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Classification of Antineutrophil Cytoplasmic Autoantibody Vasculitides

The Role of Antineutrophil Cytoplasmic Autoantibody Specificity for Myeloperoxidase or Proteinase 3 in Disease Recognition and Prognosis

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Objective. **To compare the usefulness of 3 currently used classification systems in predicting the outcomes of treatment resistance, disease relapse, end-stage renal disease (ESRD), and death in patients with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV).**

Methods. **Three classification systems were applied to 502 patients with biopsy-proven AAV: 1) the Chapel Hill Consensus Conference (CHCC) definition with categories for granulomatosis with polyangiitis (GPA) (Wegener's), microscopic polyangiitis (MPA), and kidney-limited disease; 2) the European Medicines Agency (EMA) system with categories for GPA and MPA; and 3) classification based on ANCA with specificity for myeloperoxidase (MPO ANCA) versus ANCA with specificity for proteinase 3 (PR3 ANCA). Outcomes included treatment resistance, relapse, ESRD, and death. Proportional hazards models were compared between systems using an information-theoretic approach to rank models by predictive fit. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) and *P* values are reported.**

Results. **ANCA specificity was predictive of relapse, with PR3 ANCA–positive patients almost twice as likely to relapse as those with MPO ANCA (HR 1.89 [95% CI 1.33–2.69], $P = 0.0004$), and ANCA specificity had the best predictive model fit (model rank 1) compared to the CHCC and EMA systems. The CHCC and EMA systems did not predict relapse. By ANCA specificity, categories of GPA, MPA, and kidney-limited disease did not distinguish differences in probability of relapse-free survival. None of the systems predicted treatment resistance, ESRD, or death.**

Conclusion. **ANCA specificity independently predicts relapse among patients with AAV with renal disease. Classification and diagnostic systems that incorporate ANCA specificity, such as PR3 ANCA–positive MPA and MPO ANCA–positive MPA, provide a more useful tool than the clinical pathologic category alone for predicting relapse.**

The name of a disease should be informative about clinical and pathologic phenotypes, etiology, and pathogenesis (when known), natural history, and response to therapy. It should permit the differentiation of similar diseases that have different outcomes. Optimally, the name of a disease should reflect its underlying etiology. In 1994, the Chapel Hill Consensus Conference (CHCC) aimed to standardize nomenclature and definitions for vasculitis, including microscopic polyangiitis (MPA), Wegener's granulomatosis, Churg-Strauss syndrome, and polyarteritis nodosa (1). In 2007, the European Medicines Agency (EMA) classification system (2) proposed the same disease names but different definitions that refined and expanded the 1990 American College of Rheumatology classification system (3). Since that time, granulomatosis with polyangi-

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itis (GPA) (Wegener's) has been proposed as an alternative term for Wegener's granulomatosis and will be used in place of Wegener's granulomatosis for the remainder of this article (4).

The CHCC nomenclature was meant to provide disease definitions. Neither the CHCC nor the EMA classification system provides diagnostic criteria that enable practicing physicians to discriminate MPA from GPA. The advent of widespread antineutrophil cytoplasmic antibody (ANCA) testing and accumulating evidence that ANCAs may participate in causing small-vessel vasculitis (5) have spawned the terms ANCA-associated vasculitis (AAV), ANCA vasculitis, or ANCA disease as overarching terms for MPA, GPA, and kidney-limited disease that aid patients and clinicians in therapeutic decision-making. This approach has substantial value yet may mask real differences in disease phenotype and prognosis unless the ANCA specificity is included in the diagnosis.

We sought to evaluate the utility of 3 classification systems in predicting the outcomes of treatment resistance, disease relapse, end-stage renal disease (ESRD), and death in a cohort of patients with AAV. The classification systems compared for this project were a system based on the CHCC definitions (1), the EMA classification system (2), and classification based on ANCA serologic specificity. We hypothesized that ANCA with specificity for myeloperoxidase (MPO ANCA) versus ANCA with specificity for proteinase 3 (PR3 ANCA) would provide a more useful classification system in distinguishing both clinical phenotype and prognosis in AAV than either the CHCC or the EMA system alone. We also studied the added value of appending the ANCA specificity to the CHCC categories.

PATIENTS AND METHODS

Cohort description. The inception cohort included patients in whom biopsy-proven AAV (including kidney-limited disease) was diagnosed between January 1985 and December 2007 and who were followed up by the Glomerular Disease Collaborative Network, as previously described (6). ANCA tests were done by indirect immunofluorescence microscopy or antigen-specific enzyme-linked immunosorbent assays (ELISAs). Patients were categorized as having cytoplasmic ANCA, PR3 ANCA, or both (referred to collectively as PR3 ANCA) or perinuclear ANCA (pANCA), MPO ANCA, or both (referred to collectively as MPO ANCA). Patients having only pANCA were required to have a negative antinuclear antibody test result. Histologic confirmation was based on a kidney, lung, or upper respiratory tract biopsy, consistent with pauci-immune small-vessel vasculitis or glomerulonephritis, with or without granulomatous inflammation. All renal biopsy specimens were evaluated by personnel at the University of North Carolina Nephropathology Laboratory. A small cohort of additional patients in our population who were persistently ANCA negative were excluded from the ANCA-positive cohort and statistical modeling, but they are described as a group with respect to the 3 classification systems. Patients were excluded if they had specificity for both PR3 ANCA and MPO ANCA, had a diagnosis of Churg-Strauss syndrome, or had disease overlapping with any other autoimmune disorder.

Our proposed system of describing AAV based on PR3 and MPO specificity was compared to 2 established classification systems, those of the CHCC (1) and the EMA (2). Each patient was assigned a clinical phenotype for each system as well as ANCA specificity, clinical disease manifestations, and outcomes, all of which were recorded from review of medical records. The EMA system describes clinical phenotypes as GPA or MPA, with a priority inclusion of any ear, nose, and throat (ENT) involvement as GPA, while the CHCC classification includes these GPA and MPA phenotypes with an additional category for kidney-limited disease (1,2). All patients were classified according to the CHCC and EMA systems through discussion and a consensus decision among 3 investigators (SL, SLH, and RJF). Organ involvement was determined using previously described criteria (6–8), and detailed information was recorded.

Outcomes of interest included treatment resistance, time to relapse, ESRD, and death, as previously described (6–8). Briefly, treatment resistance was defined as persistence or new appearance of any extrarenal manifestation of vasculitis despite immunosuppressive therapy and/or progressive decline in renal function in the setting of active urinary sediment. Relapse was defined as the reactivation of vasculitis in any organ system. The definition of disease relapse required an initial response to treatment; therefore, patients with treatment-resistant disease were not included among those with disease relapse. ESRD was defined as the long-term need for renal replacement therapy. Death from any cause was noted. The frequency of ANCA type, ranked from lowest to highest frequency of PR3 ANCA across clinical phenotype categories, was plotted by various organ system combinations, which were not mutually exclusive.

Statistical analysis. Univariate comparisons of the prevalence of each outcome (treatment resistance, relapse, ESRD, and death) across classification systems were first evaluated with chi-square tests. Kaplan-Meier estimates were used to plot the probability of relapse-free survival over time, and log rank tests were performed to evaluate univariate differences in relapse-free survival according to subgroups.

Receiver operating characteristic curve analysis was used to assess the prediction ability of each model by individual classification systems, with a concordance index (C-index) reported for each model. Classification systems with a C-index >0.65, indicating adequate model fit, were then directly compared for each outcome using an information-theoretic approach, which is a system for comparing models using multimodel inferences that allows direct comparison of the models of the 3 classification systems (9,10).

This approach uses the delta (Δ) of Akaike's information criterion (AIC), Akaike weights (or model probabilities), and evidence ratios to assess which model (and corresponding

system) best predicted each outcome (9,10). An additional bias correction term (AICc) was used instead of AIC (10). The evidence ratio of interest was between the estimated best model (delta AICc = 0) and each compared model (10).

Model averaging, which includes all information from the 3 classification system models together, weighted by model fit, was used to obtain point estimates, 95% confidence intervals (95% CIs), and *P* values for specific predictors of interest (9,10). Logistic regression models were used to assess factors associated with treatment resistance, with odds ratios (ORs) and 95% CIs reported. Proportional hazards models were used to evaluate the risk in terms of time to relapse, ESRD, and death, with hazard ratios (HRs) and 95% CIs provided.

Models were evaluated first with only the classification systems of interest, then controlling for potential confounding factors, with models controlling for potential confounders reported in the results. Predictors found in previous analyses to be predictors of each outcome in a subgroup of this cohort (6,11) were evaluated in the multivariable model averaging. In addition to the classification systems, control variables within each model system included the following: for relapse, disease involvement in the lungs and upper respiratory airways; for treatment resistance, age, race, and initial treatment (with or without cyclophosphamide); for ESRD, age, race, peak creatinine level at entry, initial treatment (with or without cyclophosphamide), and vasculitis of the skin; and, for death, age, peak creatinine level at entry, and initial treatment (with or without cyclophosphamide). Treatment with cyclophosphamide as a first therapy regimen after diagnosis typically included intravenous pulse (0.5–1 gm/m^2 per month) or oral (1–2 mg/kg per day) doses in conjunction with oral corticosteroids and frequently methylprednisolone as well. Treatment without cyclophosphamide included initial treatment with corticosteroids alone or in conjunction with other immunosuppressive regimens including azathioprine, mycophenolate mofetil, and cyclosporine. Therapy was not randomly assigned. The peak serum creatinine level (reported as both μmoles/liter and mg/dl) was noted as the highest measurement at the time of diagnosis and prior to beginning treatment. The racial groups compared were white and nonwhite, since only 14% of the cohort was nonwhite.

The majority of the factors have been well described in the literature, but the control of skin involvement at onset has only been seen in our prior evaluation of predictors, where it was associated with a protective effect against ESRD (HR 0.20 [95% CI 0.06–0.75], $P = 0.02$) (6). ENT involvement was included in the multivariable model as a potential predictor of relapse. As a sensitivity analysis, all models reevaluated patients with MPA and patients with kidney-limited disease as a single group, using the CHCC system.

A proportional hazards model was used to evaluate the effect of categorical subgroups defined by ANCA specificity and CHCC definitions, controlling for lung and upper respiratory tract involvement of the disease. Analyses were done using SAS statistical software, version 9.2.

RESULTS

Study cohort. Initially, 523 patients were considered for study inclusion. All patients were ANCA positive with a biopsy-proven pauci-immune small-vessel vasculitis. Of those, 502 were finally included in the study. Of the 21 patients who were excluded, 9 had been reported as being ANCA positive, but the actual specificity results as determined by indirect immunofluorescence and/or ELISA were not available. One patient was excluded for both PR3 ANCA and MPO ANCA positivity, 4 were excluded because of a diagnosis of Churg-Strauss syndrome, and 7 were excluded because long-term disease outcomes were not available.

In addition to the 523 ANCA-positive patients, we identified 12 patients who were consistently ANCA negative. Those 12 patients were not considered for inclusion by study design, as they could not be analyzed within the ANCA specificity system. However, understanding the particular interest surrounding the clinical entity of ANCA-negative pauci-immune vasculitis, we provide a thorough description of this group in the Discussion.

A detailed description of our study population (n = 502) is shown in Table 1. Kidney involvement was present in 488 patients, as confirmed by renal biopsy in 466 patients and by active urinary sediment with or without renal insufficiency in 22 patients. A diagnostic

Table 1. Description of the study cohort (n = 502)*

Followup after diagnosis of AAV, months	40.5 ± 44.9
Age at diagnosis, years	56.5 ± 18.7
Female, no. (%)	234 (47)
Caucasian, no. (%)	433 (86)
Lung involvement, no. (%)	252 (50)
Skin involvement, no. (%)	115 (23)
ENT involvement, no. (%)	185 (37)
Kidney involvement, no. (%)	488 (97)
Gastrointestinal involvement, no. (%)	59 (12)
Nerve involvement, no. (%)	60 (12)
Peak creatinine level at entry, mg/dl	4.6 ± 3.6
Acute dialysis at onset, no. (%)	94 (19)
Initial induction therapy, no. (%)	
No treatment	19 (4)
Corticosteroids alone	53 (11)
Cyclophosphamide (intravenous) and prednisone	238 (47)
Cyclophosphamide (oral) and prednisone	166 (33)
Other immunosuppressive therapy	26 (5)
Response to initial induction therapy, no. (%)†	
Treatment resistance	109 (23)
Complete remission (all therapy discontinued)	217 (45)
Remission sustained with therapy	157 (32)
Months to outcome	
Relapse (n = 147, among 374 who had a response)	31.3 ± 38.4
ESRD (n = 161)	39.2 ± 40.2
Death (total, n = 139)	50.6 ± 53.9
Death (censored by ESRD, n = 80)	52.7 ± 62.5

* Except where indicated otherwise, values are the mean ± SD. AAV = antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis; ENT = ear, nose, and throat; ESRD = end-stage renal disease.
† n = 483 (19 patients who were not treated were excluded).

kidney biopsy was performed in 466 of 502 patients (93%), while the remaining 36 patients (7%) underwent a diagnostic biopsy in other tissue (22 of these 36 patients had an active urinary sediment). Among the 466 patients who underwent a kidney biopsy, 103 (22%) also underwent a diagnostic biopsy in ≥1 additional organs or tissues. The most common sites for nonrenal biopsies (n = 137) included the lung (n = 61), skin (n = 42), and sinuses (n = 17, with an additional 17 sinus biopsies that were nondiagnostic).

Analysis of clinical phenotype and response to therapy. Although the CHCC and EMA use identical names for disease categories, there were substantial discrepancies in the allocation of patients into specific clinical pathologic categories between the 2 systems. Seventy-eight percent of patients classified as having MPA using the CHCC system were considered to have GPA by the EMA algorithm. As a consequence, the EMA system identified the majority of patients (324 [65%] of 502) as having GPA. In contrast, this diagnosis was far less frequent within the CHCC system (117 [23%] of 502; $P < 0.0001$). The difference between classification systems in GPA was predominantly due to the priority inclusion of ENT involvement as GPA by the EMA system. Specifically, we found 185 patients (37%) with ENT involvement, with 100% classified as having GPA by the EMA system by definition, and with 87 patients (47%) classified as having GPA by the CHCC system. The distribution of ANCA specificity was also different between these 2 systems. Using the CHCC system, 74% of patients diagnosed as having GPA were PR3 ANCA positive, whereas in the EMA algorithm only 54% of patients diagnosed as having GPA were PR3 ANCA positive. Using the CHCC definitions, 59% of MPA patients were MPO ANCA positive, compared to 75% of those with MPA by the EMA system. MPO ANCA was the dominant serotype (81%) among patients with kidney-limited disease, a category that is grouped with MPA within the EMA system.

Treatment resistance was evaluated in 483 of 502 patients, excluding the 19 patients who received no treatment. Relapse was evaluated in 374 patients, as patients were not considered able to relapse if they received no treatment (n = 19) or were resistant to treatment (n = 109). ESRD was reached in 161 of the 502 patients (32%), and 139 of 502 died (28%).

A number of univariate differences in outcomes among the various classification systems are displayed in Table 2. Treatment resistance was not markedly different across the CHCC and EMA classification systems, but was more common among those with MPO ANCA (27%) than among those with PR3 ANCA (17%) ($P = 0.016$). The rate of relapse differed across CHCC classification. Those identified as having GPA were most likely to relapse (60%), those with MPA had an intermediate risk of relapse (37%), and those with kidney-limited disease were least likely to relapse (19%) ($P < 0.0001$). According to the EMA system, those with GPA were also more likely to relapse than those with MPA, but the risks of relapse were closer (44% versus 30%; $P = 0.0071$). PR3 ANCA–positive patients relapsed more than MPO ANCA–positive patients

Table 2. Frequency of short- and long-term outcomes across classification systems*

Classification system, disease (n)	Treatment resistance (n = 109/483)	Relapse (n = 147/374)	ESRD (n = 161/502)	Death (n = 139/502)
Chapel Hill Consensus Conference				
GPA (117)	20/117 (17)	58/97 (60)	24/117 (21)	20/117 (17)
MPA (264)	56/255 (22)	74/199 (37)	80/264 (30)	79/264 (30)
Kidney-limited disease (121)	33/111 (30)	15/78 (19)	57/121 (47)	40/121 (33)
P	0.0711	<0.0001	<0.0001	0.0091
European Medicines Agency				
GPA (324)	68/317 (22)	110/249 (44)	92/324 (28)	84/324 (26)
MPA (178)	41/166 (25)	37/125 (30)	69/178 (39)	55/178 (31)
P	0.4244	0.0071	0.0214	0.2520
ANCA specificity				
MPO ANCA (283)	72/270 (27)	57/198 (29)	105/283 (37)	89/283 (31)
PR3 ANCA (219)	37/213 (17)	90/176 (51)	56/219 (26)	50/219 (23)
P	0.0160	<0.0001	0.0069	0.0349

* Values are the number/total number (%) of patients. ESRD = end-stage renal disease; GPA = granulomatosis with polyangiitis (Wegener's); MPA = microscopic polyangiitis; ANCA = antineutrophil cytoplasmic antibody; MPO ANCA = ANCA with myeloperoxidase specificity; PR3 ANCA = ANCA with proteinase 3 specificity.

Table 3. Comparison of classification system modeling and estimates for classification systems using model averaging for disease relapse, treatment resistance, ESRD, and death*

System modeling, classification system, classification category	ΔAICc per system model	Model weight	Model averaging		
			Model rank	*P*	HR or OR (95% CI)†
Disease relapse					
PR3 ANCA/MPO ANCA	0.000	0.989	1		
MPO ANCA					Reference
PR3 ANCA				0.0004	1.888 (1.328–2.686)
CHCC	11.651	0.003	3		
MPA					Reference
Kidney-limited disease				0.978	0.999 (0.961–1.034)
GPA				0.963	1.001 (0.962–1.042)
EMA	9.516	0.003	2		
MPA					Reference
GPA				0.935	0.995 (0.879–1.126)
Treatment resistance					
PR3 ANCA/MPO ANCA	1.93	0.256	2		
MPO ANCA					Reference
PR3 ANCA				0.744	0.952 (0.709–1.278)
CHCC	4.47	0.072	3		
MPA					Reference
Kidney-limited disease				0.966	0.997 (0.850–1.168)
GPA				0.961	1.004 (0.841–1.120)
EMA	0	0.672	1		
MPA					Reference
GPA				0.257	1.312 (0.817–2.132)
ESRD					
PR3 ANCA/MPO ANCA	2.849	0.154	3		
MPO ANCA					Reference
PR3 ANCA				0.907	1.009 (0.871–1.168)
CHCC	0	0.641	1		
MPA					Reference
Kidney-limited disease				0.186	1.302 (0.880–1.926)
GPA				0.693	0.923 (0.619–1.375)
EMA	2.288	0.204	2		
MPA					Reference
GPA				0.759	1.029 (0.855–1.239)
Death					
PR3 ANCA/MPO ANCA	0	0.495	1		
MPO ANCA					Reference
PR3 ANCA				0.417	1.141 (0.830–1.568)
CHCC	3.952	0.069	3		
MPA					Reference
Kidney-limited disease				0.987	1.001 (0.900–1.113)
GPA				0.951	0.996 (0.863–1.149)
EMA	0.251	0.437	2		
MPA					Reference
GPA				0.488	1.113 (0.822–1.508)

* ΔAICc = delta of Akaike's information criterion with an additional bias correction term (see Patients and Methods); PR3 ANCA = antineutrophil cytoplasmic antibody with proteinase 3 specificity; MPO ANCA = ANCA with myeloperoxidase specificity; CHCC = Chapel Hill Consensus Conference; MPA = microscopic polyangiitis; GPA = granulomatosis with polyangiitis (Wegener's); EMA = European Medicines Agency.

† Hazard ratios (HRs) and 95% confidence intervals (95% CIs) are shown for disease relapse, end-stage renal disease (ESRD), and death. Odds ratios (ORs) and 95% CIs are shown for treatment resistance.

(51% versus 29%). There were also variations in both ESRD and death within each of the 3 classification systems (Table 2).

Among the 12 patients who were ANCA negative, 9 were documented as negative by both immunofluorescence and antigen-specific ELISA, and the other 3 were documented as negative by immunofluorescence alone, with antigen specificity not evaluated. According

to the CHCC definitions, 2 of these patients were classified as having MPA, 7 as having GPA, and 3 as having kidney-limited disease. By the EMA system, 4 were categorized as having MPA and 8 as having GPA. Although these distributions were not formally compared, they were generally similar to those seen in the overall ANCA-positive cohort. Of note, 7 of the 12 ANCA-negative patients had disease involvement restricted to a single organ or system, including the 3 with kidney-limited disease.

Prognostic ability of classification systems for clinical outcomes. Each of the 3 candidate classification system models for relapse had adequate fit, with C statistics ranging from 0.86 to 0.89. The information-theoretic modeling approach for the outcome of time to relapse revealed that classification using ANCA specificity alone (PR3 versus MPO) had the best predictive model fit (model rank 1) among the 3 classification models, with the lowest delta AICc of 0.00 and the highest weight of 0.989 (Table 3). The other systems had weights at or approaching zero (Table 3), indicating that they did not provide predictive value for time to relapse. ANCA specificity was strongly predictive of relapse, with PR3 ANCA–positive patients almost twice as likely to relapse as those with MPO ANCA positivity (HR 1.89 [95% CI 1.33–2.69], $P = 0.0004$) (Table 3). These results are displayed graphically in Figure 1A, which shows the probability of relapse-free survival over time by ANCA specificity.

The only other predictor of relapse in the multivariable model was pulmonary involvement of the disease (HR 1.7 [95% CI 1.2–2.4], $P = 0.004$). Upper respiratory tract disease involvement, which has been an inconsistent predictor of relapse across cohorts (6,11), did not predict relapse in this analysis (HR 1.07 [95% CI 0.75–1.51], $P = 0.71$). In the sensitivity analysis, the same model-averaging results were seen when MPA and kidney-limited disease were grouped together in the CHCC system, with ANCA specificity remaining the best predictive model and PR3 ANCA and lung involvement remaining the significant predictors with similar point estimates and CIs (for PR3 ANCA: HR 1.89 [95% CI 1.33–2.69], $P = 0.0004$) (for lung involvement: HR 1.68 [95% CI 1.18–2.40], $P = 0.004$).

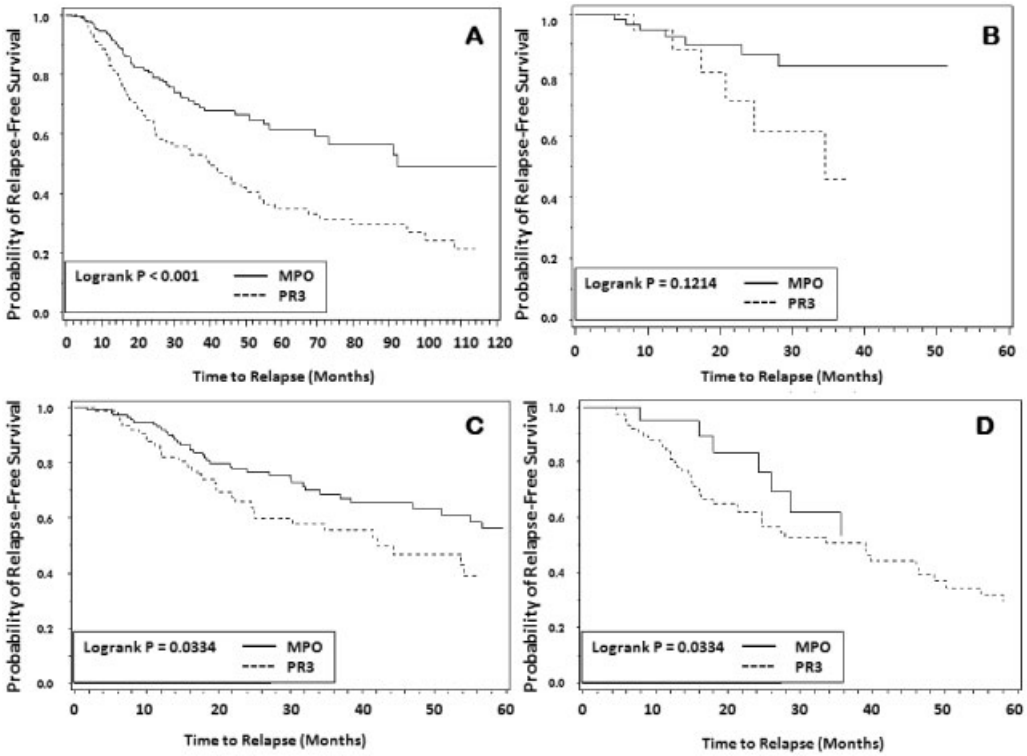

Figure 1. Probability of relapse-free survival by antineutrophil cytoplasmic antibody (ANCA) specificity for myeloperoxidase (MPO) and proteinase 3 (PR3) (**A**) and by MPO ANCA positivity and PR3 ANCA positivity within classification groups of the Chapel Hill Consensus Conference definitions, including kidney-limited disease (**B**), microscopic polyangiitis (**C**), and granulomatosis with polyangiitis (Wegener's) (**D**).

Table 4. Multivariable HRs for time to relapse by CHCC disease categories for MPO ANCA and PR3 ANCA specificities*

ANCA specificity, disease definition category (n)	HR (95% CI)†	*P*
MPO ANCA, KLD (56)	Reference	NA
MPO ANCA, MPA (121)	1.56 (0.70–3.48)	0.276
MPO ANCA, GPA (21)	1.36 (0.47–3.90)	0.568
PR3 ANCA, KLD (20)	2.49 (0.89–6.95)	0.081
PR3 ANCA, MPA (79)	2.45 (1.07–5.63)	0.035
PR3 ANCA, GPA (77)	3.15 (1.34–7.40)	0.009

* KLD = kidney-limited disease; NA = not applicable (see Table 3 for other definitions).
† The proportional hazards model for these results controlled for disease involvement of the lung and upper airways.

The probability of relapse-free survival over time by MPO ANCA positivity and PR3 ANCA positivity within each CHCC disease group (kidney-limited disease, MPA, and GPA) is shown in Figures 1B–D. Within each disease subgroup, there was a trend for those with PR3 ANCA to be more likely to relapse. The statistical power of multivariable modeling was limited but revealed a clear trend for all 3 CHCC categories among PR3 ANCA–positive patients to have similar and consistently higher risks (HRs of 2.45–3.15) than the categories among MPO ANCA–positive patients (HRs of 1.0–1.56) (Table 4). Results were similar using the EMA categories by ANCA specificity (data not shown).

Given the consistent results for ANCA specificity as a predictor of relapse, we sought to better understand organ involvement of the disease by ANCA specificity. Categories of organ system involvement were ranked by their prevalence of PR3 ANCA and inversely by their prevalence of MPO ANCA (Figure 2). Patients with kidney-limited disease or any form of vasculitis without radiographic or histologic proof of granulomatous inflammation were more likely to have MPO ANCA, and those with the most compelling evidence for necrotizing granulomatous inflammation were most likely to have PR3 ANCA. For instance, the majority of patients with kidney-limited disease had MPO ANCA (81%), while almost all patients with bone destruction or saddle nose deformity had PR3 ANCA (94%).

Each of the 3 classification system models for treatment resistance, ESRD, and death had adequate fit, with C statistics for treatment resistance of 0.70 for all 3 models and of 0.78 and 0.79 for ESRD and death, respectively. In comparing models, there were slight differences between classification systems in the multivariable modeling for each outcome; however, none of the 3 classification systems were found to be better

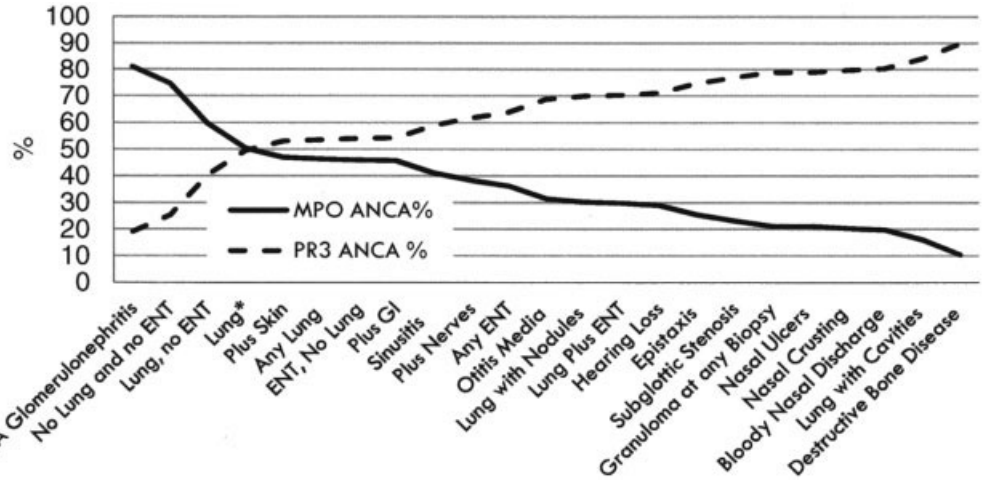

Figure 2. Frequency of PR3 ANCA and MPO ANCA specificities by a variety of clinical phenotypes (organ groupings are not mutually exclusive). No lung and no ear, nose, and throat (ENT) = vasculitis in any organ except the lungs and the ENT system; lung, no ENT = vasculitis localized in the lungs but not in the ENT system; lung* = vasculitis localized in the lungs without indicative markers (nodules or cavities) or histologic proof (granulomas) of granulomatous inflammation; plus skin = vasculitis localized at any organ plus dermal involvement; any lung = any type of pulmonary vasculitis such as pulmonary hemorrhage, infiltrates, nodules, cavities, granulomas, or respiratory arrest; ENT, no lung = vasculitis localized in the ENT system but not in the lungs; plus gastrointestinal (GI) = vasculitis localized at any organ plus involvement of the GI tract; plus nerves = vasculitis localized at any organ plus involvement of the nerves; any ENT = any type of vasculitic manifestation of the ENT system; lung with nodules = vasculitis localized in the lungs with radiographic proof of nodules; lung plus ENT = any type of pulmonary vasculitis plus any type of vasculitic manifestation of the ENT system (see Figure 1 for other definitions).

independent predictors of these outcomes (Table 3). Results were similar for each of these outcomes for the sensitivity analyses when MPA and kidney-limited disease were grouped together in the CHCC system. For the outcome of treatment resistance, treatment category and race were the only significant predictors.

Those not treated with cyclophosphamide at initial diagnosis were twice as likely to be resistant to therapy as those who received cyclophosphamide (OR 2.1 [95% CI 1.2–3.6], $P = 0.011$). Those of nonwhite race were also twice as likely to be treatment resistant (OR 2.0 [95% CI 1.1–3.7], $P = 0.016$).

For ESRD, controlling for classification systems, age, race, skin involvement, peak creatinine level at entry, and treatment category, statistically significant predictors included peak serum creatinine level at entry (HR 1.15 per unit increase in mg/dl [95% CI 1.11–1.19], $P < 0.0001$) and nonwhite race (HR 1.7 versus whites [95% CI 1.1–2.6], $P = 0.018$). Evaluation of predictors for death (n = 139 deaths) revealed that when controlling for classification systems, age, ANCA specificity, peak creatinine level at entry, and treatment category, predictor variables included age (HR 1.05 [95% CI 1.04–1.07], $P < 0.00001$) and peak serum creatinine level at entry (HR 1.11 per unit increase in mg/dl [95% CI 1.06–1.16], $P = 0.00002$). When death was censored by the date of ESRD (n = 80 deaths), there was still no predictive value from the classification systems. Other predictors for death had equivalent risk estimates (age and peak creatinine level at entry).

DISCUSSION

We envision a classification system for AAV to be not only terms to label and describe the disease, but also a functional tool for assisting clinicians with disease recognition, treatment, and prognosis. We focused on issues we consider critical for patient management—the clinical phenotype and prediction of disease course.

The question of prognosis in AAV is critically important for clinicians. Because the vast majority of patients respond to standard induction treatment (12,13), the question is how to weigh the risk of relapse against the risk of long-term maintenance therapy to prevent relapse. In this study, disease relapse was found to be independently predicted by PR3 ANCA specificity, a finding consistent with previous studies (6,14), but not by other classification systems. These PR3 ANCA–positive patients may be the ones in whom prolongation of immunosuppressive therapy after achievement of remission is reasonable, although there are few direct data to support the contention that relapse can be prevented by the use of current therapies (6,8,15–17).

A wide range of manifestations of vasculitis involving multiple anatomic sites and tissues was observed and was found to correlate strongly with ANCA specificity. The association between PR3 ANCA or MPO ANCA and the anatomic site of vasculitic involvement and/or the presence of granulomatous inflammation was particularly interesting. The majority of patients with kidney-limited disease had MPO ANCA positivity (81%), and those with destructive lesions of the upper airways had PR3 ANCA positivity (94%). When vasculitis was expanded from the kidney-limited variant to involve the gastrointestinal or respiratory tract, MPO ANCA positivity was less frequent and PR3 ANCA positivity increased. Moreover, among 52 patients in our cohort who had histologic proof of granulomatous inflammation at any site, 79% had PR3 ANCA positivity and 21% had MPO ANCA positivity. The principle that diseases associated with MPO ANCA and PR3 ANCA are clinically distinct is essential to the categorization of ANCA-associated small-vessel vasculitis based on antibody specificity.

Several hypotheses could explain the correlation of disease expression with ANCA serotype. Among them, the entrance portal and/or nature of any potential environmental "pathogen," including its ability to be distributed in the body, could predict ANCA type. In addition, the availability of the target antigen in the tissue or organ (18) or the genetic background of any particular individual may explain ANCA type. In this regard, it is interesting that PR3 ANCA positivity is predominant in northern Europe, whereas MPO ANCA positivity is predominant in Japan and China (19,20). ANCA disease associated with environmental factors, such as silica (21), microbes (22), medications (23), or concomitant disease (24), usually demonstrates a predominance of a specific ANCA type. Various genes have been closely associated with AAV (25,26). If the disease is genetically driven in the direction of a specific phenotype, this might be influenced by the ANCA specificity. However, the extent to which any gene might influence the clinical phenotype of vasculitis, in what proportion of patients, and in any particular patient is not known. Different pathogenic effects of autoantibodies against PR3 versus MPO could confer different manifestations of disease (27,28). This could be explained by differences in external or internal triggering events, differences in activation of effector cells, or differences in innate or

adaptive immune responses that are activated by PR3 ANCA versus MPO ANCA (21,29–34).

The CHCC and EMA classification systems failed to provide a consistent ability to predict AAV outcomes. This results in part from differences in disease "definitions." For instance, the EMA system overrepresents the diagnostic category of GPA (2), because essentially any upper respiratory tract involvement is considered to be in this category according to the criteria of the American College of Rheumatology (3). Seventy-eight percent of patients classified as having MPA by the CHCC system were instead classified as having GPA by the EMA system. Interestingly, the distribution of ANCA types differs significantly between the CHCC classification and the EMA system. PR3 ANCA positivity is predominant in patients deemed as having GPA by the CHCC definitions (74%), yet there is almost a 1:1 ratio for PR3 ANCA (54%) and MPO ANCA (46%) by the EMA model in patients with GPA. Long-standing clinical experience (35–37) has shown that most patients with ongoing active GPA have PR3 ANCA positivity (38–40), although sensitivity differs across studies (38–40).

Patients with pauci-immune small-vessel vasculitis who were ANCA negative were not included in the statistical analyses for this study, but were described. Only 2.2% of patients in our registry were known to be persistently ANCA negative in clinical ANCA assays. Various proportions of patients with pauci-immune small-vessel vasculitis fail to demonstrate ANCA positivity across study cohorts, with studies demonstrating 10–30% across all types of pauci-immune small-vessel vasculitis (41), but this phenomenon is rarer in our population. Ideally, patients should be tested for ANCAs when the disease is active and prior to initiation of therapy, to avoid the effect of immunomodulation. This becomes even more critical with the use of interventions that eliminate antibodies, such as plasmapheresis and B cell depletion. ANCA-negative patients in our cohort demonstrated symptoms of AAV indistinguishable from those in ANCA-positive patients, as also reported by others (42).

The strong predictive value of PR3 ANCA positivity and lung involvement for relapse in this study is consistent with previous studies (6,11,43). ENT involvement was not predictive of relapse in this analysis. Prior analyses have shown only a weak or nonsignificant association with prediction of relapse (6,11).

With respect to treatment resistance, the predictors of being nonwhite and having induction therapy without cyclophosphamide were in accord with the evaluation in our previous cohort (6). Other potential predictors of treatment resistance previously evaluated include sex and age, which were not significant predictors in this evaluation, having shown inconsistent results in previous cohorts (6,11). Older age and higher baseline creatinine levels as predictors of death are consistent with a recent report that older age and higher organ damage, as measured by the Vasculitis Damage Index (44), were predictors of death in a cohort of 50 patients with GPA (45). Higher serum creatinine levels and the need for acute or chronic dialysis have also been shown to represent a specific form of damage that contributes to mortality in small-vessel vasculitis (46). Evaluation of predictors of death found in other studies, such as pulmonary hemorrhage (7), or adverse treatment events and level of disease activity (47) were beyond the scope of this study.

Limitations of this study include that this cohort was derived from a registry of patients recruited by nephrologists, and therefore the vast majority of patients had ANCA-associated glomerulonephritis at presentation, alone or in combination with other organ involvement. However, the prevalence of kidney involvement in AAV is reported to be as high as 75–90% (48), and therefore our population likely represents the majority of patients with this disease (49). Furthermore, kidney involvement renders a significant effect on patients' quality of life, as morbidity and mortality are high, particularly among those with ESRD. Thus, studying patients with kidney involvement is useful for any specialist seeing patients with small-vessel vasculitis.

Other limitations, inherent to community-based cohort studies conducted over a long period of time, include a lack of uniform treatment protocols and differences in general clinical practice. Additionally, tests for ANCAs have evolved with time and were not standardized across clinics; however, there is acceptable consistency between earlier ANCA test methods and the commercial kits that are currently used (50).

Classification systems are designed to provide a standard method of describing groups of patients, not only to facilitate categorizing patients for clinical trials and comparing results among trials in the medical literature, but above all to assist in patient care. Etiology, the constellation of symptoms, and other predictors of outcome should be included in classification systems if they facilitate patient care. Because ANCA specificity not only is implicated in pathogenesis and correlates with clinical symptoms, but more importantly helps predict the outcome of disease, it is appropriate to include ANCA specificity in the diagnostic classification.

This approach is feasible now that ANCA testing is widely available and reliable. We recommend that PR3 ANCA and MPO ANCA be used in conjunction with the terms MPA, GPA, and pauci-immune glomerulonephritis in categorizing patients within the spectrum of AAV.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Lionaki had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lionaki, Hogan, Senior, Nachman, J. C. Jennette, Falk.

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Analysis and interpretation of data. Lionaki, Blyth, Hogan, Hu, Senior, Nachman, J. C. Jennette, Falk.

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