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Is There a Role for IgA/C3 Ratio in IgA Nephropathy Prognosis? An Outcome Analysis on An European Population

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Keywords. IgA/C3 ratio, IgA nephropathy, renal survival, MESTC classification, prognostic factors

Original Paper

Introduction. Serum immunoglobulin A (IgA)/C3 ratio has been reported as a predictor of histological lesions and prognosis in asian patients with IgA nephropathy (IgAN). Since its validity in other populations is unclear, we aimed to evaluate the relationship between IgA/C3 ratio and renal outcome in Caucasian European patients with biopsy-proven IgAN.

Methods. We conducted a retrospective, observational study on 95 patients with primary IgAN patients diagnosed between 2010 to 2017 (70% male, age 41 (34 to 49) years, eGFR 39.4 (25.2 to 56.5) mL/min, proteinuria 1.7 (0.8 to 3.0) g/g). The primary study composite end-point was doubling of serum creatinine, ESRD (dialysis or renal transplant) or death, whichever came first.

Results. Median follow-up was 30 (95% CI: 27.5 to 32.4) months; 11% developed ESRD, 10% experienced serum creatinine doubling, and 1% died. The endpoint was reached by 21% of the patients. They had lower eGFR, higher proteinuria and hematuria, and lower serum albumin. The distribution in Oxford classes was alike. The AUROC for IgA/C3 ratio was 0.60 (95% CI: 0.45 to 0.74) and generated an optimal cut-off of 2.91 (sensitivity 68%, specificity 55%). The mean event-free survival of the whole cohort was 5.2 (95% CI: 4.7 to 5.8) years. Patients with IgA/C3 ratio < 2.9 had a tendency to better renal survival ($P > .05$). In Cox proportional hazard ratio model, the independent predictors of a poorer event-free survival were higher serum creatinine, higher proteinuria and increased IgA/C3 ratio, while renin angiotensin system inhibitors predicted better outcome.

Conclusion. Our study reports evidence that supports IgA/C3 ratio as a reasonable predictor of IgAN prognosis in European patients.

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INTRODUCTION

IgA nephropathy (IgAN) has a variably reported risk of decline in kidney function, with a 10-year risk of end stage renal disease (ESRD) ranging between 5 and 60%.[1,2] Variability regarding the clinical course of patients with IgAN may be related to multiple factors, including differences in clinical patterns, care practices inconsistency and geographic prevalence.[3,4] Thus, identification of novel risk factors for IgAN progression at the time of diagnosis remains a central issue. In previous studies patients with increased serum immunoglobulin A/complement C3 (IgA/C3) ratios were more likely to be diagnosed with IgAN.[5-7] Thereafter, few authors aimed to evaluate whether the IgA/C3 ratio can serve as a prognosis marker.[8-10] However, these

studies were performed in Asian patients and had conflicting results. Thus, replication in other ethnic groups is needed to evaluate the validity of IgA/C3 in IgAN prognosis. Therefore, we aimed to evaluate the relationship between IgA/C3 ratio and renal outcome in Caucasian European patients with biopsy-proven IgAN.

MATERIALS AND METHODS

Patient Selection

We conducted a retrospective, observational study on all patients with histologically proved primary IgAN from January 2010 to December 2017 (n = 215) at "Dr. Carol Davila" Teaching Hospital of Nephrology, Bucharest, Romania. Those with ages under 18 (n = 3), those whose kidney biopsy specimen contained less than 8 glomeruli (n = 4), with secondary cause of IgAN (n = 42), with insufficient clinical data (n = 62) or with less than 12 months follow-up at 06/01/2018 (n = 9) were excluded from the analysis, leaving a final population of 95 patients. The diagnosis of IgAN was based on optical microscopy, immunofluorescence (dominant IgA in the mesangium) and electron-microscopy (para-mesangial electron-dense deposits). All renal specimens were assessed according to the 2016 revised Oxford Classification by two independent pathologists.[11]

Clinical and Histological Parameters

The clinical variables acquired from the patient's medical records at the time of kidney biopsy were age, gender, Charlson comorbidity index,[12] obesity (defined as a body mass index over 30 kg/m^2), diabetes mellitus and arterial hypertension (defined as blood pressure over 140/90 mmHg or use of antihypertensive agents), therapy with renin-angiotensin-aldosterone system inhibitors (RASI) and immunosuppressive medication (IS).

Laboratory data included serum creatinine, estimated glomerular filtration rate (eGFR, calculated by CKD-EPI equation), serum albumin, proteinuria (g/g creatinine), haematuria (cells/mmc), IgA/C3 ratio, serum cholesterol, triglycerides and uric acid.

IgA and C3 levels were measured immediately after blood sample collection using a turbidimetric immunoassay with reagents adjusted according to the IFCC/CRM 470. The serum IgA/C3 ratio was calculated from individual serum IgA and C3 values.

Study End-points

The primary study composite end-point was defined as doubling of serum creatinine, ESRD (dialysis or renal transplant) or death, whichever came first.

Statistical Analysis

Continuous variables were expressed either as mean or median and 95% confidence interval (95% CI) and categorical variables as percentages. Differences between groups were assessed in case of continuous variables by student *t* test or by Mann-Whitney test, according to their distribution, and in case of categorical variables by Pearson χ^2 test.

The probability of event-free survival was assessed by Kaplan-Meyer method and the log-rank test was used for comparisons. Univariate and multivariate (Cox proportional hazard ratio) analyses were performed to identify independent predictors of the end-point. The results of Cox analyses are expressed as a hazard ratio (HR) and 95% CI.

Due to the lack of standardized cut-off point for serum IgA/C3 ratio, receiver operating curve (ROC) was drawn to examine the performance and determine the optimal cutoff for predicting an endpoint event. Optimal cut-off values were chosen according to a balance of sensitivity and specificity. In all analyses, *P* values are two-tailed and all *P* values less than .05 were considered statistically significant. Statistical analyses were performed using the SPSS program (SPSS version 20, Chicago, IL).

Ethics

The study was conducted with the provisions of the Declaration of Helsinki and the protocol was approved by the local ethics committee.

RESULTS

Study Population

The study population included 95 patients (70% male). At the time IgAN diagnosis, their age was 41 (34 to 49) years, eGFR was 39.4 (25.2 to 56.5) mL/min/ 1.73m^2, proteinuria was 1.7 (0.8 to 3.0) g/g and most of patients had arterial hypertension (85%). The median comorbidity index evaluated with Charlson score was 2.0 (0 to 3) (Table 1). On histopathologic assessment, mesangial hypercellularity was present in 80% of patients,

Table 1. Baseline Characteristics of the Whole Population and Composite Endpoint Groups Comparison

Variables	All (n = 95)	Composite Endpoint		*P*
		Yes (n = 19)	No (n = 76)	
Age, y	41 (34 to 49)	40 (33 to 47)	41 (34 to 49)	> .05
Male Gender, %	70	84	66	> .05
Charlson Comorbidity Index	2 (0 to 3)	2 (2 to 3)	2 (0.0 to 2.5)	> .05
Obesity, %	37	32	38	> .05
Diabetes mellitus, %	8	11	7	> .05
Hypertension, %	85	95	83	> .05
Serum Creatinine, mg/dL	1.8 (1.3 to 2.6)	5.3 (1.5 to 7.1)	1.8 (1.3 to 2.4)	< .05
eGFR, mL/min/ 1.73m^2	39.4 (25.2 to 56.5)	11.9 (8.3 to 54.5)	40.4 (29.1 to 58.2)	< .05
Proteinuria, g/g Creatinine	1.7 (0.8 to 3.0)	2.7 (1.0 to 4.7)	1.5 (0.8 to 2.5)	< .05
Haematuria, cells/mm^3	185 (39 to 240)	230 (120 to 365)	150 (30 to 230)	< .05
Cholesterol, mg/dL	215 (177 to 259)	198 (174 to 238)	220 (182 to 259)	> .05
Triglycerides, mg/dL	150.5 (106 to 248)	146 (89 to 270)	155 (108 to 242)	> .05
Serum albumin, g/dL	4.1 (3.7 to 4.4)	3.7 (3.1 to 4.3)	4.2 (3.8 to 4.4)	< .05
Uric acid, mg/dL	7.2 (5.9 to 8.5)	7.2 (6.0 to 8.7)	7.1 (5.7 to 8.4)	> .05
IgA/C3 Ratio	2.9 (2.1 to 3.6)	3.3 (2.5 to 3.8)	2.7 (2.0 to 3.6)	> .05
Renal Biopsy				
M1, %	80	76	81	> .05
E1, %	23	32	21	> .05
S1, %	52	42	55	> .05
T1/2, %	22 / 5	21 / 11	22 / 4	> .05
C1/2, %	16 / 10	16 / 21	16 / 7	> .05
MESTC Score	2 (1 to 3)	2 (1 to 3)	2 (1 to 3)	> .05
Treatment, %				
Immunosuppression Therapy	57	63	55	> .05
RASI	66	33	74	< .05

eGFR, estimated glomerular filtration rate; sCr, serum creatinine; IgAN, IgA nephropathy; M1, mesangial hypercellularity; E1, endocapillary hypercellularity; S1, segmental glomerulosclerosis; T1/2, tubular atrophy and interstitial fibrosis > 25%; C1/2, crescents in at least one glomerulus; ESRD, end-stage renal disease

endocapillary hypercellularity in 23%, segmental glomerulosclerosis in 52%, tubular atrophy and interstitial fibrosis > 25% (T1 + T2) in 27 and 26% showed crescents in at least one glomerulus. The median MESTC score was 2.0 (1 to 3) (Table 1).

Approximately two thirds of the studied patients received RASI, while more than half had received some form of immunosuppressive treatment during the observation period (24% only steroids, 68% steroids and cyclophosphamide, and 8% steroids and other immunosuppressors) (Table 1). The median follow-up time was 30 (95% CI: 27.5 to 32.4) months. Of the entire cohort, 11% developed ESRD, 10% experienced serum creatinine doubling and 1% died.

Composite Endpoint Group Comparison

Twenty one percent of the studied patients (n = 19) reached the composite endpoint. They had lower eGFR, higher proteinuria and hematuria, and lower serum albumin. The distribution in MESTC

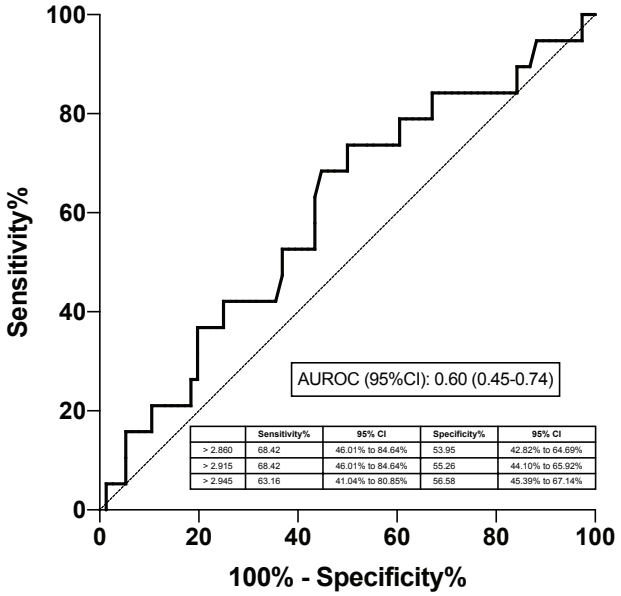

Figure 1. Sensitivity and Specificity of IgA/C3 Ratio to Identify Correctly the Composite Endpoint (Doubling of Serum Creatinine, ESRD (Dialysis or Renal Transplant) or Death, Whichever Came First)

classes was similar in both groups.

Patients who did not reach the composite endpoint were more often treated with RASI, but there were no differences regarding the usage of immunosuppressive therapy (Table 1).

Because there is no standardized cut off for the IgA/C3 ratio, we performed receiver operating curve (ROC) analysis in order to dermine the optimal value. The area under the receiver operating characteristic curve (AUROC) for IgA/C3 ratio was 0.6 (95% CI: 0.45 to 0.74). The optimal cut-off for IgA/C3 ratio generated from the AUROC was 2.91, with a sensitivity and a specificity of 68% and 55%, respectively. Therefore, a serum IgA/C3 ratio above 2.91 was considered a risk factor IgAN progression in the present study (Figure 1).

Comparison Between High and Low IgA/C3 Ratio Groups

Fifty-one percent of the patients had IgA/C3 higher than 2.9. There were no differences at the time of IgAN diagnosis between the two groups regarding the known risk factors for progression: age, hypertension, eGFR, proteinuria, hematuria, Oxford classification, or treatment. However, patients with IgA/C3 ratio higher than 2.9 reached the composite endpoint more often (Table 2). We found no differences when analyzing the IgA/C3 ratio across the MESTC classes. However, patients with class T1/2 had a trend to higher IgA/C3 ratio as compared to T0 (Figure 2).

Renal Survival Analysis

The mean event-free survival of the whole

Table 2. Baseline Characteristics and Outcome of IgAN Patients with IgA/C3 < 2.9 Group and IgA/C3 ≥ 2.9 Group

Variables	IgA/C3 < 2.9 (n = 47)	IgA/C3 ≥ 2.9 (n = 48)	*P*
Age, y	42 (34 to 54)	40.5 (34.0 to 45.5)	> .05
Male Gender, %	68	71	> .05
Charlson Comorbidity Index	2 (0 to 3)	2.0 (1.5 to 2.0)	> .05
Obesity, %	38	35	> .05
Diabetes Mellitus, %	7	9	> .05
Hypertension, %	81	90	> .05
Serum Creatinine, mg/dL	1.7 (1.2 to 2.7)	1.9 (1.5 to 2.6)	> .05
eGFR, mL/min/ 1.73m^2	42.2 (27.3 to 62.3)	35.8 (24.5 to 49.9)	> .05
Proteinuria, g/g Creatinine	2.0 (0.8 to 3.5)	1.5 (0.8 to 2.5)	> .05
Haematuria, cells/mm^3	190 (50 to 270)	165 (29 to 230)	> .05
Cholesterol, mg/dL	219 (192 to 262)	207.0 (174.0 to 246.5)	> .05
Triglycerides, mg/dL	150.5 (103 to 216)	154.0 (109.0 to 263.5)	> .05
Serum Albumin, g/dL	4.0 (3.7 to 4.5)	4.1 (3.8 to 4.4)	> .05
Uric Acid, mg/dL	6.6 (5.4 to 7.8)	7.6 (6.5 to 8.5)	< .05
Renal biopsy			
M1 (%)	81	79	> .05
E1 (%)	23	23	> .05
S1 (%)	51	54	> .05
T1/2 (%)	13 / 4	31 / 6	> .05
C1/2 (%)	17 / 15	15 / 4	> .05
MESTC score	2 (1 to 3)	2.5 (2.0 to 3.0)	> .05
Treatment (%)			
Immunosuppression therapy	57	56	> .05
RASI	60	72	> .05
Outcome (%)			
Double sCr	2	17	< .05
ESRD	13	8	> .05
Kidney end-point (double sCr or ESRD)	15	25	> .05
Death	-	2	> .05
Composite end-point (double sCr, ESRD, death)	15	27	> .05

eGFR, estimated glomerular filtration rate; sCr, serum creatinine; IgAN, IgA nephropathy; M1, mesangial hypercellularity; E1, endocapillary hypercellularity; S1, segmental glomerulosclerosis; T1/2, tubular atrophy and interstitial fibrosis > 25%; C1/2, crescents in at least one glomerulus; ESRD, end-stage renal disease

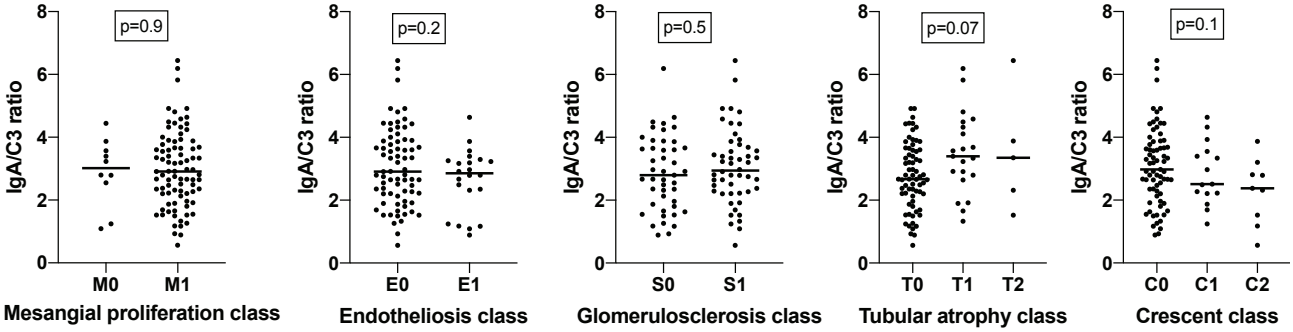

Figure 2. IgA/C3 Ratio Distribution Across MESTC Classes

population was 5.2 (95% CI: 4.7 to 5.8) years. In univariate analysis, patients with IgA/C3 ratio < 2.9 had a tendency to better mean event-free survival, 5.7 (95% CI: 5.1 to 6.3) vs. 4.5 (95% CI: 3.7 to 5.3) years ($P > .05$) (Figure 3).

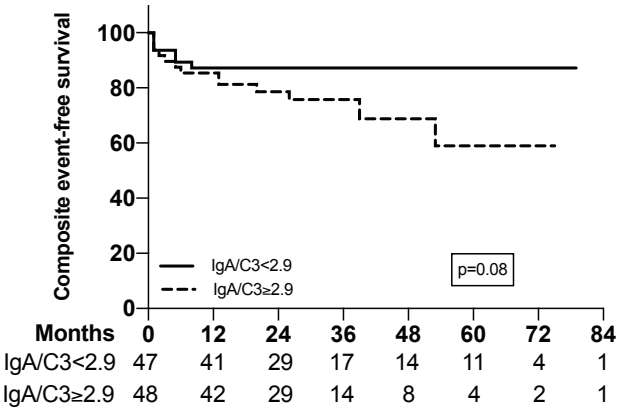

Figure 3. IgA/C3 ratio is associated with renal survival (Kaplan-Meyer analysis, Log Rank test; the number of patients at risk are shown below the graph).

The crude hazard ratio for the composite endpoint in IgA/C3 ratio < 2.9 versus ≥ 2.9 was 1.28 (95% CI: 0.89 to 1.84; $P > .05$). In the multivariate Cox proportional hazard ratio model, the independent predictors of a poorer event-free survival were higher serum creatinine, higher proteinuria and increased IgA/C3 ratio, while RASI therapy predicted a better outcome (Table 3).

DISCUSSION

We aimed to evaluate the relationship between IgA/C3 ratio and renal outcome in European patients with primary IgAN. IgA/C3 ratio was associated with renal survival independent of the known risk factors for IgAN progression. Moreover, increased IgA/C3 ratio -above 2.9- was a reasonable prognostic marker for renal survival. Currently, the chain of pathogenic events in IgAN has been translated into a four hit-mechanism: circulating immune complexes (hit three) composed of galactose-deficient IgA1 (hit one) and galactose-

Table 3. Prognostic factors analysis (Cox proportional hazard model for composite endpoints)

Variables	Univariate (HR, 95% CI)	*P*	Adjusted Model (HR, 95% CI)	*P*
Age, y	0.99 (0.95 to 1.03)	> .05	1.01 (0.94 to 1.08)	> .05
Male Gender vs. Female	0.41 (0.12 to 1.41)	> .05	0.37 (0.07 to 1.77)	> .05
Charlson Score	1.16 (0.93 to 1.44)	> .05	0.69 (0.41 to 1.16)	> .05
Hypertension (Yes vs. No)	0.27 (0.03 to 2.05)	> .05	0.45 (0.03 to 5.36)	> .05
Serum Creatinine, mg/dL	1.98 (1.55 to 2.52)	< .001	1.86 (1.35 to 2.57)	< .001
Proteinuria, g/g Creatinine	1.29 (1.13 to 1.47)	< .001	1.36 (1.09 to 1.68)	< .05
Haematuria, cells/mm3	1.00 (1.00 to 1.00)	> .05	1.00 (0.99 to 1.00)	> .05
IgA/C3 Ratio	1.28 (0.89 to 1.84)	> .05	1.94 (1.16 to 3.26)	< .05
Triglycerides, mg/dL	1.00 (0.99 to 1.00)	> .05	1.00 (0.99 to 1.00)	> .05
MESTC Score	1.33 (0.92 to 1.94)	> .05	0.93 (0.59 to 1.44)	> .05
IS (No vs. Yes)	0.75 (0.29 to 1.90)	> .05	1.13 (0.30 to 4.12)	> .05
RASI (No vs. Yes)	5.72 (2.08 to 15.75)	< .05	5.40 (1.28 to 22.69)	< .05

Cox regression (composite end-point)
eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; IS, immunosuppression; RASI, renin angiotensin system inhibitors

deficient IgA1 – specific autoantibodies (hit two) deposit in the glomerulus, leading to mesangial cells proliferation and glomerular injury (hit four).[3,13] Since C3 and IgA mesangial codeposition is present at immunofluorescence in more than 90% of patients, complement activation has been incriminated in IgAN pathogenesis.[14,15] Alternative and lectin pathways of the complement seem to be responsible for the activation systemically on circulating immune complexes and locally in glomeruli.[15] Regardless of the two involved pathways, C5b generation triggers the formation of the membrane attack complex (C5b-9) and contribute to glomerular injury.[16,17] Therefore, both IgA and C3 are pivotal players in IgAN pathogenesis. Glomerular deposition of IgA1 and IgA1-IgG immune complexes leads to lower serum C3 levels, together with elevated serum IgA this result in a higher IgA/C3 ratio, which could be used as a prognostic biomarker for IgAN.[18]

Although more than half of the patients with IgAN have elevated serum IgA, the actual polymeric IgA levels have limited diagnostic utility.[19] The C3 level is almost always normal or slightly reduced. However, serum IgA/C3 ratio has poor sensitivity but reasonable specificity in IgAN diagnosis.[18] Moreover, increased IgA levels in presence of moderate albuminuria, elevated blood pressure and increased IgA/C3 ratio $\geq$ 3 have a good ability to separate IgAN from other glomerular diseases causing hematuria, with a correct diagnosis rate of over 75%.[20] Similarly, Maeda *et al* reported that three of the following four markers can distinguish IgAN from other primary renal diseases: (1) more than five red blood cells in urinary sediments, (2) persistent proteinuria (urinary protein of more than 0.3 g/d), (3) serum IgA levels of more than 315 mg/dL, and (4) a serum IgA/C3 ratio of more than 3.01.[7]

Different complement fractions have been shown to have prognostic value in IgAN. Kim *et al*. reported that decreased serum C3 level (i.e. under 90 mg/dL) predicted poor renal survival, defined as doubling of serum creatinine and renal replacement theray initiation.[9] Moreover, in a number of studies from Asia, high serum IgA/C3 ratio -above 3 to 4.5- was a sign of progressive disease, but this has not been confirmed in other ethnic populations.[7,8,10,20,21] We report the first european study that confirms the prognostic value of IgA/C3 ratio in IgAN renal prognosis. This is important since previous data were obtained from Asian cohorts, in whom the natural history of IgAN may be different from European derived populations.[22]

Interestingly, previous studies have found that the serum IgA/C3 ratio can differentiate IgAN patients with severe histological lesions from those with mild histological lesions.[23-25] However, we found no relationship between IgA/C3 ratio and the MESTC classes. This might be due to the fact that the patients from our study have more advanced IgAN in comparison with previous reports: older age, lower eGFR, higher proteinuria and increased proportion of high blood pressure.[26] Several risk factors for progressive IgAN at diagnosis have been confirmed in our study, including higher serum creatinine, heavier proteinuria and absence of RASI treatment.[1] Our study has several limitations that are worth noting. Due to the retrospective nature of the study, our results may be influenced by other variables which were not considered. Moreover, the small number of patients may prevent strong conclusions. Also, our study population has some features which hamper results generalization: more advanced IgAN -suggested by lower eGFR, higher proteinuria, distinct distribution of MESTC lesions- and higher risk of progression as compared with other reports despite of a shorter follow-up.

CONCLUSION

In conclusion, the results of the present study support IgA/C3 ratio as a reasonable predictor of IgAN prognosis in European patients. However, additional large-scale studies are needed for the validation of the cut-off ratio in other populations.

CONFLICT OF INTEREST

All listed authors declare no conflict of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent is not required due to the

retrospective deidentified dataset from local renal biopsy registry.

DATA AVAILABILITY STATEMENT

Data will be made available under reasonable request.

AUTHORS' CONTRIBUTIONS

Research idea and study design: GS, GM; data acquisition: NP, BB, AZ, SS; data analysis/ interpretation: GS, GM; statistical analysis: GS, GM; supervision or mentorship: SS, AZ, GM; writing original draft: GS. Each author contributed important intellectual content during manuscript drafting or revision. All authors read and approved the final manuscript.

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