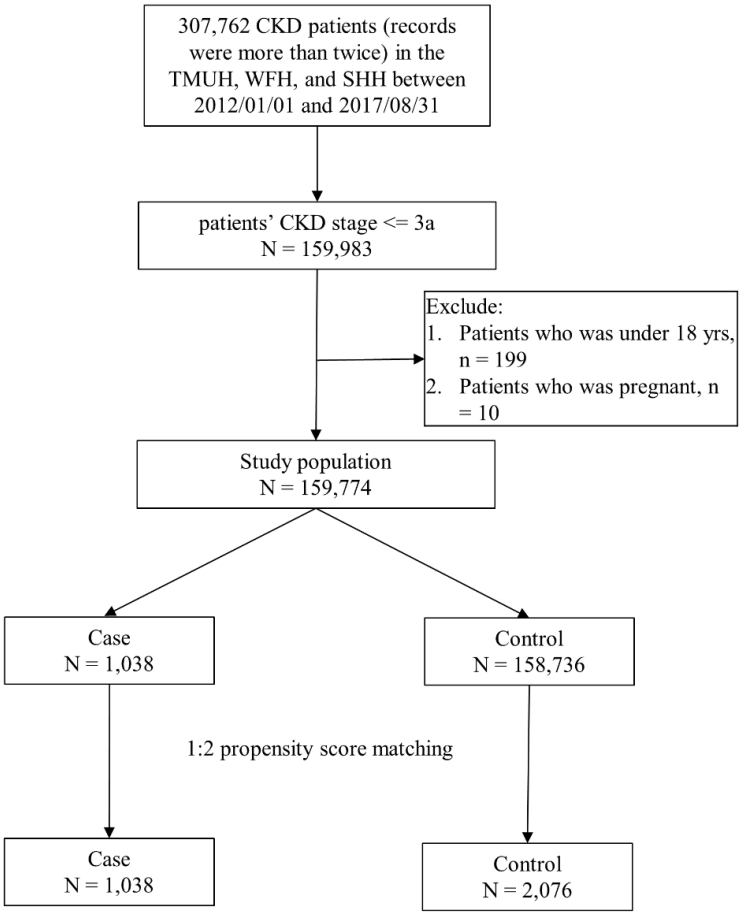

Figure 1. Flow chart of study population.

Figure 1. Flow of patient selection for the study cohort.
From January 2012 to August 2017, 307,762 patients with chronic kidney disease (CKD) with more than two visits to the participating hospitals were identified in the institutional and clinical research database of Taipei Medical University. Adult nonpregnant patients with CKD who met the specific criteria of stage I–IIIa CKD were regarded as patients with early CKD. Those who participated in the Early CKD Care Program comprised the case group, and those not participating in the program served as the control group. We conducted 1:2 propensity score matching with age, sex, estimated glomerular filtration rate, and CKD stage to reduce selection bias in the control group.

107x109mm (300 x 300 DPI)

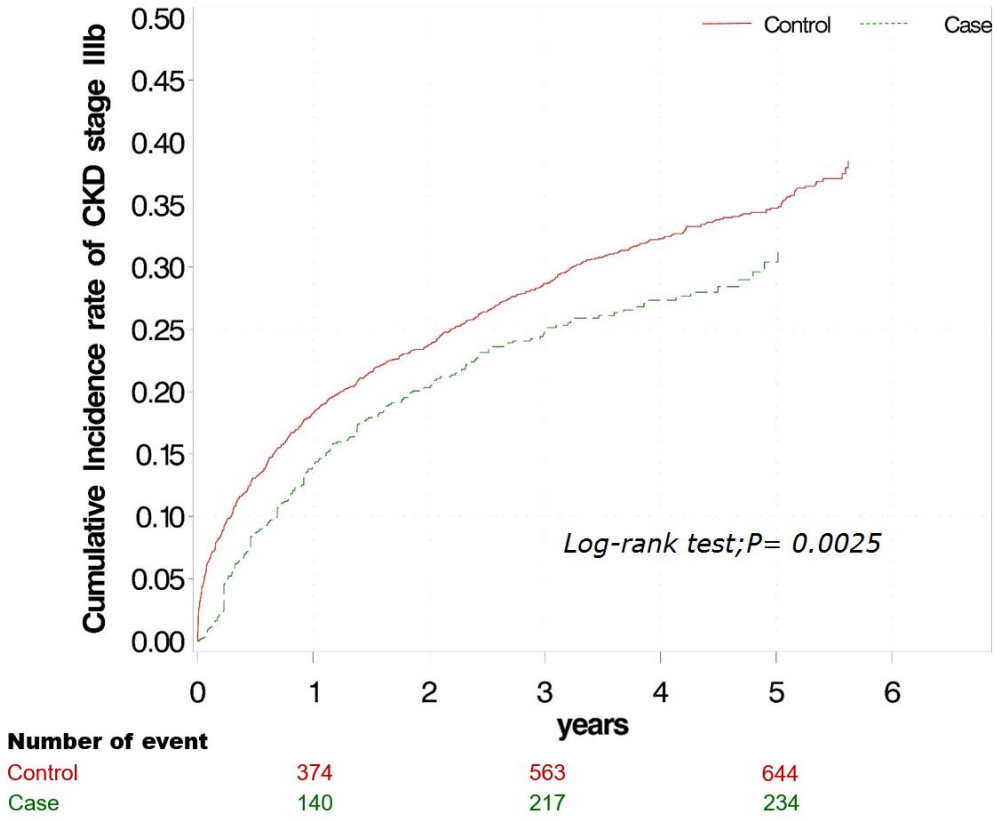

Figure 2. Cumulative incidence of progression to chronic kidney disease (CKD) stage IIIb in patients with stage I–IIIa CKD in case and control groups.
Kaplan–Meier analysis revealed that the cumulative incidence of progression to CKD stage IIIb was significantly higher in patients with stage I–IIIa CKD who did not participate in the Early CKD Care Program compared with that of those who participated in the program, during the follow-up period (log-rank test, P = 0.025)

95x80mm (300 x 300 DPI)

Early Chronic Kidney Disease Care Program delay kidney function deterioration in patients with Stage I–IIIa chronic kidney disease: an observational cohort study

Shu-Fen Niu, Chung-Kuan Wu, Nai-Chen Chuang, Ya-Bei Yang, Tzu-Hao Chang

Supplementary material

Table S1. International Classification of Diseases, ninth Revision, Clinical Modification codes used to identify comorbid conditions in this study.

Table S1. International Classification of Diseases, ninth Revision, Clinical Modification codes used to identify comorbid conditions in this study.

Co-morbid diseases	Corresponding ICD-9-CM codes
Hypertension	401.x–405.x
Diabetes mellitus	250.x
Gout	274.x
Hyperlipidemia	272.x
Heart disease	410.x–414.x; 420.x–429.x
Cerebrovascular disease	430.x–438.x

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,6,7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6,7,8.9
Bias	9	Describe any efforts to address potential sources of bias	8,9,16
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	8,9
		(*d*) If applicable, explain how loss to follow-up was addressed	8,9
		(*e*) Describe any sensitivity analyses	8,9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,10
		(b) Give reasons for non-participation at each stage	9,10
		(c) Consider use of a flow diagram	23
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10,24,25
		(b) Indicate number of participants with missing data for each variable of interest	9,10,23
		(c) Summarise follow-up time (eg, average and total amount)	10,11,12,23
Outcome data	15*	Report numbers of outcome events or summary measures over time	11,12,23,26,27
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11,12,23,24,25,26,27,28
		(*b*) Report category boundaries when continuous variables were categorized	11,12,23,24,25,26,27,28
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11,12,27,28
Discussion			
Key results	18	Summarise key results with reference to study objectives	12,13,14,15,16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13,14,1,16,17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Early Chronic Kidney Disease Care Program delays kidney function deterioration in patients with Stage I–IIIa chronic kidney disease: An observational cohort study in Taiwan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-041210.R2
Article Type:	Original research
Date Submitted by the Author:	30-Dec-2020
Complete List of Authors:	Niu, Shu-Fen; Shin Kong Wu Ho Su Memorial Hospital, Department of Nursing Wu, Chung-Kuan; Shin Kong Wu Ho Su Memorial Hospital, Division of Nephrology,Department of Internal Medicine Chuang, Nai-Chen; Taipei Medical University, Clinical Data Center, Office of Data Science Yang, Ya-Bei; Shin Kong Wu Ho Su Memorial Hospital, Division of Cardiovascular Surgery Chang, Tzu-Hao; Taipei Medical University Hospital, Clinical Big Data Research Center
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Public health
Keywords:	Chronic renal failure < NEPHROLOGY, Nephrology < INTERNAL MEDICINE, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Early Chronic Kidney Disease Care Program delays kidney function deterioration in patients with Stage I–IIIa chronic kidney disease: An observational cohort study in Taiwan

Shu-Fen Niu[1,2,3], Chung-Kuan Wu[4,5], Nai-Chen Chuang[6], Ya-Bei Yang[7], Tzu-Hao Chang[8,9]

Reprints and correspondence:

Address to Chung-Kuan Wu, MD, PhD

Division of Nephrology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

No.95, Wenchang Rd., Shilin Dist., Taipei City 11101, Taiwan

Tel: +886-2-2833-2211 ext. 2385 Fax: +886-28389491

E-mail: m008533@ms.skh.org.tw

Or

Tzu-Hao Chang, PhD

Clinical Big Data Research Center, Taipei Medical University Hospital, Taipei, Taiwan

No.250, Wu-Hsing st., Xinyi Dist., Taipei City 11031, Taiwan

Tel: 886-2-6638-2736 #1508 Fax: +886-2-66380233

E-mail: kevinchang@tmu.edu.tw

ABSTRACT

Objectives: To investigate the effect of the Early CKD Care Program on CKD progression in patients with CKD stage I–IIIa

Design: Observational cohort study

Setting: Taipei Medical University Research Database from three affiliated hospitals.

Participants: Adult nonpregnant patients with CKD stage I–IIIa from Taipei Medical University Research Database between January 1, 2012 and August 31, 2017 were recruited. These patients were divided into Early CKD Care Program participants (case) and nonparticipants (control). The models were matched by age, sex, estimated glomerular filtration rate, and CKD stage with 1:2 propensity score to reduce bias between two groups.

Outcome measures: The risks of CKD stage I–IIIa progression to IIIb between Early CKD Care Program participants and nonparticipants.

Results: Compared with the control group, the case group demonstrated more comorbidities and higher proportions of hypertension, diabetes mellitus, gout, dyslipidemia, heart disease, and cerebrovascular disease, but had lower risk of progression to CKD stage IIIb before and (HR, 0.72; 95% CI, 0.61–0.85) and after (aHR, 0.67; 95% CI, 0.55–0.81) adjustments. Moreover, Kaplan–Meier analysis revealed the cumulative incidence of CKD stage IIIb was significantly lower in the

case group than in the control group. Finally, the program was an independent protective factor against progression to stage IIIb, especially in patients with CKD stage IIIa before (HR, 0.72; 95% CI, 0.61–0.85) and after (aHR, 0.67; 95% CI, 0.55–0.81) adjustments.

Conclusions: The Early CKD Care Program is an independent protective factor against progression of early CKD.

Strengths and limitations of this study

- The study provides the information on the preventive effect of the Early CKD Care Program on CKD progression
- The patients in our study were recruited from the greater Taipei area, which might not be representative of all clinical situations in Taiwan because of the urban–rural medical disparity
- Selection bias should be considered for participants owing to their motivation and role of medical personnel
- The clinical outcome focuses on the progression of early CKD, rather than major adverse cardiac events or mortality

Introduction

Chronic kidney disease (CKD) is recognized as a global health concern[1] because its overall prevalence in the general population is more than 10%. CKD prevalence ranged from 11.7% to 15.1%, with stages I-V accounting for 2.8%–4.2%, 2.7%–5.3%, 6.4%–8.9%, 0.3%–0.5%, and 0.1%, respectively. Therefore, most patients with CKD are in the early stages,[2] in which they may have no symptoms or signs.[3] Such early disease stages are not easily discovered and diagnosed by primary care physicians; therefore, most patients had not consulted a nephrologist, with fewer than 6% of the patients had consulting a nephrologist even for stage III CKD.[4] Without appropriate response or management of early CKD, it progresses to advanced CKD and finally to end-stage renal disease (ESRD), which usually requires management with dialysis. Therefore, exponential growth in medical costs[5] is expected. Despite treatment, patients with ESRD have poor quality of life and high mortality risk.[6]

In CKD stages I-II, an optimal outcome can be achieved with adequate assessment, diagnosis, and treatment.[4] The US Centers for Disease Control and Prevention recommends that early CKD progression prevention should include testing for and controlling CKD risk factors as well as maintaining a healthy weight through a balanced diet and physical exercise.[7] Moreover, early monitoring and treatment in conjunction with lifestyle adjustments can improve the revisit rate of patients with

CKD and delay renal function reduction.[8]

In Taiwan, more than 85,000 patients require dialysis and the related National Health Insurance (NHI) expenditure reached NT$44.9 billion in 2017. To reduce kidney function deterioration, improve the quality of life, reduce the burden on the NHI program, and achieve the goal of prioritizing prevention over management, Taiwan's Ministry of Health and Welfare launched the Early CKD Care Program aimed at active management of stage I–IIIa CKD.[9,10] However, the effectiveness of intervention in delaying kidney function deterioration warrants exploration. Therefore, this study explored the effects of an intervention-based Early CKD Care Program in reducing kidney function deterioration in patients with stage I–IIIa CKD.

Materials and Methods

Data Source.

This cohort study obtained information on patients with CKD stages I-IIIa in the institutional and clinical research database of Taipei Medical University (CRDB). This database contains the electronic health and medical records of more than 3 million patients from three affiliated hospitals, namely Taipei Medical University Hospital (TMUH), Wan Fang Hospital (WFH), and Shuang Ho Hospital (SHH). This study was exempted from a full review and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB-201803022).

Study Design and Cohort.

Figure 1 illustrates the patient selection process for the study cohort. From the CRDB, we identified patients with CKD who had more than two medical return visits between January 1, 2012, and August 31, 2017. We enrolled those who met the following criteria of CKD stages I-IIIa: patients with normal renal function but who present signs of kidney damage such as proteinuria, hematuria, and other conditions with eGFR ≥ 90 mL/min/1.73 m2; patients with kidney damage with eGFR 60–89.9 mL/min/1.73 m2; and patients with eGFR 45–59.9 mL/min/1.73 m2, respectively. We excluded patients aged < 18 years and those who were pregnant. The remaining patients were divided into the case group, those who participated in the Early CKD Care Program with P4301C, P4302C, or P403603C treatment codes, and the control group, consisting of those who did not participate in the Early CKD Care Program.

Outcome Measures and Comorbidity.

Major comorbidities diagnosed before the index date, according to claims data, were defined as baseline comorbidities. The comorbidities were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for hypertension, DM, gout, hyperlipidemia, heart disease, and cerebrovascular disease, as shown in Supplementary Table S1. Other baseline demographic data included age, sex, eGFR, CKD stage, and number of comorbidities.

Here, the eGFR was calculated as 186 × creatinine−1.154 × age−0.203 (× 0.742 for female), and the number of comorbidities was defined as the sum of the aforementioned comorbidities in the year prior to the enrollment date. The outcome of the study was patient progression to CKD stage IIIb during the study period.

The Early CKD Care Program.

The Bureau of NHI in Taiwan launched the Early CKD Care Program in 2011. Patients who participated in the program constitute this study's case group. The program involved (i) referral to a nephrologist and provision of medication for hypertension, diabetes, and hyperlipidemia to delay kidney function deterioration, avoid damage caused by improper medication, and prevent complications; (ii) CKD case managers enrolled these patients and provided nursing education and lifestyle consultations and routinely monitored disease progress and conducted renal function tests, urinalysis, and urine albumin–creatinine or protein–creatinine ratio evaluations. The CKD case managers informed the doctors and patients' families regarding medical practice and care-giving. The nursing education provided during the enrollment period included the following: (i) teaching the basic structure and functions of kidneys; (ii) introducing the common symptoms of kidney conditions as well as the examination values; (iii) explaining daily care and prevention of kidney conditions; (iv) communicating the importance of routine monitoring; (v)

communicating the importance of consulting a doctor before using medication; (vi) introducing kidney needle biopsy; (vii) introducing hyperlipidemia, hypertension, DM, kidney conditions, and their complications; and (viii) explaining dietary instructions. Lifestyle recommendations included the following: smoking cessation; weight loss, particularly for those with BMI > 25 kg/m2 or men and women with a waist circumference of >90 and >80 cm, respectively; daily protein intake < 1.5 gm/kg; prevention of routine or excessive alcohol consumption; adequate exercise; and daily salt intake < 100 mEq. Routine physical examinations were conducted at least once every 6 months for CKD stages I-IIIa, and urine protein, urine creatinine, serum creatinine, LDL, and HbA1c were tested. The control group received routine care and was not enrolled or monitored by CKD case managers.

Statistical Analysis.

Descriptive statistics were used to summarize the demographic data. Continuous variables are presented as mean and standard deviation, and categorical variables are presented as the number of enrollees and percentage (%). The models were matched by age, sex, estimated glomerular filtration rate, and CKD stage with 1:2 propensity score to reduce bias between the case group and the control group. Considering that the number of participants in the case group (n = 1,038) were substantially smaller than those in the control group (n = 158,736), we chose a greedy and nearest neighbor

matching for propensity score matching algorithm. Before PSM, we used Student's t test to assess age and eGFR; and the chi-squared test or Fisher's exact test were used for sex, CKD stage, number of comorbidities, hypertension, DM, gout, heart disease, hyperlipidemia, and cerebrovascular disease. After PSM, we evaluated the differences between matched pairs using the signed rank test for continuous data and McNemar's test for binary data. Multivariable Cox proportional hazards models were matched to all the candidate variables, including comorbidity numbers, hypertension, DM, gout, hyperlipidemia, heart disease, and cerebrovascular disease to determine the risk factors for patients progressing to CKD stage IIIb.. Subgroup analysis was used to determine the risk factors for patients progressing to CKD stage IIIb from baseline CKD stage IIIa or the stages before it. A two-sided statistical test at 5% significance was used. Analyses were performed using SAS (version 7.11; SAS Institute, Cary, NC, USA).

Patient and public involvement.

The study used de-identified data from the institutional and Taipei Medical University Research Database (TMURD). No patients were involved in developing the research question or in determining the outcome measures. Patients were not involved in designing the study. There are no plans to disseminate the results of this study to any participants.

Results

Study Population Characteristics

Table 1 presents the characteristics of the study population. Before PSM, a total of 159,774 patients with stage I–IIIa CKD were enrolled from the participating hospitals, including 1,038 in the case group and 158,736 in the control group. All the variables were significantly different between the two groups (all $P < 0.001$). Age was significantly higher in the case group than in the control group. By contrast, eGFR was significantly lower in the case group than that in the control group. The proportions of sex, CKD stage IIIa, hypertension, DM, gout, hyperlipidemia, heart disease, cerebrovascular disease, and proportion of number of comorbidity were significantly higher in the case group than in the control group. To reduce bias, 1:2 PSM was used to match the age, sex, eGFR, and CKD stage. After PSM, 3,114 patients with stage I–IIIa CKD from the participating hospitals during the study period were finally enrolled in the study, including 1,038 in the case group and 2,076 in the control group. The proportion of hypertension, DM, gout, heart disease, hyperlipidemia, cerebrovascular disease, and proportion of number of comorbidities remained significantly higher in the case group than in the control group (all $P < 0.001$). Distribution of eGFR amongst cases and controls during the follow-up period was shown in supplementary Table S2.

Association of Early CKD Care Program and Risk Factors with Early CKD Progression

Table 2 lists the crude hazard ratios (HRs) and adjusted HRs (aHRs) of all variables for stage I–IIIa CKD that progressed to CKD stage IIIb during the study period. Compared with patients in the control group, the HR for progression to CKD stage IIIb was 0.72 (95% confidence interval [CI], 0.61–0.85) for those participating in the Early CKD Care Program. After adjustments for the variables listed in Table 1, those in the control group still exhibited significant risk for progression to CKD stage IIIb (aHR, 0.67; 95% CI, 0.55–0.51). In addition, DM, heart disease, or cerebrovascular disease in patients with stage I–IIIa CKD were significant risk factors for progression to CKD stage IIIb. The Kaplan–Meier curves for the cumulative incidence of progression to CKD stage IIIb was significantly higher in patients with stage I–IIIa CKD who did not participate in the Early CKD Care Program (control group) than the curves in those who participated in the program (case group) during the follow-up period (log-rank test, P= 0.0025; Figure 2). The median follow-up duration was 3.0 (1.0–4.7) years. Deterioration to CKD stage IIIb within 1, 3, and 5 years was respectively noted 374, 563, and 644 patients in the control group and 140, 217, and 234 patients in the case group.

Association of Early CKD Care Program and risk factors between CKD stage I-

II and CKD stage IIIa with Early CKD Progression

Of the 3114 patients with stage I–IIIa CKD in this study, 1,382 patients with CKD stages I–II and the remaining 1,732 patients were in stage IIIa. Table 3 lists the crude HRs and aHRs of all variables for the progression of CKD from stage I–IIIa to IIIb during the study period. In the CKD stages I-II subgroup, the Early CKD Care Program, the number of comorbidities, and comorbid hypertension, DM, gout, heart disease, hyperlipidemia, and cerebrovascular disease had no significant influence on the progression of CKD from stage I-II to IIIb even after adjustment for the variables. However, in the stage IIIa CKD subgroup, compared with those in the control group, the HR for progression to CKD stage IIIb in those with participated in the Early CKD Care Program was 0.72 (95% CI, 0.60–0.87). After adjustments for the variables listed in Table 1, participation in the program remained a significant protective factor against progression to CKD stage IIIb (aHR, 0.67; 95% CI, 0.55–0.81). In addition, compared with patients with stage IIIa CKD but without DM, those with DM were at a greater risk of progression to CKD stage IIIb (HR, 1.26; 95% CI, 1.01–1.57 and aHR, 1.69; 95% CI, 1.16–2.47). Compared with patients without heart disease with CKD stage IIIa, those with heart disease with CKD stage IIIa were at a greater risk for progression to CKD stage IIIb after adjustment for the variables (aHR, 1.65; 95% CI, 1.12–2.45).

Discussion

In this clinical observational study, we demonstrated that patients with stage I–IIIa CKD who participated in the Early CKD Care Program exhibited significantly delayed deterioration of renal function to CKD stage IIIb compared with nonparticipants, particularly those patients in stage IIIa. We also observed that DM, heart disease, and cerebrovascular disease are risk factors for deterioration of renal function in patients with stage I–IIIa CKD.

Compared with the control group, the case group had a higher mean age, a lower eGFR, a higher proportion of CKD stage IIIa, and more comorbidities before PSM. In the real-life clinical scenario, these disparities are reasonable. First, patients with stage I and II CKD typically have no noticeable symptom;[4] hence, they are usually not referred to a nephrologist. Second, patients with CKD stage IIIa are more likely to manifest clinical symptoms than patients with earlier stages of the disease and, therefore, consult a nephrologist or seek medical attention. Third, patients with CKD IIIa with more comorbidities are more likely to be referred to a nephrologist than are those with fewer comorbidities. Fourth, older patients with more comorbidities are also more likely to be referred to specialists than younger patients with same comorbidities. CKD managers frequently encourage patients with clinical symptoms and those who consulted a nephrologist, have more comorbidities, or are older to

participate in the Early CKD Care Program. Therefore, PSM was used to match variables such as age, sex, eGFR, and CKD stage to reduce the bias of basic characteristics between the two groups during further analysis.

After PSM, we observed that the case group still showed more comorbidities such as hypertension, DM, gout, dyslipidemia, heart disease, and cerebrovascular disease, than the control group. Hypertension and CKD are closely interlinked. Uncontrolled hypertension can accelerate CKD progression;[11] thus, blood pressure control is essential to prevent CKD progression.[12] DM is also a major cause of CKD and a risk factor for CKD progression.[13-15] Compared with those without DM, patients with DM have a 3.8-fold higher risk of developing CKD.[15] Amongst patients with type 2 DM, 42.3% have kidney injury.[2] Compared with CKD patients without DM, those with DM developed CKD earlier and experienced more severe CKD complications.[16] Intracellular hyperglycemia leads to endothelial dysfunction, increased oxidative stress, and protein accumulation on the vascular wall, which cause vascular complications.[17]

In addition to hypertension and DM, gout is independently associated with CKD.[18] Patients with hyperuricemia are particularly susceptible to gout development. Hyperuricemia is an independent risk factor for CKD, and hyperuricemia treatment may delay CKD progression.[19, 20] Chronic hyperuricemia is associated with

hypertension, metabolic syndrome, CKD, and cardiovascular disease.[21] Dyslipidemia is a risk factor for CKD, and CKD causes alterations in the lipoprotein profile. Therefore, the dyslipidemia–CKD relationship is reciprocal. [22] Hypertension, DM, and dyslipidemia are major causes of cardiovascular and cerebrovascular disease in patients with CKD. Treatment of hypertension, DM, and dyslipidemia in CKD patients can reduce the occurrence of cardiovascular events and improve associated outcomes.[23] Given the links between these diseases, the high proportion of heart and cerebrovascular disease observed in the case group may be expected. In theory, CKD in patients with many comorbidities should progress more rapidly from stage I–IIIa to IIIb than those with fewer comorbidities. However, in our study, despite having more comorbidities, the case group had better renal outcomes than the control group. Therefore, the Early CKD Care Program may be assumed to be instrumental in delaying renal function deterioration.

The effect of the Early CKD Care Program on the progression of CKD from early stages to stage IIIb was analyzed. We found that participation in the program significantly delayed the progression of CKD from stage IIIa to IIIb, however, we also observed no significant results for the progression of CKD from stages I-II to IIIb. Although the case group had low HRs for stage IIIb CKD compared with the control group, this difference was nonsignificant. CKD progression from stage I-II to

IIIb may require some time, which could explain why few patients in the control group with stage I-II CKD progressed to stage IIIb during the follow-up period. Although some studies have developed clinical predication models for CKD, the study groups in these investigations generally had stage III- IV CKD and ESRD was defined as the outcome.[24,25] No clinical predication model has yet been designed for stages I-II or IIIa-IIIb CKD. Further investigation employing clinical predication models for early-to-advanced CKD are warranted. Figure 2 illustrates that the protective effect of the Early Chronic Kidney Disease Care Program was sustained over the follow-up period, although the difference in cumulative incidence rate between the two groups gradually increased. The decrease of the slope over time may be attributed to the fact that patients who overcame the decline of their eGFR to less than 45 for over 1 year had good compliance or few comorbidities.

In our clinical study, patients with stage I–IIIa CKD with DM, heart disease, or cerebrovascular disease exhibited considerable risk of progression to stage IIIb CKD. These results are similar to the findings of the KEEP[4] and a population-level cohort study by Tonelli.[26] Besides other conditions, DM and heart disease are also significant risk factors for the progression of CKD from stage IIIa to IIIb. Therefore, in addition to the Early CKD Care Program, the Diabetes Shared Care Program (DSCP), which has been proven to reduce cardiovascular and cerebrovascular events and mortality

risks,[27] may be implemented.

The current study had some limitations that may affect the interpretation of the results. First, the CRDB only included data from three educational medical institutions located in New Taipei City and Taipei City in Taiwan. The greater Taipei area has adequate medical resources and, thus, may not be representative of all clinical situations in Taiwan on account of the urban–rural medical disparity. Second, our study cannot completely eliminate concerns related to selection bias because this phenomenon may be attributed to multiple reasons, including differential rates of death, and cause-specific models could feature assumptions that do not necessarily resolve competing risk issues. Third, the clinical outcome of our study was limited to the progression of early CKD; this work does not provide a comprehensive assessment of cardiovascular events and mortality. Fourth, the study did not take the potential effects of reversible kidney injury into account. Finally, the ethnicity of most of Taiwan's population is Chinese; thus, the results may not be generalizable to populations of other ethnic backgrounds.

In conclusion, the results of this study revealed that patients with stage I–IIIa CKD who participated in the Early CKD Care Program benefit from a reduction in renal function deterioration. As such, this program should be promoted and implemented, especially amongst those with stage IIIa CKD. More research is needed to understand

what type of participants in the Early Chronic Kidney Disease Care Program and which aspects of the Program yield the more effective results.

Author affiliations

[1]Department of Nursing, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

[2]Department of Nursing, Fu Jen Catholic University, New Taipei, Taiwan

[3]College of Nursing, Taipei Medical University, Taipei, Taiwan

[4]Division of Nephrology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

[5]School of Medicine, Fu-Jen Catholic University, New Taipei, Taiwan

[6]Clinical Data Center, Office of Data Science, Taipei Medical University, Taipei, Taiwan

[7]Division of Cardiovascular Surgery, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

[8]Graduate Institute of Biomedical Informatics, Taipei Medical University, Taipei, Taiwan

[9]Clinical Big Data Research Center, Taipei Medical University Hospital, Taipei, Taiwan

Acknowledgments None

Contributors All authors reviewed the manuscript. S.-F.N. collected and interpreted the data and wrote the manuscript. N.-C.C. and T.-H.C. ran the data and performed statistical analyses. S.-F.N. and C.-K.W. determined the concept and design of this study. Y.-B.Y. contributed to the manuscript revision. T.-H.C. and C.-K.W. helped to write the manuscript and conceived the study.

Funding This study was supported by grant from the Ministry of Science and Technology, Taiwan (MOST 109-2314-B-341-003-MY3).

Competing interests None declared

Ethics approval The study was approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB-201803022).

Provenance and peer review Not commissioned; externally peer reviewed

Data availability statement No additional data are available.

References

1. Bello AK, Levin A, Tonelli M *et al*. Assessment of Global Kidney Health Care Status. JAMA 2017; 317(18):1864-81

2. Hill NR, Fatoba ST, Oke JL *et al*. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One 2016;11(7):e0158765

3. Stenvinkel P. Chronic kidney disease: a public health priority and harbinger of premature cardiovascular disease. J Intern Med 2010; 268(5):456-67

4. Agrawal V, Jaar BG, Frisby XY *et al.* Access to health care among adults evaluated for CKD: findings from the Kidney Early Evaluation Program (KEEP). American journal of kidney diseases : the official journal of the National Kidney Foundation 2012; 59(3 Suppl 2):S5-15

5. Mills KT, Xu Y, Zhang W *et al.* A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int 2015; 88(5):950-7

6. Webster AC, Nagler EV, Morton RL *et al.* Chronic Kidney Disease. The Lancet 2017; 389(10075):1238-52

7. Saran R, Robinson B, Abbott KC *et al.* US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States. American journal of kidney diseases : the official journal of the National Kidney Foundation 2019; 73(3S1):A7-A8

8. Yamagata K, Makino H, Iseki K *et al.* Effect of Behavior Modification on Outcome in Early- to Moderate-Stage Chronic Kidney Disease: A Cluster-Randomized Trial. PLoS One 2016; 11(3):e0151422

9. Stack AG. Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. American journal of kidney diseases : the official journal of the National Kidney Foundation 2003;

41(2):310-8

10. Lin MY, Cheng LJ, Chiu YW *et al.* Effect of national pre-ESRD care program on expenditures and mortality in incident dialysis patients: A population-based study. PLoS One 2018; 13(6):e0198387

11. Ku E, Lee BJ, Wei J *et al.* Hypertension in CKD: Core Curriculum 2019. American journal of kidney diseases : the official journal of the National Kidney Foundation 2019; 74(1):120-31

12. Kusaba T, Kimura K. [Management of hypertension in CKD patients]. Nihon Rinsho 2008; 66(9):1747-52

13. Dare AJ, Fu SH, Patra J *et al.*Renal failure deaths and their risk factors in India 2001–13: nationally representative estimates from the Million Death Study. The Lancet Global Health 2017; 5(1):e89-e95

14. Wen CP, Cheng TYD, Tsai MK *et al.* All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. The Lancet 2008; 371(9631):2173-82

15. McCullough PA, Steigerwalt S, Tolia K *et al.* Cardiovascular disease in chronic kidney disease: data from the Kidney Early Evaluation Program (KEEP). Curr Diab Rep 2011; 11(1):47-55

16. Winocour PH. Diabetes and chronic kidney disease: an increasingly common

multi-morbid disease in need of a paradigm shift in care. Diabet Med 2018; 35(3):300-5

17. Peters E, van Elsas A, Heemskerk S *et al.* Alkaline phosphatase as a treatment of sepsis-associated acute kidney injury. J Pharmacol Exp Ther 2013; 344(1):2-7

18. Roughley MJ, Belcher J, Mallen CD *et al.*Gout and risk of chronic kidney disease and nephrolithiasis: meta-analysis of observational studies. Arthritis Res Ther 2015; 17:90

19. Zhao G, Huang L, Song M *et al.*Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies. Atherosclerosis 2013; 231(1):61-8

20. Ishihara M, Urushido M, Hamada K *et al.* Sestrin-2 and BNIP3 regulate autophagy and mitophagy in renal tubular cells in acute kidney injury. Am J Physiol Renal Physiol 2013; 305(4):F495-509

21. Borghi C, Rosei EA, Bardin T *et al.* Serum uric acid and the risk of cardiovascular and renal disease. J Hypertens 2015; 33(9):1729-41

22. Bermudez-Lopez M, Arroyo D, Betriu A *et al.* New perspectives on CKD-induced dyslipidemia. Expert opinion on therapeutic targets 2017; 21(10):967-76

23. Galvao TF, Araujo ME, Penha AP *et al.* Statins for early stage chronic kidney disease: an overview of reviews. Cardiovascular & hematological disorders drug

targets 2014; 14(3):205-11

24. Tangri N, Stevens LA, Griffith J *et al.* A predictive model for progression of chronic kidney disease to kidney failure. JAMA 2011; 305(15):1553-9

25. Hasegawa T, Sakamaki K, Koiwa F *et al.* Clinical prediction models for progression of chronic kidney disease to end-stage kidney failure under pre-dialysis nephrology care: results from the Chronic Kidney Disease Japan Cohort Study. Clin Exp Nephrol 2019; 23(2):189-98

26. Tonelli M, Muntner P, Lloyd A *et al.* Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. The Lancet 2012; 380(9844):807-14

27. Kornelius E, Chiou JY, Yang YS *et al.* The Diabetes Shared Care Program and Risks of Cardiovascular Events in Type 2 Diabetes. The American journal of medicine 2015; 128(9):977-85

Figure 1. Flow of patient selection for the study cohort.

From January 2012 to August 2017, 307,762 patients with chronic kidney disease (CKD) with more than two visits to the participating hospitals were identified in-Taipei Medical University Research Database (TMURD). Adult nonpregnant patients with CKD who met the specific criteria of stage I–IIIa CKD were regarded as patients with early CKD. Those who participated in the Early CKD Care Program comprised the case group, and those not participating in the program served as the control group. We conducted 1:2 propensity score matching with age, sex, estimated glomerular filtration rate, and CKD stage to reduce selection bias in the control group.

Figure 2. Cumulative incidence of progression to chronic kidney disease (CKD) stage IIIb in patients with stage I–IIIa CKD in case and control groups.

Kaplan–Meier analysis revealed that the cumulative incidence of progression to CKD stage IIIb was significantly higher in patients with stage I–IIIa CKD who did not participate in the Early CKD Care Program compared with that of those who participated in the program, during the follow-up period (log-rank test, $P = 0.02$)

Table 1. Baseline characteristics of enrollees

	Before propensity score matching				After propensity score matching			
	Total n = 159,774 N (%)	Case group n = 1,038 N (%)	Control group n = 158,736 N (%)	*P* value	Total n = 3,114 N (%)	Case group n = 1,038 N (%)	Control group n = 2,076 N (%)	*P* value
Age	59.1 ± 16.1	66.4 ± 12.8	59.1 ± 16.1	< 0.0001	66.6 ± 14.4	66.4 ± 12.8	66.7 ± 15.2	0.5917
Sex, male	89933 (56.3)	697 (67.2)	89236 (56.2)	< 0.0001	2054 (66.0)	697 (67.2)	1357 (65.7)	0.3358
eGFR	79.2 ± 14.0	62.2 ± 12.9	79.3 ± 13.9	< 0.0001	62.2 ± 13.2	62.2 ± 12.9	62.2 ± 13.3	0.8842
CKD Stage				< 0.0001				0.6009
1	44066 (27.6)	53 (5.1)	44013 (27.7)		166 (5.3)	53 (5.1)	113 (5.4)	
2	96435 (60.4)	418 (40.3)	96017 (60.5)		1216 (39.1)	418 (40.3)	798 (38.4)	
3a	19273 (12.1)	567 (54.6)	18706 (11.8)		1732 (55.6)	567 (54.6)	1165 (56.1)	
Comorbidity number				< 0.0001				< 0.0001
0	81576 (51.1)	66 (6.4)	81510 (51.4)		977 (31.4)	66 (6.4)	911 (43.9)	
1	33519 (21.0)	221 (21.3)	33298 (21.0)		698 (22.4)	221 (21.3)	477 (23.0)	
2	25865 (16.2)	303 (29.2)	25562 (16.1)		712 (22.9)	303 (29.2)	409 (19.7)	
3+	18814 (11.8)	448 (43.2)	18366 (11.6)		727 (23.4)	448 (43.2)	279 (13.4)	
Hypertension	44998 (28.2)	755 (72.7)	44243 (27.9)	< 0.0001	1448 (46.5)	755 (72.7)	693 (33.4)	< 0.0001
DM	22601 (14.2)	399 (38.4)	22202 (14.0)	< 0.0001	780 (25.1)	399 (38.4)	381 (18.4)	< 0.0001
Gout	7563 (4.73)	257 (24.8)	7306 (4.6)	< 0.0001	374 (12.0)	257 (24.8)	117 (5.6)	< 0.0001
Hyperlipidemia	28629 (17.9)	549 (52.9)	28080 (17.7)	< 0.0001	882 (28.3)	549 (52.9)	333 (16.0)	< 0.0001

Heart disease	30692 (19.2)	318 (30.6)	30374 (19.1)	< 0.0001	779 (25.0)	318 (30.6)	461 (22.2)	< 0.0001
Cerebrovascular disease	12143 (7.6)	132 (12.7)	12011 (7.6)	< 0.0001	356 (11.4)	132 (12.7)	224 (10.8)	< 0.0001

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; DM, diabetes mellitus.

Matched variables were age, sex, eGFR, and CKD stage.

Table 2. Univariable and multivariable Cox regression analysis for the risk of CKD I-IIIa progression to CKD IIIb among the Early Chronic Kidney Disease Care Program and other risk factors (n = 3,114)

	Univariable		Multivariable*	
	HR (95%CI)	*P* value	aHR (95%CI)	*P* value
Group				
Control	ref		ref	
Case	0.72 (0.61, 0.85)	< 0.0001	0.67 (0.55, 0.81)	< 0.0001
Comorbidity number				
0	ref		ref	
1	0.99 (0.77, 1.29)	0.9687	0.80 (0.54, 1.17)	0.2438
2	0.94 (0.73, 1.21)	0.6374	0.54 (0.29, 1.02)	0.0592
3+	1.16 (0.93, 1.46)	0.1931	0.46 (0.17, 1.23)	0.1195
Hypertension				
No	ref		ref	
Yes	0.98 (0.82, 1.16)	0.7803	1.24 (0.85, 1.81)	0.2654
DM				
No	ref		ref	
Yes	1.30 (1.07, 1.58)	0.0075	1.72 (1.23, 2.41)	0.0015
Gout				
No	ref		ref	
Yes	0.86 (0.67, 1.11)	0.2577	1.25 (0.87, 1.77)	0.2241
Hyperlipidemia				
No	ref		ref	
Yes	0.98 (0.81, 1.19)	0.8467	1.26 (0.88, 1.80)	0.2152
Heart disease				
No	ref		ref	
Yes	1.29 (1.06, 1.58)	0.0132	1.70 (1.20, 2.40)	0.0027
Cerebrovascular disease				
No	ref		ref	
Yes	1.36 (1.04, 1.78)	0.0270	1.59 (1.12, 2.27)	0.0104

DM, diabetes mellitus; aHR, adjusted hazard ratio; CI, confidence interval.

*The multivariable model was adjusted for all variables.

Table 3. Univariable and multivariable Cox regression analysis for the risk of baseline stage < 3a progression to stage 3b and stage 3a progression to stage 3b among the Early Chronic Kidney Disease Care Program and other risk factors

	Baseline Stage < 3a n = 1,382				Baseline Stage = 3a n = 1,732			
	Univariable		Multivariable*		Univariable		Multivariable*	
	HR (95%CI)	*P* value	aHR (95%CI)	*P* value	HR (95%CI)	*P* value	aHR (95%CI)	*P* value
Group								
Control	ref		ref		ref		ref	
Case	0.75 (0.52, 1.08)	0.1244	0.75 (0.48, 1.17)	0.2059	0.72 (0.60, 0.87)	0.0005	0.34 (0.51, 0.80)	< 0.0001
Comorbidity number								
0	ref		ref		ref		ref	
1	0.61 (0.33, 1.12)	0.1090	0.50 (0.20, 1.26)	0.1420	1.09 (0.82, 1.46)	0.5593	0.87 (0.56, 1.35)	0.5345
2	0.82 (0.49, 1.38)	0.4528	0.59 (0.14, 2.48)	0.4753	0.95 (0.71, 1.27)	0.7322	0.51 (0.25, 1.05)	0.0664
3+	0.99 (0.57, 1.72)	0.9617	0.64 (0.06, 6.54)	0.7025	1.18 (0.91, 1.52)	0.2062	0.39 (0.13, 1.20)	0.1013
Hypertension								
No	ref		ref		ref		ref	
Yes	0.93 (0.63, 1.36)	0.6964	1.10 (0.45, 2.66)	0.7025	0.99 (0.81, 1.20)	0.8805	1.32 (0.86, 2.03)	0.2019
DM								
No	ref		ref		ref		ref	
Yes	1.48 (0.94, 2.34)	0.0932	1.99 (0.87, 4.54)	0.1032	1.26 (1.01, 1.57)	0.0385	1.69 (1.16, 2.47)	0.0065
Gout								

No	ref		ref		ref		ref	
Yes	0.79 (0.43, 1.46)	0.4536	1.05 (0.45, 2.43)	0.9181	0.89 (0.67, 1.19)	0.4329	1.34 (0.90, 1.99)	0.1525
Hyperlipidemia								
No	ref		ref		ref		ref	
Yes	0.73 (0.48, 1.11)	0.1404	0.76 (0.34, 1.70)	0.5014	1.07 (0.87, 1.33)	0.5204	1.52 (0.99, 2.30)	0.0507
Heart disease								
No	ref		ref		ref		ref	
Yes	1.20 (0.74, 1.93)	0.4599	1.47 (0.70, 3.12)	0.3093	1.24 (0.99, 1.56)	0.0618	1.65 (1.12, 2.45)	0.0124
Cerebrovascular disease								
No	ref		ref		ref		ref	
Yes	1.78 (0.97, 3.28)	0.0644	1.89 (0.84, 4.26)	0.1247	1.25 (0.92, 1.70)	0.1602	1.48 (0.99, 2.21)	0.0576

DM, diabetes mellitus; HR, hazard ratio; aHR, adjusted HR.

*The multivariable model was adjusted for all variables.

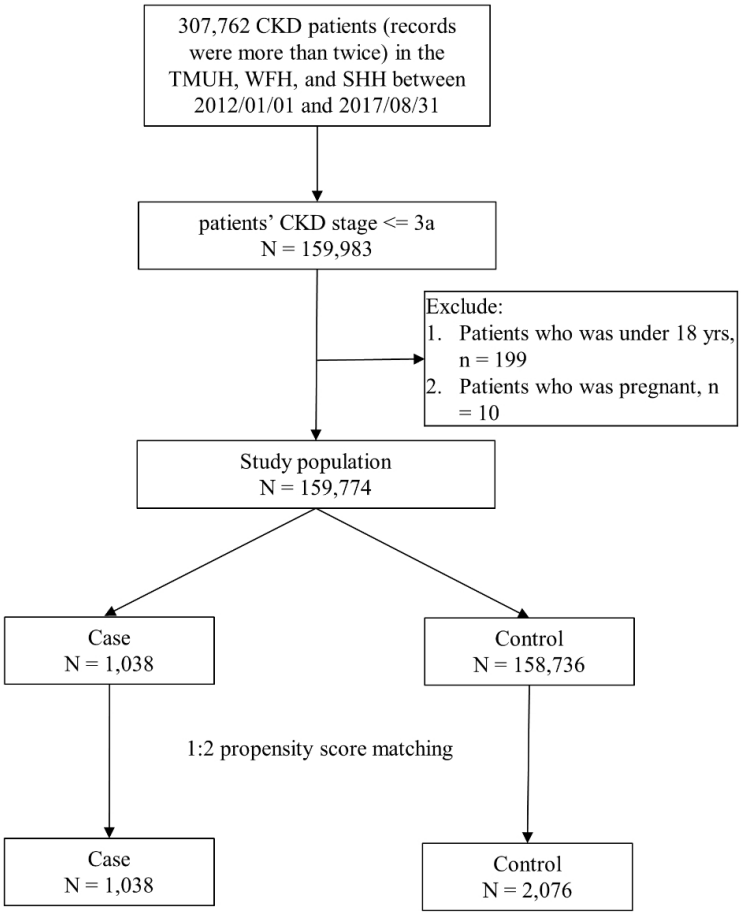

Figure 1. Flow chart of study population.

Figure 1. Flow of patient selection for the study cohort.
From January 2012 to August 2017, 307,762 patients with chronic kidney disease (CKD) with more than two visits to the participating hospitals were identified in the institutional and clinical research database of Taipei Medical University. Adult nonpregnant patients with CKD who met the specific criteria of stage I–IIIa CKD were regarded as patients with early CKD. Those who participated in the Early CKD Care Program comprised the case group, and those not participating in the program served as the control group. We conducted 1:2 propensity score matching with age, sex, estimated glomerular filtration rate, and CKD stage to reduce selection bias in the control group.

107x109mm (300 x 300 DPI)

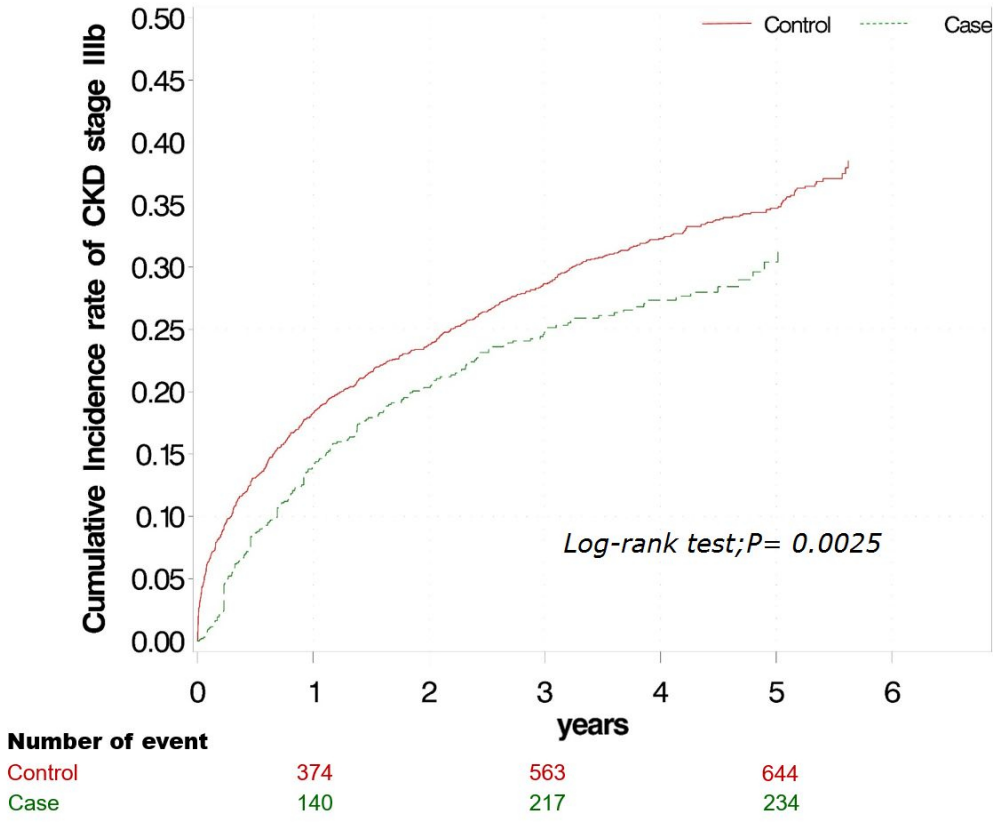

Figure 2. Cumulative incidence of progression to chronic kidney disease (CKD) stage IIIb in patients with stage I–IIIa CKD in case and control groups.
Kaplan–Meier analysis revealed that the cumulative incidence of progression to CKD stage IIIb was significantly higher in patients with stage I–IIIa CKD who did not participate in the Early CKD Care Program compared with that of those who participated in the program, during the follow-up period (log-rank test, P = 0.025)

95x80mm (300 x 300 DPI)

Early Chronic Kidney Disease Care Program delays kidney function deterioration in patients with Stage I–IIIa chronic kidney disease: An observational cohort study in Taiwan

Shu-Fen Niu, Chung-Kuan Wu, Nai-Chen Chuang, Ya-Bei Yang, Tzu-Hao Chang

Supplementary material

Table S1. International Classification of Diseases, ninth Revision, Clinical Modification codes used to identify comorbid conditions in this study.

Table S2. Distribution of eGFR amongst cases and controls during the follow-up period.

Table S1. International Classification of Diseases, ninth Revision, Clinical Modification codes used to identify comorbid conditions in this study.

Co-morbid diseases	Corresponding ICD-9-CM codes
Hypertension	401.x–405.x
Diabetes mellitus	250.x
Gout	274.x
Hyperlipidemia	272.x
Heart disease	410.x–414.x; 420.x–429.x
Cerebrovascular disease	430.x–438.x

Table S2. Distribution of eGFR amongst cases and controls during the follow-up period.

	eGFR				
	Control (n = 2076)		Case (n = 1038)		p-value
	N	Mean ± SD	N	Mean ± SD	
Follow-up time					
Baseline	2076	62.2 ± 13.3	1038	62.2 ± 12.9	0.8842
1 year	479	67.0 ± 26.0	398	63.3 ± 17.9	**0.0122**
2 years	385	65.4 ± 24.5	239	65.5 ± 19.6	0.9406
3 years	301	63.0 ± 24.1	143	66.5 ± 19.3	0.0970
5 years	181	56.7 ± 20.9	17	59.1 ± 13.9	0.6338

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,6,7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6,7,8.9
Bias	9	Describe any efforts to address potential sources of bias	8,9,16
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	8,9
		(*d*) If applicable, explain how loss to follow-up was addressed	8,9
		(*e*) Describe any sensitivity analyses	8,9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,10
		(b) Give reasons for non-participation at each stage	9,10
		(c) Consider use of a flow diagram	23
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10,24,25
		(b) Indicate number of participants with missing data for each variable of interest	9,10,23
		(c) Summarise follow-up time (eg, average and total amount)	10,11,12,23
Outcome data	15*	Report numbers of outcome events or summary measures over time	11,12,23,26,27
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11,12,23,24,25,26,27,28
		(*b*) Report category boundaries when continuous variables were categorized	11,12,23,24,25,26,27,28
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11,12,27,28
Discussion			
Key results	18	Summarise key results with reference to study objectives	12,13,14,15,16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13,14,1,16,17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.