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Clinicopathological Characteristics of Adult IgA Nephropathy: A Retrospective Cohort Study

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Background

- IgA nephropathy (IgAN) is the most prevalent primary glomerulonephritis worldwide[1]
- IgAN is often progressive and when uncontrolled, or poorly controlled, can lead to end-stage kidney disease (ESKD)[2-4]
- Few studies have reported on the kidney-biopsy associated histological characteristics in adult IgAN patients

Objective

- To describe the demographic, clinical, and kidney biopsy histological characteristics among a sample of US adult patients with IgAN at time of kidney biopsy

Methods

Study design and data source

- This is a descriptive, non-interventional, retrospective cohort study of data collected from patients in the United States (US) with IgAN from the Arkana Biopsy database from January 1, 2016 to May 31, 2020

Inclusion criteria, exclusion criteria, index dates

- Patients who: (1) were 18+ yrs., (2) had at least 1 IgAN positive kidney biopsy during study period (January 1, 2016 – May 31, 2020), and (3) had no prior kidney transplant

Arkana laboratories

- Arkana Laboratories provides renal pathology, serology, molecular pathology, and neuropathology services, from healthcare institutions across 40 states in the US
- Patient clinical characteristics are retrospectively collected at time of biopsy

Histology

- Standard renal biopsy processing techniques were used, including light, immunofluorescence, and electron microscopy[5]
- Light microscopy samples were fixed in formalin, embedded in paraffin and serially cut at 3 microns and stained with hematoxylin and eosin, Jones methenamine silver, Masson trichrome, and periodic acid–Schiff reagent
- Tissue for immunofluorescence was snap frozen, embedded in OCT and sections were cut at 4 mm and stained with fluorescein-tagged polyclonal rabbit anti-human antibodies to IgG, IgA, IgM, C3, C1q, fibrinogen, and k- and l-light chains (Dako, Carpenteria, CA) for 1 hour, and rinsed; a coverslip was applied using aqueous mounting media
- For electron microscopy, 1 mm cubes were removed from the ends of the biopsy sample, dehydrated with graded alcohols and embedded in Epon/Araldite resin. 1-micron sections were cut with an ultramicrotome and stained with toluidine blue and examined with a light microscope for glomerular evaluation. Thin sections were cut at 60 nm and examined in a Jeol JEM 1011 electron microscope (Jeol, Tokyo, Japan) and photomicrographs taken at 4,000, 12,000 and 20,000 x magnification.

Measures and statistical analyses

- Categorical variables were summarized using frequencies and percentages, continuous variables were summarized using means, standard deviations, medians, and interquartile ranges

RESULTS

Table 1. Demographics and Clinical Characteristics of Adult Patients with IgAN at Time of Kidney Biopsy

	N	%
Overall	4,384	100.0%
Age		
Mean (SD)	47.7 (16.6)	
Median (IQR)	46.0 (34-60)	
Min, Max	18, 93	
Sex		
Female	1,636	37.3%
Male	2,748	62.7%
Race/Ethnicity	3,004	68.5%
White	2,176	72.4%
Black	225	7.5%
Latinx	231	7.7%
Asian	247	8.2%
Other	125	4.2%
Year of biopsy		
2016	802	18.3%
2017	819	18.7%
2018	1,011	23.1%
2019	1,261	28.8%
2020 (up to May 31)	491	11.2%
Hypertension	3,236	73.8%
Yes	2,857	88.3%
No	379	11.7%
Creatinine	3,835	87.5%
Mean (SD)	3.0 (3.0)	
Median (IQR)	2.0 (1.3-3.5)	
Min - Max	0.2 - 34.4	
eGFR with race modifier*	2,674	61.0%
Mean (SD)	42.6 (32.5)	
Median (IQR)	33.4 (17.7-58.2)	
Min - Max	1.6 - 213.7	
CKD stage with race modifier*	2,674	61.0%
Stage 1	317	11.9%
Stage 2	327	12.2%
Stage 3	832	31.1%
Stage 3A	308	11.5%
Stage 3B	524	19.6%
Stage 4	643	24.0%
Stage 5	555	20.8%
eGFR without race modifier*	3,835	87.5%
Mean (SD)	42.4 (32.1)	
Median (IQR)	33 (17.7-57.9)	
Min - Max	1.3 - 184.4	
CKD stage without race modifier*	3,835	87.5%
Stage 1	444	11.6%
Stage 2	477	12.4%
Stage 3	1,194	31.1%
Stage 3A	435	11.3%
Stage 3B	759	19.8%
Stage 4	915	23.9%
Stage 5	805	21.0%
Arteriosclerosis	4,208	96.0%
Absent or no comment	1,068	25.4%
Minimal or mild	1,054	25.0%
Moderate	960	22.8%
Marked or severe	1,126	26.8%
Arteriolosclerosis	4,371	99.7%
Absent or no comment	1,985	45.4%
Minimal or mild	1,074	24.6%
Moderate	618	14.1%
Marked or severe	694	15.9%
Proteinuria (UPC)	2,285	52.1%
Mean (SD)	3.5 (3.4)	
Median (IQR)	3.0 (1.0-5.0)	
Min - Max	0.0 - 34.0	
Nephrotic (≥3.0 g/g)	1,027	44.9%
Non-nephrotic (<3.0 g/g)	1,258	55.1%
Hematuria	2,965	67.6%
Present	2,767	93.3%
Absent	198	6.7%

Abbreviations: SD, standard deviation; **eGFR**, estimated glomerular filtration rate; **CKD**, chronic kidney disease; **IQR**, interquartile range; **UPC**, urine protein to creatine ratio. *eGFR calculated using CKD-EPI equation.[6]

Table 2. Frequency of IgAN Study Population Risk by eGFR and Albuminuria Category Among Patients with Available eGFR and Albuminuria Data (N=2,176)

Prognosis of CKD by GFR and Albuminuria Categories			Albuminuria* Categories Description and Range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol		A2 Moderately increased 30-299 mg/g 3-29 mg/mmol		A3 Severely increased ≥300 mg/g ≥30 mg/mmol	
			N	%	N	%	N	%
eGFR Categories** (ml/min/1.73m²) Description and Range	G1 Normal or high	≥90	.	.	36	1.7%	268	12.3%
	G2 Mildly decreased	60-90	1	0.0%	33	1.5%	298	13.7%
	G3a Mildly to moderately decreased	45-59	.	.	24	1.1%	245	11.3%
	G3b Moderately to severely decreased	30-44	.	.	33	1.5%	413	19.0%
	G4 Severely decreased	15-29	.	.	20	0.9%	472	21.7%
	G5 Kidney failure	<15	.	.	5	0.2%	328	15.1%

Abbreviations: CKD, chronic kidney disease; **eGFR**, estimated glomerular filtration rate. Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk (Kidney Disease: Improving Global Outcomes (KDIGO) 2012); *Albuminuria measured by converting UPC (urine protein to creatine ratio) by applying a factor of 1.43 (KDIGO, 2012); **Calculated using CKD-EPI equation without race modifier.

- Two-thirds of patients with IgAN were male, the mean age was approximately 48 years, and nearly 90% of patients had hypertension
- Most patients were White, while less than 10% were Black, LatinX, or Asian race/ethnicity
- The median urine protein to creatine ratio (UPC) was 3.0 g/g and nearly half of the population was nephrotic
- A large majority of patients (98.6%) presented with 2+ IgA and 85.5% with Negative/Trace IgG and IgM on immunofluorescence staining (data not shown)
- Two-thirds of these patients with IgAN had presence of segmental sclerosis and/or adhesion of tuft to Bowman Capsule; approximately one quarter of the patient sample presented with interstitial fibrosis and tubular atrophy (IFTA) >50%
- A greater proportion of patients with IgAN exhibited mild or moderate mesangial hypercellularity compared to endocapillary hypercellularity
- More than three quarters of IgAN patients presented with No Crescents (C0) (Fig. 1F) and most had Negative/Trace Fibrinogen (data not shown)
- High levels of variability were observed in proportion of patients exhibiting 3+ for C3, Kappa, and Lambda

Limitations

- Although this study presents a large sample of US adult patients with IgAN with demographic, clinical, and histological data collected at time of kidney biopsy, the ability to generalize results to the global IgAN patient population is limited

Discussion & Conclusions

- Most US patients with IgAN were diagnosed at CKD stage ≥3 (regardless of race modifier) and high MEST-C scores for S and T, which suggests significant disease duration at the time of kidney biopsy
- Strategies for earlier awareness and detection of IgAN are needed to facilitate therapeutic intervention in high-risk patients, thereby preventing progression to ESKD and attendant consequences

Disclosures & Funding

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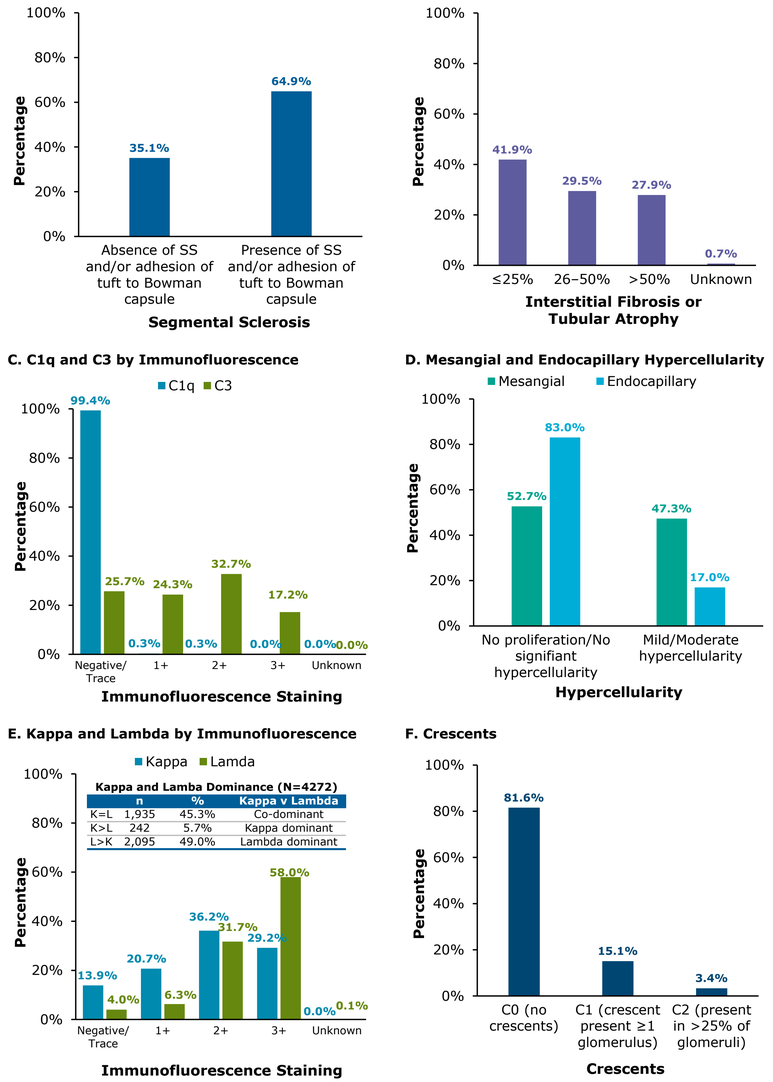
Figure 1. Distribution of Kidney Biopsy Histological Characteristics in Patients with IgAN at Time of Kidney Biopsy (N=4,384)



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