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# Rate of kidney function decline and factors predicting progression of kidney disease in type 2 diabetes mellitus patients with reduced kidney function: A nationwide retrospective cohort study

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## Abstract

Currently, the data on independent risk factors for the progression of kidney disease in type 2 diabetes mellitus (T2DM) patients with CKD are limited. This study aimed to investigate CKD progression in T2DM patients who have reduced kidney function with baseline estimated glomerular filtration rate (eGFRs) between 15 and 59 mL/min/1.73 $m^2$. This study was composed of a nationwide retrospective cohort of adult T2DM patients from 831 public hospitals in Thailand during the year 2015. T2DM patients with CKD stages 3 and 4 were followed up, until development of CKD stage 5, requirement of chronic dialysis, loss to follow-up, death, or 31 May 2018, whichever came first. Cox proportional hazard regression was utilized for analysis. A total of 8464 participants were included; 30.4% were male. The mean age was 69 ± 10 years. The mean eGFR was 45 ± 11 mL/min/1.73 $m^2$. The incidence of CKD stage 5 or the need for chronic dialysis was 16.4 per 1000 person-years. The annual rate of eGFR decline during a mean follow-up of 29 months was −2.3 mL/min/1.73 $m^2$; 14.4% had a rapid decline in eGFR. The risk factors associated with progression to CKD stage 5 or the need for chronic dialysis were diabetes duration, systolic blood pressure,

serum uric acid, albuminuria, and baseline eGFR. Conversely, older age and the use of renin-angiotensin aldosterone system blockade were associated with decreased risks for rapid CKD progression and incidence CKD stage 5 or dialysis. This study identifies multiple predictive risk factors that support a multifaceted approach to prevent progression of advanced CKD.

**KEYWORDS**

albuminuria, chronic kidney disease, end-stage kidney disease, glomerular filtration rate, type 2 diabetes mellitus

## 1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease with worldwide prevalence and causes increased morbidity and mortality.[1,2] T2DM and its sequelae can contribute to significant global health burden. It is frequently complicated by CKD, which is an emerging global public health issue.[3,4] Approximately 35% of adult patients with T2DM have CKD and incidence rates of end-stage kidney disease (ESKD) due to diabetic nephropathy, have been reported as high as 804.0 per 100 000 person-years.[5,6] Long-term renal replacement therapy and its associated high costs have placed increasing burdens on the national health insurance system in recent years.[7]

Several predictors for decline in estimated glomerular filtration rate (eGFR) and progression to ESKD have been identified.[8–11] However, the course of renal disease progression is heterogeneous and complex in T2DM, due to individual patient characteristics and disease-specific conditions.[12,13] Although these studies had identified risk factors for the development of advanced kidney disease or a rapid decline in renal function in T2DM with CKD, the findings of these studies were limited due to small population sizes and short-term follow-up.[9–13] In addition, reported risk and protective factors for CKD progression among T2DM patients were conflicting.[14–16]

This observational cohort study is performed in T2DM patients with reduced kidney function (baseline eGFR of 15-59 mL/min/1.73 $m^2$). Our aim is to assess the incidence and risk factors of CKD stage 5 or the need for chronic dialysis, the prevalence, and associated risk factors for a rapid decline in renal function.

## 2 | PATIENTS AND METHODS

### 2.1 | Study design and population

This study was comprised of a nationwide, multicenter, observational cohort in Thailand with data obtained from a secondary analysis of the DM/HT dataset from 1 January 2015 through 31 December 2015. Patients receiving care at clinics and public hospitals of the Thai Ministry of Public Health in the Thailand National Health Security Office's program were included in a nationwide survey annually. Goal of the survey was to assess the status of medical care in T2DM patients. T2DM patients with age ≥ 35 years receiving regular medical care more than 12 months at the aforementioned 831 clinics and public hospitals prior to study enrolment were included in this DM/HT dataset.[17] Only the patients receiving primary care in Bangkok and university hospitals were included. This study utilized a two-stage stratified cluster sampling design for selection of a nationally and provincially representative sample of T2DM patients in Thailand. The initial stage of sample collection consisted of the provinces that constituted 77 strata. The second stage of sample collection was the at the hospital level in each province, which were stratified into five strata, according to the hospital. These five strata consisted of regional (>500 beds), provincial (200-500 beds), large community (80-120 beds), medium community (60 beds), and small community (10-30 beds) hospitals. This study included all regional ($n$ = 25), provincial ($n$ = 70), and community ($n$ = 736) hospitals. Of the 736 community hospitals, 10%, 20%, and 70% were large, medium, and small community hospitals, respectively. All patients were recruited from outpatient clinic. Prior to enrollment, a written informed consent was obtained. This study was approved by both the Institutional Review Board of the Royal Thai Army Medical Department and the Ethical Review Committee for Research in Human Subjects, the Ministry of Public Health of Thailand (IRB number 0445/2556). Data were collected by trained research nurses into a case record form after reviewing medical records. Medical Research Network of the Consortium of Thai Medical Schools' central data management team ensured that the data process collection was performed per study protocol. Data management team performed inquiries to study sites and verified data. Site monitoring was randomly performed in approximately 10% of study sites. This study was reported according to

the STrengthening The Reporting of OBservational Studies in Epidemiology (STROBE) guidelines.[18]

As this study aimed to investigate CKD progression in T2DM patients with reduced kidney function, only patients with baseline eGFR of 15 to 59 mL/min/1.73 $m^2$ were included in this analysis. Patients who had baseline eGFR of less than 15 or greater than 60 mL/min/1.73 $m^2$ or those who were on chronic dialysis were excluded.

## 2.2 | Data collection

Baseline clinical characteristics, demographics, anthropometrics, medications, and laboratory data were collected from the medical record. Blood pressure was measured by trained nurses using a mercury sphygmomanometer with appropriate upper arm cuff size after patients had sat quietly for at least 5 minutes. eGFR was calculated with chronic kidney disease epidemiology collaboration equation[19] based on the most recent outpatient creatinine. eGFR is categorized into three groups based on KDIGO guidelines for CKD[20]: 45 to 59 mL/min/1.73 $m^2$ (stage 3A), 30 to 44 mL/min/1.73 $m^2$ (stage 3B), and 15 to 29 mL/min/1.73 $m^2$ (stage 4). The urinary albumin excretion was estimated based on the spot urine albumin-to-creatinine ratio. Moderately and severely increased albuminuria was defined as urinary albumin-to-creatinine ratio of 30 to 299 and ≥300 mg/g, respectively.

Patients returned annually for clinic follow-up visits. During the follow-up visit, information on the eGFR and whether the patient was dialysis dependent was obtained. Patients were followed up until the development of nondialysis dependent CKD stage 5 or requirement of dialysis, loss to follow-up, death, or 31 May 2018, whichever came first.

## 2.3 | Outcome assessment

The primary outcomes of interest were the incidence of CKD stage 5 (defined as eGFR < 15 mL/min/1.73 $m^2$) and initiation of chronic dialysis.

Secondary outcome was rapid decline in eGFR, defined as a decrease in eGFR ≥ 5 mL/min/1.73 $m^2$ in 1 year.[20,21] For each patient, a linear regression model of eGFR by time was created, and the slope of the regression line was used to estimate a patient's annual change in eGFR.

## 2.4 | Statistical analysis

Continuous variables are presented as mean ± SD (SD). Categorical variables are presented as a count with percentage of the whole. Incidence of CKD stage 5 or dialysis-dependence was calculated as ([total number of new CKD stage 5 or dialysis dependence] × 1000% [total patient-years of follow-up]). Univariate regression analysis was initially performed. Multivariate regression analysis with inclusion of all variables with $P$ value < 0.05 in univariate analysis was subsequently performed using a stepwise backward selection method to identify independent risk factors for the outcomes of interest. Cox proportional hazard analysis was used for time-to-event analysis of incident CKD and dialysis dependence. Logistic regression was used to identify a rapid decline in eGFR, and linear regression was used for the annual change in eGFR. A $P$-value <0.05 was considered statistically significant. All statistical analyses were performed using STATA version 14.1 (StataCorp, College Station, TX).

# 3 | RESULTS

## 3.1 | Baseline characteristics

A total of 8464 adult T2DM patients with a baseline eGFR of 15 to 59 mL/min/1.73 $m^2$ were enrolled during the study period. The baseline clinical characteristics are shown in Table 1. Of these patients, 2571 (30.4%) were male. The mean age was 69 ± 10 years. The mean duration from diagnosis of diabetes was 10 ± 6 years. Eighty-nine percent of patients had hypertension, 74% had dyslipidemia, 7% had coronary artery disease, 7% had diabetic retinopathy, and 4% had cerebrovascular disease. Medications use included 33% on insulin, 55% on RAAS blockers, 73% on statins, and 62% on antiplatelets. The mean BMI was 25.0 ± 4.5 kg/$m^2$. The mean systolic blood pressure and diastolic blood pressure were 135 ± 16 and 73 ± 10 mm Hg, respectively. The mean hemoglobin A1c (HbA1c) was 7.8 ± 2.0%. The mean serum uric acid was 6.8 ± 1.8 mg/dL. The mean eGFR was 45 ± 11 mL/min/1.73 $m^2$. Fifty-four percent of patients had CKD stage 3A, 34% had CKD stage 3B, and 12% had CKD stage 4. In all, 14.4% had albuminuria with 11.5% of that percentage labeled as moderately increased and 2.9% as severely increased.

During a mean follow-up of 29 months, 335 (4%) patients developed CKD stage 5 or required dialysis. Among this subgroup of patients, 284 (85%) were nondialysis dependent, 29 (9%) received hemodialysis, and 22 (7%) received peritoneal dialysis. The incidence of CKD stage 5 or the need for chronic dialysis among T2DM with CKD stages 3 and 4 was 16.4 per 1000 person-years. The rate of annual eGFR decline was 2.3 mL/min/1.73 $m^2$, and 1140 (14.4%) patients had a rapid decline in eGFR (Table 2). CKD stage 3A had a higher rate of annual eGFR decline with CKD stages 3B and 4 following behind, respectively (Table 2).

**TABLE 1** Baseline characteristics

| Characteristics | All |
|---|---|
| N (%) | 8464 |
| Age (years) | 69.3 ± 9.5 |
| Male | 2571 (30.4) |
| Duration of diabetes (y) | 9.9 ± 5.7 |
| Hypertension | 7559 (89.3) |
| Dyslipidemia | 6238 (73.7) |
| Gout | 868 (10.3) |
| Coronary artery disease | 552 (6.5) |
| Cerebrovascular disease | 350 (4.1) |
| Diabetic retinopathy | 569 (6.7) |
| Smoking | 162 (1.9) |
| Metformin | 4185 (49.4) |
| Sulfonylurea | 4576 (54.1) |
| Insulin | 2810 (33.2) |
| RAAS blockade | 4645 (54.9) |
| Statins | 6195 (73.2) |
| Antiplatelets | 5235 (61.9) |
| Body mass index (kg/m$^2$) | 25.0 ± 4.5 |
| Systolic blood pressure (mm Hg) | 135.1 ± 16.1 |
| Diastolic blood pressure (mm Hg) | 72.7 ± 10.4 |
| Baseline HbA1c (%) | 7.8 ± 2.0 |
| Serum uric acid (mg/dL) | 6.8 ± 1.8 |
| Albuminuria | 1217 (14.4) |
| Normal or mildly increased | 7247 (85.6) |
| Moderately increased | 973 (11.5) |
| Severely increased | 244 (2.9) |
| eGFR (mL/min/1.73 m$^2$) | 44.6 ± 10.7 |
| Baseline CKD stage | |
| CKD stage 3A | 4586 (54.2) |
| CKD stage 3B | 2893 (34.2) |
| CKD stage 4 | 985 (11.6) |
| Mean observation time (mo) | 29.1 ± 5.5 |

*Note*: Continuous variables are presented as means ± SD. Categorical variables are presented as a count with percentage.
Abbreviation: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; RAAS blockade, renin angiotensin aldosterone blockade.

**TABLE 2** Outcomes

| Outcomes | |
|---|---|
| CKD stage 5 or dialysis | 335 (4.0) |
| CKD stage 5 not on dialysis | 284 (84.8) |
| Hemodialysis | 29 (8.7) |
| Peritoneal dialysis | 22 (6.6) |
| Time at risk (person-years) | 20 480 |
| Incidence of CKD stage 5 or dialysis (per 1000 person-years) | 16.4 |
| Annual eGFR decline (mL/min/1.73 m$^2$/y) | 2.3 ± 0.1 |
| Rate eGFR decline of CKD stage 3A | 2.8 ± 8.9 |
| Rate eGFR decline of CKD stage 3B | 1.9 ± 7.5 |
| Rate eGFR decline of CKD stage 4 | 1.3 ± 7.7 |
| Rapid decline eGFR (decrease ≥5 mL/min/1.73 m$^2$/y) | 1140 (14.4) |

*Note*: Continuous variables are presented as means ± SD. Categorical variables are presented as a count with percentage.
Abbreviation: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

## 3.2 | Risk factors for CKD stage 5 or dialysis dependence among T2DM with reduced kidney function

The multivariate analysis identified the following risk factors for incident CKD stage 5 or dialysis dependence: increased duration from diagnosis of T2DM (HR 1.17 per 5-year increase, 95% CI 1.01-1.35); increased systolic blood pressure (HR 1.13 per 10-mm Hg increase, 95% CI 1.01-1.27); increased baseline serum uric acid (HR 1.24 per 1 mg/dL increase, 95% CI 1.13-1.36); presence of albuminuria (HR 1.62, 95% CI 1.04-2.51), particularly severely increased albuminuria (HR 1.59, 95% CI 1.02-2.49); and decreased baseline eGFR (HR 3.03 per 10 mL/min/1.73 m$^2$ decrease, 95% CI 2.30-4.00). Compared to CKD stage 3A, CKD stage 3B was associated with HR of 3.47 (95% CI 1.56-7.76) and CKD stage 4 was associated with HR of 24.09 (95% CI 11.31-51.32) for an increased risk of incident CKD stage 5 or dialysis dependence. In contrast, older age (HR 0.64, 95% CI 0.53-0.78) and use of RAAS blockers (HR 0.39, 95% CI 0.24-0.64) were associated with a decreased risk of incident CKD stage 5 or dialysis dependence (Table 3).

## 3.3 | Factors associated with a rapid eGFR decline in T2DM with reduced kidney function

In the multivariate analysis, a rapid decline in eGFR was associated with an increased duration of T2DM (OR 1.20 per 5-year increase, 95% CI 1.07-1.33), history of coronary artery disease (OR 1.86, 95% CI 1.16-2.96), increased systolic blood pressure (OR 1.13 per 10 mm Hg increase, 95% CI 1.02-1.26), increased baseline serum uric acid

**TABLE 3** Risk factor of CKD stage 5 or the need for chronic dialysis among type 2 DM with reduced kidney function analysis using Cox proportional hazard model

| Parameters | Person-years of exposure | Events (incidence rate/1000 person-years) | Crude HR (95% CI) | *P* value | Adjusted HR (95% CI) | *P* value |
|---|---|---|---|---|---|---|
| Age (per 10 y increase) | | | 0.82 (0.74-0.91) | <.001 | 0.64 (0.53-0.78) | <.001 |
| Gender | | | | | | |
| Female | 14 210.4 | 229 (16.1) | 1 (reference) | | — | — |
| Male | 6270.5 | 106 (16.9) | 1.02 (0.81-1.28) | .89 | — | — |
| Duration of diabetes (per 5 y increase) | | | 1.16 (1.06-1.27) | .001 | 1.17 (1.01-1.35) | .04 |
| Hypertension | 18 312.4 | 312 (17.0) | 1.58 (1.04-2.41) | .03 | — | — |
| Dyslipidemia | 15 155.0 | 238 (15.7) | 0.83 (0.66-1.06) | .13 | — | — |
| Gout | 2142.8 | 51 (23.8) | 1.40 (1.04-1.88) | .03 | — | — |
| Coronary artery disease | 1365.7 | 41 (30.0) | 1.81 (1.31-2.51) | <.001 | — | — |
| Cerebrovascular disease | 852.3 | 17 (19.9) | 1.25 (0.77-2.03) | .38 | — | — |
| Diabetic retinopathy | 1426.8 | 39 (27.3) | 1.54 (1.10-2.15) | .01 | — | — |
| Smoking | 391.6 | 5 (12.8) | 0.76 (0.31-1.84) | .54 | — | — |
| RAAS blockade | 11 239.2 | 58 (5.2) | 0.18 (0.14-0.24) | <.001 | 0.39 (0.24–0.64) | <.001 |
| Statins | 15 084.0 | 240 (15.9) | 0.85 (0.67-1.08) | .18 | — | — |
| Antiplatelets | 12 692.8 | 190 (15.0) | 0.79 (0.64-0.98) | .03 | — | — |
| Body mass index (per 5 kg/m$^2$ increase) | | | 0.85 (0.76-0.96) | <.01 | — | — |
| Systolic blood pressure (per 10 mm Hg increase) | | | 1.19 (1.11-1.27) | <.001 | 1.13 (1.01–1.27) | 0.04 |
| Diastolic blood pressure (per 10 mm Hg increase) | | | 0.98 (0.79-1.21) | .84 | - | — |
| Baseline HbA1c < 7.0% | 5282.7 | 64 (12.1) | 0.89 (0.66-1.21) | .45 | - | — |
| Serum uric acid (per 1 mg/dL increase) | | | 1.40 (1.29-1.51) | <.001 | 1.24 (1.13–1.36) | <.001 |
| Any albuminuria | 2961.9 | 81 (27.3) | 1.77 (1.37-2.27) | <.001 | 1.62 (1.04–2.51) | .03 |
| Normal | 17 519 | 254 (14.5) | 1 (reference) | | 1 (reference) | |
| Moderately increased | 2363.3 | 59 (25.0) | 1.65 (1.24-2.19) | .001 | 1.27 (0.95-1.69) | .11 |
| Severely increased | 598.7 | 22 (36.7) | 2.19 (1.42-3.39) | <.001 | 1.59 (1.02–2.49) | .04 |
| Baseline eGFR (per 10 mL/min/1.73 m$^2$ decrease) | | | 3.51 (3.03-4.05) | <.001 | 3.03 (2.30–4.00) | <.001 |
| CKD stage 3A | 11 024.1 | 29 (2.6) | 1 (reference) | | 1 (reference) | |
| CKD stage 3B | 7106.1 | 79 (11.1) | 3.83 (2.50-5.86) | <.001 | 3.47 (1.56–7.76) | <.01 |
| CKD stage 4 | 2350.8 | 227 (96.6) | 32.44 (22.03-47.76) | <.001 | 24.09 (11.31–51.32) | <.001 |

Abbreviation: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HR, hazard ratio; RAAS blockade, renin angiotensin aldosterone blockade.

(OR 1.29 per 1 mg/dL increase, 95% CI 1.20-1.40), and presence of severely increased albuminuria (OR 2.04, 95% 1.09-3.81). A decreased risk for rapid decline in eGFR was associated with use of RAAS blockers (OR 0.61, 95% CI 0.46-0.82), and decreased baseline eGFR (OR 0.58 per 10 mL/min/1.73 m$^2$ decrease, 95% CI 0.49-0.68) (Table 4).

### 3.4 | Factors associated with annual eGFR change in T2DM with reduced kidney function

The multivariate analysis identified older age, increased duration of T2DM, history of coronary artery disease,

**TABLE 4** Factor associated with a rapid decline in GFR among type 2 DM with reduced kidney function using multiple logistic regression analysis

| Parameters | Prevalence (%) | Crude OR (95%CI) | *P* value | Adjusted OR (95% CI) | *P* value |
|---|---|---|---|---|---|
| Age (per 10 y increase) | | 0.96 (0.90-1.02) | .21 | — | — |
| Gender | | | | — | — |
| Female | 784 (14.3) | 1 (reference) | | — | — |
| Male | 356 (14.7) | 1.03 (0.90-1.18) | .67 | — | — |
| Duration of diabetes (per 5 y increase) | | 1.09 (1.03-1.15) | <.01 | 1.20 (1.07–1.33) | .001 |
| Hypertension | 1044 (14.8) | 1.34 (1.07-1.68) | .01 | — | — |
| Dyslipidemia | 838 (14.4) | 0.99 (0.85-1.14) | .84 | — | — |
| Gout | 140 (17.1) | 1.26 (1.03-1.52) | .02 | — | — |
| Coronary artery disease | 116 (22.1) | 1.76 (1.42-2.18) | <.001 | 1.86 (1.16–2.96) | .01 |
| Cerebrovascular disease | 59 (17.9) | 1.31 (0.98-1.75) | .07 | — | — |
| Diabetic retinopathy | 121 (22.4) | 1.80 (1.45-2.22) | <.001 | — | — |
| Smoking | 20 (13.2) | 0.90 (0.56-1.44) | .65 | — | — |
| RAAS blockade | 513 (11.9) | 0.63 (0.56-0.72) | <.001 | 0.61 (0.46–0.82) | .001 |
| Statins | 826 (14.3) | 0.95 (0.83-1.10) | .49 | — | — |
| Antiplatelets | 712 (14.5) | 1.02 (0.90-1.16) | .75 | — | — |
| Body mass index (per 5 kg/m$^2$ increase) | | 0.98 (0.91-1.04) | .48 | — | — |
| Systolic blood pressure (per 10 mmHg increase) | | 1.11 (1.07-1.16) | <.001 | 1.13 (1.02–1.26) | <.01 |
| Diastolic blood pressure (per 10 mmHg increase) | | 1.11 (0.99-1.24) | .08 | — | — |
| Baseline HbA1c < 7.0% | 246 (12.1) | 0.90 (0.80-1.01) | .06 | — | — |
| Serum uric acid (per 1 mg/dL increase) | | 1.25 (1.18-1.32) | <.001 | 1.29 (1.20–1.40) | <.001 |
| Any albuminuria | 216 (18.9) | 1.47 (1.25-1.73) | <.001 | 1.38 (0.67-1.98) | .08 |
| Normal | 924 (13.7) | 1 (reference) | | 1 (reference) | |
| Moderately increased | 156 (17.1) | 1.31 (1.08-1.57) | <.01 | 1.20 (0.79-1.82) | .39 |
| Severely increased | 60 (25.8) | 2.19 (1.62-2.96) | <.001 | 2.04 (1.09–3.81) | .03 |
| Baseline eGFR (per 10 mL/min/1.73 m$^2$/ decrease) | | 0.85 (0.80-0.91) | <.001 | 0.58 (0.49–0.68) | <.001 |
| CKD stage 3A | 690 (16.3) | 1 (reference) | | 1 (reference) | |
| CKD stage 3B | 336 (12.4) | 0.73 (0.63-0.83) | <.001 | 0.46 (0.33-0.63) | <.001 |
| CKD stage 4 | 114 (12.1) | 0.71 (0.57-0.88) | .001 | 0.31 (0.19-0.53) | <.001 |

Abbreviation: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HR, hazard ratio; RAAS blockade, renin angiotensin aldosterone blockade.

diabetic retinopathy, increased systolic blood pressure, increased baseline HbA1c, increased baseline serum uric acid, and presence of albuminuria as factors associated with a greater annual eGFR decline, whereas use of RAAS blocker, increased BMI, higher diastolic blood pressure, and decreased baseline eGFR were associated with a decreased annual eGFR decline (Table 5).

## 4 | DISCUSSION

In this nationwide study of T2DM patients with reduced kidney function, there was a predominance of patients with female sex, older age, hypertension, dyslipidemia, and use of medications such as RAAS blockers, statin, and antiplatelets. Our study showed that incidence of CKD stage 5 or the requirement for chronic dialysis for

**TABLE 5** Factor associated with annual change in eGFR among type 2 DM with reduced kidney function using multiple linear regression analysis

| Parameters | Crude standardized coefficient | *P* value | Adjusted standardized coefficient | *P* value |
|---|---|---|---|---|
| Age (years) | −0.14 | <.001 | −0.18 | <.001 |
| Male | −0.05 | <.001 | — | — |
| Duration of diabetes (years) | −0.08 | <.001 | −0.06 | .01 |
| Hypertension | −0.08 | <.001 | — | — |
| Dyslipidemia | −0.01 | .20 | — | — |
| Gout | −0.06 | <.001 | — | — |
| Coronary artery disease | −0.06 | <.001 | −0.05 | .04 |
| Cerebrovascular disease | −0.01 | .46 | — | — |
| Diabetic retinopathy | −0.08 | <.001 | −0.06 | .02 |
| Smoking | 0.01 | .63 | — | — |
| RAAS blockade | 0.05 | <.001 | 0.10 | <.001 |
| Statins | −0.02 | .04 | — | — |
| Antiplatelets | −0.02 | .04 | — | — |
| Body mass index (kg/m$^2$) | 0.04 | <.01 | 0.04 | .06 |
| Systolic blood pressure (mm Hg) | −0.08 | <.001 | −0.07 | <.01 |
| Diastolic blood pressure (mm Hg) | 0.03 | <.01 | 0.06 | .02 |
| Baseline HbA1c (%) | −0.02 | .08 | −0.06 | .02 |
| Serum uric acid (mg/dL) | −0.25 | <.001 | −0.25 | <.001 |
| Albuminuria | −0.07 | <.001 | −0.05 | .03 |
| Moderately increased albuminuria | −0.04 | .001 | −0.03 | .04 |
| Severely increased albuminuria | −0.07 | <.001 | −0.05 | <.001 |
| Initial CKD stage (3a-4) | 0.07 | <.001 | 0.07 | <.01 |

Abbreviation: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; RAAS blockade, renin angiotensin aldosterone blockade.

patients in Thailand was similar to a report from Belgium,[22] but lower than the reported incidence rate in the United States.[2,23,24] Possible explanations for the lower incidence than reported in the United States was that our patients had less albuminuria, decreased length of diabetes, less obesity, early diabetic medication use, increased RAAS blocker use, more dietary fiber, less acid-ash diet, and less acidosis.[25]

The prevalence of a rapid decline in eGFR in this study was similar to an Italian report.[9] The rate of annual eGFR decline in this study was comparable to a prior report from Japan[26] and Canada.[27] Our study's annual eGFR decline was greater than those reported from a healthy population,[28] an Italian cohort,[9] and the chronic renal insufficiency cohort.[23] This difference in annual eGFR decline may be due to different baseline characteristics and environmental exposures, varying proportion of patients on optimal treatment, and a different proportion of patients at high risk. For instance, our study had a higher prevalence of hypertension and a lower rate of RAAS blockers use, and hypertension and diabetes are intrinsically linked to vascular injury and progression to advanced renal disease.[29,30] Pathologically, hypertension in T2DM could increase glomerular capillary hydraulic pressure and single nephron glomerular filtration rate. These mechanisms can cause increased proteinuria, inflammation, and glomerular cell injury[31,32] leading to an accelerated rate of eGFR decline annually.

We also identified risk factors for incident CKD stage 5 or dialysis dependence. These included increased duration of diabetes, systolic blood pressure, serum uric acid, and albuminuria. This study's findings were similar to many reports from the United States,[30,33] Italy,[9] Japan,[26] and Belgium[22] which report albuminuria as an important risk factor for rapid eGFR decline and progression to end-stage kidney disease in patients with T2DM with reduced kidney function, independent from blood pressure control. Our report also confirms that severely

increased albuminuria is strongly predictive for progression to advanced renal disease or long-term dialysis. Previous studies in Pima Indians and Japanese patients with type 2 diabetes showed that severely increased albuminuria predicts ESKD.[34,35] With regard to blood pressure this study confirms that high systolic blood pressures in T2DM are associated with a steep decline in kidney function.[36]

Additional risk factors for both a decline in annual eGFR and a more rapid decline in renal function in T2DM with reduced kidney function included coronary artery disease. This may be due to the shared parallel pathophysiology of atherosclerotic disease resulting in micro- and macro-vascular disease.[37] However, our study failed to demonstrate a statistically significant association between coronary artery disease and incident CKD stage 5 or dialysis dependence. Possible explanations include insufficient power due to the smaller number of patients or due to a drop out effect as these high-risk patients may die before developing ESKD.[38] Other comorbidities such as gout and diabetic retinopathy were also statistically significantly associated with an annual change in renal function. Previous reports[39–41] demonstrated that gout and hyperuricemia could increase the annual decline in renal function via several proposed mechanisms, such as intrarenal endothelial dysfunction, vascular smooth muscle proliferation,[42] and tubulointerstitial fibrosis[39] via renal tubulointerstitial injury and inflammation from uric acid crystal and NSAIDs use.[40] The association between diabetic retinopathy and rate of eGFR decline was similar to a prior study from Japan.[11] It is hypothesized that this association between diabetic retinopathy and kidney disease[43] is due to the shared hyperglycemic and microvascular pathophysiological risk factors.[44] A previous study indicated that age was associated with a decline in eGFR.[45] Our study also supports that age had linear association with annual decline renal function. On the other hand, our result showed the association of old age diverged on incident CKD stage 5 or dialysis dependence. According to a US veteran cohort,[46] Taiwan[10] and Belgium cohort[22] have identified that younger age is in fact an independent risk factor for developing ESKD. This phenomenon could explain by age-period-cohort effect.[47] This effect may be due to the increased mortality rate in older T2DM patients with a reduced renal function who die before reaching the development of ESKD.[38] Another explanation of this effect is that elderly patients with reduced renal function may have different pathophysiological or genetic traits that place them at lower risk for advanced-stage renal disease than other younger patients.[48] Results from International Network of Chronic Kidney Disease (iNETCKD) cohort studies also corroborate our findings.[49] The lower baseline renal function was associated with a greater annual change in eGFR and an increased risk of incident CKD stage 5 or the requirement for chronic dialysis. A previous cohort[22] also showed that patients with advanced stage CKD at baseline had a greater chance of developing ESKD. On the contrary, our results show that advanced stage CKD at baseline was inversely associated with annual eGFR decline and a rapid decline in eGFR. This could be explained by more advanced stage CKD patients receiving more intensified treatment for prevention of a rapid decline eGFR in the CKD clinic.

Our study demonstrated that higher baseline HbA1c was associated with an annual decrease in renal function. Our result was similar to previous cohort from Taiwan. Findings showed the association of baseline HbA1c and decline renal function in addition to blood pressure and peripheral arterial stiffness.[50] A recent meta-analysis from randomized controlled trials had shown that RAAS blockade reduces the composite outcome of renal replacement therapy and doubling of serum creatinine, but it did not slow the rate of eGFR decline in T2DM patients with nondialysis-dependent CKD stages 3 to 5.[14] Our study also supports RAAS blockers as a strongly independent protective factor for development of incident CKD stage 5 or dialysis dependence, and was inversely associated with both a rapid decline in renal function and an annual decrease in renal function. Our study also found that increased BMI was not a risk factor for advanced CKD, a rapid decline of eGFR, and annual eGFR decline. These results are similar to those originating from the United States,[51] Canada,[52] and Uruguay,[53] but are contrasting to an Italian report suggesting that morbid obesity and by proxy, BMI, was associated with a rapid decline in eGFR.[9] In addition, several cohorts from Japan and Taiwan also failed to demonstrate BMI as a risk factor for developing ESKD.[10,13] Our results pertaining to BMI and renal function may be explained by the shorter follow-up period, a greater proportion of our patients being in the overweight category rather than obese, or that a higher BMI in CKD stages 3 and 4 may represent a better nutritional status that is less commonly found in uremic patients.[54] An increase in diastolic blood pressure was associated with a lower annual eGFR decline. The reason for this association is unknown. A possible mechanism may be that lower diastolic blood pressures are found with vascular calcification and arterial stiffening,[55,56] both of which are found in patients with advanced CKD.

There are several strengths of this large-scale population-based nationwide representative cohort. Our statistical analysis for associations between each clinical variable and outcome of interest utilized Cox proportional hazard model, multiple logistic regression analysis, and multiple linear regression analysis that accounted for several possible confounders such as age, gender, smoking, BMI, duration of diabetes, blood pressure,

comorbidities, medications, baseline eGFR, serum uric acid, and urinary albumin excretion. Comorbidities consisted of hypertension, dyslipidemia, diabetic retinopathy, coronary artery disease, cerebrovascular disease, and gout. In the final adjusted model, medications adjusted for included RAAS blockers, statins, and antiplatelet agents. Lastly, our study analyzed eGFR using the CKD-EPI formula, which is now recommended in current practice.

Following are the limitations of the study. First, data collection was performed via retrospective medical record review, therefore missing diagnoses or incomplete data records cannot be identified or corrected. In addition, by performing a retrospective review that included only patients with available eGFR, we may have selected for a population at higher risk for progressive CKD as medical providers were likely checking this level due to medical concern. Second, only half of the participating centers used isotope dilution-mass spectrometry-traceable enzymatic method for the measurement of serum creatinine. However, all centers did have their own laboratory standard quality control system that applied to local practice. Third, we lack kidney biopsy data that might show the cause of differences in the rate of renal progression. Furthermore, we did not have mortality data, and this may cause an underestimation of advanced-stage renal disease. Fourth, this study does not demonstrate whether treatment with antidiabetic drugs or glycemic control would decrease the incidence of advanced CKD or slow its progression. Fifth, although this was a nationwide, multicenter cohort study, the patient population in this study was predominantly elderly female, and thus, might limit generalizability of the study to population in other countries. Lastly, the urinary albumin value from the parent dataset was markedly different in laboratory testing techniques. This may cause misclassification of severity for patients with albuminuria.

Our findings may help focus current research into the mechanism and treatment of CKD in patients with T2DM. It may also assist in developing individual and public health strategies for the prevention of CKD progression in type 2 diabetes with pre-existing advanced kidney disease. The identification of high-risk factors may allow earlier modification of risk factors for progression, and the institution of protective factors to slow the rate of renal function decline. The avoidance of end-stage kidney disease has far-reaching impacts on morbidity, mortality, and healthcare expenditure for our patients.

## 5 | CONCLUSION

This study provides further evidence in support of the factors that predict end-stage kidney disease in type 2 diabetes mellitus patients with reduced renal function. It also identifies risk factors for an annual eGFR decline or those at risk for rapid decline in kidney function. These factors include blood pressure, serum uric acid, RAAS blockers, and albuminuria. Development of widespread multifactorial intervention on the multiple predictive risk factors found in our study should be implemented to reduce the healthcare burden.

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## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

## AUTHOR CONTRIBUTIONS

All authors had access to the data and a role in writing this manuscript.

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