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Original Article

ORIGINAL ARTICLE

The coexistence of diabetic retinopathy and diabetic nephropathy is associated with worse kidney outcomes

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ABSTRACT

Background. Up to 50–60% of patients with diabetes have non-diabetic kidney disease (NDKD) on kidney biopsy. Diabetic retinopathy (DR) is a microvascular complication of diabetes frequently associated with diabetic nephropathy (DN). The objective of the current study was to investigate the kidney outcomes and survival in patients with biopsy diagnoses of DN and NDKD according to the presence of DR.

Methods. We conducted an observational, multicentre and retrospective study of the pathological findings of renal biopsies from 832 consecutive patients with diabetes from 2002 to 2014 from 18 nephrology departments. The association of DR with kidney replacement therapy (KRT) or survival was assessed by Kaplan–Meier and Cox regression analyses.

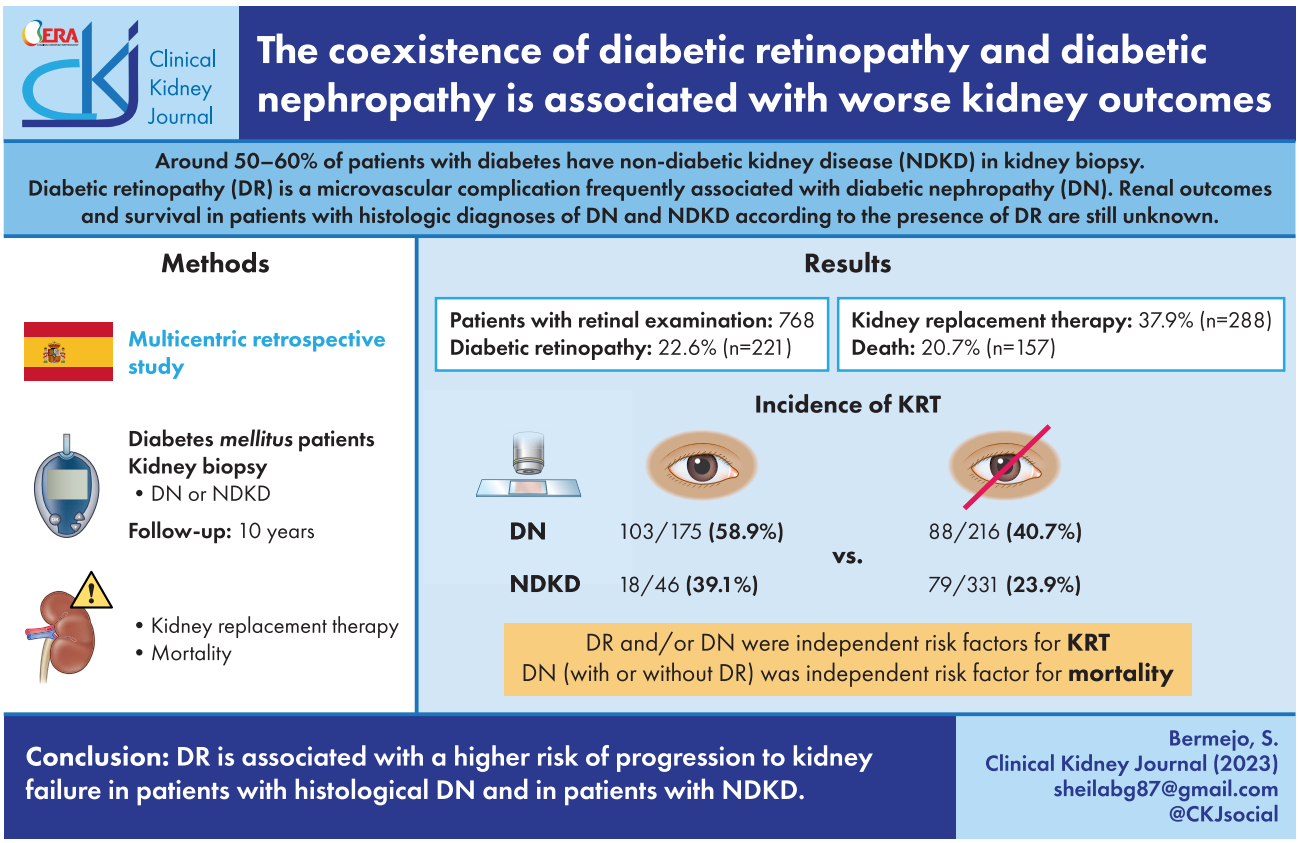
Results. Of 832 patients with diabetes and renal biopsy, 768 had a retinal examination and 221/768 (22.6%) had DR. During a follow-up of 10 years, 288/760 (37.9%) patients with follow-up data needed KRT and 157/760 (20.7%) died. The incidence of KRT was higher among patients with DN (alone or with NDKD) and DR [103/175 (58.9%)] than among patients without DR [88/216 (40.7%), $P < .0001$]. The incidence of KRT was also higher among patients with only NDKD and DR than among those without DR [18/46 (39.1%) versus 79/331 (23.9%), $P < .0001$]. In multivariate analysis, DR or DN were independent risk factors for KRT {hazard ratio [HR] 2.48 [confidence interval (CI) 1.85–3.31], $P < .001$}. DN (with or without DR) was also identified as an independent risk factor for mortality [HR 1.81 (CI 1.26–2.62), $P = .001$].

Conclusions. DR is associated with a higher risk of progression to kidney failure in patients with histological DN and in patients with NDKD.

LAY SUMMARY

Renal biopsies in patients with diabetes are increasing and up to 50–60% of patients with diabetes have non-diabetic kidney disease (NDKD). Diabetic retinopathy (DR) is a microvascular complication of diabetes frequently associated with diabetic nephropathy (DN). The objective of the current study was to investigate the renal prognosis and survival in patients with DN with or without DR. We demonstrated that the diagnosis of diabetic microangiopathy in terms of DR and/or DN is crucial since it confers a worse renal prognosis, indicating patients at risk for progression to end-stage kidney disease.

GRAPHICAL ABSTRACT



Keywords: diabetes mellitus, diabetic kidney disease, diabetic nephropathy, kidney biopsy, type 2 diabetes

INTRODUCTION

Diabetes mellitus (DM) is one of the most important health problems worldwide. In 2021 there were 537 million people affected by DM and this number is expected to increase to 783 million by the year 2045 [1]. Approximately one-third of patients with DM will develop chronic kidney disease (CKD) in their lifetime [2]. The spectrum of CKD in patients with DM is wide and can be classified as diabetic nephropathy (DN), diabetic kidney disease (DKD) and non-diabetic kidney disease (NDKD). DKD is defined as patients with CKD [an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 and/or a urinary albumin:creatinine ratio (UACR) ≥30 mg/g for ≥3 months] in which the cause of CKD is attributed to DM. The diagnosis of DKD is clinical, without histological evidence. The term DN is used when diabetic lesions are identified through renal biopsy. When histological lesions different from DM are observed, the term NDKD is used [3]. DN and NDKD can coexist. Thus kidney biopsy is key to identify patients with DM and NDKD. It has been previously demonstrated that patients with DM and DN have a worse renal prognosis. Thus kidney biopsy provides information on the risk of progression to end-stage kidney disease (ESKD) [4].

Overall, the micro- and macroangiopathic complications of DM should be evaluated to stratify risk, identify treatable complications and guide therapy [5]. Both microangiopathies, diabetic retinopathy (DR) and DN, frequently coexist in patients with type 2 DM [6]. The severity of DR is associated with progression to ESKD [7, 8], the development of cardiovascular disease [9] and mortality [8, 10, 11]. However, in most studies the diagnosis of DKD was clinical suspicion, thus a diagnosis of biopsy-proven DN was not available. A few studies have observed that the severity of DR is correlated with kidney injury scores for glomerular injury, interstitial fibrosis and diffuse lesions in patients with biopsy-proven DN [12, 13]. Some typical glomerular lesions of DN, such as Kimmelstiel–Wilson nodules, are associated with DR. Furthermore, patients with biopsy-proven DN and more severe DR have a higher risk of progression to ESKD [13]. However, this study enrolled patients that were not contemporary, had a limited sample size and did not assess NDKD.

The objective of the current study was to assess the renal prognosis and survival of patients with biopsy-proven DN or NDKD with or without DR in a large contemporary cohort of patients with diabetes and kidney biopsy.

MATERIALS AND METHODS

Patients

This is a retrospective cohort study involving 18 nephrology departments from the Spanish Group for the Study of Glomerular Diseases (GLOSEN), the Catalonian Group for the Study of Glomerular Diseases (GLOMCAT) and the Spanish Group of Diabetic Nephropathy (GEENDIAB). Data from kidney biopsies performed in patients with diabetes from 2002 to 2014 were collected. The Healthcare Ethics Committee of Parc de Salut Mar, Barcelona, Spain approved the study protocol (CEIC2013/5468/I).

Clinical and laboratory parameters

Patient demographic characteristics were recorded (age, gender and race), along with a history of hypertension, dyslipidaemia, duration of DM and the presence or absence of DR, DN, ischaemic heart disease, stroke, peripheral vasculopathy, malignancy and systemic diseases. Furthermore, information on treatment with renin–angiotensin–aldosterone system (RAAS) blockers, oral antidiabetics, insulin, statins and aldosterone antagonists was collected. At the time of kidney biopsy, weight, height, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. Laboratory data included serum creatinine, eGFR according to the Modification of Diet in Renal Disease four-variable equation (expressed in ml/min/1.73 m^2), urea, glucose, 24-h proteinuria, UACR, urine protein:creatinine ratio (UPCR), microhaematuria, autoimmunity markers and viral serology (anti-hepatitis C virus), surface antigen of the hepatitis B virus and anti-human immunodeficiency virus. The indications of kidney biopsy were classified as nephrotic syndrome, acute kidney injury (AKI), nephrotic proteinuria in patients with diabetes for <5 years, nephrotic proteinuria without DR, abrupt decrease in eGFR, presence of micro-/macrohaematuria, signs or symptoms of systemic disease and proteinuria >1 g/24 h (excluding nephrotic) in patients with diabetes for <5 years. Kidney biopsies were reviewed for this study at every participating centre. The morphological characteristics found in the biopsy (number of glomeruli, diffuse or nodular mesangial expansion, global or segmental sclerosis, percentage of glomerulosclerosis and an increase of basement glomerular membrane) and the final diagnoses were collected. Based on the diagnoses, the kidney biopsies were classified into DN (with or without NDKD) and NDKD. Follow-up was conducted at 1, 3, 5 and 10 years after kidney biopsy, including serum creatinine, eGFR, glycaemia, 24-h proteinuria, UACR, UPCR, need for KRT and death.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 20.0 (IBM, Armonk, NY, USA) and Stata version 15.1 (StataCorp, College Station, TX, USA). The quantitative variables are expressed as mean and standard deviation (SD) and the qualitative variables as percentages. The distribution of variables was assessed using the Kolmogorov–Smirnov test. Univariate comparisons between groups were performed using a chi-squared test for categorical variables and one-way analysis of variance for comparing means. With the purpose of studying patients' survival and the need for KRT, we performed Kaplan–Meier curves and logrank tests. Cox regression analysis were performed to identify the independent risk factors for mortality and for the start of KRT. A *P*-value <.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 832 patients with diabetes and kidney biopsy were screened for this study. The most relevant clinical and analytical data at the time of kidney biopsy and histological diagnoses have been previously reported [4]. Of the participants in the original study, 768 had retinal study data and were analysed (Fig. 1, Table 1, Supplementary Table 1). Outcomes were available for 760 participants with retinal study data. A total of 221/768 patients (26.6%) had DR. Of these, 145 (65.6%) had DN alone, 30 (13.6%) had ND associated with NDKD and 46 (20.8%) had NDKD. Patients with DN had a higher prevalence of DR (Table 2). The distribution of patients regarding the presence of DR and renal histological diagnosis is provided in Table 2. Patients with DN-NDKD had lower renal function and a lower prevalence of cardiovascular disease and hypertension compared with those with isolated DN (Supplementary Table 1).

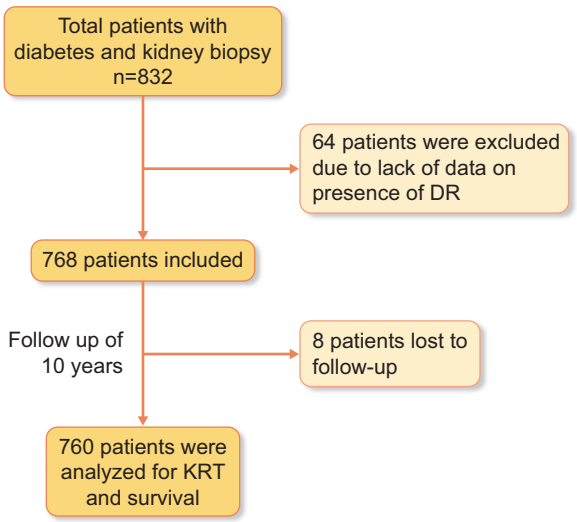


Figure 1: Flowchart of patients included in the present study: 768 with retinal study data were included and 760 of these had information on KRT and mortality outcomes.

Relationship between DR and DN

Among participants with retinal study data, a total of 305 patients (39.7%) had isolated DN on kidney biopsy, 377 (49.1%) had NDKD and 86 (11.2%) had DN-NDKD. Among patients with DN, 83.3% ($n = 274$) had diffuse mesangial expansion, 62% ($n = 204$) had nodular mesangial expansion and 10.6% ($n = 35$) had focal and segmental glomerulosclerosis. Nodular mesangial expansion was more common in patients with DR than in those without DR among patients with isolated DN or DN-NDKD (72.2% versus 55.1%, $P = .001$ and 65.5% versus 28.6%, $P < .001$, respectively). We did not find any differences in other types of histological lesions regarding the presence of DR.

Relationship between DR and kidney outcomes

A total of 288/760 (37.9%) patients with outcome data required KRT within a median follow-up of 10 years. Of these, 121/288 (42%) had DR. The incidence of KRT was 191/391 (48.9%) among patients with DN: 153/305 (50.2%) among patients with isolated DN and 38/86 (44.2%) among patients with DN-NDKD (P = not significant). The incidence of KRT was 97/377 (25.7%) among patients with NDKD who did not have DN.

Among patients with DN (isolated DN or DN-NDKD), the incidence of KRT was higher among patients with DR than among patients without DR [103/175 (58.9%) versus 88/216 (40.7%), $P < .001$]. Among patients with NDKD only, the incidence of KRT was higher among patients with DR than among patients without DR [18/46 (39.1%) versus 79/331 (23.9%), $P = .024$].

In actuarial survival analysis (Kaplan–Meier curves), patients with DR had a higher incidence of KRT than those without DR ($P < .001$) (Fig. 2A). Furthermore, patients with DN (with or without NDKD) had a higher incidence of KRT than those without DN ($P < .001$) (Fig. 2B). We did not evidence differences in the incidence of KRT between patients with isolated DN and those with DN-NDKD (Supplementary Figure 1). Patients with DR or DN had a higher incidence of KRT than those with neither DN nor DR ($P = .02$) (Fig. 2C).

In the Cox regression analysis (Table 3), the presence of DR and the presence of DN were independently associated with incident KRT after adjustment for sex, age, serum creatinine and proteinuria. In a second Cox regression model adjusted for the same variables but replacing the independent variables DR and DN with a composite variable consisting of the presence of DR or DN (encompassing both isolated DN and DN-NDKD), the presence of DR or DN was associated with incident KRT.

Relationship between DR and mortality

A total of 157/760 (20.7%) patients with mortality data died within a median follow-up of 10 years. Among patients with

Table 2: Distribution of patients regarding the presence of DR and renal histological diagnosis.

	Kidney biopsy			
Retinal examination	DN	NDKD	DN-NDKD	Total
DR	145	46	30	221
No DR	160	331	56	547
No data	24	36	4	64
Total	329	413	90	832

Table 1: Baseline population characteristics regarding the presence of DR.

Characteristics	All patients ($n = 768$)	Presence of DR (n = 221)	Absence of DR ($n = 547$)
Age (years), mean ± SD	61.3 ± 12.9	57.1 ± 12.4	63 ± 12.7
Male, *n* (%)	576 (75.0)	162 (73.3)	414 (75.7)
Hypertension, *n* (%)	668 (87)	200 (90.5)	468 (85.6)
Type 1 DM, *n* (%)	59 (7.7)	35 (15.8)	24 (4.4)
Time of evolution of DM (years), mean ± SD	11 ± 9	14.1 ± 9.6	9.5 ± 7.8
Dyslipidaemia, *n* (%)	541 (70.4)	146 (66.1)	395 (72.2)
Ischaemic heart disease, *n* (%)	131 (17.1)	40 (18.1)	91 (16.6)
Stroke, *n* (%)	89 (11.6)	32 (14.5)	57 (10.4)
Peripheral vasculopathy, *n* (%)	145 (18.9)	71 (32.1)	74 (13.5)
SBP (mmHg), mean ± SD	144.5 ± 25.3	148.9 ± 26.2	142.9 ± 24.8
DBP (mmHg), mean ± SD	77.2 ± 12.2	78.7 ± 13.1	76.6 ± 11.8
Creatinine (mg/dl), mean ± SD	2.7 ± 2.2	3.1 ± 2.3	2.6 ± 2.2
Glycosylated haemoglobin (%), mean ± SD	6.9 ± 1.6	7.2 ± 1.8	6.8 ± 1.6
Proteinuria (g/24 h), median (IQR)	2.84 (1.30–5.54)	3.00 (1.41–6.19)	2.8 (1.29–5.20)
Microhaematuria, *n* (%)	263 (34.2)	83 (37.6)	180 (32.9)

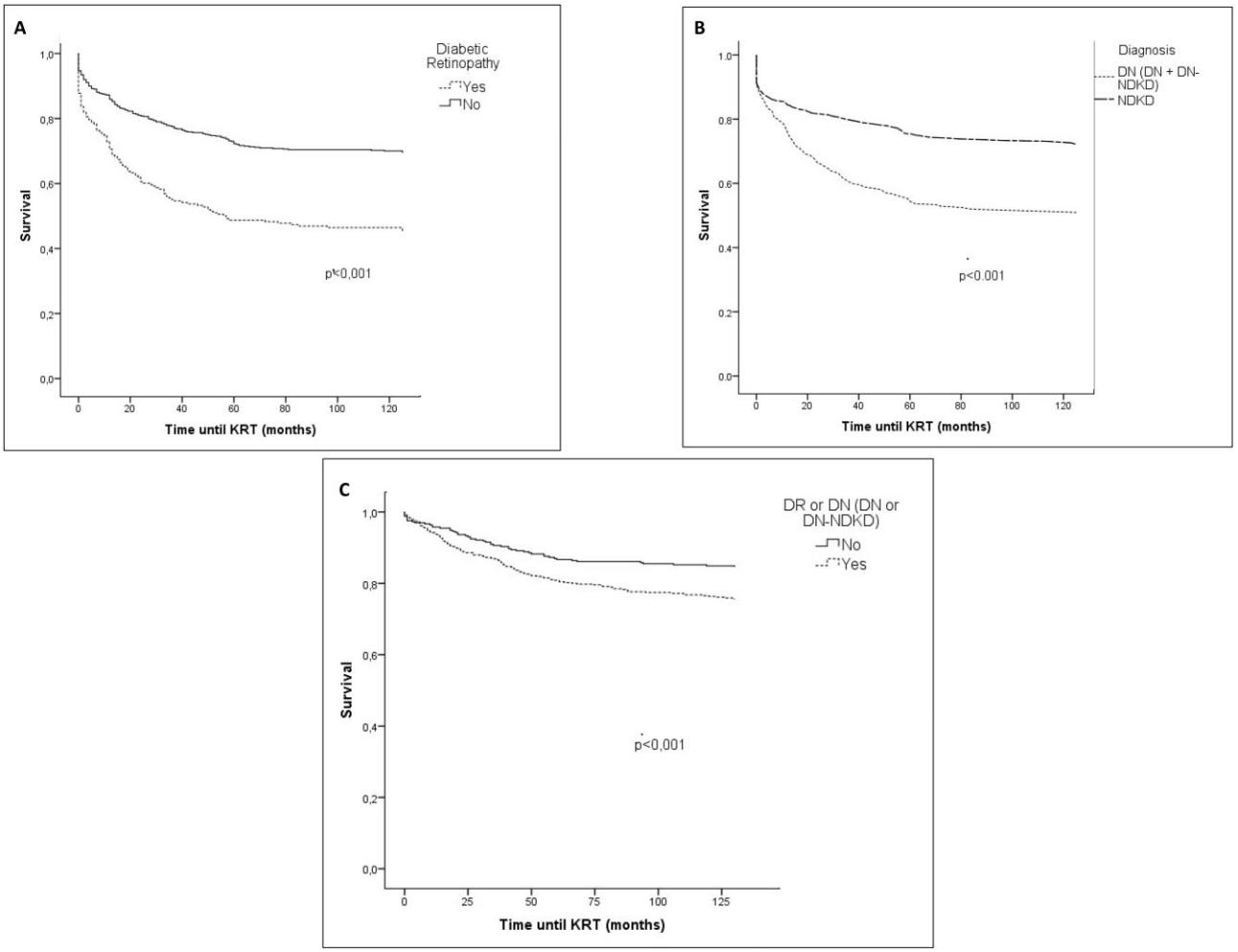


Figure 2: Analysis of KRT outcomes according to the presence of **(A)** DR, **(B)** histological diagnosis and **(C)** the presence of DR or DN versus neither DR nor DN.

Table 3: Multivariate: Cox regression analysis for identifying risk factors for need of KRT.

Variables	HR	95% CI	*P*-value
Model 1			
Age (years)	1.02	1.004–1.03	.005
Sex (men versus woman)	1.29	0.97–1.23	.085
Proteinuria (g/24 h)	1.061	1.03–1.09	<.001
Serum creatinine (mg/dl)	1.245	1.2–1.29	<.001
DR (yes versus no)	1.517	1.15–2	.004
DN or DN-NDKD (yes versus no)	1.985	1.48–2.67	<.001
Model 2			
Age (years)	1.02	1.01–1.03	.001
Sex (men versus woman)	1.33	1.004–1.76	.047
Proteinuria (g/24 h)	1.07	1.04–1.09	<.001
Serum creatinine (mg/dl)	1.25	1.2–1.29	<.001
DR or DN (DN and DN-NDKD) (yes versus no)	2.48	1.85–3.31	<.001

Dependent variable: need of KRT.

DR, mortality was 57/221 (26.7%) and among those without DR it was 100/547 (18.3%) ($P = .014$). Mortality was 99/391 (25.3%) among patients with DN, 76/305 (24.9%) among patients with isolated DN, 23/86 (26.7%) among patients with DN-NDKD and 58/377 (15.4%) among patients with NDKD who did not have DN.

Among patients with DN (isolated or with coexistent NDKD), we did not evidence differences in mortality between patients with DR and without DR [50/175 (28.6%) versus 49/216 (22.7%), P = not significant]. Similar results were obtained for patients with NDKD, in whom mortality was 7/46 (15.2%) and 51/331 (15.4%; P = not significant) for patients with and without DR, respectively.

In actuarial survival analysis (Kaplan–Meier curves), patients with DR had higher mortality than those without DR ($P < .001$) (Fig. 3A) and patients with DN (with or without NDKD) had higher mortality than those without DN ($P = .008$) (Fig. 3B). We did not evidence differences in mortality between patients with isolated DN and those with DN-NDKD (Supplementary Figure 2). Patients with DR or DN had higher mortality than those with neither DN nor DR ($P = .002$) (Fig. 3C).

In the Cox regression analysis (Table 4), the presence of DN was associated with mortality after adjustment for sex, age, creatinine and proteinuria {hazard ratio [HR] 1.67 [95% confidence interval (CI) 1.15–2.43], $P = .007$}. The association of DR with mortality did not reach statistical significance ($P = .056$). In a second Cox regression model adjusted for the same variables but replacing the independent variables DR and DN with a composite variable consisting of the presence of DR or DN (encompassing both

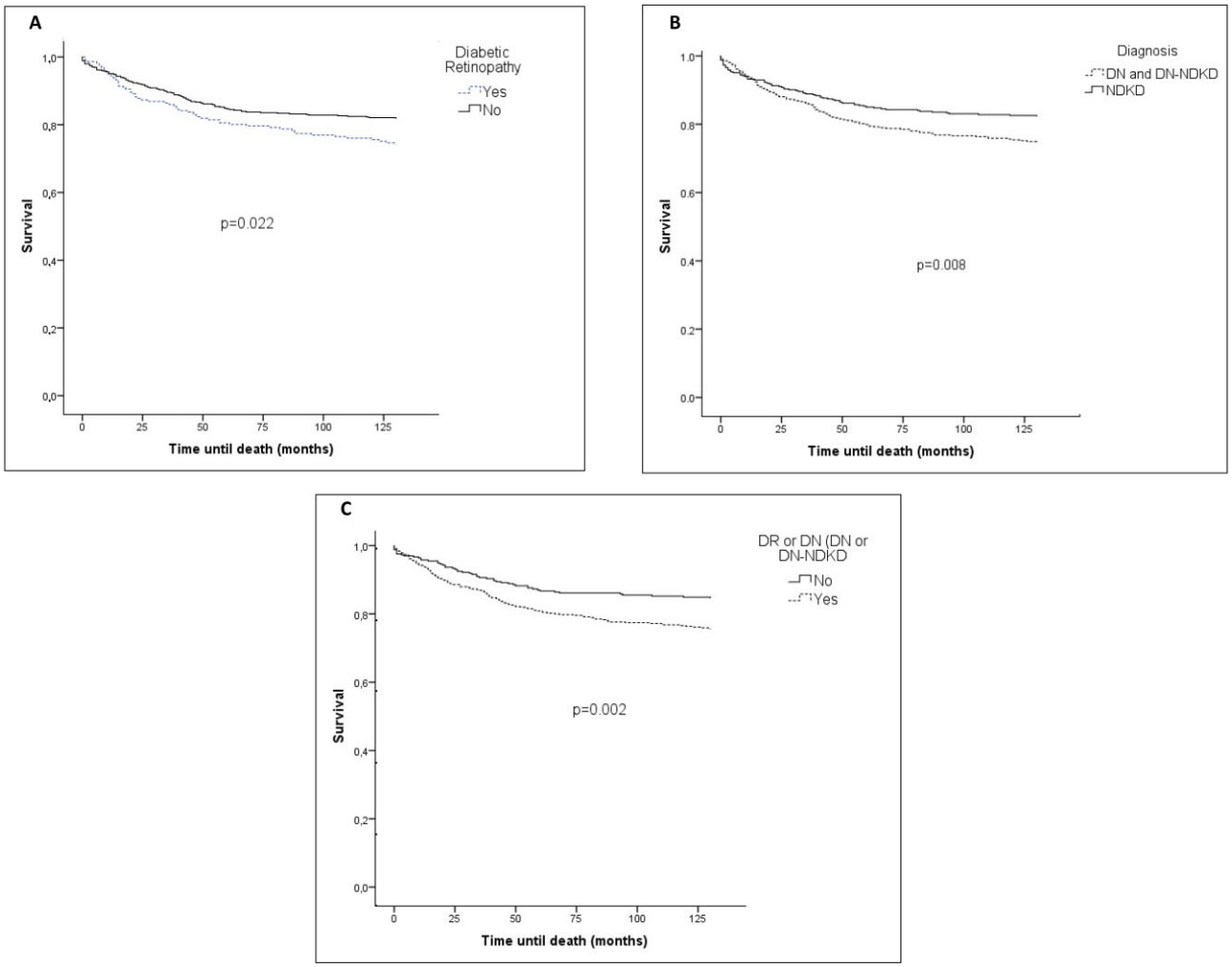


Figure 3: Analysis of patient survival according to the presence of **(A)** DR, **(B)** histological diagnosis and **(C)** the presence of DR or DN versus neither DR nor DN.

isolated DN and DN-NDKD), the presence of DR or DN was an independent risk factor for mortality.

DISCUSSION

In the present multicentre cohort study of 768 biopsied patients with diabetes, approximately two-thirds had NDKD as a unique or contributing cause of renal disease. The main finding was that the presence of DR was an independent risk factor for a need for KRT in both patients with histological DN and in those with histological NDKD and the highest risk was observed in patients who presented both DR and DN.

The present cohort represents the largest European cohort analysed for the association of DR with kidney and patient survival among patients categorized according to the presence of DN on kidney biopsy. Sharma *et al.* [14] and Liu *et al.* [15] published the kidney biopsy findings for 620 and 1604 patients with DM in the modern era from the USA and China, respectively, but did not explore the relationship between DR and DN and outcomes such as KRT or mortality. Regarding the present cohort, we previously described the prevalence and predictors of NDKD and observed worsened renal survival and increased mortality in patients with DM and histological DN [4]. We have now explored the association of DR with kidney histology as well as with kidney and survival outcomes overall and according to underlying histological findings.

In 1998, Scharwtz *et al.* [12] observed that in 17 patients with biopsy-proven DN, the presence of advanced DN with Kimmelstiel–Wilson nodules was more frequently associated with DR than the presence of mesangial sclerosis. In the present study, the presence of nodular sclerosis on the kidney biopsy was also more frequently associated with DR. Additionally, patients with DR, DN or a combination of both had a worse renal prognosis. DR is known as a microangiopathic complication of DM, as is DN [6–8]. As patients with diabetes with proteinuria and DR are considered at high risk for DN, kidney biopsy is often not performed [16, 17]. A higher severity of DR is associated with adverse kidney outcomes [6–8]. DR has also been related to the development of cardiovascular disease [9] and mortality [9–11]. However, none of these studies characterized the underlying kidney disease histologically and it was unknown whether DN was present. In accordance with previous studies, we found a significant prevalence of NDKD among patients with DM who underwent kidney biopsy, emphasizing the need to characterize and treat the underlying kidney condition [4].

To our knowledge, few studies have related DR with biopsy-proven DN. Yamanouchi *et al.* [13], published a retrospective study that included a cohort of biopsy proven DN (n = 232)

Table 4: Multivariate Cox regression analysis for identifying risk factors for mortality.

Variables	HR	95% CI	P-value
Model 1			
Age (years)	1.04	1.02–1.06	<.001
Sex (men versus woman)	1.13	0.77–1.67	.54
Proteinuria (g/24 h)	1.02	0.98–1.06	.277
Serum creatinine (mg/dl)	1.08	1.01–1.15	.022
DR (yes versus no)	1.45	0.99–2.14	.056
DN or DN-NDKD (yes versus no)	1.67	1.15–2.43	.007
Model 2			
Age (years)	1.04	1.01–1.03	<.001
Sex (men versus woman)	1.08	0.74–1.58	.689
Proteinuria (g/24 h)	1.02	0.98–1.06	.294
Serum creatinine (mg/dl)	1.09	1.02–1.16	.009
DR or DN (DN and DN-NDKD) (yes versus no)	1.81	1.26–2.62	.001

Dependent variable: mortality.

from 1985 to 2017. They categorized the severity of DR into mild proliferative DR, moderate non-proliferative DR, severe non-proliferative DR and proliferative DR. More severe DR was an independent risk factor for kidney failure. However, this study excluded patients with NDKD. These results are concordant with findings in the present article, in which DR was identified as an independent risk factor for incident KRT in patients with either DN or NDKD. Thus the observation in the Japanese population was expanded to include all underlying nephropathies as assessed by kidney biopsy, as well as participants with a different genetic and environmental background. Furthermore, the present study supports the idea that the combination of DR and DN further increases the risk of adverse kidney outcomes in patients with diabetes as compared with patients with isolated DR or isolated DN. In this regard, Simo *et al.* [9] showed that DR and microalbuminuria were independent risk factors for coronary artery calcification, but their combined presence further increased the risk of coronary artery calcification.

The present study has certain limitations because of its retrospective nature. Kidney biopsies were interpreted by different pathologists from different hospitals and kidney biopsies with a diagnosis of DN were not classified according to Tervaert *et al.* [18] due to insufficient information. Finally, DR was not categorized according to severity. However, the study also had some strengths, including the large sample size and its multicentric nature, the assessment of risk for adverse outcomes in diabetic patients with both DN and NDKD and the fact that the study provided information on outcomes in a 21st century cohort.

In summary, the assessment of DR plays a key role in risk stratification of diabetic patients for kidney and mortality risks. Patients with DR have worse renal prognosis, regardless of the presence of DN or NDKD. In patients with DN, a coexistent diagnosis of DR, representing another microangiopathic complication, further impairs the renal prognosis. Monitoring for DR should be part of the integral evaluation of patients with diabetes and kidney disease, as it allows identification of those at higher risk for closer monitoring, evaluation of compliance and adaptation of the treatment strategy to delay the need for KRT, and likely of premature death. Future prospective studies should focus on optimizing the diagnosis, treatment and outcomes of patients with diabetes, DR and kidney disease, independent of the underlying kidney histology.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

M.J.S. and X.F. collaborated on the original idea and study design. All authors contributed to the inclusion of patients in the cohort. S.B. and M.J.S. collaborated on the statistical analysis and wrote the article. All authors approved the final version of the submitted manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

S.B. reports honorarium for conferences, consulting fees and advisory boards from AstraZeneca, Boehringer, Bayer and Mundipharma. M.J.S. reports personal fees from Novo Nordisk, Jansen, Mundipharma, AstraZeneca, Esteve, Fresenius, Ingelheim Lilly, Vifor, ICU, Pfizer, Bayer, Travere Therapeutics and GE Healthcare and grants and personal fees from Boehringer Ingelheim, outside the current study. N.M. reports honoraria from Alexion and GSK. N.G.-F. paticipates on scientific advisory virtual of Mundipharma, honoraria for lectures of Astellas and medical Statistics Consulting and payment for expert testimony of Baxter, Viforpharma and Fresenius. B.F.-F. has received grants from Esteve and Astrazeneca and have worked for Cátedra UAM-mundipharma. B.F.-F. has received consultancy or speaker fees or travel support from Astrazeneca, Bayer, Menarini, Novo-Nordisk BoeringerInheilm and Mundipharma. B.F.F is Editor for Nefroplus. B.F.-F. has received travel support from Astrazeneca, Bayer, Menarini, Novo-Nordisk BoeringerInheilm and Mundipharma. B.F.-F. has been advisor for Astrazeneca, Bayer, Menarini, Novo-Nordisk Boeringer Inheilm and Mundipharma. M.P. reports consulting fees and payment for honoraria from Alexion, Novartis, Otsuka, Vifor, GSK, Travere. M.J.S. is Editor Emeritus of CKJ. The rest of authors have no conflicts of interest to declare.

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