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ORIGINAL RESEARCH

Diagnostic significance of antineutrophil cytoplasmic antibody (ANCA) titres: a retrospective case-control study

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ABSTRACT

Objectives To investigate the reliability of elevated titres of antineutrophil cytoplasmic antibody (ANCA) and to identify a cut-off titre in discriminating between ANCA-associated vasculitides (AAV) and its mimickers.

Methods This retrospective observational single-centre study included patients over 18 years with positive myeloperoxidase (MPO)-ANCA and/or proteinase 3 (PR3)-ANCA immunoassays over an 8-year period (January 2010 to December 2018), via their electronic medical files. Patients were classified according to the 2022 ACR/EULAR criteria and alternative diagnoses categorised either as non-AAV autoimmune disorders (ANCA-AI) or disorders without autoimmune features (ANCA-O). Findings from the AAV group were compared with those of ANCA-AI and ANCA-O groups and followed by a multivariate logistic stepwise regression analysis of features associated with AAV.

Results 288 ANCA-positive patients of which 49 had AAV were altogether included. There was no difference between patients between the ANCA-AI (n=99) and the ANCA-O (n=140) groups. The AUC for titres discriminating AAV from mimickers was 0.83 (95% CI, 0.79 to 0.87). The best threshold titre, irrespective of PR3-ANCA or MPO-ANCA, was 65 U/mL with a negative predictive value of 0.98 (95% CI, 0.95 to 1.00). On multivariate analysis, an ANCA titre ≥65 U/mL was independently associated with AAV with an OR of 34.21 (95% CI 9.08 to 129.81; p<0.001). Other risk factors were: pulmonary fibrosis (OR, 11.55 (95% CI, 3.87 to 34.47, p<0.001)), typical ear nose and throat involvement (OR, 5.67 (95% CI, 1.64 to 19.67); p=0.006) and proteinuria (OR, 6.56 (95% CI, 2.56 to 16.81; p<0.001)).

Conclusion High PR3/MPO-ANCA titres can help to discriminate between AAV and their mimickers in patients presenting with small-calibre vasculitides, with a threshold titre of 65 U/mL and above.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Antineutrophil cytoplasmic antibody (ANCA) positivity can be found in situations other than ANCA-associated vasculitides (AAV). Only a previous retrospective study, using multiple immunoassays, had shown that higher ANCA levels and multiple affected organs were associated with AAV.

WHAT THIS STUDY ADDS

⇒ This study confirms that an ANCA-proteinase 3 or ANCA-myeloperoxidase cut-off titre (ie, 65 U/mL and above) when associated with 2022 EULAR/ACR classification criteria in patients presenting with small-vessel vasculitides, can be used to distinguish AAV from alternative autoimmune or non-autoimmune diseases with a negative predictive value of 98%.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides a pragmatic approach to the diagnostic dilemma associated with ANCA positivity in cases that cannot rely on histopathological evidence of systemic vasculitides. Adding a threshold approach to the diagnostic workup may assist clinicians in reassessing concerns for differentials.

INTRODUCTION

Antineutrophil cytoplasmic antibodies (ANCA) have been closely associated with small-calibre vessel necrotising vasculitis.[1] In the 2012 Chapel Hill Consensus Conference Nomenclature, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) are classified as ANCA-associated vasculitis (AAV).[1] More recently, the American College of Rheumatology and the European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria have placed emphasis on the positivity of antiproteinase 3 (PR3-) or antimyeloperoxidase (MPO-) ANCA to, respectively, classify GPA and MPA.[2–4] According to such threshold scores, ANCA positivity is weighted sufficiently high to classify AAV in a setting of medium-vessel or small-vessel vasculitis once alternative diagnoses have been

eliminated.[2–4] However, in the absence of histological evidence of AAV, clinicians must rely on ANCA status and are required to eliminate differential diagnoses of vasculitis mimickers.

Clinical findings have been highly suggestive of ANCA pathogenicity and various in vitro studies have characterised processes such as the activation of neutrophils and monocytes, complement-mediated inflammation and the release of neutrophil extracellular traps leading to endothelial injury.[5 6] A 2020 meta-analysis found that PR3-ANCA immunoassays had a pooled sensitivity for AAV ranging from 79.8% to 86.6%, and a pooled specificity of 96.8% to 98.3%.[7] In the same study, sensitivity and specificity were of 58.1% and 95.6% for MPO-ANCA immunoassays. Unsurprisingly, previous case-series and studies have illustrated situations in which ANCA positivity did not reflect AAV (ie, infection, inflammatory bowel disease, connective tissue disease and so on).[7–10] Furthermore, ANCA titres have been found to incompletely correlate with disease activity and/or treatment response, and their clinical significance for relapse remains controversial.[11–13] Studies that have sought to evaluate the sensitivity and specificity of ANCA cut-off values for a clinical diagnosis of AAV are scarce.[9]

Based on previous but extremely limited experience—and given the emphasis placed on ANCA positivity and its putative involvement in AAV pathophysiology—we hypothesised that the probability of AAV increased with higher ANCA titres. Our study aimed to investigate the reliability of elevated titres of ANCA in discriminating between AAV and its mimickers and to identify a titre cut-off value that could be used in clinically relevant situations.

MATERIAL AND METHODS

Study population

This retrospective observational study included patients with ANCA-positive immunoassays treated at the University Hospital of Nice, France. The study period spanned 8 years from 1 January 2010 to 31 December 2018.

Subjects were identified via a database search of ANCA results provided by the Immunology laboratory. Patients aged 18 years or older with one or more positive MPO-ANCA and/or PR3-ANCA tests were included. Diagnosis of disease was directly obtained from electronic records (and, in some cases, paper records). When necessary, findings were reclassified according to Chapel Hill Consensus Conference definitions and 2022 ACR/EULAR classification criteria, based on available clinical and pathological data. Those that lacked information on ANCA titre or for whom diagnosis was unclear were excluded from the study.

The ANCA-positive patients were then categorised into three groups: (i) those with AAV, (ii) those with a non-AAV autoimmune disorder (ANCA-AI) and (iii) those without autoimmune features (ANCA-O).

Data collection

Data were extracted from the patients' digital medical files. Recorded findings included demographics, clinical characteristics (such as comorbidities, symptoms at presentation leading to ANCA testing, number of affected organs) and laboratory parameters (ie, C reactive protein, eosinophil count, proteinuria, creatinine level and antinuclear antibodies testing). The dates of ANCA testing and their titre were systematically specified. Organ features were assessed and recorded, when available, as per the different domains of the Birmingham Vasculitis Activity Score and five factor score.[14 15]

Immunoassays and antibody testing

ANCA quantification was performed using the multiplexed FIDIS immunoassay and Luminex technology, according to the instructions of the manufacturer. The upper reference limit for PR3-ANCA and MPO-ANCA titres was 20 U/mL. Antinuclear antibodies (ANA) were also recorded and considered positive for titres of 1/160 or higher.

Statistical analysis

Categorical variables were expressed as counts with percentages, and continuous variables as medians with their IQR. Normality and heteroskedasticity of the baseline demographic, clinical and biology characteristics were assessed using the Shapiro-Wilk and Levene's tests, respectively. Wilcoxon-Mann-Whitney tests compared differences between two groups of non-normally distributed data with a Nemenyi *post hoc* analysis. For normally distributed continuous variables, Student's t-test was used. For categorical variables, a χ^2 test or a Fischer's exact test was performed according to the number of patients to be compared. All analyses were two-tailed.

To evaluate the diagnostic value of ANCA titres, findings from the AAV group were compared with those of ANCA-AI and ANCA-O groups. Logistic regressions were performed with areas under (curve) (AUC) for the receiver operating curves (ROC) expressed with their 95% CI. Youden's index helped to define the optimal threshold for ANCA titres within our cohort. The patients were then classified as positive or negative according to the estimated threshold, followed by multivariate logistic stepwise regression analyses of previously identified risk factors of AAV on univariate analysis ($p<0.05$). For all comparisons, $p<0.05$ were considered statistically significant. Statistical analyses were performed with R[16] and the online application EasyMedStat (V.3.18, www.easymedstat.com).

Ethics and data protection

Data were anonymised on collection and stored in an electronic repository hosted by our Institution, in compliance with *Commission Nationale de l'Informatique et des Libertés* regulations, under the reference number 2022—EI-027.

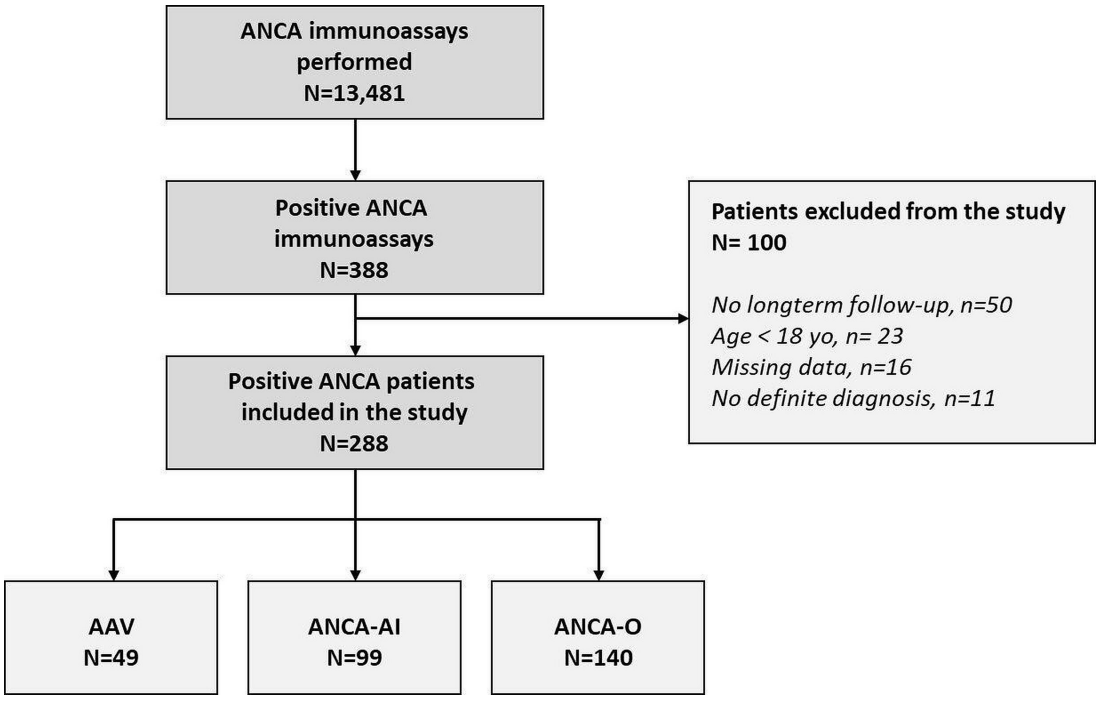

Figure 1 Study flowchart. AAV, ANCA-associated vasculitides; ANCA, antineutrophil cytoplasmic antibody; ANCA-AI, ANCA-positive patients with a non-AAV autoimmune disorder; ANCA-O, ANCA-positive patients with autoimmune features; N or n, number of subjects.

RESULTS

ANCA-associated diagnoses and patient characteristics

Over the course of the study period, 13 481 ANCA studies were performed, of which 388 (2.9%) were positive. Ultimately, 288 ANCA-positive patients were included: 49 in the AAV group, 99 in the ANCA-AI group and 140 in the ANCA-O group (figure 1). In the AAV group, 33 patients were diagnosed with MPA and 16 with GPA. The ANCA-AI group included vasculitides of all calibre vessels (online supplemental table S1).

Patient characteristics are presented in table 1 and were found to be significantly different between the AAV, ANCA-AI and ANCA-O groups for demographics, ANCA titres and selected organ involvement. Lung (n=30/49) and kidney (n=21/49) impairment as well as higher proteinuria were more frequently found in AAV, but there was a greater proportion of patients with articular (n=51/99), cutaneous (n=29/99) and/or intestinal involvement (n=24/99) in the ANCA-AI group. PR3-ANCA were overall the most prevalent and were mostly expressed in the ANCA-AI and ANCA-O groups.

ANCA titres and their diagnostic performance

Median ANCA titres were significantly higher in patients with AAV (table 1), and titres were not statistically different between ANCA-AI and ANCA-O groups (p=0.531).

ROC curve analysis of ANCA titres discriminating patients with AAV from controls (ie, ANCA-AI and ANCA-O groups combined) found an AUC of 0.89 (95% CI, 0.85 to 0.93) (figure 2A). The best threshold value of ANCA titre was 65 U/mL that was associated with a sensitivity of 0.94 (95%CI, 0.83 to 0.99) and a specificity of 0.73 (95%CI, 0.67 to 0.78) (table 2). The negative predictive value was 0.98 (95% CI, 0.95 to 1.00) for ANCA, irrespective of PR3 or MPO status. PR3-ANCA performed better than MPO-ANCA with, respectively, AUCs of 0.92 (95%CI, 0.86 to 0.98) (figure 2B) and 0.86 (95%CI, 0.79 to 0.92) (figure 2C). A 106 U/mL threshold could be preferred to separate AAV from mimickers for patients with PR3-ANCA (table 2).

Multivariate analysis

Based on the previous results (table 1), the following variables were included in the stepwise multivariate logistic regression model: interstitial lung disease, ear nose and throat (ENT) involvement, joint and bone involvement, ANCA titre ≥65 U/mL, ANCA-PR3 status, proteinuria and ANA positivity of ≤1:160.

ANCA titre was found to be an independent diagnostic biomarker for distinguishing AAV from mimickers. ORs for specific organ involvement, proteinuria and the ANCA-titre threshold are presented in table 3.

When 2022 ACR/EULAR classification criteria were applied to ANCA-AI patients who presented with small-/medium-vessel vasculitis (n=11), 8 were wrongly classified as GPA. The ANCA titre cut-off of 65 U/mL helped to correctly reclassify patients (online supplemental table S2).

DISCUSSION

This study found that a high ANCA titre, regardless of PR3 or MPO targets, can be used to discriminate between AAV and their mimickers. Patients with an ANCA cut-off

Table 1 Demographics, clinical and biological features of patients with positive ANCA testing

				P value		
	AAV n=49	ANCA-AI n=99	ANCA-O n=140	AAV vs ANCA-AI	AAV vs ANCA-O	ANCA-AI vs ANCA-O
Age, mean, years±SD	65.4±13.6	53.4±19.9	57.7±16.7	**<0.001**	**0.004**	0.067
Female gender, n (%)	28 (57)	60 (61)	49 (35)	0.821	**0.011**	**<0.001**
Organ involvement at ANCA determination:						
Lung, n (%)	30 (63)	21 (21)	29 (21)	**<0.001**	**<0.001**	0.999
Kidney, n (%)	21 (60)	4 (10)	6 (13)	**<0.001**	**<0.001**	0.745
ENT, n (%)	15 (31)	3 (3)	15 (11)	**<0.001**	**0.002**	**0.027**
Skin, n (%)	5 (10)	29 (29)	20 (14)	**0.019**	0.626	**0.008**
Nervous system, n (%)	5 (10)	11 (11)	11 (8)	**0.999**	0.559	0.496
Digestive tract, n (%)	5 (10)	24 (24)	24 (17)	**0.058**	0.356	0.236
Eye, n (%)	2 (4)	5 (5)	7 (5)	**0.999**	0.999	0.999
Joints and bone, n (%)	12 (25)	51 (52)	15 (11)	**0.004**	**0.029**	**<0.001**
Antimyeloperoxidase, n (%)	34 (69)	47 (47)	46 (33)	**0.019**	**<0.001**	**0.032**
Antiproteinase 3, n (%)	15 (31)	52 (53)	94 (67)	**0.019**	**<0.001**	**0.032**
ANCA titre, median (IQR)	186(106; 423)	37(27; 77)	36(27; 59)	**<0.001**	**<0.001**	0.531
MPO ANCA titre, median (IQR)	184(95; 330)	41(28; 93)	36(26; 74)	**<0.001**	**<0.001**	0.458
PR3 ANCA titre, median (IQR)	502(137; 764)	36(27; 72)	37(28; 55)	**<0.001**	**<0.001**	0.979
CRP level, median, mg/L (IQR)	46(7; 99)	6(1; 26)	8(1; 45)	**<0.001**	**<0.001**	0.275
Serum creatinine level (mcg/L), median (IQR)	181(85; 308)	73(56; 88)	74(63; 88)	**<0.001**	**<0.001**	0.260
Urine protein-to-creatinine ratio, median (IQR)	1.1(0.3; 1.8)	0.1(0.1; 0.2)	0.2(0.1; 0.7)	**<0.001**	**<0.001**	0.090

P-values set in boldface indicate statistical significance.

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; ANCA-AI, non-AAV autoimmune disorders; ANCA-O, non-autoimmune disorders; CRP, C reactive protein; ENT, ear nose and throat (involvement); n, number of events.

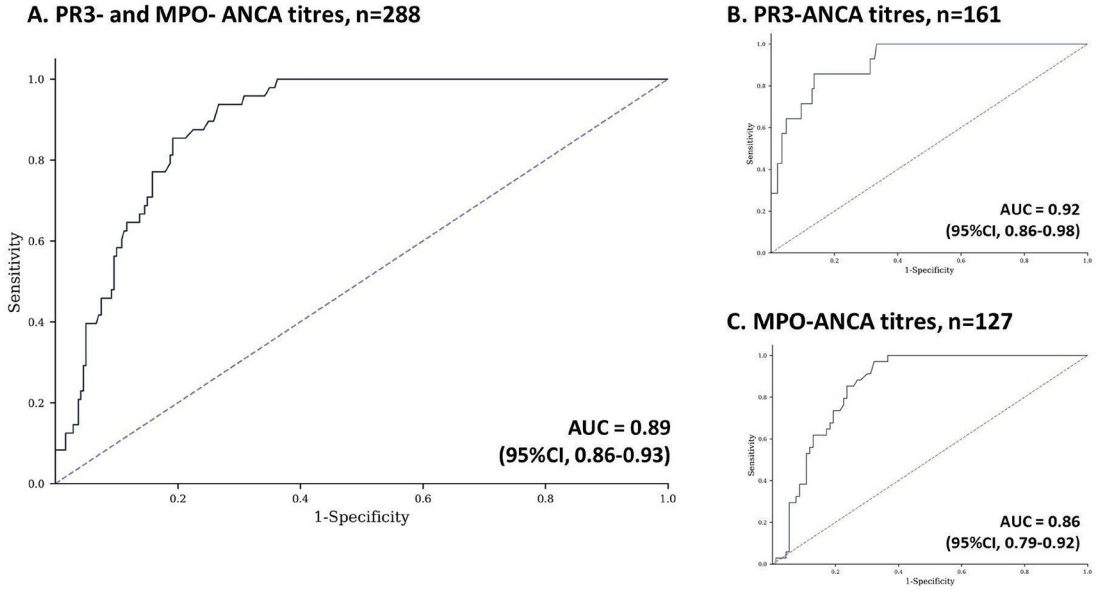

Figure 2 ROC with calculated AUC and their 95% CI for identifying patients with ANCA-associated vasculitides. (A) ROC for PR3-ANCA and MPO-ANCA titres. (B) ROC for PR3-ANCA titres. (C) ROC for MPO-ANCA titres. ANCA, antineutrophil cytoplasmic antibody; AUC, area under the curve; MPO, myeloperoxidase; PR3, proteinase 3; ROC, receiver operating curves.

Table 2 Study of ANCA titre cut-off values for the diagnosis of AAV

	N	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Accuracy (95% CI)	AUC (95% CI)
All patients with ANCA titres of ≥65 U/mL	288	0.94 (0.83 to 0.99)	0.73 (0.67 to 0.78)	0.41 (0.36 to 0.46)	0.98 (0.95 to 1.00)	0.76 (0.71 to 0.81)	0.89 (0.85 to 0.93)
PR3-ANCA-positive patients with ANCA titres ≥106 U/mL	161	0.86 (0.57 to 0.98)	0.86 (0.79 to 0.91)	0.36 (0.27 to 0.47)	0.98 (0.96:–1.00)	0.86 (0.79 to 0.91)	0.92 (0.86 to 0.98)
MPO-ANCA-positive patients with ANCA titres ≥65 U/mL	127	0.94 (0.80 to 0.99)	0.69 (0.58 to 0.78)	0.52 (0.45 to 0.60)	0.97 (0.89 to 1.00)	0.76 (0.67 to 0.83)	0.86 (0.79 to 0.92)

ANCA, antineutrophil cytoplasmic antibody; AUC, area under the ROC curve; MPO, myeloperoxidase; N, number of subjects; PR3, proteinase 3.

Table 3 Logistic regression analysis evaluating the diagnostic value of univariate findings for AAV

	OR (95% CI)	P value
Interstitial lung disease or pulmonary fibrosis	11.55 (3.87 to 34.47)	**<0.001**
Typical ENT involvement	5.67 (1.64 to 19.67)	**0.006**
Positive ANA, titre ≤1/160	0.18 (0.05 to 0.74)	**0.017**
ANCA titre ≥65 U/mL	34.21 (9.08 to 129.81)	**<0.001**
Proteinuria*	6.56 (2.56 to 16.81)	**<0.001**
Positive PR3-ANCA	0.64 (0.23 to 1.78)	0.392

P-values set in boldface indicate statistical significance.
*OR is expressed for each one unit increase.
ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ENT, ears nose and throat; PR3, proteinase 3.

value of 65 U/mL and above (irrespective of ANCA-PR3 or ANCA-MPO positivity), and for whom small-vessel vasculitides were considered, were more likely to present with AAV. Our findings argue that the ANCA titre can be of diagnostic value when alternative diagnoses such as non-vasculitides inflammatory diseases, infection and even non-AAV vasculitides are suspected.

This is not the first study to assess the diagnostic value of ANCA titres.[9] However, to the best of our knowledge, it is the largest and the first to suggest that an ANCA cut-off value when added to the 2022 ACR/EULAR classification criteria can be of practical use for the diagnosis of GPA and MPA.

We chose a pragmatic approach to classifying patients for whom small-to-medium-size vessel vasculitides could be suspected, by further sorting patients without AAV into two categories of differential diagnoses (ie, ANCA-AI and ANCA-O). As previously stated, ANCA titres were not significantly different in the latter two categories, highlighting once again that low-ANCA to medium-ANCA titres can be expressed in non-vasculitis disorders.[7 14 17] However, unlike previous studies, ANCA-PR3 positivity was more commonly found in patients without AAV. Pathogenicity of ANCA is complex and involves overlapping factors.[6] Further differences in phenotypes may explain the range and clinical expression of AAV, and perhaps even discrepancies in findings between studies.[18]

Performance of a 65 U/mL cut-off ANCA titre was remarkably good. Taken independently, its negative predictive value of 98% underscores its practical usefulness in eliminated alternate diagnoses. Understandably, its positive predictive value was low and reflects the low prevalence of AAV among the spectre of 'ANCA-associated disorders'. Other findings were also independently associated with AAV. These were ENT involvement, lung disease and proteinuria—often significantly weighted items of the ACR/EULAR 2022 classification criteria for GPA or MPA.[3 4] The 2022 criteria for GPA found a 94.6% specificity but a lower sensitivity of 83.8%;[3] specificity and sensitivity, in regard to MPA criteria, were respectively

92.5% and 82.4%.[4] By adding an ANCA threshold, sensitivity of the narrow-scoped criteria (that were not meant for diagnosis) is increased. On the other hand, positive ANA was independently associated with AAV mimickers.

Our findings echo those of Houben *et al* who also found that higher ANCA levels and multiple affected organs were associated with AAV.[9] In that study, four different immunoassays were used for ANCA testing and a threshold of ≥4 times the upper limit was chosen. In our study, the threshold value is approximately of ≥3 times the upper limit given for the immunoassay.

ANCA positivity has been studied as a marker of disease activity and, most notably, in guiding maintenance therapy in AAV.[19 20] It has been argued that an increase in titres, rather than ANCA-positivity, is associated with relapse over a timeframe of 6–12 months.[20 21] It would also seem that such findings are mostly associated with renal disease.[21] The caveat is that older studies tend to unequivocally use immunofluorescence and enzyme immunoassays in heterogeneous populations that have often received immunosuppressive induction treatment.[22] At the diagnosis stage, this is however not a major consideration but emphasises that variations in ANCA titres could suggest less active disease that are usually more complicated to characterise.

Our study does have its limitations—the most important of which, being its retrospective nature and the identification of patients solely through their ANCA status. This implies that 'ANCA-negative' AAV and EGPA were overlooked, although such forms are mostly renal, rarely systemic and remain exceptional.[23] Therefore, we believe that such a drawback does not significantly impact our message. Of note, other small-vessel vasculitides required either the positivity of a specific marker (ie, cryoglobulinemia) and/or histopathological evidence of the disease. As a single-cohort study, the cut-off values that were identified cannot be extrapolated, despite using the same immunoassay throughout the entire study-period. Furthermore, patients were mostly Caucasian and not all diagnoses were supported by histological evidence. Despite these shortcomings, our findings are in line with available data from the only previous study on this topic.[9] One of the strengths of our work is its pragmatic and clinical approach to diagnostic dilemmas in daily practice. Our cohort is significantly large for a single-centre study despite the low prevalence of AAV, with more than 13 000 patients screened for AAV over an 8-year period. We also studied AAV in relation to a relatively high number of 'mimickers'.[7 9]

CONCLUSION

An ANCA-PR3 or ANCA-MPO cut-off titre of 65 U/mL and above, when associated with 2022 EULAR/ACR classification criteria in patients presenting with small-vessel vasculitides, can be used to diagnose AAV and its mimickers. Prospective studies validating an ANCA-titre threshold-based approach might help clinicians to better discriminate between AAV and alternative diagnoses.

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Competing interests None declared.

Patient consent for publication Not applicable.

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