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ORIGINAL ARTICLE

Kidney biopsy chronicity grading in antineutrophil cytoplasmic antibody-associated vasculitis

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

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

Correspondence to: Sanjeev Sethi; E-mail: sethi.sanjeev@mayo.edu

ABSTRACT

Background. Kidney biopsy is valuable for prognostic assessment of renal outcomes in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with glomerulonephritis (AAV-GN) but the impact of chronic changes is not determined.

Methods. We conducted a retrospective cohort study of myeloperoxidase (MPO)- or proteinase 3 (PR3)-ANCA-positive patients with AAV and active renal disease. We applied the Mayo Clinic Chronicity Score (MCCS) and validated and evaluated its implications on outcome prediction in AAV-GN.

Results. We analyzed 329 patients with kidney biopsies available to score. The extent of chronicity was graded by MCCS as minimal [102 (31.0%)], mild [106 (32.2%)], moderate [86 (26.1%)] and severe [35 (10.6%)]. The MCCS grades correlated with the degree of renal function impairment at presentation [mean estimated glomerular filtration rate (eGFR) 48.3 versus 29.2 versus 23.7 versus 18.5 mL/min/1.73 m^2, respectively; $P < 0.0001$]. Higher degrees of the individual components of the MCCS (glomerulosclerosis, interstitial fibrosis, tubular atrophy and arteriosclerosis) were associated with lower median eGFR ($P < 0.0001$) and decreased event-free [kidney failure (KF) and death] survival ($P = 0.002$, $P < 0.0001$, $P < 0.0001$ and $P = 0.017$, respectively). Patients with lower MCCS grades recovered renal function more frequently ($P < 0.0001$). Increasing MCCS grades were associated with decreased renal recovery ($P = 0.001$), more frequent events and shorter time to KF ($P < 0.0001$), KF and death ($P < 0.0001$) and death ($P = 0.042$), independent of the remission induction treatment used (cyclophosphamide or rituximab). The MCCS stratified renal outcomes for each MCCS grade and can be used in clinical practice as a cutoff for KF prediction (MCCS ≥ 4).

Conclusions. Chronic changes on kidney histology independently predict renal function, outcomes and response to treatment in AAV-GN.

Keywords: ANCA, glomerulonephritis, kidney biopsy, Mayo Clinic Chronicity Score

INTRODUCTION

Glomerulonephritis (GN) is a frequent presentation of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) [1–3] and an important factor of morbidity and mortality [4, 5]. The most common cause of rapidly progressive GN that presents on kidney biopsy as a pauci-immune necrotizing crescentic GN is AAV-GN, with negative or few immune deposits on indirect immunofluorescence [3, 6]. Kidney biopsy is valuable to establish the diagnosis of AAV-GN [1, 7]. The prognostic utility of kidney histology in AAV-GN has been predominantly based on glomerular pathology [8–17].

Chronic changes are increasingly recognized as an important component of native kidney biopsy evaluation and as strong predictors of renal outcomes in kidney diseases [18, 19]. Chronic changes involve all components of the renal parenchyma and include glomerulosclerosis (GS), interstitial fibrosis (IF), tubular atrophy (TA) and arteriosclerosis [18]. In AAV-GN, characteristic acute lesions of fibrinoid necrosis and crescents are often accompanied by varying degrees of GS, IF, TA and arteriosclerosis [20]. The chronic lesions may appear within weeks or months after the injury or develop slowly in the absence of any apparent acute lesions [7, 18]. GS, interstitial fibrosis and tubular atrophy (IFTA) and moderate to severe arteriosclerosis are independently associated with outcomes in several glomerular diseases [19]. Chronic changes are generally irreversible and have a major bearing on kidney function and are as important as the underlying disease etiology in predicting the prognosis, guiding treatment and assessing treatment response [7, 18].

The Mayo Clinic Chronicity Score (MCCS) was developed by a group of nephrologists and pathologists as a systematic

KEY LEARNING POINTS

What is already known about this subject?

1. Chronic changes are increasingly recognized as an important component of native kidney biopsy evaluation and as strong predictors of renal outcomes in kidney diseases.
2. In antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis with glomerulonephritis (AAV-GN), tubulointerstitial changes predict the estimated glomerular filtration rate (eGFR) at baseline and a moderate to severe Mayo Clinic Chronicity Score (MCCS) grade predicted worse renal outcomes over a period of 12 months based only on eGFR.
3. The stratification of patients according to ANCA specificity [myeloperoxidase (MPO) versus proteinase 3 (PR3) AAV-GN] conveys prognostic information, as differences in severity and outcomes between these groups have been reported.

What this study adds?

1. Based on 329 kidney biopsies from patients with AAV-GN, we show that increasing MCCS grades were associated with decreased renal recovery to eGFR $\geq$30 mL/min/1.73 m^2 ($P < 0.0001$) after 12 months, lower probability of recovery from dialysis ($P = 0.001$), more frequent events and shorter time to kidney failure (KF) ($P < 0.0001$) at 12 months, KF and death ($P < 0.0001$) at 24 months and death ($P = 0.042$) at 10 years, independent of the remission induction treatment used.
2. Patients with MPO AAV-GN showed more severe eGFR impairment along with higher MCCS grades and higher degrees of glomerulosclerosis and interstitial fibrosis and tubular atrophy when compared with PR3 AAV-GN, but the degree of eGFR improvement was not different between groups of AAV-GN.
3. The MCCS grades correlated with eGFR in both MPO and PR3 AAV-GN, whereas the Berden classes correlated with eGFR in patients with MPO AAV-GN but not PR3 AAV-GN. This observation suggests that the MCCS chronicity grades are as important as the ANCA status when studying outcomes of AAV-GN.

What impact this may have on practice or policy?

1. The MCCS is a practical tool for accurate prognostic prediction in AAV-GN, has a very low interobserver variability and is not limited by the presence of an adequate number of glomeruli in the biopsy specimen. Therefore stratification using scores based solely on glomerular abnormalities should be reconsidered.
2. The MCCS allows the establishment of an objective cutoff to stratify the risk of progressing to KF. In AAV-GN, a score $\geq$4 was related with increased risk for KF. This may prove useful as a criterion when comparing data in clinical practice and clinical trials of AAV-GN.

and semiquantitative approach to score and grade chronic changes on kidney biopsy in various disease entities so that the chronicity grading might provide prognostic information in various glomerular diseases, including AAV-GN [21]. To apply the MCCS grade, GS, IF and TA are first scored from 0 to 3 according to the percentage of involvement of each compartment (<10, 10–25, 26–50 and >50%) and arteriosclerosis is scored from 0 to 1 according to the degree of intimal thickening. Subsequently the scores are added to grade the overall severity of the chronic lesions into four grades: minimal (0–1), mild (2–4), moderate (5–7) and severe (8–10) [18].

The present study on kidney histology from patients with AAV-GN was conducted to grade kidney biopsies of AAV-GN based on the MCCS classification, evaluate clinical characteristics and outcomes in response to remission induction treatments based on the MCCS chronicity grades and compare the performance of the MCCS grading to a previously validated Berden classification.

MATERIALS AND METHODS

Study cohort and patient characteristics

This study is based on the Mayo Clinic ANCA-associated vasculitis cohort comprising 1830 patients evaluated from 1 January 1996 to 31 December 2015 with the last follow-up on 31 December 2017 [22]. The present study is based on the 329 patients from this cohort who were identified with myeloperoxidase (MPO)- or proteinase 3 (PR3)-ANCA, active renal disease and at least one follow-up visit beyond their index date and an available kidney biopsy to grade, as described previously [18]. All patients fulfilled the American College of Rheumatology criteria and Chapel Hill consensus definition for granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) [23–25]. Of the 1830 AAV patients, 1363 were excluded due to the following: 1018 patients had no kidney involvement, 268 had no active renal disease, 32 had no follow-up visit, 23 patients were non-eligible and 22 were classified as eosinophilic granulomatosis with polyangiitis. Of the remaining 467 patients with AAV-GN, kidney biopsies were available to score in 329 patients.

Renal function assessment

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [26, 27]. Further categorization of severity of kidney failure (KF) at baseline for the determination of

predictors of outcomes included the eGFR cutoff (<15 and ≥15 mL/min/1.73 m^2).

Kidney biopsies and histopathological scores

Kidney biopsies were performed according to clinical practice. The MCCS was applied following the principles previously described for chronic changes scoring and grading [18]. In addition, based on the glomerular lesions, the biopsies were reviewed and scored by the Berden classification as focal, if ≥50% normal glomeruli present; crescentic, if ≥50% glomeruli with cellular crescents present; mixed, if <50% normal, <50% crescentic or <50% sclerotic; and sclerotic, if ≥50% globally sclerotic glomeruli [17]. Kidney biopsies with no glomeruli or medulla only were considered inadequate.

Outcomes assessment

The date of renal involvement diagnosis (index date) was registered for the calculation of outcome time points. The Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS/WG) was used to quantify disease activity at presentation and during the follow-up [28]. Remission was defined by a BVAS/WG of 0, independent of the dose of prednisone. This event was assessed at different time points during the follow-up. Relapse was defined as an increase in the BVAS/WG >1 that resulted in therapy changes (increases in doses of maintenance/remission therapy or the start of a new remission induction cycle) and were classified as major or minor according with the Rituximab in ANCA-associated Vasculitis trial criteria [29]. The number of relapses after achievement of remission, type of relapse (major or minor), organ involvement (renal versus nonrenal) and the BVAS/WG at the time of relapse were recorded.

Kidney disease progression was determined by the development of KF, defined as an eGFR <15 mL/min/1.73 m^2 or the need to initiate renal replacement therapy. Renal recovery was defined as independence of renal replacement therapy for those in whom this therapy was initiated, as improvement of eGFR to values ≥30 mL/min/1.73 m^2 (if severe renal disease at diagnosis), improvement on renal function (if nonsevere renal disease at diagnosis) or sustained eGFR ≥30 mL/min/1.73 m^2. The date of death was recorded to assess patient survival. Response to treatment was analyzed as the time to renal outcomes stratified per remission induction treatment received. KF and the 'combined events' endpoint of KF and/or death at 12 and 24 months and at 10 years and renal recovery to an eGFR ≥30 mL/min/1.73 m^2 were the outcomes selected to define the prognostic ability of the histopathological scores.

Statistical analysis

Categorical variables were presented as number (percent) and continuous variables were presented as mean [standard deviation (SD)] if they were normally distributed as determined by the Shapiro–Wilk test or as median [interquartile range (IQR)] if nonnormal. For comparisons of categorical variables between groups, the Pearson's chi-square test was used if the number of elements in each cell was ≥5; the Fisher's exact test was used otherwise. For comparison of two categories of continuous variables between groups, an unpaired Student's *t*-test for independent samples was used for distributions consistent with normality and the Mann–Whitney U-test was used otherwise. For comparison of more than two categories of continuous variables between groups, an analysis of variance (ANOVA) test was used for distributions consistent with normality and the Kruskal–Wallis test was used otherwise.

Logistic regression models were developed to examine the predictive role of the eGFR and histopathological baseline biopsy classification in the clinical outcomes. Variables were considered for the multivariate logistic regression models if they occurred before the development of the outcome of interest, had <10% missing values, had a P-value <0.05 in the univariable analysis and were clinically plausible. The final model was determined using both clinical and statistical criteria, taking into consideration collinearity, interaction and the number of patients who experienced the outcome of interest. The odds ratios (ORs) with 95% confidence intervals (CIs) were reported when appropriate.

The Kaplan–Meier method was used to assess the cumulative incidence of remission, time to relapse, cumulative incidence of KF, time to death (survival) and cumulative incidence of combined events of KF and/or death at the more relevant time points. Cox proportional hazards regression models were used to determine predictive factors for the outcomes. We report the hazard ratio (HR) with a 95% CI when appropriate [30]. We treated the patient's observation as right censored: we included the observation in the survival analysis up to the last point at which the outcome was known to have not yet occurred. In addition, to estimate potential threshold values of the MCCS that could help predict KF, we analyzed the score as a continuous variable and modeled the natural cubic spline in Cox proportional hazards models. SPSS Statistics for MacOS version 25 (IBM, Armonk, NY, USA), R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and the R package 'smoothHR' were used for data analysis [31].

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 (Figure 1). Baseline demographics and outcomes for these 329 patients are presented in Supplementary Tables S1 and S2, respectively. Remission (BVAS/WG = 0) was achieved in 215 (65.3%) patients at 6 months and in 263 (79.9%) patients during the follow-up. Renal remission was observed in 225 (68.4%) patients at 6 months and in 270 (82.1%) patients during the follow-up. Relapses were documented in 88 (26.7%) patients, of which 53 (60.2%) had a renal relapse. Dialysis was required in 50 (15.2%) patients. By the end of the follow-up [median 5.9 years (IQR 3.0–11.3)], 75 patients (22.8%) with renal involvement had died.

Kidney biopsy findings

The kidney biopsies were scored and graded according to the MCCS into chronicity grades of minimal [102 (31.0%)].

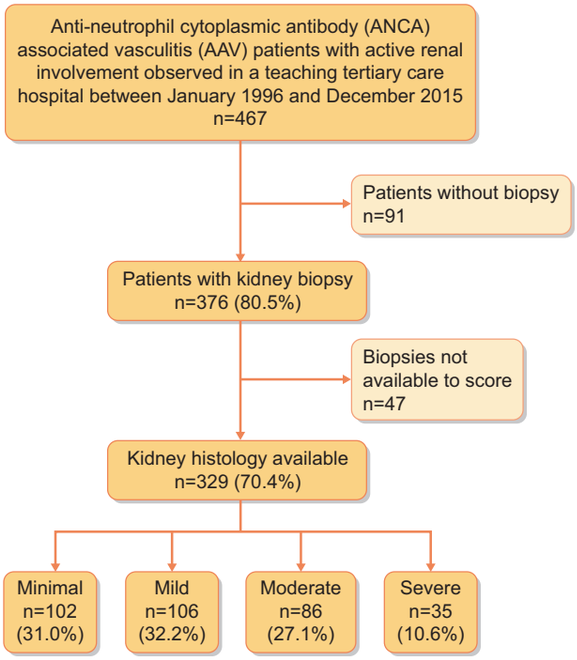

FIGURE 1: Strengthening the Reporting of Observational Studies in Epidemiology flowchart for the selection of the patient with active renal involvement in AAV-GN. Active renal involvement was defined by the presence of active, biopsy-proven, pauci-immune glomerulonephritis; red blood cell casts on urine microscopy or an increase in serum creatinine (SCr) >30% (or a >25% decrease in creatinine clearance) attributed to active vasculitis. Kidney biopsies were scored for chronicity based on the MCCS grading system into minimal, mild, moderate and severe.

mild [106 (32.2%)], moderate [86 (26.1%)] and severe [35 (10.6%)] (Table 1). Based on the extent of the glomerular lesions, the kidney biopsies were classified by the Berden classification into focal [117 (35.6%)]. crescentic [60 (18.2%)], mixed [107 (32.5%)] and sclerotic [45 (13.7%)]. Representative examples of each grade and category are shown in Figure 2.

Relationship of MCCS grades and clinical findings at first detection of active renal disease

The distribution of the clinical characteristics based on the MCCS grades is shown in detail in Table 1. Patients classified as minimal MCCS grade in the kidney biopsy were slightly younger (minimal 60 years versus mild 68 versus moderate 64 versus severe 65; $P = 0.003$) (Table 1). Patients with GPA most frequently had minimal or mild MCCS chronicity grades on the kidney biopsy, and among all cases with minimal chronicity grades, more had GPA (55.9%) than MPA (44.1%) (Table 1). In addition, as shown in Table 1, among patients with greater than minimal MCCSgrades, more patients had MPA (56.6, 69.8 and 65.7% with mild, moderate and severe chronicity grades, respectively) than GPA (43.4, 30.2 and 34.3%, respectively). Similarly, while the same fraction of patients with a minimal MCCS grade had MPO-ANCA and PR3-ANCA, as the chronicity grades increased, the fraction of patients who wereMPO-ANCA positive increased and those who were PR3- ANCA positive decreased (mild: 63.2% MPO versus 36.8% PR3; moderate: 72.2% versus 27.9%; severe: 77.1% versus 22.9%; Table 1).

The diagnosis of MPA and MPO AAV-GN increased in the last two decades, whereas the diagnosis of GPA and PR3 AAV-GN decreased in the last decade. There was no statistically significant difference in the distribution of patients regarding the severity of clinical manifestations as determined by the BVAS/WG score. There were no statistically significant differences in the distribution of the type of disease presentation (new diagnosis versus relapse), in the remission induction treatment assignment, treatment with intravenous methylprednisolone, administration of plasma exchange or maintenance/remission treatment strategy per category (Table 1).

The mean eGFR at baseline correlated with the overall MCCS grades and decreased in a gradient from minimal to severe chronicity grade (minimal 48.3 versus mild 29.2 versus moderate 23.7 versus severe 18.5 mL/min/1.73 m^2; $P < 0.0001$). Similarly, the mean eGFR at 6, 12, 18 and 24 months correlated with the overall MCCS grades ($P < 0.0001$ for 6, 12 and 18 months; $P = 0.002$ for 24 months). In both MPO and PR3 AAV-GN patients, the mean eGFR at baseline correlated with the overall grades (MPO: minimal 34.3 versus mild 27.9 versus moderate 24.8 versus severe 10.8 mL/min/1.73 m^2; $P = 0.001$; PR3: minimal 49.3 versus mild 27.9 versus moderate 29.9 versus severe 24.9 mL/min/1.73 m^2; $P < 0.0001$). Furthermore, the individual components of the MCCS grades correlated with the median eGFR: higher degrees of GS, IF, TA and arteriosclerosis were associated with a lower median eGFR at baseline (Figure 3A) and at 6, 12, 18 and 24 months (data not shown). Higher degrees of GS, IF, TA and arteriosclerosis were associated with an increased risk of KF at 12 months and 10 years (Figure 3B).

Renal recovery

In order to evaluate renal recovery we analyzed the improvement of eGFR as the achievement or maintained values of eGFR $\geq$30 mL/min/1.73 m^2 over a period of 12–24 months. Patients with lower MCCS chronicity grades showed increased rates of renal recovery (minimal 83.8% versus mild 68.5% versus moderate 52.4% versus severe 39.3%; $P < 0.0001$) and higher rates of dialysis independence (minimal 90.2% versus mild 88.3% versus moderate 85.7% versus severe 54.3%; $P < 0.0001$) (Table 2). When stratified for MPO- or PR3-ANCA status, eGFR was consistently lower in patients with MPO-ANCA [26.7 versus 39.0 mL/min/1.73 m^2 ($P = 0.003$, baseline), 37.8 versus 51.8 mL/min/1.73 m^2 ($P = 0.025$, 6 months), 39.3 versus 51.3 mL/min/1.73 m^2 ($P = 0.012$, 12 months), 40.5 versus 50.8 mL/min/1.73 m^2 ($P = 0.021$, 18 months), 40.2 versus 46.9 mL/min/1.73 m^2 (non-significant, 24 months)] (Supplementary Figure S1). The median degree of eGFR recovery was not different between MPO- and PR3-ANCA patients in any of the time points evaluated (Supplementary Figure 1).

We analyzed the combined endpoint of renal recovery in patients who achieved remission by 12 months. Using the

Table 1. Clinical characteristics of patients with AAV AAV-GN based on MCCS grade

Characteristics	Minimal [$n = 102$ (31.0%)]	Mild [$n = 106$ (32.2%)]	Moderate [$n = 86$ (26.1%)]	Severe [$n = 35$ (10.6%)]	P-value*
Age at diagnosis (years), median (IQR)	60 (47–68)	68 (58–75)	64 (54–74)	65 (53–75)	**0.003**
Male, *n* (%)	62 (60.8)	53 (50.0)	43 (50.0)	16 (45.7)	0.270
Presentation, *n* (%)					0.562
New diagnosis	78 (76.5)	88 (83.0)	66 (76.7)	26 (74.3)	
Relapse	24 (23.5)	18 (17.0)	20 (23.3)	9 (25.7)	
AAV, *n* (%)					**0.003**
MPA	45 (44.1)	60 (56.6)	60 (69.8)	23 (65.7)	
GPA	57 (55.9)	46 (43.4)	26 (30.2)	12 (34.3)	
ANCA specificity, *n* (%)					**0.004**
MPO	51 (50.0)	67 (63.2)	62 (72.2)	27 (77.1)	
PR3	51 (50.0)	39 (36.8)	24 (27.9)	8 (22.9)	
BVAS/WG at diagnosis, median (IQR)	8 (6–9)	8 (7–10)	8 (7–10)	7 (7–10)	0.592
Organ involvement classified using BVAS/WG at diagnosis, *n* (%)					
General	29 (28.4)	23 (21.7)	14 (16.3)	7 (20.0)	0.245
Cutaneous	9 (8.8)	4 (3.8)	4 (4.7)	1 (2.9)	0.336
Mucous membranous/eye	11 (10.8)	4 (3.8)	8 (9.3)	1 (2.9)	0.150
Ear, nose and throat	31 (30.4)	23 (21.7)	17 (19.8)	5 (14.3)	0.155
Cardiovascular	0 (0.0)	2 (2.0)	1 (1.2)	1 (2.9)	0.501
Gastrointestinal	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.517
Pulmonary	49 (48.0)	49 (46.2)	31 (36.0)	13 (37.1)	0.297
Renal	–	–	–	–	–
Neurologic	6 (5.9)	3 (2.8)	5 (5.8)	0 (0.0)	0.414
Rapidly progressive glomerulonephritis, *n* (%)	32 (33.4)	39 (39.0)	28 (33.7)	11 (31.4)	0.307
Alveolar hemorrhage BVAS/WG at diagnosis, *n* (%)	19 (18.6)	16 (15.1)	10 (11.6)	7 (20.0)	0.524
Cardiovascular risk factors, *n* (%)					
Arterial hypertension	64 (62.7)	77 (72.6)	54 (62.8)	29 (82.9)	0.073
Diabetes mellitus	7 (6.9)	21 (19.8)	23 (26.7)	6 (17.1)	**0.004**
Dyslipidemia	31 (30.4)	35 (33.0)	28 (32.6)	10 (28.6)	0.950
BMI >30 kg/m^2	26 (27.7)	33 (33.3)	23 (28.0)	9 (30.0)	0.821
Laboratory findings					
Hemoglobin (g/dL), median (IQR)	10.7 (9.5–12.2)	10.0 (8.8–11.8)	9.8 (9.0–11.3)	9.8 (9.0–11.4)	**0.042**
eGFR at diagnosis (mL/min/1.73 m^2), mean (SD)	48.3 (35.8)	29.2 (22.3)	23.7 (14.6)	18.5 (16.1)	**<0.0001**
eGFR at diagnosis <30 mL/min/1.73 m^2, *n* (%)	39 (38.2)	66 (62.3)	62 (72.1)	32 (91.4)	**<0.0001**
eGFR at diagnosis <15 mL/min/1.73 m^2, *n* (%)	10 (11.5)	23 (26.7)	19 (26.0)	14 (42.4)	**0.003**
Remission induction therapy, *n* (%)					0.182
CYC	63 (61.8)	67 (63.2)	55 (64.0)	21 (60.0)	0.842
Rituximab	30 (29.4)	24 (22.6)	18 (20.9)	6 (17.1)	0.217
Mycophenolate mofetil	8 (7.8)	9 (9.8)	8 (10.5)	4 (12.1)	0.853
Remission induction adjuvant therapy, *n* (%)					
IV methylprednisolone at induction remission	51 (50.0)	66 (62.3)	47 (54.7)	16 (45.7)	0.213
Plasma exchange therapy	15 (14.7)	18 (17.0)	10 (11.6)	3 (8.6)	0.555
Maintenance treatment, *n* (%)					0.079
Azathioprine	36 (36.4)	34 (32.7)	24 (28.2)	8 (22.9)	
Mycophenolate mofetil	29 (29.3)	26 (25.0)	27 (31.8)	11 (31.4)	
Rituximab	16 (16.2)	6 (5.8)	11 (12.9)	2 (5.7)	
CYC	6 (6.1)	5 (4.8)	4 (4.7)	3 (8.6)	
Prednisone	12 (12.1)	33 (31.7)	19 (22.4)	11 (31.4)	

BMI, body mass index; IV, intravenous.

Remission induction treatment was conducted with oral corticosteroids (with or without IV methylprednisolone) together with either oral cyclophosphamide (2 mg/kg/day for 6 months) or rituximab (IV, 375 mg/m^2 of body surface area once weekly for 4 weeks).

*$P < 0.05$ is considered significant (Pearson chi-square test for categorical variables, ANOVA for continuous variables normally distributed and Kruskal–Wallis test for continuous variables with skewed distribution) and is shown in bold.

Kaplan–Meier method, the chronicity grades displayed prognostic information for the combined endpoint of eGFR ≥30 mL/min/1.73 m^2 and remission ($P = 0.001$) (Figure 4A).

Vasculitis and renal outcomes

A comparable number of patients per MCCS grade achieved remission (BVAS/WG = 0) at 6 months or renal remission at 6 months (Table 2). Patients with a severe chronicity grade were at higher risk for KF, for combined events of KF and/or death and the need of renal replacement therapy at any of the analyzed time points throughout the observation period ($P < 0.0001$). There were no differences in the frequency of the outcomes when stratified by MPO- or PR3-ANCA. Overall, patient survival was lower in patients with a severe chronicity grade ($P = 0.052$) (Table 3).

Using the Kaplan–Meier method, the chronicity grades displayed prognostic information for the renal outcomes of

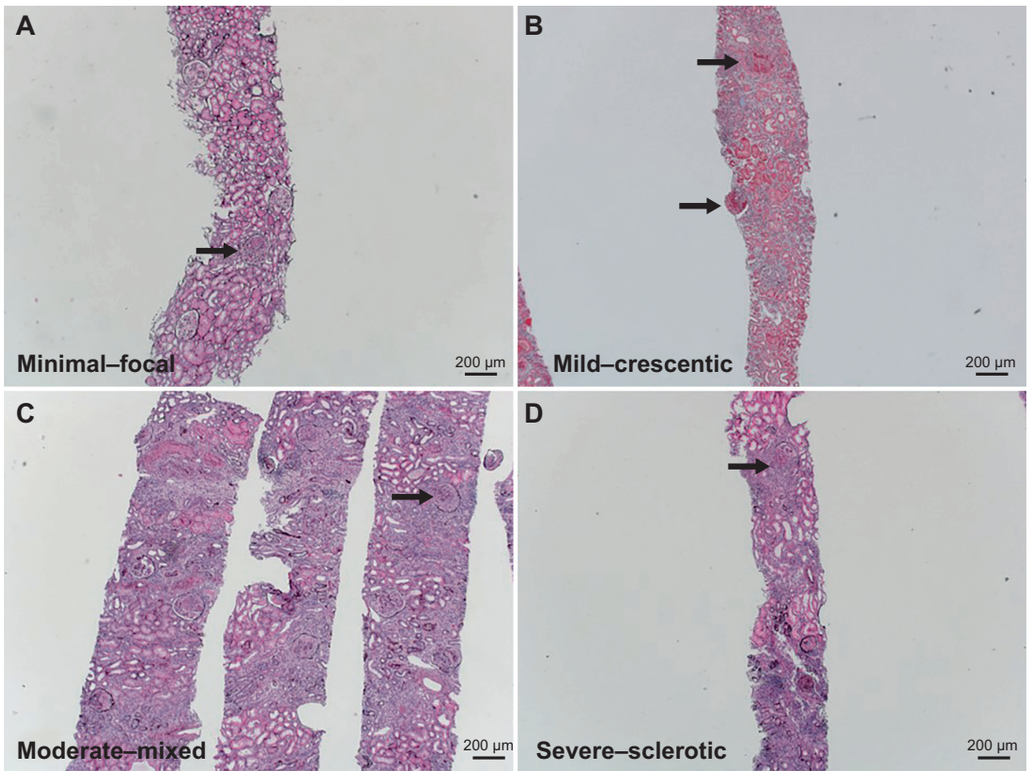

FIGURE 2: Light microscopy of kidney biopsy findings in AAV-GN according with the MCCS grading and Berden classification: (**A**) minimal, focal; (**B**) mild, crescentic; (**C**) moderate, mixed; (**D**) severe, sclerotic. Arrows point to cellular crescents.

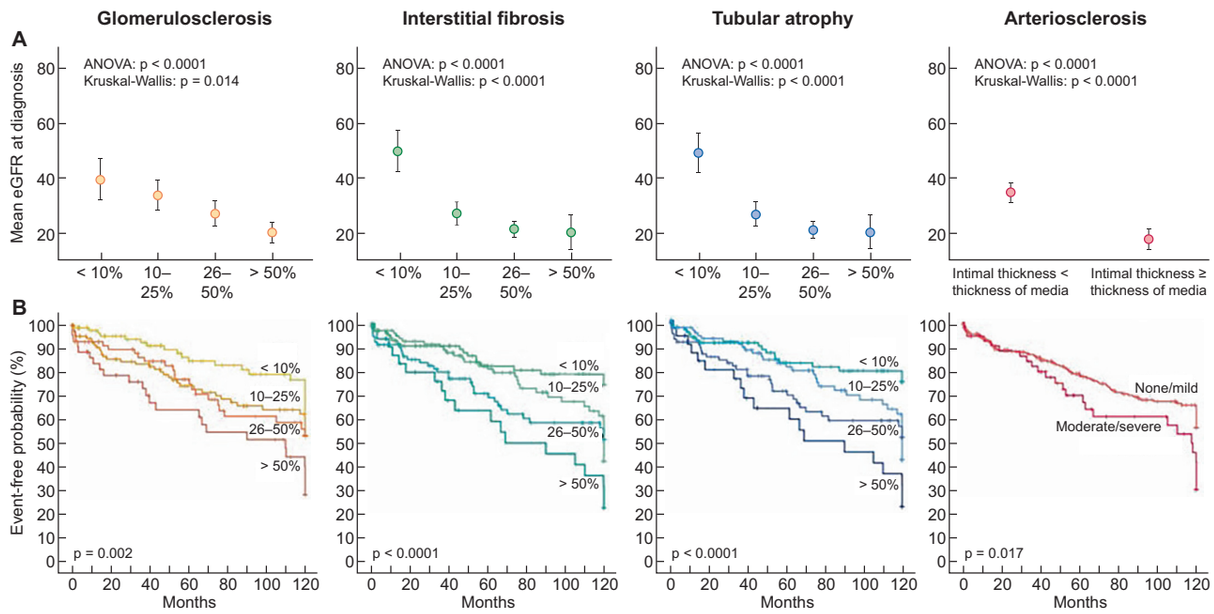

FIGURE 3: The categories of each histologic component of the MCCS are strongly and independently correlated with (**A**) renal function at baseline and (**B**) are associated with kidney disease progression and decreased event-free survival (KF and/or death).

KF at 12 months and combined events of KF and/or death over 24 months ($P < 0.0001$) (Figure 4B and C). There were no differences between the assigned categories in the time to remission at 6 months, to relapse at 12 months and to patient survival at 24 months.

Using multivariable Cox regression, we determined that moderate and severe MCCS grades and baseline eGFR were risk factors for KF at 12 months, adjusted for age at AAV-GN diagnosis and for patients with severe renal involvement (eGFR <30 mL/min/1.73 m^2) (Table 3 and Supplementary Table S3).

Table 2. Outcomes of AAV-GN based on MCCS grade

Outcomes	Minimal [$n = 102$ (31.0%)[	Mild [$n = 106$ (32.2%)]	Moderate [$n = 86$ (26.1%)]	Severe [$n = 35$ (10.6%)]	P-value*
Vasculitis activity, *n* (%)					
Remission					
6 months	74 (82.2)	64 (73.6)	56 (75.7)	21 (65.6)	0.142
Total[a]	87 (95.6)	79 (91.9)	68 (91.9)	29 (87.9)	0.494
Complete remission					
6 months	21 (27.3)	14 (17.9)	16 (23.5)	6 (21.4)	0.578
Total[a]	60 (69.8)	54 (62.8)	43 (58.9)	12 (36.4)	**0.010**
Relapse					
18 months	16 (16.3)	11 (10.9)	14 (17.3)	5 (16.1)	0.605
Total	29 (31.2)	19 (20.7)	28 (36.8)	12 (36.4)	0.101
Renal relapse					
Total[a]	20 (69.0)	12 (60.0)	14 (56.0)	7 (58.3)	0.784
Death					
24 months	5 (4.9)	8 (7.5)	8 (9.3)	4 (11.4)	0.543
10 years	10 (9.8)	23 (21.7)	18 (20.9)	9 (25.7)	0.059
Total[a]	14 (13.7)	26 (24.5)	24 (27.9)	11 (31.4)	0.052
Renal, *n* (%)					
Renal recovery					
24 months	62 (83.8)	50 (68.5)	33 (52.4)	11 (39.3)	**<0.0001**
KF					
12 months	4 (3.9)	13 (12.3)	19 (22.1)	13 (37.1)	**<0.0001**
10 years	9 (9.4)	19 (19.0)	23 (27.7)	18 (51.4)	**<0.0001**
Total[a]	10 (9.8)	19 (19.0)	25 (30.1)	18 (51.4)	**<0.0001**
Dialysis	10 (9.8)	12 (11.7)	12 (14.3)	16 (45.7)	**<0.0001**
Combined events of KF and/or death, *n* (%)					
24 months	11 (11.5)	19 (19.0)	23 (27.7)	15 (42.9)	**0.001**
10 years	16 (15.7)	36 (34.0)	33 (38.4)	23 (65.7)	**<0.0001**
Total[a]	19 (19.8)	37 (37.0)	37 (44.6)	24 (68.6)	**<0.0001**
Time to event (months), median (IQR)					
Remission	3.4 (2.3–5.9)	4.1 (3.0–6.0)	4.4 (2.8–6.0)	5.3 (3.0–6.0)	0.200
Relapse	20.0 (14.4–63.0)	13.5 (11.7–76.3)	17.3 (9.2–37.1)	20.5 (4.5–57.7)	0.755
Death	54.0 (12.5–111.0)	47.0 (13.0–81.5)	45 (16.5–123.3)	38.0 (10.9–105.0)	0.853
ESRD	15.7 (1.3–51.1)	1.2 (0.0–20.5)	3.3 (0.1–19.1)	2.7 (0.1–26.9)	0.494
Combined events	15.7 (4.6–53.3)	19.6 (1.1–79.2)	6.8 (0.8–33.6)	4.6 (0.3–55.3)	0.239
Time of FU after renal involvement (years), median (IQR)	7.8 (3.3–12.3)	6.2 (3.5–10.3)	5.5 (2.8–11.9)	3.8 (2.2–10.5)	0.248

[a] Total refers to the number of occurrences during all follow-up time.
*$P < 0.05$ is considered significant (Pearson chi-square test for categorical variables, ANOVA for continuous variables normally distributed and Kruskal–Wallis test for continuous variables with skewed distribution) and is shown in bold.

The same relationship was not observed for survival at 12 months (Supplementary Table S4).

Among the 207 MPO AAV-GN patients, 73 (35.3%) of the patients had MPO AAV-GN limited to the kidney and 134 (64.7%) had MPO AAV-GN with systemic disease. In each group, 15 patients evolved to KF at 12 months (11.2% versus 20.15%; P = 0.068).

Response to treatment

MCCS performance. *KF prediction using MCCS.* The ability of the MCCS ability to predict KF was further explored by the development of regression models using only histological variables, the continuous score or by the combination of histologic and clinical variables (Table 4). The histologic models based on the grading and in all the categories included in the MCCS were robust. Minimal grade was protective [HR 0.183 (95% CI 0.066–0.508); P = 0.001] while moderate and severe grades were predictors of KF at 12 months [HR 1.863 (95% CI 1.049–3.310); P = 0.034 and HR 3.429 (95% CI 1.817–6.471); P < 0.0001, respectively] and GS, IF and TA were predictors of KF (GS: P = 0.001; IF and TA: P = 0.003) while arteriosclerosis was not (P = 0.075). However, in PR3 AAV-GN, GS could not predict the risk for renal outcomes. In the multivariable analysis of the grading model, the risk increased according to the severity grade. In the multivariable analysis using all the categories graded, IF had more weight in the estimation of risk, but this observation was not statistically significant (Table 4). In addition, we evaluated the performance of the MCCS as a continuous predictor: an increase of 20% in the total score (2 points) was associated with a 29% increased risk for KF [HR 1.294 (95% CI 1.174–1.428); P < 0.0001] (Table 4). We determined that an MCCS ≥4 was the optimal cutoff point for the risk of progression to KF at 12 months [HR 4.776 (95% CI 2.384–9.571); P < 0.0001]. Furthermore, in order to analyze the threshold related with increased risk for KF at 10 years, we fitted models with splines to the total MCCS: patients with scores ≥4 in the MCCS had 3.5 times more risk to progress to KF [HR 3.506 (95% CI 2.066–5.952); P < 0.0001] and event-free survival was lower (Supplementary Figure S2). The cutoff was discriminative even after stratification by ANCA status. Finally, by

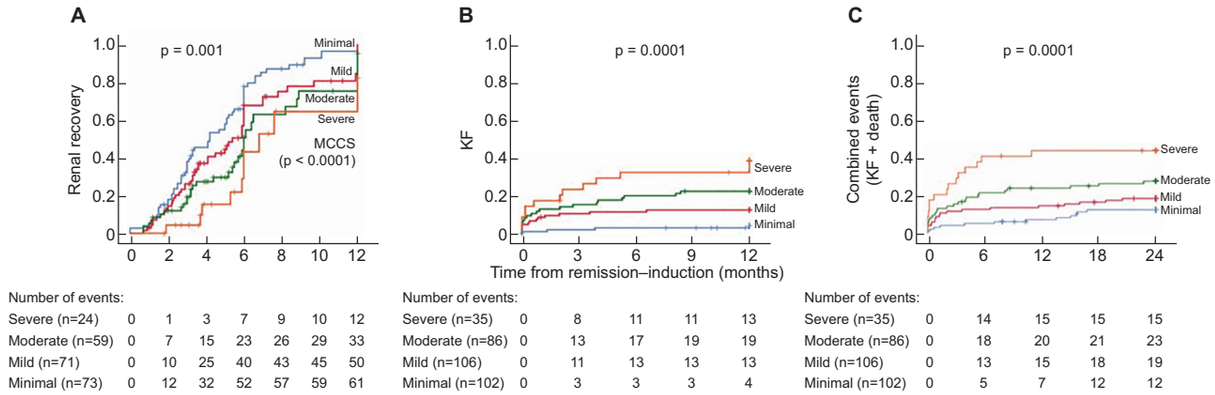

FIGURE 4: Kaplan–Meier plots of renal outcomes. (**A**) Renal recovery (with minimal eGFR ≥30 mL/min/1.73 m^2) and remission for 12 months: 61 versus 50 versus 33 versus 10, mean time to event 4.6 versus 5.9 versus 6.7 versus 7.9 months; P = 0.001. (**B**) KF at 12 months (minimal versus mild versus moderate versus severe): 4 versus 13 versus 19 versus 13 events, mean time to event 11.7 versus 10.7 versus 9.9 versus 8.7 months; P < 0.0001. (**C**) Combined events of KF and/or death over 24 months (minimal versus mild versus moderate versus severe): 12 versus 19 versus 23 versus 15 events, mean time to event 22.1 versus 20.6 versus 18.7 versus 14.8 months; P < 0.0001.

Table 3. Multivariable Cox regression analysis of the predictive factors for KF at 12 months in patients with AAV-GN

	Multivariable Cox regression	
KF at 12 months	HR (95% CI)	P-value*
MCCS grade		**0.028**
Minimal	1.00 (reference)	
Mild	1.897 (0.612–5.878)	0.267
Moderate	**3.435 (1.166–10.119)**	**0.012**
Severe	**4.340 (1.390–13.551)**	**0.004**
eGFR at AAV-GN diagnosis	**1.082 (1.041–1.119)**	**<0.0001**
eGFR ≤30 mL/min/1.73 m^2	1.244 (0.265–5.814)	0.782
Age ≥60 years at AAV-GN diagnosis	1.133 (0.610-2.105)	0.693

*P < 0.05 is considered significant (multivariable Cox regression) and is shown in bold.

combining clinical and histologic variables, we determined that an MCCS ≥4 and eGFR at renal involvement diagnosis were independent predictors and the main determinants of KF at 12 months, adjusted for eGFR <30 mL/min/1.73 m^2 and age ≥60 years (Table 4).

Comparison of MCCS grades with Berden classification. Direct concordance between individual categories was observed in 165 kidney biopsies (50.2%) (Supplementary Figure S3A and Table S5), permissive or histopathological concordance was observed in 290 (88.1%) (Supplementary Figure S3B) and the remaining 39 (11.9%) were considered completely discordant (Supplementary Figure S3C). The IFTA scores increased proportionally along with a higher Berden category of severity (P < 0.0001). Similarly, lower MCCS grades had a lower glomerular component (P < 0.0001).

eGFR correlation with MCCS grade and Berden classification was observed for patients with MPO AAV-GN. In contrast, MCCS grades correlated with eGFR recovery at 12 months in PR3 AAV-GN patients (P = 0.030) while the Berden classification could not stratify eGFR appropriately through different classes in PR3 AAV-GN at any time point evaluated. In addition, the Berden classification did not show discriminative power for the prediction of eGFR at 24 months or for outcome prediction in patients with eGFR ≥30 mL/min/1.73 m^2.

Using Cox proportional hazards models and Kaplan–Meier analysis we observed that crescentic and mixed classification defined two groups with similar risk profiles for the outcomes and that, in some of the outcomes evaluated, patients classified as crescentic had a worse prognosis than patients classified has mixed (Supplementary Figure S4 and Table S6).

Activity index using the percentage of cellular crescents/necrotizing lesions. The extent of cellular crescents/necrotizing lesions in each case was calculated to generate an activity index (AI). The AI was graded 0–4 depending on the percentage of glomeruli involved by cellular crescents/necrotizing lesions: no crescents/necrosis, 0; 1–10%, 1; 11–25%, 2; 26–50%, 3; and >50%, 4. Patients with higher AIs were more likely to evolve to KF at 12 months and combined events of KF and death at 24 months and the time to KF at 12 months was also shorter (P = 0.001) (Table 5).

DISCUSSION

Our study shows that the MCCS is a valid prognostic tool for the independent assessment of renal outcomes and survival in AAV-GN. The grading of GS, IF, TA and arteriosclerosis showed that higher degrees of involvement of each component was correlated with lower eGFR at diagnosis and increased risk of kidney disease progression in patients with AAV-GN. The MCCS stratified patients with AAV-GN into four grades according to the severity of kidney involvement: minimal, mild, moderate and severe. Patients with minimal or mild MCCS grades were younger and more likely to have GPA, PR3-ANCA and recovery of renal function to eGFR ≥30 mL/min/1.73 m^2. In contrast, patients with moderate and severe MCCS grades were more like to have MPA and be MPO-ANCA positive. In addition, eGFR was lower in patients with MPO AAV-GN from baseline throughout all the time points evaluated. Furthermore, higher degrees of chronicity grades were

Table 4. Cox proportional hazards regression analyses for clinical and histologic predictors of KF in patients with AAV-GN at 12 months

	Univariable		Multivariable	
MCCS grading model	HR (95% CI)	P-value*	HR (95% CI)	P-value*
Minimal	**0.183 (0.066–0.508)**	**0.001**	1.00 (reference)	
Mild	0.755 (0.400–1.423)	0.384	3.288 (1.072–11.139)	0.147
Moderate	**1.863 (1.049–3.310)**	**0.034**	**6.136 (2.087–18.039)**	**0.001**
Severe	**3.429 (1.817–6.471)**	**<0.0001**	**11.186 (3.645–34.328)**	**<0.0001**
MCCS histologic model				
Glomerulosclerosis, %		**0.001**		0.195
≤10	1.00 (reference)		1.00 (reference)	
11–25	1.123 (0.465–2.709)	0.797	1.258 (0.476–3.322)	0.184
26–50	2.193 (0.937–5.131)	0.070	1.325 (0.473–3.709)	0.592
>50	**4.187 (1.831–9.575)**	**0.001**	2.245 (0.719–7.012)	0.164
Interstitial fibrosis, %		**0.003**		0.567
≤10	1.00 (reference)		1.00 (reference)	
11–25	1.921 (0.766–4.815)	0.164	1.695 (0.608–4.722)	0.313
26–50	**3.210 (1.342–7.687)**	**0.009**	2.155 (0.708–6.559)	0.176
>50	**5.393 (2.052–14.176)**	**0.001**	2.439 (0.643–9.246)	0.190
Tubular atrophy, %		**0.003**		
≤10	1.00 (reference)		–	[a]
11–25	1.961 (0.782–4.915)	0.151	–	[a]
26–50	**3.243 (1.354–7.765)**	**0.008**	–	[a]
>50	**5.448 (2.073–14.320)**	**0.001**	–	[a]
Arteriosclerosis		0.075		0.234
None/mild	1.00 (reference)		1.00 (reference)	
Moderate/severe	1.811 (0.942–3.481)		1.509 (0.766–2.972)	
MCCS score model				
Continuous	**1.294 (1.174–1.428)**	**<0.0001**	–	[b]
MCCS ≥4	**4.776 (2.384–9.571)**	**<0.0001**	–	[b]
Combined model				
MCCS ≥4	–	–	**3.340 (1.508–6.098)**	**0.002**
eGFR at diagnosis	–	–	**1.086 (1.043–1.130)**	**<0.0001**
eGFR ≤30 mL/min/1.73 m^2	–	–	1.277 (0.169–3.623)	0.755
Age at diagnosis ≥60 years	–	–	1.190 (0.459–1.540)	0.574

[a] Collinearity with interstitial fibrosis (as expected).
[b] Not performed since the categorical variable was derived from the continuous variable.
*P < 0.05 is considered significant (uni- and multivariable Cox regression) and is shown in bold.

Table 5. KF and combined events of KF and death according to the AI

Outcomes	AI: 0 *n* (%)	AI: 1 *n* (%)	AI: 2 *n* (%)	AI: 3 *n* (%)	AI: 4 *n* (%)	*P-value
KF						
12 months	2 (9.5)	3 (13.0)	4 (5.1)	9 (10.3)	23 (26.4)	**0.001**
KF and death						
24 months	2 (9.5)	5 (21.7)	7 (9.0)	14 (16.1)	31 (35.6)	**<0.0001**

The AI is scored based on the percentage of glomeruli with cellular crescents/necrotizing lesions. No cellular crescents/necrotizing lesions, 0; 1–10%, 1; 11–25%, 2; 26–50%, 3; >50%, 4.
* P < 0.05 is considered significant (uni- and multivariable Cox regression) and is shown in bold.

associated with a higher risk for renal outcomes of KF and combined events of KF and/or death, with decreased survival and with decreased probability of achieving recovery of renal function to an eGFR ≥30 mL/min/1.73 m^2. The prognostic ability of the MCCS was independent of the remission induction treatment [cyclophosphamide (CYC) or rituximab (RTX)] and an MCCS ≥4 predicted KF in AAV-GN. However, although MCCS ≥4 is predictive of KF in AAV-GN, it does not indicate that therapy should be changed or withheld. It should also be pointed out that while IFTA alone is responsible for 60% of the MCCS grade, the addition of a glomerulosclerosis score and arteriosclerosis score to complete the total MCCS grade helps in earlier separation of the MCCS grades compared with IFTA alone.

Empirical evidence and reproducibility of the application of the MCCS was provided in the three-center study by Srivastava *et al.* [19], who evaluated 676 biopsies from patients with several glomerular diseases for semiquantitative scores in 13 categories of histopathology. In this study, IF, TA, GS and arteriosclerosis were independently associated with kidney disease progression in different renal diseases with predominant glomerular or tubulointerstitial or vascular involvement [19]. This study concluded that chronicity scoring may provide significant prognostic information over and above clinical information and assessment of glomerular lesions alone [19].

The combined evaluation of GS, IFTA and arteriosclerosis reflects the overall kidney response to injury [32–34]. The degree of IFTA has been suggested as one of the main determinants for KF and death in different kidney diseases. In lupus nephritis (LN), studies showed that IFTA is a strong predictor of KF and death independent of LN class, leading to the

recommendation of adding chronicity grades to the International Society of Nephrology/Renal Pathology Society classification of LN [35–37]. In immunoglobulin A nephropathy, studies have shown that chronic changes are the most important histological predictors of the outcome [38–40]. In C3 glomerulopathy, the total chronicity score was determined as the principal histological predictive factor for KF [41, 42]. In diabetic nephropathy, the severity of chronic changes, especially GS and IFTA, are related with renal outcomes [43]. The present study shows that the MCCS grade also stratifies patients with AAV-GN into groups with different profiles of eGFR, renal recovery and risk for renal outcomes.

Stopping the progression of kidney injury to KF is one of the most challenging unmet needs in the treatment of AAV-GN [44]. We show that higher degrees of IFTA correlate with lower eGFR and increased risk for unfavorable renal outcomes. Additionally, patients with minimal and mild MCCS grades usually recover renal function to an eGFR $\geq$30 mL/min/1.73 m^2 and dialysis independence, whereas patients with moderate or severe MCCS grades evolve more frequently to KF or combined events of KF and/or death. Consequently the MCCS grades are important predictors of renal function recovery and allow the identification of patients at higher risk for kidney disease progression at the time of diagnosis.

The presence of MPO-ANCA in AAV-GN has been associated with chronic damage at the time of diagnosis and thus more severe disease [5, 9, 45–47]. Here we show that eGFR was consistently lower in patients with MPO AAV-GN, but the degree of eGFR improvement was not different when compared with PR3 AAV-GN. Patients with MPO AAV-GN showed more severe eGFR impairment with higher MCCS grades and higher degrees of GS and IFTA when compared with PR3 AAV-GN, suggesting an indolent but relentless mechanism of kidney injury associated with chronic damage in MPO AAV-GN. In contrast, patients with PR3 AAV-GN showed less eGFR impairment, lower degrees of GS and IFTA and less correlation with the degree of GS, suggesting a more acute inflammatory kidney injury. In contrast, the outcomes are not as dependent on the ANCA status but are concordant with the MCCS grading (Supplementary Table S7). Patients with MPO AAV-GN classified as severe have the same incidence of renal outcomes as patients with PR3 AAV-GN classified as severe. Taken together, our results indicate that the MCCS chronicity grades provide important prognostic information about the outcomes of AAV-GN than ANCA status alone.

It is also pertinent to discuss that many patients of AAV-GN are older and have hypertension that may contribute to arteriosclerosis, which may be unrelated to AAV. However, it is unlikely that arteriosclerosis on its own shifts the balance of the MCCS grade, as it accounts for only 10% of the total MCCS grade, and moderate to severe arteriosclerosis is required to obtain a score of 1 in the MCCS grade. Furthermore, when we compared patients with none/mild arteriosclerosis to patients with moderate/severe arteriosclerosis, we did not observe a significant difference in the proportion of patients with hypertension or with older age ($\geq$60 years) between the two groups (Supplementary Table S8).

A comparison of the MCCS with the Berden classification, which is based only on the glomerular compartment, has been called for [48]. The histopathological clinical validation cohort study by Berden et al. [17] comprised 100 patients included in the CYCAZAREM (CYC versus AZA for Early Remission of vasculitis) trial, who received CYC for remission-induction treatment [49]. In accordance with the standard of care for remission induction treatment in AAV-GN in 2010, the score was not initially validated in patients treated with RTX, and subsequent validation studies included only patients treated with CYC [45]. We now show that the MCCS is also valuable for prognostic stratification in patients treated with RTX, which is consistent with the previous identification of TA as a predictor of renal function at 1 year in patients treated with RTX [50]. In addition, the sole evaluation of the glomerular compartment for prognosis prediction in AAV-GN by the application of the Berden histopathological classification has proven to be only partially useful for prognostic stratification. Several studies have shown that the renal outcomes were not accurately discriminated between patients classified as crescentic or mixed [17, 51, 52]. Thus it has been suggested that other prognostic factors, including tubulointerstitial features, should be considered. This prompted the development of the Brix score, but this only includes two levels of IFTA ($\leq$25% and >25%) combined with the percentage of normal glomeruli and eGFR at baseline [53]. In contrast, our study shows that IF 26–50% and IF >50% are associated with different risks for KF at 12 months and the levels of chronic changes (GS, IFTA and arteriosclerosis) correlate with different degrees of eGFR impairment and risk for renal outcomes. Therefore the four levels of IFTA represent a more accurate grading, contributing to the ability of MCCS grading to discriminate renal outcomes.

We do acknowledge that chronicity grading is not the only parameter that correlates with outcomes, and AI might be another important factor to consider in the biopsy findings. Indeed, we show that the percentage of glomeruli involved by cellular crescents/necrotizing lesions also correlates with outcomes at 12 and 24 months. Thus reporting both the AI along with the MCCS chronicity grade might be the optimal way of reporting the prognostic indexes in AAV-GN, creating an AI and chronicity index similar to that seen in LN. However, our current studies focus on the chronicity grading and further studies are required to combine the two indexes in a meaningful way.

This study has limitations inherent to its retrospective design, including possible confounding by indication bias related with clinical management decisions and non-protocolized follow-up intervals. Also, our cohort consists of a Midwestern US white population with predominantly Scandinavian and Northern European ethnic backgrounds, therefore the results may not be generalizable.

Despite these limitations, this is the largest cohort of active AAV-GN documented by kidney histology providing a detailed analysis of clinical characteristics and outcomes in response to different treatments in real clinical practice. Furthermore, the data come from a single center with detailed availability of clinical information and kidney biopsy slides and reports. An advantage of the MCCS grading is that it is heavily weighted toward assessment of tubulointerstitial scarring, and unlike the

Berden classification, it is not dependent on an adequate number of glomeruli in the biopsy. Crescents and necrosis in AAV-GN are focal lesions, and it is possible that biopsies containing inadequate/fewer glomeruli may lead to an erroneous Berden class. Finally, the GS and IFTA are easy to score by the MCCS, with low interobserver variability, thus allowing very consistent grading [18, 54, 55].

Our study fills important gaps in the literature. First, we demonstrate the importance of evaluating the interstitial compartment and determining the degree of IF and TA for the accurate clinical categorization and estimation of the risk profile of patients with AAV-GN. Second, this is the first representative cohort study that extensively evaluates the clinical characteristics and outcomes (KF) in the populations generated by the application of the MCCS grade in AAV-GN, stratified by MPO versus PR3 AAV-GN. Finally, we were able to confirm the utility of kidney histology on prognostic prediction in an AAV-GN population treated with RTX.

In conclusion, our results demonstrate that chronic changes in kidney histology estimated by the MCCS have an impact on prognosis prediction and for evaluation of treatment response in patients with AAV-GN. Accounting for tubulointerstitial parameters on kidney histology improved the accuracy of the evaluation of outcomes and response to treatments in AAV-GN when compared with classifications that rely only on the glomerular component. Assessment of chronic lesions from kidney biopsy findings may allow the selection of candidates who may benefit from specific future treatments designed to modify the progression to KF in AAV-GN, such as antifibrotic agents.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

M.C.M., U.S., F.C.F and S.S. designed the study. M.C.M. abstracted the data. M.C.M. and S.S. reviewed and scored the biopsies. M.C.M., U.S., F.C.F. and S.S. analyzed the data. M.C.M. performed the statistical analysis. M.C.M., U.S., F.C.F. and S.S. drafted and revised the article. All authors provided input for the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

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