The patient journey for immunoglobulin A nephropathy: diagnostic delay and change in kidney function from first clinical sign

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BACKGROUND

- Immunoglobulin A nephropathy (IgAN) is a rare kidney disorder involving inflammation of the glomeruli.[1]
- Patients with IgAN frequently present with hematuria and/or proteinuria as an early clinical sign.[2,3] A definitive diagnosis of IgAN requires a kidney biopsy.[4]
- However, the absence of overt signs and symptoms during the initial stages of disease often results in a delay in diagnosis, which may translate to a loss in kidney function.[2]
- At present, the time from first clinical sign to biopsy-confirmed diagnosis of IgAN is unknown.

OBJECTIVES

- To describe the time from first clinical sign to biopsy-confirmed diagnosis of IgAN and change in kidney function during this period.
- To assess the association between time to diagnosis and end-stage kidney disease (ESKD).

METHODS

- In this retrospective analysis using electronic health records (EHR) data provided by Geisinger, adult patients receiving care between January 2004 and February 2021 with a kidney biopsy-confirmed diagnosis of IgAN were identified.
- The first clinical sign of IgAN was defined as the first positive hematuria and/or proteinuria result prior to IgAN diagnosis.
- Patients were required to have ≥6 months of data availability before their first clinical sign and no evidence of ESKD or kidney transplant prior to the first clinical sign.
- Patient characteristics and comorbidities were summarized during the 6-month period prior to the first clinical sign, overall, and by quartiles of time to diagnosis.
- Time from first clinical sign to diagnosis and change in estimated glomerular filtration rate (eGFR) during this period were assessed overall, and by quartiles of time to diagnosis.
- Kaplan-Meier analysis was used to estimate the proportion of patients with incident ESKD following IgAN diagnosis.

RESULTS

- Among 227 patients with biopsy-confirmed diagnosis of IgAN in the data, 117 patients (mean age 46.7 ± 19.4, 43.6% female) met the criteria for this study. (**Table 1**, **Figure 1**)
- Among these patients, 56.6% presented with hematuria and proteinuria on the same day; 24.8% presented with proteinuria alone and 19.7% presented with hematuria alone as their first clinical sign. (**Table 1**)
- Overall, 15.4% of patients had Stage 3 CKD and 6% had an acute kidney injury during the 6-month period prior to the first clinical sign. Charlson Comorbidity Index (CCI) was relatively consistent among the four diagnostic lag quartiles (mean 0.71 ± 1.36); however, patients in the quartile with the longest diagnostic lag had the highest CCI (mean 0.95 ± 1.78). (**Table 1**)
- Overall, median time from first clinical sign to diagnosis was 5.0 months (interquartile range [IQR]: 0.9, 29.3).
  - Among patients included in the eGFR analysis, quartiles of time to diagnosis were as follows, in months: 1st (0.5, 3.7); 2nd (3.7, 14.7); 3rd (14.7, 51.4); 4th (51.4, 184.7).
  - A subgroup of patients who developed Stage 5 CKD between their first clinical sign and IgAN diagnosis was identified (n = 17). These patients exhibited a longer and more variable diagnostic lag than the overall cohort (median time from first clinical sign to diagnosis 32.3 months [IQR: 1.3, 89.5]).
- Overall, mean monthly decrease in eGFR during time to diagnosis was 1.8 mL/min/1.73m^2, and mean total decline was 19.7 mL/min/1.73m^2.
  - Patients in the highest quartile of time to diagnosis had the largest total decrease in eGFR: mean monthly decline of 0.4 mL/min/1.73m^2, mean total decline of 36.0 mL/min/1.73m^2. (**Table 2**)
  - Patients in the first quartile of time to diagnosis had the largest mean monthly decline in eGFR of 4.8 mL/min/1.73m^2. (**Table 2**)
- Among patients included in the eGFR analysis, 21 patients developed ESKD by the end of the follow-up period. (**Table 3**)

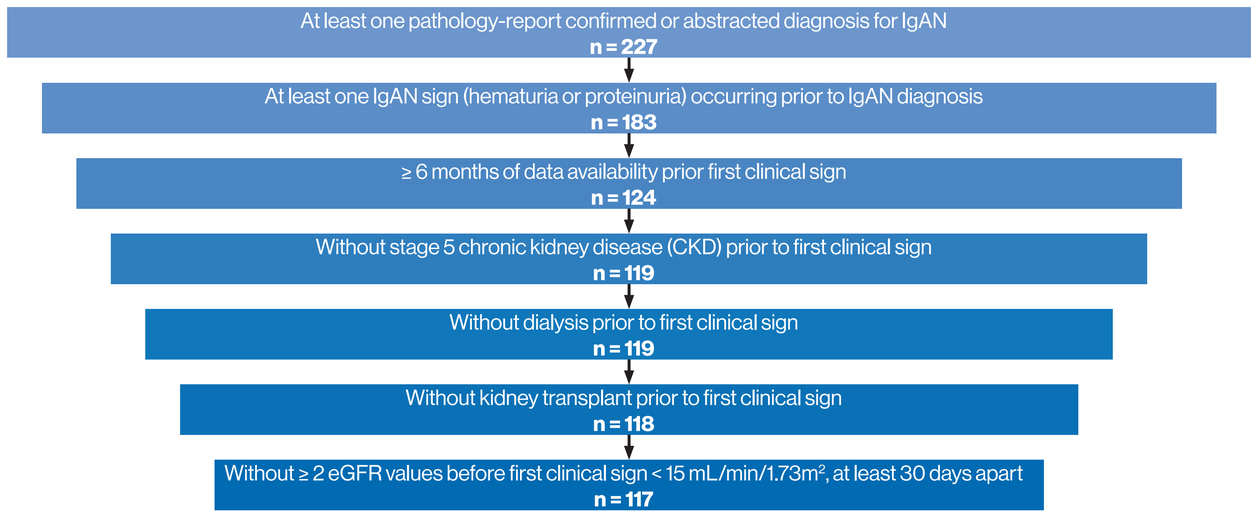
Table 1. Patient characteristics during the 6-month period prior to first clinical sign, by time to biopsy-confirmed diagnosis

	Overall N = 117	Quartiles of diagnostic lag among eGFR patient sample*: Patients in Q1 (0.5, 3.7) n = 22	Patients in Q2 (3.7, 14.7) n = 21	Patients in Q3 (14.7, 51.4) n = 21	Patients in Q4 (51.4, 184.7) n = 21
Patient characteristics†					
Age					
Mean ± SD	46.68 ± 19.40	48.71 ± 26.06	45.89 ± 19.56	43.90 ± 15.26	48.99 ± 15.97
Gender					
Female	51 (43.59%)	9 (40.91%)	9 (42.86%)	9 (42.86%)	12 (57.14%)
Male	66 (56.41%)	13 (59.09%)	12 (57.14%)	12 (57.14%)	9 (42.86%)
Race					
Asian	3 (2.56%)	2 (9.09%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Black or African American	4 (3.42%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (4.76%)
White	110 (94.02%)	20 (90.91%)	21 (100.00%)	19 (90.48%)	20 (95.24%)
Ethnicity					
Hispanic or Latino	4 (3.42%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)
Not Hispanic or Latino	107 (91.45%)	21 (95.45%)	20 (95.24%)	20 (95.24%)	19 (90.48%)
Unknown	6 (5.13%)	1 (4.55%)	1 (4.76%)	1 (4.76%)	0 (0.00%)
Insurance type					
Commercial	76 (64.96%)	11 (50.00%)	13 (61.90%)	16 (76.19%)	14 (66.67%)
Medicaid	4 (3.42%)	1 (4.55%)	1 (4.76%)	1 (4.76%)	1 (4.76%)
Medicare	28 (23.93%)	6 (27.27%)	5 (23.81%)	4 (19.05%)	5 (23.81%)
Other	9 (7.69%)	4 (18.18%)	2 (9.52%)	0 (0.00%)	1 (4.76%)
First clinical sign					
Hematuria and proteinuria	65 (55.56%)	11 (50.00%)	15 (71.43%)	11 (52.38%)	9 (42.86%)
Hematuria only	23 (19.66%)	5 (22.73%)	3 (14.29%)	4 (19.05%)	5 (23.81%)
Proteinuria only	29 (24.79%)	6 (27.27%)	3 (14.29%)	6 (28.57%)	7 (33.33%)
Kidney-related conditions					
Stage 1 CKD	15 (12.82%)	4 (18.18%)	2 (9.52%)	5 (23.81%)	4 (19.05%)
Stage 2 CKD	8 (6.84%)	3 (13.64%)	2 (9.52%)	2 (9.52%)	0 (0.00%)
Stage 3 CKD	18 (15.38%)	4 (18.18%)	4 (19.05%)	5 (23.81%)	2 (9.52%)
Stage 4 CKD	7 (5.98%)	3 (13.64%)	2 (9.52%)	0 (0.00%)	2 (9.52%)
Acute kidney injury	7 (5.98%)	2 (9.09%)	1 (4.76%)	1 (4.76%)	0 (0.00%)
Charlson Comorbidity Index (CCI)					
CCI					
Mean ± SD	0.71 ± 1.36	0.74 ± 1.69	0.73 ± 1.03	0.50 ± 0.82	0.95 ± 1.78

*Quartile values are in months; †Means and standard deviations are shown for continuous characteristics; counts and percentages are shown for categorical characteristics, unless otherwise noted.

CKD, Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; Q, quartile; SD, Standard Deviation.

Figure 1. Sample selection of patients with IgAN



*Diagnoses of IgAN were identified using the pathology report or chart abstraction; †Hematuria and proteinuria were identified using ICD codes or lab results.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy.

Table 2. Total and monthly change in eGFR (mL/min/1.73m²), by time to biopsy-confirmed diagnosis*

	Overall N = 85	Quartiles of diagnostic lag among eGFR patient sample†: Patients in Q1 (0.5, 3.7) n = 22	Patients in Q2 (3.7, 14.7) n = 21	Patients in Q3 (14.7, 51.4) n = 21	Patients in Q4 (51.4, 184.7) n = 21
Total change in eGFR					
Mean ± SD	-19.68 ± 29.50	-10.76 ± 19.11	-8.31 ± 19.15	-24.01 ± 37.47	-36.04 ± 31.26
Median (IQR)	-13.68 (-31.40, -0.38)	-2.13 (-15.89, -0.08)	7.13 (-12.13, -0.38)	-19.76 (-42.38, -1.53)	-29.77 (-44.53, -22.58)
Monthly change in eGFR					
Mean ± SD	-1.79 ± 4.29	-4.78 ± 6.79	-1.18 ± 2.22	-0.61 ± 3.23	-0.44 ± 0.42
Median (IQR)	-0.47 (-2.04, -0.08)	-0.91 (-8.88, -0.04)	-0.76 (-2.14, -0.09)	-0.79 (-1.32, -0.08)	-0.35 (-0.61, -0.17)

*This analysis excludes patients who did not have at least two eGFR values >30 days apart. The first eGFR value was the first lab value that occurred within three months before the first clinical sign up until the diagnostic date, the second eGFR value was the last lab value that occurred after the first clinical sign and before the diagnostic date;. †Quartile values are in months.

eGFR, estimated glomerular filtration rate; IQR, interquartile range; Q, quartile; SD, standard deviation.

Table 3. Summary of ESKD during the follow-up period, by time to biopsy-confirmed diagnosis*,†

	Number of patients‡,§	Patients with ESKD	Proportion without ESKD at year 1	Proportion without ESKD at year 2	Proportion without ESKD at year 3
Overall#	72	21	82.56%	82.56%	71.82%
Patients in Q1 (0.5, 3.7)	20	5	83.03%	83.03%	76.64%
Patients in Q2 (3.7, 14.7)	20	8	70.00%	70.00%	70.00%
Patients in Q3 (14.7, 51.4)	17	5	88.24%	88.24%	69.33%
Patients in Q4 (51.4, 184.7)	15	3	92.31%	92.31%	64.62%

*The follow-up period was defined as the time from IgAN diagnosis until the last available encounter; †ESKD was defined as the earliest of the following: Stage 5 CKD diagnosis, dialysis, kidney transplant, or ≥2 eGFR values <15 mL/min/1.73m² at least 30 days apart; ‡This analysis was restricted to patients included in the eGFR analysis with a diagnostic lag quartile; §Patients with ESKD prior to the index date were excluded from this analysis; #Quartile values are in months.

ESKD, end-stage kidney disease; Q, quartile.

LIMITATIONS

- As with all EHR-based studies, the databases used in this study may be subject to coding errors or data omission.
- This study was conducted using EHR data provided by Geisinger. Therefore, the results might not be generalizable to populations outside of this health system.
  - Additionally, because patients may seek care outside of the health system, the analysis was subject to missing patient visits that occur outside of the system and were therefore not visible in the data.
- Finally, this study sought to identify the first clinical sign of IgAN, which may be subject to left-censoring due to data availability. To mitigate this risk, a sensitivity analysis was conducted among patients with at least 2 years of data availability prior to the first observed clinical sign, and results were confirmed to be consistent with the overall analysis.

CONCLUSIONS

- A substantial proportion of patients with kidney biopsy-confirmed IgAN experienced delay from first clinical sign to diagnosis.
- During diagnostic lag, kidney function decreased, particularly among patients in the upper quartile of time to diagnosis.
- It is not known whether earlier detection of IgAN may help preserve kidney function and improve patient outcomes in IgAN, but these data suggest efforts to test such a hypothesis and shorten time to diagnosis so as to improve patient care, are warranted.
- This study provides a better understanding of factors that impact the length of patient journey to diagnosis.

References

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Disclosures

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