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Influence of guideline adherence and parameter control on the clinical outcomes in patients with diabetic nephropathy

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ABSTRACT

Introduction We assessed the association between guideline adherence and outcomes of clinical parameter control and end-stage kidney disease (ESKD), and further studied the effect of parameter control on ESKD for Chinese patients with diabetic nephropathy (DN).

Research design and methods In this retrospective study, 1128 patients with DN (15,374 patient-visit samples) diagnosed by renal biopsy were enrolled. Samples were classified as adherence and nonadherence based on whether prescribed drugs conformed to medication regimen and drug contraindication recommended by guidelines, including American Diabetes Association (ADA) and Chinese guidelines. Guideline adherence rate was calculated on all samples for antihyperglycemic, antihypertensive and lipid-lowering treatments. Clinical parameter control was compared after 3–6 months' therapy between two groups by generalized estimating equation models. Time-dependent Cox models were applied to evaluate the influence of guideline adherence on ESKD. Latent class mixed model was used to identify distinct trajectories for parameters and their ESKD risks were compared using Cox proportional-hazards models.

Results Guideline adherence rate of antihyperglycemic therapy was the highest, with 72.87% and 68.15% of samples meeting ADA and Chinese guidelines, respectively. Adherence was more likely to have good glycated hemoglobin A1c (HbA1c) control (ADA: OR 1.46, 95% CI 1.12 to 1.88; Chinese guideline: OR 1.42, 95% CI 1.09 to 1.85) and good blood pressure control (ADA: OR 1.35, 95% CI 1.03 to 1.78; Chinese guideline: OR 1.39, 95% CI 1.08 to 1.79) compared with nonadherence. The improvement of patient's adherence showed the potential to reduce ESKD risk. For proteinuria, low-density lipoprotein cholesterol (LDL-C), systolic blood pressure and uric acid, patients in higher-value trajectory group had higher ESKD risk. Proteinuria and LDL-C trajectories were most closely related to ESKD risk, while the risk was not significantly different in HbA1c trajectories.

Conclusions Guideline adherence and good control of proteinuria and LDL-C in clinical practice are important and in need for improving clinical outcomes in patients with DN.

INTRODUCTION

Diabetic nephropathy (DN) is a chronic kidney disease (CKD) caused by diabetes mellitus, which is the main cause of end-stage

Significance of this study

What is already known about this subject?
► Adherence to guideline associates with improved clinical outcome in patients with type 2 diabetes with renal disease. However, there was no evidence for patients with diabetic nephropathy (DN) diagnosed by renal biopsy.
► The relationship between the longitudinal changes in clinical parameters and end-stage kidney disease (ESKD) risk was not clear.

What are the new findings?
► For patients with biopsy-proven DN, guideline adherence was associated with better glycemic and blood pressure control, and showed the potential to reduce ESKD risk by comprehensively assessing the antihyperglycemic, antihypertensive and lipid-lowering treatments.
► The continuous control of proteinuria, low-density lipoprotein cholesterol (LDL-C), systolic blood pressure and uric acid were more likely to reduce ESKD risk, particularly in proteinuria and LDL-C.
► Glycated hemoglobin A1c level was not associated with ESKD risk.

How might these results change the focus of research or clinical practice?
► This study demonstrates that guideline adherence and good control of proteinuria and LDL-C in patients with DN are important in improving prognosis. It provides theoretical evidence to help in establishing the policies of standardized treatment for DN.

kidney disease (ESKD) at present.[1] Approximately 20%–40% of patients with diabetes have progressed to DN.[2,3] In China, the prevalence of DN is also increasing.[4–6] In order to standardize the diagnosis and treatment of DN, multi-version clinical practice guidelines were formulated.[7–11] These guidelines involved diagnosis, treatment goals, therapeutic strategies and so on. It was emphasized that patients with DN should adopt a

comprehensive treatment of antihyperglycemic therapy, hypertension control and lipid management on the basis of changing their lifestyle in order to slow the progression of DN.

In theory, the development of various guidelines can help to guide the diagnosis and treatment of the clinician and improve the prognosis of patients. However, in actual practice, are the treatments of patients with DN in China accordant with guidelines? Is guideline adherence conducive to the improvement of clinical parameter control and long-term outcome? How about the association between longitudinal changes in clinical parameters and outcome in patients with DN? The interpretation of these questions will help improve the treatment strategies of patients with DN with more guideline-concordance and real-world evidence integrated, assisting clinicians with most effective prescriptions.

Some published studies assessed the adherence to guidelines for patients with type 2 diabetes with renal disease and the guideline was interpreted relatively simply.[12–15] For example, Eder et al[12] assessed the guideline adherence with respect to metabolic and blood pressure control, use of renin–angiotensin system–blocking agents, statins and acetylsalicylic acid for patients with type 2 diabetes with and without renal disease. Chen et al[13] only assessed whether patients adjusted the dose of oral antidiabetic agents or avoided using them in patients with type 2 diabetes with moderate to severe CKD. Nevertheless, neither of the studies elaborated on the guideline-recommended medication regimen, namely which drug therapy should be chosen and how to combine drugs for precise patients grouped by their clinical conditions and medication history. Chen et al[15] assessed the association between oral antidiabetic drug treatment concordance with guidelines and related economic and clinical outcomes in patients with type 2 diabetes and stage 3 to 5 CKD. However, there was no evidence for patients with DN diagnosed by renal biopsy. Also, they did not comprehensively assess the antihyperglycemic, antihypertensive and lipid-lowering treatments. As far as we know, there was no study to assess the effect of longitudinal trajectories in clinical parameter (ie, increasing, stable or decreasing) on ESKD for patients with DN.

Therefore, our study aimed to fill this gap. We first extracted the medication regimens and drug contraindications of patients with DN in American Diabetes Association (ADA) and Chinese guidelines, and further evaluated the guideline adherence to antihyperglycemic, antihypertensive and lipid-lowering treatments comprehensively. Then we analyzed the influence of guideline-concordant treatment on clinical outcomes in terms of short-term clinical parameter control and long-term ESKD occurrence. In addition, latent class mixed model was used to identify longitudinal trajectory groups for clinical parameters, and further it was studied how different trajectory groups were associated with ESKD risk in patients with DN.

RESEARCH DESIGN AND METHODS
Study population
A total of 1906 patients with biopsy-proven DN in the Nanjing Diabetic Nephropathy Registry from January 2003 to December 2018 were reviewed. At our institution, the general indication for renal biopsy is persistent albuminuria or decreased serum creatinine, with a particular emphasis on sudden-onset overt proteinuria, obvious hematuria or rapidly progressive glomerular nephropathy.[16] Patients meeting one of the following criteria were excluded: (1) patients with other renal diseases (such as membranous nephropathy and IgA nephropathy); (2) patients who had received kidney transplantation or dialysis before enrollment; (3) DN not caused by type 2 diabetes; (4) less than 14 days from enrollment to the occurrence of ESKD; (5) follow-up time was less than 1 year and no ESKD occurred; (6) patients without estimated glomerular filtration rate (eGFR) record. Finally, 1128 patients were enrolled with 15,374 follow-up visits from the enrollment time to outcome event (online supplementary figure S1).

Clinical data collection
The baseline and follow-up data of the patients were obtained from the Nanjing Diabetic Nephropathy Registry database. The time when a patient was diagnosed by renal biopsy was regarded as enrollment time, which was also baseline time. Eligible patients were followed up from the time of biopsy until the earliest outcome event (patient transferred out, death, study end date, ESKD occurrence). The follow-up visits of these patients were performed two to four times per year based on the patient's individual condition. At baseline, demographic information (eg, sex and age) and disease history (eg, diabetes and atherosclerotic cardiovascular disease (ASCVD)) were collected. At baseline and each follow-up visit, laboratory test results, current and previous medications in prescriptions were collected. The laboratory test results included glycated hemoglobin A1c (HbA1c), blood pressure (BP), uric acid (UA), proteinuria (PRO), serum creatine (SCr), low-density lipoprotein cholesterol (LDL-C) and so on, and the medications in prescriptions included antihyperglycemic drugs, antihypertensive drugs and lipid-lowering drugs.

The eGFR was estimated using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula.[17] ESKD was defined as eGFR $<15\,\mathrm{mL/min/1.73\,m^2}$ for over 3 months, with initiation of dialysis or transplantation.

Selection of guidelines
In this study, multi-version guidelines including ADA guideline for 2018[8] and Chinese guideline[9] were selected for comparative analysis. In addition, some drugs metabolized or excreted in the kidney, so in patients with renal insufficiency, the decrease of renal excretion or the clearance of its active metabolites can lead to adverse reactions such as hypoglycemia.[18] Therefore, another two national guidelines supplemented the drug contraindications

when eGFR was below $60\,mL/min/1.73\,m^2$ for Chinese guideline in this study.[10 11] Treatment strategies in domestic and international guidelines were summarized in online supplementary table S1.

Statistical analysis

In this study, the guideline-concordant evaluation and associated clinical outcomes were given at both sample level and patient level. We defined a sample as a follow-up visit merged with diagnosis, laboratory tests and treatments (online supplementary figure S1B), so there were multiple samples for one patient. Taking the antihyperglycemic therapy of ADA guideline for example, the flowchart of sample inclusion when evaluating the influence of guideline adherence on short-term/long-term outcome is shown in online supplementary figure S2. The following analysis was performed separately for domestic and international guidelines.

The guideline adherence rate was calculated at sample level. For each kind of guideline, we partitioned all samples into adherence and nonadherence based on whether the type and number of prescribed medications conformed to guideline recommendations and the drugs that should be completely avoided at low eGFR were discontinued. The short-term clinical outcomes were defined as target achievement rate of the key parameters, namely the percentages of samples with (1) HbA1c $< 7\%$, (2) both systolic BP <130 and diastolic BP <80 mm Hg, and (3) LDL-C <1.8 mmol/L for very-high-risk, LDL-C <2.6 mmol/L for high-risk (very-high-risk: have a definite history of ASCVD; high-risk: diabetic patients without history of ASCVD). Then we compared these clinical outcomes in short term (after 3–6 months' therapy) between the two groups. The generalized estimating equation (GEE) models with an exchangeable correlation structure were used to account for correlation between samples within the same patient when evaluating the association between guideline-concordant treatment and short-term clinical outcomes.[19] The models were also performed to control potential confounding factors including age, sex, eGFR and corresponding parameters (HbA1c or systolic BP, diastolic BP or LDL-C, triglyceride (TG)) measured at baseline or current visit. In order to evaluate the influence of guideline versions published in different years, we divided ADA guidelines from 2003 to 2018 into five groups according to the similarity in the antihypertensive treatment regimen and BP control target (online supplementary table S2). The 2007, 2012, 2014, 2016 and 2018 versions of ADA were selected as representative of each group to study the association between guideline adherence and BP-goal achieving rate.

Then, we performed the long-term effect evaluation results at patient level. For each patient, we first computed its patient's adherence rate with regard to antihyperglycemic therapy, hypertension control and lipid management, respectively, through dividing the number of guideline-adherent visits by the total number of visits, that is, to quantify the extent to which each

patient complied with the guidelines. In the whole population, we further illustrated the relationship between patient's adherence rate and ESKD occurrence rate. To avoid the sharp variability in less visit number, patients with a visit number of 5 or greater were selected to evaluate the long-term clinical outcome. In addition, to evaluate the influence of exposing to different guidelines, taking hypertension control of ADA guideline for an example (online supplementary table S2), we illustrated the relationship between patient's adherence rate and ESKD occurrence rate based on multi-version ADA guidelines that the different visits of the patient were exposed to.

Considering that the adherence for a patient to 2018 version of guidelines was time varying and the follow-up time for different patients were varied, the time-dependent Cox models were used to evaluate the influence of guideline adherence on long-term outcome of ESKD.[20] The models were adjusted for sex, age, eGFR, duration of diabetes and time-dependent covariates (HbA1c, systolic BP, diastolic BP, LDL-C, TG, PRO, UA).

Trajectory analyses

In order to illustrate how changes in clinical parameters were associated with the prognosis of patients with DN, latent class mixed model (LCMM) was used to identify distinct longitudinal trajectory groups for each key clinical parameter using R package "lcmm".[21] LCMM enables agnostic detection of multiple subpopulations with distinct longitudinal patterns of clinical parameter.[22 23] Compared with the traditional method, trajectory analyses may be more beneficial to identify dynamic patterns over time for laboratory test records in their individual patients rather than average changes in all of their patients. Thus, we used LCMM to fit the longitudinal records with different numbers of trajectory groups in various polynomial (linear, quadratic and cubic) terms. Best models were chosen with the following key criteria: sufficient patient number in each class and relatively low Bayesian Information Criterion. Furthermore, Cox proportional-hazards models were applied to analyze how different trajectory groups were associated with the occurrence of ESKD.

Potential confounding factors were adjusted stepwise in each Cox model. Model 1 adjusted for demographic factors (age and sex). Model 2 further adjusted for the visit number during the follow-up period and the laboratory test results (including HbA1c, systolic BP, diastolic BP, TC, TG, LDL-C, HDL-C, UA) measured at baseline. Model 3 further adjusted for the baseline eGFR. In order to determine whether the results of the study were affected by changing the follow-up time, we performed the sensitivity analysis by changing the inclusion time span of the trajectory and repeating the aforementioned analysis. All p values were two tailed, and p value <0.05 was considered statistically significant.

Table 1 Baseline characteristics of study participants

Baseline characteristics	Values
Age, years	50.17±9.37
Male sex	778 (69%)
Duration of diabetes, years	9.13±6.56
HbA1c, %	6.70±1.23
Uric acid, µmol/L	388.43±96.21
Total cholesterol, mmol/L	5.22±1.71
HDL-C, mmol/L	1.13±0.39
LDL-C, mmol/L	3.11±1.35
Triglyceride, mmol/L	1.55 (1.11–2.14)
Systolic BP, mm Hg	136.89±20.83
Diastolic BP, mm Hg	78.25±10.88
Proteinuria, g/24 h	1.59 (0.71–3.35)
Serum creatine, mg/dL	1.29 (0.89–1.86)
eGFR (mL/min/1.73 m^2)	58.98 (38.36–92.03)
Follow-up, years	3.26 (1.56–5.53)
Anemia, %	49.91
ASCVD, %	16.9

Values for continuous variables given as mean±SD or median (IQR); for categorical variables, as count (percentage).
ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

RESULTS
Baseline characteristics
Of the 1128 patients enrolled in the study, 778 were male (69%). At the time of biopsy, the mean age was 50.17±9.37 years and the mean duration of diabetes was 9.13±6.56 years. The median follow-up period was 3.26 (IQR, 1.56–5.53) years. The median baseline serum creatinine level was 1.29 (IQR, 0.89–1.86) mg/dL and the median eGFR was 58.98 (IQR, 38.36–92.03) mL/min/1.73 m^2 (table 1). The ADA guideline adherence rates at baseline for antihyperglycemic, antihypertensive and lipid-lowering treatment were 55.10%, 42.09% and 30.54%, respectively. The Chinese-guideline adherence rates at baseline were 43.88%, 45.15% and 19.63%, respectively.

Adherence to guidelines and achievement of control targets
As shown in table 2, the overall guideline adherence rate for antihyperglycemic therapy was the highest. ADA-guideline adherence rate and Chinese-guideline adherence rate for antihyperglycemic therapy were 72.87% and 68.15%, respectively. Since ADA guideline just mentioned drug contraindications for antihyperglycemic therapy but not for hypertension control and lipid management, we just evaluated the compliance with the medication regimens in ADA guideline for antihypertensive and lipid-lowering treatment. For antihypertensive treatment, ADA-guideline adherence rate

and Chinese-guideline adherence rate were 36.00% and 37.78%, respectively. ADA-guideline adherence rate and Chinese-guideline adherence rate for lipid management were 36.98% and 28.97%, respectively.

The short-term clinical outcomes between adherence and nonadherence were compared in table 3. After confounder adjustment by GEE models, for both ADA and Chinese guidelines, the adherence was more likely to have good HbA1c control (ADA: OR 1.46, 95% CI 1.12 to 1.88; Chinese guideline: OR 1.42, 95% CI 1.09 to 1.85), good blood pressure control (ADA: OR 1.35, 95% CI 1.03 to 1.78; Chinese guideline: OR 1.39, 95% CI 1.08 to 1.79) than nonadherence. Since there is no specified control goal of blood lipid in ADA guideline, the lipid-goal achieving rate was not assessed for ADA guideline. For Chinese guideline, we found no statistically significant difference between adherence and nonadherence (OR 1.18, 95% CI 0.85 to 1.62).

The guideline adherence and associated BP-goal achieving rate are shown based on guidelines published in different years in online supplementary table S3. There is an irregularity between the guideline adherence rate and guideline version, as the guideline adherence rate with ADA guideline in 2016 was the highest (55.12%). Interestingly, the BP-goal achieving rate is closely related to the BP control target. The BP-goal achieving rate if concordant with ADA guideline in 2016 was the highest (55.71%) due to a relatively high goal of 140/90 mm Hg. We also found among the five versions of ADA guidelines that guideline-adherent treatments tend to have better BP-goal achieving rate than nonadherence.

Adherence to guidelines and the risk of ESKD
The curves in A, B, E and F were with an obvious downward trend as a whole (online supplementary figure S3), which means that the higher the patient's adherence rate, the lower the ESKD occurrence rate. It was indicated that the improvement of patient's adherence showed the potential to reduce ESKD risk. Although the curve was fluctuated in online supplementary figure S3D, the whole curve still showed a slight downward trend. While in online supplementary figure S3C the curve was fluctuated horizontally, it was indicated that there was no obvious trend in illustrating the relationship between the patient's adherence rate and ESKD occurrence rate for lipid management of ADA guideline. In addition, similar trends have been found in patients with a visit number of 5 or greater (online supplementary figure S4) and multiversion ADA guidelines–based adherence rate (online supplementary figure S5).

The influence of guideline adherence on ESKD was evaluated using time-dependent Cox models (table 4). After adjustment for confounders, adherence to Chinese guideline was associated with a decrease in ESKD risk for antihyperglycemic therapy (adjusted HR 0.74; 95% CI 0.58 to 0.95; p=0.016), hypertension control (adjusted HR 0.66; 95% CI 0.50 to 0.87; p=0.004) and

Table 2 ADA and Chinese guideline adherence rate for antihyperglycemic therapy, hypertension control and lipid management in patients with diabetic nephropathy

Treatment strategies	ADA guideline			Chinese guidelines		
	Total sample number*	Adherence sample number	Guideline adherence rate (%)	Total sample number	Adherence sample number	Guideline adherence rate (%)
Antihyperglycemic therapy						
Medication rule	6925	5343	77.16	6925	5066	73.16
Monotherapy	1221	802	65.68	1221	537	43.98
Dual therapy	464	140	30.17	296	53	17.91
Triple therapy	248	26	10.48	248	26	10.48
Combination injectable therapy	1234	1017	82.41	1118	960	85.87
Short-term intensive insulin therapy	–	–	–	284	132	46.48
Continue therapy†	3758	3358	89.36	3758	3358	89.36
Drug contraindications	9176	8720	95.03	9176	8621	93.95
Rules and contraindications	6864	5002	**72.87**	6864	4678	**68.15**
Hypertension control						
Medication rule	3336	1201	**36.00**	3407	1345	39.48
Monotherapy	505	454	89.90	505	463	91.68
Dual therapy	808	212	26.24	818	267	32.64
Triple therapy	705	25	3.55	732	52	7.10
Quadruple therapy	653	3	0.46	687	43	6.26
Continue therapy†	665	507	76.24	665	520	78.20
Drug contraindications	–	–	–	9937	9490	95.50
Rules and contraindications	–	–	–	3303	1248	**37.78**
Lipid management						
Medication rule	11 002	4069	**36.98**	7299	3405	46.65
Statin	10 538	3918	37.18	4118	1240	30.11
Statin and additional LDL-lowering therapy	163	19	11.66	162	18	11.11
Fibrate	301	132	43.85	301	132	43.85
Continue therapy†	–	–	–	487	427	87.68
Drug contraindications	–	–	–	5319	4806	90.36
Rules and contraindications	–	–	–	5693	1649	**28.97**

Bold values denote overall adherence rate of guidelines.
*The total sample number of each group represented the number of patient visits meeting the situation mentioned in corresponding rule in online supplementary table S1. The adherence sample number indicated the number of patient visits in which prescribed medications conformed to guideline-rule recommendations. Thus, guideline adherence rate was calculated through dividing the adherence sample number by the total sample number.
†Continue therapy: continued previous treatment when tolerated and target achieved.
ADA, American Diabetes Association.

lipid management (adjusted HR 0.52; 95% CI 0.39 to 0.71; p<0.001), while adherence to ADA guideline was associated with a decrease in ESKD risk for antihyperglycemic therapy (adjusted HR 0.71; 95% CI 0.55 to 0.9; p=0.006). However, no significant association existed between adherence to ADA guideline and ESKD risk for hypertension control (adjusted HR 0.89; 95% CI 0.66 to 1.21; p=0.471) and lipid management (adjusted HR 0.95; 95% CI 0.76 to 1.19; p=0.658).

Longitudinal trajectory of key clinical parameters and the risk of ESKD

The median number of follow-up visits was 9.0 (IQR 5.0–16.0) and median follow-up time is 3.26 (IQR 1.56–5.53) years. During the first 2 years of follow-up, about 70% of participants did not develop ESKD in the study. Therefore, we performed the longitudinal trajectory analysis on the key parameters in the first 2 years from the enrollment, and analyzed the association between

Table 3 Evaluation result for short-term parameter control between adherence and nonadherence with respect to antihyperglycemic therapy, hypertension control and lipid management

Parameter	Target	Guideline	Groups	Total sample number	Target achievement sample number	Target achievement rate (%)	P value*	Adjusted OR (95% CI)†	Adjusted p value†
HbA1c	<7%	ADA	Adherence	2182	1621	74.29	<0.001	1.46 (1.12 to 1.88)	0.004
			Nonadherence	726	416	57.30		Reference	
		Chinese guidelines	Adherence	2136	1592	74.53	<0.001	1.42 (1.09 to 1.85)	0.010
			Nonadherence	774	447	57.75		Reference	
BP	<130/80 mm Hg	ADA	Adherence	583	200	34.31	<0.001	1.35 (1.03 to 1.78)	0.029
			Nonadherence	1188	202	17.00		Reference	
		Chinese guideline	Adherence	615	203	33.01	<0.001	1.39 (1.08 to 1.79)	0.010
			Nonadherence	1247	207	16.60		Reference	
LDL-C	Very-high-risk: <1.8mmol/L, high-risk: <2.6mmol/L‡	Chinese guideline	Adherence	374	128	34.22	<0.001	1.18 (0.85 to 1.62)	0.321
			Nonadherence	1402	341	24.32		Reference	

*P value was obtained via χ^2 test.

†Adjusted OR and p value were obtained via generalized estimating equations models to adjust for age, sex, eGFR and corresponding parameters (HbA1c or systolic BP, diastolic BP or LDL–C, TG) measured at baseline or current visit.

‡Very-high-risk: have a definite history of ASCVD; high-risk: diabetic patients without history of ASCVD.

ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LDL–C, lowdensity lipoprotein cholesterol; TG, triglyceride.

Table 4 Associations between guideline adherence and ESKD risk using time-dependent Cox models

	ADA guideline		Chinese guideline	
	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Antihyperglycemic therapy	0.71 (0.55 to 0.9)	0.006	0.74 (0.58 to 0.95)	0.016
Hypertension control	0.89 (0.66 to 1.21)	0.471	0.66 (0.50 to 0.87)	0.004
Lipid management	0.95 (0.76 to 1.19)	0.658	0.52 (0.39 to 0.71)	<0.001

Adjusted HR and p value were obtained via time-dependent Cox models to adjust for sex, age, eGFR, duration of diabetes and time-dependent covariates (HbA1c, systolic BP, diastolic BP, LDL-C, TG, PRO, UA).
ADA, American Diabetes Association; BP, blood pressure; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; PRO, proteinuria; TG, triglyceride; UA, uric acid.

different trajectory groups and ESKD occurrence from the third year.

The distinct trajectory groups of each clinical parameter are shown in figure 1. For proteinuria, we identified four distinct trajectories marked with Class 1–4 orderly: low stable (in black), moderate stable (in red), rising (in green) and declining (in blue) (figure 1A). After trajectory grouping, we compared their ESKD risk using Cox proportional-hazards models. Compared with low-stable proteinuria trajectory group (PRO-Class 1), the full multivariable-adjusted HR of ESKD was 8.29 (95% CI 4.81 to 14.28, p<0.001) for the rising proteinuria trajectory group (PRO-Class 3) and 7.46 (95% CI 3.45 to 16.14, p<0.001) for the declining proteinuria trajectory group (PRO-Class 4), as described in figure 1F and online supplementary table S4 (model 3). It was indicated that

compared with low-stable trajectory group (PRO-Class 1), participants with rising proteinuria trajectory group (PRO-Class 3) were at 8.29-fold higher risk of ESKD and participants with declining proteinuria trajectory group (PRO-Class 4) were at 7.46-fold higher risk of ESKD in fully adjusted analyses. For HbA1c, four distinct trajectory groups were identified and illustrated in figure 1E. Patients with DN with higher HbA1c trajectory did not have a higher risk of ESKD (p>0.05) compared with those with a low-stable HbA1c trajectory. For other parameters including LDL-C, systolic blood pressure (SBP) and UA, the results for the full multivariable-adjusted HR of ESKD showed that participants with higher trajectory were associated with higher risk of ESKD (figure 1B–D). Rising PRO trajectory (PRO-Class 3) and EX-high unstable LDL-C trajectory (LDL-Class 4) were most closely
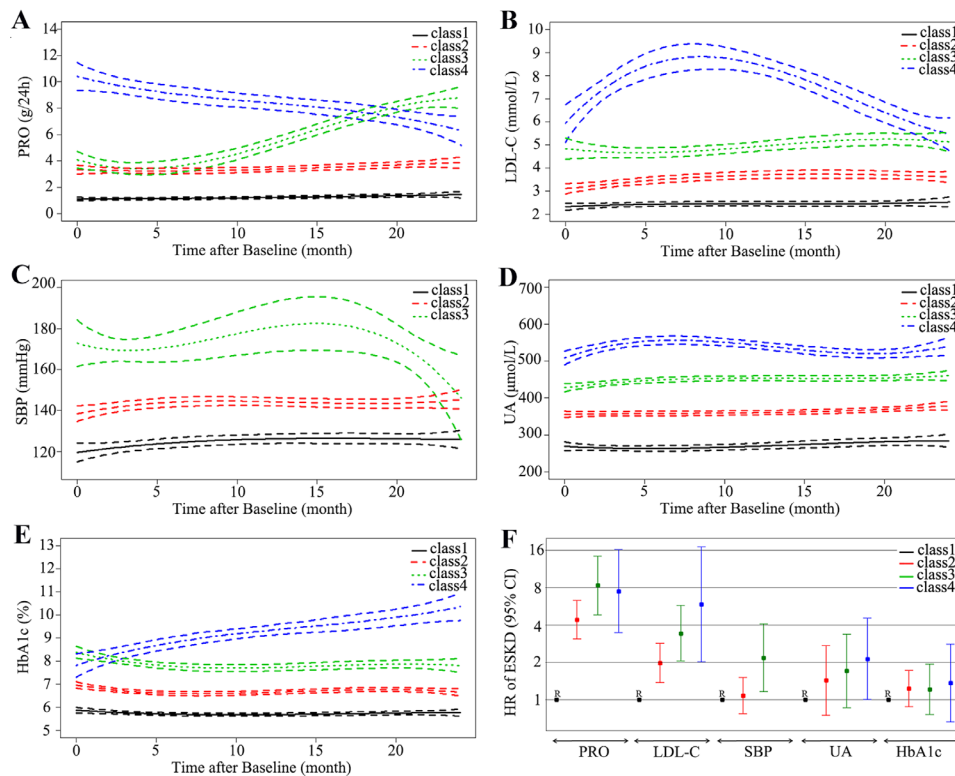

Figure 1 Trajectory modeling identified multiple distinct trajectory groups with 95% CIs (between dashed lines) for PRO (A), LDL-C (B), SBP (C), UA (D), HbA1c (E). The ESKD risks were compared according to trajectory groups of those key clinical parameters with fully adjusted HRs (low-stable trajectory as reference) (F). ESKD, end-stage kidney disease; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; PRO, proteinuria; SBP, systolic blood pressure; UA, uric acid.

associated with increased risk of ESKD (figure 1F). In summary, except HbA1c, the continuous control of PRO, LDL-C, SBP and UA was more likely to reduce ESKD risk, particularly in PRO and LDL-C. The results of sensitivity analysis by changing the inclusion time span of the trajectory from 2 years to 3 years were similar (online supplementary table S5).

DISCUSSION

To our knowledge, this is the first study to assess guideline-concordant treatment and associated clinical outcomes in patients with DN diagnosed by renal biopsy. The guideline adherence rates of ADA and Chinese guideline were similar. However, guideline adherence of treatments for patients with DN in China still needs to be improved, especially for antihypertensive and lipid-lowing treatment. We found that guideline-concordant treatments were associated with improved clinical outcomes, achieving good control of blood glucose and BP and showing the potential to reduce ESKD risk in the long term. Except HbA1c, the longitudinal trajectory analysis of PRO, LDL-C, SBP and UA indicated that good continuous control of these key parameters was associated with reduced ESKD risk, particularly for PRO and LDL-C.

Some previous study found guideline-concordant treatment was associated with better clinical outcomes.[15 24] Similarly, we found that adherence to Chinese guideline was associated with a decrease in ESKD risk for antihyperglycemic therapy, hypertension control and lipid management among Chinese patients with DN. However, it seems that no significant association existed between adherence to ADA guideline and ESKD risk for hypertension control and lipid management in our study. It may be because that ADA guideline just mentioned drug contraindications for antihyperglycemic therapy but not for hypertension control and lipid management.[8] So we just evaluated the compliance with the medication regimens in ADA guideline for antihypertensive and lipid-lowering treatment. Some patients in the adherence group tend to have higher ESKD risk if taking those drugs that should be discontinued at low eGFR, which probably leads to no significant difference in ESKD risk between adherence and nonadherence for hypertension control and lipid management of ADA guideline.

Proteinuria is an established marker of kidney damage, a risk factor for progression of CKD and a potent risk factor for mortality among the diabetic population.[25 26] Our results are in agreement, and it was found that proteinuria was most closely related to ESKD risk among those clinical parameters, and the prognosis could be improved by continuous good control of proteinuria. In addition, previous studies showed that the level of BP, lipid and UA were closely related to the progression of kidney disease in patients with DN.[27–30] This was consistent with the longitudinal trajectory results of LDL-C, SBP and UA in this study, and all of them showed that patients in the

trajectory group with higher value were associated with higher ESKD risk.

Our study showed that no difference in ESKD risk was observed among HbA1c trajectory groups. Studies exploring the impact of glycemic control on ESKD are limited and yield somewhat inconsistent results. Several studies have similar results to our study, indicating that lowering blood glucose did not appreciably reduce the incidence of ESKD.[31–33] We discuss the possible reason in our study as follows. In the ADVANCE-ON study, to analyze the effect of intensive glucose control on ESKD by baseline CKD status, participants were divided into those with CKD stage 1, stage 2 and stage ≥3.[34] A graded reduction in the strength of the effect was seen as CKD stage increased and intensive glucose control did not reduce the incidence of ESKD in participants with CKD stage ≥3. In our study, the proportion of participants with CKD stage ≥3 was 39%, which was quite higher than some studies that have similar results with our study, like VADT (14%) and UKPDS (10%) studies.[35] This may be a possible reason why HbA1c level was not associated with ESKD risk. In addition, in patients with CKD, lower or higher HbA1c levels may be observed than would be expected from measured glucose control[36] because HbA1c is influenced by many factors including the lifespan of red blood cells, recombinant human erythropoietin, blood transfusions, iron supplements and anemia.[37–40] Those interfering and confounding factors may lead to erroneous HbA1c values. Glycated albumin was not influenced by those factors, which may replace HbA1c to further explore the relationship between glycemic control and ESKD in patients with DN.[37 41]

The strengths of this study are twofold. First, the data of patients with DN used for adherence and effectiveness evaluation are of good quality. They consist of the medical records for a large number of Chinese patients with DN and cover a long time span with median follow-up time of 3.26 (IQR 1.56–5.53) years. Second, the methods to investigate the influence of guideline adherence and parameter control on the clinical outcomes are comprehensive, including GEE models, Cox proportional-hazards models and latent class mixed model. We consider the guideline adherence of three types of treatments (antihyperglycemic, antihypertensive and lipid-lowing therapy) in both ADA and Chinese guidelines, and evaluate two types of outcomes (the control of clinical parameters in the short term and the occurrences of ESKD in the long term). In this study, considering the correlation between visit samples within the same patient, guideline adherence and its effect on control target achievement of parameters were evaluated through GEE models. Furthermore, considering that adherence to a specific guideline for a patient was time varying and the follow-up time for different patients was varied, the time-dependent Cox models have been applied to solve this problem and evaluate the influence of guideline adherence on long-term outcome of ESKD. Finally, to investigate the effect of parameter

control on ESKD, an advanced method of LCMM was applied to identify the trajectory groups in clinical parameters at patient level, and associated ESKD risks in different trajectory groups were compared using Cox proportional-hazards models with sensitivity analysis.

However, our study has its limitations. First, it was a single-center retrospective study and the selection bias may exist. Some patients with incomplete follow-up data were not included in the study. Second, since the information of drug dosage was incomplete, we did not consider the drug dosage adjustment in patients with DN. Also, the incomplete death records did not allow us to build up competitive risk models. Third, we only measure guideline adherence without any measures of patients' adherence to prescription. Finally, although the guidelines increasingly emphasize personalized treatment, in this study unified therapeutic targets were selected (eg, HbA1c<7%) without considering personalized control targets for individual patients.

In conclusion, the results in this retrospective study suggested that adherence to guidelines can help patients with DN patients to reach therapeutic targets and improve long-term prognosis. At the same time, the importance of strict control of proteinuria and LDL-C in patients with DN was emphasized. It provides the real-world evidence to help in establishing the policies of standardized treatment for DN in China.

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