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A Pathological Scoring System to Predict Renal Outcome in Diabetic Nephropathy

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Key Words
Diabetic nephropathy · Renal biopsy · Pathology · Scoring system · Prediction · End-stage renal disease

Abstract
Background: With the association between diabetic nephropathy (DN) and renal outcome being increasingly clear, we aimed at creating a new DN pathological scoring system that could predict the renal outcome. ***Methods:*** We studied 205 patients with DN confirmed by renal biopsy, sometime between March 1985 and January 2010, who met the inclusion criteria. Renal biopsy included clinical parameters and Tervaert classifications. Hazard ratios (HRs) for death-censored end-stage renal disease (ESRD) were estimated by adjusted Cox proportional-hazards regression. The overall pathological risk score (D-score) was calculated by summing the products of beta coefficient and bootstrap-inclusion fractions, its predictive utility evaluated by Kaplan-Meier methods and c-statistics for a 10-year risk of ESRD. ***Results:*** The D-scores of glomerular classes 1, 2A, 2B, 3, and 4 were, respectively, 0, 3, 4, 6, and 6. Those of interstitial fibrosis and tubular atrophy classes 0, 1, 2, and 3 were 0, 7, 9, and 11, and those of interstitial inflammation classes 0, 1, and 2 were 0, 3, and 4, respectively. The D-score of hyalinosis class 2 was 3 and that of arteriosclerosis class 2 was 1. So, a patient's D-score could be 0–25. HRs for ESRD in patients with D-score ≤14, 15–18, 19–21, and 22–25 were, respectively, 1.00 (reference) 16.21 (95% confidence interval (CI), 1.86–140.90), 19.78 (95% CI, 2.15–182.40), and 45.46 (95% CI, 4.63–446.68) after adjusting for clinical factors. The c-statistics suggested a better predictive ability for a 10-year renal death with models that included the D-score. ***Conclusion:*** Prediction of DN patients' renal outcome was better with the D-score than without it. Patients with a D-score ≤14 had excellent renal prognosis.
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Introduction

Diabetic nephropathy (DN) is the single most common cause of end-stage renal disease (ESRD) in adults in many countries and is considered a main reason for the

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elevation of the number of ESRD patients [1]. Several large studies showed that a high urinary albumin-to-creatinine ratio and a low estimated glomerular filtration rate (eGFR) are predictors for diabetic ESRD and death [2–5]. In addition to these clinical parameters, after the development of pathological classification of DN by Tervaert et al. [6], several studies suggested that both glomerular and interstitial damage are independently associated with ESRD [7–10]. But it remained unknown how much the separate sorts of damage revealed by renal biopsy – with varying degrees of severity for each patient – impact the overall renal outcome. What is their net cumulative effect on DN patients? Without that knowledge, renal biopsy is an uncertain predictor of renal outcome, and it is less clear when and for whom renal biopsy is indicated. To address this problem, we aimed at creating a new pathological scoring system for DN patients that would factor in for each patient, the weighted effect of all the kinds of renal damage that the patient had sustained, allowing prediction of the patient's renal outcome.

Methods

Data about this study's population were detailed in our previous study [7]. Briefly, from the 310 patients with diabetes mellitus at our center who underwent renal biopsy from March 1985 to January 2010 – and whose DN was confirmed by the Tervaert classification [6] – 205 were enrolled in this retrospective study and followed until ESRD, death, or the end of follow-up. We defined DN as a kidney disease attributable to diabetes and pathologically confirmed by the criteria of Tervaert et al. The exclusion criteria were kidney transplantation, coexistence of other renal disease (except for nephrosclerosis), eGFR less than 10 ml/min/1.73 m^2 at the time of renal biopsy, and the renal biopsy having obtained fewer than five glomeruli (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000431333).

The patients' baseline clinical data were obtained from medical records. The data included sex, age, body mass index (BMI), blood pressure (BP), eGFR, serum albumin, hemoglobin (Hb), hemoglobin A1c (HbA1c), proteinuria, urinary red blood cell (RBC), presence of diabetic retinopathy, and type of diabetes at the time of renal biopsy. The indications of renal biopsy (inclusion criteria) were, basically, proteinuria more than 0.5 g/day or atypical DN such as renal involvement without diabetic retinopathy and/or with urinary RBC. Renal tissue was obtained by needle biopsy and specimens were processed for light microscopy, immunofluorescence, and electron microscopy (EM), as described previously [11]. DN was diagnosed by two or more researchers who were pathologists or nephrologists. The diagnosis and histological scoring were reevaluated by the same pathologists/nephrologists according to the criteria of Tervaert et al. The glomerular scores were classified as: class 1, glomerular basement membrane thickening (>395 nm in females, >430 nm in males) by EM without any of the other glomerular criteria detailed below for classes 2, 3, or 4; class 2A, mild mesangial expansion (the expanded mesangial area is smaller than the mean area of capillary lumen) in >25% of the observed mesangial areas; class 2B, severe mesangial expansion (the expanded mesangial area is larger than the mean area of capillary lumen) in >25% of the total observed mesangial areas; class 3, nodular sclerosis known as Kimmelstiel-Wilson lesion and <50% global glomerulosclerosis; and class 4, >50% global glomerulosclerosis (although the Tervaert classification used Roman numerals for the classes of glomerular lesions, for simplicity's sake we used regular numerals for the classes of all the different kinds of renal damage). Interstitial fibrosis and tubular atrophy (IFTA) scores were classified as: 0, absent; 1 (mild), <25%; 2 (moderate), 25–50%; and 3 (severe), >50% of the total area. Interstitial inflammation was scored as: 0, absent; 1 (mild), inflammation related only to IFTA; and 2 (advanced), inflammation in areas without IFTA. Arteriolar hyalinosis was scored as: 0, absent; 1 (mild), hyalinosis of, at least, one arteriole; and 2 (advanced), hyalinosis of more than one arteriole. Arteriosclerosis was scored in the most severely affected artery as: 0, no intimal thickening; 1 (mild), intimal thickening that was less than the medial thickness; and 2 (advanced), intimal thickening that was greater than the medial thickness. The presence of exudative lesions was also evaluated.

The primary endpoint of this study was ESRD, which was defined as the initiation of chronic dialysis. No patient received renal transplantation during follow-up.

Statistical Analysis

Data were summarized using proportions, means (±SD) as appropriate. Since competing risks exerted little influence in this study's results, results of the Kaplan-Meier survival estimate would approximate the 10-year cumulative incidence (risks) of ESRD [12]. Hazard ratios (HRs) of ESRD for each stage of pathological variables were estimated using the Cox proportional hazards regression model after adjusting for clinical factors: age, gender, eGFR, proteinuria, BP control (<130/80 mm Hg) or lack thereof, BMI, HbA1c, presence of urinary RBC, presence of diabetic retinopathy, duration of diabetes, and type of diabetes. The measurement of proteinuria was transformed into natural logarithms because of the skewed distribution. Because the correlation coefficient was high between pathological variables (e.g. the glomerular score and IFTA score (r = 0.665)), HRs of stages in each pathological variable was separately analyzed to avoid multicollinearity.

In order to provide information about the relative importance of each pathological variable for ESRD prediction, bootstrap inclusion fractions (BIFs) were calculated by the bootstrap aggregating method with 500 resamplings [13–15]. To generate a simple integer-based point score for each stage in the pathological variables, scores were given by multiplying the beta coefficient by 5, multiplying by the estimated BIF of the pathological variable, and rounding to the nearest integer. The overall pathological risk score (D-score) (i.e. diabetic pathological score, or D-score) for each patient was calculated by summing the scores of all components.

The calculated D-score was divided into four groups. The cutoff value was evaluated by quartile of the 10-year risk of ESRD. To examine the goodness of fit of the scoring system to the data, we compared the renal survival curves in each group using the Kaplan-Meier method. To further assess the utility of the score, we used the area under the receiver-operating characteristics (ROC) curve (c-statistics) for the 10-year risk of ESRD with 10-

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Table 1. Patient characteristics (n = 205)

Clinical findings		Pathological findings		
Male, %	73	Glomerular	1	6%
Age, years	55.9±13.0		2A	21%
BMI, kg/m^2	24.0±4.0		2B	27%
sBP/dBP, mm Hg	146±21/82±13		3	28%
eGFR, ml/min/1.73 m^2	44.4±22.9		4	18%
≥90	6%	IFTA	0	9%
60 to <90	25%		1	27%
45 to <60	24%		2	32%
30 to <45	22%		3	32%
15 to <30	20%	Interstitial inflammation	0	12%
<15	3%		1	80%
Proteinuria, g/day	3.22±3.27		2	8%
<0.5	15%	Arteriolar hyalinosis	0	8%
0.5 to <1.0	10%		1	9%
1.0 to <3.5	44%		2	83%
≥3.5	31%	Arteriosclerosis	0	9%
Serum albumin, g/dl	3.2±0.7		1	50%
Hemoglobin, g/dl	12.1±2.4		2	42%
Diabetic retinopathy, %	69	Exudative lesion	0	41%
Urinary RBC, %	11		1	59%
Duration of diabetes, years	15.1±7.9			
Type 1 DN, %	11			
ACEi/ARB, %	64			

sBP/dBP = Systolic/diastolic blood pressure; RBC = red blood cells; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

fold cross-validation [15]. The patients' data set was randomly split in deciles, with model development in nine of the ten and testing in one of the ten, repeated ten times. The net reclassification index (NRI), after inclusion of D-score in the risk model without it, was also calculated. All statistical analyses were performed using the Stata 13.1 software (Stata Corporation, College Station, Tex., USA).

Results

Of the 310 patients who were diagnosed with DN by renal biopsy, 205 met the inclusion criteria of this study; their characteristics are detailed in table 1. Of the 205 patients (73% men; mean age, 55.9 ± 13.0 years; mean proteinuria, 3.22 ± 3.27 g/day; and mean eGFR, 44.4 ± 22.9 ml/min/1.73 m^2), 183 had type 2 diabetes (89%), and 141 had diabetic retinopathy (69%). Other baseline characteristics were shown in our previous report [7]. The mean follow-up was 5.57 ± 5.75 years.

The distribution of DN glomerular pathological classification was 13 patients in class 1 (6%), 44 in class 2A (21%), 55 in class 2B (27%), 57 in class 3 (28%), and 36 patients in class 4 (18%). With the IFTA scoring, 18 patients had none (9%), IFTA was mild in 55 patients (27%), moderate in 66 (32%), and severe in 66 (32%). Scoring showed that interstitial inflammation was absent in 25 patients (12%), mild in 163 (80%), and advanced in 17 (8%). Arteriolar hyalinosis was absent in 16 patients (8%), mild in 19 (9%), and advanced in 170 (83%). Arteriosclerosis was absent in 17 patients (9%), mild in 95 (50%), and advanced in 80 (42%). Of the 205 patients, 121 (59%) had exudative lesions.

When we looked at the correlation coefficient between pathological and clinical factors, there were strong correlations (r > 0.5) between eGFR and glomerular classification and between eGFR and IFTA (online suppl. table 1). Moreover, there were strong correlations within pathological scores: glomerular lesions and IFTA, IFTA and hyalinosis, interstitial inflammation and hyalinosis, and IFTA and exudative lesions. Because of these strong correlations within pathological factors, we included pathological factors as separate items in the Cox proportional hazards model for analyzing factors associating with ESRD.

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Table 2. HR, BIF, and score in each pathological class

Pathological classification		HR	95% CI	p value	β-Coefficient	BIF	Score
Glomerular	1	1.00			0	0.42	0
	2A	4.80	0.72–31.87	0.10	1.57		3
	2B	8.24	1.19–57.25	0.03	2.11		4
	3	15.06	2.11–107.64	0.007	2.71		6
	4	14.33	1.90–108.09	0.01	2.66		6
IFTA	0	1.00			0	0.604	0
	1	11.57	1.30–102.62	0.03	2.45		7
	2	17.37	1.80–167.62	0.01	2.85		9
	3	37.99	3.73–387.32	0.002	3.64		11
Interstitial inflammation	0	1.00			0	0.236	0
	1	14.49	1.57–134.02	0.02	2.67		3
	2	24.68	2.42–251.88	0.007	3.32		4
Hyalinosis	0, 1	1.00			0	0.474	0
	2	3.24	1.07–9.81	0.04	1.18		3
Arteriosclerosis	0	1.00			0	0.164	0
	1	1.29	0.27–6.08	0.75	0.25		0
	2	2.05	0.41–10.14	0.38	0.72		1
Exudative		1.26	0.72–2.23	0.41	0.24	0.06	0

Adjusted by age, gender, eGFR, proteinuria, BP control (<130/80 mm Hg) or lack thereof, BMI, HbA1c, urinary RBC, DM retinopathy, duration of diabetes, and type of diabetes.

Multivariate Analysis and Development of the Scoring System

Next, we analyzed the HRs for ESRD of DN patients in each pathological class after adjusting for clinical factors: age, gender, eGFR, proteinuria, BP control (<130/80 mm Hg) or lack thereof, BMI, HbA1c, urinary RBC, DM retinopathy, duration of diabetes, and type of diabetes. With class 1 as reference, the HRs of glomerular classes 2A, 2B, 3, and 4 were, respectively, 4.80 (95% confidence interval (CI), 0.72–31.87), 8.24 (95% CI, 1.19–57.25), 15.06 (95% CI, 2.11–107.64), and 14.33 (95% CI, 1.90–108.09). With 0 as reference, the HRs of IFTA classes 1, 2, and 3 were, respectively, 11.57 (95% CI, 1.30–102.62), 17.37 (95% CI, 1.80–167.62), and 37.99 (95% CI, 3.73–387.32). Those of interstitial inflammation class 1 and 2 were, respectively (0 as reference), 14.49 (95% CI, 1.57–134.02) and 24.68 (95% CI, 2.42–251.88). With 0 or class 1 as reference, the HR of hyalinosis class 2 was 3.24 (95% CI, 1.07–9.81). The HRs of arteriosclerosis classes 1 and 2 were, respectively (0 as reference), 1.29 (95% CI, 0.27–6.08) and 2.05 (95% CI, 0.41–10.14). The HR of exudative lesions was 1.26 (95% CI, 0.72–2.23) (table 2).

In order to calculate the pathological score, we gave a weight to each pathological factor and summed the products of the beta and that weight. We initiated the bootstrap aggregating method and calculated the BIF for assessing the weight of each pathological factor. The BIFs of glomerular lesion, IFTA, interstitial inflammation, hyalinosis, arteriosclerosis, and exudative lesion – after bootstrapping 500 times – were, respectively, 42.0, 60.4, 23.6, 47.4, 16.4, and 6.6%. Table 2 shows the components of the D-score after multiplying the beta coefficient by 5, multiplying by the estimated BIF of each pathological variable, and rounding to the nearest integer. Scores of glomerular classes 1, 2A, 2B, 3, and 4 were 0, 3, 4, 6, and 6, respectively. With 0 as reference, the scores of IFTA classes 1, 2, and 3 were 7, 9, and 11, respectively, and those of interstitial inflammation classes 1 and 2 were 3 and 4. The score of hyalinosis class 2 was 3, and that of arteriosclerosis class 2 was 1. So, the possible range of D-scores was 0–25.

Evaluation of the Scoring System

According to the quartile of the 10-year risk of ESRD in our population, we divided patients into four groups, those with D-score ≤14 (n = 33), 15–18 (n = 32), 19–21 (n = 70), and 22–25 (n = 70). The 10-year renal survival in patients with D-score ≤14, 15–18, 19–21, and 22–25 was, respectively, 96% (77–99), 65% (40–81), 30% (16–

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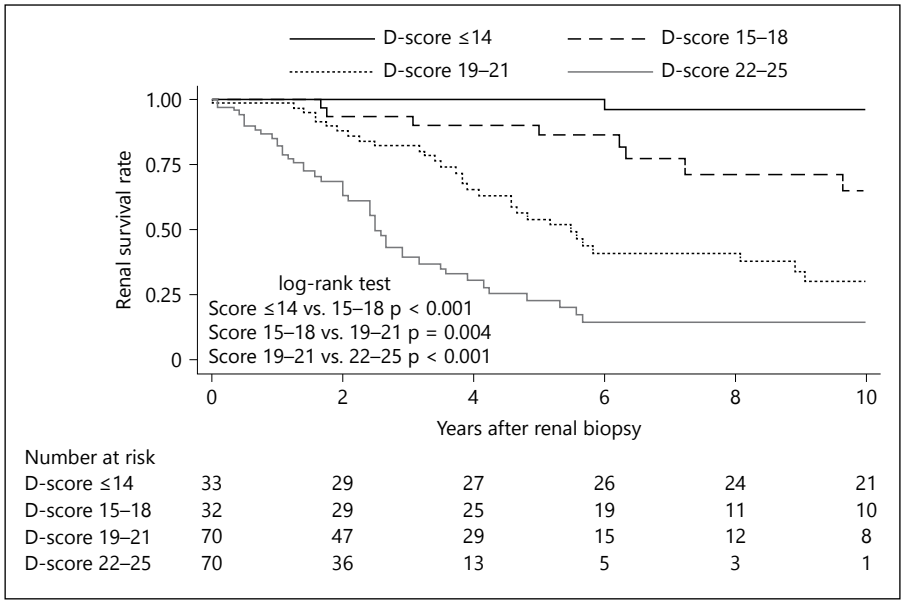

Fig. 1. Renal survival rates after renal biopsy by pathological score (D-score) divided into four groups (in order of increasing D-score).

Table 3. Factors affecting ESRD in patients with diabetic nephropathy

Variables	HR (95% CI)	p value
D-score		
≤14	1.00	
15–18	16.21 (1.86–140.90)	0.01
19–21	19.78 (2.15–182.40)	0.008
22–25	45.46 (4.63–446.68)	0.001
eGFR, ml/min/1.73 m^2		
per each 5	2.12 (1.41–3.18)	<0.001
per –10	1.46 (1.24–1.73)	<0.001
Proteinuria, g/day		
<0.5	1.00	
0.5–3.49	2.45 (0.85–7.12)	0.10
≥3.5	3.86 (1.25–11.91)	0.02
Age, per 10 years	0.67 (0.52–0.87)	0.002
Gender, female	1.22 (0.72–2.08)	0.46
BP, <130/80 mm Hg	0.62 (0.33–1.18)	0.15
BMI, per 1 kg/m^2	0.93 (0.87–0.99)	0.03
HbA1c, per 1%	0.91 (0.80–1.04)	0.16

Other adjusted factors includes urinary red blood cell, diabetic retinopathy, diabetes duration, and type of diabetes.

45), and 14% (5–26). Renal survival curves after renal biopsy, when considered by D-score subgroups, were significantly different from each other ($p < 0.01$, log-rank test) (fig. 1). After adjusting for age, gender, eGFR, proteinuria, BP control, BMI, HbA1c, presence of urinary RBC, presence of DM retinopathy, diabetes duration, and type of diabetes – and with ≤14 as reference – the HRs for ESRD of patients with D-score 15–18, 19–21, and 22–25 were, respectively, 16.21 (95% CI, 1.86–140.90), 19.78 (95% CI, 2.15–182.40), and 45.46 (95% CI, 4.63–446.68) (table 3). Very similar results were seen when we analyzed HRs for renal death or death (data not shown). In addition to age, eGFR, and proteinuria, which are known as important predictors for renal death, the D-score appeared to be a significant predictor of ESRD after biopsy.

The area under the ROC curve with a 10-fold cross-validation was used to compare the ability of different factors to predict the 10-year risk of ESRD. When comparing c-statistics, a model that included D-score (with 10-fold cross-validation) in addition to age, eGFR, and proteinuria, showed a slight improvement from 0.9013 (0.8608–0.9418) to 0.9317 (0.8984–0.9649) (table 4; fig. 2), although it was not statistically significant ($p = 0.27$). Furthermore, the NRI also showed better reclassification (NRI: 0.24; 95% CI, –0.02 to 0.49; $p = 0.09$). Therefore, in addition to clinical parameters, the D-score might have improved the prediction of a 10-year risk of ESRD in our population.

Discussion

In this study, we aimed at developing a new pathological scoring system for DN in order to estimate the renal damage associate with ESRD. Previously, we found that

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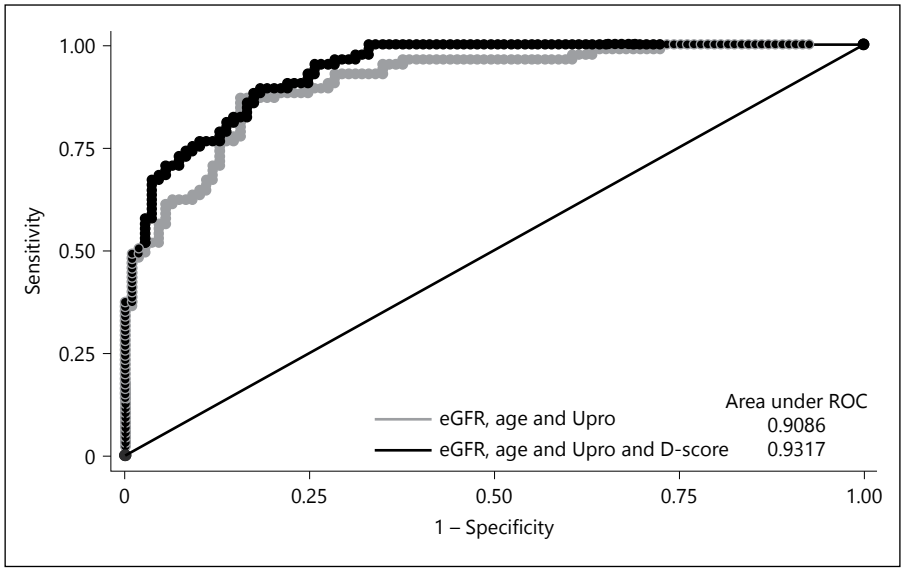

Fig. 2. The ROC curves for predicting ESRD within 10 years by scoring systems with and without the D-score.

Table 4. Comparison of the ROC curves for predicting ESRD within 10 years

	Area under ROC
Age	0.6903 (0.6183–0.7624)
Upro	0.7786 (0.7160–0.8411)
Score	0.7802 (0.7185–0.8419)
eGFR	0.8291 (0.7733–0.8848)
Age + Upro	0.8162 (0.7588–0.8736)
Upro + eGFR	0.8637 (0.8155–0.9120)
Age + eGFR	0.8687 (0.8199–0.9175)
Age + eGFR + Upro	0.9013 (0.8608–0.9418)
Upro + eGFR + score	0.9091 (0.8710–0.9473)
Age + eGFR + Upro + score	0.9317 (0.8984–0.9649)

Upro = Proteinuria; score = pathological score of diabetic nephropathy.

not only a glomerular lesion, but also IFTA and interstitial inflammation had a strong impact on the renal prognosis [7]. Several other reports have also suggested the importance of these pathological lesions in assessing the renal outcome [8, 10, 16]. Nevertheless, because the correlation between organ changes in the kidney is so complex [7], the net effect of kidney damage on renal prognosis remained unknown. Here, we report the development of a new scoring system to assess the net effect of renal pathological damage based on the most recent pathological classification of DN. In addition, our study showed that the D-score is an independent predictor for renal outcome even after adjusting for age, eGFR, proteinuria, and other clinical factors.

The D-score may solve some important problems raised by renal outcome studies that rely on biopsy findings. First of all, this new scoring system makes it possible to evaluate the net pathological staging damage caused by diabetes mellitus, and that evaluation may make comparison between clinical and pathological factors easier, and allow clinicians to consider the importance of renal biopsy for predicting renal outcomes. Second, this scoring system shows the different impacts of pathological changes in glomerular lesions, IFTA, interstitial inflammation, arteriolar hyalinosis, arteriosclerosis, and exudative lesions on renal outcomes – and this may support better prediction for renal outcome at bedside. Third, since pathological lesions are closely associated with each other, we must always pay attention to the multicollinearity problem that attends the presence of two or more pathological covariates in multivariate analyses. The D-score could solve the problem raised in the analyses that use many pathological variables.

The clinical importance of renal biopsy for DN is still debated. Iseki et al. reported better survival for patients whose dialysis started after renal biopsies than for those starting dialysis without a renal biopsy, suggesting the importance of pathological assessment for better patient management [17]. On the other hand, the KDOQI guideline 2007 reported that, in most cases, careful screening of diabetic patients can identify those who have DN without a renal biopsy. Kidney biopsy may be required if normoalbuminuric patients have a decreased GFR [18]. Al-

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though the long-term renal outcome of diabetic patients with normoalbuminuria and renal insufficiency is still unclear, Shimizu et al. reported that their pathological findings were classified as being of the diabetic glomerular lesion type and of the tubulointerstitial and vascular lesions type, as well as nephrosclerosis [19], suggesting the importance of a histological evaluation even in the early stage of DN. Moreover, it is known that renal structural damage in diabetic patients is heterogeneous [20] and each lesion is independently associated with ESRD [7, 8, 10, 16]. Based on these findings – and our results – the structural evaluation by a renal biopsy specimen may be more important than previously thought for understanding the physiology of renal damage and clinical management. There are close relationships between pathological findings and renal function and proteinuria [7, 9]. That is why the ability to predict ESRD was not greatly improved by adding D-score to the prediction models with eGFR, age, and proteinuria. However, our analyses showed some advantage to including D-score in the prediction – even though it was not significant probably due to the limited number of study samples.

There were several limitations in this study. First, selection bias necessarily exists in this kind of biopsy study. Considering how difficult it is to perform randomized trials in biopsy studies, the only possible solution to minimize the bias would be performing a large scale and/or multicenter cohort study. Second, given the nature of the biopsy studies, the limited number of patients restricted further analyses, taking into account various factors that might have affected the renal outcome. Nevertheless, compared with previous biopsy studies of DN, ours is based on a relatively large cohort with a very long follow-up. Third, since this is an observational study, a clear evaluation of the treatment effect is not included. For example, BP control and HbA1c at baseline were not selected as statistically significant prognostic factors for ESRD because results might be changed if we included the treatment factor during follow-up in the analyses. Although there is no optimal strategy for treatment of DN, some treatments could reduce proteinuria and the rate of disease progression – like renin-angiotensin blockade or antidiabetic drugs. However, when we factored various treatment options into account in the multivariate analyses, the results were very similar. Fourth, an external validation of the new scoring system was lacking in this study. Although we performed a 10-fold cross-validation, further external validation studies would be needed to confirm the new scoring system. Finally, because our cohort consisted of patients with a relatively advanced DN, further studies including patients in early-stage DN would be needed to evaluate and update the scoring system. Based on our experience, although, the need for renal biopsy with patients in early-stage DN is not high, a scoring system targeting this study's population should be the most useful one in the clinical setting.

In summary, we created a new pathological scoring system for DN to predict patients' renal outcome. Based on this D-score system, we could, indeed, predict renal outcome, and we found that if the D-score is less than 15, the predicted renal outcome is excellent. Furthermore, our analyses suggest that a model, including this new pathological score, predicts the patients' renal outcome better than those without it. The aim of this study was not to recommend renal biopsy studies. Rather, we believe that if renal biopsy has been performed, all the information should be used for the patients' better outcome, including diagnosis, choice of treatment strategy, and prediction of their renal outcome. We hope our scoring system can improve clinicians' understanding, resulting in better outcomes. Further studies are needed to confirm the utility of our scoring system and to determine the best candidates for renal biopsy among DN patients.

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Disclosure Statement

There are no conflicts of interest to declare.

References

1 Mauer M, Fioretto P, Woredekal Y, et al: Diabetic nephropathy; in Schrier RW (ed): Disease of the Kidney and Urinary Tract. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 2083–2127.

2 Feldt-Rasmussen B: Is there a need to optimize glycemic control in hemodialyzed diabetic patients? Kidney Int 2006;70:1392–1394.

3 Berhane AM, Weil EJ, Knowler WC, et al: Albuminuria and estimated glomerular filtration rate as predictors of diabetic end-stage renal disease and death. Clin J Am Soc Nephrol 2011;6:2444–2451.

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4 Ninomiya T, Perkovic V, de Galan BE, et al: Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 2009;20:1813–1821.
5 Wada T, Haneda M, Furuichi K, et al: Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes. Clin Exp Nephrol 2013;18:613–620.
6 Tervaert TW, Mooyaart AL, Amann K, et al: Pathologic classification of diabetic nephropathy. J Am Soc Nephrol 2010;21:556–563.
7 Mise K, Hoshino J, Ubara Y, et al: Renal prognosis a long time after renal biopsy on patients with diabetic nephropathy. Nephrol Dial Transplant 2014;29:109–118.
8 Okada T, Nagao T, Matsumoto H, et al: Histological predictors for renal prognosis in diabetic nephropathy in diabetes mellitus type 2 patients with overt proteinuria. Nephrology (Carlton) 2012;17:68–75.
9 Oh SW, Kim S, Na KY, et al: Clinical implications of pathologic diagnosis and classification for diabetic nephropathy. Diabetes Res Clin Pract 2012;97:418–424.
10 Shimizu M, Furuichi K, Toyama T, et al: Long-term outcomes of Japanese type 2 diabetic patients with biopsy-proven diabetic nephropathy. Diabetes Care 2013;36:3655–3662.
11 Mise K, Hoshino J, Ueno T, et al: Clinical implications of linear immunofluorescent staining for immunoglobulin G in patients with diabetic nephropathy. Diabetes Res Clin Pract 2014;106:522–530.
12 Gooley TA, Leisenring W, Crowley J, et al: Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999;18:695–706.
13 Royston P, Sauerbrei W: Bootstrap assessment of the stability of multivariable models. Stata J 2009;9:547–570.
14 Breiman L: Bagging predictors. Machine Learning 1996;24:123–140.
15 Steyerberg EW: Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. New York, Springer, 2010.
16 An Y, Xu F, Le W, et al: Renal histologic changes and the outcome in patients with diabetic nephropathy. Nephrol Dial Transplant 2015;30:257–266.
17 Iseki K, Miyasato F, Uehara H, et al: Outcome study of renal biopsy patients in Okinawa, Japan. Kidney Int 2004;66:914–919.
18 KDOQI: KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007;49(2 suppl 2):S12–S154.
19 Shimizu M, Furuichi K, Yokoyama H, et al: Kidney lesions in diabetic patients with normoalbuminuric renal insufficiency. Clin Exp Nephrol 2014;18:305–312.
20 Wolf G, Ritz E: Diabetic nephropathy in type 2 diabetes prevention and patient management. J Am Soc Nephrol 2003;14:1396–1405.

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