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CKD progression in patients with complement 3 glomerulopathy (C3G) in a US multi-center assessment

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KEY FINDINGS & CONCLUSIONS

- In this real-world US cohort, despite supportive care, there was progression of CKD among patients with C3G, highlighting a need for novel treatments to improve patient outcomes
- Relative to non-progressors, patients who progressed to a higher CKD stage had numerically higher rates of advanced CKD stage and tended to be more likely to have post-transplant recurrent C3G
- Patients with post-transplant C3G recurrence at the index date tended to have a shorter median time to CKD stage progression and poor CKD stage progression-free rate estimates
- This analysis observed no difference in the median time to CKD stage progression among patients with normal and decreased baseline C3 level

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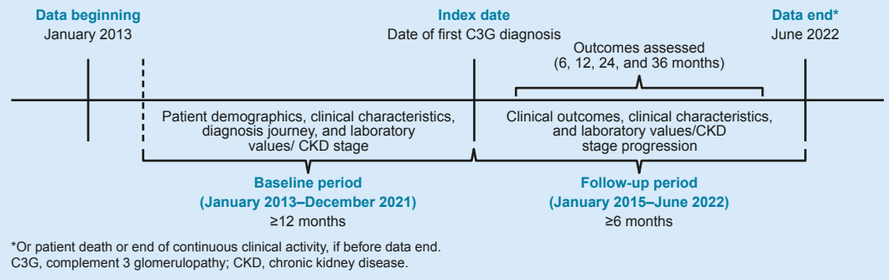
INTRODUCTION

- C3G is a complex, rare, glomerulonephritis characterized by the accumulation of C3 in the glomeruli, caused by the dysregulation of the alternative complement pathway[1–4]
- Approximately 50% of adults living with C3G develop kidney failure within 10 years of diagnosis and subsequently require dialysis or transplant[2,5]
- Many patients with C3G remain stable for years despite persistent proteinuria, but rapid fluctuations in proteinuria may occur, associated with episodes of acute kidney deterioration, often in the absence of obvious triggering events[2]
- There are currently no validated treatment strategies or approved therapies for C3G[6]
- In this study, using real-world EHR data, we characterize disease progression in a cohortof US patients diagnosed with C3G, stratified by C3 level at the index date and kidneytransplant status

METHODS

- This was a retrospective cohort study of patients within the US Optum Life Science Clinical EHR database who received a C3G diagnosis between January 2015 and June 2022 (**Figure 1**)
- A C3G diagnosis was identified by the presence of a diagnostic code (ICD-10-CM or SNOMED CT) for C3G; the index date was the date of the first C3G diagnosis
  - Included patients were ≥12 years of age at the index date and had ≥1 C3G diagnosis between January 2015 and June 2022
  - Patients were required to have ≥12 months of available clinical data before the index date (baseline period) and ≥6 months after the index date (follow-up period)
  - Patients were followed for a minimum of 6 months until death, end of data availability, or end of continuous clinical activity (June 2022)
- CKD stage at the index date was defined using the eGFR value closest to the index date; if eGFR data were not available within 1 month of the index date, CKD stage was defined using the CKD stage diagnosis code closest to the index date
  - If a patient had a procedure code for dialysis during baseline, their CKD stage was defined as CKD stage 5/kidney failure
  - Progression was assessed between the index date and follow-up timepoints in all patients with CKD stage <5 at the index date who had adequate data (based on laboratory values, diagnosis codes, or dialysis procedure codes); patients with lower CKD stage at the index date versus follow-up were considered progressors
- Patients were stratified by baseline C3 level (decreased [<77 mg/dL] or normal [≥77 to <201 mg/dL], among those with C3 laboratory data) and kidney transplant status at the index date (post-transplant recurrent C3G or C3G in the native kidney)
  - Post-transplant recurrent C3G was defined as documentation of a kidney transplant before C3G diagnosis at the index date
- Continuous variables were summarized by means and SDs; categorical variables were summarized by counts and percentages
- The time to CKD stage progression and time to kidney failure was estimated using Kaplan–Meier analyses

Figure 1. Study design



*Or patient death or end of continuous clinical activity, if before data end.
C3G, complement 3 glomerulopathy; CKD, chronic kidney disease.

RESULTS

- In the US Optum Life Science Clinical EHR database, 415 patients had ≥1 diagnosis for C3G
  - A total of 284 patients met the study inclusion criteria, and 188 were assessed for progression
  - Of the 188 patients assessed for CKD stage progression, 14 had post-transplant recurrent C3G and 174 had C3G in the native kidney at the index date
  - Progression was assessed in 24 patients with decreased C3 and 47 patients with normal C3 at the index date

Demographic and clinical characteristics

- Demographic and clinical characteristics of patients with CKD stage progression assessed, stratified by post-index date CKD stage progression status, are presented in **Table 1**
- Most patients were White (76.6%), 47.9% were female, and the mean age at the index date was 51.4 years (SD: 20.0 years)
- In patients with CKD stage progression, relative to non-progressors:
  - CKD stage ≥3 was more prevalent at the index date (59.1% and 38.4%)
  - ACEi or ARB use was numerically higher 12 months after (and including) the index date (61.7% and 46.6%)
  - The mean UPCR was numerically higher (3.7 g/g and 2.3 g/g)
  - The mean Charlson Comorbidity Index score was numerically higher (2.8 and 1.8)
  - More patients tended to have post-transplant recurrent C3G (10.4% and 2.7%)
  - Normal C3 levels were slightly more prevalent (68.1% and 62.5%)

CKD stage progression from the index date

- The time to CKD stage progression, stratified by index C3 level and kidney transplant status, is presented in **Figure 2**
- Of 188 patients assessed for CKD stage progression, progression occurred in 115 patients (61.2%), and 54 (28.7%) progressed to CKD stage 5/kidney failure
- The median time to CKD stage progression was 12.6 months (95% CI: 9.4, 17.7)
  - Progression-free rate estimates were 62.2% and 34.6% at 6 and 36 months, respectively
- For all groups, the median time to CKD stage 5/kidney failure was not reached

Patients stratified by C3 level at the index date

- Of 188 patients assessed for CKD stage progression, C3 level was assessed in 71 patients (37.8%)
- CKD stage progression occurred in 15 patients (62.5%) with decreased C3 levels (n=24) and 32 patients (68.1%) with normal C3 levels (n=47)
- The median time to CKD stage progression among patients with normal C3 levels was 9.4 months (95% CI: 4.3, 18.6), and among patients with decreased C3 levels was 9.4 months (95% CI: 7.0, NR)

Patients stratified by post-transplant recurrent C3G and C3G in the native kidney at the index date

- CKD stage progression occurred in 12 (85.7%) patients with post-transplant recurrent C3G (n=14) and 103 (59.2%) patients with C3G in the native kidney (n=174)
- The median time to CKD stage progression was numerically lower in patients with post-transplant recurrent C3G (0.5 months [95% CI: 0.1, NR]) relative to patients with C3G in the native kidney (13.9 months [95% CI: 10.1, 21.7])

Post-index date treatment in patients with CKD stage progression

- Data for treatments received by patients who progressed to a higher CKD stage are presented in **Table 2**
- Supportive therapy (71.4% and 38.9%) and ACEi or ARB use (ACEi, 33.3% and 22.2%, and ARB, 42.9% and 22.2%) were numerically higher in patients with CKD stage progression at 36 months post-index date than in those who progressed at 6 months post-index date

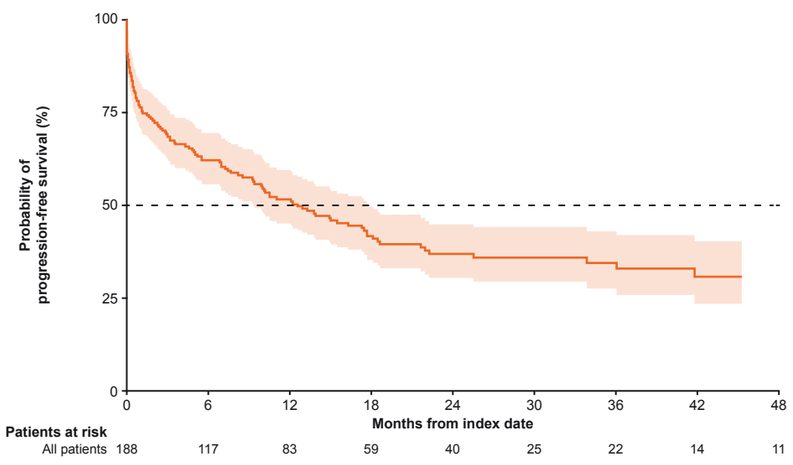
Table 1. Patient demographic and clinical characteristics

Characteristic	Patients with CKD stage progression assessed during the follow-up period* n=188	Non-progressors n=73	CKD stage progressors n=115
Age at the index date, years			
Mean ± SD	51.4 ± 20.0	48.1 ± 19.9	53.5 ± 19.8
Sex, n (%)			
Female	90 (47.9)	36 (49.3)	54 (47.0)
Male	98 (52.1)	37 (50.7)	61 (53.0)
Race, n (%)			
African American	20 (10.6)	4 (5.5)	16 (13.9)
Asian	5 (2.7)	4 (5.5)	1 (0.9)
White	144 (76.6)	54 (74.0)	90 (78.3)
Other/unknown	19 (10.1)	11 (15.1)	8 (7.0)
CKD stage within 1 month of the index date†, n (%)			
Stage 1	41 (21.8)	22 (30.1)	19 (16.5)
Stage 2	51 (27.1)	23 (31.5)	28 (24.3)
Stage 3	45 (23.9)	15 (20.5)	30 (26.1)
Stage 4	36 (19.1)	13 (17.8)	23 (20.0)
Stage 5/kidney failure‡	15 (8.0)	0	15 (13.0)
Treatments 1 month before (and including) the index date, n (%)			
CV-related	97 (51.6)	23 (31.5)	74 (64.3)
ACEi	49 (26.1)	15 (20.5)	34 (29.6)
ARBs	32 (17.0)	9 (12.3)	23 (20.0)
CS (oral/IV)	52 (27.7)	11 (15.1)	41 (35.7)
Immunosuppressive agents	25 (13.3)	4 (5.5)	21 (18.3)
Eculizumab	3 (1.6)	2 (2.7)	1 (0.9)
ACEi or ARB use 12 months after (and including) the index date, n (%)			
Yes	105 (55.9)	34 (46.6)	71 (61.7)
No	83 (44.1)	39 (53.4)	44 (38.3)
Baseline Charlson Comorbidity Index score			
Mean ± SD	2.4 ± 2.6	1.8 ± 2.4	2.8 ± 2.6
C3G-related procedures during the baseline period, n (%)			
Kidney biopsy	45 (23.9)	13 (17.8)	32 (27.8)
Kidney transplant§	14 (7.4)	2 (2.7)	12 (10.4)
Hemodialysis‖	12 (6.4)	1 (1.4)	11 (9.6)
Baseline C3 level¶, n (%)			
C3 level assessed	71 (37.8)	24 (32.9)	47 (40.9)
Decreased (<77 mg/dL)	24 (33.8)	9 (37.5)	15 (31.9)
Normal (≥77 to <201 mg/dL)	47 (66.2)	15 (62.5)	32 (68.1)
Laboratory values 90 days after (and including) the index date¶			
Proteinuria status#, n (%)			
Proteinuria status assessed	74 (39.4)	21 (28.8)	53 (46.1)
Normal (<0.2 g/g)	10 (13.5)	4 (19.0)	6 (11.3)
Subnephrotic (≥0.2 to <3.5 g/g)	42 (56.8)	12 (57.1)	30 (56.6)
Nephrotic (≥3.5 g/g)	22 (29.7)	5 (23.8)	17 (32.1)
UPCR (g/g), mean ± SD	3.3 ± 4.5	2.3 ± 2.6	3.7 ± 5.0
eGFR (mL/min/1.73m²), n (%)**			
eGFR assessed	157 (83.5)	52 (71.2)	105 (91.3)
<30	46 (29.3)	11 (21.2)	35 (33.3)
≥30	111 (70.7)	41 (78.8)	70 (66.7)
Mean ± SD	56.9 ± 34.7	71.6 ± 35.8	49.6 ± 31.8

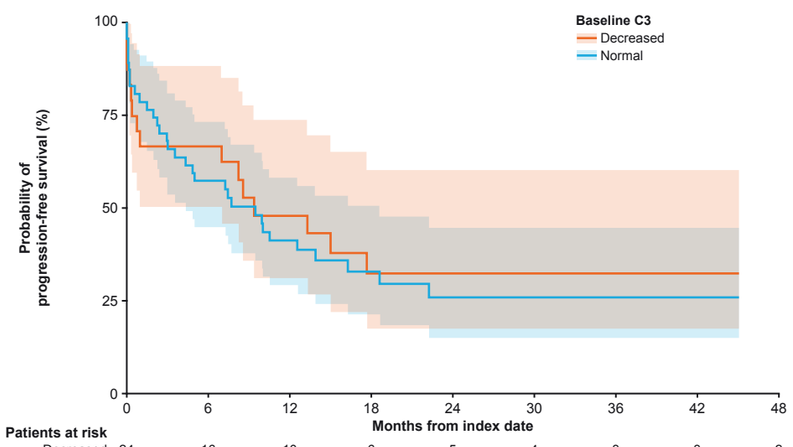
*Patients with a lower CKD stage at the index date than at the follow-up timepoint were considered progressed; †CKD stage was defined using the eGFR value closest to the index date. If eGFR data were not available within 1 month of the index date, CKD stage was defined using the CKD diagnosis code closest to the index date; CKD stage 3 includes stage 3a, stage 3b, and unspecified stage 3; ‡If a patient had a procedure code for dialysis within 1 month of the index date, their CKD stage was defined as CKD stage 5/kidney failure; §Kidney transplant during baseline, or diagnosis code in baseline indicating a prior kidney transplant; ‖Hemodialysis was identified by the presence of a procedure code on the visit closest to the index during the baseline period; ¶Assessed using data closest to the index date; #Proteinuria was assessed using UPCR (urinalysis); proteinuria status was based on the definition from Kaminska et al.[7]; **eGFR values were either calculated with the CKD-EPI creatinine equation (2021) for patients ≥18 years of age or reported by Optum (Schwartz formula) for patients <18 years of age.
ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; C3, complement component 3; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CS, corticosteroids; eGFR, estimated glomerular filtration rate; SD, standard deviation; UPCR, urine total protein to creatinine ratio.

Figure 2. Time to CKD stage progression

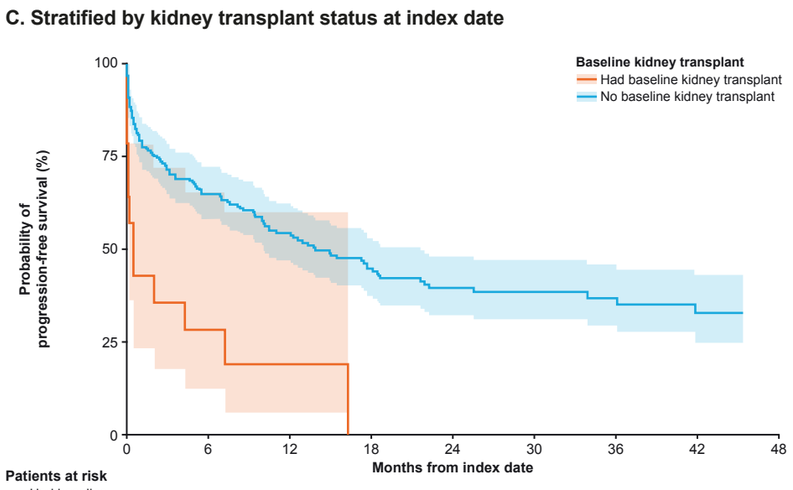
A. CKD stage progression in the overall population



B. Stratified by C3 level at index date



C. Stratified by kidney transplant status at index date



C3, complement component 3; CKD, chronic kidney disease.

Table 2. Post-index date C3G-related treatments in CKD stage progressors

C3G-related treatment	Patients with CKD stage progression at post-index date follow-up* 6 months† n=18	12 months‡ n=28	24 months‡ n=24	36 months‡ n=21
Supportive therapy§	7 (38.9)	11 (39.3)	13 (54.2)	15 (71.4)
ACEi	4 (22.2)	8 (28.6)	7 (29.2)	7 (33.3)
ARBs	4 (22.2)	4 (14.3)	8 (33.3)	9 (42.9)
Immunosuppressive therapy	6 (33.3)	14 (50.0)	7 (29.2)	7 (33.3)
Immunosuppressive agents	4 (22.2)	3 (10.7)	3 (12.5)	3 (14.3)
CS (oral/IV)	4 (22.2)	12 (42.9)	5 (20.8)	6 (28.6)
Eculizumab	0	0	1 (4.2)	0

*Progression was assessed between CKD stage at the index date and CKD stage at the follow-up timepoint among patients with a CKD stage <5 at the index date; patients with a lower CKD stage at the index date than at the follow-up timepoint were considered progressed; patients with CKD stage 3 unspecified at the index date and CKD stage 4 or 5 at the follow-up timepoint were considered progressed; †6 months from the index date ±1 month; ‡12, 24, or 36 months from the index date ± 3 months; §Supportive therapy is defined as treatment with either ACEi or ARBs.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; CS, corticosteroids; IV, intravenous.

LIMITATIONS

- As with all EHR-based studies, the diagnosis codes and data recorded in the database may be subject to human or technical error or data omission
- The subgroup population sizes were small and not powered for statistical comparison
- CKD stage was derived using a combination of diagnosis codes, procedure codes, and eGFR values, and therefore, may not reflect the actual CKD stage for each patient; progression, which was dependent upon CKD stages, may not reflect the true disease progression of the patient
- Patients with a C3G diagnosis at the index date and documentation of a kidney transplant were assumed to have recurrent C3G and, therefore, categorized as having post-transplant recurrent C3G
- The analysis required patients to have ≥6 months of continuous clinical activity, which may lead to the underestimation of the proportions of patients with select clinical events, such as progression
- The progression free survival analyses were unadjusted with covariates and confounding variables

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; C3, complement component 3; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CM, Clinical Modification; CS, corticosteroids; CT, Clinical Terms; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EHR, electronic health record; ICD, International Classification of Diseases; IV, intravenous; NR, not reached; SD, standard deviation; SNOMED, Systematized Nomenclature of Medicine; UPCR, urine total protein to creatinine ratio; US, United States.

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Disclosures

BN, **CA**, **KPM**, and **JN** are employees of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA. **IP**, **MLE**, **AA**, and **JS** are employees of Analysis Group, Boston, Massachusetts, USA, which has received consulting fees from Novartis. **PC** has consultancy agreements with Chinook, Novartis, and Otsuka, and has received research funding from Calliditas, Novartis, and Travere.

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