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ORIGINAL RESEARCH

Comparative study of granulomatosis with polyangiitis subsets according to ANCA status: data from the French Vasculitis Study Group Registry

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ABSTRACT

Objective To investigate whether antineutrophil cytoplasm antibody (ANCA)-negative and myeloperoxidase (MPO)-ANCA–positive granulomatosis with polyangiitis (GPA) differ from proteinase-3 (PR3)-ANCA–positive GPA.

Methods Diagnostic characteristics and outcomes of newly diagnosed French Vasculitis Study Group Registry patients with ANCA-negative, MPO-ANCA–positive or PR3-ANCA–positive GPA satisfying American College of Rheumatology criteria and/or Chapel Hill Conference Consensus Nomenclature were compared.

Results Among 727 GPA, 62 (8.5%) were ANCA-negative, 119 (16.4%) MPO-ANCA–positive and 546 (75.1%) PR3-ANCA–positive. ANCA-negative patients had significantly ($p<0.05$) more limited disease (17.7% vs 5.8%) and less kidney involvement (35.5% vs 58.9%) than those PR3-ANCA–positive or MPO-ANCA–positive, with comparable relapse-free (RFS) and overall survival (OS). MPO-ANCA–positive versus PR3-ANCA–positive and ANCA-negative patients were significantly more often female (52.9% vs 42.1%), older (59.8 vs 51.9 years), with more frequent kidney involvement (65.5% vs 55.2%) and less arthralgias (34.5% vs 55.1%), purpura (8.4% vs 17.1%) or eye involvement (18.5% vs 28.4%); RFS was similar but OS was lower before age adjustment. PR3-positive patients' RFS was significantly lower than for ANCA-negative and MPO-positive groups combined, with OS higher before age adjustment. PR3-ANCA–positivity independently predicted relapse for all GPA forms combined but not when comparing only PR3-ANCA–positive versus MPO-ANCA–positive patients.

Conclusions Based on this large cohort, ANCA-negative versus ANCA-positive patients more frequently had limited disease but similar RFS and OS. MPO-ANCA–positive patients had similar RFS but lower OS due to their older age. PR3-ANCA–positive GPA patients' RFS was lower than those of the two other subsets combined but that difference did not persist when comparing only PR3 versus MPO-ANCA–positive patients.

Key messages

What is already known about this subject?

- Evidence suggests that antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) might be better classified as proteinase-3 (PR3)-positive or myeloperoxidase (MPO)-positive AAV than based on their phenotypic characteristics, but the data remain controversial for granulomatosis with polyangiitis (GPA).

What does this study add?

- Patients with ANCA-negative GPA more frequently had limited disease than those ANCA–positive but relapse-free (RFS) and overall survival (OS) rates were similar.
- RFS of MPO-ANCA–positive GPA patients was comparable to those of patients with PR3-ANCA–positive and ANCA-negative disease, but their OS rate was lower because of their older age.
- PR3-ANCA–positive GPA patients' RFS was lower than those of the two other subsets combined but that difference did not persist when comparing only PR3 versus MPO-ANCA–positive patients.

How might this impact on clinical practice or further developments?

- These new findings reinforce that ANCA specificity must systematically be added (as a prefix) to the phenotype (GPA) but regardless of ANCA status, patients with GPA retain a high relapse rate.

INTRODUCTION

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAVs) are necrotising vasculitides, predominantly affecting small vessels and associated with autoantibodies

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directed against neutrophil proteins: proteinase-3 (PR3) or myeloperoxidase (MPO). The Chapel Hill Conference Consensus (CHCC) defined granulomatosis with polyangiitis (GPA) according to clinical and histological features, including necrotising granulomatous inflammation, usually involving the upper and lower respiratory tract, and common necrotising glomerulonephritis and granulomatous and non-granulomatous extravascular inflammation.[1] The European Medicines Agency algorithm was proposed for epidemiological studies to classify AAVs according to disease types: GPA, microscopic polyangiitis (MPA) or eosinophilic GPA.[2] Those patients identified as having GPA according to the CHCC Nomenclature or that algorithm[1 2] are more likely to relapse than those with MPA.[3–7] Among Caucasian patients clinically diagnosed with GPA, 65%–75% are PR3-ANCA–positive, 20%–30% are MPO-ANCA–positive, with the remaining 5% having no detectable ANCA.[6] However, Chinese and Japanese GPA patients predominantly express MPO-ANCA.[8 9]

Accumulating evidence suggests that ANCA specificity is a major determinant of AAV presentation and outcomes and that these clinical syndromes may be better classified as PR3-positive or MPO-positive AAVs.[4–6 10–14] It has been recommended that ANCA specificity and the phenotype be used to categorise patients within the AAV spectrum.[1 4] However, studies on only GPA patients yielded conflicting results, when evaluating whether ANCA-negative and MPO-ANCA–positive subsets differ from PR3-ANCA–positive patients.[8 9 13 15–17] Based on a German cohort that included 177 GPA patients, those MPO-ANCA–positive more frequently had limited disease without severe organ involvement, especially less kidney involvement and subglottic stenosis; less frequently required cyclophosphamide or rituximab; and were less likely to relapse than PR3-ANCA–positive patients.[13] In contrast, a pooled analysis of data from randomised controlled trials that included 321 GPA patients was unable to demonstrate major clinical differences between MPO-ANCA–positive and PR3-ANCA–positive patients.[16] Furthermore, with mean follow-up at 18 months, the relapse risk was more closely associated with the AAV than ANCA specificity. Similar results were obtained in a retrospective analysis of a single-centre cohort of 150 AAVs, with 94 GPA, for whom relapse-free remission was better predicted by clinical GPA or MPA phenotypes than the ANCA subtype.[17] The limited data available on ANCA-negative and MPO-ANCA–positive GPA, and discordant findings concerning the contributions of AAV and ANCA specificities to the initial phenotype and relapse risk for GPA patients prompted further investigations involving larger patient subsets.

The French Vasculitis Study Group (FVSG) Registry is a national database of AAV patients, whose clinical and laboratory information has been collected prospectively and longitudinally, thereby enabling description of clinical characteristics and long-term outcomes of a large cohort including GPA.[18] The data from all GPA patients entered in this database were extracted and analysed to determine whether ANCA-negative and MPO-ANCA–positive GPA represent a clinically distinct subset—differing from proteinase-3 (PR3)-ANCA–positive GPA—with different outcomes within AAV, and whether ANCA status and specificity should be taken into account to predict relapse and adapt therapy.

METHODS

Patients

This multicentre analysis was conducted on patients with newly diagnosed GPA entered prospectively into the FVSG Registry from 1983 to 2018. This database includes information from vasculitis patients referred to FVSG members, those who participated in our network's trials[19] and whose follow-up was pursued. Investigators from >60 French centres regularly contribute that information. For study enrolment, patients' GPA diagnoses had to meet the 1990 American College of Rheumatology classification criteria and/or revised CHCC Nomenclature.[1 20] All diagnoses of patients who fulfilled those criteria were reassessed independently by two of the authors (XP, MI) considering their entire clinical histories. All FVSG Registry patients gave their informed consent. Only patients entered in the Registry at diagnosis and followed for ≥6 months or who died within 6 months of entry were included. Patients with insufficient information were excluded.

Definitions

In accordance with EULAR recommendations, the following definitions were applied[21]: remission, the absence of signs of 'new/worsening' disease activity according to the Birmingham Vasculitis Activity Score (BVAS=0) version 3[22]; and relapse, the reoccurrence or new appearance of disease activity attributable to active vasculitis. Limited GPA was defined according to the revised CHCC Nomenclature and referred particularly to disease confined to the upper or lower respiratory tract, or the eye.[1] Severe GPA was defined as posing an immediate threat to either the patient's life or vital organ function.[23]

Data collection and analysis

Demographic, clinical and biological information was collected on electronic case-report forms at diagnosis (baseline) and each follow-up visit. Information at diagnosis and outcomes were compared among ANCA-negative, MPO-ANCA–positive and PR3-ANCA–positive GPA patients.

Statistical analyses

Quantitative variables are reported as mean±SD or median (IQR) and qualitative variables as number (percentages). Continuous variables were compared with Student's t-test or Mann-Whitney U test, and categorical variables with χ^2 test or Fisher's exact test, as appropriate. Kaplan-Meier estimations of relapse-free survival (RFS)

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and overall survival (OS) probabilities were compared using log-rank tests. RFS was calculated from GPA diagnosis to relapse, death or end of follow-up, whichever occurred first. OS was calculated from GPA diagnosis to death or the last follow-up visit. To identify independent predictors of RFS or OS, univariable and multivariable Cox regression analyses assessed potential associations with patient demographics, clinical, laboratory and therapeutic parameters. Results are expressed as HR and 95% CIs. A p value ≤0.05 defined significance. Statistical analyses were computed with R V.3.2.2 software (R Core Team, 2015, R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement statement

Patients and the public were not involved in the design, conduct, reporting or dissemination of this research.

RESULTS

Overall description at diagnosis of FVSG Registry patients with GPA

The Registry database enrolled 795 patients with new-onset GPA.[18] For the 727 with complete baseline clinical details, including ANCA-immunoassay results, median follow-up was 3.7 (1.8–6.6) years, 62 (8.5%) were ANCA-negative, 119 (16.4%) MPO-ANCA–positive and 546 (75.1%) PR3-ANCA–positive (table 1). Their RFS and OS probabilities (table 2) are shown in figure 1A,B according to ANCA specificity.

Comparison of 62 ANCA-negative versus 665 PR3-ANCA–positive or MPO-ANCA–positive patients

Histological findings supported GPA diagnosis for 29 (47%) ANCA-negative patients. Among the 33 patients with no histological support of a GPA diagnosis, 21 had chronic sinusitis, otitis media or mastoiditis for >3 months, 12 had X-ray evidence of fixed pulmonary infiltrates, nodules or cavitations present for >1 month, seven had 2+ haematuria and 2+ proteinuria on urinalysis, and four had subglottic stenosis, bloody nasal discharge and crusting for >1 month, or nasal ulceration.[2] At diagnosis, ANCA-negative patients had limited disease significantly more frequently than those PR3-ANCA–positive and MPO-ANCA–positive combined, less kidney involvement and peripheral neuropathy resulting in a lower baseline BVAS (table 1). They significantly less frequently received intravenous or oral cyclophosphamide induction therapy or methylprednisolone infusions, and had received a lower initial glucocorticoid dose. Their RFS and OS rates did not differ (table 2, figure 2A,B).

Comparison of 119 MPO-ANCA–positive versus 608 PR3-ANCA–positive or ANCA-negative patients

MPO-ANCA–positive patients versus PR3-ANCA–positive and ANCA-negative patients combined, were significantly more often female, older, with more frequent kidney involvement but less frequent arthralgias, purpura or eye involvement (table 1). Their mean baseline BVAS and induction therapies were comparable. Their RFS rate was similar but OS was lower (table 2, figure 3A,B).

Comparison of 546 PR3-positive versus 181 ANCA-negative or MPO-positive patients

Patients with PR3-ANCA–positive GPA, compared with ANCA-negative and MPO-positive patients combined, were significantly younger at diagnosis, had significantly less frequent limited GPA, more frequent arthralgias and purpura. They had significantly received intravenous or oral cyclophosphamide more frequently and higher initial glucocorticoid dose. Compared with ANCA-negative and MPO-positive groups, PR3-positive patients' RFS rate was lower but their OS rate higher (table 2, figure 4A,B).

Univariable and multivariable predictors of death or relapse for the entire GPA cohort

Univariable analyses selected only the PR3-ANCA–positivity as being associated with a higher relapse-risk probability, which persisted even after adjustment (table 3). Multivariable analysis retained age and congestive heart failure as significant and independent predictors of death and not MPO-ANCA–positivity (table 3).

Univariable and multivariable predictors of death or relapse for PR3-ANCA or MPO-ANCA–positive GPA patients

Excluding ANCA-negative GPA patients from the analysis, predictors of death remain unchanged but PR3-ANCA–positivity was no longer associated with an increased relapse-risk probability (table 4).

DISCUSSION

Based on data from one of the largest cohorts of GPA patients, ANCA status was associated with patients' phenotypes, and ANCA-negativity and MPO-ANCA–positivity distinguished distinct subsets. ANCA-negative GPA patients, compared with those ANCA-positive, more frequently had limited disease but similar RFS and OS rates. Relapse probability for MPO-ANCA–positive GPA patients was similar to those of ANCA-negative and PR3-ANCA–positive patients but their OS was lower because of their older age. PR3-ANCA–positivity was independently associated with a higher relapse probability when all GPA patients were considered but was not retained when comparing only PR3-ANCA–positive versus MPO-ANCA–positive subgroups. Thus, there was no appreciable difference in relapse rate between ANCA-positive GPA patients based on ANCA type and regardless of ANCA status, patients with GPA retain a high relapse rate.

Several classification criteria have been proposed to define syndromes within the AAV spectrum and then categorise patients accordingly.[1 20] They all relied on combinations of clinical, radiographic and histological findings. In practice, they poorly predicted outcomes and prognoses.[4 12] Several lines of evidence suggest that classifying patients by ANCA specificity produces more clearly defined groups than their classification by clinical diagnosis (GPA vs MPA).[4 12] However, although demonstrated

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Table 1 Main clinical characteristics and treatments at diagnosis of 727 French Vasculitis Study Group Registry GPA patients according to ANCA specificity

Characteristic	Overall n=727	P value (PR3-ANCA$^+$ vs MPO-ANCA$^+$ vs ANCA$^-$)	No ANCA n=62	P value (ANCA$^-$ vs PR3-ANCA$^+$ and MPO-ANCA$^+$)	MPO-ANCA$^+$ n=119	P value (MPO-ANCA$^+$ vs PR3-ANCA$^+$ and ANCA$^-$)	PR3-ANCA$^+$ n=546	P value (PR3-ANCA$^+$ vs MPO-ANCA$^+$ and ANCA$^-$)
Sex, female	319 (43.9)	0.082	28 (45.2)	0.94	63 (52.9)	0.04	228 (41.8)	0.06
Age at diagnosis, years, mean (SD)	53 (16.3)	<0.001	52.5 (16.5)	0.79	59.8 (17.2)	<0.001	51.6 (15.7)	<0.001
Limited GPA	50 (6.9)	0.002	11 (17.7)	0.001	8 (6.7)	0.55	31 (5.7)	0.04
Severe GPA	83 (11.4)	0.08	2 (3.2)	0.09	17 (14.3)	0.71	64 (11.7)	0.75
General	592 (81.4)	0.83	51 (82.3)	0.99	99 (83.2)	0.70	442 (81)	0.66
Fever >38.5°C	304 (41.8)	0.05	23 (37.1)	0.51	39 (32.8)	0.04	242 (44.3)	0.02
Weight loss >3 kg within 3 months	329 (45.3)	0.16	21 (33.9)	0.08	53 (44.5)	0.94	255 (46.7)	0.20
Arthralgias	376 (51.7)	<0.001	27 (43.5)	0.23	41 (34.5)	<0.001	308 (56.4)	<0.001
Myalgias	197 (27.1)	0.30	15 (24.2)	0.70	39 (32.8)	0.16	143 (26.2)	0.39
Ear, nose and throat	582 (80.1)	0.53	49 (79.0)	0.96	91 (76.5)	0.35	442 (81)	0.35
Sinusitis	297 (40.9)	0.44	28 (45.2)	0.56	43 (36.1)	0.30	226 (41.4)	0.67
Rhinitis	390 (53.6)	0.28	29 (46.8)	0.32	59 (49.6)	0.38	302 (55.3)	0.14
Nasal crusts	276 (38)	0.10	16 (25.8)	0.05	44 (37)	0.05	216 (39.6)	0.15
Epistaxis	138(19)	0.04	7 (11.3)	0.15	16 (13.4)	0.12	115 (21.1)	0.02
Saddle nose	9 (1.2)	0.06	0 (0)	0.75	4 (3.4)	0.07	5 (0.9)	0.33
Nasal obstruction	183 (25.2)	0.64	18 (29.0)	0.56	27 (22.7)	0.57	138 (25.3)	0.99
Otitis	166 (22.8)	0.32	11 (17.7)	0.40	23 (19.3)	0.38	132 (24.2)	0.16
Lung	492 (67.7)	0.35	37 (59.7)	0.21	83 (69.7)	0.67	372 (68.1)	0.72
Alveolar haemorrhage	130 (17.9)	0.21	7 (11.3)	0.21	26 (21.8)	0.27	97 (17.8)	0.98
Massive alveolar haemorrhage and/or Hb <90 g/L	35 (4.8)	0.16	1 (1.6)	0.36	3 (2.5)	0.30	31 (5.7)	0.09
Lung nodules	303 (41.7)	0.61	25 (40.3)	0.93	45 (37.8)	0.41	233 (42.7)	0.39
Lung infiltrate	134 (18.4)	0.44	6 (9.7)	0.18	18 (15.1)	0.29	62 (11.4)	0.58
Subglottic stenosis	11 (1.5)	0.07	3 (4.8)	0.09	2 (1.7)	1.00	6 (1.1)	0.22
Kidney	414 (56.9)	<0.001	22 (35.5)	0.001	78 (65.5)	<0.05	314 (57.5)	0.66
Serum creatinine median (µmol/L)	93 (73–177)	<0.001	77 (63–100)	<0.001	113 (78–199)	<0.001	92 (74–174.5)	<0.001

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Table 1 Continued

Characteristic	Overall n=727	P value (PR3-ANCA$^+$ vs MPO-ANCA$^+$ vs ANCA$^-$)	No ANCA n=62	P value (ANCA$^-$ vs PR3-ANCA$^+$ and MPO-ANCA$^+$)	MPO-ANCA$^+$ n=119	P value (MPO-ANCA$^+$ vs PR3-ANCA$^+$ and ANCA$^-$)	PR3-ANCA$^+$ n=546	P value (PR3-ANCA$^+$ vs MPO-ANCA$^+$ and ANCA$^-$)
Serum creatinine >150 µmol/L	162/563 (28.8)	0.06	7/42 (16.7)	0.10	34/94 (36.2)	0.11	121/427 (28.3)	0.77
Rise in creatinine level >30%	178 (24.5)	<0.05	9 (14.5)	0.08	37 (31.1)	0.09	132 (24.2)	0.81
Proteinuria	256 (35.2)	0.004	10 (16.1)	0.002	45 (37.8)	0.59	201 (36.8)	0.14
Haematuria	280 (38.5)	<0.001	9 (14.5)	0.001	54 (45.4)	0.11	217 (39.7)	0.27
Need for dialysis	41 (5.6)	0.10	0 (0)	0.09	9 (7.6)	0.48	32 (5.9)	0.79
Mucocutaneous	232 (31.9)	0.14	17 (27.4)	0.52	30 (25.2)	0.11	185 (33.9)	0.06
Purpura	114 (15.7)	0.01	6 (9.7)	0.24	10 (8.4)	0.02	98 (17.9)	0.005
Livedo reticularis	26 (3.6)	0.49	1 (1.6)	0.61	6 (5.0)	0.50	19 (3.5)	0.99
Gangrene	16 (2.2)	0.33	3 (4.8)	0.30	2 (1.7)	0.94	11 (2.0)	0.76
Eye	195 (26.8)	0.07	19 (30.6)	0.58	22 (18.5)	0.03	154 (28.2)	0.17
Exophthalmos	24 (3.3)	0.83	2 (3.2)	1.00	5 (4.2)	0.75	17 (3.1)	0.80
Episcleritis	67 (9.2)	0.13	4 (6.5)	0.58	6 (5.0)	0.12	57 (10.4)	0.07
Scleritis	30 (4.1)	0.16	1 (1.6)	0.48	2 (1.7)	0.22	27 (4.9)	0.09
Cardiovascular	115 (15.8)	0.53	7 (11.3)	0.40	21 (17.6)	0.65	87 (15.9)	0.98
Pericarditis	31 (4.3)	0.21	0 (0)	0.16	5 (4.2)	1.00	26 (4.8)	0.35
Myocarditis	9 (1.2)	0.34	1 (1.6)	1.00	3 (2.5)	0.35	5 (0.9)	0.33
Congestive heart failure	10 (1.3)	0.49	0 (0)	0.77	1 (0.8)	0.35	9 (1.6)	0.47
Gastrointestinal	76 (10.5)	0.55	5 (8.1)	0.67	10 (8.4)	0.53	61 (11.2)	0.34
Abdominal pain	41 (5.6)	0.47	2 (3.2)	0.57	9 (7.6)	0.44	30 (5.5)	0.91
Perforation	2 (0.3)	0.042	0 (0)	1.00	1 (0.8)	0.74	1 (0.2)	1.00
Neurological	215 (29.6)	0.79	16 (25.8)	0.59	35 (29.4)	1.00	164 (30.0)	0.70
Central nervous system	21 (2.9)	0.18	4 (6.5)	0.18	2 (1.7)	0.58	15 (2.7)	0.89
Peripheral neuropathy	143 (19.7)	0.06	5 (8.1)	0.025	25 (21.0)	0.78	113 (20.7)	0.27
BVAS at diagnosis, mean (SD)	17.5 (8.8)	0.001	13.3 (8.1)	<0.001	18.2 (8.6)	0.36	17.8 (8.7)	0.10
Histology supporting GPA diagnosis	324 (44.6)	0.935	29 (46.8)	–	53 (44.5)	–	242 (44.3)	–
Intravenous cyclophosphamide	561 (77.2)	<0.001	35 (56.5)	<0.001	86 (72.3)	0.20	440 (80.6)	<0.001

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Table 1 Continued

Characteristic	Overall n=727	P value (PR3-ANCA$^+$ vs MPO-ANCA$^+$ vs ANCA$^-$)	No ANCA n=62	P value (ANCA$^-$ vs PR3-ANCA$^+$ and MPO-ANCA$^+$)	MPO-ANCA$^+$ n=119	P value (MPO-ANCA$^+$ vs PR3-ANCA$^+$ and ANCA$^-$)	PR3-ANCA$^+$ n=546	P value (PR3-ANCA$^+$ vs MPO-ANCA$^+$ and ANCA$^-$)
Oral cyclophosphamide	41 (5.6)	0.001	10 (16.1)	0.001	6 (5.0)	0.93	25 (4.6)	<0.05
Rituximab	50 (6.9)	0.66	3 (4.8)	0.69	10 (8.4)	0.60	37 (6.8)	0.99
Methotrexate	33 (4.5)	0.13	6 (9.7)	0.09	5 (4.2)	1.00	22 (4.0)	0.35
Glucocorticoids	709 (97.5)	0.10	58 (93.5)	0.09	116 (97.5)	1.00	535 (98)	0.27
Glucocorticoid, mg/day mean (SD)	60 (50–70)	0.006	50.2 (29.7)	0.05	52.0 (23.0)	0.03	59.1 (21.4)	0.002
Methylprednisolone pulse	208 (28.6)	0.06	10 (16.1)	0.03	39 (32.8)	0.33	159 (29.1)	0.66
Plasma exchanges	57 (7.8)	0.21	2 (3.2)	0.24	7 (5.9)	0.50	48 (8.8)	0.13

Values are expressed as number (percentage) unless stated otherwise.
ANCA, antineutrophil cytoplasm antibody; GPA, granulomatosis with polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3.

Table 2 Relapse-free survival and overall survival of 727 granulomatosis with polyangiitis patients according to ANCA specificity

	Overall n=727	P value (PR3-ANCA$^+$ vs MPO-ANCA$^+$ vs ANCA$^-$)	No ANCA n=62	P value (ANCA$^-$ vs PR3-ANCA$^+$ and MPO-ANCA$^+$)	MPO-ANCA$^+$ n=119	P value (MPO-ANCA$^+$ vs PR3-ANCA$^+$ and ANCA$^-$)	PR3-ANCA$^+$ n=546	P value (PR3-ANCA$^+$ vs MPO-ANCA$^+$ and ANCA$^-$)
Relapse-free survival								
5-year (95% CI)	38.6% (34.3 to 43.4)	0.12	56.2% (43.8 to 72.1)	0.18	47.2% (36.0 to 61.7)	0.17	35.4% (30.7 to 40.9)	0.04
10-year (95% CI)	19.4% (14.7 to 25.5)		37.0% (22.7 to 60.2)		32.7% (20.5 to 52.0)		14.8% (10.0 to 21.9)	
Overall survival								
5-year (95% CI)	92.6% (90.3 to 95.0)	0.0058	93.0% (86.6 to 89.9)	0.92	83.9% (75.2 to 93.5)	0.001	94.2% (91.8 to 96.7)	<0.01
10-year (95% CI)	86.8% (82.9 to 90.9)		85.7% (75.0 to 98.0)		81.5% (72.1 to 92.1)		88.1% (83.5 to 92.9)	

ANCA, antineutrophil cytoplasm antibody; MPO, myeloperoxidase; PR3, proteinase-3.

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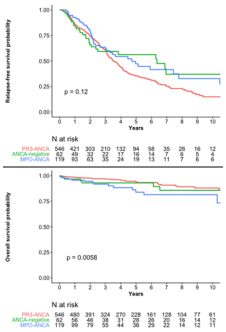


Figure 1 (A) Relapse-free survival and (B) overall survival probabilities for the 727 patients with granulomatosis with polyangiitis according to their ANCA status. ANCA, antineutrophil cytoplasm antibody; MPO, myeloperoxidase; PR3, proteinase-3.

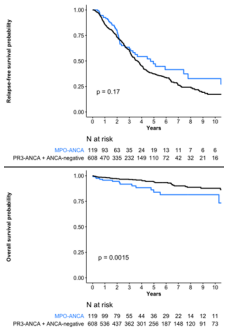


Figure 3 (A) Relapse-free survival and (B) overall survival probabilities for the 119 ANCA-MPO–positive granulomatosis with polyangiitis (GPA) patients versus 608 PR3-ANCA–positive and ANCA-negative GPA patients combined. ANCA, antineutrophil cytoplasm antibody; MPO, myeloperoxidase; PR3, proteinase-3.

when GPA and MPA patients were considered together, data from observational studies and pooled trials yielded discordant outcome results for GPA patients according to ANCA specificity.[13 16 24] We hypothesised that those discrepancies could result from too few GPA patients studied and aimed to clarify those findings by analysing the data from one of the largest GPA subsets.

Herein, ANCA-negative GPA patients more frequently had limited GPA and less kidney involvement, thereby justifying their less aggressive treatments. Very few authors have investigated this patient subset, which represents 8.5% of our GPA cohort and approximately 5% of GPA patients described in the literature.[6] Our observed sex ratio of ~1 was unable to confirm the significant female predominance reported, perhaps attributable to chance in that smaller study.[16] However, our results are in line with lower BVAS, primarily due to the lower likelihood of kidney involvement in ANCA-negative GPA patients. At the same time, these findings are consistent with previous findings suggesting that non-severe or limited GPA is more frequently ANCA-negative.[25] In agreement with pooled-trial data showing that the ANCA-negative GPA patients' relapse rate was similar to those PR3-positive,[16] we found that the ANCA-negative GPA patients' RFS and OS rates were similar to those of PR3-ANCA–positive or MPO-ANCA–positive GPA subsets. Also, it was recently reported that the risk of limited-GPA relapse was similar to that of systemic GPA.[26] Our high relapse and mortality rates for patients with ANCA-negative GPA highlight that it is not always a benign disease and should be managed accordingly, with regular follow-up.

FVSG Registry patients with MPO-ANCA–positive GPA were more often older women, as usually reported.[8 9 13 15 16] Our results also agree with the classical 10-year age discrepancy between patients with MPO-ANCA versus PR3-ANCA.[4 8 27–29] Herein, this subset had significantly less frequent arthralgias, purpura or eye involvement, consistent with the data from the only other study that also included >100 MPO-ANCA–positive GPA patients.[9] No such significant disease-manifestation differences were observed in studies with smaller enrolments of MPO-ANCA–positive GPA patients.[16 17 30] Our MPO-ANCA–positive GPA patients also had significantly more frequent kidney involvement (65.5%), unlike this subset in German and Chinese cohorts.[9 13] Further studies are still required to address these discrepancies. Our MPO-positive patients' RFS rate was similar

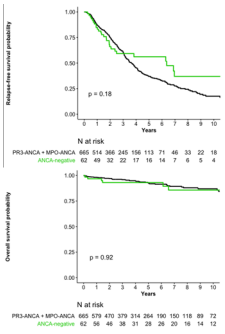


Figure 2 (A) Relapse-free survival and (B) overall survival probabilities for the 62 ANCA-negative granulomatosis with polyangiitis patients versus 665 PR3-ANCA–positive and MPO-ANCA–positive GPA patients. ANCA, antineutrophil cytoplasm antibody; MPO, myeloperoxidase; PR3, proteinase-3.

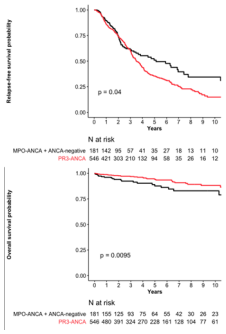


Figure 4 (A) Relapse-free survival and (B) overall survival probabilities for the 546 PR3-ANCA–positive granulomatosis with polyangiitis (GPA) patients versus 181 MPO-ANCA–positive and ANCA-negative GPA patients combined. ANCA, antineutrophil cytoplasm antibody; MPO, myeloperoxidase; PR3, proteinase-3.

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Table 3 Univariable and multivariable analyses of factors associated with death and relapse for the entire Registry cohort of 727 granulomatosis with polyangiitis patients

	Death				Relapse			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Factor	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.07 (1.04 to 1.09)	<0.001	1.07 (1.04 to 1.09)	<0.001	0.99 (0.99 to 1.00)	0.520		
Female	0.64 (0.37 to 1.08)	0.09			1.03 (0.78 to 1.19)	0.773		
Lung	0.46 (0.88 to 2.90)	0.123			0.98 (0.78 to 1.22)	0.864		
Alveolar haemorrhage	2.14 (1.23 to 3.72)	0.006			1.08 (0.83 to 1.42)	0.547		
Renal	3.19 (1.77 to 5.79)	0.0001			1.02 (0.83 to 1.26)	0.827		
Serum creatinine >150 µmol/L	2.16 (1.24 to 3.76)	0.006			0.92 (0.70 to 1.21)	0.572		
Skin	1.42 (0.84 to 2.40)	0.180			1.04 (0.83 to 1.29)	0.734		
Ear, nose and throat	0.77 (0.42 to 1.41)	0.409			1.12 (0.86 to 1.47)	0.396		
Eye	0.75 (0.42 to 1.34)	0.347			1.02 (0.81 to 1.28)	0.826		
Cardiovascular	2.70 (1.56 to 4.70)	0.0004			1.06 (0.80 to 1.42)	0.653		
Congestive heart failure	10.73 (4.56 to 25.22)	<0.0001	3.20 (1.12 to 9.16)	0.029	0.69 (0.22 to 2.14)	0.521		
Gastrointestinal	1.27 (0.54 to 2.97)	0.571			0.97 (0.67 to 1.41)	0.905		
Neurological	1.61 (0.96 to 2.69)	0.067			0.98 (0.78 to 1.24)	0.926		
BVAS	1.07 (1.04 to 1.10)	<0.001			0.99 (0.98 to 1.00)	0.283		
Anti-myeloperoxidase	2.25 (1.28 to 3.94)	0.004			0.82 (0.60 to 1.12)	0.219		
Anti-proteinase-3	0.51 (0.30 to 0.85)	0.01	0.43 (0.18 to 1.03)	0.060	1.31 (1.01 to 1.69)	0.040	1.29 (1.00 to 1.68)	0.047
ANCA negative	1.04 (0.47 to 2.29)	0.921			0.76 (0.51 to 1.13)	0.185		
Intravenous CYC	–	–			0.85 (0.66 to 1.10)	0.232		
Oral CYC	–	–			0.63 (0.37 to 1.07)	0.091		
Rituximab	–	–			0.77 (0.43 to 1.38)	0.385		
Methotrexate	–	–			1.02 (0.63 to 1.65)	0.912		

ANCA, antineutrophil cytoplasm antibody; BVAS, Birmingham Vasculitis Activity Score.

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Table 4 Univariable and multivariable analyses of factors associated with death and relapse for the 665 granulomatosis with polyangiitis antineutrophil cytoplasm antibody-positive patients

	Death				Relapse	
	Univariable analysis		Multivariable analysis		Univariable analysis	
Factor	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.07 (1.04 to 1.09)	<0.001	1.07 (1.04 to 1.09)	<0.001	1.00 (0.80 to 1.24)	0.999
Female	0.58 (0.33 to 1.02)	0.061			0.99 (099 to 1.00)	0.561
Lung	1.62 (0.85 to 3.07)	0.141			0.98 (0.78 to 1.24)	0.921
Alveolar haemorrhage	2.10 (1.17 to 3.78)	0.012			1.06 (0.80 to 1.40)	0.665
Renal	3.32 (1.71 to 6.45)	0.0001			1.03 (0.77 to 1.20)	0.744
Serum creatinine >150 µmol/L	1.87 (1.03 to 3.38)	0.038			0.86 (0.65 to 1.13)	0.292
Haemodialysis	3.37 (1.51 to 7.53)	0.003			1.31 (0.83 to 2.06)	0.240
Skin	1.42 (0.82 to 2.47)	0.206			1.01 (0.78 to 1.24)	0.912
Ear, nose and throat	0.77 (0.42 to 1.41)	0.409			1.11 (0.84 to 1.45)	0.445
Eye	0.74 (0.39 to 1.38)	0.349			1.08 (0.85 to 1.36)	0.513
Cardiovascular	2.52 (1.40 to 4.53)	0.001			1.03 (0.76 to 1.38)	0.838
Congestive heart failure	9.57 (3.77 to 24.3)	<0.0001	4.58 (1.79 to 11.70)	0.001	0.70 (0.22 to 2.19)	0.547
Gastrointestinal	0.98 (0.35 to 2.74)	0.976			0.87 (0.59 to 1.30)	0.521
Neurological	1.43 (0.82 to 1.48)	0.205			1.00 (0.79 to 1.27)	0.949
Birmingham Vasculitis Activity Score	1.07 (1.03 to 1.10)	<0.001			0.99 (0.97 to 1.00)	0.169
Anti-myeloperoxidase	2.33 (1.31 to 4.14)	0.003			0.80 (0.60 to 1.12)	0.159
Anti-proteinase-3	0.39 (0.22 to 0.70)	0.001	0.43 (0.18 to 1.03)	0.057	1.28 (0.93 to 1.75)	0.119
Intravenous cyclophosphamide	–	–			0.85 (0.64 to 1.11)	0.244
Oral cyclophosphamide	–	–			0.72 (0.40 to 1.28)	0.267
Rituximab	–	–			0.73 (0.40 to 1.34)	0.319
Methotrexate	–	–			1.1 (0.65 to 1.84)	0.719

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to those of ANCA-negative and PR3-positive subgroups, in accordance with the similar relapse rates observed across ANCA specificities among GPA patients in several cohorts.[9 16 17] In addition, in several studies, the relapse risk was associated more closely with AAV type than ANCA specificity.[16 17] We also found that there was no detectable difference in relapse rate between ANCA-positive GPA patients based on ANCA type. Taken together, those findings illustrated that GPA patients are at high risk of relapse, regardless of their ANCA status/specificity at diagnosis and confirmed that GPA phenotype remains a major factor associated with the probability of relapse.[4 6] In addition, our observed lower OS rate of these older GPA patients did not remain statistically significant after adjustment for age at diagnosis, as observed in most studies.[12 27 31]

Our 546 PR3-ANCA–positive GPA patients represent one of the largest groups yet constituted, with median follow-up exceeding 3 years, enabling identification of long-term outcomes with a sufficient level of evidence.[14 32] Compared with the other subsets, PR3-positive patients' RFS rate was lower. That finding agrees with accumulating knowledge that PR3-positivity is independently associated with a higher relapse risk for AAV patients[10 12] and allows us to extend the relapse risk associated with PR3-postivity to the subgroup of GPA.[4 14 24] Our results demonstrate that GPA classification and diagnostic criteria incorporating ANCA-specificity are more useful than the clinical diagnosis alone to predict relapse and that PR3-ANCA–positivity was the sole factor significantly associated with a higher probability of relapse among all GPA. GPA patients' high relapse risk should lead to appropriate patient education and vigilant monitoring to assure more favourable clinical outcomes. With the advent of rituximab as maintenance therapy, the treatment paradigm has changed from managing frequent relapses on maintenance methotrexate or azathioprine to adjusting rituximab duration to further limit relapses.[33] However, the higher reported risk of severe SARS-CoV-2 infection in rituximab-treated patients may have changed the risk/benefit of maintenance rituximab approach. Recommendations for the management of COVID-19 vaccination and prophylaxis in patients receiving rituximab for systemic vasculitis have been proposed.[34] Since most of those relapses were minor and rapidly treated,[18] the higher relapse rate of our PR3-ANCA–positive GPA patients was not associated with shorter long-term survival, as previously reported.[10 30] In contrast, better OS of PR3-ANCA–positive patients could be explained by the fact that MPO-ANCA–positive patients were older and had poorer renal outcomes, as in most cohorts.[4 12 28–30]

Our results add important clarifying information to the ongoing discussion of the relative contributions of ANCA specificity, as opposed to AAV clinical diagnosis, to GPA phenotype and outcomes. They reconcile the seemingly contradictory literature data and open the way for more tailored treatment, based not only on the AAV type but also on ANCA specificity. Current trials already take this dichotomy into account by stratifying enrolment according to ANCA specificity[35 36] or even by including exclusively patients with one ANCA specificity (ClinicalTrials.gov Identifier: NCT00405860 or NCT03920722 for MPO-ANCA–positive and NCT03967925 for PR3-ANCA–positive patients). Our data suggest, even among patients receiving a clinically based GPA diagnosis, that those PR3-ANCA–positive are more prone to relapse than those of the two other subsets combined. Patients with critical organ damage that could become life-limiting if further injury occurs (eg, lungs and kidneys) or those at high risk of relapse, such as those who have previously relapsed or whose PR3-ANCA test is positive, should receive longer rituximab maintenance therapy, as already proposed,[33 37] and new therapeutic strategies should be evaluated (ClinicalTrials.gov Identifier: NCT03967925).

Our study has major strengths. Our Registry collected the clinical characteristics and long-term outcomes of patients, originating from several medical specialties, enabling analysis according to immunoassay results of a truly representative distribution of different GPA presentations and evolutions. ANCA-negative GPA patients were also included and we enrolled more than twice the number of patients reported in each of the previous studies,[4 9 13 15 16] thereby characterising one of the largest GPA-patient populations ever analysed. All diagnoses were reassessed independently by two of the authors, who considered patients' entire follow-up.

Some limitations also need to be addressed. This study enrolled patients over a long period, during which general clinical practices evolved. Very few Asian patients were enrolled and it is not clear whether our results can be extrapolated to them. Even though patients had to meet the 1990 American College of Rheumatology GPA classification criteria and/or revised CHCC Nomenclature to be enrolled and were reassessed considering their entire clinical histories, some patients without documented evidence of vasculitis in the ANCA-negative subset may have been misclassified. The analysis was conducted retrospectively, engendering all the biases inherent to such a design, including that all relapses occurring during follow-up may not have been captured. However, all patient information was entered prospectively into the FVSG Registry database. Although ANCA-PR3–positivity was associated with a higher relapse risk in the multivariable analysis of our entire GPA population, that finding was mitigated in the subgroup analysis restricted to ANCA-positive patients, perhaps because clinicians may have already prescribed those patients longer maintenance therapies and the detection of a potential small difference may require an even larger sample size.

In conclusion, our results finally reconcile the seemingly contradictory data reported in the GPA literature and support the concept that ANCA specificity enables identification of distinct GPA subsets with clinical and prognostic relevance. ANCA-negative GPA patients more frequently had limited disease but RFS and OS rates comparable to the other subgroups. MPO-ANCA–positive

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GPA patients and the other subsets had similar RFS rates, with their lower OS rate being attributable to their older age. PR3-ANCA–positive GPA patients' RFS was lower than those of the two other subsets combined but that difference did not persist when comparing only PR3 versus MPO-ANCA–positive patients and it did not lead to a lower OS rate. These new findings support adding ANCA specificity to the phenotype and taking it into account, along with a history of relapse or damage, when discussing therapeutic strategies for those patients diagnosed with GPA.

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Collaborators Other investigators are listed in the online supplemental appendix.

Contributors XP, MI and LG designed the study and were involved in acquisition, analysis and interpretation of data. CP was involved in acquisition and interpretation of data. AK, PC, FM, TQ, FL, MH were involved in acquisition of data. 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. XP accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Cochin University Hospital Ethics Committee (ID: AAA-2020-08033). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Additional data may be obtained upon reasonable request.

Author note We propose to list and designate all the site investigators as 'collaborators' as per Medline designation. This means their names are searchable on Medline. This is an important method to appropriately recognise the work of the many coinvestigators of this study and is consistent with approaches taken by major journals for such work. A full list of collaborators is provided in the online supplemental appendix 1. Several authors of this publication are members of the European Reference Network for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases, Project ID No. 739543.

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