Glucose Regulation States and Renal Outcomes in Patients with Preserved Kidney Function

Keywords
diabetes mellitus, chronic kidney disease, prediabetes, estimated glomerular filtration rate, mortality

Abstract

Introduction
We investigated the associations between glucose regulation states and the risks of adverse renal outcomes and all-cause mortality in a large outpatient population.

Material and methods
We retrospectively identified patients with a baseline estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m2 between 2010 and 2022. Patients were categorized into glucose regulation states according to their history of diabetes and glycated hemoglobin (HbA1c) levels. Data on each patient's renal function were obtained from electronic medical records, and survival status was confirmed through March 2023. The outcomes of interest included adverse renal outcome (≥40% reduction of eGFR from baseline) and all-cause mortality.

Results
A total of 43,422 patients were analyzed. After a median follow-up of 6.9 years, patients with diabetes, stratified by HbA1c levels (<7.0%, 7.0 to <9%, and ≥ 9%), exhibited a significantly higher risk of adverse outcomes (adjusted HR 1.922, 2.376 and 3.306, respectively, all p<0.001) compared with those with normal glucose tolerance. In contrast, there was no significant difference in adverse outcomes between patients with prediabetes and those with normal glucose tolerance (adjusted HR 1.090, p=0.107).

Conclusions
Compared with normal glucose tolerance, patients with diabetes had a higher risk of adverse outcomes, even among those with an HbA1c <7%. Maintaining glycemic control within the non-diabetic range may help mitigate long-term adverse renal outcomes.

Title: Glucose Regulation States and Renal Outcomes in Patients with Preserved Kidney Function

Running head: Glucose Regulation States versus Adverse Renal Outcomes

Introduction

Prediabetes, defined as impaired glucose metabolism that does not meet the diagnostic criteria for diabetes, imposes a substantial global disease burden. In 2021, the global prevalence of prediabetes ranged from 5.8% to 9.1%, depending on the diagnostic criteria used [1]. In Taiwan, the burden is even higher, with an estimated prevalence of 21.08% between 2019 and 2020 [2]. Moreover, patients with prediabetes face an increased risk of diabetes-related complications and all-cause mortality [3]. Given its high prevalence and associated complications, prediabetes represents a major public health concern.

Diabetic nephropathy is the leading cause of incident end-stage renal disease in Taiwan [4]. While the association between diabetes and adverse renal outcomes is well established [5], including a dose-response relationship between elevated glycated hemoglobin (HbA1c) and kidney function decline [6], the renal risk associated with prediabetes remains controversial. Two major meta-analyses have reported conflicting results [7,8]. However, these meta-analyses may have been affected by bias due to several limitations in the included studies, including indirect assessment of prediabetes, relatively short follow-up periods, and inadequate adjustment for potential confounders. A recent prospective cohort study demonstrated an increased risk of chronic kidney disease (CKD) in patients with prediabetes, even after accounting for progression to

diabetes [9]. However, this association was no longer significant after full adjustment for established CKD risk factors.

Owing to the conflicting evidence and limitations of previous studies, further robust investigations are warranted to clarify the impact of prediabetes on kidney function outcomes. Therefore, we conducted this study to investigate the associations between different glucose regulation states (normal glucose tolerance, prediabetes, and diabetes stratified by HbA1c: <7.0%, 7.0 to <9.0%, and ≥ 9.0%) and the risk of adverse renal outcomes in a large outpatient population with baseline estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m².

Materials and Methods

This was a retrospective cohort study, and the study protocol was approved on July 8, 2025 (Approval number: CE25495A) by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan. We conducted this study in accordance with the Declaration of Helsinki. A waiver of informed consent was granted by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan, due to the retrospective study design and minimal risk to the study subjects. We collected data from electronic medical records between 2010 and 2022. Collected data included demographic characteristics, medical history, and laboratory measurements, such as serum creatinine, fasting plasma glucose, HbA1c, and lipids profiles.

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [10]. Patients with a baseline eGFR <60 mL/min/1.73 m^2 or missing serum creatinine data were excluded from the analysis. Patients without a diagnosis of diabetes and who were not receiving glucose-lowering

therapy in outpatient clinics were classified as having normal glucose tolerance or prediabetes based on HbA1c levels (<5.7% and 5.7 to 6.4%, respectively). Patients with a diagnosis of diabetes or who had received glucose-lowering therapy in outpatient clinics were stratified according to their mean HbA1c levels during the first year of follow-up (diabetes with HbA1c <7.0%, diabetes with HbA1c 7.0 to <9.0%, and diabetes with HbA1c ≥ 9.0%). Patients having type 1 diabetes, missing HbA1c data, or a follow-up period of less than one year were excluded from the analysis.

Data on all-cause mortality were obtained from the Ministry of Health and Welfare, R.O.C., with analyses performed on de-identified data. We determined each patient's final eGFR and calculated the change from baseline, expressed as eGFR change per year. We compared the rate of eGFR decline among five glucose regulation groups: normal glucose tolerance, prediabetes, and diabetes stratified by HbA1c (<7.0%, 7.0 to <9.0%, and ≥ 9.0%). The primary outcomes of this study were a 40% decline in eGFR and a composite outcome of a 40% decline in eGFR or all-cause mortality. We selected a 40% decline in eGFR as the primary outcome because it has been associated with over a ten-fold increased risk of kidney failure compared with individuals with stable eGFR [11]. In addition, a 40% reduction in eGFR over 2–3 years has been accepted by multiple international agencies and regulatory bodies as a surrogate endpoint for kidney disease progression in clinical trials [12-14]. This endpoint is currently recognized by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [15].

We conducted all statistical analyses using the Statistical Package for the Social Sciences (IBM SPSS version 22.0; International Business Machines Corp., NY, USA). Patients were stratified according to their glucose regulation states: normal glucose

tolerance, prediabetes, and diabetes categorized by HbA1c (<7.0%, 7.0 to <9.0%, and ≥ 9.0%). Between-group differences in clinical variables were assessed for statistical significance using the Student's t-test for continuous variables and the Chi-square test for categorical variables. Kaplan-Meier survival curves were used to compare survival without a 40% eGFR decline among the five groups. Cox-proportional hazard models with multivariate adjustment for age, sex, body mass index, hypertension, cardiovascular disease, and low-density lipoprotein cholesterol were conducted to determine the risk of primary outcomes among the five groups. As a sensitivity analysis, the study population was stratified by baseline HbA1c levels (<5.7%, 5.7 to 6.4%, 6.5 to <7%, 7 to <9%, and ≥ 9%), and the associations between the five HbA1c categories and the primary outcome were examined. A two-sided p value <0.05 was considered statistically significant for the aforementioned statistical analyses.

Results

A total of 43,422 patients with baseline eGFR ≥ 60 mL/min/1.73 m^2 were analyzed, and their baseline characteristics are presented in Table I. Patients with diabetes (n=29,377) were older (57.5 ± 12.9 vs 51.6 ± 13.6 years, p<0.001), had a higher body mass index (26.3 ± 4.8 vs 24.5 ± 4.2 kg/m^2, p<0.001), a higher rate of hypertension (65.0% vs 46.1%, p<0.001), and a higher fasting plasma glucose (140.4 ± 58.9 vs 94.1 ± 11.9 mg/dl, p<0.001) and HbA1c (7.08 ± 1.25 vs 5.61 ± 0.07 %, p<0.001), than those with no history of diabetes and HbA1c <5.7%. Between-group differences in the other variables were modest (Table I).

Patients with diabetes were grouped according to their mean HbA1c levels during the first year of follow-up (<7.0%, 7.0 to <9.0%, and ≥ 9.0%, Table II). Among the five

groups (normal glucose tolerance, prediabetes, and diabetes stratified by HbA1c: <7.0%, 7.0 to <9.0%, and ≥ 9.0%), the baseline eGFR was found to be higher in patients with diabetes and HbA1c ≥ 9.0% (p<0.001). Nevertheless, they experienced a greater decline in eGFR than patients with HbA1c <5.7% (eGFR change per year -2.97 ± 6.37 vs -2.23 ± 3.18, p<0.001) over a median follow-up of 6.9 years.

Figure 1 shows event (≥ 40% decline in eGFR)-free survival among the five groups. Compared with patients with HbA1c <5.7% (normal glucose tolerance), those with diabetes had lower event-free survival, particularly in patients with HbA1c ≥ 9.0% (Log-rank p<0.001). Using patients with HbA1c <5.7% as the reference group, those with HbA1c 5.7 to 6.4% (prediabetes) experienced a similar risk of 40% decline in eGFR (HR 0.972, 95% CI 0.870 to 1.086, p=0.615, Table III). Nevertheless, patients with diabetes had a significantly higher risk after multivariate adjustment. Moreover, the risk increased along with the elevation in HbA1c (Table III). Similar findings were observed when the composite outcome of a 40% decline in eGFR or all-cause mortality was used as the dependent variable.

Table IV shows the associations between the five baseline HbA1c categories (<5.7%, 5.7 to 6.4%, 6.5 to <7%, 7 to <9%, and ≥ 9%) and the primary outcome. Using patients with a baseline HbA1c <5.7% as the reference group, those with a baseline HbA1c of 5.7 to 6.4% had a modestly lower risk of a 40% decline in eGFR (HR 0.910, 95% CI 0.854 to 0.969, p=0.004). The risk was significantly higher among patients with baseline HbA1c levels of 6.5 to <7%, 7 to <9%, and ≥ 9% (all p<0.001, Table IV). Similar results were noted for the composite outcome of a 40% decline in eGFR and all-cause mortality.

Table V shows the associations between glucose regulations states and renal outcomes across age subgroups (<65 years and ≥ 65 years), using the composite outcome of a 40% decline in eGFR or all-cause mortality as the dependent variable. The findings were consistent with the results prevented in Tables III and IV. Similarly, consistent associations between glucose regulation states and renal outcomes were observed across sex subgroups (male and female), as shown in Table VI.

Discussion

Our findings indicate that patients with diabetes are at a higher risk of adverse renal outcomes and all-cause mortality, even among those achieving an HbA1c <7%. Conversely, no significant difference in adverse outcomes was observed between individuals with prediabetes and those with normal glucose tolerance. Therefore, beyond the established importance of maintaining an HbA1c <7% in patients with existing diabetes, our study highlights the potential significance of maintaining glycemic control within the non-diabetic range as a strategy for mitigating renal function decline.

Large population-based randomized controlled trials have demonstrated that glycemic control reduces adverse renal events, with protective effects lasting over a decade [16-18]. Furthermore, a clear dose-response relationship exists, with each 1% increase in HbA1c associated with an approximate 12% higher risk of developing diabetic nephropathy [6]. Consistent with previous studies, our patients with diabetes and HbA1c <7% experienced a lower risk of a 40% decline in eGFR compared with those with HbA1c ≥ 9%. Similar findings were observed for the composite outcome.

While the association between overt diabetes and renal damage is well established, the relationship between prediabetes and adverse renal outcomes remains controversial.

An umbrella review demonstrated that prediabetes was positively associated with an increased risk of all-cause mortality and a moderate increase in the incidence of CKD [3]. However, this finding is attenuated by the fact that it was based on two meta-analyses with conflicting results [7,8]. Crucially, the meta-analysis reporting a positive association exhibited substantial methodological heterogeneity. Most included studies did not demonstrate a significant association, particularly those defining CKD solely on the basis of eGFR [19,20]. These studies were generally limited by small sample sizes, the use of less accurate risk prediction equations for eGFR calculation, and a primary focus on metabolic syndrome defined by fasting blood glucose [21,22]. While various diagnostic criteria exist for prediabetes, HbA1c-based definitions demonstrate greater specificity and modestly superior discrimination for the risk of clinical complications [23]. Furthermore, the only study within the systematic review that reported a significantly increased renal risk among prediabetic patients was limited by inadequate adjustment for confounding factors, as its multivariate models accounted for only age and gender [24].

While some studies have reported contrasting results, numerous investigations have produced findings consistent with our results. For instance, a large cohort study from the Atherosclerosis Risk in Communities (ARIC) study found no significant association between prediabetes and the risk of developing CKD or ESRD over a median follow-up period of 14 years [25]. Consistently, similar results have been reported in two other major cohort studies, the ESTHER Study and the Dallas Heart Study, as well as in studies conducted in Asian populations [26-28]. Notably, these

investigations defined prediabetes using HbA1c, calculated eGFR with validated equations, and adjusted for key confounders. The methodological rigor of these studies, which closely parallels our own design, provides strong support for the conclusion that prediabetes may not be independently associated with adverse renal outcomes.

A recent prospective cohort study, conducting a further analysis of the ARIC cohort, evaluated whether the risks of clinical outcomes associated with prediabetes were partially or entirely attributable to progression to overt diabetes [9]. Over a maximum follow-up of 30 years, prediabetes was initially associated with a 1.2-fold increased long-term risk of CKD after adjustment for age and gender. Interestingly, even after accounting for progression to diabetes, 80% of the excess CKD risk in the prediabetes group persisted. However, the elevated risk was attenuated to non-significance after adequate adjustment for established CKD risk factors, including hypertension, lipid profiles, and smoking (as shown in the electronic supplementary material). Furthermore, a meta-analysis using Mendelian randomization to approximate a randomized controlled trial demonstrated that prediabetes was not associated with CKD, regardless of whether it was defined by HbA1c or fasting blood glucose [7]. In summary, these robust findings from recent literature align closely with our study and strongly suggest that prediabetes does not have a direct causal effect on CKD.

Despite these findings, it is important to emphasize that the lack of an observed association does not indicate the absence of risk; rather, prediabetes does not appear to be an independent risk factor after adjustment for major confounders. Abnormal glucose regulation is an important risk factor for CKD, although many confounders not addressed in our study—such as body weight changes, medication use, and dietary factors [29,30]—may influence both glucose control and its impact on adverse renal

outcomes. Another important finding of our study was that early optimal glycemic control (HbA1c <7%) in patients with diabetes was associated with a lower risk of adverse renal outcomes compared with poor glycemic control (HbA1c ≥ 9%).

To the best of our knowledge, few studies have investigated the association between long-term glycemic control and clinically significant renal outcomes (e.g. a 40% eGFR decline from baseline) across different glucose regulation states (normal, prediabetes, and diabetes). Our study helps address this critical knowledge gap. The strengths of our study include the large sample size, the relatively long follow-up period, and consideration of multiple confounding factors. However, our findings must be interpreted in light of several limitations. First, this was a retrospective, single-center cohort study, which may limit the generalizability of our findings to broader populations. Our study cohort, in which more than half of the patients had hypertension and approximately one-quarter had cardiovascular disease, may represent a population with greater clinical complexity than the general population. It is possible that the follow-up period was too short to detect differences in the risk of adverse outcomes between patients with normal glucose tolerance and those with prediabetes. Second, we did not have data on blood pressure or blood pressure lowering drugs, and only 38.0% (n=16,516) of the study population had available urine albumin to creatinine ratio (UACR) data. Patients with no UACR data had a lower prevalence of hypertension (57.0% vs 65.3%, p<0.001) and cardiovascular disease (24.9% vs 30.3%, p<0.001), as well as lower HbA1c levels (6.42 ± 1.15 vs 7.11 ± 1.11 %, p<0.001), compared with those with available UACR data. Therefore, we did not include UACR in the analysis in Tables III-VI, as doing so could introduce significant selection bias. After adjustment for UACR in a multivariate model, using the composite outcome of a 40% decline in

eGFR or all-cause mortality as the dependent variable, the HRs for prediabetes, diabetes with HbA1c <7%, diabetes with HbA1c 7 to <9%, and diabetes with HbA1c ≥ 9% were 1.242 (95% CI 0.901 to 1.711), 1.299 (95% CI 0.964 to 1.751), 1.440 (95% CI 1.068 to 1.942), and 1.580 (95% CI 1.153 to 2.165), respectively. The corresponding p values were 0.186, 0.085, 0.017, and 0.005, respectively. These findings were similar to the results shown in Tables III-VI. Third, we did not account for the effects of glucose lowering drugs, such as sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide-1 agonists. In our cohort, only prescription records were available, without detailed information on dosage or duration of therapy. The proportions of our patients with prescription records for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the normal glucose tolerance, prediabetes, and diabetes groups were 33.3%, 37.0%, and 50.8%, respectively. The rates for sodium-glucose co-transporter 2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and statins were 1.0%/0.8%/22.4%, 0.7%/0.4%/4.3%, and 49.0%/50.0%/62.2%, respectively. The differences between normal glucose tolerance and prediabetes were only modest. We believe that the differences in the use of these medications are unlikely to have significantly influenced our finding that there were no significant differences in the risks of adverse outcomes between patients with normal glucose tolerance and those with prediabetes. The use of these medications may help reduce the risk among patients with well-controlled diabetes. We examined the associations between diabetes subgroups (HbA1c <7%, HbA1c 7 to <9%, and HbA1c ≥ 9%) and renal outcomes, stratified by the use or non-use of SGLT-2 inhibitors/GLP-1 receptor agonists. Compared with patients with normal glucose tolerance, the HRs for patients with diabetes who were treated with SGLT-2 inhibitors or GLP-1 receptor agonists were 1.811 (95% CI 1.608 to 2.040),

1.839 (95% CI 1.642 to 2.058), and 2.731 (95% CI 2.335 to 3.193) for those with HbA1c <7%, HbA1c 7 to <9%, and HbA1c ≥ 9%, respectively. The corresponding HRs for patients with diabetes who were not treated with SGLT-2 inhibitors or GLP-1 receptor agonists were 1.710 (95% CI 1.546 to 1.892), 2.328 (95% CI 2.098 to 2.584), and 3.417 (95% CI 3.015 to 3.873), respectively. All p values for the aforementioned analyses were <0.001. These findings were consistent with the results prevented in Tables III-VI. Fourth, population categorization was based on the mean HbA1c level during the first year of follow-up (without an oral glucose tolerance test), which may introduce immortal time bias and misclassification bias. Accordingly, our findings should be interpreted as reflecting the impact of early glycemic exposure rather than long-term glycemic burden. Fifth, although we addressed the issue of competing risk bias by analyzing a composite outcome that included all-cause mortality, residual competing risk cannot be entirely excluded because cause-specific hazards were not explicitly modeled. Despite the aforementioned limitations, our results highlight the importance of maintaining glycemic control within the non-diabetic range to improve renal outcomes.

In conclusion, we have demonstrated that patients diagnosed with type 2 diabetes, even amongst those achieving the target HbA1c <7%, experienced a significantly higher risk of adverse renal outcome when compared to individuals with normal glucose tolerance. Conversely, patients diagnosed with prediabetes did not appear to experience a higher risk. Our findings suggest that maintaining glycemic control within the non-diabetic range may help mitigate long-term adverse renal outcomes.

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Declaration of Competing Interest: The authors declare that they have no competing interests.

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Figure Legends:

Figure 1. Event (≥ 40% decline in eGFR)-free survival curve among the five groups. (normal, prediabetes, diabetes with HbA1c <7.0%, diabetes with HbA1c 7.0 to <9.0%, and diabetes with HbA1c ≥ 9.0%).

Glucose Regulation States and Renal Outcomes in Patients with Preserved Kidney Function

Study population and designs

Study population (N = 43,422)

- ✓ Review EMRs during 2010-2022
- ✓ Baseline eGFR ≥ 60 mL/min/1.73 m^2
- ✓ Confirm survival status by March 2023

Follow up eGFR

Patients with no diabetes

- Normal glucose tolerance HbA1c <5.7%
- Prediabetes HbA1c 5.7 to 6.4%

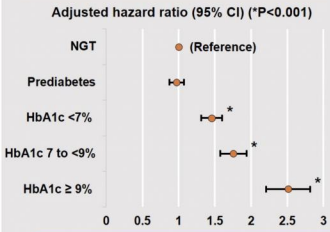
Patients with diabetes

- HbA1c <7.0%
- HbA1c 7.0 to <9.0%
- HbA1c ≥ 9.0%

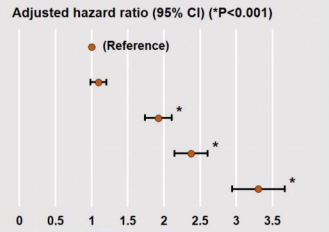
Results

Median follow-up period of 6.9 years

40% decline in eGFR



40% decline in eGFR or all-cause mortality



Conclusions

Patients with diabetes had a higher risk of adverse renal outcomes, even in those who had an HbA1c <7%. Maintaining glycemic control within the non-diabetic range may help mitigate long-term adverse outcomes.

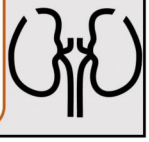


Table I – Baseline characteristics of the study population according to glucose regulation states

	HbA1c <5.7%	HbA1c 5.7 to 6.4%	Diabetes	P
N	2160	11885	29377	
Age, years	51.6 ± 13.6	55.0 ± 12.4	57.5 ± 12.9	<0.001
Male, n (%)	1222 (56.6)	6375 (53.6)	16529 (56.3)	<0.001
Body mass index, kg/m^2	24.5 ± 4.2	25.3 ± 4.2	26.3 ± 4.8	<0.001
Hypertension, n (%)	995 (46.1)	6036 (50.8)	19103 (65.0)	<0.001
Cardiovascular disease, n (%)	594 (27.5)	3414 (28.7)	7695 (26.2)	<0.001
eGFR, mL/min/1.73 m^2	92.9 ± 18.9	90.9 ± 16.5	91.3 ± 17.3	<0.001
Total cholesterol, mg/dl	195.8 ± 43.6	197.3 ± 44.4	186.0 ± 46.6	<0.001
HDL cholesterol, mg/dl	56.0 ± 16.2	54.0 ± 15.8	48.9 ± 14.4	<0.001
LDL cholesterol, mg/dl	122.5 ± 37.8	124.3 ± 37.8	113.4 ± 37.5	<0.001
Triglycerides, mg/dl	131.6 ± 115.6	141.3 ± 119.9	173.1 ± 240.4	<0.001
FPG, mg/dl	94.1 ± 11.9	98.7 ± 13.7	140.4 ± 58.9	<0.001
HbA1c, %	5.61 ± 0.07	5.89 ± 0.15	7.08 ± 1.25	<0.001

Data are presented as mean ± SD or numbers (percentages). eGFR, estimated glomerular filtration rate. FPG, fasting plasma glucose. HbA1c, glycated hemoglobin. HDL, high-density lipoprotein. LDL, low-density lipoprotein. UACR, urine albumin to creatinine ratio.

Table II – eGFR changes according to glucose regulation states and HbA1c levels

	Normal HbA1c <5.7%	Prediabetes HbA1c 5.7 to 6.4%	Diabetes HbA1c <7.0%	Diabetes HbA1c 7.0 to <9.0%	Diabetes HbA1c ≥ 9.0%	P
Number of patients	2160	11885	16728	10422	2227	
Duration of follow-up, days	2885 ± 1263	2642 ± 1292	2517 ± 1269	2350 ± 1262	2027 ± 1194	<0.001
eGFR, mL/min/1.73 m^2						
At baseline	92.9 ± 18.9	90.9 ± 16.5	89.8 ± 16.6	92.3 ± 17.3	97.3 ± 20.2	<0.001
At follow-up	77.3 ± 19.3	77.0 ± 18.5	75.3 ± 22.2	77.3 ± 24.6	83.2 ± 28.0	<0.001
Change from baseline	-15.6 ± 16.8	-13.9 ± 15.7	-14.5 ± 19.1	-14.9 ± 21.0	-14.1 ± 23.6	<0.001
Change per year	-2.23 ± 3.18	-2.14 ± 3.70	-2.33 ± 4.66	-2.54 ± 5.36	-2.97 ± 6.37	<0.001

Data are presented as mean ± SD. eGFR, estimated glomerular filtration rate. HbA1c, glycated hemoglobin.

Table III – Associations of glucose regulation states with renal outcomes and all-cause mortality

	Adjusted HR (95% CI)[a]	P
Dependent variable: 40% decline in eGFR		
Normal glucose tolerance (HbA1c <5.7%)	1 (reference)	
Prediabetes (HbA1c 5.7 to 6.4%)	0.972 (0.870 to 1.086)	0.615
Diabetes (HbA1c <7%)	1.457 (1.311 to 1.620)	<0.001
Diabetes (HbA1c 7 to <9%)	1.755 (1.575 to 1.955)	<0.001
Diabetes (HbA1c ≥ 9%)	2.509 (2.206 to 2.854)	<0.001
Dependent variable: 40% decline in eGFR or all-cause mortality		
Normal glucose tolerance (HbA1c <5.7%)	1 (reference)	
Prediabetes (HbA1c 5.7 to 6.4%)	1.090 (0.982 to 1.120)	0.107
Diabetes (HbA1c <7%)	1.922 (1.739 to 2.125)	<0.001
Diabetes (HbA1c 7 to <9%)	2.376 (2.146 to 2.630)	<0.001
Diabetes (HbA1c ≥ 9%)	3.306 (2.940 to 3.718)	<0.001

[a]Adjusted for age, sex, body mass index, hypertension, cardiovascular disease, and low-density-lipoprotein cholesterol. eGFR, estimated glomerular filtration rate. HbA1c, glycated hemoglobin.

Table IV – Associations of baseline HbA1c with renal outcomes and all-cause mortality

	Adjusted HR (95% CI)[a]	P
Dependent variable: 40% decline in eGFR		
Baseline HbA1c <5.7%	1 (reference)	
Baseline HbA1c 5.7 to 6.4%	0.910 (0.854 to 0.969)	0.004
Baseline HbA1c 6.5 to <7%	1.197 (1.112 to 1.289)	<0.001
Baseline HbA1c 7 to <9%	1.418 (1.324 to 1.518)	<0.001
Baseline HbA1c ≥ 9%	1.863 (1.732 to 2.004)	<0.001
Dependent variable: 40% decline in eGFR or all-cause mortality		
Baseline HbA1c <5.7%	1 (reference)	
Baseline HbA1c 5.7 to 6.4%	0.972 (0.917 to 1.030)	0.331
Baseline HbA1c 6.5 to <7%	1.469 (1.374 to 1.570)	<0.001
Baseline HbA1c 7 to <9%	1.735 (1.631 to 1.845)	<0.001
Baseline HbA1c ≥ 9%	1.934 (1.810 to 2.066)	<0.001

[a]Adjusted for age, sex, body mass index, hypertension, cardiovascular disease, and low-density-lipoprotein cholesterol. eGFR, estimated glomerular filtration rate. HbA1c, glycated hemoglobin.

Table V – Associations between glucose regulation states and renal outcomes across age subgroups

Dependent variable: 40% decline in eGFR or all-cause mortality	Adjusted HR (95% CI)[a]	P
Age <65 years		
Normal glucose tolerance (HbA1c <5.7%)	1 (reference)	
Prediabetes (HbA1c 5.7 to 6.4%)	1.079 (0.951 to 1.224)	0.237
Diabetes (HbA1c <7%)	1.881 (1.667 to 2.123)	<0.001
Diabetes (HbA1c 7 to <9%)	2.416 (2.136 to 2.731)	<0.001
Diabetes (HbA1c ≥ 9%)	3.275 (2.843 to 3.773)	<0.001
Age ≥ 65 years		
Normal glucose tolerance (HbA1c <5.7%)	1 (reference)	
Prediabetes (HbA1c 5.7 to 6.4%)	1.110 (0.920 to 1.339)	0.276
Diabetes (HbA1c <7%)	1.826 (1.525 to 2.186)	<0.001
Diabetes (HbA1c 7 to <9%)	2.112 (1.759 to 2.535)	<0.001
Diabetes (HbA1c ≥ 9%)	2.842 (2.303 to 3.508)	<0.001

[a]Adjusted for sex, body mass index, hypertension, cardiovascular disease, and low-density-lipoprotein cholesterol. eGFR, estimated glomerular filtration rate. HbA1c, glycated hemoglobin.

Table VI – Associations between glucose regulation states and renal outcomes across sex subgroups

Dependent variable: 40% decline in eGFR or all-cause mortality	Adjusted HR (95% CI)[a]	P
Male		
Normal glucose tolerance (HbA1c <5.7%)	1 (reference)	
Prediabetes (HbA1c 5.7 to 6.4%)	0.982 (0.857 to 1.124)	0.788
Diabetes (HbA1c <7%)	1.691 (1.487 to 1.923)	<0.001
Diabetes (HbA1c 7 to <9%)	2.090 (1.834 to 2.381)	<0.001
Diabetes (HbA1c ≥ 9%)	2.998 (2.576 to 3.489)	<0.001
Female		
Normal glucose tolerance (HbA1c <5.7%)	1 (reference)	
Prediabetes (HbA1c 5.7 to 6.4%)	1.116 (0.946 to 1.316)	0.194
Diabetes (HbA1c <7%)	1.742 (1.485 to 2.045)	<0.001
Diabetes (HbA1c 7 to <9%)	2.209 (1.877 to 2.600)	<0.001
Diabetes (HbA1c ≥ 9%)	3.401 (2.824 to 4.094)	<0.001

[a]Adjusted for age, body mass index, hypertension, cardiovascular disease, and low-density-lipoprotein cholesterol. eGFR, estimated glomerular filtration rate. HbA1c, glycated hemoglobin.

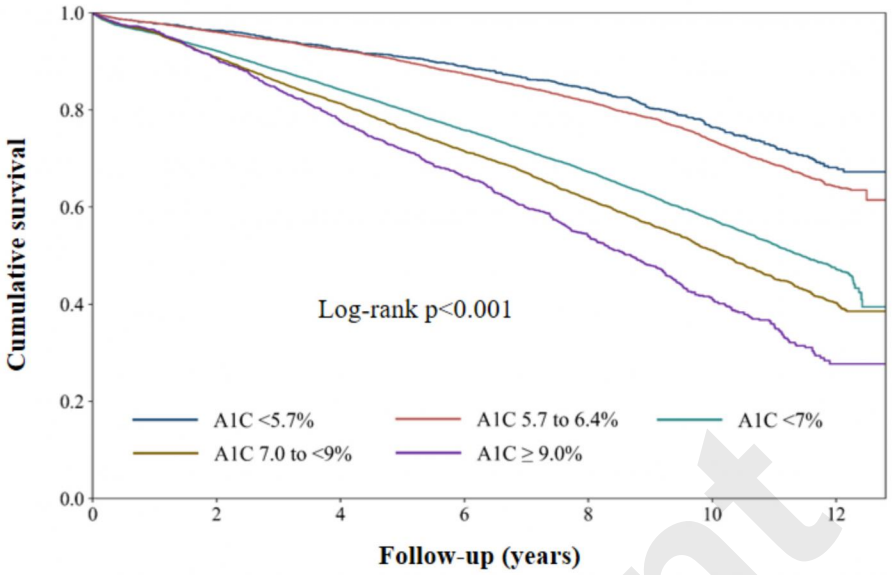


Figure 1. Event (≥ 40% decline in eGFR)-free survival curve among the 5 groups. (normal, prediabetes, diabetes with HbA1c <7.0%, diabetes with HbA1c 7.0 to <9.0%, and diabetes with HbA1c ≥ 9.0%)