KI REPORTS
KIReports.org

"Normal" Glomerular Score Correlates With Outcomes in Antineutrophil Cytoplasmic Autoantibody–Associated Vasculitis With Glomerulonephritis

Marta Casal Moura[1], Fernando C. Fervenza[2], Ulrich Specks[1] and Sanjeev Sethi[3]

[1]Division of Pulmonary and Critical Care, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA; [2]Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA; and [3]Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

Correspondence: Sanjeev Sethi, Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First Street, SW, Rochester, Minnesota 55901, USA. E-mail: sethi.sanjeev@mayo.edu

Received 26 September 2024; revised 8 November 2024; accepted 12 November 2024; published online 20 November 2024

Kidney Int Rep (2025) **10,** 596–600; https://doi.org/10.1016/j.ekir.2024.11.019
KEYWORDS: ANCA; glomerulonephritis; kidney biopsy; normal glomerular score

INTRODUCTION

Glomerulonephritis (GN) is a frequent presentation of antineutrophil cytoplasmic antibody–associated vasculitis (AAV),[1] and an important factor of morbidity and mortality.[2] The kidney biopsy in AAV-GN typically shows necrotizing and crescentic GN. The biopsy may also show sclerosing lesions along with glomeruli that do not show either necrotizing, crescentic, or sclerosing lesions.[3] Kidney biopsy is used to determine the prognosis in AAV-GN. The most used system is the Berden classification, which is based on both the extent of glomerular involvement by necrotizing and crescentic lesions and the extent of glomerular scarring.[4] Recently, we proposed a classification to predict end-stage kidney disease (ESKD) based not on the active necrotizing and crescentic lesions, but on the extent of chronic changes present on the kidney biopsy.[5] A combination of clinical and kidney biopsy findings has also been proposed to predict ESKD development at 36 months.[6]

An important finding on kidney biopsy in AAV-GN is not just the presence of necrotizing and crescentic lesions (active lesions) or the glomerulosclerosis (chronic lesions), but the presence of glomeruli that are not involved by either active or chronic lesions but appear normal on light microscopy. Although normal appearing glomeruli are factored in when estimating the extent of active and chronic lesions in the above-mentioned classifications, studies with a large number of cases to better estimate the risk of developing ESKD based on the extent of normal appearing glomeruli have not been done. The percentage of normal appearing glomeruli in an AAV-GN biopsy are easy to calculate and does not require expertise such as evaluating type of crescent, degree of interstitial fibrosis, and raises the possibility of being implemented by artificial inteligence[7]

In this study, we show that the percentage of normal glomeruli on kidney biopsy correlates with development of ESKD in AAV-GN. The study design, definitions, outcomes, and methodology are described in the Supplementary Material.

RESULTS

Patient Characteristics and Clinical Outcomes

Of the 467 patients with active AAV-GN identified during the study period, 329 (70.4%) had kidney histology available to grade and score (Supplementary Figure S1). Renal remission was observed in 225 patients (68.4%) at 6 months and in a total of 270 patients (82.1%) during the follow-up. Relapses were documented in 88 patients (26.7%), of which 53 (60.2%) had a renal relapse. Dialysis was required in 50 patients (15.2%). By the end of the follow-up (median of 5.9 years [interquartile range: 3.0–11.3]), 75 patients (22.8%) had died.

Kidney Biopsy Findings

The kidney biopsies had in a median (interquartile range) of 16 (12–23) glomeruli, 5 (2–7) crescents, 7 (4–11)

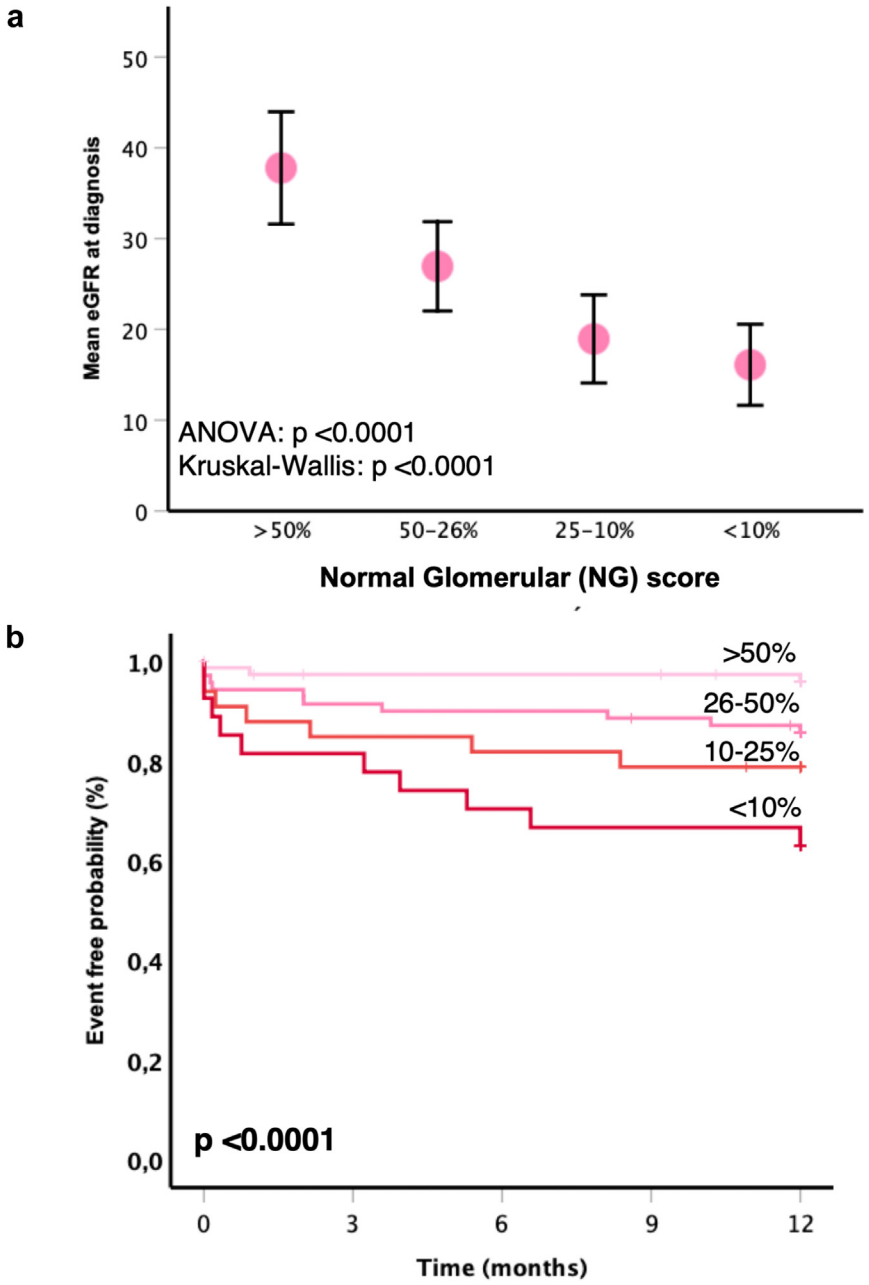

Figure 1. (a) Estimated glomerular filtration rate and (b) end-stage kidney disease at 12 months based on NG score. NG score is divided into (i) very low NG score $<$ 10% of normal glomeruli $=$ 0, (ii) low NG 10%–25% of normal glomeruli $=$ 1; (iii) moderate NG score 26%–50% of normal glomeruli $=$ 2; and (iv) high NG score $>$50% of glomeruli $=$ 3. NG, normal glomerular.

normal glomeruli, and normal glomerular (NG) score of 43.3% (23.5–64.3). The kidney biopsies were scored into the following: (i) high NG score, 121 (36.8%) cases; (ii) moderate NG score, 108 (32.8%) cases; (iii) low NG score, 63 (19.1%) cases; and (iv) very low NG score, 37 (11.2%) cases (Supplementary Figure S1 and Supplementary Table S1). There was no difference in the median number of glomeruli present in the biopsy by each category ($P = 0.535$). The patients were equally distributed according to antineutrophil cytoplasmic antibody specificity. Representative kidney biopsies of each group are shown in Supplementary Figure S2.

NG Score Correlates With Clinical Findings at First Detection of Active Renal Disease

The distribution of the clinical characteristics based on the NG score is shown in detail in Supplementary Table S2. The patients were equally distributed between categories in terms of age, sex, clinical phenotype, antineutrophil cytoplasmic antibody specificity, and severity of clinical manifestations as determined by the Birmingham vasculitis activity score for Wegener granulomatosis score. There were no statistically significant differences in the distribution of the type of disease presentation (new diagnosis vs. relapse), or

Table 1. Outcomes of antineutrophil cytoplasmic antibody–associated vasculitis glomerulonephritis based on NGS categories ($n = 329$)

NGS clinical categories	High NG score (>50%) $n = 121$ (36.8%)	Moderate NG score (26%–50%) $n = 108$ (32.8%)	Low NG score (10%–25%) $n = 63$ (19.1%)	Very low NG score (< 10%) $n = 37$ (11.2%)	*P*-value[a]
Outcomes					
Vasculitis activity, *n* (%)					
Remission					
6 mo	73 (75.3)	76 (84.4)	41 (80.4)	20 (69.0)	0.243
Total[b]	96 (92.3)	88 (93.6)	51 (92.7)	28 (90.3)	0.942
Complete remission					
6 mo	18 (20.9)	22 (25.3)	10 (20.8)	7 (23.3)	0.899
Total[b]	60 (59.4)	60 (64.5)	29 (54.7)	20 (64.5)	0.654
Relapse					
12 mo	10 (8.8)	9 (8.5)	9 (14.8)	2 (5.7)	0.434
Total[b]	28 (24.8)	28 (26.7)	14 (22.6)	7 (18.9)	0.446
Death					
12 mo	7 (5.8)	3 (2.8)	2 (3.2)	3 (8.1)	0.466
24 mo	10 (8.3)	8 (7.4)	3 (4.8)	4 (10.8)	0.718
Total[b]	30 (24.8)	19 (17.6)	14 (22.2)	12 (32.4)	0.272
Renal, *n* (%)					
Renal recovery					
6 mo	57 (79.2)	44 (64.7)	25 (62.5)	7 (30.4)	<0.0001
ESKD					
12 mo	8 (6.6)	14 (13.0)	12 (19.0)	15 (40.5)	<0.0001
24 mo	10 (8.3)	15 (13.9)	14 (22.2)	16 (43.2)	<0.0001
Total[b]	15 (12.4)	20 (18.5)	18 (28.6)	18 (48.6)	<0.0001
Dialysis	7 (6.9)	13 (14.0)	10 (18.9)	12 (38.8)	<0.0001
Combined events of kidney failure and/or death, *n* (%)					
24 mo	18 (14.9)	18 (16.7)	16 (25.4)	17 (45.9)	<0.0001
Total[b]	36 (29.8)	32 (29.6)	27 (42.9)	24 (64.9)	<0.0001
Time to event, median (IQR) mo					
Remission	3.7 (2.2–5.9)	3.6 (2.3–6.0)	5.0 (3.0–5.9)	5.9 (3.2-6.7)	0.042
Relapse	23.4 (5.9–39.0)	15.9 (10.7–74.8)	11.5 (4.0–28.9)	30.1 (11.8–60.6)	0.245
Death	61.5 (13.0–105.3)	37.0 (16.0–52.0)	36.0 (14.3–120.3)	56.0 (5.9–98.0)	0.843
ESKD	3.8 (0.6–54.2)	4.0 (0.4–51.1)	3.9 (0.0–25.1)	1.2 (0.07–6.6)	0.515
Combined events	23.0 (2.2–75.8)	16.4 (2.0–51.0)	15.0 (0.2–32.5)	3.2 (0.1–62.3)	0.168
Time of FU after renal involvement, median (IQR) years	8.2 (3.3–12.3)	5.2 (3.1–11.7)	6.9 (3.0–11.9)	6.8 (3.5–13.0)	0.930

AAV, antineutrophil cytoplasmic antibody–associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; BVAS/WG, Birmingham vasculitis activity score for Wegener Granulomatosis; eGFR, estimated glomerular filtration rate; FU, follow-up; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; IQR, interquartile range; MCCS, Mayo Clinic Chronicity Score; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.
[a]*P*-value < 0.05 is considered significant (Pearson χ^2 test for categorical variables, analysis of variance test for continuous variables normal distributed and Kruskal-Wallis test for continuous variables with skewed distribution).
[b]"Total" refers to the number of occurrences during all follow-up time.

maintenance-remission treatment strategy per category. More patients with very low NG score received cyclophosphamide for remission-induction (Supplementary Table S2). The frequency of treatment with i.v. methylprednisolone and treatment with plasma exchange varied across categories ($P = 0.025$ and $P = 0.032$, respectively) (Supplementary Table S2).

Mean estimated glomerular filtration rate at baseline correlated with the NG score and decreased in a gradient from high to very low NG score (high NG score with 37.5 vs. moderate NG score with 23.6 vs. low NG score with 17.0 vs. very low NG score with 12.0 ml/min per 1.73 m^2; $P < 0.0001$) (Supplementary Table 2). The NG score correlated with median estimated glomerular filtration rate: lower NG score was associated with lower median estimated glomerular filtration rate at baseline (Figure 1a).

Outcomes Stratified According to NG Score

ESKD at 12 months and dialysis were more frequent in patients with very low NG score (very low NG score with 40.5% vs. low NG score with 19.0% vs. moderate NG score with 13.0% vs. high NG score with 6.6% of ESKD at 12 months, $P < 0.0001$; very low NG score with 38.9% vs. low NG score with 18.9% vs. moderate NG score with 14.0% vs. high NG score with 6.9% of dialysis, $P < 0.0001$) (Figure 1b and Table 1). Renal recovery at 6 months was more frequent in patients with high NG score (high NG score with 79.2% vs. moderate NG score with 64.7% vs. low NG score with

62.5% vs. very low NG score with 30.4% of renal recovery, $P < 0.0001$) (Table 1).

Using the Kaplan Meier method, the NG score displayed prognostic information for the renal outcomes of ESKD at 12 months ($P < 0.0001$) (Figure 1b). Using univariable Cox regression, we determined that the NG score is protective for the development of ESKD at 12 months (Supplementary Table S3).

DISCUSSION

A characteristic of AAV-GN is that the necrotizing and crescentic lesions do not involve all the glomeruli and varying numbers of normal appearing glomeruli are present on the kidney biopsy. We hypothesized that the percentage of normal appearing glomeruli (NG score) correlates with the recovery potential and renal outcomes. Our study shows that the NG score is a valid simple prognostic tool for the independent assessment of renal outcomes in AAV-GN. Thus, lower NG scores (≤25% of normal glomeruli) correlated with lower estimated glomerular filtration rate at diagnosis and strongly correlated with progression to ESKD at 12 months.

There are multiple classifications to help in guiding management and assessing outcomes in AAV-GN.[1,4–6,8] The most commonly used classification is the Berden classification which is based on the extent of glomerular involvement by necrotizing and crescentic lesions, and the extent of glomerular scarring.[1,4] The Berden classification has proven only partially useful for prognosis for ESKD development, because there is significant overlap between the various groups of the Berden classification. Several studies have shown that commonly evaluated renal outcomes such as ESKD were not accurately discriminated between patients classified as crescentic or mixed Berden classes.[4] The Mayo Clinic Chronicity Score has also been used to grade chronic changes on kidney biopsy in various disease entities, including AAV-GN; and more recently, the Mayo Clinic Chronicity Score was proposed as a valuable alternative to establish the prognosis in patients with AAV-GN because it independently predicted kidney function, outcomes (ESKD at 12 months, ESKD at 24 months, and combined ESKD and/or death at 24 months), and response to treatment.[5] Lastly, a combination of kidney biopsy findings with clinical features result in a renal risk score to predict development of ESKD at 36 months.[6] All the above classifications hold merit but are somewhat difficult to use and as mentioned earlier, there is overlap between different classes. These classifications in some way include normal glomeruli along with other lesions but do not form the basis of any class or grade.

The percentage of normal glomeruli as a marker for recovery is an easy concept to envision, it does not require expertise to quantify, and can be easily implemented across medical practice.

In conclusion, our study shows that the NG score correlates with renal outcomes in AAV-GN. NG score is simple to use and is useful for risk stratification of renal outcomes in patients with AAV-GN.

DISCLOSURE

FCF received unrestricted grants from Genentech Inc., South San Francisco, CA. All the other authors declared no competing interests.

AUTHOR CONTRIBUTIONS

MCM, US, FCF, and SS designed the study. MCM abstracted the data. MCM and SS reviewed and scored the biopsies. MCM, US, FCF, and SS analyzed the data. MCM performed the statistical analysis. MCM, US, FCF, and SS drafted and revised the paper. All the authors provided input for the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) flowchart for the selection of the patient with active renal involvement in Anti-Neutrophil Cytoplasmic Antibodies (ANCA) associated vasculitis (AAV) glomerulonephritis (GN).

Figure S2. Kidney biopsy showing (a) very low normal glomerular score, (b) low normal glomerular score, (c) moderate normal glomerular score, and (d) high normal glomerular score.

Table S1. Distribution of kidney histopathology elements and classification according to normal glomerular score categories ($n = 329$).

Table S2. Clinical characteristics of patients with antineutrophil cytoplasmic antibody–associated vasculitis glomerulonephritis based on the normal glomerular score categories ($n = 329$).

Table S3. Cox univariable analysis of the normal glomerular score as protective factor for end-stage kidney disease development at 12 months in patients with antineutrophil cytoplasmic antibody–associated vasculitis glomerulonephritis.

REFERENCES

1. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. *Nat Rev Dis Primers*. 2020;6:71. https://doi.org/10.1038/s41572-020-0204-y

2. AAE SJ, Stegeman CA, Stegeman CA. Renal survival in proteinase 3 and myeloperoxidase ANCA-associated systemic vasculitis. *Clin J Am Soc Nephrol*. 2013;8:1709–1717. https://doi.org/10.2215/CJN.01020113
3. Jennette JC. Rapidly progressive crescentic glomerulonephritis. *Kidney Int*. 2003;63:1164–1177. https://doi.org/10.1046/j.1523-1755.2003.00843.x
4. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Neprhol*. 2010;21:1628–1636. https://doi.org/10.1681/ASN.2010050477
5. Casal Moura M, Fervenza FC, Specks U, Sethi S. Kidney biopsy chronicity grading in antineutrophil cytoplasmic antibody associated vasculitis. *Neprhol Dial Transpl*. 2022;37:1710–1721. https://doi.org/10.1093/ndt/gfab250
6. Brix SR, Noriega M, Tennstedt P, et al. Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int*. 2018;94:1177–1188. https://doi.org/10.1016/j.kint.2018.07.020
7. Huo Y, Deng R, Liu Q, Fogo AB, Yang H. AI applications in renal pathology. *Kidney Int*. 2021;99:1309–1320. https://doi.org/10.1016/j.kint.2021.01.015
8. Aasarod KBL. Renal histopathology and clinical course in 94 patients with Wegener's granulomatosis. *Nephrol Dial Transplant*. 2001;16:953–960. https://doi.org/10.1093/ndt/16.5.953