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International Journal of Clinical Nephrology

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Research Article

Clinical Factors Associated with Non-Diabetic Renal Disease in Diabetic Latin American Patients, Histopathological Findings, and Predictive Model

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Received Date: January 17, 2023; **Accepted Date:** May 11, 2023; **Published Date:** May 23, 2023

Citation: Jennifer Garay., Jorge Pinilla., Luis F. Arias., Mauricio Restrepo., José M. Ustariz., et all (2023), Clinical Factors Associated with Non-Diabetic Renal Disease in Diabetic Latin American Patients, Histopathological Findings, and Predictive Model, *International Journal of Clinical Nephrology*. 5(2); **DOI:**10.37579/2834-5142/047

Abstract

The prevalence of diabetes was reported by the World Health Organization from 180 million in 1980 to 422 million in 2014, differentiating those patients who have diabetes but it is not the cause of kidney damage and is actually in the presence of non-diabetic renal disease (NDRD) or who, in addition to having diabetic nephropathy, simultaneously suffer from another illness that is aggravating kidney function and is susceptible to a therapeutic intervention other than glycemic control that allows improving renal survival.

The present analysis of 201 biopsies from native kidneys in diabetes mellitus patients from the pathology department of the University of Antioquia at the San Vicente Hospital clinical laboratory was a retrospective cohort study. The kidney biopsy report that 41% of patients had diabetic nephropathy, 16% mixed, and 43% NDRD, the most frequent histological finding was focal segmental glomerulosclerosis; in the univariate and multivariate analysis, two independent predictors were identified, each year above the mean age (56 years) increases the risk of presenting NDRD (OR, 1.05; 95% CI, 1.02–1.09; p = 0.002) in the KB. Diabetic retinopathy significantly decreases the occurrence of NDRD (OR, 0.23; 95% CI, 0.09–0.60; p = 0.002). Our findings on the potential predictive strategies, the model with the clinical variables age, diabetic retinopathy, and time of diabetes offered the best predictive performance. The area under the discrimination curve was 0.75 (95% CI, 0.67-0.81) with an acceptable Hosmer Lemeshow test, and calibration can be useful when deciding whether to perform a kidney biopsy.

Keywords: diabetes mellitus; kidney biopsy; diabetic nephropathy; non-diabetic renal disease; focal segmental glomerulosclerosis; iga nephropathy; acute tubulointerstitial nephritis

Introduction

The dramatic increase in the prevalence of diabetes reported by the World Health Organization from 180 million in 1980 to 422 million in 2014, plus the high projected growth for 2050 in low and middle-income countries (1, 2) and the association with cardiovascular outcomes, chronic kidney disease (CKD) and mortality (3,4,5), support the interest in differentiating those patients who have diabetes. Still, it is not the leading cause of kidney damage among those with non-diabetic renal disease (NDRD) or who, in addition to diabetic nephropathy, simultaneously suffer from other illnesses that are aggravating kidney function and are susceptible to a

therapeutic intervention other than glycemic control that allows improvement in renal outcomes (6,7).

To be able to discriminate diabetic kidney disease, which is a clinical diagnosis, from diabetic nephropathy (DN) alone or combined with another kidney pathology (mixed), is only possible by a kidney biopsy (KB) (8,9). Still, given the risk of the procedure, the clinician's skill is required to define the patients who benefit from an invasive diagnostic test. The indications described in the literature for type 1 diabetes mellitus include microhematuria, absence of diabetic retinopathy, unusual alteration of renal function or immunological alterations (10), and for type 2 diabetes mellitus are the sudden onset of proteinuria, proteinuria in the absence of diabetic retinopathy, active urine sediment, rapidly declining kidney function, and diabetes less than ten years (11). A meta-analysis that included 48 studies evaluating KB results in diabetic patients showed a wide range of prevalence of DN (6.5-94%) versus NDRD (3-82.9%) and mixed (4 -45.5%) in their analysis. The most frequent histopathological findings are Focal Segmental Glomerulosclerosis (FSGS), IgA Nephropathy (IgAN), and acute tubulointerstitial nephritis (ATIN) (12). Therefore, there is still a lack of consensus on when to perform KB in this population. We aimed to identify the possible clinical and laboratory factors in diabetic patients associated with the occurrence of NDRD in KB.

Methods

Design and patients

From January 2011 to February 2022, the pathology department of the University of Antioquia at the San Vicente Hospital received a total of 6780 kidney biopsies, of which 201 biopsies were of patients ≥14 years old with native kidneys and diagnosis of diabetes mellitus, that were included in this retrospective cohort study. The indications for KB included acute presentations with persistent renal impairment following acute kidney injury or non-acute presentations with atypical clinical features including (1) sub-nephrotic or nephrotic-range proteinuria or nephrotic syndrome and (2) the presence of microscopic hematuria; or (3) rapid progressive chronic kidney disease.

Data Collection

Data were collected from hospital records and the KB registry at the pathology department; final reports were checked individually. All biopsy reports included the results examined under light microscopy (stained with hematoxylin & eosin, periodic acid-Schiff, Masson's trichrome, and Jones methenamine silver and with other histochemical stains Congo red if was necessary) and immunofluorescence (for IgA, IgG, IgM, C3, C1q, κ, and λ). Still, only 18.4% had electron microscopy to examine glomerular basement membrane thickness or clarify selected cases. Non-sclerosed and sclerosed glomeruli were counted to ascertain the degree of scarring. Glomeruli with global sclerosis and glomeruli with segmental lesions were quantified as percentages of total glomeruli or viable glomeruli, respectively. IFTA scores were classified according to the estimated rate seen in the cortical area of the biopsy sample as follows: absent (grade 0) as 0%; mild (grade 1) <25%; moderate (grade 2) 25-50%, and severe (grade 3) >50% of the total area (13). DN was diagnosed and graded according to the Renal Pathology Society classification in two groups: 1) combine grades 1 and 2 described as early DN, and 2) grades 3 and 4 Kimmelstiel-Wilson nodules described as advanced DN. (14)

Clinical variables: we collected patients' demographic information (age, sex), prespecified laboratory and clinical variables, duration of diabetes, and retinopathy status at the biopsy. Baseline renal function was recorded using the serum creatinine measurements at least three months before the KB. Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration method (CKD-EPI) (15). Retinal status was recorded from clinical records at the last assessment. We also follow the previously available serum creatinine before End-Stage Kidney Disease (ESKD) or death. Our main objectives of interest were a) to identify the possible clinical and laboratory association factors of diabetic patients for the appearance of NDRD in KB; b) To compare patient and ESKD (defined as the need for renal replacement therapy) in patients with diabetic versus nondiabetic renal disease; c) Identify risk factors associated with all-cause mortality in the cohort. Patients were followed from the time of renal biopsy until study endpoints or February 2022. The following clinical definitions were used nephrotic-range proteinuria,24-hour urine protein >3500 mg/d; nephrotic syndrome as defined by the KDIGO guidelines (16), 24-hour urine protein >3500 mg/d plus hypoalbuminemia (less than 3 mg/dl) plus hyperlipidemia and edema; hematuria, >5 red blood cells per high-power field; pyuria, >5 white blood cells per high-power field (17); acute kidney disease according to KDIGO guidelines (18), >0.3 mg/dl baseline serum creatinine in less than three months.

Statistical analysis

Qualitative variables were compared using Fisher's test or chi-square as appropriate. Continuous variables depend on whether they followed a normal distribution with means and standard deviations and those did not differ by median and interquartile range. To compare quantitative variables, Student's t-test was used for variables that followed normality and Wilcoxon's t-test for those that did not follow normality.

A logistic regression analysis was carried out for the primary outcome. The dependent variable was NDRD, and the following variables were entered into the model, conforming to their behavior in the univariate analysis. According to the background in the literature (age, glomerular filtration rate, hematuria, retinopathy, and albuminuria) for this, a stepwise logistic regression model was assessed with the clinical variables of interest, and those that in the univariate analysis had a lower p-value of 0.25.

For the second aim, we performed a Kaplan-Meier survival curve using as start date, the time of the biopsy until the ESKD or death from all causes or censoring by the last follow up, comparing DN with NDRD by log-rank test. A Cox proportional hazards regression analysis was performed for the third objective and identified possible factors associated with renal survival and patient survival using the time of biopsy as the start date until death from all causes for patient survival or ESKD. The variables in the univariate analysis had a p of less than 0.25. According to the literature for the event's development, clinically relevant ones were entered into the Cox regression model. Finally, several prediction models were proposed in an exploratory manner through various logistic regression analyses. The outcome variable was defined as the final biopsy result of any NDRD or mixed versus DN alone in all cases. The independent variables were initially included according to a previous literature review. The variables were selected by a step-by-step method using a significance level of $p < 0.1$. No imputation of missing data was performed. The performance of the different models was evaluated through their discrimination and calibration properties through the C statistic and the Hosmer-Lemeshow test with their corresponding graphs. All analyses were performed using STATA Statistical Software, version 14 (College Station, TX: StataCorp LP). The San Vicente Hospital Ethics Committee approved this study.

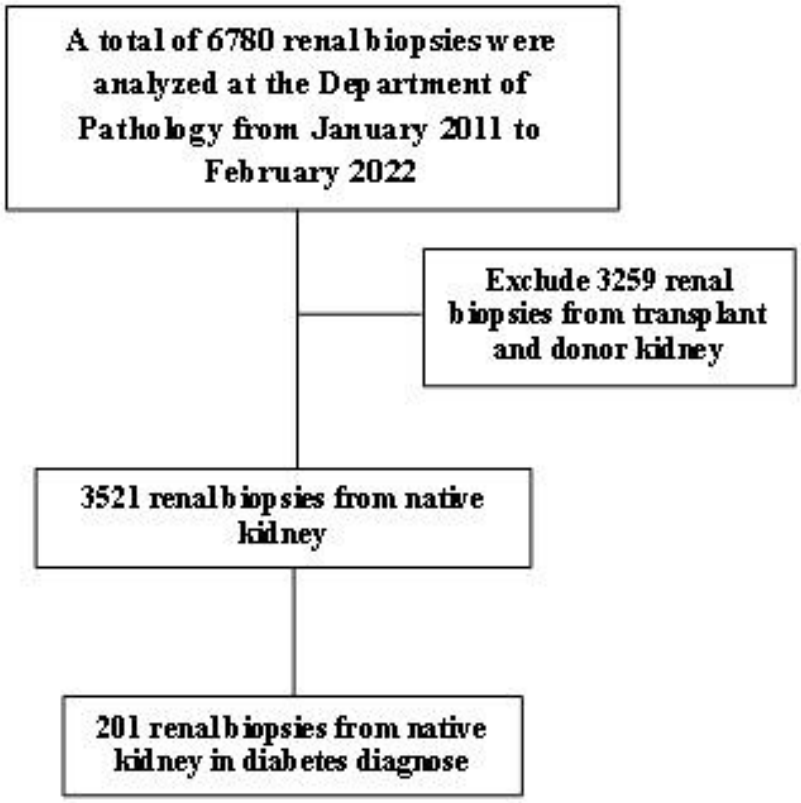

Figure 1: Sampling methodology for patients with kidney biopsy diagnosed with diabetes mellitus from January 2011 to February 2022 at the Department of Pathology Antioquia at University and San Vicente Hospital.

Results

A total of 201 patients diagnosed with diabetes mellitus older than 14 years underwent KB during the study period from January 2011 to February 2022 (fig 1). The mean ± SD age was 56 ± 13 years, the median diabetes mellitus duration 7 (IQR 3 – 13) years, with glycosylated hemoglobin (HbA1c) 7.2(6,4-9,0), and the median serum creatinine was 2 mg/dl, and retinopathy was present in 33% of the cohort. The KB reports that 41% of patients had DN, 16% mixed, and 43% NDRD. 84% of the patients had high blood pressure, and 76% received Angiotensin-Converting Enzyme (ACEIs) or Inhibitors Angiotensin II receptor blockers (ARBs). The 3 most common causes leading to biopsy were nephrotic syndrome 36.3% (n=73), proteinuria 30.3% (n=61) and acute kidney injury 18.9% (n=38), table 1.

Histopathological findings

Of the eighty-three DN alone, 92.7% (n=77) present advanced DN classified as grades 3 and 4 containing Kimmelstiel-Wilson nodules, and only 50.6% had diabetic retinopathy. The most frequent histological finding in the KB from the NDRD patients was focal segmental glomerulosclerosis (FSGS), found in twenty-three patients (26.7%), followed by IgA nephropathy. Mixed (NDRD plus DN) most prevalent was tubulointerstitial nephritis with fourteen (45%) individuals, and just six patients (18.7%) had a glomerulopathy in this subgroup, see table 2.

Characteristics	Total n = 201 n (%)	Diabetic Nephropathy n= 83 (41%)	Diabetic Nephropathy plus other n = 32 (16%)	Non-diabetic renal disease n = 86 (43%)	p-Value
Sociodemographic					
Sex – Male	107 (53%)	43 (52%)	15 (47%)	49 (57%)	0.590
Residence – Urban	125 (62%)	48 (58%)	16 (50%)	61 (71%)	0.063
Clinical					
Age, media (years) mean ± SD	56 ± 13	52 ± 12	56 ± 11	61 ± 14	<0.001
Weight (kg) mean ± SD	75 ± 14	74 ± 14	74 ± 12	76 ± 15	0.629
Systolic blood pressure (mmHg) at the time of kidney biopsy mean ± SD	133 ± 16	136 ± 17	132 ± 12	131 ± 16	0.165
Diastolic blood pressure (mmHg) at the time of kidney biopsy median ± SD	76 ± 10	77 ± 10	77 ± 8	76 ± 9	0.526
Medical history					
Diabetes mellitus					
Type 1	16 (8%)	11 (13%)	1 (3%)	4 (5%)	0.077
Type 2	185 (92%)	72 (87%)	31 (97%)	82 (95%)	

DM duration (years) Median (I.Q.R.)	7 (3 - 13)	10 (5 - 17)	8 (3 - 13)	5 (2 - 10)	<0.001
Hypertension	168 (84%)	71 (86%)	29 (91%)	68 (79%)	0.075*
Obesity	70 (35%)	26 (31%)	12 (38%)	32 (37%)	0.632
Chronic kidney disease	97 (48%)	42 (51%)	15 (47%)	40 (47%)	0.823
Dyslipidemia	123 (61%)	49 (59%)	20 (63%)	54 (63%)	0.895
Alcohol	34 (17%)	15 (18%)	6 (19%)	13 (15%)	0.791
Smoking	65 (32%)	19 (23%)	12 (38%)	34 (40%)	0.053
Drug abuse	4 (2%)	2 (2%)	1 (3%)	1 (1%)	0.661
Biomass smoke exposure	16 (8%)	-	9 (28%)	7 (8%)	<0.001
Retinopathy	67 (33%)	42 (51%)	14 (44%)	11 (13%)	<0.001
ACEIs or ARBs	153 (76%)	63 (76%)	27 (84%)	63 (73%)	0.244
Verapamil use	13 (6%)	3 (4%)	1 (3%)	9 (10%)	0.176
Statins use	113 (56%)	46 (55%)	19 (59%)	48 (56%)	0.837
Diabetes medication					
Insulin	77(38%)	43(52%)	14(44%)	20(23%)	0.723
Metformin	53(26%)	11(13%)	7(22%)	35(42%)	0.054
Insulin + metformin	24(12%)	10(12%)	3(9.4%)	11(13%)	0.145
SGLT2i +/- metformin	7(3.5%)	1(1.2%)	1(3.1%)	5(5.8%)	0.625
Other medication*	40(20%)	18(22%)	7(22%)	15(17%)	0.078
Laboratories					
Creatinine (mg/dl)	2.0 (1.3 – 3.3)	1.9 (1.3 – 3.1)	2.4 (1.6 – 3.9)	1.9 (1.0 – 3.1)	0.157
Glomerular filtration rate (ml/min)	32 (17 – 55)	34 (21 – 53)	29 (13 – 41)	33 (17 – 68)	0.195
24-hour urine protein (mg/24 h)	3347 (1375 – 6185)	3985 (2100 – 6627)	2419 (800 – 8100)	2285 (885 – 5414)	0.068
HbA1c (%)	7.2 (6.4 – 9.0)	7.7 (6.5 – 9.3)	7.3 (6.4 – 10.2)	6.9 (6.3 – 8.3)	0.097
Hemoglobin (g/dl)	11 (9 – 13)	11 (9 – 12)	11 (10 – 12)	13 (10 – 14)	<0.001
Hematocrit (%)	33 (28 – 40)	31 (27 – 36)	32 (27 – 35)	36 (29 – 44)	<0.001
Glycemia (mg/dl)	144 (114 – 205)	159 (116 – 230)	167 (135 – 248)	132 (107 – 174)	0.013
Total Cholesterol (mg/dl)	189 (154 – 255)	183 (147 – 233)	246 (185 – 273)	185 (147 – 254)	0.115
LDL Cholesterol (mg/dl)	106 (80 – 154)	106 (83 – 137)	147 (94 – 175)	102 (78 – 154)	0.282
Albumin (g/dl)	3.2 (2.5 – 3.6)	3.0 (2.5 – 3.5)	3.0 (2.4 – 3.5)	3.4 (2.7 – 3.8)	0.071
Parathyroid hormone (pg/ml)	93 (52 – 164)	107 (63 – 164)	120 (56 – 196)	73 (48 – 144)	0.122
Albumin-to-creatinine ratio					
<30 (mg/g)	28 (14%)	8 (10%)	7 (22%)	13 (15%)	0.054
30-300 (mg/g)	52 (26%)	16 (19%)	7 (22%)	29 (34%)	
>300 (mg/g)	109 (54%)	54 (65%)	13 (41%)	42 (49%)	
Unknown	12 (6%)	5 (6%)	5 (16%)	2 (2%)	
Pyuria	52 (26%)	17 (20%)	12 (38%)	23 (27%)	0.130
Hematuria	62 (31%)	22 (27%)	10 (31%)	30 (35%)	0.560

SD, Standard deviation; IQR, interquartile Range; HbA1c, glycosylated hemoglobin; ACEIs, Angiotensin-Converting Enzyme; ARBs, Inhibitors Angiotensin II receptor blockers, SGTL2i sodium-glucose cotransporter 2 inhibitors

Table 1: Descriptive analysis of patients diagnosed with diabetes mellitus with a kidney biopsy.

	Total n = 118 (%)	Non-Diabetic Renal Disease n= 86 (%)	Diabetic Nephropathy plus other n = 32 (%)
Acute Tubulointerstitial Nephritis	30 (25.4)	16 (18.6)	14 (45)
FSGS	24 (20.3)	23 (26.7)	1 (3.1)
IgA nephropathy	13 (11)	11 (12.8)	2 (6.2)
Membranous nephropathy	11 (9.3)	9 (10.5)	2 (6.2)
ANCAS	6 (5.1)	6 (7)	0
MPGN	6 (5.1)	5 (5.8)	1(3.1)
ATN	7 (5.9)	3 (3.5)	4(12.5)
Chronic Interstitial Nephritis	4 (3.4)	3 (3.5)	1(3.1)
Amyloidosis	2 (1.7)	2 (2.3)	0
Hypertensive nephropathy	2 (1.7)	2 (2.3)	0
Monoclonal gammopathy	3 (2.5)	2 (2.3)	1(3.1)
Post-infectious glomerulonephritis	3 (2.5)	2 (2.3)	1(3.1)
Thin basement membrane nephropathy	1 (0.8)	1 (1.16)	0
Lupus Nephritis	2 (1.7)	1 (1.16)	1(3.1)

Pyelonephritis	3 (2.5)	0	3 (9.4)
C3 nephropathy	1 (0.8)	0	1 (3.1)
FSGS, Focal segmental glomerular sclerosis; ANCAS: neutrophil anti-cytoplasmic antibodies glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; ATN, acute tubular necrosis			

Table 2. Histopathological findings in patients with non-diabetic renal disease and diabetic nephropathy plus another diagnosis.

Factors associated with non-diabetic kidney disease in kidney biopsy

Two independent predictors were identified in the univariate and multivariate analysis; each year above the mean age (56 years) increases the risk of presenting NDRD (OR, 1.05; 95% CI, 1.02–1.09; p = 0.002) in the KB. The diabetic retinopathy significantly decreases the occurrence of NDRD (OR, 0.23; 95% CI, 0.09–0.60; p = 0.002), see table 3.

Variable	Univariate analysis			Multivariate analysis		
	OR	CI 95%	p-Value	OR	CI 95%	p-Value
Age	1.05	1.02 – 1.08	<0.001	1.05	1.02 – 1.09	0.002
Male	0.81	0.44 – 1.49	0.500	1.00	0.44 – 2.30	0.995
Glomerular filtration rate	1.01	1.00 – 1.02	0.197	1.00	0.99 – 1.02	0.750
Hematuria	1.44	0.74 – 2.79	0.282	1.09	0.44 – 2.67	0.852
DM duration	0.92	0.88 – 0.96	<0.001	0.96	0.90 – 1.02	0.157
Retinopathy	0.13	0.06 – 0.29	<0.001	0.23	0.09 – 0.60	0.003
Albumin	1.59	1.05 – 2.39	0.027	1.60	0.85 – 3.01	0.148
Proteinuria	1.00	0.99 – 1.00	0.366	1.00	0.99 – 1.00	0.609

Table 3. Univariate and multivariate logistic regression analysis of diabetic nephropathy versus non-diabetic renal disease. Regression with all continuous quantitative variables (albumin and proteinuria do not show collinearity).

Patient and renal-censored survival diabetes nephropathy versus non-diabetic renal disease

Fifty-seven (28.3%) patients died during the follow-up, the most common cause was infection (n=30, 52.6%), continued by cardiovascular cause (n=16, 28%). The patient survival with DN rate was 52%, and for NDRD, 60% in the first year, 25% and 28% in the third year, and 12,5% and 15% in the fifth year, respectively, figure 2a. The renal survival with DN rate was 40% and for NDRD plus mixed 38% in the first year, figure 2b. There was no significant difference between patients and renal survival if they presented DN or NDRD.

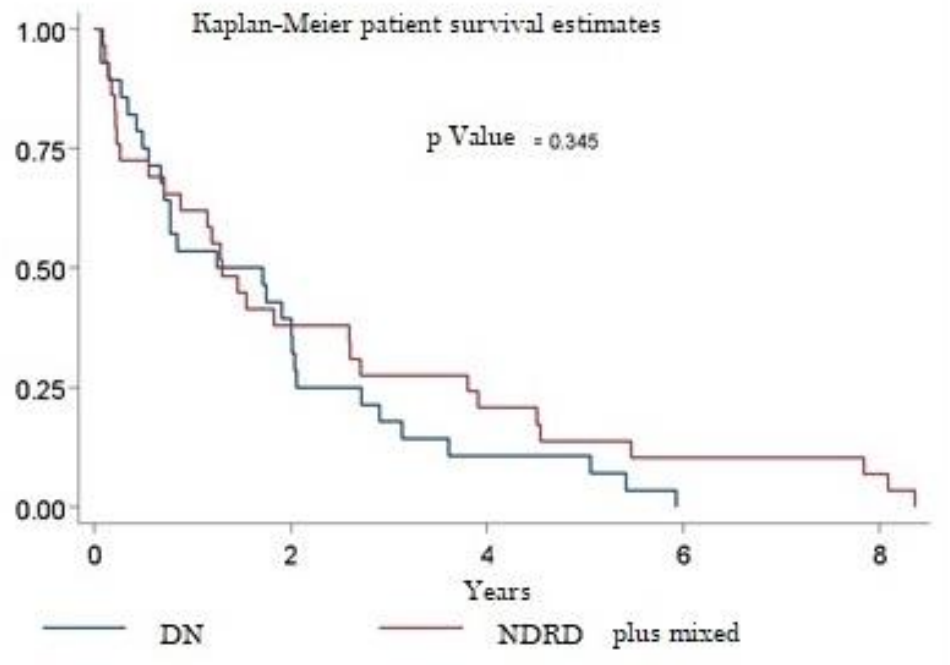

Figure 2. (a) Patient survival rates for diabetic nephropathy versus mixed (diabetic nephropathy plus non-diabetic renal disease). (b) Renal survival rates diabetic nephropathy versus mixed (diabetic nephropathy plus non-diabetic renal disease)

Patient and renal-censored survival associated factors.

Univariable and multivariate Cox proportional hazards regression models were performed to estimate the adjusted risk for lower patient and renal survival. Patient survival multivariate analysis showed albumin >3 g/dL increases the survival of overall patients that were biopsied; HR, 0.29 (95% CI, 0.12 – 0.68; p = 0.005), as does having proteinuria of less than 3.5 g/24 hours; HR, 0.37 (95% CI, 0.15 – 0.95; p = 0.030). On the contrary, age over 56 years decreases patient survival, HR, 1.04 (95% CI, 1.01–1.06; p = 0.05). These findings were similar in the subgroup of only type 2 diabetic patients. The difference that in this population, not having hematuria was also related to better survival, HR, 0.37 (95% CI, 0.15 – 0.95; p = 0.030). Multivariate analysis showed a marked association with the decreased renal survival associated with diabetic retinopathy, HR, 3.37 (95% CI, 1.36 – 8.33; p = 0.009).

Model I. Univariable and multivariable Cox analysis of predictors of patient survival in the entire population.						
Variable	Univariate analysis			Multivariate analysis		
	HR	CI 95%	p-Value	HR	CI 95%	p-Value
Age	1.00	0.98 – 1.02	0.815	1.04	1.01 – 1.06	0.05
Sex (Male)	0.88	0.52 – 1.49	0.633	0.56	0.26 – 1.22	0.143
eGFR >60 ml/min/1.73 m2	0.76	0.39 – 1.48	0.423	0.82	0.38 – 1.76	0.607
Hematuria	0.83	0.47 – 1.47	0.520	0.54	0.23 – 1.24	0.144
DM duration (< 5 years)	0.78	0.43 – 1.43	0.426	0.74	0.33 – 1.65	0.463
Retinopathy	0.89	0.51 – 1.58	0.698	1.25	0.60 – 2.62	0.557
Albumin >3.0 gr/dl	0.60	0.32 – 1.13	0.112	0.29	0.12 – 0.68	0.004
Proteinuria <3.5 gr/24 h	1.06	0.59 – 1.92	0.848	0.37	0.15 – 0.95	0.039
Diabetic nephropathy non-diabetic renal disease	0.77	0.45 – 1.32	0.346	0.87	0.41 – 1.85	0.718
Model II. Univariable and multivariable Cox analysis of predictors of patient survival in the type 2 diabetes mellitus population						
Variable	Univariate analysis			Multivariate analysis		
	HR	CI 95%	P-Value	HR	CI 95%	P-Value
Age	1.00	0.98 – 1.02	0.884	1.04	1.00 – 1.09	0.044
Sex (Male)	0.90	0.52 – 1.56	0.697	0.55	0.24 – 1.23	0.144
eGFR>60 ml/min/1.73 m^2	0.78	0.40 – 1.52	0.460	0.91	0.42 – 2.00	0.819
Hematuria	0.81	0.45 – 1.45	0.473	0.40	0.16 -0.99	0.048
DM duration (< 5 years)	0.81	0.44 – 1.50	0.513	10.85	0.37 – 1.92	0.693
Diabetic retinopathy	0.87	0.47 – 1.59	0.647	1.34	0.62 - 292	0.459
Albumin >3.0 gr/dl	0.66	0.34 – 1.26	0.204	0.28	0.11 – 0.68	0.005
Proteinuria <3.5 gr/24 h	0.96	0.52 – 1.78	0.901	0.33	0.13 – 0.86	0.024
Diabetic nephropathy non-diabetic renal disease	0.76	0.44 – 1.34	0.349	0.78	0.35 – 1.78	0.559
Model III. Univariable and multivariable Cox analysis of predictors renal survival in the entire population.						
Variable	Univariate analysis			Multivariate analysis		
	HR	CI 95%	p-Value	HR	CI 95%	p-Value
Age	0.98	0.96 – 1.00	0.066	0.98	0.95 – 1.01	0.181
Sex (Male)	0.75	0.42 – 1.33	0.327	0.72	0.34 – 1.53	0.395
eGFR >60 ml/min/1.73 m^2	0.99	0.98 – 1.01	0.353	0.98	0.96 – 1.00	0.029
Hematuria	0.90	0.48 – 1.70	0.751	11.02	0.42 – 2.46	0.962
DM duration (< 5 years)	1.00	0.96 – 1.04	0.983	0.96	0.91 – 1.02	0.183
Retinopathy	2.22	1.18 – 4.17	0.013	3.37	1.36 – 8.33	0.009
Albumin >3.0 gr/dl	1.00	0.73 – 1.38	0.999	0.90	0.57 – 1.42	0.648
Proteinuria <3.5 gr/24 h	1.00	1.00 – 1.00	0.806	1.00	1.00 – 1.00	0.132
Diabetic nephropathy, non-diabetic renal disease	0.91	0.51 – 1.65	0.768	1.17	0.54 – 2.54	0.697

Table 4. Univariable and multivariable Cox analysis for overall patient survival and renal survival.

During the exploration of potential predictive strategies, the model with the clinical variables age, diabetic retinopathy, and time of diabetes offered the best predictive performance. The area under the discrimination curve was 0.75 (95% CI, 0.67-0.81) with an acceptable Hosmer Lemeshow test and calibration plot, figure 3.

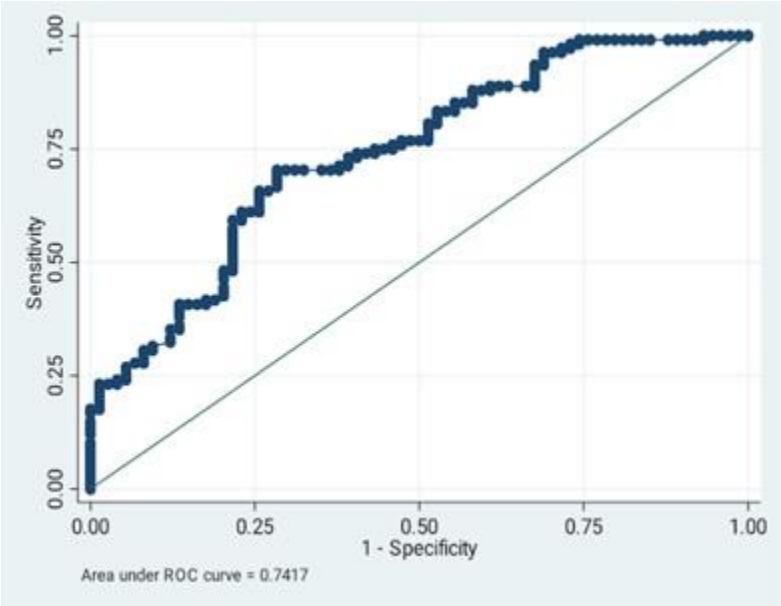

Figure 3. Predictive strategies, a model with clinical variables age, diabetic retinopathy, and time of diabetes

Discussion

We present our retrospective cohort study in a reference pathology center of diabetic patients who underwent KB in the last decade. The most frequent indication for KB was proteinuria, whether in the nephrotic range or not. In general, KB was a safe procedure, with just 3.98% minor complications and no death caused by it.

NDRD in patients with diabetes has a wide range in prevalence (12,19-23); this phenomenon is perhaps due to the lack of consensus on the indications for KB from each center (24). In our cohort, the prevalence of NDRD alone was 43%, like those found in the largest cohorts in Europe and the USA, 49.6% and 35.4%, respectively (25,26). Focal segmental glomerulosclerosis was the most prevalent glomerulopathy within the NDRD alone in our study, followed by ATIN, IgAN, and membranous nephropathy, which differs from previous reports literature, in which IgAN was the main finding (27-34). In a study previously carried out by our group that included the review of glomerular disease in 1040 kidney biopsies in the general population, this same distribution of prevalence was also found, which is a similar tendency in Latin America and black race (35). These results are important because they are pathologies susceptible to other treatments that impact better kidney outcomes (36,37).

In the logistic regression model for the occurrence of NDRD, we identified as associated factors the older age (OR, 1.05; 95% CI, 1.02–1.09; p = 0.002) and the absence of diabetic retinopathy (OR, 0.23; 95% CI, 0.09–0.60; p = 0.002), this data is also support by the meta-analysis published by Liang et al. (38), who reported an inversely proportional relationship between the presence of retinopathy and the diagnosis of NDRD. Many researchers have long considered diabetic retinopathy a clinical characteristic of advanced diabetes that would rule out the need for KB in diabetic patients with renal deterioration signs (39,40). But older age (>56 years) has not been previously described as an associated factor as far as we know from the review carried out by our group.

The Cox analysis showed that a normal albumin level (HR, 0.29; p = 0.004) and sub-nephrotic proteinuria (HR, 0.37; p = 0.030) had better patient survival. The predictive component of proteinuria with the progression of kidney disease and cardiovascular mortality has been widely described as worse renal survival with higher amounts [41]. While advanced age (HR, 1.04; p = 0.05) was established as a factor associated with less survival, older individuals are usually linked to other comorbidities that are also frequent in both diabetic patients and those with chronic kidney disease (42-44), which can contribute to the sum of mortality rates (45,46). To our knowledge, after reviewing the available literature, our study was the first to describe independent factors related to better patient survival in a cohort of diabetic patients with KB.

On the other hand, patients with an eGFR >60 ml/min had better survival, while the presence of diabetic retinopathy was the only independent factor related to worse renal survival. Tan et al. (47) compared NDRD with ND, finding that renal prognosis was generally better with NDRD without specifying associated aspects. Also, Bermejo et al. (48) identified the presence of DN or NDRD plus DN as factors associated with higher mortality in their cohort. Also, in another study, Bermejo et al. (49) related advanced age, peripheral vascular disease, increased creatinine levels, and DN as risk factors for poor renal survival.

We analyzed the type 2 DM subgroup again older age was correlated with less patient survival. Likewise, the absence of hematuria stands out as a protective factor in terms of survival (<5 erythrocytes/high power field), adding to the normal albumin, and not having proteinuria in the nephrotic range. Previously Garcia-Martin et al. (50) linked microhematuria as the leading independent factor for NDRD, but no other study has this association with patient survival. Diabetic patients with isolated diabetic DN may present microhematuria of glomerular origin and have been described in DN as between 5% and 75%. This variation is related to estimating hematuria (≥3 or >10 erythrocytes/field). This presence of red blood cells of glomerular origin in DN is due to alterations in the glomerular basement membrane or to microaneurysms that can rupture [51-55]

Since no single variable has sufficient concordance with the final histological result, it is impossible to rely on a single parameter to make the final clinical decision to perform a KB. However, there is the possibility of building multivariate models that take advantage of the predictive properties of a set of variables simultaneously and support clinical decision-making [56]. In our study, the model with the variables age, retinopathy, and years with diabetes seems to work as a sensitive strategy to rule out DN alone and more strongly justifies a KB in diabetic patients.

Our study has limitations related to being retrospective. In addition, the subjectivity is related to histopathological studies. On the other hand, there is a selection bias since the biopsies are only from diabetic patients with a high suspicion of NDRD. The presence of proteinuria was one of the indications, so our results could be overestimated the true prevalence of NDRD.

Finally, NDRD is a frequent condition, as demonstrated by this cohort of Mestizo (Latino) patients; in addition, the identification of some characteristics such as the older age of the patient as well as the absence of retinopathy can be helpful when deciding whether to perform a KB because the high correlation to have other findings than DN on the histopathological results.

References

1. International Diabetes Federation. IDF Diabetes Atlas. International Diabetes Federation, editor, Brussels, Belgium, 2017
2. Lopez-Lopez J, Garay J, Wandurraga E, Camacho PA, Higuera-Escalante F, Cohen D, Lopez-Jaramillo P. The simultaneous assessment of glycosylated hemoglobin, fasting plasma glucose and oral glucose tolerance test does not improve the detection of type 2 diabetes mellitus in Colombian adults. PLOS ONE. 2018 Apr 13;13(4):e0194446. DOI: 10.1371/journal.pone.0194446
3. International Hypoglycaemia Study Group. Hypoglycemia, cardiovascular disease, and mortality in diabetes: epidemiology, pathogenesis, and management. Lancet Diabetes Endocrinol. 2019 May;7(5):385-396. DOI: 10.1016/S2213-8587(18)30315-2. Epub 2019 Mar 27. Erratum in: Lancet Diabetes Endocrinol. 2019 Jun;7(6):e18.
4. Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The Global Epidemiology of Diabetes and Kidney Disease. Adv Chronic Kidney Dis. 2018 Mar;25(2):121-132. DOI: 10.1053/j.ackd.2017.10.011.
5. Jansson SP, Andersson DK, Svärdsudd K. Mortality trends in subjects with and without diabetes during 33 years of follow-up. Diabetes Care. 2010 Mar;33(3):551-6. DOI: 10.2337/dc09-0680.
6. Gonzalez Suarez, M. L., Thomas, D. B., Barisoni, L. & Fornoni, A. Diabetic nephropathy: Is it time yet for a routine kidney biopsy? World J. Diabetes 4, 245–255 (2013).
7. Sharma, S. G. et al. The modern spectrum of renal biopsy findings in patients with diabetes. Clin. J. Am. Soc. Nephrol. 8, 1718–1724 (2013).
8. Kritmetapak K, Anutrakulchai S, Pongchaiya C, et al. Clinical and pathological characteristics of non-diabetic renal disease in type 2 diabetes patients. Clin Kidney J. 2018; 11: 342–347.
9. Bi H, Chen N, Ling G, et al. Nondiabetic renal disease in type 2 diabetic patients: a review of our experience in 220 cases. Ren Fail. 2011; 33:26–30.
10. Hommel E, Carstensen H, Skott R, et al. Prevalence and causes of microscopic haematuria in Type 1 (insulin-dependent) diabetic patients with persistent proteinuria. Diabetologia. 1987; 30: 627–630.
11. Erdogmusa S, Kiremitcib S, Kendi Celebia ZK, et al. non-diabetic kidney disease in type 2 diabetic patients: prevalence, clinical predictors and outcomes. Kidney Blood Press Res. 2017; 42: 886–893.
12. Fiorentino M, Bolignano D, Tesar V, Pisano A, Biesen WV, Tripepi G, D'Arrigo G, Gesualdo L; ERA-EDTA Immunonephrology Working Group. Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies. Nephrol Dial Transplant. 2017 Jan 1;32(1):97-110. DOI: 10.1093/ndt/gfw070.
13. Racusen LC, Solez K, Colvin RB, Bonsib SM, Castro MC, Cavallo T, Croker BP, Demetris AJ, Drachenberg CB, Fogo AB, Furness P, Gaber LW, Gibson IW, Glotz D, Goldberg JC, Grande J, Halloran PF, Hansen HE, Hartley B, Hayry PJ, Hill CM, Hoffman EO, Hunsicker LG, Lindblad AS, Yamaguchi Y, et al. The Banff 97 working classification of renal allograft pathology. Kidney Int. 1999 Feb;55(2):713-23. DOI: 10.1046/j.1523-1755.1999.00299.x.
14. Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, Ferrario F, Fogo AB, Haas M, de Heer E, Joh K, Noël LH, Radhakrishnan J, Seshan SV, Bajema IM, Bruijn JA; Renal Pathology Society. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010 Apr;21(4):556-63. DOI: 10.1681/ASN.2010010010.
15. Camargo EG, Soares AA, Detanico AB, et al. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is less accurate in patients with type 2 diabetes when compared with healthy individuals. Diabet Med 2011;28:90–95
16. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021 Oct;100(4S): S1-S276. DOI: 10.1016/j.kint.2021.05.021.
17. Krishnan A., Levin A. Análisis de laboratorio de la enfermedad renal: tasa de filtración glomerular, análisis de orina y proteinuria In Yu, A. S. L., Chertow, G. M., Luyckx, V., Marsden, P. A., Skorecki, K., & Taal, M. W. (Eds.). (2021). Brenner Y Rector. El Rinon (11th ed.). Elsevier. 23, 732-757
18. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179-84. DOI: 10.1159/000339789. Epub 2012 Aug 7.
19. Mou S, Wang Q, Liu J, Che X, Zhang M, Cao L, Zhou W, Ni Z. Prevalence of non-diabetic renal disease in patients with type 2 diabetes. Diabetes Res Clin Pract. 2010 Mar;87(3):354-9. DOI: 10.1016/j.diabres.2009.11.012.
20. Premalatha G, Vidhya K, Deepa R, Ravikumar R, Rema M, Mohan V. Prevalence of non-diabetic renal disease in type 2 diabetic patients in a diabetes Centre in Southern India. J Assoc Physicians India. 2002 Sep;50:1135-9.
21. Zhuo L, Zou G, Li W, Lu J, Ren W. Prevalence of diabetic nephropathy complicating non-diabetic renal disease among Chinese patients with type 2 diabetes mellitus. Eur J Med Res. 2013 Feb 22;18(1):4. DOI: 10.1186/2047-783X-18-4.
22. Fan JZ, Wang R. Non-diabetic renal disease in patients with type 2 diabetes: a single Centre study. Intern Med J. 2018 Apr;48(4):451-456. DOI: 10.1111/imj.13708.
23. Santoro D, Torreggiani M, Pellicanò V, Cernaro V, Messina RM, Longhitano E, Siligato R, Gembillo G, Esposito C, Piccoli GB. Kidney Biopsy in Type 2 Diabetic Patients: Critical Reflections on Present Indications and Diagnostic Alternatives. Int J Mol Sci. 2021 May 21;22(11):5425. DOI: 10.3390/ijms22115425.
24. Hsieh JT, Chang FP, Yang AH, Tarng DC, Yang CY. Timing of kidney biopsy in type 2 diabetic patients: a stepwise approach. BMC Nephrol. 2020 Apr 15;21(1):131. DOI: 10.1186/s12882-020-01794-w.
25. Bermejo S, González E, López-Revuelta K, Ibernon M, López D, Martín-Gómez A, Garcia-Osuna R, Linares T, Díaz M, Martín N, Barros X, Marco H, Navarro MI, Esparza N, Elias S, Coloma A, Robles NR, Agraz I, Poch E, Rodas L, Lozano V, Fernández B, Hernández E, Martínez MI, Stanescu RI, Moirón JP, García N, Goicoechea M, Calero F, Bonet J, Galceran JM,

Liaño F, Pascual J, Praga M, Fulladosa X, Soler MJ. Risk factors for non-diabetic renal disease in diabetic patients. Clin Kidney J. 2020 Jan 3;13(3):380-388. doi: 10.1093/ckj/sfz177.

26. Sharma SG, Bomback AS, Radhakrishnan J, Herlitz LC, Stokes MB, Markowitz GS, D'Agati VD. The modern spectrum of renal biopsy findings in patients with diabetes. Clin J Am Soc Nephrol. 2013 Oct;8(10):1718-24. DOI: 10.2215/CJN.02510213.
27. Mak SK, Gwi E, Chan KW, et al. Clinical predictors of non-diabetic renal disease in patients with non-insulin-dependent diabetes mellitus. Nephrol Dial Transplant 1997; 12: 2588–2591
28. Wong TYH, Choi PCL, Szeto CC et al. Renal outcome in type 2 diabetic patients with or without coexisting non-diabetic nephropathies. Diabetes Care 2002; 25: 900–905
29. Bi H, Chen N, Ling G, et al. Nondiabetic renal disease in type 2 diabetic patients: a review of our experience in 220 cases. Ren Fail 2011; 33: 26–30
30. Suzuki D, Takano H, Toyoda M, et al. Evaluation of renal biopsy samples of patients with diabetic nephropathy. Intern Med 2001; 40: 1077–1084
31. Zhuo L, Ren W, Li W et al. Evaluation of renal biopsies in type 2 diabetic patients with kidney disease: a clinicopathological study of 216 cases. Int Urol Nephrol 2013; 45: 173–179
32. Schwartz MM, Lewis EJ, Leonard-Martin T et al.; The Collaborative Study Group. Renal pathology patterns in type II diabetes mellitus: relationship with retinopathy. Nephrol Dial Transplant 1998; 13: 2547–2552
33. Tan J, Zwi LJ, Collins JF, et al. Presentation, pathology and prognosis of renal disease in type 2 diabetes. BMJ Open Diabetes Res Care 2017; 5: 1–9
34. Bermejo S, Soler MJ, Gimeno J et al. Factores predictivos de nefropatía no diabética en pacientes diabéticos. Utilidad de la biopsia renal. Nefrología 2016; 36: 535–544
35. Arias LF, Henao J, Giraldo RD, Carvajal N, Rodelo J, Arbeláez M. Glomerular diseases in a Hispanic population: review of a regional renal biopsy database. Sao Paulo Med J. 2009;127(3):140-4. doi: 10.1590/s1516-31802009000300006.
36. Moledina DG, Perazella MA. Drug-Induced Acute Interstitial Nephritis. Clin J Am Soc Nephrol. 2017 Dec 7;12(12):2046-2049. DOI: 10.2215/CJN.07630717.
37. Fernández-Juárez G, Rojas-Rivera J, Logt AV, Justino J, Sevillano A, Caravaca-Fontán F, Ávila A, Rabasco C, Cabello V, Varela A, Díez M, Martín-Reyes G, Diezhandino MG, Quintana LF, Agraz I, Gómez-Martino JR, Cao M, Rodríguez-Moreno A, Rivas B, Galeano C, Bonet J, Romera A, Shabaka A, Plaisier E, Espinosa M, Egido J, Segarra A, Lambeau G, Ronco P, Wetzels J, Praga M; STARMEN Investigators. The STARMEN trial indicates that alternating treatment with corticosteroids and cyclophosphamide is superior to sequential treatment with tacrolimus and rituximab in primary membranous nephropathy. Kidney Int. 2021 Apr;99(4):986-998. doi: 10.1016/j.kint.2020.10.014.
38. Liang S, Zhang XG, Cai GY, Zhu HY, Zhou JH, Wu J, Chen P, Lin SP, Qiu Q, Chen XM. Identifying parameters to distinguish non-diabetic renal diseases from diabetic nephropathy in patients with type 2 diabetes mellitus: a meta-analysis. PLoS One. 2013 May 14;8(5):e64184. DOI: 10.1371/journal.pone.0064184.
39. Cho A, Park HC, Lee YK, Shin YJ, Bae SH, Kim H. Progression of Diabetic Retinopathy and Declining Renal Function in Patients with Type 2 Diabetes. J Diabetes Res. 2020 Jul 26;2020:8784139. DOI: 10.1155/2020/8784139
40. Soleymanian T, Hamid G, Arefi M, Najafi I, Ganji MR, Amini M, Hakemi M, Tehrani MR, Larijani B. Non-diabetic renal disease with or without diabetic nephropathy in type 2 diabetes: clinical predictors and outcome. Ren Fail. 2015 May;37(4):572-5. DOI: 10.3109/0886022X.2015.1007804.
41. Popa O, Stefan G, Capusa C, Mandache E, Stancu S, Petre N, Mircescu G. Non-diabetic glomerular lesions in diabetic kidney disease: clinical predictors and outcome in an Eastern European cohort. Int Urol Nephrol. 2021 Apr;53(4):739-747. DOI: 10.1007/s11255-020-02681-x.
42. Villén N, Guisado-Clavero M, Fernández-Bertolín S, Troncoso-Mariño A, Foguet-Boreu Q, Amado E, Pons-Vigués M, Roso-Llorach A, Violán C. Multimorbidity patterns, polypharmacy and their association with liver and kidney abnormalities in people over 65 years of age: a longitudinal study. BMC Geriatr. 2020 Jun 12;20(1):206. doi: 10.1186/s12877-020-01580-1.
43. Ahmed AK, Brown SH, Abdelhafiz AH. Chronic kidney disease in older people; disease or dilemma? Saudi J Kidney Dis Transpl. 2010 Sep;21(5):835-41.
44. Nasri H. The awareness of chronic kidney disease and aging; the focus of world kidney day in 2014. J Nephropharmacol. 2014 Jan 1;3(1):1-2
45. Crews DE. Senescence, aging, and disease. J Physiol Anthropol. 2007 May;26(3):365-72. DOI: 10.2114/jpa2.26.365.
46. London GM, Safar ME, Pannier B. Aortic Aging in ESRD: Structural, Hemodynamic, and Mortality Implications. J Am Soc Nephrol. 2016 Jun;27(6):1837-46. DOI: 10.1681/ASN.2015060617.
47. Tan J, Zwi LJ, Collins JF, Marshall MR, Cundy T. Presentation, pathology and prognosis of renal disease in type 2 diabetes. BMJ Open Diabetes Res Care. 2017 Aug 11;5(1):e000412. DOI: 10.1136/bmjdrc-2017-000412.
48. Bermejo S, Pascual J, Soler MJ. The current role of renal biopsy in diabetic patients. Minerva Med 2018; 109: 116–125
49. Bermejo S, García-Carro C, Soler MJ. Diabetes and renal disease-should we biopsy? Nephrol Dial Transplant. 2021 Jul 23;36(8):1384-1386. DOI: 10.1093/ndt/gfz248.
50. García-Martína F, González Montea E, Hernández Martíneza E, Bada Boscha T, Bustamante NE, Praga M. When to perform renal biopsy in patients with type 2 diabetes mellitus? Predictive model of non-diabetic renal disease. Nefrologia. 2020 Apr; 40 (2): 115-212
51. Saito Y, Kida H, Takeda S, Yoshimura M, Yokoyama H, Koshino Y, Hattori N: Mesangiolysis in diabetic glomeruli: Its role in the formation of nodular lesions. 1988. Kidney Int 34: 389–396.
52. Stout LC, Kumar S, Whorton EB: Focal mesangiolysis and the pathogenesis of the Kimmelstiel-Wilson nodule. 1993. Hum Pathol 24: 77–89.
53. Yoshida N, Hanai K, Murata H, Uchigata Y, Babazono T. Cross-sectional and longitudinal associations between dipstick hematuria and chronic kidney disease in patients with type 2 diabetes. Diabetes Res Clin Pract. 2021 Feb; 172: 108519. DOI: 10.1016/j.diabres.2020.108519.
54. Wu Y, Zhang J, Wang Y, Wang T, Han Q, Guo R, Zhang R, Ren H, Zhu Y, Xu H, Li L, Tong N, Liu F. The association of hematuria on kidney clinicopathologic features and renal outcome in patients with diabetic nephropathy: a biopsy-based study. J Endocrinol Invest. 2020 Sep;43(9):1213-1220. DOI: 10.1007/s40618-020-01207-7.

55. Izzedine H, Fongoro S, Pajot O, Beaufils H, Deray G. Retinopathy, hematuria, and diabetic nephropathy. Nephron. 2001 Aug;88(4):382-3. DOI: 10.1159/000046025.

56. Shipe ME, Deppen SA, Farjah F, Grogan EL. Developing prediction models for clinical use using logistic regression: an overview. J Thorac Dis. 2019 Mar;11(Suppl 4): S574-S584. DOI: 10.21037/jtd.2019.01.25.

DOI: 10.37579/2834-5142/047