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Enclosure:

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End-Stage Kidney Disease (ESKD), Chronic Kidney Disease (CKD) Progression and Mortality among a Racially/Ethnically Diverse Population with Primary Immunoglobulin A Nephropathy (IgAN)

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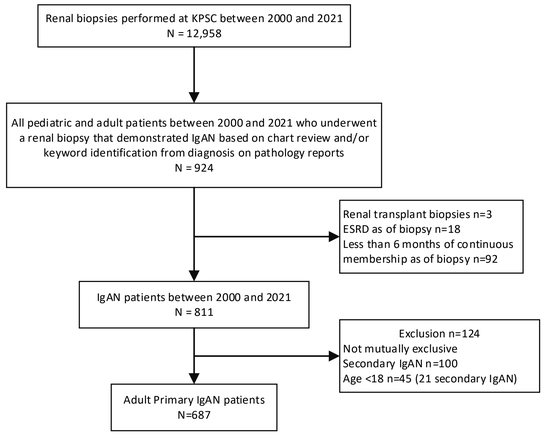
BACKGROUND

- IgAN is the most common glomerulonephritis and a leading cause of ESKD. (Storrar et al, 2022)
- Real-world data on natural history of this disease is sparse.
- This study evaluated kidney outcomes among a diverse IgAN population in an integrated US health system.

METHODS

- Longitudinal cohort study (1/1/2000-12/31/2021) was performed within Kaiser Permanente Southern California members with biopsy proven primary IgAN. Secondary IgAN was excluded.
- Primary outcome was a composite of ESKD (dialysis or transplant), CKD progression (≥ 50% decline eGFR) and/or mortality.
- Patients were followed from index biopsy until kidney outcome, mortality, or disenrollment.
- Multivariable Cox Regression was use to estimate hazard ratios (HR).

Figure 1. Consort Diagram



Onset of ESKD was defined as dialysis or renal transplant.

Secondary IgAN was defined as with concurrent lupus nephritis/ANCA vasculitis/IgA Vasculitis/Henoch-Schonlein purpura diagnosis included in pathology report, with IgA Vasculitis/Henoch-Schonlein purpura ICD diagnosis codes within 1-year prior to or after biopsy, or with Hepatitis B/Hepatitis C/Liver Cirrhosis/Liver transplant/Coeliac (Celiac) disease/Ulcerative colitis/Crohn's disease/Ankylosing spondylitis/Dermatitis herpetiformis ICD diagnosis codes within 1-year prior to biopsy.

RESULTS

Table 1. Baseline Characteristics for Adults with Primary IgAN

	White (N=165, 24.0%)	Black (N=23, 3.4%)	Hispanic (N=276, 40.2%)	Asian/Pacific Islander (N=207, 30.1%)	Other/unknown (N=16, 2.3%)	Total (N=687)
Age Mean (SD)	47.3 (16.5)	46.7 (17.1)	44.9 (14.1)	45.1 (13.9)	39.8 (9.2)	45.5 (14.7)
18 to 24	33 (20.0%)	4 (17.4%)	46 (16.7%)	24 (11.6%)	1 (6.3%)	108 (15.7%)
25 to 44	44 (26.7%)	7 (30.4%)	97 (35.1%)	92 (44.4%)	10 (62.5%)	250 (36.4%)
45 to 64	61 (37.0%)	8 (34.8%)	105 (38.0%)	67 (32.4%)	5 (31.3%)	246 (35.8%)
65+	27 (16.4%)	4 (17.4%)	28 (10.1%)	24 (11.6%)	0 (0.0%)	83 (12.1%)
Sex, n (%)						
Female	52 (31.5%)	9 (39.1%)	137 (49.6%)	122 (58.9%)	6 (37.5%)	326 (47.5%)
Male	113 (68.5%)	14 (60.9%)	139 (50.4%)	85 (41.1%)	10 (62.5%)	361 (52.5%)
Systolic blood pressure*, Mean (SD)	130.9 (14.05)	135.3 (15.21)	129.8 (13.58)	126.9 (14.95)	133.1 (8.34)	129.4 (14.18)
Diastolic blood pressure*, Mean (SD)	76.3 (10.41)	80.0 (11.30)	76.8 (9.03)	77.5 (9.45)	80.6 (7.73)	77.1 (9.57)
Hypertension[$], n (%)	105 (63.6%)	13 (56.5%)	177 (64.1%)	138 (66.7%)	10 (62.5%)	443 (64.5%)
Diabetes[$], n (%)	19 (11.5%)	1 (4.3%)	42 (15.2%)	34 (16.4%)	1 (6.3%)	97 (14.1%)
Baseline eGFR[†]						
Median (IQR)	48.9 (32.6, 68.1)	60.5 (24.4, 77.6)	52.8 (35.0, 81.2)	54.3 (36.5, 81.1)	59.6 (46.3, 78.4)	52.5 (34.9, 78.2)
90+	22 (13.3%)	2 (8.7%)	56 (20.3%)	37 (17.9%)	4 (25.0%)	121 (17.6%)
60-89	33 (20.0%)	10 (43.5%)	63 (22.8%)	52 (25.1%)	4 (25.0%)	162 (23.6%)
45-59	37 (22.4%)	2 (8.7%)	41 (14.9%)	47 (22.7%)	4 (25.0%)	131 (19.1%)
30-44	39 (23.6%)	2 (8.7%)	66 (23.9%)	36 (17.4%)	2 (12.5%)	145 (21.1%)
<30	31 (18.8%)	7 (30.4%)	48 (17.4%)	33 (15.9%)	2 (12.5%)	121 (17.6%)
Unknown	3 (1.8%)	0 (0.0%)	2 (0.7%)	2 (1.0%)	0 (0.0%)	7 (1.0%)
Treatment with immunosuppressive agents[†]	66 (40.0%)	14 (60.9%)	114 (41.3%)	83 (40.1%)	6 (37.5%)	283 (41.2%)
ACEi[$]	78 (47.3%)	6 (26.1%)	136 (49.3%)	88 (42.5%)	6 (37.5%)	314 (45.7%)
ARB[$]	27 (16.4%)	3 (13.0%)	56 (20.3%)	75 (36.2%)	6 (37.5%)	167 (24.3%)
SGLT-2i§	1 (0.6%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
Baseline urine protein creatinine ratio (UPCR)[#]						
Median (IQR)	1.6 (0.8, 3.1)	0.8 (0.3, 3.2)	1.8 (1.0, 3.5)	2.0 (1.0, 3.7)	1.5 (0.5, 3.0)	1.8 (0.9, 3.5)
<0.5	25 (15.2%)	7 (30.4%)	33 (12.0%)	18 (8.7%)	4 (25.0%)	87 (12.7%)
0.5-<1	23 (13.9%)	4 (17.4%)	28 (10.1%)	27 (13.0%)	2 (12.5%)	84 (12.2%)
1-2	49 (29.7%)	2 (8.7%)	74 (26.8%)	57 (27.5%)	3 (18.8%)	185 (26.9%)
>2	56 (33.9%)	7 (30.4%)	124 (44.9%)	99 (47.8%)	6 (37.5%)	292 (42.5%)
Unknown	12 (7.3%)	3 (13.0%)	17 (6.2%)	6 (2.9%)	1 (6.3%)	39 (5.7%)

*Based on the most recent record within 1-year prior to or as of renal biopsy. § Comorbidity and medication were based on data within 1-year prior to or as of renal biopsy. †With immunosuppressive agents during 4-week prior to and 1-year post renal biopsy. #Measurements at inpatient setting were excluded. ##record measured closest to renal biopsy during 1-year before and 30-day after biopsy was retained. Urine albumin-creatinine ratio (n=139) and total urine protein within 24hour (n=76) were converted to UPCR by divided by 700 and 1000, respectively.

Table 2: Composite Renal Outcome: Follow-up Time, Incidence Rate, Age and Time to Event

	Total f/u time (years)	Median f/u time (years) median (IQR)	No. of event	Incidence rate /1000 py (95%CI*)	Time to event (years) median (IQR)	Age at events median (IQR)
Overall (N=687)	3029	3.1 (1.3, 6.4)	258	85.2 (74.9, 96.8)	2.4 (0.6, 5.1)	49.3 (41.5, 63.2)
Excluding those with baseline eGFR<30 (N=566)	2707	3.5 (1.7, 6.8)	168	62.1 (53.5, 72.0)	3.6 (1.6, 6.3)	49.1 (42.1, 61.2)

*95% CI was generated based on Robust Poisson regression

Table 3. Adjusted Hazard Ratios – Multivariable Cox Model

	Hazard Ratio (95%CI)
Race/ethnicity (ref=White)	
Asian/Pacific Islander	0.8 (0.6, 1.2)
Black	1.2 (0.5, 2.7)
Hispanic	0.9 (0.7, 1.3)
Other/Unknown	1.1 (0.4, 3.7)
Baseline GFR (ref=60+)	
45-59	1.2 (0.8, 1.9)
30-44	2.5 (1.7, 3.6)
<30	6.2 (4.2, 9.2)
Unknown	41.1 (15.1, 111.9)
Treatment with immunosuppressive agents (yes vs. no)	0.7 (0.6, 0.96)
Baseline urine protein creatinine ratio (UPCR) (ref=[UPCR<0.5])	
0.5-<1	2.7 (1.4, 5.4)
1-2	3 (1.6, 5.4)
>2	5.8 (3.3, 10.1)
Unknown	1.8 (0.9, 3.6)
Age (Ref= 18-29)	
30-64	0.6 (0.4, 0.9)
65+	0.5 (0.3, 0.8)
Sex (male vs. female)	1.3 (1.03, 1.7)
Hypertension (yes vs no)	1.6 (1.1, 2.2)
Diabetes (yes vs no)	2 (1.4, 2.8)
Hematuria (yes vs no)	0.5 (0.4, 0.6)

Figure 2. Cumulative Incidence of Composite Renal Outcome by uPCR

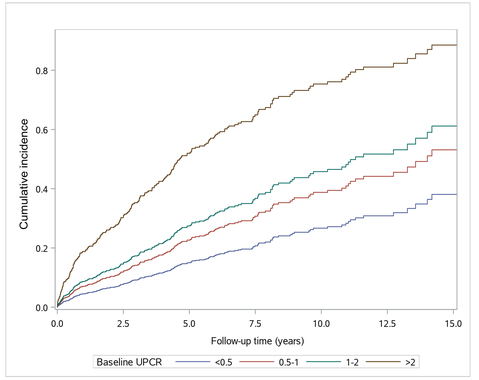
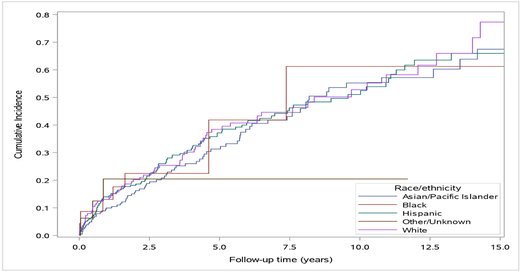


Figure 3. Cumulative Incidence of Composite Renal Outcome by Race/Ethnicity



- Among 687 patients with IgAN, the mean age was 45.5 (SD 14.7) yrs. with 53% males, 40% Hispanic/Latino, 30% Asian/Pacific Islander, 24% White, 3% Black, and 39% with eGFR<45).
- At biopsy, median eGFR was 58 and mean urine protein creatinine ratio (uPCR) was 2.6 g/g.
- A total of 258 (38%) had a kidney outcome (49 ESKD, 22 mortality, and 187 CKD progression) with median time to outcome of 2.4 years (3.6 years among eGFR>30 patients). The composite kidney outcome rate was 85.2 (per 1,000 person-years).
- A total of 182 patients had ESKD in the observation period.
- Median time to ESKD was 2.6 years (4.7 years among eGFR<30 patients).
- ESKD rate was 56.1 (per 1,000 person-years), over the median follow-up duration of 3.4 years.

CONCLUSIONS

- We observed a high rate of kidney outcomes among a diverse IgAN population.
- Baseline uPCR, eGFR, sex, hypertension, diabetes, hematuria, and age were associated with CKD progression, ESKD, and mortality.
- We also observed kidney outcomes among those with uPCR 0.5-1 who are traditionally considered "low-risk".
- Individuals with uPCR 1-2 and 0.5-1 had similar trajectory in the probability of developing the composite kidney outcomes.
- We did not observe differences in outcomes by race/ethnicity
- Our findings demonstrate the high risk for kidney outcomes across all proteinuria levels and across race/ethnicity among patients with IgAN .

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Reference:
1. Storrar, J, Chinnadurai R, Sinha S, Kalra P. The epidemiology and evolution of IgA nephropathy over two decades: a single center experience. PLOS ONE 17(8): e0268421. https://doi.org/10.1371/journal.pone.0268421

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