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Prognostic nomogram and score to predict renal survival of patients with biopsy-proven diabetic nephropathy

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ABSTRACT

Aims: Both clinical and pathogenetic markers for accurate prediction of end-stage renal disease in diabetic nephropathy (DN) are lacking. This study aimed to establish an effective prognostic nomogram and a score for renal survival (RS) in biopsy-proven DN.

Methods: Analyses were derived from 110 DN patients who underwent renal biopsy at China-Japan Friendship Hospital between January 2006 and May 2018 with DN as the only glomerular disease diagnosis. The prognostic ability of 34 baseline clinicopathologic parameters was evaluated using univariate and multivariate Cox regression analyses. The predictive accuracy and discriminative ability of the final model were measured using the calibration curve and concordance index (C-index). Internal validation of the model was assessed using bootstrap resampling.

Results: Urinary proteinuria excretion, stages of chronic kidney disease, glomerular hyalinosis, and extracapillary hypercellularity were independent prognostic factors for RS, and all were selected into the nomogram. The calibration curve for the probability of survival showed good agreement between the prediction by nomogram and actual observation. The C-index for predicting survival was 0.79 (95% confidence interval (CI) 0.72–0.86). A high C-index value of 0.76 indicated good internal validation. The prognostic score had the potential to delineate two prognosis groups with median RS of 24 and 70 months, respectively.

Conclusions: The proposed nomogram and score provide a useful individualized risk estimate of renal prognosis in patients with DN.

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1. Introduction

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) worldwide. Furthermore, the prevalence of diabetes is rising dramatically [1], which suggests an increasing prevalence of DN in the future [2]. Published data [3,4] indicate that 20–40% of individuals with diabetes will develop chronic kidney disease (CKD), and 19% show signs of later stages of kidney disease. To date, markers for accurate prediction of the time from DN to ESRD are inadequate and mainly rely on several clinical factors, such as albuminuria and glomerular filtration rate (GFR) [5]. In clinical practice, patients with a typical course of DN usually do not undergo renal biopsy. Pathologic phenotypes of DN are thus very limited in the biopsied population. Whether pathologic lesions have clinical prognostic value warrants further research.

To standardize DN scoring and to analyze pathologic variations in DN, the Working Group of the Renal Pathology Society (RPS) developed a pathologic classification for DN in 2010 [6]. Given that the RPS classification is based on the most "severe" findings and that additional features, such as segmental sclerosis (SS), extracapillary hypercellularity (EXHC), and glomerular hyalinosis [7–10], are not included in the RPS scoring, Mottl et al. [9] provided a more detailed characterization of light-microscopic pathologic lesions in 2018 to further quantify the risk for diabetic ESRD. Unfortunately, their study had extensive missing data on several important clinical prognostic parameters, such as hemoglobin A1c (HbA1c), systolic blood pressure (SBP), and the duration of diabetes. The effect of these data when added to clinicopathologic data needs to be determined by other studies.

In addition, nomograms have been increasingly used by clinicians for survival prediction as a new standard in oncology and medicine [11–13], as they can provide simple-to-use digital interfaces and increase predictive power by integration of multiple independent predictors. However, to date, no single study is available that evaluates a prognostic nomogram for ESRD-free survival prediction in DN patients. Accordingly, the aims of our study were to (1) determine whether SS and EXHC could represent a distinct pathogenetic phenotype of DN, and (2) develop a novel prognostic nomogram and a score for RS using a broad spectrum of clinicopathologic parameters available at baseline in the hope that it could be used to accurately and conveniently predict RS in DN and thereby guide adjuvant therapy.

2. Materials and methods

2.1. Patients and study design

A retrospective study was conducted on a cohort of patients with type 1 or type 2 diabetes and nephropathy who underwent native renal biopsy at China-Japan Friendship Hospital between January 2006 and May 2018 with isolated DN as the only pathologic diagnosis. The following exclusions were made: coincident non-diabetic renal disease (NDRD), eGFR < 15 ml/min/1.73 m^2 at baseline, inadequate renal tissue (fewer than five glomeruli by renal biopsy), and no follow-up information (Fig. 1).

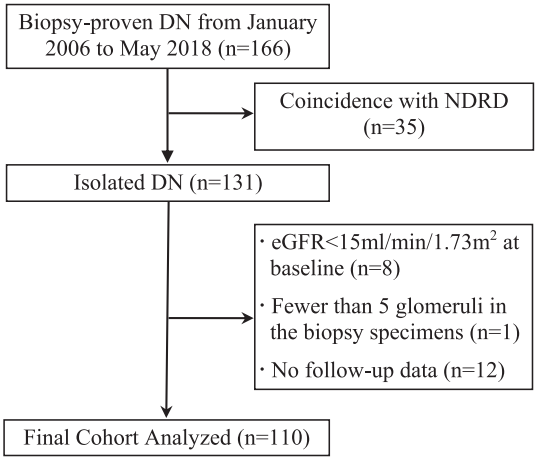

Fig. 1 – Flowchart of study participants. DN, diabetic nephropathy; NDRD, non-diabetic renal disease; eGFR, estimated glomerular filtration rate.

This study protocol was approved by the institutional ethics committee of China-Japan Friendship Hospital on human research (2018-43-K32). All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the Declaration of Helsinki of 1975, revised in 2008. Informed consent was obtained from each patient before renal biopsy.

2.2. Endpoints

The follow-up time was assessed from the time of renal biopsy to one of four endpoints: ESRD (i.e., the commencement of chronic renal replacement therapy or kidney transplantation), death, loss to follow-up, or the study end date of December 31, 2018. The primary endpoint was renal survival (RS), defined as the duration from renal biopsy to ESRD or death. None of the patients received kidney transplantation during follow-up.

2.3. Clinical and laboratory data

Clinicians collected clinical and laboratory data from electronic medical records, including age, gender, body mass index (BMI), duration of diabetes, presence of diabetic retinopathy (DR), number of erythrocytes in urine sediment, 24-hour urinary protein excretion (UPE), serum albumin (ALB), serum creatinine, blood urea nitrogen, fasting blood glucose (FBG), HbA1c, hemoglobin (Hb), serum uric acid, total cholesterol (TCH), triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood pressure, use of hypoglycemic agents, and history of cardiovascular events (CVEs). The estimated GFR (eGFR) was calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14], and categorized according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline [5].

2.4. Definitions

According to the Chinese Society of Health Management [15], overweight was defined as a BMI $\geq$ 24 kg/m^2, and obesity was defined as a BMI $\geq$ 28 kg/m^2. Following the current clinical practice recommendations of the American Diabetes Association (ADA), <7% was considered a reasonable HbA1c level for adults [16]. Hematuria was defined as the excretion of more than five erythrocytes per high-power field in urine sediment from at least two of three consecutive urine specimens. According to the classifications from the guidelines for the management of dyslipidemia in Chinese adults [17], dyslipidemia was defined as TCH $\geq$ 5.2 mmol/L, triglycerides $\geq$ 1.7 mmol/L, LDL-C $\geq$ 3.4 mmol/L, HDL-C < 1.0 mmol/L, or treatment with any lipid-lowering medication. Hyperuricemia was defined as serum uric acid $\geq$420 μmol/L in males or $\geq$360 μmol/L in females. Hypoalbuminemia was defined as serum ALB < 30 g/L. Anemia was defined as Hb concentration <130 g/L in males and <120 g/L in females according to the 2012 KDIGO guidelines for anemia in CKD [5]. The presence of DR was defined as any degree and/or severity according to the Early Treatment Diabetic Retinopathy Study severity scale [18]. CVEs were defined as a positive medical history of cardiovascular disease, including myocardial infarction, angina, acute coronary syndrome, revascularization events (coronary artery surgery and percutaneous transluminal coronary angioplasty), significant coronary stenosis (defined as $\geq$70%) [19], and stroke.

2.5. Pathology review of renal biopsy specimens

The indications for renal biopsy were as follows: unexplained hematuria, absence of diabetic retinopathy, abrupt increase in serum creatinine or proteinuria, rapid worsening of renal function, and renal failure in patients without macroalbuminuria. All renal biopsy specimens were processed at China-Japan Friendship Hospital and evaluated routinely by (1) light microscopy on formalin-fixed, paraffin-embedded tissue using hematoxylin-eosin (H&E), periodic acid-Schiff, silver methenamine, and Masson-trichrome staining; (2) immunofluorescence microscopy on frozen tissue using antibodies specific for IgG, IgA, IgM, C3, C1q, and fibrin; and (3) transmission electron microscopy on tissue fixed in Trump's EM fixative and processed into resin blocks.

Pathologic scoring was performed according to the criteria developed by Mottl et al. [9]; the definitions of pathologic scoring are summarized in Table 2. Classification of DN was performed according to the RPS DN classification [6] with the following classes of glomerular lesions. Class I was defined as mild or nonspecific light microscopy changes and glomerular basement membrane (GBM) thickening (GBM > 395 nm in females and >430 nm in males, without any of the criteria mentioned below for Class II, III, or IV. Class II was defined as mesangial expansion in >25% of the observed mesangium, but not meeting the criteria for Class III or IV (IIa, expanded mesangial area < capillary lumen; IIb, expanded mesangial area > capillary lumen). Class III was defined as nodular sclerosis (presence of at least one convincing Kimmelstiel–Wilson (K-W) lesion and <50% global glomerulosclerosis). Class IV was defined as advanced diabetic glomerulosclerosis (global glomerular sclerosis in >50% of glomeruli). Scoring was performed by two nephropathologists, with discrepancies solved by consensus. The evaluators who carried out renal biopsy review were unaware of patients' clinical outcomes.

2.6. Statistical analysis

All statistical analyses were performed using R version 3.5.2 (Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). All tests were two-sided, with the statistical significance level set at $p < 0.05$. Categorical variables were grouped based on clinical and pathological findings, and decisions on the groups were made before modeling. Cox-proportional-hazard models were performed to estimate the hazard ratio (HR) and 95% confidence interval (CI) for parameters associated with RS. The association of the baseline parameters with RS was first assessed using univariate log-rank tests, and those with p-values < 0.10 were entered into a final multivariate Cox regression model [20]. To provide the clinicians with a quantitative tool to estimate the individual post-diagnosis RS probability at 1, 3, and 5 years, a nomogram was built based on the multivariate Cox regression analysis.

Accuracy of the final model was verified using two parameters: discrimination and calibration. The predictive performance and the discrimination ability of the nomogram were measured using the concordance index (C-index) [21]. C-index values range from 0.5 to 1.0, larger C-index values indicate more accurate prognostic prediction. Generally, a C-index value $\geq$ 0.70 suggests a good fit [22]. The apparent performance was also assessed using a calibration plot to provide unbiased survival predictions in groups of similar patients [21]. Internal validation of the final multivariate model was performed with a bootstrap sample procedure to calculate a relatively corrected C-index [23].

For estimation at the population level, a prognostic score was built from the weighted sum of each independent variable, with the weights equal to the β-coefficient from the multivariate Cox model. To provide a range of risk, patients were divided into low-risk and high-risk groups according to the median of the prognostic score. The discrimination abilities of the different prognostic scores produced were assessed with the C-index by considering risk group classification.

3. Results

3.1. Clinicopathologic characteristics of patients

As shown in Fig. 1, of the 166 patients with biopsy-proven DN during the study period, 110 met the inclusion criteria and were included in this study. Of these 110 patients, 108 had type 2 diabetes (98.2%). The median age at baseline was 54.0 (range 26.0–74.0) years. The median number of glomeruli of the 110 biopsy specimens was 22.5 (range 8–65). The baseline clinicopathologic characteristics of the development cohort are tabulated in Tables 1 and 2.

Table 1 – Clinical characteristics of patients with diabetic nephropathy.

Clinical parameters	Missing data, n (%)	Cohort (n = 110)	
		No. of patients	%
Male sex	0	79	71.82
Age, years, median (range)	0	54 (26–74)	
BMI, kg/m^2	0		
<24		34	30.91
24~<28		46	41.82
≥28		30	27.27
Diabetes duration, yr	0		
<5		18	16.36
5~<10		28	25.46
≥10		64	58.18
Hematuria	0	36	32.73
Anemia	0	81	73.64
Hypoalbuminemia	0	29	26.36
UPE, g/24 h	0		
<1		11	10.0
1~<3.5		27	24.55
≥3.5		72	65.45
HbA1c (≥7%)	9 (8.2%)	58	57.43
Stages of CKD*	0		
CKD stage 1		15	13.64
CKD stage 2		29	26.36
CKD stage 3a		24	21.82
CKD stage 3b		22	20.0
CKD stage 4		20	18.18
Hyperuricemia	0	44	40.0
Dyslipidemia	0	86	78.18
DR	0	95	86.36
PDR	12 (11%)	31	31.63
History of hypertension	0		
None		9	8.18
Grade 1 hypertension		8	7.27
Grade 2 hypertension		18	16.36
Grade 3 hypertension		75	68.18
SBP (≥140 mmHg)	0	73	66.36
DBP (≥90 mmHg)	0	31	28.18
History of CVE	0	28	25.45
Number of antihypertensive agents	0		
None		7	6.36
1~2		72	65.45
≥3		31	28.18
Using ACEI or ARB	0	91	82.73
Hypoglycemic agents	0		
OHA therapy		28	25.45
Insulin therapy		82	74.55

BMI, body mass index; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; 24 h-UPE, 24-hour urinary proteinuria excretion; CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVE, cardiovascular event; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type I receptor blocker; OHA, oral hypoglycemic agent; Insulin therapy, treatment with insulin including basal supported oral hypoglycemic agent.

* Stages of CKD were classified based on eGFR calculated using the creatinine-based CKD-EPI equation [14].

3.2. *Renal progression and RS in the cohort*

The median follow-up duration was 27.4 (range 6.0–127.6) months. ESRD occurred in 48 individuals (43.6%) during follow-up. A total of 10 patients died during follow-up: 2 died before reaching ESRD, and 8 died after progression to ESRD. The median RS was 40.3 (95% CI 27.2–53.3) months; the 1-, 3-, and 5-year RS rates were 89.6%, 52.0%, and 40.0%, respectively.

3.3. *Prognostic factors for RS*

Only 7 of 34 evaluated baseline clinicopathologic parameters were associated with RS in the univariate Cox analyses at a p-value < 0.1. These were anemia, UPE, CKD stages, K-W nodules, glomerular hyalinosis, EXHC, and interstitial fibrosis. The multivariate Cox analysis showed that only four predictors were independently associated with RS, namely UPE, CKD stages, glomerular hyalinosis, and EXHC (Table 3).

Table 2 – Pathological characteristics of patients with diabetic nephropathy.

Pathologic scores	Scoring definitions	Cohort (n = 110)	
		No. of patients	%
RPS DN class[a]			
I	Mild or nonspecific LM changes with GBM thickening	0	0
IIa	Mild mesangial expansion	10	9.09
IIb	Severe mesangial expansion	29	26.36
III	Nodular sclerosis	64	58.18
IV	Advanced diabetic glomerulosclerosis	7	6.36
Mild mesangial expansion[b*#]			
0	None	60	54.55
1	1%~25%	22	20.0
2	>25%	28	25.45
Severe mesangial expansion[b*]			
0	None	12	10.91
1	1%~25%	7	6.36
2	26%~50%	24	21.82
3	51%~75%	27	24.55
4	>75%	40	36.36
Global glomerulosclerosis[b*#]			
0	None	26	23.64
1	1%~25%	50	45.45
2	>25%	34	30.9
Presence of K-W nodules[b*#]			
0	None	42	38.18
1	1%~25%	24	21.82
2	26%~50%	33	30.0
3	>50%	11	10.0
SS[b*$]			
0	None	31	29.09
1	Present	79	70.91
Mesangiolysis[b*#]			
0	None	36	32.73
1	1%~25%	51	46.36
2	>25%	23	20.9
Glomerular hyalinosis[b*]			
0	None	41	37.27
1	Present	69	62.73
EXHC[b*$]			
0	None	94	85.45
1	Present	16	14.55
Interstitial fibrosis[b#]			
1	1%~25% cortex	32	29.09
2	26%~50% cortex	65	59.09
3	>50% cortex	12	11.82
Interstitial inflammation[b]			
0	None	6	5.45
1	<25% of interstitial fibrotic regions	99	90.0
2	≥25% of interstitial fibrotic regions	5	4.55
Arteriolosclerosis[b]			
1	No thickening of wall	3	2.73
2	Thickened wall with patent lumen	28	25.45
3	Severely or completely narrowed lumen	79	71.82
Arteriosclerosis[b]			
0	None	7	6.36
1	Intimal fibrosis < 25% media thickness	28	25.45
2	Intimal fibrosis 25–49% media thickness	31	28.18
3	Intimal fibrosis ≥ 50% media thickness	41	37.27
Missing	–	3	2.73

RPS, Renal Pathology Society; DN, diabetic nephropathy; GBM, glomerular basement membrane; SS, segmental sclerosis; EXHC, extracapillary hypercellularity; LM, light microscopy.

[a] Scores were defined by the RPS Diabetic Nephropathy Classification [6].

[b] Scoring definitions were done according to Mottl et al [9].

[*] Glomerular lesions were scored as % of the glomeruli.

[#] For analyses, scores of 2, 3, and 4 were collapsed together as 2 for mild mesangial expansion, global glomerulosclerosis, and mesangiolysis. Scores of 3 and 4 were collapsed together as 3 for the presence of K-W nodules, and interstitial fibrosis.

[$] Owing to the limited data on the presence of either SS or EXHC, both SS and EXHC were divided into two groups: none and present.

Table 3 – Univariate associations between candidate predictors and survival and multivariate Cox regression analysis for the prediction of survival.

Variable	Univariate analysis		Multivariate analysis		
	HR (95% CI)	*p*	*β*	HR (95% CI)	*p*
Clinical characteristics					
Anemia	1.94 (0.90–4.18)	0.09	0.67	1.97 (0.72–5.37)	0.18
UPE, g/24 h					
1~<3.5	6.03 (0.76–47.80)	0.09	1.51	4.51 (0.46–43.87)	0.19
≥3.5	13.28 (1.78–99.16)	0.01	2.07	7.97 (0.99–68.75)	0.05
CKD stages					
CKD stage 2	1.50 (0.47–4.77)	0.49	0.63	1.88 (0.49–7.24)	0.36
CKD stage 3a	2.55 (0.73–8.89)	0.14	0.81	2.26 (0.58–8.81)	0.24
CKD stage 3b	3.86 (1.19–12.52)	0.02	1.37	3.93 (1.01–15.37)	<0.05
CKD stage 4	5.20 (1.71–15.84)	0.004	1.35	3.85 (1.05–14.11)	<0.05
Pathologic characteristics					
K-W nodules					
1%~25%	1.14 (0.50–2.60)	0.75	−0.15	0.86 (0.31–2.37)	0.76
26%~50%	2.07 (1.04–4.12)	0.04	0.38	1.46 (0.69–3.09)	0.32
≥51%	1.51 (0.55–4.17)	0.43	0.08	1.09 (0.36–3.29)	0.88
Glomerular hyalinosis	5.37 (2.38–12.14)	<0.001	1.81	6.10 (2.30–16.17)	<0.001
EXHC	2.14 (0.88–5.2)	0.07	1.27	3.55 (1.30–9.71)	<0.05
Interstitial fibrosis					
26%~50% cortex	2.11 (0.99–4.45)	0.05	0.28	1.32 (0.51–3.44)	0.57
≥51% cortex	2.56 (1.07–6.08)	0.03	0.74	2.12 (0.72–6.17)	0.17

HR, hazard ratio; CI, confidence interval; UPE, urinary proteinuria excretion; CKD, chronic kidney disease; EXHC, extracapillary hypercellularity. *β* is the regression coefficient.

As displayed in Fig. 2A–D, patients who presented with nephrotic-range proteinuria, later stages of CKD, glomerular hyalinosis, or EXHC had significantly worse RS than those who did not. The median RS for patients with proteinuria in the nephrotic range was 37.2 (95% CI 28.4–46.1) months *vs.* 73.2 (95% CI 57.5–88.9) for non-nephrotic range proteinuria. The median RS was 67.1 (95% CI 50.9–83.3) months in CKD stage 1–2 patients and 36.4 (95% CI 28.6–44.2) in CKD stage 3–4 patients. The median RS values were 30.1 (95% CI 24.7–35.4) for patients with glomerular hyalinosis and 27.1 (95% CI 17.9–36.3) for those with EXHC.

3.4. *Prognostic nomogram for RS*

The final model integrating all significant independent factors for RS was developed and is shown as a nomogram (Fig. 3) that provides simple-to-use individual survival estimations for DN patients. For example, a DN patient with a UPE of 2.5 g/24 h (7 points), CKD stage 2 (2 points), presence of glomerular hyalinosis (8 points), and EXHC (4 points) would have a total of 21 points, which corresponds to estimated 1-, 3-, and 5-year RS likelihood of 80%, 30%, and 10%, respectively.

3.5. *Performance assessment and internal validation of the final model*

The nomogram had a C-index of 0.79 (95% CI 0.72–0.86), which indicates good discrimination ability. The calibration plots showed optimal agreement between the model prediction and actual observation for predicting RS probability at 1, 3, and 5 years (Fig. 4). With respect to internal validation, the C-index was confirmed to be 0.76 through bootstrapping validation, suggesting good discrimination.

3.6. *Prognostic score for ESRD risk stratification*

A second model based on the final multivariate Cox analysis used the independent variables to develop a prognostic score to predict risk of time to diabetic ESRD. The score for an individual patient was the weighted sum of the individual predictors, with weights equal to the regression coefficients in the final model; scores were calculated as follows: prognostic score = 2.12 * (1 if UPE ≥ 3.5 g/24 h) + 1.46 * (1 if CKD stage 4) + 1.65 * (1 if glomerular hyalinosis present) + 0.89 * (1 if EXHC present). Based on the median prognostic score, patients were categorized into two risk groups: a low-risk group (n = 51; score < 3.01) and a high-risk group (n = 59; score ≥ 3.01). The median RS values were 70.0 and 24.2 months for the low-risk and high-risk groups, respectively ($p < 0.001$) (Fig. 5). The risk stratification groups based on the prognostic score predicted RS with a C-index of 0.71 (95% CI 0.65–0.77).

4. Discussion

This is a detailed study of the association between clinicopathologic findings of DN and clinical outcome. We found that RS in DN could be predicted using a combination of UPE, stages of CKD, glomerular hyalinosis, and EXHC. A novel clinicopathologic prognostic nomogram was developed by modelling the above factors to predict the 1-, 3-, and 5-year RS for patients with DN. This model showed moderately high discrimination and sufficient calibration. In addition, a baseline prognostic score was developed, which could serve as a

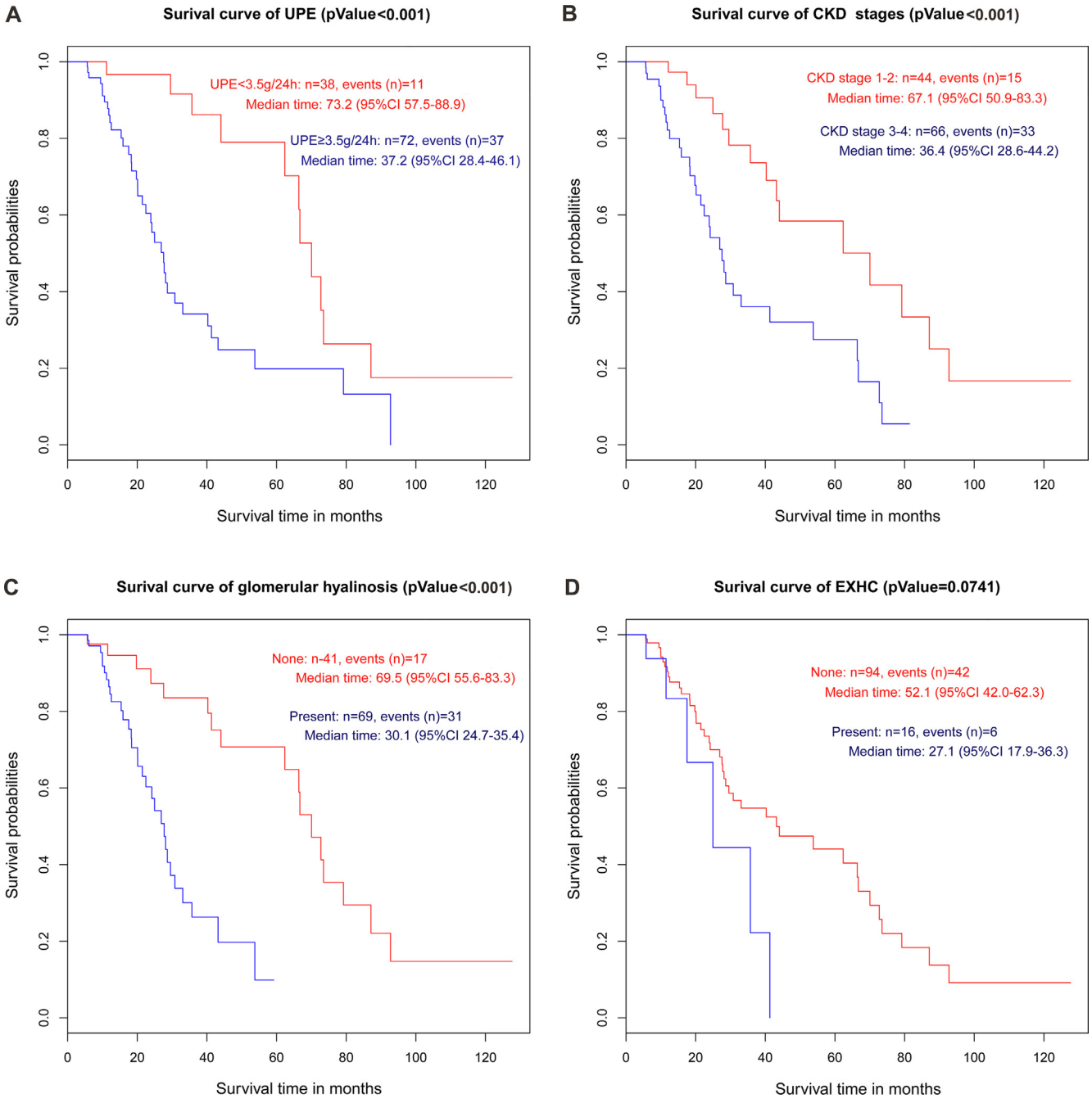

Fig. 2 – Kaplan–Meier curves of cumulative survival according to clinicopathologic characteristics. (A) UPE, (B) CKD stages, (C) glomerular hyalinosis, and (D) EXHC. UPE, urinary protein excretion; CKD, chronic kidney disease; EXHC, extracapillary hypercellularity.

complementary tool in clinical practice to produce a classification of patients into well-identified ESRD-risk populations.

The 2012 KDIGO guidelines provide a simple classification that helps predict the risk of ESRD in CKD [5]. This classification is based on three clinical factors: the cause of the disease, the degree of albuminuria, and the GFR. In patients with DN, owing to the limited pathologic phenotypes, proteinuria and eGFR are currently the main prognostic markers for diabetic ESRD [24,25], though few potential pathogenetic markers have been identified [9,26]. In the present study, for the sake of building a simple-to-use and better model, we graded the baseline UPE and groups of eGFR to convert them into categorical variables. Our study supports the role of UPE and eGFR as independent prognostic factors for RS.

Pathogenic markers of time to ESRD are currently lacking. To determine which pathologic variations are independently suggestive of the risk for diabetic ESRD, Mottl et al. [9] provided a more detailed characterization of light-microscopic pathologic changes based on RPS DN class in 2017 [6]. They identified SS and EXHC as novel and poor prognostic indicators of time from DN to ESRD. Unfortunately, data on several important clinical factors, such as HbA1c, systolic blood pres-

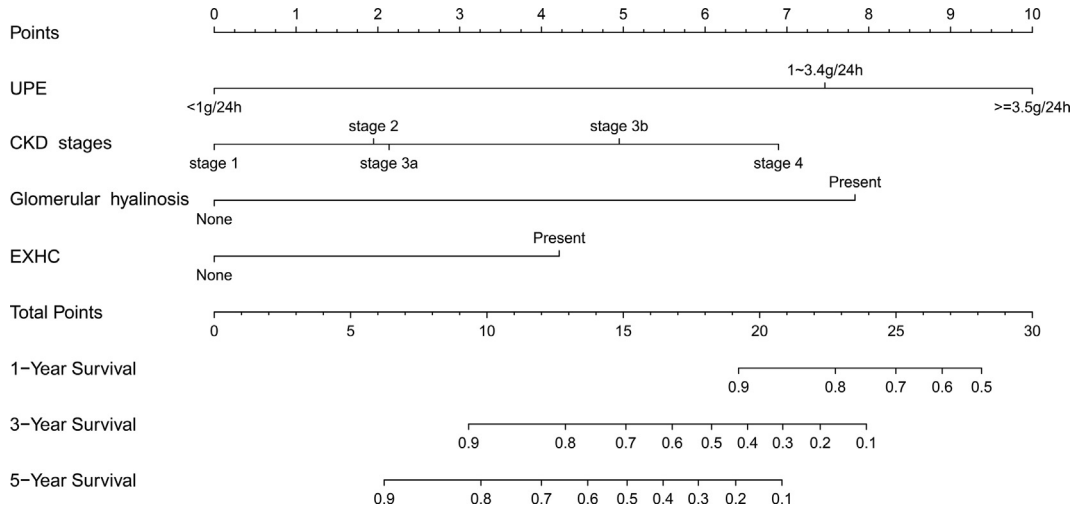

Fig. 3 – Prognostic nomogram to predict individual renal survival probability in patients with diabetic nephropathy. The nomogram allows the user to obtain 1-, 3-, and 5-year renal survival corresponding to a patient's combination of variables. Points are assigned for each variable by drawing a straight line upward from the corresponding value to the "Points" line. Then, sum the points received for each variable, and locate the number on the "Total Points" axis. To speculate the patient's renal survival after 1-, 3-, or 5-years, a straight line must be drawn down to the corresponding "1-Year Survival, 3-Year Survival, or 5-Year Survival" probability axis. UPE, urinary protein excretion; CKD, chronic kidney disease; EXHC, extracapillary hypercellularity.

sure, and diabetes duration, were extensively missed in their study. However, we found no independent predictive role for ESRD after we added these complete data in our study. Thus, we consider that these clinical factors may not play a major role in DN progression.

On the other hand, we found that EXHC, other than SS, was an independent predictor of clinical progression to diabetic ESRD. EXHC in the present study referred to hyperplasia of either podocyte or parietal epithelial cells. Thus, EXHC resampled the EXHC of pseudocrescents of collapsing focal segmental glomerulosclerosis in 6 (5.5%) patients, and that of crescents of glomerulonephritis in 10 (9.1%) patients. Only a few studies with very small sample sizes, apart from a relatively large cohort of patients with DN [9], have reported "crescents" [8,27] or "pseudoocrescents" [7] in DN, all of which reported a lower incidence of EXHC than in our cohort. The prevalence of EXHC in our cohort was 14.5%, which is similar to the results observed in the only study with a large sample published in 2018 [9]. Some investigators consider that the percentage of diabetic glomeruli associated with crescents may be related to the severity of vascular disease [8]. Here, we showed that EXHC is a prognostic marker of time to diabetic ESRD. The presence of EXHC in renal biopsy specimens of patients with diabetes may provide guidance for future research.

Hyalinosis can be present within the glomerular tuft under endothelial cells (fibrin cap) or under parietal epithelial cells (capsular drop) in DN [10]. Exudative lesions in afferent and efferent arterioles are called hyalinized afferent and hyalinized efferent arterioles, respectively. Glomerular hyalinosis in the present study referred to either fibrin cap lesions or capsular drop lesions in glomerular tufts, and in most instances, they coexisted. As a result, an additional interesting conclusion of the present study is that the presence of glomerular hyalinosis is another independent predictor of time to diabetic ESRD. Stout et al. observed that fibrin cap lesions were infrequent in minimal diabetic changes but were easily found in advanced diabetic changes [28]. To our knowledge, few studies have evaluated the association between glomerular hyalinosis and renal outcome [9]. This is the first report to demonstrate that the presence of glomerular hyalinosis is an independent predictor of time to diabetic ESRD, which will lay a foundation for further research.

Nomograms have increasingly become an important component of modern medical decision-making [11,12]. They can make the results of prediction models clear by showing visual graphical interfaces, thus providing accurate predictions for specified end points. Unfortunately, no nomogram has been developed to date for the prediction of time to ESRD in DN patients. Therefore, this was the major aim of the present study. Eventually, four independent parameters (UPE, CKD stages, glomerular hyalinosis, and EXHC) were incorporated into the nomogram, all of which are easily available and measurable. The baseline prognostic score can serve as a supplement to classify patients into well-identified ESRD risk populations; it is not a replacement of the nomogram. It is worth noting that the difference in cutoff points between the risk score and the development cohort should be explored further to give a more reasonable spread of risk. A large study that includes two or three prognostic risk groups will be important to determine this.

Our study has several strengths. The main strength is that we used complete clinical data and detailed pathologic characterization of light microscopic pathologic lesions to generate the prediction models for RS. Next in importance is the development of the nomogram and the risk score, either of which can be applied in clinical practice to be predictive of RS in DN patients. Moreover, this is the first report in which

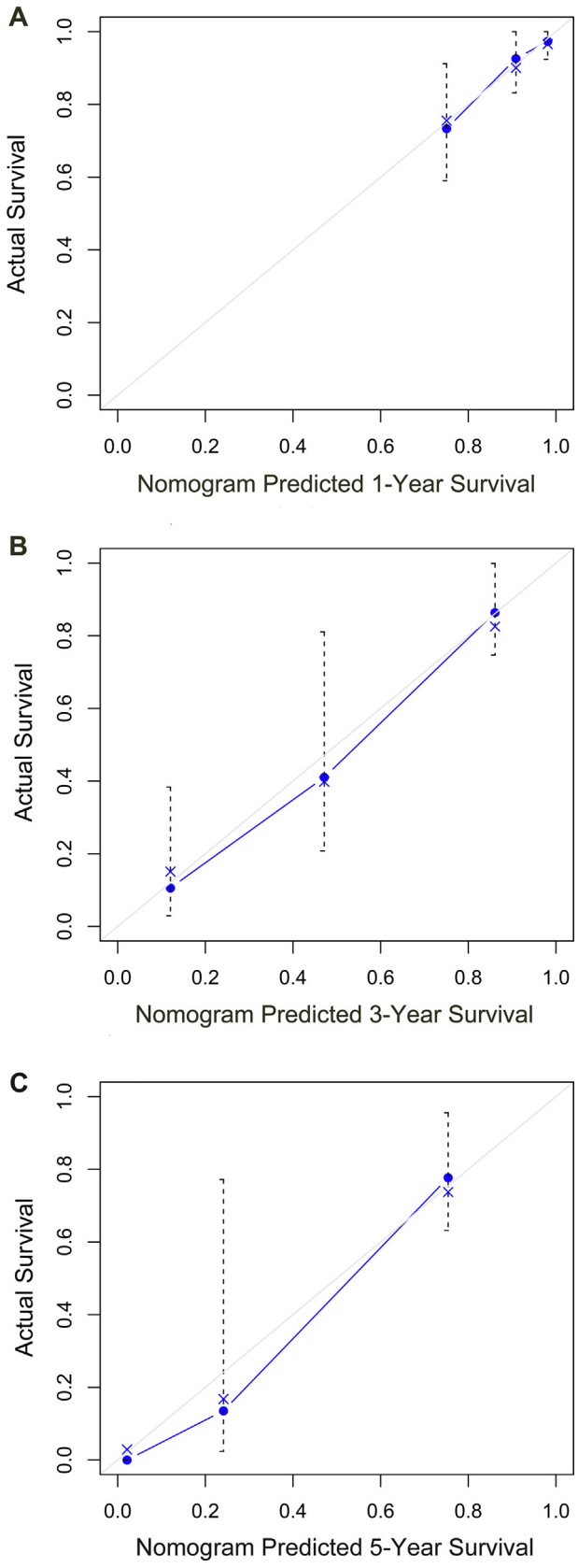

Fig. 4 – Calibration curves for predicting renal survival at 1 and 3 years. Nomogram-predicted probability of renal survival is plotted on the x-axis, and actual renal survival is plotted on the y-axis.

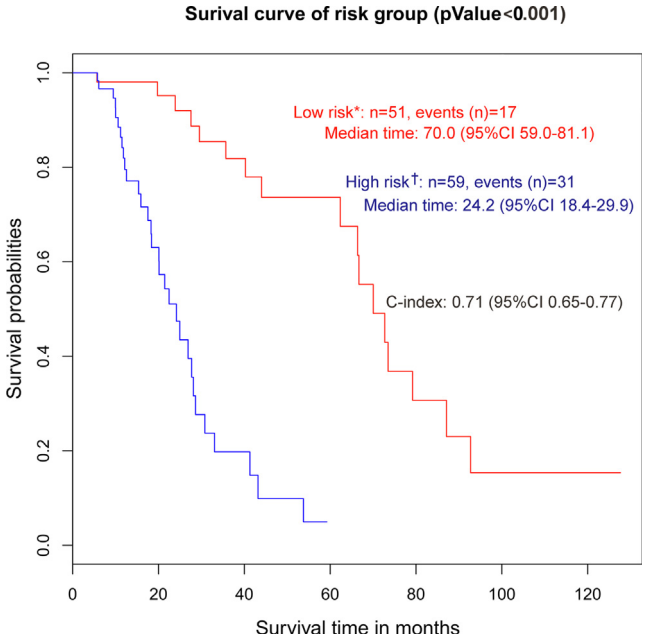

Fig. 5 – Kaplan–Meier curves of cumulative survival according to the prognostic score group for the two risk groups. * Low-risk group: score <3.01 or nomogram total points <14; † High-risk group: score ≥3.01 or nomogram total points ≥14.

a nomogram was applied for the survival prediction of DN patients. Finally, the blinded evaluation of renal biopsy is another strength of this study.

However, this study has several limitations. First, the nomogram and score were established based on retrospective data obtained from a single institution. Validating the models prospectively, or at least in independent patient groups, is warranted. Second, the biopsied patients with diabetic kidney disease in the present study were clinically atypical and thus may not represent those with DN in the general population. Third, this study primarily included patients with advanced type 2 diabetes. Therefore, a larger study with a broad spectrum of disease severity by diabetes type is required to test the effect of the models and further improve their clinical utility.

In conclusion, the nomogram and score proposed in this study can be considered to accurately predict renal prognosis in DN in clinical practice and may help in decision-making regarding management of DN. Additional studies are required to determine whether they can be applied to other independent population-based databases and thus to improve the clinical utility of the model via a prospective, multicenter study that includes protocol renal biopsies in all enrolled patients and different ethnic groups.

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Declaration of Competing Interest

None.

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None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107809.

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