Renal prognosis a long time after renal biopsy on patients with diabetic nephropathy

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ABSTRACT

Background. A new classification of diabetic nephropathy was reported by Tervaert et al., but the association between pathological findings and the clinical outcomes remains unclear.

Keywords: diabetic nephropathy, pathological classification, renal prognosis

Methods. Among 310 patients with diabetes mellitus who underwent renal biopsy from March 1985 to January 2010 and were confirmed to have diabetic nephropathy according to the Tervaert’s classification, 205 patients were enrolled in this study. Cox proportional hazard regression analysis was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for death-censored renal death. Each regression analysis employed two levels of multivariate adjustment.
have been started for each disease. However, there is still no uniform classification for DN, even though it is the most frequent cause of ESRD. A working group that included Tervaert et al. [7] has proposed a new pathological classification of DN that is intended to improve communication between renal pathologists and clinicians, to provide a logical basis for prognostic interventional studies and to improve clinical management and efficiency. They expected that classifying the severity of disease in patients with pure DN could help to unravel various pathways leading to glomerulosclerosis, thus providing new possibilities for intervention to prevent the progression of DN.

In the present study, the renal prognosis of patients with DN classified according to Tervaert’s criteria was followed for a long time.

**METHODS**

**Patients and study design**

Among 310 patients with diabetes mellitus who underwent renal biopsy at our hospital from March 1985 to January 2010 and were confirmed to have DN, 205 patients were considered to be eligible and were enrolled in this study. DN was diagnosed by at least two renal pathologists and/or nephrologists, and the diagnosis was re-evaluated according to Tervaert’s classification [7]. Exclusion criteria were kidney transplantation, coexistence of other renal diseases except for nephrosclerosis, estimated glomerular filtration rate (eGFR) <10 mL/min per 1.73 m² at the time of renal biopsy and obtaining fewer than five glomeruli by renal biopsy (Figure 1).

**Assessment of laboratory data and definitions**

HbA₁c was measured by high-performance liquid chromatography according to the standards of the Japanese Diabetes Society (normal range: 4.3–5.8%). Hematuria was defined as the detection of more than five erythrocytes per high-power field in at least two of three consecutive urine tests. All patients with hematuria had no more than one to five white blood cells...
per high-power field, no urinary tract malignancy and no stone disease. The average annual values were calculated for urinary protein excretion, systolic and diastolic blood pressure, HbA1c and hemoglobin during follow-up. When data for any of these variables were not available during follow-up, the average of the observations before and after the missing value was calculated and used. We employed U-Pro (g/gCr) if U-Pro (g/day) was not available.

Renal biopsy and pathological classification

All renal biopsies were performed based on the decisions by our department and/or primary doctor. Basically, indications of renal biopsy were proteinuria more than 0.5 g/day or atypical DN such as renal involvement without diabetic retinopathy and/or with hematuria. Renal tissue was obtained by needle biopsy. For light and electron microscopy, the biopsy specimens were processed according to standard procedures. Sections were stained with hematoxylin–eosin, periodic acid-Schiff, Weigert's elastica-van Gieson, Masson trichrome, or periodic acid methamine silver stain. The mean number of glomeruli was 17.0 ± 11.1 (range, 5–63). Classification of DN and histological scoring were done according to the criteria of Tervaert et al. [7]. The glomerular classification was as follows and light microscopic changes in the glomerular basement membrane and epithelial foot process effacement by electron microscopy had no influence on the classification. Class I was defined as glomerular basement membrane thickening (>395 nm in females or >430 nm in males) without any of the criteria mentioned below for classes II, III or IV. The glomerular basement membrane of other cases from class II, III or IV was directly compared to the glomerular classes in Table 1. Patients in class I were significantly younger than patients in the other classes. The mean eGFR was signiﬁcantly lower for patients in classes IIB or III than for those in classes I or IIA, and also signiﬁcantly lower.

End point

The primary end point was renal death, which was defined as commencement of dialysis due to ESRD. None of the patients received kidney transplantation during follow-up.

Statistical analysis

Data were summarized as percentages or the mean (±standard deviation [SD]) as appropriate. Categorical variables were analyzed with the \( \chi^2 \) test or Fisher’s exact test as appropriate, and continuous variables were compared using t-test, Mann–Whitney U-test, Kruskal–Wallis H-test or ANOVA, as appropriate. Correlations among each histopathological finding were evaluated by Spearman’s correlation. Cumulative survival was estimated with Kaplan–Meier survival curves, and was compared by using the log-rank test. The Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for death-censored renal death. In the Cox proportional hazards model 1, each HR was adjusted for age, gender, eGFR, type of diabetes, urinary protein excretion, systolic blood pressure, body mass index and HbA1c at the time of renal biopsy. Also, in Model 2, each HR was adjusted for the above plus diabetic retinopathy and red blood cells in urinary sediment at the time of renal biopsy. A P-value of <0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed using SPSS (version 20.0, Chicago, IL, USA).

RESULTS

Of the 310 patients screened, 205 met the study entry criteria. A flowchart showing the disposition of the patients is displayed in Figure 1. The mean follow-up period was 62.9 ± 68.3 months.

Of the 205 patients, 150 were men (73.2%). The mean (±SD) age at the time of renal biopsy was 55.9 ± 13.0 years (range: 21–83 years). A total of 183 patients (89.3%) had type 2 diabetes, and 141 patients (68.8%) had diabetic retinopathy. Mean body mass index (BMI) was 24.0 ± 4.0 kg/m². The mean systolic and diastolic blood pressures at admission were 145.7 ± 20.6 and 123.0 ± 12.3 mmHg, respectively. The mean baseline serum creatinine level was 1.65 ± 0.95 mg/dL (0.4–5.5), the mean creatinine clearance rate was 49.8 ± 28.3 mL/min (6.0–175.6) and the mean eGFR was 44.3 ± 22.6 mL/min per 1.73 m² (10.0–123.0) [9]. Urinary protein excretion was 3.22 ± 3.27 g/day (0.03–21.9). The mean hemoglobin was 12.1 ± 2.4 g/dL (6.6–17.9), mean HbA1c was 7.3 ± 1.9%, serum albumin was 3.2 ± 0.7 g/dL, total cholesterol was 217.4 ± 61.2 mg/dL, triglycerides were 169.4 ± 90.9 mg/dL and low-density lipoprotein (LDL) cholesterol was 141.0 ± 52.3 mg/dL (Table 1).

Clinical findings at the time of renal biopsy and the number of glomeruli obtained by biopsy are compared among the glomerular classes in Table 1. Patients in class I were significantly younger than patients in the other classes. The eGFR was significantly lower for patients in classes IIB or III than for those in classes I or IIA, and also significantly lower.
Urinary protein excretion was significantly higher in class III or IV patients than in class I, IIA or IIB patients, as well as in class IIB patients than in class I or IIA patients. HbA1c was significantly lower for patients in class IV than for those in all other classes. The hemoglobin was significantly lower in class IV patients than in those from classes I, IIA and IIB, and it was also significantly lower in class IIB or III patients than in those with lower classes.

### Table 1. Baseline clinical findings and the number of glomeruli obtained by renal biopsy in groups stratified according to the glomerular classification of diabetic nephropathy

|                      | All (n=205) | Class I (n=13) | Class IIA (n=44) | Class IIB (n=55) | Class III (n=57) | Class IV (n=36) |
|----------------------|-------------|----------------|------------------|------------------|------------------|-----------------|
| Male (%)             | 73.2 (n=150)| 61.5 (n=8)    | 86.4 (n=38)     | 70.9 (n=39)     | 59.6 (n=34)      | 86.1 (n=31)     |
| Age (year)           | 55.9 ± 13.0 | 40.2 ± 13.4   | 57.1 ± 13.5a    | 53.9 ± 13.1a    | 57.5 ± 10.6a     | 60.6 ± 11.5a    |
| BMI (kg/m²)          | 24.0 ± 4.0  | 26.5 ± 4.4    | 24.7 ± 4.2      | 25.3 ± 3.7b     | 23.6 ± 4.3b      | 23.6 ± 3.3b     |
| sBP (mmHg)           | 145.7 ± 20.6| 136.5 ± 14.0  | 139.8 ± 20.8    | 143.3 ± 15.8    | 151.2 ± 23.1b,d,f| 151.3 ± 21.7b,d|
| dBP (mmHg)           | 81.7 ± 12.8 | 81.2 ± 15.5   | 80.8 ± 11.3     | 80.8 ± 11.0     | 82.4 ± 13.7      | 83.1 ± 14.9     |
| s-Cr (mg/dL)         | 1.65 ± 0.95 (0.4–5.5) | 0.98 ± 0.30 (0.4–1.5) | 1.20 ± 0.51 (0.5–2.9) | 1.51 ± 0.79a,d (0.6–3.9) | 1.65 ± 0.85a,c (0.5–4.2) | 2.63 ± 1.18ac,eg (1.0–5.5) |
| Ccr (mL/min)         | 49.8 ± 28.3 | 78.3 ± 21.9   | 65.5 ± 30.6     | 51.9 ± 26.2a,d  | 42.0 ± 22.5a,c   | 28.9 ± 18.3a,c,e,g |
| eGFR (ml/min/1.73 m²)| 44.3 ± 22.6 | 68.8 ± 22.1   | 56.9 ± 22.4     | 45.6 ± 19.9a,d  | 40.0 ± 19.3a,c   | 24.7 ± 11.3a,c,e,g |
| U-Pro (g/day)        | 3.22 ± 3.27 | 0.81 ± 0.50   | 1.35 ± 1.77     | 3.36 ± 3.36a,c  | 4.27 ± 3.51a,c,e | 4.66 ± 3.29a,c,e |
| s-Alb (g/dL)         | 7.3 ± 1.9   | 7.9 ± 1.4     | 7.4 ± 1.6       | 7.6 ± 2.0       | 7.5 ± 2.1        | 6.4 ± 1.4a,c,d,g |
| HbA1c (%)            | 12.1 ± 2.4  | 14.8 ± 1.7    | 13.6 ± 1.8      | 12.1 ± 2.2a,c   | 10.9 ± 1.8a,c,f  | 10.9 ± 2.3a,c,f |
| Hb (g/dL)            | 68.8 (n=141)| 15.4 (n=2)    | 43.2 (n=19)     | 76.4 (n=42)a,c  | 86.0 (n=49)a,c   | 80.6 (n=29)a,c  |
| Retinopathy (%)      | 10.7 (n=22) | 15.4 (n=2)    | 9.1 (n=4)       | 14.5 (n=8)      | 12.3 (n=7)       | 2.8 (n=1)       |
| Type1 DM (%)         | 10.7 (n=22) | 15.4 (n=2)    | 9.1 (n=4)       | 10.9 (n=6)      | 19.3 (n=11)      | 2.8 (n=1)       |
| RBC in urinary sediment (%) | 63.9 (n=131) | 15.4 (n=2) | 63.6 (n=28)a | 67.3 (n=37)a  | 77.2 (n=44)a  | 55.6 (n=20)b,h  |
| ACE-I or ARB (%)     | 2.1 ± 1.4   | 0.5 ± 0.8     | 1.6 ± 1.3a      | 2.1 ± 1.3a      | 2.7 ± 1.5a,c,f   | 2.4 ± 1.3a,c    |
| Number of antihypertensive agent | 7.8 (n=16) | 0 | 2.3 (n=1) | 1.8 (n=1) | 14.0 (n=8)f | 16.7 (n=6)df |
| ESA (%)              | 30.2 (n=62) | 7.7 (n=1)     | 38.6 (n=17)b    | 30.9 (n=17)     | 29.8 (n=17)      | 27.8 (n=10)     |
| Insulin therapy (%)  | 49.3 (n=101)| 15.4 (n=2)    | 34.1 (n=15)     | 54.5 (n=30)b,d  | 63.2 (n=36)a,c  | 50.0 (n=18)b,d  |
| Number of glomeruli  | 17.0 ± 11.1 | 11.9 ± 10.9   | 12.7 ± 6.7      | 14.8 ± 8.8      | 23.3 ± 13.2a,c,e | 17.6 ± 10.7bd,h |

BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure; s-Cr, serum creatinine; Ccr, creatinine clearance rate; eGFR, estimated glomerular filtration rate; U-Pro, urinary protein excretion; s-Alb, serum albumin; Hb, hemoglobin; retinopathy, diabetic retinopathy; RBC in urinary sediment, red blood cells >5/HPF in sediment; ACE-I or ARB, use of an angiotensin-converting enzyme inhibitor or angiotensin II type I receptor blocker, respectively; ESA, erythropoietin-stimulating agents; OHA, oral hypoglycemic agent; insulin therapy, treatment with insulin including basal supported oral therapy.

aP < 0.01: versus class I.
bP < 0.05: versus class I.
cP < 0.01: versus class IIA.
dP < 0.05: versus class IIA.
eP < 0.01: versus class IIB.
fP < 0.05: versus class IIB.
gP < 0.01: versus class III.
hP < 0.05: versus class III.
Coexistence of diabetic retinopathy was significantly more frequent in patients from classes IIIB, III, and IV than in those from classes I or IIA. Treatment with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II type I receptor blockers (ARB) was significantly less frequent and significantly fewer antihypertensive agents were used by class I patients than by patients from the other classes.

Clinical findings during the follow-up period and at final follow-up are shown in Table 2 for each glomerular class. Average urinary protein excretion during follow-up was greater in patients from classes III and IV than in those from classes I, IIA or IIB. Average Hba1c was significantly lower in class IV patients than in those from the other classes. There were no significant differences in the use of ACE-I or ARB during follow-up among the patients from different glomerular classes, except between those from classes I and IIA. At final follow-up, class I patients were using significantly fewer antihypertensive agents than patients from the other classes.

Renal death occurred in 88 patients during follow-up, and the number of renal deaths in each glomerular class is shown in Table 2. A total of 17 patients died during follow-up, with the cause of death being heart disease in 2, infection in 3 (pneumonia in 2 and lower limb gangrene in 1), stroke in 2 (cerebral hemorrhage and cerebral infarction in 1 each), hepatic disease in 2 (hepatic encephalopathy in 1 and bleeding varices in 1), malignancy (cholangiocarcinoma) in 1, gastrointestinal hemorrhage in 1, acute exacerbation of interstitial pneumonia in 1 and undefined in 5.

Kaplan–Meier survival curves stratified according to the glomerular class, the scores for IFTA, interstitial inflammation, arteriolar hyalinosis or arteriosclerosis, and the presence of exudative lesions are shown in Figure 2. There was a significant

![113](Renal prognostic of diabetic nephropathy)
difference in the renal survival rate among most of the glomerular classes, except between class I versus IIA, class IIB versus III and class III versus IV (Figure 2a). There was also a significant difference in renal survival among each IFTA score or interstitial inflammation score, except between interstitial inflammation scores of 1 and 2 (Figure 2b and c). Furthermore, there was a significant difference in renal survival among each arteriolar hyalinosis score (Figure 2d) and among each arteriosclerosis score (Figure 2e).
class III was significantly higher than class IIB, and compared with class IIB, the overall HR for renal survival between glomerular class IIA and classes III or IV was larger and that we studied patients with worse renal function, as well as a difference of the renal prognosis between DN with diffuse lesions and DN with nodular lesions [11–13]. With regard to tubulointerstitial lesions, Ueno et al. [14] found that interstitial expansion combined with thickening of the tubular basement membrane existed before the onset of proteinuria and these changes progressed in parallel with glomerular and arteriolar lesions. White et al. [15] reported a significant correlation between an increase of the interstitial volume and decreased creatinine clearance, while proteinuria was only correlated with glomerular pathology.

After Tervaert’s pathological classification of DN was proposed, Okada et al. evaluated renal biopsy specimens from 69 patients with type 2 diabetes and frank proteinuria. They found that the glomerular class was not a significant independent variable, but IFTA and interstitial inflammation were independently associated with the renal end point (HR: 3.36, 95% CI: 1.21–9.32 and HR: 4.74, 95% CI: 1.26–17.91, respectively). They also found no significant difference in renal survival between glomerular classes IIA and IIB combined (diffuse lesions) and glomerular class III (nodular lesions) [10]. In addition, Oh et al. performed renal biopsy in 126 patients with type 2 DM and frank proteinuria from January 2000 to December 2007, revealing that 50 patients had pure DN, 65 had nondiabetic renal disease (NDRN) and 11 had coexisting DN and NDRN. ESRD occurred in 44.0% of the DN group, 18.2% of the mixed group and 12.3% of the NDRD group (P < 0.001 by the χ² test). Among patients with pure DN, the 5-year renal survival rate was estimated to be 100.0% in class I (n = 2) and class IIA (n = 6), 75.0% in class IIB (n = 12), 66.7% in class III (n = 9) and 38.1% in class IV (n = 21) (P = 0.002) [16].

In our retrospective study, IFTA and interstitial inflammation had a strong impact on the renal prognosis, as well as in Okada’s study [10], and this result was also in agreement with the findings reported for other renal diseases such as IgA nephropathy and lupus nephritis [17, 18]. However, with respect to glomerular lesions, there was a significant difference in the renal survival rate between glomerular class IIA and classes IIB or III in our study, unlike the findings of Okada [10]. The reasons for this discrepancy may be that our cohort was larger and that we studied patients with worse renal

### DISCUSSION

Before Tervaert’s classification was proposed, some authors reported a relation between mesangial matrix volume and renal function, as well as a difference of the renal prognosis between DN with diffuse lesions and DN with nodular lesions [11–13]. With regard to tubulointerstitial lesions, Ueno et al. [14] found that interstitial expansion combined with thickening of the tubular basement membrane existed before the onset of proteinuria and these changes progressed in parallel with glomerular and arteriolar lesions. White et al. [15] reported a significant correlation between an increase of the interstitial volume and decreased creatinine clearance, while proteinuria was only correlated with glomerular pathology.

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### Table 3. Correlation coefficients among histopathological findings

|                         | Glomerular class | IFTA | Interstitial inflammation | Arteriolar hyalinosis | Arteriosclerosis | Exudative lesion |
|-------------------------|------------------|------|---------------------------|-----------------------|-----------------|------------------|
| Glomerular class        | –                | 0.66 | 0.43                      | 0.40                  | 0.33            | 0.46             |
| IFTA                    | –                | –    | 0.47                      | 0.48                  | 0.46            | 0.52             |
| Interstitial inflammation| –                | –    | –                         | 0.55                  | 0.27            | 0.33             |
| Arteriolar hyalinosis    | –                | –    | –                         | –                     | 0.31            | 0.36             |
| Arteriosclerosis         | –                | –    | –                         | –                     | –               | 0.20             |
| Exudative lesion         | –                | –    | –                         | –                     | –               | –                |

IFTA, interstitial fibrosis and tubular atrophy scores.
function. Actually, among our 222 patients with pure DN (including those with an eGFR < 10 mL/min per 1.73 m²), there was a significant difference in the renal survival rate among each glomerular class (data not shown). Moreover, our analysis clearly showed that the HR for class III (DN with nodular lesions) was significantly higher than that for class IIB (DN with diffuse lesions), even after adjusting for other variables. On the other hand, the estimated 5-year renal survival rate in our subjects was lower for each glomerular class compared with the pure DN subjects studied by Oh et al. [16], possibly because of differences in the background factors of the patients.

This study had several limitations. First, it had a relatively small sample size and all of the subjects were Japanese. However, this study was the first investigation of the relationship between the renal prognosis and all pathological findings, including early DN (glomerular class I), unlike previous studies. Second, this was a retrospective cohort study and the indications for renal biopsy were not standardized, making it undeniable that there was selection bias in our study. Third, factors related to treatment during follow-up that could have a strong influence on the renal prognosis, such as use of renin-angiotensin inhibitors (ACE-I and ARB), glycemic control and blood pressure control, were not adequately examined and adjusted. However, there were no significant differences of ACE-I or ARB use during follow-up among the glomerular classes, except between classes I and IIA. The reason for the low rate of ACE-I or ARB use in class I was that fewer patients had hypertension in this class than in other classes, as indicated by the average systolic blood pressure during follow-up and the final number of antihypertensive agents. With respect to glycemic control during follow-up, there were no marked differences among the glomerular classes, and this was supported by the average HbA1c and hemoglobin levels during follow-up as well as the final use of erythropoietin-stimulating agents. In our study, there was no significant difference in the average HbA1c during follow-up among the glomerular classes, except for classes III and IV. The lowest hemoglobin and the highest rate of final use of erythropoietin-stimulating agents may have been associated with the significantly lower HbA1c in class IV than in the other classes. With regard to blood pressure control, average systolic and diastolic blood pressures during follow-up were lower than at baseline for each glomerular class, while the number of antihypertensive agents in use showed an increase at final follow-up. However, the average systolic blood pressure during follow-up exceeded 140 mmHg in classes III and IV, being significantly higher than in classes I, IIA and IIB.

Fourth, the minimum number of glomeruli required for the classification of glomerular lesions was five in this study. Therefore, inclusion of patients with only a few glomeruli in our study may have influenced the classification of renal pathology, especially in patients who had late-stage DN such as glomerular classes III and IV because of the large number of glomeruli with global sclerosis in those classes. However, more glomeruli were obtained by biopsy in classes III or IV than in classes I, IIA or IIB (Table 1), and fewer than 10 glomeruli were rarely obtained (8 (14%) in class III and 7 (19%) in class IV). Finally, the formula used to estimate GFR in our study was derived from the Modification of Diet in Renal Disease (MDRD) Study equation [9]. According to Horio, the precision of the Japanese GFR equations used in our study was significantly better at a GFR of 0–29 mL/min per 1.73 m² and was statistically equivalent at a GFR of 30–59 mL/min per 1.73 m² and was significantly worse at GFRs of 60–89 or 90–119 mL/min per 1.73 m² compared with the coefficient-modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on serum creatinine (0.813 × CKD-EPIcr) [19]. This study included many patients with a GFR of <60 mL/min per 1.73 m² (77% estimated by the Japanese GFR equations), and our estimated GFR values were valid for those patients. However, it is undeniable that the estimated GFR values for patients with less advanced CKD (GFR >60 mL/min per 1.73 m²) were of lower validity than if we had employed the coefficient-modified CKD-EPI equation.

Table 4. Factors affecting renal outcome at baseline; adjusted for patient sex, age and body mass index (BMI)

| Model 1 | HR   | 95% CI       | P-value |
|---------|------|--------------|---------|
| U-Pro   | 1.13 | 1.05–1.21    | 0.001   |
| eGFR    | 0.95 | 0.93–0.96    | <0.001  |
| sBP     | 1.01 | 1.00–1.02    | 0.09    |
| HbA1c   | 0.89 | 0.80–1.01    | 0.07    |
| DM type | 0.47 | 0.23–0.95    | 0.04    |
| Model 2 |      |              |         |
| U-Pro   | 1.12 | 1.04–1.20    | 0.002   |
| eGFR    | 0.95 | 0.93–0.96    | <0.001  |
| sBP     | 1.01 | 1.00–1.02    | 0.06    |
| HbA1c   | 0.89 | 0.79–1.02    | 0.08    |
| DM type | 0.44 | 0.22–0.88    | 0.02    |
| RBC in urinary sediment | 1.73 | 0.90–3.34 | 0.10 |
| Retinopathy | 0.95 | 0.56–1.62 | 0.85 |

Model 1 includes duration from renal biopsy to event, patient sex, age, BMI, urinary protein excretion (U-Pro), estimated glomerular filtration rate (eGFR), systolic blood pressure (sBP), HbA1c and type of diabetes (DM type). Model 2 includes duration from renal biopsy to event, patient sex, age, BMI, U-Pro, eGFR, sBP, HbA1c, DM type, red blood cells (RBC) in urinary sediment and presence/absence of diabetic retinopathy (Retinopathy). Reference and abbreviation: U-Pro, per 1 g/day; eGFR, per 1 mL/min per 1.73 m²; sBP, per 1 mmHg; HbA1c, per 1%; DM type, type 2 diabetes is referent. RBC in urinary sediment: red blood cells ≤5/HPF in urinary sediment is referent. Red blood cells in urinary sediment were classified as ≤5/HPF and >5/HPF. Retinopathy: Absence of diabetic retinopathy is referent. HR, hazard ratio; CI, confidence interval.
FIGURE 3: Univariate and multivariate Cox proportional hazard models by pathological variables at renal end point. Model 1: adjusted for age, gender, estimated glomerular filtration rate, type of diabetes, urinary protein excretion, systolic blood pressure, body mass index and HbA1c at the time of renal biopsy. Model 2: adjusted for the above plus diabetic retinopathy and red blood cells in urinary sediment at the time of renal biopsy. HR: hazard ratio, 95% CI: 95% confidence interval. G-class, glomerular class; IFTA, interstitial fibrosis and tubular atrophy scores; interinfra, interstitial inflammation scores; hyalinosis, arteriolar hyalinosis scores; A-sclerosis, arteriosclerosis scores; exudative, presence of exudative lesions.
In conclusion, we examined whether Tervaert’s pathological classification could predict the renal prognosis of patients with DN. Cox proportional hazards analysis showed that HRs were much higher for higher glomerular classes and higher tubulointerstitial lesion scores. The progression of glomerular, tubulointerstitial and vascular lesions was associated with renal survival, suggesting that Tervaert’s pathological classification of DN is useful for predicting the renal prognosis.

**AUTHORS’ CONTRIBUTIONS**

The contributions of the authors are detailed as follows: K.M. contributed to analysis and interpretation of data including pathological findings, and to writing the manuscript and collecting clinical data including follow-up. J.H. contributed to analysis and interpretation of data and writing the manuscript. Y.U. contributed to analysis and interpretation of data and writing the manuscript. K.S. contributed to managing patients and assessing data. R.H. contributed to managing patients and assessing data. E.H. contributed to managing patients and assessing data. M.Y. contributed to managing patients and assessing data. N.H. contributed to managing patients and assessing data. T.S. contributed to managing patients and assessing data. N.S. contributed to managing patients and assessing data. T.F. contributed to classification of pathological findings. K.O. contributed to classification of pathological findings. S.H. contributed to managing patients and assessing data. K.T. contributed to analysis and interpretation of data.

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**CONFLICT OF INTEREST STATEMENT**

None declared.

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