Non-Diabetic Kidney Disease Confirmed by Biopsy in Patients with Diabetes: A Single-Center Registry Report

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Keywords. Diabetes mellitus; Diabetic kidney disease; Kidney biopsies; Histopathology

Introduction. Diabetic kidney disease (DKD) is a major complication of diabetes mellitus (DM), often leading to kidney failure. This study was designed to assess the prevalence and clinicopathological correlations of biopsy-confirmed non-diabetic kidney disease (NDKD) in patients with diabetes.

Method. A retrospective analysis was conducted by including 547 diabetic patients who underwent kidney biopsies. Data on demographics, laboratory results (including serum creatinine and urine protein levels), clinical symptoms, medical history, and histopathological diagnoses were collected.

Result. Among the patients, 261 (47.7%) were diagnosed with DKD, while 286 (52.3%) had NDKD. The most prevalent histopathological finding in NDKD was membranous glomerulonephritis (13.9%), followed by focal and segmental glomerulosclerosis (9.7%) and IgA nephropathy (5.7%). Key predictors for DKD included longer duration of diabetes mellitus (odds ratio [OR]: 1.12), elevated HbA1c levels (OR: 1.26), and the presence of retinopathy at the time of biopsy (OR: 7.97), all with $P < .05$. No significant differences were observed in the frequency of hematuria between the DKD and NDKD groups.

Conclusion. Membranous glomerulonephritis was the most common diagnosis among NDKD patients. The findings suggest a strong correlation between the duration of diabetes mellitus, the presence of retinopathy, and HbA1c levels with DKD development, indicating a need for revised criteria for kidney biopsy decisions in diabetic individuals to enhance diagnostic accuracy and treatment strategies.

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INTRODUCTION

Diabetes mellitus (DM) has become a global epidemic, affecting close to half a billion individuals worldwide. This number is expected to increase by 25% by 2030 and by 51% by 2045.[1,2]

Diabetic kidney disease (DKD) is characterized by increased urine albumin excretion, a decreased glomerular filtration rate (GFR), or both. It is a major complication affecting 20% to 40% of individuals with DM.[1,2] Economic and governmental policies may be behind the racial/ethnic difference in DKD epidemiology.[3]

Non-diabetic kidney disease (NDKD) can also occur in patients with DM either independently or alongside DKD, with reported prevalence rates varying widely from about 3% to 83% across different studies. Accurately diagnosing these patients is essential for forecasting the progression

of their disease and determining the most suitable treatment strategies.[3,4]

The timing and indications for kidney biopsy in diabetic patients are often based on expert opinion or policies of individual centers, and not according to a universal consensus. Kidney biopsy is typically conducted in diabetic patients exhibiting a rapid decline in estimated GFR (eGFR) greater than 5 cc/min/1.73m^2 per year, a sudden onset of marked proteinuria in patients with a relatively short duration of diabetes mellitus, or a 5 to 10 fold increase in albuminuria over less than 1-2 years. Additionally, biopsy may be warranted if there is hematuria and no diabetic retinopathy.[3,4]

The frequency of histological subtypes of NDKD, as reported in biopsy specimens, has been found to exhibit considerable heterogeneity, depending on the study region. However, meta-analyses have identified membranous glomerulonephritis, IgA nephropathy, and focal and segmental glomerulosclerosis as the most common types of histopathologic diagnosis.[3,4]

This study was conducted to determine the frequency of diabetic kidney disease (DKD) and non-diabetic kidney disease (NDKD), as well as their various subtypes, among diabetic patients who underwent renal biopsy at Hasheminejad Kidney Center (HKC), as the largest referral nephrology center in Iran. Additionally, we aimed to define the clinicopathologic correlation and the risk factors of NDKD in diabetic patients to assist clinicians in deciding whether to perform a kidney biopsy on those with signs of kidney involvement.

MATERIALS AND METHOD

This retrospective observational study included 547 individuals with diabetes mellitus from a total of 6548 patients who underwent kidney biopsy at Hasheminejad Kidney Center (HKC), Tehran, Iran, between 1998 and 2023. Patients with increased creatinine levels due to urinary tract infections or obstructions were not considered for biopsy.

Demographic, laboratory data including serum creatinine level (SCr), the amount of 24-hour urine protein, hematuria, hemoglobin A1c (HbA1c), erythrocyte sediment rate (ESR), serum albumin, hemoglobin, antinuclear antibody (ANA), anti-double stranded DNA antibody (anti ds-DNA antibody) and antineutrophilic cytoplasmic antibody (ANCA), duration of the diagnosis of diabetes mellitus, existence of retinopathy or underlying hypertension, and histopathological diagnosis were extracted from the kidney biopsy registry of HKC. eGFR was calculated with the CKD-EPI formula.

Patients diagnosed histopathologically with DKD and those with NDKD were compared based on their clinical and laboratory characteristics. We also categorized pure acute tubulointerstitial nephritis (ATIN) and mixed DKD/NDKD in the NDKD subgroup, and ATIN coexisting with DKD in the DKD group.

The Mann-Whitney U test and Student's t-test were applied to analyze skewed and normally distributed data, respectively. Categorical variables were compared using the chi-square test. Univariate logistic regression analysis was employed to identify independent predictors of DKD, with outcomes expressed as odds ratios (OR) accompanied by 95% confidence intervals (CI). Receiver operating characteristic (ROC) curve analysis was conducted to establish optimal cut-off values for HbA1c levels and duration of DM in predicting DKD presence. A *P*-value less than 0.05 was regarded as statistically significant.

RESULTS

Our study was conducted on 547 patients with a diagnosis of DM at the time of kidney biopsy, of whom 53.6% were male and 46.4% female. The mean age was 54.2 ± 13.3 years, and the mean baseline 24-hour proteinuria and SCr were 4652 ± 4179 mg/24h and 3.89 ± 3.06 mg/dL, respectively.

In pathologic examination, DKD was detected in 261 (47.7%) patients and NDKD (pure or in combination with DKD) in 286 (52.3%) (Figure 1). There was no statistically significant difference between the DKD and NDKD groups in terms of sex and age (Table 1).

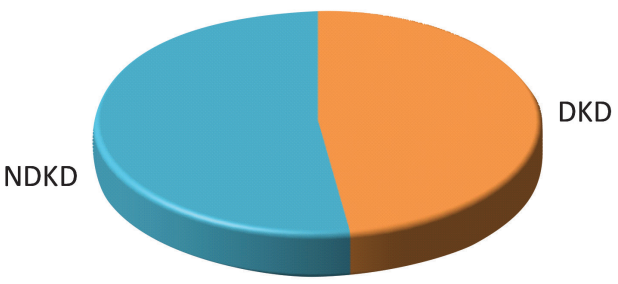

Figure 1. Distribution of Histopathological Diagnosis in Diabetic Patients who underwent a Kidney Biopsy (1998-2023).
DKD: Diabetic Kidney Disease, NDKD: Non- Diabetic Kidney Disease

Table 1. Demographic, Laboratory, and Clinical Features in DKD and NDKD Groups

	Total	DKD[1]	Non-DKD	*P*
Patient Number (%)	547 (100)	261 (47.7)	286 (52.3)	
Sex (male %)	53.6	55.9	51.4	.28
Mean Age (years) *	54.2 ± 13.3	54.11 ± 13.6	54.4 ± 13	.77
Duration of Diabetes Mellitus (years) **	7 (3- 12)	10 (5- 15)	5.5 (2- 10)	< .001
Frequency of Hypertension[2] (%)	387 (70.7)	205 (78.5)	178 (62.2)	< .001
Mean Scr[3] Level at Admission (mg/dL) *	3.89 ± 3.06	4.45 ± 3.04	3.37 ± 2.99	< .001
Mean GFR[4] at Admission (mL/min)	32.9 ± 29	24.6 ± 22.2	40.4 ± 32.3	< .001
Mean Amount of Proteinuria (mg/24h) *	4652 ± 4179	4810 ± 4192	4511 ± 4170	.428
Frequency of Nephrotic Range Proteinuria[5] (%)	275 (54.9)	139 (57)	136 (52.9)	.334
Frequency of Nephritic Syndrome[6] (%)	26 (4.8)	6 (2.3)	20 (7)	.01
Scr > 1.4 at Admission (mg/dL) (%)	429 (78.9)	229 (88.1)	200 (70.4)	< .001
Frequency of Hematuria[7] (%)	77 (53.5)	139 (57.2)	138 (50.2)	.11
Frequency of Retinopathy (%)	103 (52.8)	76 (29.1)	27 (9.4)	< .001
Mean ESR Level (mm/hr) [8]*	60.7 ± 34.3	64.5 ± 32.7	57.2 ± 35.4	.03
Mean Albumin Level* (g/dL)	3.17 ± 0.67	3.23 ± 0.61	3.12 ± 0.72	.121
Mean HbA1c Level (%) *	7.11 ± 1.49	7.41 ± 1.55	6.89 ± 1.42	.034
Mean Hemoglobin Level (g/dL) **	10.4 (3.1)	9.7 (2.3)	11.5 (3.1)	< .001
Frequency of Positive Rheumatologic Tests[9] (%)	40 (7.3)	12 (4.6)	28 (9.8)	.02
Frequency of Low Complement level (%) (C3, C4 or CH50)	45 (8.4)	25 (9.6)	20 (7)	.272

*Mean ± Standard Deviation ** Median (Inter Quartile Range). 1. Diabetic kidney disease, 2. Blood pressure ≥ 140/90 mmHg, 3. Serum Creatinine, 4. Glomerular filtration rate according to the CKD-EPI formula, 5. Proteinuria ≥ 3500 mg/24h, 6. Presence of Hematuria, hypertension, and creatinine rise from baseline, 7. Red blood cell ≥ 3/ HPF in urine sediment, 8. Erythrocyte sediment rate, 9. Positive antinuclear antibody or anti-ds-DNA antibody, or antineutrophilic cytoplasmic antibody.

Membranous glomerulonephritis (13.9%) was the most common histopathologic diagnosis of NDKD, followed by focal and segmental glomerulosclerosis (9.7%), IgA nephropathy (5.7%), tubulointerstitial nephritis (6.6%), and others (31.4%). (Figure 2).

Overall, 383 (78.5%) patients had a diagnosis of hypertension at the time of kidney biopsy, including 205 (78.5%) patients in DKD and 178 (62.2%) in NDKD groups ($P < .001$). At the time of biopsy, in patients with DKD and NDKD, the mean SCr level was 4.45 ± 3.04 mg/dL and 3.37 ± 2.99 mg/dL, ($P < .001$), and the mean 24-hour proteinuria was 4810 ± 4192 mg/24h and 4511 ± 4170 mg/24h, respectively ($P = .428$) (Table 1).

The median (interquartile range [IQR]) duration of DM in the DKD group was 10 years [5- 15], which was significantly longer than that in the patients with NDKD, which was 5 years [2- 10] ($P < .001$). In the DKD group, 36 patients (13.7%) had no previous history of DM, and six patients (2.2%) had SCr levels above 1.4 mg/dL without proteinuria. Also, the history of diabetic retinopathy was more common in DKD compared to NDKD patients, i.e., in 76 (29.1%) and 27 (9.4%) patients, respectively ($P < .001$) (Table 1).

As shown in Table 1, the mean amount of 24-hour proteinuria and serum albumin level were similar in both groups. There was no significant difference in the frequency of hematuria between the two groups (P 0.11). The mean hemoglobin level was lower, whereas the mean ESR was higher in DKD compared to the NDKD patients. Nephritic syndrome (the presence of hematuria, hypertension, and elevated creatinine) was less frequent in the DKD group. Positive rheumatologic tests, including ANA, anti-ds-DNA antibody, and ANCA, were more common in the NDKD group, with a frequency of 7%.

As detailed in Table 2, the factors predicting the presence of DKD in histology included a longer duration of diabetes mellitus (OR: 1.12, 95% confidence interval (CI): 1.07–1.16, $P < .001$), high level of HbA1c (OR 1.26, 95% CI: 1.013–1.57, $P = .038$) and the presence of retinopathy at the time of kidney biopsy (OR 7.97, 95% CI: 4.2–15.1, $P < .001$). The duration of diabetes mellitus of more than 9.5 years and HbA1c of more than 7.35 were predictors of DKD in our study. However, because of the low area under the curves (AUC) of both variables (0.69 and 0.6, respectively, i.e., below 0.7), their cut-off points were not considered significant.

We identified a significant annual increase in kidney biopsy frequency among diabetic patients

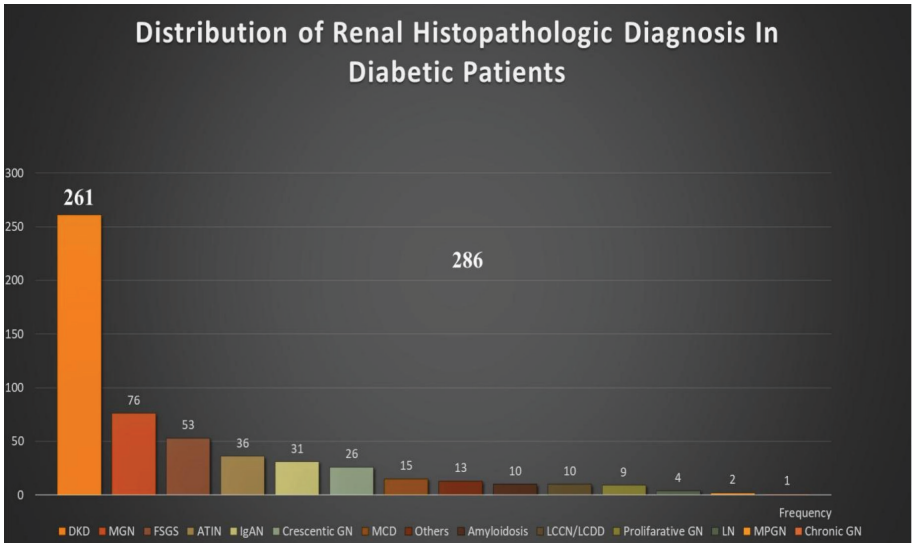

Figure 2. Distribution of renal histopathologic diagnosis in diabetic patients.
DKD: Diabetic kidney disease, MGN: Membranous Glomerulonephritis, FSGS: Focal Segmental Glomerulosclerosis, IgAN: Immunoglobulin-A Nephropathy, ATIN: Tubulointerstitial nephritis without diabetic kidney disease, GN: Glomerulonephritis, MPGN: Membranoproliferative Glomerulonephritis, MCD: Minimal Change disease, LCDD: Light chain deposition disease, LCCN: light chain cast nephropathy, LN: Lupus nephritis.

Table 2. Predictive factors for DKD (Regression analysis)

Factor	OR*	95% CI**	*P*
Duration of diabetes (years)	1.12	1.07 - 1.16	< .001
Presence of Retinopathy	7.97	4.2 - 15.1	< .001
HbA1c (%)	1.26	1.013 - 1.57	.038

*Odds Ratio, ** Confidence Interval

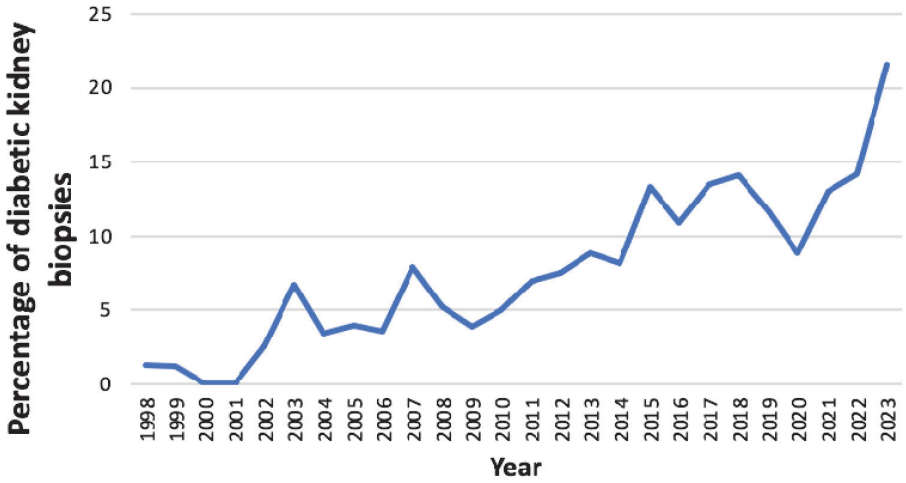

Figure 3. Temporal Trend of the Percentage of Diabetic Patients among Patients who Underwent Kidney Biopsy from 1998 to 2023.

over the 24 years of study in the HKC since 1998, as shown in Figure 3.

DISCUSSION

In this study, we present 547 diabetic patients who underwent a kidney biopsy between 1998 and 2023 in HKC. The prevalence of DKD and NDKD was 47.7% and 52.3 %, respectively.

In diabetic patients presenting with atypical symptoms of DKD, including the absence of diabetic retinopathy, a shorter duration of diabetes mellitus, microscopic hematuria, a sudden increase

in proteinuria, and a lower HbA1c, kidney biopsy is a fundamental approach for differentiating between DN, NDKD, and mixed DN/NDKD.[4]

Due to the importance of NDKD in modifying the therapeutic approach of diabetic patients, some studies have classified pure NDKD and mixed DKD/NDKD as a single NDKD group.[5,6] This approach aligns with our methodology.

The prevalence of NDKD tends to differ according to the biopsy selection criteria employed in different institutions. Diabetic patients with non-nephrotic-range proteinuria are not routinely biopsied, and patient selection for kidney biopsy strongly depends on expert opinion or policy of the centers.[3]

In a study by Sharma, which included 620 diabetic patients from the United States, the prevalence of DKD, NDKD, and mixed DKD/NDKD was 37%, 36% and 27%, respectively.[7] In a meta-analysis conducted by Tong-X *et al.* in 2020, among 5,304 patients, the prevalence of DKD, NDKD, and mixed DKD/NDKD was found to be 18.1%, 40.6% and 41.2%, respectively.[4]

In a meta-analysis of 48 studies including 4,876 participants, the prevalence of NDKD ranged from 3% to 82.9% in different centers.[3]

The NDKD prevalence of 52% in our center may reflect both the local epidemiology and the policy for biopsy of azotemic or proteinuric diabetic patients. In our study, MGN was the most frequent histopathological diagnosis (13.9%), followed by FSGS (9.7%), ATIN (6.6%), and IgAN (5.7%). In our study, cases of FSGS occurring in the context of diabetic nephropathy, referred to as secondary FSGS, were categorized as DKD.

In a review of 40 studies in 2020, MGN (24.1%) was reported as the most common NDKD in Asia, Africa, and Europe, with a prevalence of 24.1%, 15.1% and 22.6%, respectively. These findings were also confirmed in three Chinese studies.[8-10]

Another review of 48 studies by Fiorentino revealed that MGN was the most common diagnosis in nine studies, particularly those from Korea, Japan, and the United Kingdom, with larger populations.[11-13] Overall, the review by Fiorentino identified IgAN as the most prevalent NDKD, which was predominantly observed in Asia (21.3%), Europe (8.2%), and America (9.4%).[3]

Moreover, IgAN was identified as the most prevalent NDKD in 16 studies, with larger study populations varying from 109 to 220 patients originating from China, Japan, and the Czech Republic.[14-17]

In two studies conducted on 567 and 232 patients, FSGS was identified as the most prevalent NDKD in Austria and America.[18,19]

In our study, univariate logistic analyses demonstrated that a shorter duration of diabetes mellitus, the presence of nephritic syndrome, a lower HbA1c level, positive rheumatologic tests, and the absence of DR were associated with an increased probability of NDKD. On the other hand, the prevalence of hypertension was found to be lower in the NDKD group. There was no significant difference between the two groups in terms of the amount of proteinuria, the presence of hematuria, or serum albumin level.

The majority of studies have demonstrated that the presence of diabetic retinopathy and a duration of DM, exceeding 5-10 years, were associated with an increased risk of developing DKD.[3,4,20-24] In the meta-analysis conducted by Liang *et al.*, 23.6% of DKD patients did not have diabetic retinopathy, which is comparable to the rate of 24% observed in our study.[25] This suggests that the absence of retinopathy may predict NDKD, but does not exclude DKD. This was also compatible with a study by Dong, which included 248 patients with type 2 diabetes mellitus (T2DM) who underwent kidney biopsy. The absence of retinopathy had the highest diagnostic efficiency, with a sensitivity of 92.11% and a specificity of 82.29% and was the independent risk factor for the development of NDKD (OR, 44.696, 95% CI [15.91-125.566]), $P < .01$. Also, the history of DM more than 5 years with OR of 4.63 (95% CI, 1.721-12.486, $P < .01$) was an independent risk factor for the development of NDKD.[26]

In another meta-analysis, a longer duration of diabetes mellitus, a higher HbA1c level, the presence of diabetic retinopathy, nephrotic range proteinuria, and a higher systolic blood pressure level were found to be associated with DKD.[3]

Retinopathy was the most effective predictor for DKD in the study by Wang, included 422 patients with T2DM (with AUC of 0.852, sensitivity of 78.9% and specificity of 91.5%), also the combination of four predictors including duration of diabetes mellitus, retinopathy, systolic blood pressure and serum albumin, demonstrated an AUC of 0.938, with 88.1% sensitivity and 87.2% specificity for

DKD. Multivariate logistic regression analysis identified retinopathy as the most important factor for DKD (OR 60.359; $P < .001$).[27]

Another study found that the absence of retinopathy and the presence of hematuria or proteinuria less than two grams per day were the most sensitive indicators of NDKD.[28] In a study from Japan, the absence of retinopathy and a diabetes mellitus duration of less than five years were identified as the most accurate predictors of NDKD, with a sensitivity and specificity of over 70%. Conversely, the presence of hematuria (defined as ≥5 RBCs per high-powered field) was identified as a less reliable predicator, with a sensitivity of 56% and a specificity of 58%.[29] Additionally, a meta-analysis revealed that dysmorphic red blood cells (RBCs) in urine had high specificity for predicting NDKD, while the presence of hematuria alone (without distinction of dysmorphic RBC) was not enough to distinguish between DKA and NDKD.[30] Hematuria is not an unusual finding in patients with DKD, with reported frequencies of 35% and 78% in some studies and 57% in our study.[31] It can therefore be assumed that dysmorphic RBCs and RBC casts are a more accurate predictor of the necessity for a kidney biopsy.

In a review of 17 studies, the short duration of diabetes mellitus was identified as a predictor of NDKD. Additionally, low HbA1c levels and sub-nephrotic proteinuria were observed to be predictors of NDKD. Furthermore, nephrotic range proteinuria was associated with DKD.[4]

In our study, patients with NDKD had lower serum creatinine (SCr) and higher hemoglobin compared to those with DKD. Erythrocyte sedimentation rate was slightly higher in the DKD group, with an OR of 1.006, which does not appear to be clinically significant. In the study by Chong, ESR was also not significantly related to DKD.[24]

The diagnosis of acute kidney injury (AKI) is not always straightforward in patients who lack data on their previous SCr levels. Management of diabetic patients with AKI should be the same as the general population.[3] Indeed, in our study population, ATIN is reported concurrently in the majority of histopathologic DKD samples, with varying degrees of clinical significance. Consequently, in some patients, corticosteroids had been administered, which yielded a notable therapeutic response. Therefore, kidney biopsy proved an effective means for restoring kidney function in these patients with a diagnosis of DKD.

Limitations of the study

Some of our data, including history of using nephrotoxic drugs, underlying malignancy or rheumatological diseases, systemic infections, and hepatitis B surface antigen positivity, could not be evaluated because of the small number of cases. Additionally, dysmorphic red blood cells have not been checked in urine sediments consistently.

Given the small number of patients exhibiting all three factors of diabetic retinopathy, HbA1c, and duration of diabetes mellitus, a multi-variable logistic regression assessment was not feasible.

Vascular changes had been reported alongside the primary histopathologic features in many cases; however, in our registry, only the primary pathologic diagnosis of the patients had been recorded.

CONCLUSION

The present study was conducted on 547 diabetic patients who underwent kidney biopsy, representing one of the largest studies in this field to date. Given that the study was conducted in a referral nephrology center, it is reasonable to generalize the results to the Iranian population.

MGN was identified as the most prevalent form of NDKD in diabetic patients in the present study. A brief duration of diabetes mellitus, the absence of retinopathy, and lower HbA1c levels were more prevalent in NDKD diabetic patients, thereby justifying the performance of a kidney biopsy in these patients.

Despite the current indications for kidney biopsy in diabetic patients and the introduction of some predictive characteristics for DKD and NDKD, these cannot definitively determine the need for biopsy.

As a result, new criteria for deciding whether to do a kidney biopsy on individuals suffering from diabetes mellitus are required.

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ETHICAL CONSIDERATIONS

This research was based on data from the "registry of kidney biopsies and glomerulonephritis" that

was approved by the Ethics Committee of Iran University of Medical Sciences (Ethical code No IR.IUMS.REC.1401.456). Before any intervention, all participants provided written informed consent. The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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