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Renal disease progression and associated factors in type 2 diabetes patients: A retrospective cohort study

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Abstract

Predicting renal disease progression in patients with diabetes is an important clinical and policy challenge. This study aimed to investigate the survival function of renal disease progression by assessing the doubling of serum creatinine (DSC) over time and the factors associated with DSC in patients with type 2 diabetes mellitus (T2DM). This retrospective cohort study included 3,465 T2DM patients from a tertiary hospital in Thailand. Patients' data from 2011 to 2017 were extracted from the electronic medical records. The Kaplan-Meier method and Cox's proportional hazard model were analyzed to determine the survival time of T2DM patients with DSC and the factors associated with DSC. Results showed that at the end of the follow-up period, 1,028 of 3,465 patients underwent DSC. The incidence rate of DSC was 5.0/1,000 person-months. The median survival time of DSC was 81.5 months (95% confidence interval [CI]: 79.28 – 83.74). The variables associated with an increased hazard ratio of DSC were high triglyceride level (≥200 mg/dl) (adjusted hazard ratio (aHR): 1.17, 95% CI: 1.01 – 1.34), hypertension (aHR: 1.33, 95% CI: 1.18 – 1.51), high glycated hemoglobin level (≥7.0%) (aHR: 1.27, 95% CI: 1.07–1.51), and high total cholesterol level (≥ 240 mg/dl) (aHR: 1.58, 95% CI: 1.32 – 1.87). Obesity (Body Mass Index (BMI) of ≥ 25.0 kg/m^2) was negatively associated with DSC (aHR: 0.80, 95% CI: 0.71 – 0.91). In conclusion, T2DM patients under observation had a median survival time of DSC of 6.8 years. Hypertension and uncontrolled blood glucose and lipids are predictors of renal disease progression in T2DM patients.

Keywords: Biochemical parameter, Doubling serum creatinine, Renal disease progression, Survival analysis, Type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common diseases affecting the health delivery system and occurs in 415 million people [1]. Approximately 80% of people with T2DM are living in the low- and middle-income countries [2, 3]. In addition, in Southeast Asia, the prevalence of T2DM has steadily increased [4]. For Thailand, the crude cumulative incidence rates over 8 years were estimated to be 249/10,000 for men and 220/10,000 for women [5].

T2DM is the most frequent cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [6], which requires long-term and costly care. Diabetic kidney disease (DKD) affects approximately 40% of patients with T2DM [7]. Since no symptoms are often found in the early stages, CKD is usually detected when the disease has progressed or is already at the end stage. The overall objective of continuous care for T2DM patients is to reduce the development of complications [6]. This highlights the need to identify the risk factors for the loss of kidney function early in the course of nephropathy. The identification of risk factors influencing the long-term prognosis is essential for providing effective care that can impede the development of ESRD. This study aimed to assess the progress of kidney dysfunction. Therefore, doubling of serum creatinine (DSC) was selected

as an outcome measure in monitoring CKD and not the often-used serum creatinine values [8]. As an often-used accepted endpoint measure, DSC reflects sustained changes in serum creatinine as a marker of a declining kidney function [9, 10]. It is used to calculate the estimated glomerular filtration rate (eGFR) and can be easily monitored [11].

This study intended to shed light on how T2DM contributes to CKD. Secondary data from a cohort of T2DM patients were obtained from a provincial hospital in Northeast Thailand. This study aimed to observe the development of CKD in patients with T2DM based on the demographic and clinical laboratory data. The observation time was approximately 7 years, and the DSC values over time were evaluated.

2. Materials and methods

2.1 Study design and population

The investigation intended to test the development of increasing kidney function failure in a selected group of T2DM patients retrospectively. Thus, this retrospective cohort study was based on the electronic patient records derived from a provincial hospital in Northeast Thailand, located approximately 500 km northeast of Bangkok. Patients with T2DM were diagnosed by a physician and registered at a provincial hospital. The diagnosis was based on the laboratory results and clinical features commonly used to identify patients with T2DM according to the criteria proposed by the American Diabetes Association (ADA) [12]. At baseline, patients with T2DM whose serum creatinine (s-Cr) data were available in the electronic patient records were included in the study. Patients who underwent hemodialysis or peritoneal dialysis, or had a history of a kidney transplant were excluded. Of the 29,173 T2DM patients under the hospital's care from 2011 to 2017 with available s-Cr data, we recruited the patients registered between January 1, 2011 and December 31, 2013 (accrual period); this was the most suitable period for selection because the data predominantly contained the most critical variables meeting the objective for this study and allowed a maximum observation time of 7 years. The follow-up period after the accrual period was between January 1, 2014, and December 31, 2017. As the study aimed to evaluate the progress of kidney malfunction, records of patients with normal kidney function at the start of the observation, indicated by a serum creatinine (s-Cr) value of ≤1.5 mg/dl, were used. We excluded those with an s-Cr value of >1.5 mg/dl at baseline due to the already existing renal insufficiency/ failure [13]. In addition, patients <20 years of age and those with incomplete variables were excluded. A total of 3,465 patients were finally selected for the study (Figure 1). The selection process enabled the retrieval of a sufficient number of patient records according to the estimated sample size. The sample size calculation based on Cox proportional hazards models [14] was performed using the pilot study data, which were adjusted for covariates and censored data.

Patients whose serum creatinine values twice as high as the concentration from the initial value called DSC or event was no longer followed up. Some of the participants were event free (without DSC) during the study period and hence were censored. Participants who dropped out prior to the completion of the study were also censored.

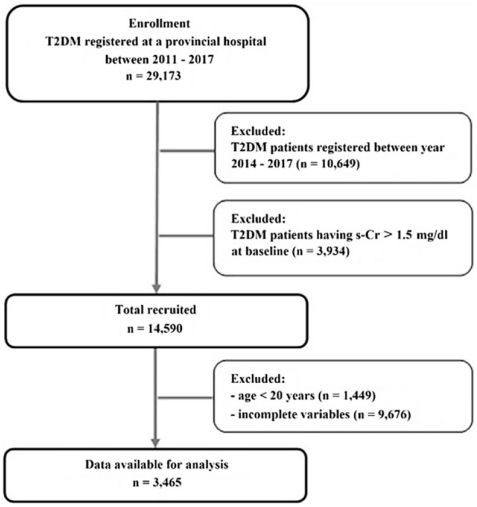

Figure 1 Flowchart of the participant selection process.

2.2 Demographic and clinical data of the study patients

The demographic data obtained upon admission included age, sex, marital status, educational level, and source of income (categorized as "occupation"). The weight and height were used to calculate the body mass index (BMI). A BMI (weight [kg]/height [m]^2) of ≥25 kg/m^2 was defined as obesity in the Asian population according to the World Health Organization (WHO) [15]. Data on smoking status and alcohol consumption were collected upon admission. Hypertension was defined as a systolic blood pressure (SBP) of >140 mmHg, a diastolic blood pressure (DBP) of >90 mmHg, or both according to the International Society of Hypertension Global Hypertension Practice Guidelines [16]. The baseline clinical laboratory data from the patients' electronic records were retrieved, including serum creatinine, hemoglobin (Hb), fasting plasma glucose (FPG), glycated hemoglobin (HbA_{1C}), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL); the levels of each laboratory parameter were measured from the patient's serum using an auto-analyzer (Furuno CA-800 analyzer). All laboratory examinations were performed following the standard procedures: s-Cr by enzymatic method, FPG by enzymatic hexokinase, HbA_{1C} by turbidimetric immunoassay, TC by CHOD-PAP method, TG by enzymatic colorimetric assay, LDL by direct enzymatic assay, and HDL by direct enzymatic assay. The eGFR was calculated using the CKD-EPI equation [17]. The cut-off values for lipid profile parameters were based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines [18]. The cut-off values used for FPG and HbA_{1C} were based on ADA criteria [12]. Due to the inherent limitations of using secondary data, additional variables of interest, such as albuminuria and cystatin C, were not continuously available in the patients' records. The provincial hospitals operate state-of-the-art clinical laboratories, under the supervision of the Ministry of Public Health of the Thai government, using approved laboratory equipment and effective clinical methods, and internal quality control was implemented in the laboratory twice a day.

2.3 Statistical analysis

STATA program version 14.0 (StataCorp, College Station, TX) was used for data processing and statistical analyses. Descriptive statistical methods were used to outline the demographic and biochemical parameters. Survival time was assessed using the Kaplan-Meier and log-rank tests. To investigate the observational association between the risk factors and DSC, a Cox regression analysis was performed. Using Cox's proportional hazards model related to DSC, the multivariable analysis was based on those factors that were significantly associated with DSC in the bivariable analysis. Backward elimination was used to remove the variables that exceeded a
p >0.05, from the likelihood ratio test. The established Kaplan-Meier statistical tool, addressed in the standard statistical nomenclature as "survival" rate, was applied in this study to describe the progress of kidney malfunction.

3. Results

3.1 Baseline characteristics of T2DM patients

The baseline characteristics of 3,465 patients confirmed to have T2DM at the time of hospital admission were obtained. Approximately 74.4% of the patients were women, while 47.4% were older adults (≥60 years old). Moreover, 93% were married, and 86.5% had graduated from primary school. Over 75% of the respondents engaged in agricultural activities. Few patients admitted that they smoked and consumed alcohol. Almost 45% of the patients were classified as overnourished or obese (Table 1).

Table 1 Baseline characteristics of the T2DM patients.

Characteristics	Number (%) (n = 3,465)
Sex	
Male	887(25.6)
Female	2,578(74.4)
Age (years)	
20–39	128(3.7)
40–59	1,695(48.9)
≥60	1,642(47.4)
Marital status	
Single	142(4.1)
Married	3,232(93.3)
Widow or divorced	91(2.6)
Education (n = 3,350)	
Primary school	2,900(86.5)
High school	277(8.3)

Table 1 Baseline characteristics of the T2DM patients (continued).

Characteristics	Number (%) (n = 3,465)
Vocational college	33(1.0)
Bachelor's degree	140(4.2)
Occupation (n = 3,335)	
Unemployed	521(15.6)
Agriculture	2,533(76.0)
Self-employed business	154(4.6)
Government official	127(3.8)
Smoking	
No smoking	3,348(96.6)
Smoking	117(3.4)
Alcohol drinking	
No drinking	3,344(96.5)
Drinking	121(3.5)
Body mass index (kg/m^2)	
<25.0	1,907(55.0)
≥25.0	1,558(45.0)

3.2 Biochemical parameters

Data on BP, serum glucose levels, and HbA_{1C}, as well as variables related to lipid status and kidney function at baseline are listed in Table 2. Approximately 40% of the patients had an SBP of ≥140 mmHg. About 20% of the patients had a DBP of ≥90 mmHg, while 43% of the patients with hypertension had either a high DBP or a high SBP. Moreover, 57% of the patients had an FPG of ≥140 mg/dl, and 80% had an HbA_{1C} value of ≥7%. The TG and LDL levels in most patients were normal. The TC level was high in 40% of the patients, while the HDL level was low in 50% of the patients.

Table 2 Blood pressure and clinical laboratory results of the T2DM patients at the time of recruitment.

Parameters	Number (%) (n = 3,465)
Systolic blood pressure (mmHg)	
<140	2,109(60.9)
≥140	1,356(39.1)
Diastolic blood pressure (mmHg)	
<90	2,788(80.5)
≥90	677(19.5)
Hypertension (mmHg)	
SBP[a] <140 or DBP[a] <90	1,958(56.5)
SBP ≥140 or DBP ≥90	1,507(43.5)
Fasting plasma glucose (mg/dl)	
<140	1,503(43.4)
≥140	1,962(56.6)
Glycated hemoglobin (%)	
<7.0	699(20.2)
≥7.0	2,766(79.8)
Total cholesterol (mg/dl)	
<200	2,120(61.2)
200–239	885(25.5)
≥240	460(13.3)
Triglyceride (mg/dl)	
<200	2,550(73.6)
≥200	915(26.4)
Low-density lipoprotein (mg/dl)	
<160	3,138(90.6)
≥160	327(9.4)
High-density lipoprotein (mg/dl)	
≥40	1,645(47.5)
<40	1,820(52.5)
Hemoglobin (g/dl)	
≥13.0 (m)[b], ≥12.0 (f)[b]	2,807(81.0)
<13.0 (m), <12.0 (f)	658(19.0)
eGFR ($ml/min/1.73m^2$)	
≥60	2,761(79.7)
<60	704(20.3)
Serum creatinine (mg/dl)	
Mean ± SD, median (Q1 : Q3)	0.88 ± 0.23, 0.90 (0.70 : 1.00)

[a]SBP = systolic blood pressure, DBP = diastolic blood pressure.
[b]m = male, f = female.

3.3 Survival time of doubling serum creatinine

For the 3,465 T2DM patients, the total follow-up time was 198,175 person-months, and 1,028 (29.7%) patients doubled their serum creatinine; therefore, 70.3% of the survival time was censored. The cumulative T2DM survival rates measured based on the DSC were 97.7% in the first year, 87.4% in 3 years, 75.5% in 5 years, and 44.8% at the end of follow-up (Figure 2). The median survival time of DSC was 81.5 months (95% confidence interval (CI): 79.28–83.74). The incidence rate of renal disease progression by DSC was 5.0 per 1,000 person-months.

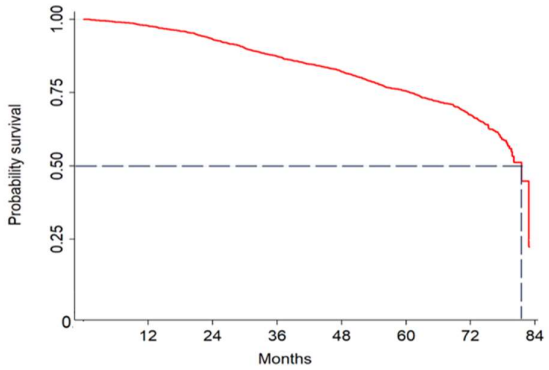

Figure 2 Progression of kidney malfunction expressed by the Kaplan-Meier method along a time axis.

3.4 Factors associated with doubling of serum creatinine

Multivariable Cox regression analysis was used to identify the factors associated with DSC. Age, hypertension, HbA_{1C}, TC, TG, and BMI were significantly associated with an increased DSC hazard ratio (HR). Patients aged 40–59 years had a significantly reduced risk of DSC, and this phenomenon was also observed among those aged 60 years and older. Therefore, those aged 20–39 years had a higher risk of developing DSC (Table 3 and Figure 3A). Similarly, patients with a BMI of ≥25 kg/m^2 had a lower risk of DSC than those with a BMI of <25 kg/m^2 (Table 3 and Figure 3B). An HbA_{1C} value of ≥7% (HR: 1.27, 95% CI: 1.07–1.51) (Table 3 and Figure 3D) and a TG level of ≥200 mg/dl (HR: 1.17, 95% CI: 1.01–1.34) contributed significantly to the model (Table 3 and Figure 3F). Patients with hypertension (HR: 1.33, 95% CI: 1.18–1.51) (Table 3 and Figure 3C) and a TC level of ≥240 mg/dl (HR: 1.58, 95% CI: 1.32–1.87) had the highest risk of DSC (Table 3 and Figure 3E).

Table 3 Multivariable Cox regression analysis of DSC in T2DM patients

Variables	Crude HR (95% CI)	Adjusted HR (95% CI)	*p*-value
Age (years)			
20–39	1	1	
40–59	0.61 (0.45–0.82)	0.59 (0.44–0.81)	0.001
≥60	0.72 (0.53–0.97)	0.71 (0.53–0.97)	0.031
Sex			
Male	1	1	
Female	0.92 (0.80–1.06)	0.91 (0.79–1.05)	0.195
Hypertension (mmHg)			
SBP <140, DBP <90	1	1	
SBP ≥140, DBP ≥90	1.34 (1.19–1.52)	1.33 (1.18–1.51)	<0.001
Glycated hemoglobin (%)			
<7.0	1	1	
≥7.0	1.26 (1.07–1.49)	1.27 (1.07–1.51)	0.005
Total cholesterol (mg/dl)			
<200	1	1	
200–239	1.02 (0.89–1.20)	0.99 (0.87–1.24)	0.895
≥240	1.66 (1.41–1.96)	1.58 (1.32–1.87)	<0.001
Triglyceride (mg/dl)			
<200	1	1	
≥200	1.28 (1.12–1.47)	1.17 (1.01–1.34)	0.032
Body mass index (kg/m^2)			
<25.0	1	1	
≥25.0	0.81 (0.72–0.92)	0.80 (0.71–0.91)	0.001

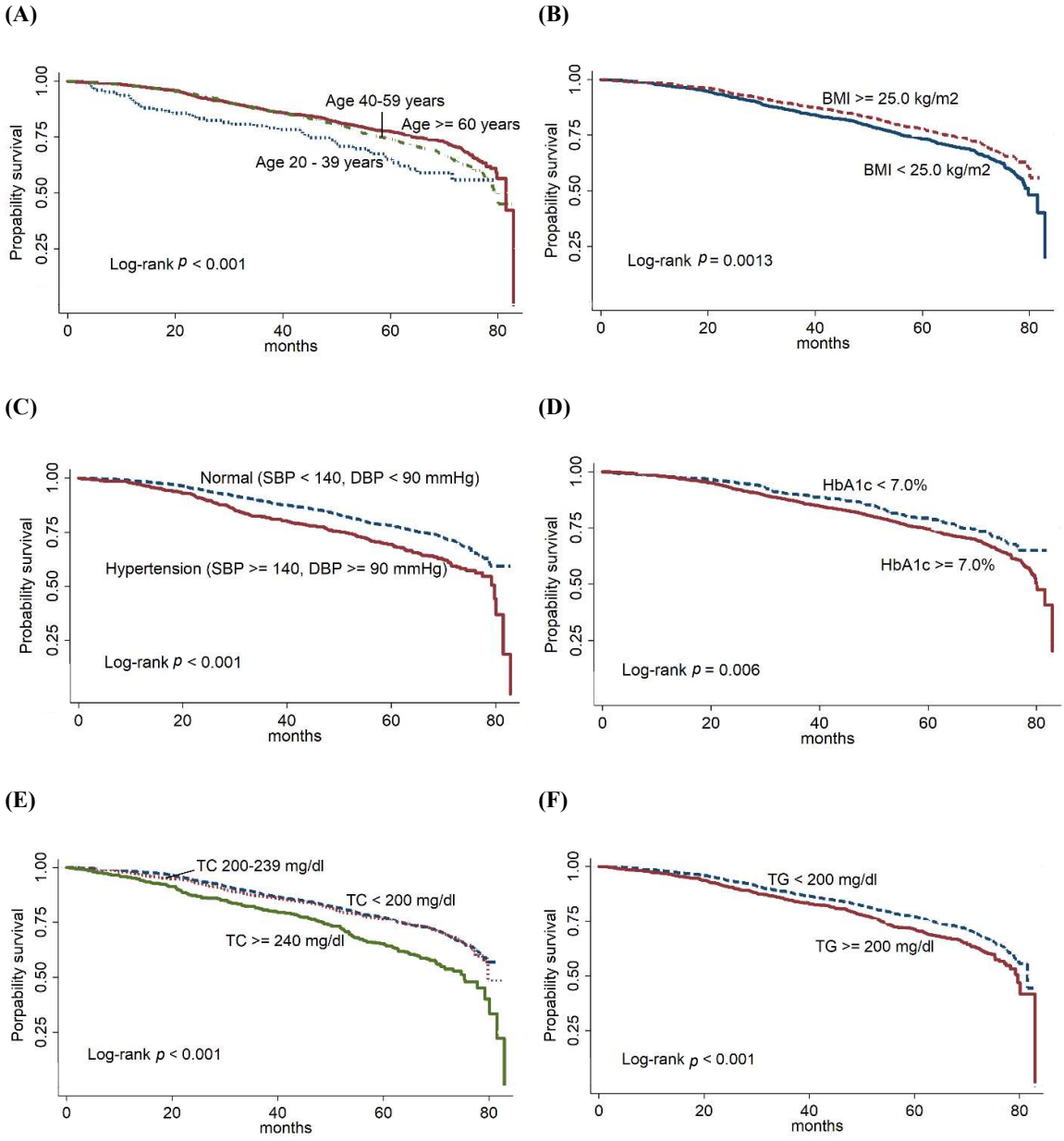

Figure 3 Cox regression and risk factors contributing to the kidney malfunction; (A) Age, (B) BMI, (C) hypertension, (D) HbA_{1C}, (E) TC, and (F) TG.

4. Discussion

The electronic hospital records of a provincial hospital in Northeast Thailand were assessed, including the 7-year retrospective data of 3,465 T2DM patients (2011–2017). The study found that the median survival time of patients with DSC was 6.8 years, and 1,028 (29.7%) patients developed kidney dysfunction as indicated by DSC. This result is consistent with that of the study by Rossing et al. (2004), who reported that 63 (28%) patients with T2DM doubled their baseline serum creatinine levels within a 6.5-year follow-up [19]. These findings support the results of a study by Vejakama et al. (2015), which found that the kidney malfunction in diabetes patients progressed more rapidly based on their GFR categories, with a median time for CKD progression of 5 to 8 years [20].

The finding that older age somehow protects T2DM patients against DSC was unexpected and needs further exploration. Hypothetically, older patients are more conscious about their health status and are more careful in adjusting their dietary intake based on their disease status. In addition, a slow progressive eGFR decline was

observed after the age of 60 years [21]. Younger age groups, who are still fully occupied in performing demanding daily activities, might have less opportunity to observe an appropriate dietary scheme. Likewise, obesity might have a protective effect on the deteriorating kidney function, as reported elsewhere [22]. The underlying mechanisms are still not entirely understood. Obesity probably increases the GFR, and neurohumoral factors causing renal vasodilation and high BP contribute to the increase in renal plasma flow [23]. However, these results contradicts to those of Fox et al. (2004), who reported that an increased BMI led to the impairment in the kidney function [24]. The difference in the study population might explain the differences in the findings. The progression of kidney disease may lower the patient's weight and BMI. Such an effect left the more affluent nourished patients, such as those at lower risk for CKD. In a longitudinal study, Galal et al. (2007) found that obese patients have an excellent probability of surviving for a long time, despite the existence of cardiovascular and renal diseases [25], which is consistent with the outcome of this study.

Poor control of blood glucose and lipids contributes to the reduction in kidney function among T2DM patients. This assumption is based on the significant contribution of high TC, high TG, and high HbA_{1C} values to the DSC model. Similar results were obtained for T2DM patients in India, Taiwan, and Thailand in terms of TG levels [26-28]. Dyslipidemia is an essential clinical abnormality in patients with DM. This study found that patients with T2DM who had high TG and TC serum concentrations had higher HRs for developing DSC (1.17 for TG and 1.58 for elevated TC). Zaman et al. (2018) also showed a positive relationship between plasma TG concentration and CKD in Thai patients with T2DM. Diabetes patients with very high TG levels (>500 mg/dl) were 3.4 times more likely to develop CKD than the regular TG group [29]. Altemtam et al. (2012) reported that a high level of serum TGs was associated with an eGFR decline [30]; Tolonen et al. (2009) also reported that patients with high TG levels were at greater risk of progression of diabetic nephropathy [31]. The elevated serum TG concentration exhibited by the patients in this study might be due to their traditional diet, especially in the northeast of Thailand. The staple diet, particularly in rural areas, includes a glutinous rice with a high glycemic index, thus resulting in the high serum TG levels in the overall population [32]. These results imply that dyslipidemia should be considered a risk factor for renal disease progression.

According to our findings, the HR for developing DSC in patients with a high HbA_{1C} concentration (≥7.0%) was 1.27 times higher than that of patients with controlled HbA_{1C} levels throughout the observation period. The majority of patients with T2DM continuously developed uncontrolled HbA_{1C}. Radcliffe et al. (2017) [33] and Wong et al. (2016) [23] pointed out that HbA_{1C} was a risk factor for DSC. Since ordinary patients are unaware that an HbA_{1C} value reflects their long-term glucose intake and cannot control the values just within a short time, the variable is a good indicator of unbalanced dietary intake in patients with diabetes. Therefore, chronic hyperglycemia is a crucial risk factor for the progression of DKD [7]. Many studies have demonstrated that strict glycemic control can delay the onset of DKD and slow its progression [34]. Clinical practice guidelines [17] recommend a target HbA_{1C} value of approximately 7.0% to prevent or delay the progression of the microvascular complications of diabetes. The same applies to the study of the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/ EDIC), revealing that patients with moderate albuminuria, but lower HbA_{1C} levels, had a lower risk of developing severe kidney dysfunction [35].

Hypertension plays a significant role in the development of pathological kidney function. Probably on an individual basis for a considerable proportion of patients, hypertensive values seemed to have contributed to the decrease in kidney function. However, it remains unclear whether kidney disease triggers an increase in BP or vice versa, as hypertension contributes to DSC [36]. Patients should be aware of the need to regularly measure their BP and seek doctors' advice once they recognize that their BP levels periodically increase.

In summary, the results fit well into the overall risk environment of populations in South and Southeast Asia, including Thailand. This applies to the main occupation that the majority of patients indicated as their economic and cultural background. Engaging in agricultural activities in tropical countries has recently emerged as an independent risk factor for kidney diseases. This probably contributed to the findings of this study [37]. In addition, part of Pakistan, India, and Thailand belong to the "stone belt." Hence, obstructive nephropathy due to urolithiasis is common. Other environmental circumstances have been assumed to cause CKD, especially in the rural areas, such as the use of pesticides, fluoride, aluminum, and cadmium [38].

This study has some limitations. Important variables such as albuminuria, medication, and treatment adherence could not be assessed. This study did not consider the final clinical status of the patient, that is, whether they died of CKD or had other comorbidities. Therefore, residual confounding may have influenced the study results. However, this study used information derived from a large number of patients and high-quality data to support the results.

5. Conclusion

Within the 7-year study period, about 30% of T2DM patients developed renal disease as having DSC with the median survival time of having DSC 6.8 years. The incidence rate of DSC was 5.0/1,000 person-months. Hypertension, uncontrolled blood glucose, and lipid levels contributed to the development of DSC. It was

unexpected that older age and overnutrition had a protective effect against DSC. When caring for T2DM patients, one should focus primarily on those whose creatinine values continuously increase. The control of hypertension, blood glucose, and blood lipids in T2DM patients should be further emphasized to prevent the progression of renal disease.

6. Ethical approval

This study relied on secondary data from the medical records of a provincial hospital after obtaining permission from the director of the hospital. The database was anonymized for confidentiality reasons, and the information of individual patients cannot be traced back. The findings presented do not specifically refer to any particular person. This study was approved by the Institutional Review Board (IRB) of Khon Kaen University, Thailand (approval no. HE622037) and the Hospital's Ethics Committee (no. 0032.125/97).

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