Persistent Disease Activity in Patients With Long-Standing Glomerular Disease

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Introduction: Glomerular diseases are characterized by variable disease activity over many years. We aimed to analyze the relationship between clinical disease activity and duration of glomerular disease.

Methods: Disease activity in adults with chronic minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and IgA nephropathy (IgAN; first diagnostic biopsy >5 years before enrollment; Of Longstanding Disease [OLD] cohort, $n = 256$) followed at Columbia University Medical Center (CUMC), was compared with disease activity of an internal and external cohort of patients with first diagnostic biopsy <5 years before enrollment drawn from the Cure Glomerulonephropathy Network (CureGN cohort, $n = 1182$; CUMC-CureGN cohort, $n = 362$). Disease activity was defined by (i) Kidney Disease: Improving Global Outcomes–recommended threshold criteria for initiation of immunosuppression in primary glomerulonephropathy (GN) and (ii) CureGN's Disease Activity Working Group definitions for activity.

Results: No significant differences were detected among the 3 cohorts in terms of age, sex, serum creatinine, and urinary protein-to-creatinine ratio. For each GN subtype, disease activity in the OLD cohort was comparable with disease activity in the entire CureGN and the CUMC-CureGN cohort. When limiting our comparisons to disease activity in incident CUMC-CureGN patients (first diagnostic biopsy within 6 months of enrollment), OLD patients demonstrated similar activity rates as incident patients.

Conclusion: Disease activity did not differ among patients with shorter versus longer duration of disease. Such survivor patients, with long-term but persistent disease, are potentially highly informative for understanding the clinical course and pathogenesis of GN and may help identify factors mediating more chronic subtypes of disease.

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With advances in the management of glomerular diseases, progression to advanced and end-stage kidney disease due to focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and IgAN is often measured in decades rather than months or years. Cohort studies on patients with longstanding glomerulonephropathies (GNs) have tried to address the impact of acknowledged risk factors on renal survival.[1,2] Most of these studies, however, have been retrospective without collection of biospecimens, limiting analyses on the pathophysiology of diseases. Hence, accurate predictors of disease behavior are still not available.

Assessment of disease activity has an important role in clinical decision-making because many components, such as proteinuria, hematuria, and blood pressure control are associated with long-term outcomes. Worsening clinical disease activity is generally considered to reflect the activity of underlying biological disease processes and often guides management decisions, such as initiation or discontinuation of immunosuppression or acquisition of a repeat renal biopsy. As we enter a realm in which biomarkers for glomerular diseases continue to emerge, the assumption that patients with a recent diagnosis have more active disease, and are therefore better suited for studying the primary biological mechanisms of GN, may be called into question. Specifically, disease onset in GN does not necessarily coincide with the histologic diagnosis, and urinary abnormalities may be detectable long before the time of kidney biopsy.

In this study, we sought to analyze the relationship between clinical disease activity and duration of GN using data from the Cure Glomerulonephropathy Network (CureGN, https://curegn.org/), a prospective multicenter cohort study on glomerular diseases funded by the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases that began enrollment in December 2014.[3] To be eligible for the Cure GN study, the first diagnostic kidney biopsy for Minimal Change Disease (MCD), FSGS, MN, or IgAN had to occur within 5 years of study enrollment. We assessed whether patients with longstanding GN (first diagnostic biopsy >5 years) still have disease activity, whether this differs from patients with a more recent diagnosis (≤5 years), and how longstanding disease influences the rate of kidney function decline.

METHODS

Participants

To determine disease activity in patients with long-standing glomerular disease, we constructed a cohort of adult patients (≥18 years) with chronic MCD, FSGS, MN, and IgAN followed at CUMC, whose first diagnostic kidney biopsy was performed >5 years from screening. We called this the OLD cohort. We then compared disease activity of the OLD cohort with disease activity of an internal and external cohort of adult patients with more recent disease diagnoses, drawn from the CureGN study and therefore all within 5 years of their first diagnostic biopsy for MCD, FSGS, MN, or IgAN. The CureGN cohort is composed of patients enrolled at CUMC (20%, internal comparison cohort) and at 69 other clinical sites (external comparison cohort).

Participants in the OLD cohort met all inclusion criteria of CureGN, with the sole exception being time of first diagnostic biopsy. Specifically, enrollment into the OLD cohort required the initial biopsy diagnosis to be >5 years from the time of first clinical encounter after December 2014. To reduce confounders, patients were excluded from the OLD cohort if they met any of the prespecified exclusion criteria for CureGN. Detailed inclusion and exclusion criteria for CureGN participants have been published elsewhere.[4]

Disease Activity

We used 2 measures of disease activity. First, we compared rates of disease activity among cohorts using Kidney Disease: Improving Global Outcomes–recommended treatment thresholds for initiation of immunosuppression in primary GN. For IgAN, this criterion was proteinuria >1000 mg/g creatinine or >1.0 g/d despite conservative therapy. For MCD/FSGS/MN, this criterion was proteinuria >3500 mg/g or >3.5 g/d, or serum albumin <3.0 g/dl if proteinuria was not available ($n = 2$), despite conservative therapy.[5] Second, we compared rates of disease activity using CureGN's Disease Activity Working Group definitions for activity, listed for each disease in Table 1. For the CureGN patients, we used disease activity at enrollment. For the OLD cohort, we assessed disease activity at the first clinical encounter after December 2014, simulating an enrollment visit for these patients.

Data Sources and Collection

Baseline clinical data for the OLD cohort were compiled from the CUMC Clinical Records Online Web Network (CROWN) and self-reported demographic information. CureGN participants' data, collected from each site on a Web-based data source (CureGNLink), were made available for analysis by the CureGN Data Coordinating Center.

Table 1. CureGN's definitions of disease activity

Diagnosis	Disease activity criteria
IgAN and HSPN	• Hematuria on urinalysis: ≥1+ (small blood, 11–25 RBC/HPF) • 24-h urine protein >500 mg • UPCR >0.3 g/g
FSGS	• 24-h urine protein >1 g (adults) • 24-h urine protein >1 g normalized to 1.73 m² BSA (children <1.73 m²) • UPCR >1 g/g
MN	• 24-h urine protein >1 g (adults) • 24-h urine protein >1 g normalized to 1.73 m² BSA (children <1.73 m²) • UPCR >1 g/g
MCD	• UPCR >1 g/g or 24-h urine >1 g • Documented by clinical records or nephrologist of the following: pattern within the past 12 months of frequently relapsing (2 relapses in 6 mo or 4 relapses in 12 mo) or corticosteroid-dependent (relapse on alternate-day corticosteroids or within 14 d of ceasing therapy with corticosteroids) nephrotic syndrome • ≥1 relapse in the 12 mo before enrollment • Immunosuppressive medication at enrollment to include current use of corticosteroids, CNI (cyclosporine or tacrolimus), mycophenolate, azathioprine, or Acthar. Additional criteria include alkylating agent (cyclophosphamide or chlorambucil) within 3 mo or rituximab or other anti-CD20 monoclonal antibody within 6 mo before enrollment

BSA, body surface area; CNI, calcineurin inhibitor; FSGS, focal and segmental glomerulosclerosis; HSPN, Henoch-Schönlein purpura nephritis; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; RBC/HPF, red blood cells per high power field; UPCR, urinary protein-to-creatinine ratio.
To define the disease as active, ≥1 criterion for each disease should be satisfied.

Statistical Analysis

Statistical analysis was performed using SPSS17.0 software (IBM Corp., Armonk, NY). Qualitative variables were expressed as number and percentage, compared using the nonparametric Kruskal-Wallis test and the Mann-Whitney test. Continuous variables were expressed as median value (interquartile range–SD) when normally distributed; data were compared using 1-way analysis of variance with Bonferroni post hoc test. A significance level of <0.05 was accepted.

Ethical Considerations

OLD patients were enrolled into an ongoing study on the genetics of chronic kidney disease, a National Institutes of Health–funded study in which patients provide written informed consent for de-identified data-sharing. All CureGN participants were informed of the protocol and gave their written consent before participating in the CureGN study. The project and subsequent manuscript were approved by the CureGN publications committee.

RESULTS

Study Population

From December 2014 through May 2018, 256 adult patients were screened at CUMC and included in the OLD cohort. During this period, 2013 patients were enrolled into the CureGN study. Fifty-three were excluded from this analysis because their first

diagnostic kidney biopsy, on review, was done >5 years before the enrollment visit. Of the remaining 1960 CureGN patients, 1182 were adults (≥18 years) at enrollment, of whom 362 (31%) had been enrolled at CUMC. Our analyses were therefore conducted comparing the abovementioned OLD cohort patients (n = 256) with longstanding glomerular disease, with both the CUMC-CureGN cohort (n = 362) and the whole CureGN adult cohort (n = 1182).

Baseline Characteristics Divided by Disease Group

Demographic data for patients included in the final analysis are summarized in Table 2, with each cohort divided by disease group (MCD, FSGS, MN, and IgAN). Age at screening did not differ among the 3 cohorts. As expected, the OLD cohort had a significantly longer course of disease compared with the CureGN and CUMC-CureGN cohorts. Therefore, patients in the OLD cohort were diagnosed at a younger age when compared with their CureGN counterparts.

Clinical and laboratory data are summarized in Table 3. No significant differences were detected in serum creatinine and proteinuria among the 3 cohorts and across the 4 disease groups. Microscopic hematuria on urinalysis was significantly lower for patients with IgAN in the OLD cohort than in CureGN patients (P < 0.001).

Overall, 75% of patients in the OLD cohort had completed at least 1 course of immunosuppression before their screening evaluation; 33% had tried at least 3 different rounds of immunosuppression. However, at the time of their screening evaluation, OLD patients were less likely than CureGN or CUMC-CureGN cohort patients to be on any immunosuppression. These rates varied by disease type: for MCD, 33% of OLD patients were on no immunosuppression (vs. 25% in CureGN and 20% in CUMC-CureGN); for FSGS, 67% of OLD patients were on no immunosuppression (vs. 53% in CureGN and 52% in CUMC-CureGN); for MN, 75% of OLD patients were on no immunosuppression (vs. 58% in CureGN and 66% in CUMC-CureGN); and for IgAN, 89% of OLD patients were on no immunosuppression (vs. 68% in CureGN and 64% in CUMC-CureGN).

Disease Activity

Using Kidney Disease: Improving Global Outcomes–recommended treatment thresholds for initiation of immunosuppression as our primary marker of disease activity, we compared rates of disease activity among the 3 cohorts (OLD, CureGN, and CUMC-CureGN) for each disease group (MCD, FSGS, MN, and IgAN) (Figure 1). The OLD cohort met these prespecified

Table 2. Demographics at enrollment by diagnosis

Demographics	MCD			FSGS			MN			IgAN			TOT		
	CureGN, *n* = 158	CUMC-CureGN, *n* = 46	OLD, *n* = 33	CureGN, *n* = 300	CUMC-CureGN, *n* = 95	OLD, *n* = 82	CureGN, *n* = 332	CUMC-CureGN, *n* = 109	OLD, *n* = 61	CureGN, *n* = 392	CUMC-CureGN, *n* = 112	OLD, *n* = 80	CureGN, *n* = 1182	CUMC-CureGN, *n* = 362	OLD, *n* = 256
Male	68 (43)	25 (54)	14 (42)	145 (48)	56 (59)	54 (66)[a]	213 (64)	70 (64)	37 (61)	229 (58)	68 (61)	49 (61)	655 (55)	219 (60)	154 (60)
Age at screening	43 (32–18.87)	42 (29–18.71)	34 (16–12.64)	43 (25–16.73)	44 (26–16.26)	43 (24–15.13)	54 (22–14.52)	55 (24–15.28)	55 (20–13.20)	39 (21–14.23)	38 (18–12.70)	42 (16–11.36)	45 (27–16.38)	44 (26–16.26)	44 (21–14.51)
Time since biopsy, yr	1.3 (2.29–1.44)	1.1 (1.81–1.23)	11 (10.00–12.66)	1.2 (2.27–1.56)	1.0 (2.25–1.56)	8.5 (8.75–7.54)	1.0 (2.35–1.47)	1.0 (2.17–1.39)	9 (9.00–9.04)	0.9 (2.27–1.52)	0.7 (2.46–1.57)	10 (8.00–4.89)	1.1 (2.33–1.51)	1.0 (2.25–1.47)	10 (9.00–8.00)
Race															
White	109 (69)	36 (78)	25 (76)	169 (56)	56 (59)	58 (71)	234 (70)	72 (66)	50 (82)	286 (73)	76 (68)	53 (66)	798 (68)	240 (66)	186 (73)
Black	24 (15)	3 (7)	3 (9)	86 (29)	15 (16)[a]	15 (18)	54 (16)	15 (14)	5 (8)	18 (5)	3 (3)	2 (3)	182 (15)	36 (10)[a]	25 (10)[a]
Asian	17 (11)	3 (7)	2 (6)	18 (6)	7 (7)	3 (4)	28 (8)	15 (14)	4 (7)	53 (14)	19 (17)	20 (25)[a]	116 (10)	44 (12)	29 (11)
Multiracial	4 (3)	2 (4)	0	4 (1)	2 (2)	1 (1)	3 (1)	0	0	7 (2)	2 (2)	2 (3)	18 (2)	6 (2)	3 (1)
Hawaiian/ Pacific Islander	0	0	0	0	0	0	0	0	0	1 (0)	0	0	1 (0)	0	0
Native American/ Alaskan Native	0	0	0	4 (1)	0	0	0	0	0	2 (1)	0	1 (1)	6 (1)	0	1 (0)
Unknown	4 (3)	2 (4)	0	19 (6)	15 (16)	0	13 (4)	7 (6)	0	25 (6)	12 (11)	0	61 (5)	36 (10)	0
Missing	0	0	3 (9)	0	0	5 (6)	0	0	2 (3)	0	0	2 (3)	0	0	12 (5)
Ethnicity															
Not Hispanic	146 (92)	42 (91)	26 (79)	245 (82)	65 (68)	64 (78)	295 (89)	98 (90)	50 (82)	321 (82)	88 (79)	68 (85)	1007 (85)	293 (81)	208 (81)
Hispanic	12 (8)	4 (9)	5 (15)[a]	49 (16)	29 (31)[a]	15 (18)	29 (9)	11 (10)	9 (15)	68 (17)	24 (21)	10 (13)	158 (13)	68 (19)	39 (15)
Unknown	0	0	0	6 (2)	1 (1)	1 (1)	8 (2)	0	0	2 (1)	0	1 (1)	16 (1)	1 (0)	2 (1)
Missing	0	0	2 (6)	0	0	2 (2)	0	0	2 (3)	1	0	1 (1)	1 (0)	0	7 (3)
Family history of kidney disease															
No	112 (71)	34 (74)	29 (88)	181 (60)	46 (48)	68 (83)[a,b]	224 (67)	73 (67)	57 (93)[a,b]	263 (67)	68 (61)	59 (74)	780 (66)	221 (61)	213 (83)[a,b]
Yes	42 (27)	12 (26)	4 (12)	113 (38)	47 (49)	17 (14)	94 (28)	33 (30)	3 (5)	116 (30)	43 (38)	20 (25)	365 (31)	135 (37)	41 (16)
Unknown	4 (3)	0	0	6 (2)	2 (2)	0	14 (4)	3 (3)	1 (2)	13 (3)	1 (1)	1 (1)	37 (3)	6 (2)	2 (1)

CUMC, Columbia University Medical Center; CureGN, Cure Glomerulonephropathy Network; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; OLD, of longstanding disease.
[a]*P* < 0.05 for comparison against CureGN cohort.
[b]*P* < 0.05 for comparison against CUMC-CureGN cohort.
Data are *n* (%) or median (interquartile range–SD).

Table 3. Clinical and laboratory data at enrollment by diagnosis

| Clinical and Laboratory Data	MCD			FSGS			MN			IgAN			TOT		
	CureGN	CUMC-CureGN	OLD	CureGN	CUMC-CureGN	OLD	CureGN	CUMC-CureGN	OLD	CureGN	CUMC-CureGN	OLD	CureGN	CUMC-CureGN	OLD
BMI	28 (9.45–8.90)	27 (5.29–6.52)	25 (7.51–7.25)	28 (8.99–13.49)	28 (7.74–8.76)	27 (8.89–7.93)	28 (8.62–18.04)	27 (8.07–28.87)	28 (7.96–10.82)	27 (7.85–7.46)	26 (7.52–6.23)	26 (5.84–4.74)	28 (8.53–11.97)	27 (7.48–16.49)	27 (6.61–7.54)
BP at enrollment, mm Hg	121/74	121/75	122/76	125/77	122/78	127/80	127/77	130/78	130/80	122/78	121/80	127/80	125/78	125/80	127/80
HTN in history	50 (32)	20 (43)	14 (42)	175 (58)	57 (60)	54 (66)	199 (60)	60 (55)	51 (84)[a,b]	217 (55)	67 (60)	59 (74)[a,b]	641 (54)	204 (56)	178 (70)[a,b]
	n = 141	n = 42	n = 32	n = 266	n = 82	n = 82	n = 300	n = 88	n = 61	n = 356	n = 97	n = 79	n = 1063	n = 309	n = 254
Creatinine (mg/dl)	0.8 (0.33–0.73)	0.9 (0.33–1.15)	0.8 (0.31–0.28)	1.3 (1.21–1.73)	1.4 (1.44–1.78)	1.3 (1.52–1.47)	1.0 (0.71–0.72)	1.0 (0.86–0.84)	1.3 (1.00–0.95)[a]	1.2 (0.95–1.20)	1.4 (1.10–1.08)	1.6 (1.27–1.18)	1.2 (0.87–1.22)	1.3 (1.08–1.24)	1.2 (1.15–1.20)
eGFR ml/min per 1.73 m^2															
≥90	72 (51)	16 (35)	19 (58)	56 (21)	12 (13)	17 (21)	89 (30)	28 (26)	7 (11)	94 (26)	20 (18)	10 (13)	311 (29%)	76 (21)	53 (21)
60≤n<90	43 (30)	15 (33)	12 (36)	57 (21)	20 (21)	22 (27)	96 (32)	25 (23)	20 (33)	81 (23)	18 (16)	22 (28)	277 (26%)	78 (22)	76 (30)
30≤n<60	23 (16)	10 (22)	1 (3)	87 (33)	22 (23)	24 (29)	85 (28)	22 (20)	22 (36)	124 (35)	41 (37)	26 (33)	319 (30%)	95 (26)	73 (29)
15≤n<30	1 (1)	0	0	46 (17)	18 (19)	13 (16)	29 (10)	13 (12)	8 (13)	49 (14)	16 (14)	19 (24)	125 (12%)	47(13)	40 (16)
<15	2 (1)	1 (2)	1 (3)	20 (8)	10 (11)	6 (7)	1 (0)	0	4 (7)	8 (2)	2 (2)	3 (4)	31 (3%)	13 (4)	14 (5)
	n = 120	n = 36	n = 25	n = 231	n = 70	n = 60	n = 267	n = 77	n = 50	n = 306	n = 85	n = 51	n = 924	n = 268	n = 186
UPCR	0.2 (0.33–0.83)	0.5 (2.25–4.59)	0.3 (3.35–8.52)	1.4 (1.21–1.73)	1.6 (3.82–3.74)	1.2 (3.70–2.86)	1.9 (0.71–0.72)	1.3 (5.40–5.03)	2.8 (5.80–3.68)	0.5 (0.95–1.20)	0.6 (1.63–2.43)	0.5 (1.51–1.24)	1.6 (0.87–1.22)	1.9 (4.03–4.38)	1.9 (4.44–4.47)
										n = 300	n = 87	n = 80			
Urinalysis: blood >1+										165 (42)	48 (43)	23 (29)[a,b]			

BMI, body mass index; BP, blood pressure; CUMC, Columbia University Medical Center; CureGN, Cure Glomerulonephropathy Network; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; HTN, hypertension; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; UPCR, urinary protein-to-creatinine ratio.
[a]$P < 0.05$ for comparison against CureGN cohort.
[b]$P < 0.05$ for comparison against CUMC-CureGN cohort.
Data are given as n (percentage) or median (interquartile range–SD).
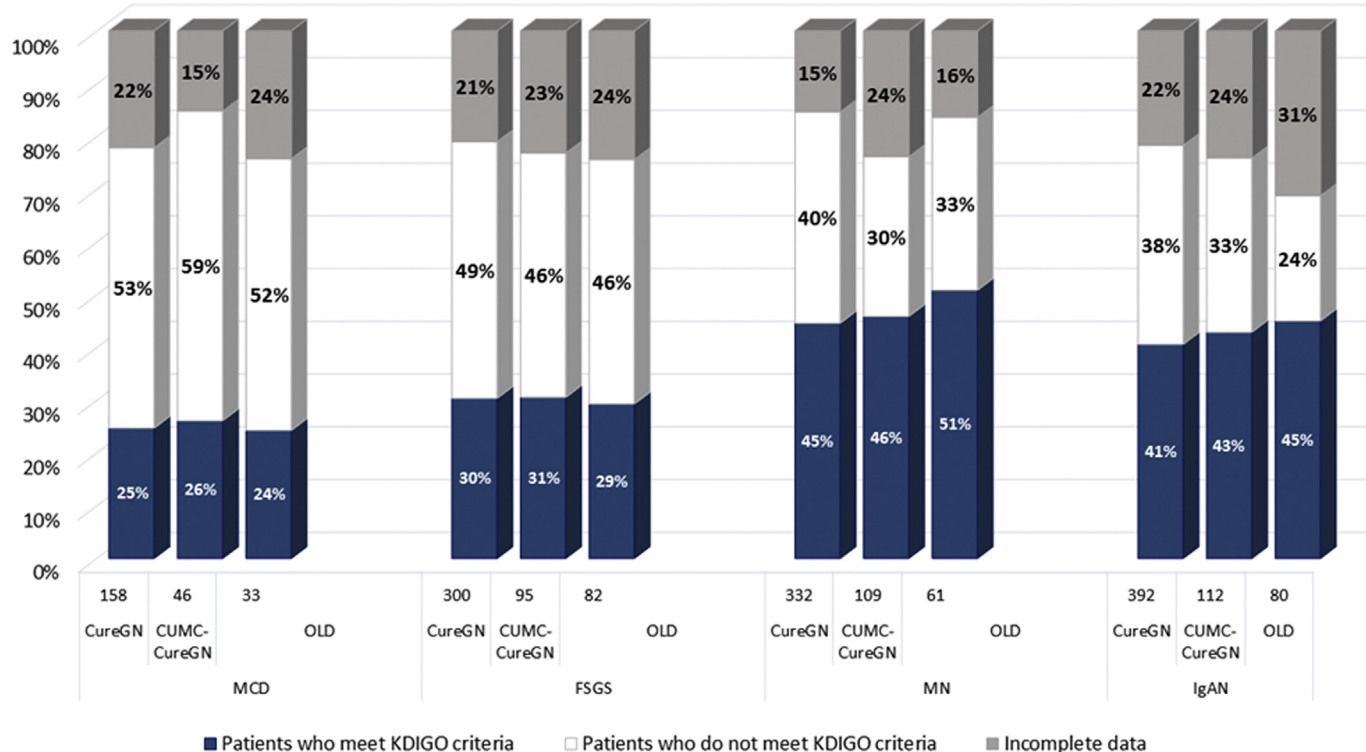
Figure 1. Treatment thresholds across disease groups. Treatment threshold cutoff for IgA nephropathy (IgAN) was urinary protein-to-creatinine ratio (UPCR) >1 g/g or 24-hour urine protein >1 g, despite optimal conservative therapy. Treatment threshold cutoff for minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (MN) was UPCR >3.5 g/g or 24-hour urine protein >3.5 g/d (or serum albumin <3.0 g/dl if proteinuria was not available), despite conservative therapy. CUMC, Columbia University Medical Center; CureGN, Cure Glomerulonephropathy Network; KDIGO, Kidney Disease: Improving Global Outcomes; OLD, of longstanding disease.

threshold criteria at rates equal to those seen in CureGN participants at enrollment. Next, we used the CureGN's Disease Activity Working Group definitions to compare disease activity (Table 1). Using these more conservative cutoffs, all 3 cohorts showed higher rates of disease activity, but we detected no difference in activity between OLD patients versus CureGN patients via this metric (Figure 2). Disease activity by cohort across diagnoses using the CureGN's Disease Activity Working Group definitions is summarized in Table 4. When we subdivided the CUMC-CureGN cohort into incident and prevalent patients (defined as diagnostic biopsy within 6 months of enrollment vs. diagnostic biopsy 6 months to 5 years before enrollment, respectively), the OLD cohort demonstrated similar activity rates as incident or prevalent CUMC-CureGN patients with MCD, FSGS, and IgAN groups. Conversely, patients with MN in the prevalent CUMC-CureGN group showed lower disease activity when compared with the OLD cohort ($P = 0.005$).

Repeat Biopsies

In the OLD cohort, 86 of 256 patients (34%) underwent a second native kidney biopsy, compared with 25 of 1182 (2%) patients in the CureGN cohort (Figure 3;

Supplementary Table S1). Patients who underwent a second biopsy were divided relatively equally among the 4 disease groups. In most cases, the repeat biopsy did not change diagnosis. In cases in which the diagnosis had changed (OLD: $n = 9$; CureGN: $n = 3$), the most common findings were segmentally sclerotic glomeruli in a patient previously diagnosed with MCD. Analyzing choices made by clinicians after additional biopsies in the OLD cohort, in 49% of the cases (50 of 103 biopsies) a change regarding immunosuppression was made, whether starting or changing immunosuppression (46%) or stopping therapy (3%). In patients with IgAN undergoing repeat biopsy for worsening proteinuria (presumed ongoing activity), only 6% had T2 lesions suggestive of advanced chronicity, 88% had mesangial proliferation (M1), and 38% had endocapillary proliferation (E1). In patients with IgAN undergoing repeat biopsy for declining eGFR without change in proteinuria (presumed chronicity), 50% had T2 lesions and 0% had E1 lesions.

DISCUSSION

Although the onset of glomerular diseases can be acute and severe, these diseases often become slowly progressive forms of chronic kidney disease. Because the

Table 4. Disease activity by cohort across diagnoses

n %	MCD	FSGS	MN	IgAN
OLD	33 (91)	82 (57)	61 (69)	80 (74)
CureGN	158 (87)	300 (57)	332 (62)	392 (74)
CUMC-CureGN	46 (87)	95 (59)	109 (55)	112 (78)
Incident[a]	11 (91)	42 (64)	39 (74)	56 (80)
Prevalent[b]	35 (86)	53 (55)	70 (44)	56 (75)

CUMC, Columbia University Medical Center; CureGN, Cure Glomerulonephropathy Network; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; OLD, of longstanding disease.
[a]Incident, diagnostic biopsy within 6 mo of enrollment vs. diagnostic biopsy 6 mo to 5 yr before enrollment.
[b]Prevalent, diagnostic biopsy 6 mo to 5 yr before enrollment.
[c]The OLD cohort was significantly more active than the CUMC-CureGN Prevalent cohort ($P = 0.005$), and the CUMC-CureGN Incident than the CUMC-CureGN Prevalent cohort ($P = 0.003$).
Data are given as number of patients in each cohort (n), and percentage of patients with active disease (%).
Disease activity between the OLD/CureGN/CUMC-CureGN cohorts, in the 4 disease subtypes, was compared using Kruskal-Wallis test: MCD, $P = 0.837$; FSGS, $P = 0.960$; MN, $P = 0.194$; IgAN, $P = 0.690$.
Disease activity between the OLD/CUMC-CureGN Incident/CUMC-CureGN Prevalent cohorts, in the 4 disease subtypes, was compared using Kruskal-Wallis test: MCD, $P = 0.773$; FSGS, $P = 0.630$; MN, $P = 0.002$[c]; IgAN, $P = 0.660$.

pattern of these diseases evolves over time, longer follow-up is required to assess patient outcomes. In this study, we examined disease activity in the 4 leading primary glomerular diseases (MCD, FSGS, MN, and IgAN), comparing activity between adult patients with longstanding disease (OLD cohort) and adult patients with recent onset of disease enrolled in the CureGN study. The median time since first diagnostic kidney biopsy for OLD patients was 10 years, compared with 1

year for CureGN-enrolled patients. Using Kidney Disease: Improving Global Outcomes–recommended treatment thresholds as a marker of persistent disease activity, we found no difference in activity status between patients in the OLD cohort and CureGN participants. We next categorized patients by CureGN's Disease Activity Working Group criteria, which were created by a group of GN experts to be as unambiguous and practically useful as possible in a large cohort, advocating sensitivity rather than specificity. Using these CureGN-based activity definitions, the OLD cohort again displayed equal disease activity rates as CureGN participants. Interestingly, the OLD cohort showed activity rates more comparable with incident patients rather than prevalent patients. Our findings highlight that, in some patients, glomerular diseases remain persistently active far into their disease course.

Incidence rates of primary glomerular diseases have been well-documented, and long-term clinical outcomes for these conditions have been reported.[6–10] Nevertheless, the literature is comparably bare in reporting persistence of disease activity many years after clinical onset. Our study presents a unique approach to this population by analyzing patients in terms of disease activity rather than their chronic kidney disease or end-stage kidney disease status. Studies on disease activity generally focus on secondary forms of GN,[11,12] or recurrence of primary GN after
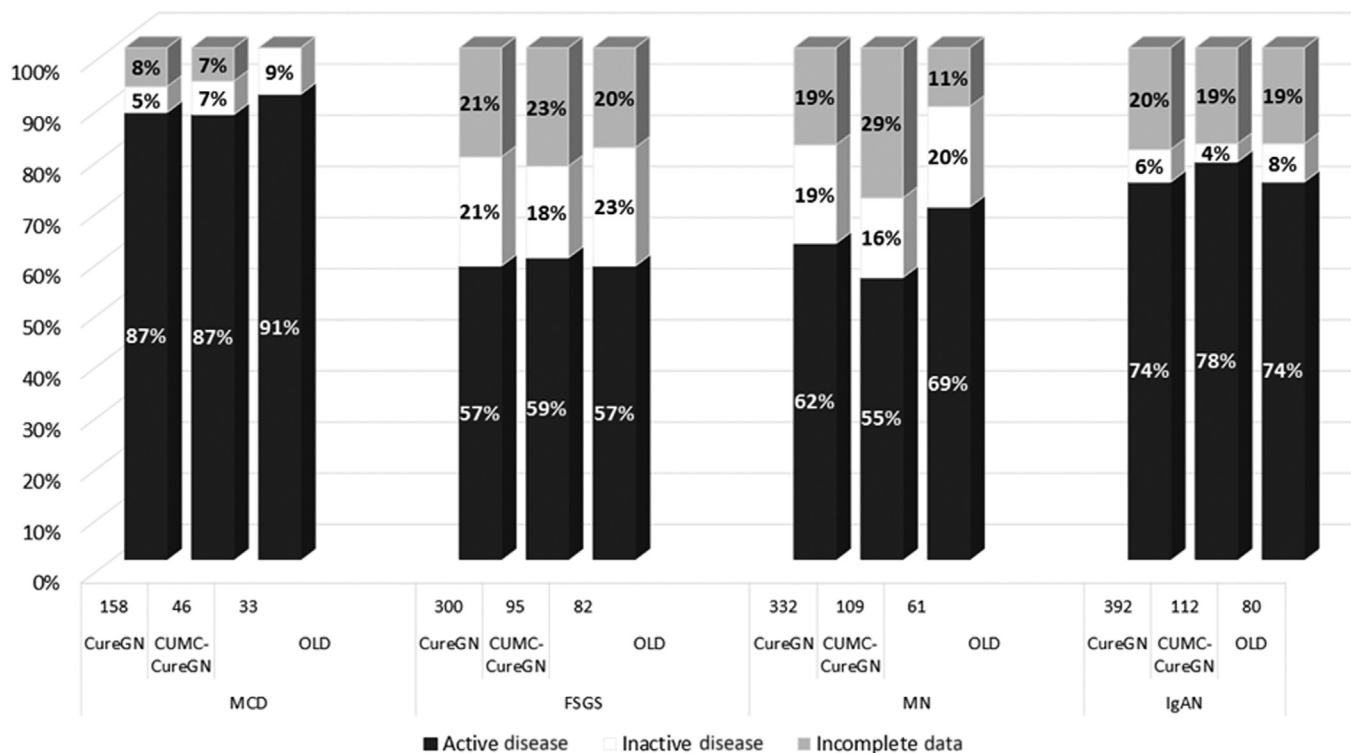
Figure 2. Disease activity at enrollment/screening according to Cure Glomerulonephropathy Network (CureGN) disease activity criteria. CUMC, Columbia University Medical Center; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; OLD, of longstanding disease.
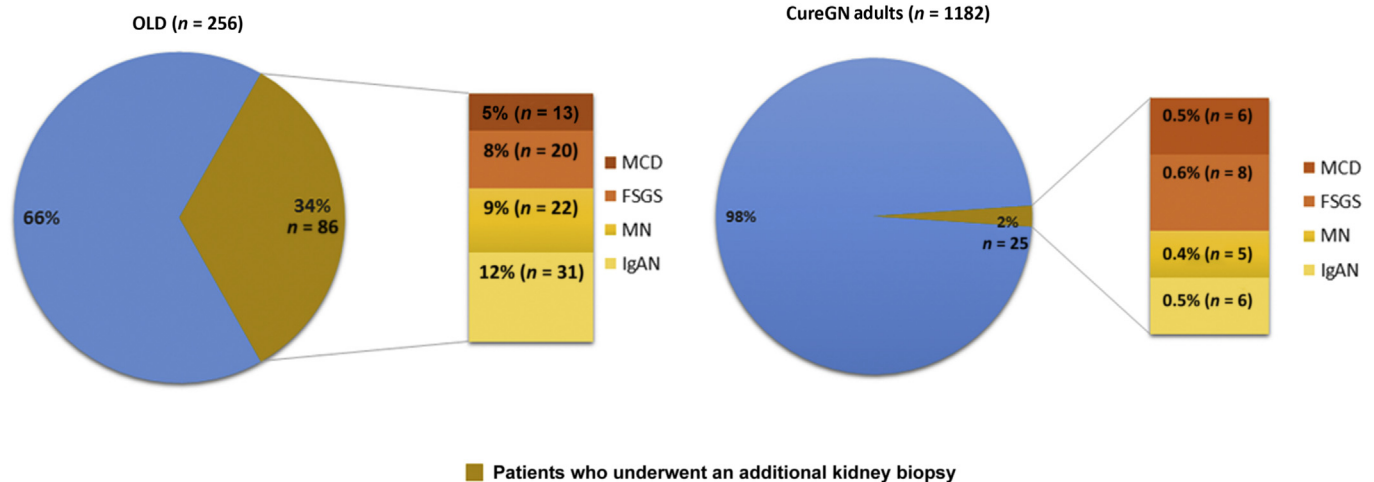
Figure 3. Proportions of patients who underwent an additional kidney biopsy across disease groups. CUMC, Columbia University Medical Center; CureGN, Cure Glomerulonephropathy Network; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; OLD, of longstanding disease.

kidney transplantation.[13,14] Patients with long-standing, primary glomerular disease are generally considered less active than patients with recent onset of the disease.

Our study stands alongside the few prior studies that have carefully examined longstanding forms of glomerular diseases in challenging this assumption. A study of 340 Chinese adults with MCD reported that nearly half continued to have flares more than 10 years past their initial presentation.[15] In our OLD cohort, the proportion of persistent MCD relapsers was even higher. Kanigicherla et al.[16] analyzed long-term outcomes of persistent disease and relapse rates in 128 patients with MN followed over a median of 12 years: 28% did not achieve remission (complete or partial), and 31% of the patients who reached partial remission experienced at least 1 relapse. In our OLD cohort, 51% of patients with MN met treatment threshold at time of screening, which is a fixed time-point, suggesting that the proportion would have been even higher during the median 10 years since biopsy. Other than proteinuria, the magnitude and persistence of hematuria during follow-up have been demonstrated to have a significant influence on the progression of disease in patients with IgAN.[17] When time-averaged, a recent study reported that, in 46% of patients with IgAN followed for a mean period of 14 years, hematuria disappeared. This proportion seems low when compared with that of our OLD cohort without hematuria (71%), but our data were collected at screening and not repeated over time. Notably, with regard to proteinuria, only 7% of the OLD patients with IgAN met criteria for complete remission.

Patients in the OLD cohort had a significantly longer disease course and were diagnosed at a younger age than their CureGN counterparts. Despite having chronic, but persistently active, disease, renal function in the OLD cohort at screening was comparable with that of CUMC-CureGN patients. Moreover, renal function over an 8-year time window was similar in the 2 cohorts, though OLD patients had been diagnosed, on average, 9 years earlier in their course than the CUMC-CureGN patients (Figure 4). Proteinuria has always been recognized as one of the most important risk factors for the decline of renal function over time in primary GN[18–21]; the effects become evident in long-term follow-up. The gap between the serum creatinine slopes of the 2 cohorts should increase over time, and thus the lack of such an increase suggests a survivor benefit in OLD patients. If younger age at diagnosis is implicated in slower decline of renal function, this must be assessed in further studies along with other potential protective factors.

The significantly higher rate of repeat biopsies in OLD patients (34%) further emphasizes marked disease activity in this population and associated clinical challenges for nephrologists. Many studies have reassessed disease activity by biopsy in lupus nephritis,[22–26] but this same sort of attention to repeat biopsies in primary GN has not been routine. In this study, the most frequent reasons why patients with MCD or FSGS were rebiopsied were therapy-resistance or corticosteroid-dependent/frequently relapsing diseases. As reaffirmed by a recent study on the clinical course of MCD with onset in adulthood,[6] a missed diagnosis of FSGS is often suggested to explain corticosteroid resistance, which occurred for 6 patients in the OLD cohort and 7 in the CureGN study. Conversely, assessing whether worsening proteinuria and/or renal function were driven by active disease or
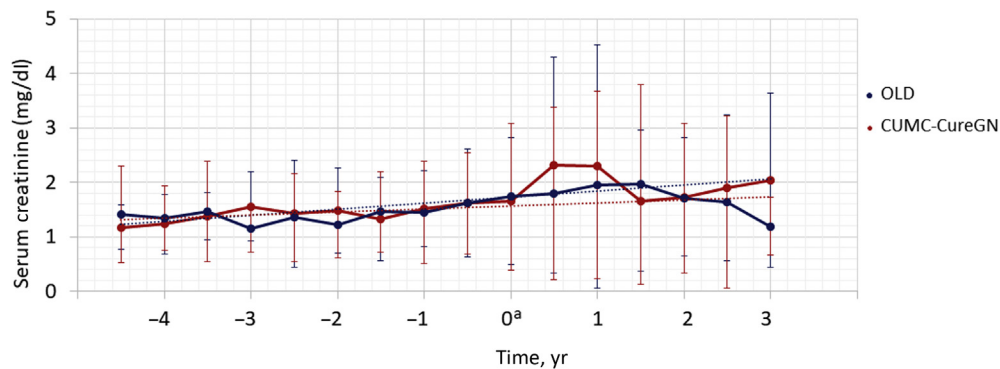
Figure 4. Serum creatinine over time in of longstanding disease (OLD) and Columbia University Medical Center (CUMC)–Cure Glomerulone-phropathy Network (CureGN) cohorts. [a]Point 0 marks enrollment/screening.

the result of a chronic process was the primary reason for second biopsies of patients with MN and IgAN. These data show the importance of histology to help decision-making in management of patients with longstanding glomerular diseases. Although the sample size of repeat biopsies in these cohorts is small, in the subgroup with IgAN, we gleaned some information on how well disease activity assessments correlate with histology using Oxford Classification scores: T2 lesions were more common in patients with presumed chronicity, whereas M1 and E1 lesions were the hallmark in patients with presumed ongoing activity. Our study has notable limitations. Principally, the OLD cohort is almost certainly affected by some degree of selection bias, as it includes patients who still require follow-up at a tertiary care center >5 years after diagnosis and presumably have better access to health care. Hence, these patients may be more active in their disease states than patients of similar disease vintage followed in nonacademic medical settings. The high repeat biopsy rate of the OLD cohort may reflect the preceding considerations. Our criteria for activity rely principally on creatinine, proteinuria, and hematuria, and do not take into account other acknowledged markers of activity and disease progression, such as phospholipase A2 (PLA2R) antibodies for MN, and blood pressure and histologic findings for all the 4 GNs. Data collection in this study was not uniform. The OLD cohort data were analyzed retrospectively; data collection on CureGN patients combined retrospective collection from chart review and prospective collection starting at enrollment. Reporter bias likely affected some data points, notably family history and medication exposures. However, the laboratory-based data points used for analysis of disease activity in this study are objective and fairly easy to confirm, limiting the effect of such bias.

In conclusion, this study identified a subset of patients with longstanding MCD, FSGS, MN, and IgAN, who had neither sustained remission nor progression to end-stage kidney disease and therefore necessitated regular nephrology care at a tertiary care center >5 years after diagnosis. These patients are notable in having clinical phenotypes similar to those of patients with newly diagnosed glomerular disease. This subset of patients likely exists within the CureGN cohort, but in the absence of reliable biomarkers, it will take a decade or more of follow-up to identify the OLD subset within the CureGN patients. Such survivor patients, with long-term but persistently active disease, may represent a special subpopulation lacking progression factors or enriched in protective factors. They are difficult to identify at time of biopsy and present a challenge to clinicians, who must balance the need to treat ostensibly active disease with side effects of second- or third-line therapies. At the moment, there are no validated biomarkers that have been shown to reflect the underlying pathological mechanisms operating in the individual GNs, and this is supported by the high rate of repeat biopsies performed in the OLD cohort. OLD patients are therefore potentially highly informative for understanding the clinical course and pathogenesis of glomerulopathies and identifying subtypes of disease. The characteristics of the OLD cohort suggest that factors mediating disease activity may be distinct from factors mediating progression. Unlocking this pathophysiology, in turn, can identify potential treatment targets for more chronic variants of disease and present a framework for personalized diagnostics and therapeutics.

APPENDIX

List of Members of the CureGN Consortium
Consortium Collaborators

The CureGN Consortium members listed as follows, from within the 4 Participating Clinical Center networks and Data Coordinating Center, are acknowledged by the authors as Collaborators (not co-authors) on this manuscript and must be indexed in PubMed as Collaborators. CureGN Principal Investigators are noted (**).

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DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTAL MATERIAL

Supplemental File (PDF)

Table S1. Indications to repeat kidney biopsies.

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