Research Article

Kidney biopsy in Type 2 Diabetes: a multicenter cross-sectional study

Supplementary Material

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Running head: Kidney biopsy indications in Type 2 diabetes

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SUPPLEMENTARY METHODS

Biopsy selection: Definitions

Type 2 diabetes was defined as self-reported T2D, history of T2D recorded in the medical record, fasting blood glucose concentration > 7mmol/l on two (or more) occasions, and/or random venous plasma glucose concentration > 11.1mmol/l.

Hypertension was defined as self-reported hypertension, history of hypertension recorded in the medical record, systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg or antihypertensive medication.

Hematuria was diagnosed by urine dipstick (considered positive from 10 erythrocytes/µL) of urine cytology, according to the policy of each center.

Diabetes duration was defined as the time from the diagnosis of diabetes to the time of the kidney biopsy.

Adverse event attributable to the kidney biopsy was defined as any event mentioned as such in the patient's record at the time of the biopsy.

Serious adverse events were defined as the need for blood transfusion, arterial embolization, prolonged stay in the hospital or death.

Biopsy indications: Definitions of the indication categories

Other atypical feature: presence of any atypical feature suggesting non-diabetic or hypertensive kidney disease (NDHKD) recorded in the patients' medical chart not listed below including acute kidney injury (AKI) stage 1 or more as defined by the KDIGO guidelines on AKI (1)). Presence of any feature compatible with this definition was considered an *other atypical feature* even if it was not mentioned as a motivation to perform the biopsy (e.g. Monoclonal gammopathy).

Recent onset of nephrotic syndrome: Occurrence of proteinuria > 3g/day or urinary-protein-to-creatinine ratio (UPCR) > 3g/g and serum albumin below 30g/l datable through apparition of clinical symptoms such as edema or anterior laboratory exam results.

Low or rapidly declining eGFR*: any decrease in eGFR considered as too fast by the referent nephrologist excluding AKI stage 1 or more but including acute kidney diseases and disorders (2).

Absence of proteinuria: Proteinuria < 0.5 g/day or UPCR > 0.5 g/g

Rapid increase in proteinuria*: any increase in proteinuria or UPCR considered as too fast by the referent nephrologist (excluding any reduction in renin-angiotensin blockade)

Short or unknown duration of diabetes: Diabetes duration considered as too low by the referent nephrologist as regard to the appearance of proteinuria or decline in eGFR. By extension, all patients with a diabetes duration lower than the maximum duration in this group was considered to have a *Short or unknown duration of diabetes.*

Presence of hematuria: >10 erythrocytes/µL or positive dipstick analysis according to the policy of each center without anatomical abnormality.

Absence of diabetic retinopathy: Absence of diabetic retinopathy with a last retinal examination in the past year.

* These atypical features are mainly based on the attending nephrologist since it was not possible to define threshold retrospectively for these features which are not defined by the guidelines or any other alternative source.

Biopsy indications: Disambiguation of atypical feature and biopsy indication appellations

To avoid further confusion between the atypical feature and the indication group defined by short duration of diabetes, hematuria and absence of diabetic retinopathy, the atypical features will be hereafter referred to as diabetes duration under 5 years, presence of hematuria and absence of diabetic retinopathy and the indication groups as *short or unknown duration of diabetes*, *presence of hematuria* and *normal retinal examination*. See supplementary material for a definition of each atypical feature.

Statistical analyses: handling of missing data

For the diabetic retinopathy status, we assumed that the nephrology team did not know the diabetic retinopathy status at the time of KB when it was not mentioned in the biopsy hospitalization report, either because of the absence of retinal examination before the biopsy or because the diabetic retinopathy status was considered irrelevant as regard to the nephrological situation. Therefore, observations for which only the diabetic retinopathy status was missing were considered as complete with an unknown diabetic retinopathy status. The *diabetic retinopathy* variable could take the following value: absence of diabetic retinopathy (=reference), unknown status, presence of non-proliferative diabetic retinopathy, or presence of proliferative diabetic retinopathy. Conversely, observations with any missing data but diabetic retinopathy status were discarded.

Statistical analyses: establishing threshold for continuous variables.

For each of them the threshold was chosen after running several logistic regressions with different values across the range of variables. The threshold with the least residual deviance was chosen for the subsequent logistic regressions (see supplementary table 1).

Statistical analyses: multivariate logistic regression.

Models were developed starting with a full model and removing sequentially the variables with the least deviance and the highest p-values from the model. This new model was tested against the previous one. We retained the last model, which did not show a significant deterioration of the fit of the model compared to the previous one. For multivariate analyses of NDHKD predictors in the sub-population without *other atypical feature*, only two models based on a non-adjusted p-value < 0.05 and similar to the final models from the total population were tested because of the few cases of NDHKD with complete data in this population.

	Residual deviance	Odds ratio	95% CI	p value
HbA1c > 7 %	478.96	0.49	[0.31-0.76]	0.001
HbA1c > 8 %	479.69	0.44	[0.25-0.74]	0.002
HbA1c > 8.5 %	481.47	0.43	[0.23-0.78]	0.005
HbA1c > 7.5 %	482.26	0.53	[0.33-0.85]	0.008
HbA1c > 9.5 %	482.47	0.33	[0.12-0.77]	0.009
HbA1c > 10 %	482.66	0.24	[0.06-0.73]	0.009
HbA1c > 6 %	484.40	0.57	[0.35-0.93]	0.025
HbA1c > 9 %	484.61	0.46	[0.21-0.92]	0.029
HbA1c > 6.5 %	486.48	0.69	[0.45-1.06]	0.088
Age > 65 y.o.	619.35	1.55	[1.07-2.25]	0.022
Age > 70 y.o.	620.39	1.52	[1.02-2.28]	0.039
Age > 60 y.o.	620.52	1.52	[1.01-2.28]	0.042
Age > 55 y.o.	620.90	1.61	[0.99-2.67]	0.053
Age > 50 y.o.	621.44	1.85	[0.94-3.83]	0.074
Age > 75 y.o.	622.28	1.49	[0.90-2.47]	0.124
Duration of diabetes > 5 years	502.17	0.44	[0.28-0.67]	<0.001
Duration of diabetes > 10 years	512.88	0.66	[0.43-1.00]	0.048
Duration of diabetes > 15 years	515.46	0.76	[0.47-1.21]	0.250
$eGFR_{CKD-EPI}$ > 15 ml/min/1.73m²	601.70	0.41	[0.27-0.61]	<0.001
$eGFR_{CKD-EPI}$ > 30 ml/min/1.73m²	607.20	0.48	[0.32-0.71]	<0.001
$eGFR_{CKD-EPI}$ > 45 ml/min/1.73m²	616.97	0.63	[0.39-0.99]	0.045
$eGFR_{CKD-EPI}$ > 90 ml/min/1.73m²	618.46	2.12	[0.84-5.57]	0.111
$eGFR_{CKD-EPI}$ > 75 ml/min/1.73m²	620.02	1.39	[0.72-2.67]	0.323
$eGFR_{CKD-EPI}$ > 60 ml/min/1.73m²	620.45	0.81	[0.46-1.40]	0.458
UPCR > 0.3 g/mmol	537.91	0.37	[0.25-0.56]	<0.001
UPCR > 0.4 g/mmol	544.85	0.42	[0.28-0.65]	<0.001
UPCR > 0.2 g/mmol	546.69	0.46	[0.31-0.69]	<0.001
UPCR > 0.5 g/mmol	550.30	0.48	[0.30-0.74]	0.001
UPCR > 0.6 g/mmol	554.27	0.53	[0.33-0.85]	0.008
UPCR > 0.1 g/mmol	555.27	0.57	[0.36-0.89]	0.015

Supplementary Table 2: Details of other atypical findings

	n (%)	% total population	% other atypical findings
Acute kidney injury	73	15.8%	24.5%
Monoclonal gammopathy	49	10.6%	16.4%
Active infectious disease and-or antibiotic therapy	29	6.3%	9.7%
ANCA	25	5.4%	8.4%
Diagnosed immunological disease with extrarenal manifestation	23	5.0%	7.7%
Extrarenal manifestations without diagnosis	18	3.9%	6.0%
Purpuric rash	17	3.7%	5.7%
Auto-antibodies	15	3.2%	5.0%
Malignancy	14	3.0%	4.7%
Recipient of non-renal solid organ transplant	11	2.4%	3.7%
Nephrotoxic exposure	6	1.3%	2.0%
Proteinuria recorded prior to diabetes onset	6	1.3%	2.0%
Cirrhosis	5	1.1%	1.7%
Other	5	1.1%	1.7%
Familial history	2	0.4%	0.7%

Supplementary Table 3: Histological lesions in patients with DN and/or HN

	Total population	Isolated DN	Isolated HN	DN and HN	p-value
n (%)	276	175 (63.4%)	35 (12.7%)	66 (23.9%)	
Number of glomeruli, median [IQR]	16 [12-20]	15[11-20]	18[14-20]	20[14-25]	**<0.001**
Glomeruli with global GS, median [IQR]	5 [2-8]	5[2-7]	6[2-7]	6.5[2-11]	0.249
Percent of glomeruli with global GS, median [IQR]	29 [17-50]	27[17-47]	32[19-46]	33.5[15-54]	0.947
Glomerular classification					**<0.001**
I	6 (3.2%)	2 (1.5%)	4 (40%)	0 (0%)	
IIa	37 (19.6%)	22 (16.5%)	3 (30%)	12 (26.1%)	
IIb	22 (11.6%)	17 (12.8%)	1 (10%)	4 (8.7%)	
III	75 (39.7%)	61 (45.9%)	1 (10%)	13 (28.3%)	
IV	43 (22.8%)	29 (21.8%)	1 (10%)	13 (28.3%)	
Uncertain	5 (2.6%)	2 (1.5%)	0 (0%)	3 (6.5%)	
IFTA					0.308
0	2 (1.1%)	2 (1.5%)	0 (0%)	0 (0%)	
1	45 (23.8%)	29 (21.8%)	1 (10%)	15 (32.6%)	
2	65 (34.4%)	44 (33.1%)	7 (70%)	14 (30.4%)	
3	76 (40.2%)	57 (42.9%)	2 (20%)	17 (37%)	
Interstitial inflammation					**0.042**
0 (<10% of cortex)	131 (69.3%)	91 (68.4%)	4 (40%)	36 (78.3%)	
1 (10%-25%)	48 (25.4%)	35 (26.3%)	4 (40%)	9 (19.6%)	
2 (26%-50%)	8 (4.2%)	6 (4.5%)	1 (10%)	1 (2.2%)	
3 (severe, >50%)	1 (0.5%)	0 (0%)	1 (10%)	0 (0%)	
Arteriosclerosis					0.056
1	95 (50.3%)	76 (57.1%)	2 (20%)	17 (37%)	
2	84 (44.4%)	49 (36.8%)	8 (80%)	27 (58.7%)	
No artery on the biopsy	2 (1.1%)	1 (0.8%)	0 (0%)	1 (2.2%)	
Arteriolar hyalinosis					0.241
0	11 (5.8%)	5 (3.8%)	0 (0%)	6 (13%)	
1	47 (24.9%)	32 (24.1%)	4 (40%)	11 (23.9%)	
2	130 (68.8%)	95 (71.4%)	6 (60%)	29 (63.0%)	

DN diabetic nephropathy, HN hypertensive nephropathy, IQR interquartile range, GS glomerulosclerosis

Supplementary Table 4: Details of NDHRD diagnoses by biopsy indications

Biopsy indications	Diagnoses
Other atypical feature	Acute interstitial nephritis: 35 (21.9%)
	IgAN: 33 (20.6%)
	ATN: 21 (13.1%)
	AAV: 18 (11.3%)
	FSGS: 8 (5%)
	MGRS: 7 (4.4%)
	Crescentic GN: 6 (3.8%)
	Membranoproliferative glomerulonephritis: 6 (3.8%)
	Acute glomerulonephritis: 5 (3.1%)
	Chronic interstitial nephritis: 4 (2.5%)
	Nephrolithiasis: 3 (1.9%)
	Lupus nephritis: 2 (1.3%)
	MCD: 2 (1.3%)
	Pyelonephritis: 2 (1.3%)
	Thrombotic microangiopathy: 2 (1.3%)
	Alport syndrome: 1 (0.6%)
	Cholesterol embolism: 1 (0.6%)
	CNI toxicity: 1 (0.6%)
	Drug nephrotoxicity: 1 (0.6%)
	Goodpasture: 1 (0.6%)
	Membranous GN: 1 (0.6%)
Recent nephrotic syndrome	MCD: 4 (40.0%)
	Acute interstitial nephritis: 3 (30.0%)
	Membranous nephropathy: 2 (20.0%)
	FSGS: 1 (10.0%)
Low or rapidly decreasing GFR	FSGS: 3 (20.0%)
	Acute interstitial nephritis: 2 (13.3%)
	IgAN: 2 (13.3%)
	Crescentic GN: 2 (13.3%)
	Chronic interstitial nephritis: 2 (13.3%)
	Membranous nephropathy: 1 (6.7%)
	ATN: 1 (6.7%)
	Nephrolithiasis: 1 (6.7%)
	Cholesterol embolism: 1 (6.7%)
Rapid increase of proteinuria	FSGS: 1 (50.0%)
	Crescentic GN: 1 (50.0%)

Supplementary Table 5 Details of NDHKD diagnoses by biopsy indications in the other atypical features group

	Acute kidney injury (n=73)	ANCA (n=25)	Purpuric rash (n=17)	Monoclonal gammopathy (n=49)
Acute interstitial nephritis	21 (28.8%)	1 (4.0%)		2 (4.1%)
IgA nephropathy	7 (9.6%)	1 (4.0%)	16 (94.1%)	
Acute tubular necrosis	16 (21.9%)			2 (4.1%)
ANCA-associated vasculitis	1 (1.4%)	16 (64.0%)		
Focal and segmental glomerulosclerosis	4 (5.5%)			
Monoclonal gammopathy of renal significance				7 (14.3%)
Membranoproliferative glomerulonephritis	2 (2.7%)			
ANCA-negative crescentic glomerulonephritis		2 (8.0%)		
Acute glomerulonephritis	3 (4.1%)		1 (5.9%)	
Chronic interstitial nephritis	1 (1.4%)			
Nephrolithiasis	3 (4.1%)			
Pyelonephritis	1 (1.4%)			
Lupus nephritis				
Thrombotic microangioapthy				
Minimal change disease				1 (2.0%)
Cholesterol embolism	1 (1.4%)			
Other drug nephrotoxicity				
Alport syndrome				
Membranous nephropathy				
Toxicity of calcineurin inhibitors				
Anti-glomerular basement membrane disease				

Supplementary Table 5 (continued): Details of NDHKD diagnoses by biopsy indications in the other atypical features group

	Diagnosed immunological disease with extrarenal manifestation (n=23)	Active infectious disease and-or antibiotic therapy (n=29)	Extrarenal manifestations without diagnosis (n=18)
Acute interstitial nephritis	4 (17.4%)	3 (10.3%)	2 (11.1%)
IgA nephropathy	3 (13.0%)		2 (11.1%)
Acute tubular necrosis			1 (5.6%)
ANCA-associated vasculitis			1 (5.6%)
Focal and segmental glomerulosclerosis		2 (6.9%)	
Monoclonal gammopathy of renal significance			
Membranoproliferative glomerulonephritis		2 (6.9%)	
ANCA-negative crescentic glomerulonephritis	1 (4.3%)		
Acute glomerulonephritis			
Chronic interstitial nephritis			1 (5.6%)
Nephrolithiasis			
Pyelonephritis			
Lupus nephritis	2 (8.7%)		
Thrombotic microangioapthy			1 (5.6%)
Minimal change disease		1 (3.4%)	
Cholesterol embolism			
Other drug nephrotoxicity		1 (3.4%)	
Alport syndrome			
Membranous nephropathy	1 (4.3%)		
Toxicity of calcineurin inhibitors			
Anti-glomerular basement membrane disease			

Supplementary Table 5 (continued): Details of NDHKD diagnoses by biopsy indications in the other atypical features group

	Auto-antibodies (n=15)	Proteinuria recorded prior to diabetes onset (n=6)	Recipient of non-renal solid organ transplant (n=11)
Acute interstitial nephritis			1 (9.1%)
IgA nephropathy	1 (6.7%)	2 (33.3%)	
Acute tubular necrosis	1 (6.7%)		
ANCA-associated vasculitis			
Focal and segmental glomerulosclerosis		2 (33.3%)	
Monoclonal gammopathy of renal significance			
Membranoproliferative glomerulonephritis			1 (9.1%)
ANCA-negative crescentic glomerulonephritis	3 (20.0%)		
Acute glomerulonephritis			1 (9.1%)
Chronic interstitial nephritis			
Nephrolithiasis			
Pyelonephritis			
Lupus nephritis			
Thrombotic microangioapthy			
Minimal change disease			
Cholesterol embolism			
Other drug nephrotoxicity			
Alport syndrome			
Membranous nephropathy			
Toxicity of calcineurin inhibitors			1 (9.1%)
Anti-glomerular basement membrane disease	1 (6.7%)		

Supplementary Table 5 (continued): Details of NDHKD diagnoses by biopsy indications in the other atypical features group

	Nephrotoxic exposure (n=6)	Malignancy (n=14)	Cirrhosis (n=5)	Familial history (n=2)	Other (n=5)
Acute interstitial nephritis	1 (16.7%)				
IgA nephropathy			1 (20.0%)		
Acute tubular necrosis		1 (7.1%)			
ANCA-associated vasculitis					
Focal and segmental glomerulosclerosis					
Monoclonal gammopathy of renal significance					
Membranoproliferative glomerulonephritis		1 (7.1%)			
ANCA-negative crescentic glomerulonephritis					
Acute glomerulonephritis					
Chronic interstitial nephritis	1 (16.7%)			1 (50.0%)	
Nephrolithiasis					
Pyelonephritis	1 (16.7%)				
Lupus nephritis					
Thrombotic microangioapthy			1 (20.0%)		
Minimal change disease					
Cholesterol embolism					
Other drug nephrotoxicity					
Alport syndrome				1 (50.0%)	
Membranous nephropathy					
Toxicity of calcineurin inhibitors					
Anti-glomerular basement membrane disease					

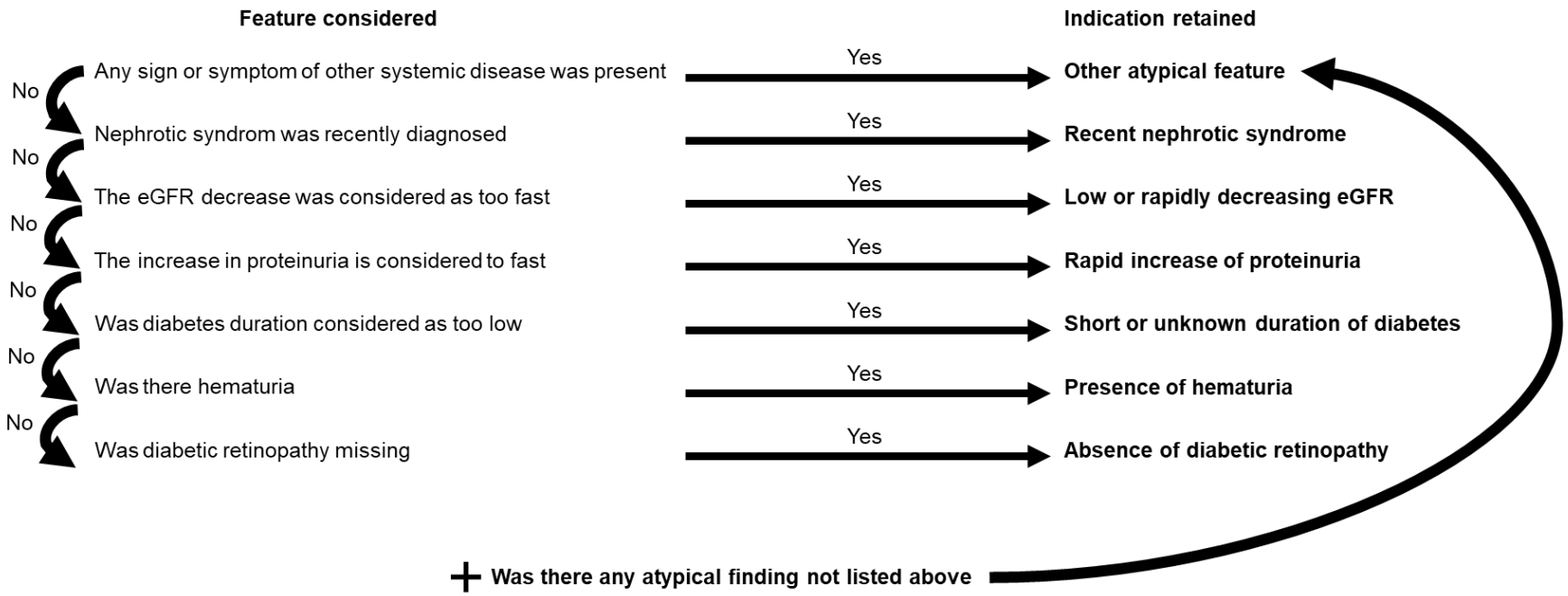
Supplementary Table 6: Comparison of patients with complete observation to the total population

	Total population	With complete observations	pvalue
n (%)	463	287 (62.0%)	
Male gender, n (%)[a]	219 (47.3%)	136 (47.4%)	1.000
Age, median [IQR] (years)[a]	65 [58;72]	65 [57;72]	0.699
Age > 65 yo, n (%)[a]	225 (48.6%)	137 (47.7%)	0.830
High blood pressure, n (%)[b]	400 (87.1%)	261 (90.9%)	0.128
eGFR(CKD-EPI), median [IQR] (ml/min/1.73m^2)[c]	25 [13;43]	25 [15;42.5]	0.672
eGFR(CKD-EPI) > 15 ml/min/1.73m^2, n (%)[c]	320 (69.4%)	210 (73.2%)	0.280
eGFR(CKD-EPI) slope, median [IQR] (ml/min/1.73m^2/month)[d]	-3.45 [-8.75;-1.16]	-3.15 [-7.09;-1.18]	0.371
UPCR, median [IQR] (g/mmol)[e]	0.29 [0.11;0.6]	0.3 [0.13;0.64]	0.430
UPCR > 0.3g/mmol, n (%)[e]	198 (47.6%)	142 (49.5%)	0.642
Hematuria, n (%)[f]	208 (46.8%)	130 (45.3%)	0.697
Diabetic retinopathy status, n (%)[a]			**0.033**
No diabetic retinopathy	234 (50.5%)	161 (56.1%)	
Non-proliferative diabetic retinopathy	63 (13.6%)	47 (16.4%)	
Proliferative diabetic retinopathy	37 (8%)	26 (9.1%)	
Unknown	129 (27.9%)	53 (18.5%)	
HbA1c, median [IQR] (%)[g]	6.9 [6.2;8.1]	7 [6.25;8.2]	0.480
HbA1c > 7% , n (%)[g]	164 (44%)	132 (46%)	0.646
Diabetes duration, median [IQR] (years)[h]	10 [4;16]	10 [4;17]	0.386
Diabetes duration > 5 years, n (%)[h]	251 (64.4%)	196 (68.3%)	0.280
Short or unkown duration of diabetes, n(%)[h]	53 (13.6%)	35 (12.2%)	0.635

Missing data: a=0 (0%) ; b=4 (1%) ; c=2 (0%) ; d=146 (32%) ; e=47 (10%) ; f=19 (4%) ; g=90 (19%) ; h=73 (16%)

Supplementary Table 7 Logistic regression analyses of predictors of NDHKD in the subpopulation without other atypical feature

	Non-adjusted			Model 1			Model 2		
	Odds ratio	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Male gender			0.8						
Yes	0.90	[0.39-2.06]	0.8						
Age > 65 yrs			0.1						
Yes	2.01	[0.88-4.75]	0.104						
High blood pressure			0.159						
Yes	0.38	[0.11-1.51]	0.137						
eGFR(CKD-EPI) > 15 ml/min/1.73m²			0.419			**0.019**			0.055
Yes	0.68	[0.28-1.79]	0.411	0.13	[0.02-0.59]	0.012	0.20	[0.05-0.80]	0.026
UPCR > 0.3g/mmol			0.424			**0.095**			0.116
Yes	0.70	[0.29-1.71]	0.422	0.30	[0.06-1.24]	0.103	0.35	[0.09-1.29]	0.124
Hematuria			**0.007**			**0.177**			0.112
Yes	3.30	[1.39-8.29]	0.008	5.31	[1.30-27.09]	0.028	4.15	[1.21-15.85]	0.028
Diabetic retinopathy			**0.002**			**0.009**			
Non-proliferative diabetic retinopathy	0.72	[0.11-2.94]	0.682	1.70	[0.18-12.27]	0.607			
Proliferative diabetic retinopathy	1.13	[0.16-4.81]	0.882	1.63	[0.07-18.33]	0.708			
Unknown	6.33	[2.38-17.31]	<0.001	14.76	[3.05-93.53]	0.002			
HbA1c > 7%			0.065			**0.013**			**0.011**
Yes	0.40	[0.14-1.06]	0.076	0.16	[0.02-0.88]	0.050	0.22	[0.04-0.87]	0.044
Diabetes duration > 5 years			0.049			**0.196**			0.112
Yes	0.40	[0.16-0.99]	0.049	0.56	[0.10-2.75]	0.470	0.45	[0.11-1.74]	0.249



Supplementary Figure 1: Schematic representation of the process of attribution of an indication to each biopsy.

Supplementary Figure 2: Atypical features compulsory or potentially present in each indication group. Biopsy indications are represented as rows and individual feature as columns. Black shaded cells represent a feature compulsory in the row indication and cannot be found in the following ones. Grey shaded cells represent features which may be present in the row indication.

Atypical feature / Biopsy indications	*Other atypical feature*	*Recent onset of nephrotic syndrome*	*Low or rapidly declining eGFR*	*Absence of proteinuria*	*Rapid increase of proteinuria*	*Short duration of diabetes*	*Presence of hematuria*	*Absence of retinopathy*
Other atypical feature								
Recent onset of nephrotic syndrome								
Low or rapidly declining eGFR								
Absence of proteinuria								
Rapid increase of proteinuria								
Short duration of diabetes								
Hematuria								
Missing diabetic retinopathy								

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