A Population-based Study Showing Better Renal Prognosis for Proteinase 3 Antineutrophil Cytoplasmic Antibody (ANCA)–associated Nephritis Versus Myeloperoxidase ANCA–associated Nephritis

Aladdin J. Mohammad and Mårten Segelmark

ABSTRACT. ***Objective.*** Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is usually differentiated based on clinical phenotypes, but recent data indicate that myeloperoxidase (MPO)-AAV is genetically distinct from proteinase 3 (PR3)-AAV. We reviewed a population-based cohort of AAV, focusing on differences in clinical and laboratory characteristics and to compare renal outcome between MPO-ANCA and PR3-ANCA nephritis.

Methods. All new cases of AAV diagnosed between 1997 and 2009 in a geographically defined area in southern Sweden were retrieved using a validated search algorithm. Data were collected from time of diagnosis and end of followup. Renal and patient survival were analyzed according to ANCA serotype.

Results. During the study period, 201 patients were diagnosed with AAV, 98 tested positive for PR3-ANCA, and 85 for MPO-ANCA. Patients with PR3-ANCA were younger, had significantly higher inflammatory activity, and had a larger number of organs involved at diagnosis, but nephritis was more prevalent among patients with MPO-associated (72/85; 85%) versus PR3-associated disease (67/98, 68%). When comparing only patients with ANCA-associated nephritis, those with MPO-ANCA were more likely to develop endstage renal disease (n = 27, 38%) than those with PR3-ANCA (n = 10, 15%), p = 0.003. The risk remained significantly elevated after adjusting for sex, age, and s-creatinine level at diagnosis (HR 2.64; 95% CI 1.25–5.58; p = 0.003). There were no significant differences in mortality rates between the 2 groups.

Conclusion. The outcome in this population-based cohort indicates that among AAV patients with nephritis, renal prognosis is better in the PR3-ANCA group, even after adjustment for sex, age, and renal function at diagnosis. (First Release June 1 2014; J Rheumatol 2014;41:1366–73; doi:10.3899/jrheum.131038)

Key Indexing Terms:
ANTINEUTROPHIL CYTOPLASMIC ANTIBODY GLOMERULONEPHRITIS
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Glomerulonephritis associated with antineutrophil cytoplasmic antibodies (ANCA-associated nephritis, AAN) is an important cause of renal insufficiency. Cohort studies indicate that 30–40% of patients with AAN eventually develop a need for renal replacement therapy. We have reported the incidence of ANCA-associated vasculitis (AAV) to be 21 per million per year in southern Sweden[1] and that 70% of these patients had AAN. A similar annual incidence of AAN (12 per million) was found in both countries when the incidence was compared between Japan and England[2]. Based on extrarenal symptoms, patients with AAV are traditionally divided into different disease entities, such as granulomatosis with polyangiitis (GPA, previously, Wegener granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss; EGPA). Even if there is a general consensus today regarding their definitions[3], disagreement remains about how to classify individual patients. Many patients exhibit overlapping phenotypes, and some change from an MPA to a GPA phenotype over time. Alternatively, AAV can be classified using serology to group patients according to their autoantibodies, i.e., as specific

From the Department of Clinical Sciences, Section of Rheumatology, Lund University; Department of Rheumatology, Skåne University Hospital, Lund; Department of Nephrology UHL, Östergötland County Council; and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden.

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A.J. Mohammad, MD, PhD, Department of Clinical Sciences, Section of Rheumatology, Lund University; Department of Rheumatology, Skåne University Hospital; M. Segelmark, MD, PhD, Department of Nephrology UHL, Östergötland County Council; Department of Medical and Health Sciences, Linköping University.

Address correspondence to Dr. A.J. Mohammad, Department of Rheumatology, Skåne University Hospital, 221 85, Lund, Sweden. E-mail: Aladdin.mohammad@med.lu.se

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for myeloperoxidase (MPO) or for proteinase 3 (PR3). A major finding in a recent genomewide association study was that MPO-ANCA and PR3-ANCA–associated vasculitis are genetically distinct entities, providing biological support for a classification based on serology[4].

From a clinical standpoint, the justification of any classification system is its ability to predict prognosis and response to therapy. One publication compared classification based on serology with one based on phenotype to predict outcome. The result showed clearly that serological was superior to phenotypic classification for predicting relapse tendency, with more frequent relapses among PR3-ANCA–positive patients. The results were independent of the algorithm used for the phenotypic classification[5].

Patients with AAV may be referred to either rheumatology or nephrology units, thus introducing a risk of selection bias in cohort studies, and all clinical trials have exclusion criteria. We developed epidemiological search tools shown to identify > 95% of all AAV cases in our study area[6]. That enabled us to study the outcome of vasculitis from a population perspective. Using data from our vasculitis registry, we present data on the clinical characteristics and outcome of AAV in a defined population in southern Sweden, focusing on differences between MPO-ANCA and PR3-ANCA AAV with nephritis.

MATERIALS AND METHODS

Study area and population. The study was conducted in a defined geographical area in southern Sweden, as described in detail[1]. Briefly, in December 2009 the population was about 701,000 and the area was 3294 km^2 (about 7% of the total population and 0.8% of the total area of Sweden). Women made up 50.4% of the study population and the age distribution was as follows: 0–14 years, 19.8%; 15–54 years, 52%; 55–64 years, 11.7%; 65–74 years, 8.7%; and ≥ 75 years, 7.8%[7].

Case ascertainment and classification. Potential cases of AAV were identified through healthcare registries using a validated search algorithm that identifies > 95% of all AAV cases[6]. All potential AAV cases were reviewed using case records. Diagnosis of small vessel vasculitis and classification of the patients into different disease entities were performed as described[6]. Patients were considered to have AAV if they had symptoms and signs compatible with small vessel vasculitis supported by histopathology, radiology, and/or serological findings, with no evidence of pseudovasculitis or secondary vasculitis; and had been classified as having GPA, MPA, or EGPA according to the European Medicine Agency 2007 algorithm[8]. All patients with a new diagnosis of AAV between 1997 and 2009 were included in the study; the comparisons, however, were limited to patients from whom positive ELISA tests for MPO-ANCA or PR3-ANCA could be retrieved. Patients were defined as having AAN if they fulfilled the following criteria: (1) had a clinical diagnosis of AAV and (2) had biopsy-proven nephritis, or (3) if not biopsied, the presence of hematuria and active urinary sediment giving a score ≥ 1 in the Birmingham Vasculitis Activity Score (BVAS) renal domain[9].

Treatment. Since 1997, the Clinical Vasculitis Network at Skåne University Hospital has issued local treatment guidelines for AAV, and these are updated every other year. Adherence to these guidelines has been good (data not shown), and thus the vast majority of patients included in the study were treated with oral cyclophosphamide (CYC, 2 mg/kg body weight/day) or intravenous CYC pulse therapy (10 pulses, each 15 mg/kg) in combination with oral corticosteroids (starting at 1 mg/kg/day). Patients with severe renal involvement (creatinine ≥ 500 μmol/l), or those with life-threatening pulmonary hemorrhage received plasma exchange. On achieving remission, patients received maintenance treatment with azathioprine or mycophenolate mofetil, usually for periods longer than 18 months. Between 2007 and the end of 2009, few patients in our area were treated with rituximab because it was used only as second- or third-line therapy during the final years of the study period.

Data collection. Demographics and clinical data were collected from time of diagnosis and included age at diagnosis, signs and symptoms at onset, diagnosis delay (time in months from first possible signs and symptoms of vasculitis to date of diagnosis); the number of organ systems involved at onset of disease was also extracted from case records. Organ involvement was recorded according to the BVAS[9]. Laboratory data were collected at the date of diagnosis including hemoglobin concentration, white blood cell count, thrombocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum creatinine (s-creatinine). Day of diagnosis was defined as the day when specific therapy was initiated; if specific therapy was never started, the day of biopsy was used instead. Renal biopsy findings were extracted by reviewing all histopathology reports. Biopsies were classified as diffuse crescentic GN if > 50% of nonsclerotic glomeruli had crescents, and as focal if crescents were < 50%. A few patients who had no crescents but had focal fibrinoid necrosis in the glomeruli were also referred to the focal group. Information on renal outcome in terms of endstage renal disease (ESRD) at any time during followup from diagnosis to May 2012 was registered. ESRD was defined as commencement of chronic dialysis or renal transplantation. Vital status and date of death were checked by the Swedish Census, which is linked to the computerized hospital files.

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Review Board in Lund (LU 283-02 and 2010-517).

Statistical analyses. Statistical analyses were performed using the Statistical Package for the Social Sciences; SPSS 20.0 for Windows (IBM SPSS 20.0.0). The differences in the frequency of organ involvement between groups were studied using the chi-square test. Patient survival and renal survival were studied using the Kaplan-Meier method in which differences between groups were investigated using the log-rank test. Differences in renal survival were also studied by Cox regression analysis. The following variables were included in the Cox regression model: (1) ANCA serotype, (2) age at diagnosis, (3) sex, and (4) s-creatinine at diagnosis. The test of normality is used to explore whether a variable is normally distributed. For normally distributed variables, data are presented as mean and SD, and Student's t-test is used for comparison between groups. Continuous, not normally distributed data are presented as median and interquartile ranges (IQR) and Mann-Whitney U test is used for comparison. For all analyses, $p < 0.05$ was considered significant.

RESULTS

Demographics. A total of 201 cases of AAV (98 women) were diagnosed between 1997 and 2009 in the study area. The patients were classified as follows: GPA, 98 patients; MPA 92; and EGPA 11. A total of 183 patients (91%) tested positive for ANCA (PR3: n = 98; MPO: n = 85) and were included in the analysis for differences based on serotype. The remaining 18 patients (14 with negative test results and 4 without any retrievable ANCA results) were excluded from further analysis. Among the 183 patients with positive ANCA results 2 were double-positive, both exhibiting predominance for MPO-ANCA; the 2 were assigned to the MPO-ANCA group.

The mean age at diagnosis for PR3-ANCA patients was

63.2 ± 15.9 years, lower than MPO-ANCA patients with 68.7 ± 14.4 years (p = 0.016). The male/female distribution was significantly skewed; women (n = 87/183, 48%) made up the majority of the MPO+ patients (48/87, 55%) compared to only 39/87 (45%) of the PR3+ patients, p = 0.024.

Organ involvement and laboratory data at presentation. Ear-nose-throat (ENT) involvement was significantly more common in the patients with PR3-ANCA (59% vs 19%, p < 0.001) while renal disease was more prevalent in MPO-ANCA–associated disease (85% vs 68%, p = 0.010). There were minor divergences in other organ manifestations but these were not statistically significant (Table 1). Patients with PR3-ANCA had a significantly greater organ involvement at diagnosis (p = 0.004, Table 1). Patients with PR3-ANCA had significantly higher inflammatory activity measured by ESR and CRP, higher thrombocyte and white blood cell counts, and a higher mean value for hemoglobin concentration (Table 1).

AAN findings. A total of 139 patients had AAN according to the study definition; demographic laboratory and histology data are shown in Table 2. There were 67 patients with positive PR3-ANCA and 72 with positive MPO-ANCA. Patients with PR3-ANCA had significantly higher inflammatory activity at diagnosis (Table 2). A larger proportion of patients with PR3-ANCA had involvement of ≥ 3 organs at diagnosis. Similarly, general symptoms and ENT involvement were significantly more common among patients with PR3-ANCA; there were no statistically significant differences in other organ involvement (Table 2).

Renal biopsies were performed in 107/139 patients (77%), 57/72 (79%) among patients with MPO-ANCA, and 50/67 (75%) with PR3-ANCA. The biopsies were nondiagnostic in 11 patients (Table 2). The most common finding in nondiagnostic renal biopsies was insufficient material (n = 4) and pauciimmune focal proliferative GN without necrosis and crescents (n = 3). The mean followup time for all patients from diagnosis to May 1, 2012, or ESRD was 4.6 ± 4.04 years. During followup, 27 of the MPO-ANCA–positive patients (38%) developed ESRD versus 10 PR3-ANCA–positive patients (15%; p = 0.003). In addition, a greater proportion of MPO-ANCA patients who were alive with a functioning native kidney at the end of followup had an estimated glomerular filtration rate below 50 ml/min/1.73 m^2 (48% vs 34%), but this difference was not statistically significant (p = 0.243). The majority of patients reaching ESRD started dialysis during the first year after diagnosis; with no difference in this

Table 1. Demographic, laboratory, and clinical characteristics of 183 patients with ANCA-associated vasculitis and ANCA positivity measured by ELISA.

	PR3-ANCA, n = 98	MPO-ANCA, n = 85	p
Sex, F/M	39/59	48/37	0.024
Diagnosis: GPA/MPA/EGPA	73/25/0	17/64/4	
Age at diagnosis, yrs	63.2 ± 15.9	68.7 ± 14.4	0.016
Diagnosis delay, mos	2 (1–4)	2 (1–5)	0.063
Laboratory results			
C-reactive protein, mg/dl	11.65 (6.5–19.1)	3.4 (0.9–12.4)	< 0.001
ESR, mm/h	77 ± 30	58 ± 35	0.004
Hemoglobin, g/dl	11.1 ± 1.82	10.6 ± 1.77	0.004
Thrombocyte count, × 10^9/l	408 (333–517)	324 (261–400)	< 0.001
White blood cell count, × 10^9/l	11.9 (9.9–15)	9.6 (7.1–13)	0.002
Creatinine, mg/dl	1.46 (0.81–3.03)	2.67 (1.21–5.19)	0.004
Patients with ≥ 3 organ systems involved, n (%)	75 (76)	48 (56)	0.004
Deaths during followup, n (%)	36 (37)	36 (42)	0.438
Organ systems involved at diagnosis			
General, n (%)	92 (94)	72 (85)	0.042
ENT, n (%)	58 (59)	16 (19)	< 0.001
Chest, n (%)	51 (52)	34 (40)	0.103
Nervous, n (%)	14 (14)	8 (9)	0.312
Cutaneous, n (%)	5 (5)	6 (7)	0.579
Mucocutaneous and eyes, n (%)	10 (10)	2 (2)	0.032
Cardiovascular, n (%)	4 (4)	4 (5)	0.837
Abdominal, n (%)	5 (5)	8 (9)	0.258
Renal, n (%)	67 (68)	72 (85)	0.01

Results are mean ± SD (normally distributed variables) or median and interquartile range (not normally distributed variables), or number and percentage. GPA: granulomatosis with polyangiitis (formerly Wegener); MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis (Churg-Strauss); ENT: ear-nose-throat; ESR: erythrocyte sedimentation rate; ANCA: antineutrophil cytoplasmic antibody; PR3: proteinase 3; MPO: myeloperoxidase.

Table 2. Demographics and laboratory data of 139 patients with AAV and renal involvement.

	PR3-ANCA n = 67	MPO-ANCA n = 72	p
Sex, F/M	24/43	36/36	0.092
Diagnosis: GPA/MPA/EGPA	42/25/0	9/62/1	
Age at diagnosis, yrs	64.8 ± 16.4	70.1 ± 14.3	0.043
Diagnosis delay, mos	2 (1–3)	2 (1–4)	0.206
Laboratory results			
C-reactive protein, mg/dl	11.8 (8.8–17.7)	4.6 (0.9–12.6)	< 0.001
ESR, mm/h	80.1 ± 29.6	64.2 ± 36.0	0.047
Hemoglobin, g/dl	10.8 ± 1.89	10.2 ± 1.68	0.05
Thrombocyte count, × 10^9/l	387 (314–483)	316 (260–386)	0.001
White blood cell count, × 10^9/l	12.5 (10–15)	9.3 (7.1–12.5)	0.001
Creatinine at diagnosis, mg/dl	2.64 (1.37–4.10)	3.05 (1.73–5.77)	0.062
Creatinine at last followup*, mg/dl	1.19 (0.85–1.60)	1.39 (1.01–1.84)	0.187
Patients with GFR < 50 ml/min at last followup*, n (%)	12/35 (34)	13/27 (48)	0.243
Patients developed ESRD, n (%)	10 (15)	27 (38)	0.003
Patients with ≥ 3 organ systems involved, n (%)	50 (75)	42 (58)	0.042
Death, n (%)	29 (43)	35 (49)	0.529
Organ system involved at diagnosis			
General, n (%)	64 (96)	60 (83)	0.021
ENT, n (%)	31 (46)	9 (13)	< 0.001
Chest, n (%)	32 (48)	29 (40)	0.374
Nervous, n (%)	7 (10)	4 (6)	0.286
Cutaneous, n (%)	4 (6)	3 (4)	0.627
Mucocutaneous and eyes, n (%)	5 (7)	1 (1)	0.078
Cardiovascular, n (%)	2 (3)	3 (4)	0.709
Abdominal, n (%)	4 (6)	8 (11)	0.281
Renal histology findings, n (%)			
Diffuse crescentic GN, pauciimmune	15 (22)	11 (15)	0.282
Diffuse crescentic GN, IF not done	2 (3)	3 (4)	0.585
Diffuse crescentic GN, granular IgG/C3	1 (1.5)	2 (3)	0.602
Focal necrotizing/crescentic GN, pauciimmune	24 (36)	22 (31)	0.509
Focal necrotizing/crescentic GN, IF not done	3 (4.5)	8 (11)	0.147
Pauciimmune small vessel vasculitis without GN	0 (0)	3 (4)	0.091
Miscellaneous or insufficient material for diagnosis	5 (8)	8 (11)	0.46
No renal biopsy performed	17 (25)	15 (21)	0.525

*Data on creatinine and GFR < 50 ml/min at last followup (May 2012), included only patients alive and with native kidney function at last followup. All other demographic, clinical, and laboratory data are based on 139 patients with renal involvement. Results are reported as mean ± SD (normally distributed variables) or median and interquartile range (not normally distributed variables), or number and percentage. AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis (formerly Wegener); MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis (Churg-Strauss); ESRD: endstage renal disease; ENT: ear-nose-throat; GN: glomerulonephritis; ESR: erythrocyte sedimentation rate; ANCA: anti-neutrophil cytoplasmic antibody; PR3: proteinase 3; MPO: myeloperoxidase; GFR: glomerular filtration rate; IF: immunofluorescence.

variable between PR3-ANCA+ (60%, 6/10) and MPO-ANCA+ (59%, 16/27) patients. Among patients with PR3-ANCA, the 1-, 5-, and 10-year renal survivals were 90.8%, 88.8%, and 77.7%. Among patients with MPO-ANCA, the corresponding findings were 77.1%, 65.6%, and 53.1% (p = 0.002; Figure 1). Removing the only patient with EGPA (MPO-ANCA–positive) from the analysis only marginally affected the result (data not shown).

When we categorized patients based on disease phenotypes, we found the 1-, 5-, and 10-year renal survival to be 89.9%, 87.4%, and 72.4% among patients classified as having GPA compared to 79.9%, 70.2%, and 60.1%, respectively, among patients with MPA (p = 0.051).

Cox regression analysis showed that patients with MPO-ANCA had a nearly 3 times higher risk of developing ESRD than PR3-ANCA–positive patients (HR 2.98; 95% CI 1.44–6.18; p = 0.003). This risk remained significantly elevated after adjustment for sex, age, and s-creatinine at diagnosis using Cox regression analysis (HR 2.64; 95% CI 1.25–5.58; 0.011; Table 3).

Patient survival. The mean time of followup for all patients

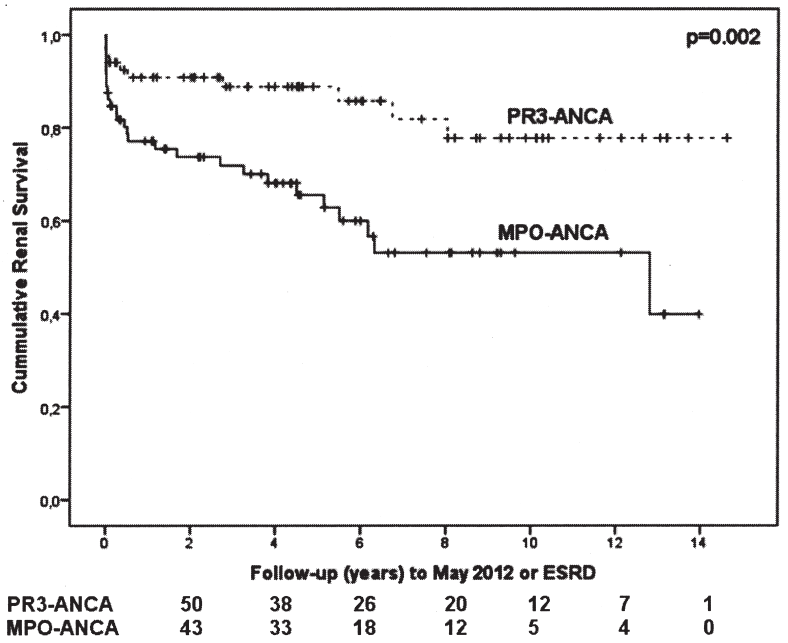

Figure 1. Renal survival by Kaplan-Meier curves according to serology type (139 patients with renal disease at diagnosis; 67 with PR3-ANCA+ and 72 with MPO-ANCA+). PR3: proteinase 3; ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase.

Table 3. Risk of endstage renal disease with nephritis.

	HR	95% CI	p
MPO+	2.64	1.25–5.58	0.011
Age at diagnosis	1.01	0.98–1.03	0.405
Sex (male)	0.96	0.68–1.34	0.815
S-creatinine	3.17	1.99–5.04	< 0.001

Cox regression analysis. MPO: myeloperoxidase.

from diagnosis to May 1, 2012, or death was 5.46 ± 4.09 years. Seventy-two patients (30 women) died during followup. For all patients, the absolute survival rate was 86.3% at 1 year, 69.4% at 5 years, and 57.1% at 10 years. The corresponding values for patients with PR3-ANCA were 86.7%, 72.4%, and 62.1% and for patients with MPO-ANCA: 85.9%, 65.9%, and 51.8% (p = 0.379; Figure 2). When analysis was restricted to patients with AAN (n = 139), the survival rate for patients with PR3-ANCA was 85.1% at 1 year, 65.8% at 5 years, and 54.8% at 10 years. The corresponding rates for patients with MPO-ANCA were 83.3%, 59.7%, and 44.3%, respectively (p = 0.377). Renal survival affected total survival as well. Survival as a group for patients who developed ESRD during followup was 78% at 1 year and 51% at 5 years compared with 86% and 67%, respectively, in patients with preserved native kidney function (p = 0.036).

DISCUSSION

In our study we compared MPO-AAV and PR3-AAV with emphasis on renal outcome. A major strength in our study is that all included patients lived in a defined geographical area, and the registry from which they were recruited was known to include > 95% of all AAV patients living in the study area[6]. This population-based perspective reduced selection bias to a minimum, resulting in a better reflection of the complete spectrum of AAV. Most other studies on the outcome of AAN are based on cohorts from either large referral centers or clinical trials[10,11,12,13,14]. Referral to centers and to studies is a multistep process, leading to differences in patient characteristics, which become evident when comparing cohorts recruited at rheumatology and nephrology units[13,15]. Another strength of our study was that the vast majority of patients were treated uniformly, according to local guidelines, which have been updated every other year since 1997.

Differences in outcome and clinical characteristics based on ANCA subtypes have been addressed in a number of studies (Table 4). However, because of heterogeneity between studies, direct comparisons are difficult or not possible. Some studies included patients with biopsy-proven disease only, while others also enrolled patients with positive ANCA and nonvasculitic diseases such as systemic lupus erythematosus[10,16].

Not surprisingly, the well-known relationship between the GPA phenotype and PR3-ANCA is reflected also in this cohort, with a larger number of involved organs, especially of the upper respiratory tract in PR3-AAV[10,11,12,15]. Patients with PR3-ANCA also had a higher degree of systemic

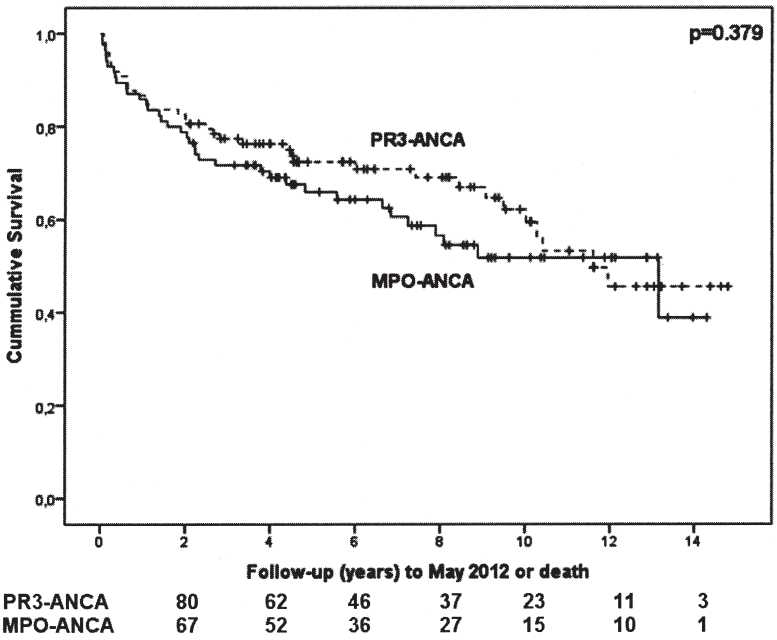

Figure 2. Patient survival by Kaplan-Meier curves according to serology type (183 patients; 98 with PR3-ANCA+ and 85 with MPO-ANCA+). PR3: proteinase 3; ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase.

Table 4. Summary of studies on renal and patient survival in patients with AAV based on ANCA serotype (C-/PR3-ANCA and P-/MPO-ANCA).

Study (reference)	Year	No. Patients	Renal Involvement	Specialty	Comparison	Case Identification	ESRD	Death
Geffriaud-Ricouard, et al[16]	1993	83	92%	Nephrology	PR3 vs MPO	Single center	No difference	No difference
Franssen, et al[18]	1995	92	75%	"Mixed"	PR3 vs MPO	Teaching hospitals	No difference	No difference
Hogan, et al[13]	1996	107	100%	Nephrology	C vs P-ANCA	Specialized units (Glomerular Disease Collaborative Network)	No difference	Worse for C-ANCA
Westman, et al[19]	1998	123	100%	Nephrology	PR3 vs MPO	Single center	Worse for PR3#	No difference
Franssen, et al[10]	1998	92	75%	"Mixed"	PR3 vs MPO	Teaching hospitals	NR	No difference
Vizjak, et al[24]	2003	135	100%	"Mixed"	PR3 vs MPO	Single center	Worse MPO	No difference
Weidner, et al[12]	2004	80	100%	Nephrology	PR3 vs MPO	Single center	No difference	Worse for PR3
Rihova, et al[25]	2005	61	100%	Nephrology	C-vs P-ANCA	Single center	No difference	No difference
Flossmann, et al[26]	2011	535	100%	Mixed	PR3 vs MPO	Multicenter clinical trials	NR	Worse for MPO
Lionaki, et al[5]	2012	502	97%	Nephrology	PR3 vs MPO	Specialized units (Glomerular Disease Collaborative Network)	Worse for MPO	Worse for MPO
de Joode, et al[20]	2013	212	100%	Nephrology	MPO vs PR3	Single center	Worse for MPO	Worse for MPO*
Present study	2013	183	76%	"Mixed"	PR3 vs MPO	Population-based	Worse for MPO	No difference

#Analysis with capture ANCA. *Significant difference during the first 6 months after diagnosis. NR: not reported; ESRD: endstage renal disease; ANCA: antineutrophil cytoplasmic antibody; PR3: proteinase 3; MPO: myeloperoxidase.

inflammation as reflected by CRP levels, ESR, and thrombocyte count. Franssen, *et al* found no differences in laboratory variables between the 2 antibody groups[10]. Renal disease was significantly more common in patients with positive MPO-ANCA disease, a finding that contrasts with a report by Weidner, *et al*[12], and a nonsignificant difference reported by Franssen, *et al*[10]. In our present study, patients with PR3-AAV were younger, and males were more prevalent in this subgroup, which is in line with other reports[12,16]. Also in line with most other studies, we found no differences in mortality rates between patients with different ANCA specificities[13,16,17,18,19]. However, there are contrasting reports[5,12,13].

The major finding in our study is a better renal survival

for patients with PR3-AAN versus patients with MPO-AAN. The relative risk of developing ESRD was only about one-third of that for patients with MPO-ANCA. The finding remained unchanged after Cox regression analysis with adjustment for sex, age, and s-creatinine level at diagnosis. In studies by Hogan, *et al* and Weidner, *et al*[12,13], no differences were seen in renal survival between patients with different ANCA specificities, while in a study by Westman, *et al*[19], 32% of patients with PR3-ANCA developed ESRD compared with 21% of patients with MPO-ANCA, but the difference was not statistically significant. This raises the questions of why our findings differ from others and how the difference in outcome can be explained. There are several possibilities. The low degree of selection bias in our population-based cohort gives credence to our results. Patients with PR3-AAN with good prognosis might not tend to be referred to nephrology units, and thus be underrepresented in such cohorts, skewing results. Naturally there could be genetic differences between populations resulting in, for instance, a lower proportion of PR3-ANCA nephritis and a different mix between patients with good and bad prognosis. Another possibility for differences in outcome could have to do with time of diagnosis. High awareness of AAV within our medical community could lead to early diagnosis, which could accentuate differences in prognosis between serotypes. In a similar fashion, differences in treatment regimens and followup could influence outcome. In a recently published series from the Netherlands with 212 patients with AAN, PR3-ANCA was also associated with a better outcome[20]. However, renal relapses in the PR3-ANCA group during followup attenuated the difference between MPO- and PR3-ANCA over time. Centralized followup, with 3 visits per year and laboratory samples in between, which is standard care in our area, might have led to rapid diagnosis and smaller effect of relapses on renal survival in our patients with PR3-ANCA. Naturally we cannot exclude that our findings may have occurred by chance; such risk is around 1% as the p value in the Cox regression analysis was 0.011.

If PR3-AAN has a better renal prognosis, even when s-creatinine at diagnosis is taken into account, the most probable reason is differences in reversible damage at time of diagnosis. Histologically significant differences in renal biopsies have been reported between patients with MPO-AAN and those with PR3-AAN. Patients with MPO-ANCA exhibited more chronic lesions and more fibrosis, while PR3-ANCA was associated with more acute lesions[18,21]. In our previous study on organ damage in prevalent cases, we found an almost complete separation between damage in the renal system and nasal damage when using the Vasculitis Damage Index[22], suggesting a good renal prognosis for patients with severe upper respiratory involvement. In AAN as well as in many other renal diseases, the degree of chronic tubulointerstitial changes is an important predictor of outcome. A new histological classification system of AAN has recently been published, which clearly emphasizes the role of sclerotic lesions for prognosis[23]. A shortcoming of our study is that it does not include any histological reevaluation of the specimens and that all the included patients had not undergone renal biopsy. Subsequently we cannot certify that histological differences explain our findings.

The clinical rationale for dividing patients into different subgroups must be that such a division results in better precision for predicting outcome and response to therapy. If 2 classification systems perform equally, the easier-to-use system is preferable. There is no doubt that ELISA specificity of ANCA is a rapid and robust tool for classification of AAN. Earlier studies indicated separation based on ELISA specificity of ANCA to be better than classification algorithms based on extrarenal disease manifestations to predict relapses[5]. Here we present data that ELISA specificity is linked to renal prognosis. Together with the recent findings, indicating ELISA specificities to be linked to different sets of genes, our data reinforce the case for a classification system based on serology[4]. Our findings should be taken into consideration at least when performing clinical trials in AAN; stratification into MPO-AAN and PR3-AAN seems prudent.

In this population-based cohort we found a statistically significantly better renal prognosis for patients with PR3-AAN than for those with MPO-AAN, even after correction for sex, age, and renal function at diagnosis.

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