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Original article

DIFFUSE ALVEOLAR HEMORRHAGE IN ANCA-ASSOCIATED VASCULITIS: MPO-ANCA VERSUS PR3-ANCA

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Abstract

Introduction: Diffuse alveolar hemorrhage (DAH) is a severe manifestation of ANCA-associated vasculitis (AAV) with significant morbidity and mortality. Although clinical differences between myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA vasculitis have been described, data specifically focused on patients presenting with DAH remain limited. The aim of this study was to compare the clinical characteristics and outcomes of MPO-ANCA and PR3-ANCA patients with DAH.

Materials and methods: We conducted a retrospective single-center study including adult patients hospitalized with ANCA-associated DAH between January 2015 and May 2023 at a university hospital in Buenos Aires, Argentina. Clinical characteristics, laboratory findings, treatment strategies, and outcomes were compared according to ANCA specificity.

Results: Forty patients were included; 26 (65%) were PR3-ANCA positive and 14 (35%) were MPO-ANCA positive. Patients with MPO-ANCA were older at presentation (55.9 ± 14.3 vs. 46.5 ± 13.5 years, p = 0.045) and more frequently developed acute kidney injury (92.9% vs. 50.0%, p = 0.013). Clinical presentation, treatment approaches, requirement for mechanical ventilation, and mortality rates were similar between groups. Overall in-hospital mortality was 22.5%, and one-year mortality was 30.0%.

Conclusion: In this cohort of patients with ANCA-associated DAH, MPO-ANCA positivity was associated with older age and more frequent renal involvement, whereas short-term mortality did not differ according to ANCA specificity. These findings contribute to the characterization of this uncommon and severe manifestation of AAV.

Key words: antibodies, antineutrophil cytoplasmic, pulmonary hemorrhage, myeloperoxidase, proteinase 3, acute kidney injury

Resumen

Hemorragia alveolar difusa asociada a vasculitis ANCA: MPO-ANCA versus PR3-ANCA

Introducción: La hemorragia alveolar difusa (HAD) es una manifestación grave de las vasculitis asociadas a anticuerpos anticitoplasma de neutrófilos (ANCA), con una elevada morbimortalidad. Si bien se han descrito diferencias clínicas entre las vasculitis asociadas a MPO-ANCA y PR3-ANCA, la información específica en pacientes con HAD es limitada. El objetivo de este estudio fue comparar las características clínicas y los desenlaces de pacientes MPO-ANCA y PR3-ANCA con HAD.

Materiales y métodos: Se realizó un estudio retrospectivo unicéntrico que incluyó pacientes adultos hospitalizados con HAD asociada a ANCA entre enero de 2015 y mayo de 2023 en un hospital universitario de Bue-

nos Aires, Argentina. Se compararon las características clínicas, los hallazgos de laboratorio, las estrategias terapéuticas y los desenlaces según la especificidad ANCA.

Resultados: Se incluyeron 40 pacientes; 26 (65%) fueron PR3-ANCA positivos y 14 (35%) MPO-ANCA positivos. Los pacientes MPO-ANCA presentaron mayor edad al diagnóstico (55.9 ± 14.3 vs. 46.5 ± 13.5 años; p = 0.045) y desarrollaron con mayor frecuencia lesión renal aguda (92.9% vs. 50.0%; p = 0.013). La presentación clínica, las estrategias terapéuticas, el requerimiento de ventilación mecánica y la mortalidad fueron similares entre ambos grupos. La mortalidad intrahospitalaria fue del 22.5% y la mortalidad acumulada al año fue del 30.0%.

Conclusión: En esta cohorte de pacientes con HAD asociada a ANCA, la positividad para MPO-ANCA se asoció con mayor edad y mayor compromiso renal, mientras que la mortalidad a corto plazo no difirió según la especificidad ANCA. Estos hallazgos contribuyen a caracterizar esta manifestación infrecuente y grave de las vasculitis asociadas a ANCA.

Palabras clave: anticuerpos anticitoplasma de neutrófilos, hemorragia pulmonar, mieloperoxidasa, proteinasa 3, lesión renal aguda

KEY POINTS
Current knowledge

- Diffuse alveolar hemorrhage is an uncommon but severe manifestation of ANCA-associated vasculitis associated with substantial morbidity and mortality. Clinical differences between MPO-ANCA and PR3-ANCA vasculitis have been described, but data focused specifically on patients with diffuse alveolar hemorrhage remain limited, particularly in Latin America.

Contribution of the article to current knowledge

- This Argentine cohort provides regional data on the clinical presentation, treatment, and outcomes of patients with ANCA-associated diffuse alveolar hemorrhage. MPO-ANCA-positive patients were older and had a higher frequency of acute kidney injury than PR3-ANCA-positive patients, whereas organ support requirements and short-term mortality were similar between groups.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic necrotizing vasculitis that predominantly affects small- to medium-sized vessels and includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Most patients with AAV have circulating ANCAs directed against specific antigens within neutrophil cytoplasmic granules, most commonly myeloperoxidase (MPO) and proteinase-3 (PR3)[1].

Beyond their diagnostic value, ANCA specificities are increasingly recognized as clinically relevant, as MPO-ANCA and PR3-ANCA positive patients display distinct clinical phenotypes, patterns of organ involvement, and long-term outcomes[2,3]. PR3-ANCA is more frequently associated with granulomatosis with polyangiitis and typically correlates with a cytoplasmic immunofluorescence pattern (cANCA), often presenting with upper respiratory tract and pulmonary involvement. In contrast, MPO-ANCA is more commonly associated with microscopic polyangiitis and typically correlates with a perinuclear immunofluorescence pattern (pANCA), frequently presenting with renal involvement. Diffuse alveolar hemorrhage (DAH) is one of the most severe and life-threatening manifestations of ANCA-associated vasculitis, affecting approximately 10-30% of patients and associated with reported mortality rates ranging from 20% to 50% in the acute phase[3,4].

Although several studies have explored the clinical differences between MPO-ANCA and PR3-ANCA positive patients in AAV, data specifically addressing these distinctions in patients presenting with diffuse alveolar hemorrhage remain limited[5,6].

Recent investigations suggest that MPO-ANCA positive patients may exhibit distinct patterns of organ involvement and potentially poorer renal outcomes compared with PR3-ANCA positive patients[7]. However, the prognostic impact of ANCA specificity on short-term outcomes and mortality in patients presenting with DAH remains incompletely defined. Furthermore, therapeutic responses and the need for organ support may vary among these subgroups, highlighting the potential clinical relevance of ANCA specificity in this setting.

The primary aim of this study was to compare the clinical characteristics and outcomes of MPO-ANCA-positive and PR3-ANCA-positive patients presenting with diffuse alveolar hemorrhage secondary to ANCA-associated vasculitis. Secondary objectives included evaluating organ support requirements (hemodialysis and mechanical ventilation), in-hospital mortality, and treatment patterns according to ANCA specificity.

Materials and methods

We conducted a retrospective comparative cohort study at a tertiary-level University Hospital in Buenos Aires, Argentina, from January 2015 to May 2023. We systematically reviewed the medical records of hospitalized patients using the following search terms: "ANCA," "vasculitis," "diffuse alveolar hemorrhage," "alveolar hemorrhage," "Wegener's granulomatosis," "granulomatosis with polyangiitis," "Churg-Strauss," "eosinophilic granulomatosis with polyangiitis," and "microscopic polyangiitis." Records identified through these search terms were subsequently reviewed manually to identify patients with diffuse alveolar hemorrhage and to determine whether the hemorrhage was associated with ANCA-associated vasculitis.

Eligible patients were aged ≥18 years and diagnosed with ANCA-associated vasculitis (AAV) according to the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria[6]. All patients had positive anti-MPO or anti-PR3 antibodies. Diffuse alveolar hemorrhage (DAH) was defined by the presence of new pulmonary infiltrates on chest imaging together with either: (1) the clinical triad of hemoptysis, a decrease in hemoglobin ≥2 g/dL within 7 days in the absence of an alternative bleeding source, and pulmonary infiltrates; or (2) bronchoalveolar lavage findings compatible with alveolar hemorrhage, defined by the presence of >20% hemosiderin-laden macrophages, consistent with previously published definitions[3]. Chest computed tomography (CT) was performed at admission in all patients to confirm pulmonary infiltrates. Bronchoscopy was performed when clinically indicated.

We excluded patients younger than 18 years and those with double-positive ANCA serology (both anti-MPO and anti-PR3 positive), ANCA-negative vasculitis, non-immune DAH, or immune-mediated DAH not associated with ANCA-associated vasculitis. Patients with positive anti-glomerular basement membrane antibodies were also excluded. Additional exclusions included patients with incomplete medical records or missing ANCA specificity data, and those lost to follow-up before the one-year assessment.

ANCA testing was performed using indirect immunofluorescence (IFI) in all 40 patients. The normal value was considered negative (<1/20). Anti-PR3 and anti-MPO antibodies were measured using an enzyme-linked immunosorbent assay (ELISA). Patients were stratified into two groups based on ANCA specificity. The MPO-ANCA group comprised patients positive for anti-MPO antibodies and negative for anti-PR3 antibodies.

We systematically collected baseline demographic characteristics (age, sex, smoking history), clinical manifestations at presentation, laboratory findings (hemoglobin levels, leukocyte count, acute-phase reactants, renal function, and urinalysis), imaging studies, instituted treatments (corticosteroids, immunosuppressive agents, plasma exchange), organ support requirements (mechanical ventilation, hemodialysis), and outcomes (in-hospital mortality, one-year mortality). Active urinary sediment was defined as the presence of proteinuria (>300 mg in a 24-hour urine collection), red blood cell casts, or dysmorphic red blood cells (>80% of total red blood cells). Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria[8].

Statistical analysis

Continuous variables are presented as means and standard deviations, and categorical variables as frequencies and percentages. For comparative analysis between the MPO-ANCA and PR3-ANCA groups, continuous variables were compared using Student's t-test or Mann-Whitney U test, as appropriate, while categorical variables were compared using the chi-square test or Fisher's exact test. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA).

One-year mortality was defined as all-cause mortality occurring during hospitalization or within 12 months after admission.

The study protocol was approved by the Hospital's Institutional Review Board (protocol number 16581).

Results

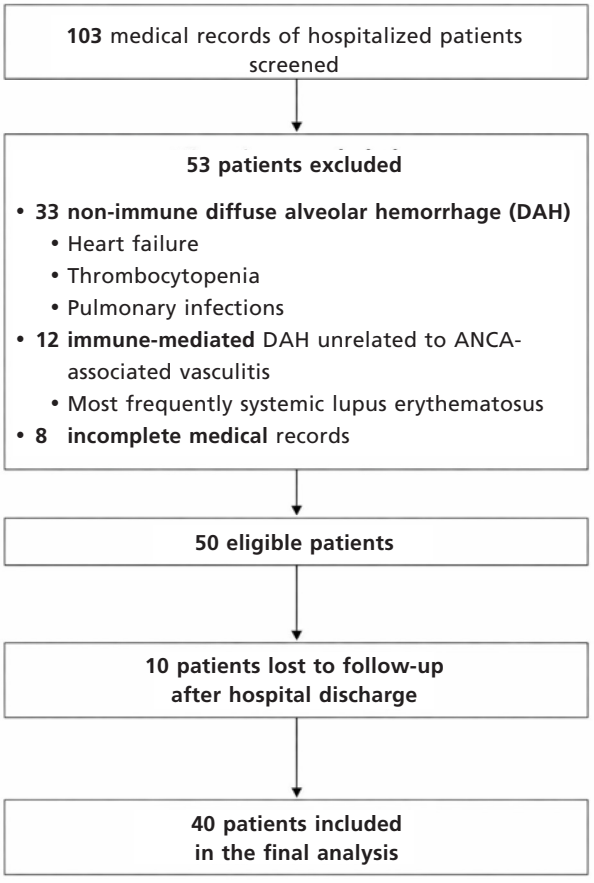
A total of 103 medical records identified through predefined search terms were reviewed. Fifty-three cases were excluded, including 33 patients with non-immune diffuse alveolar hemorrhage (DAH), most commonly due to heart failure, thrombocytopenia, or pulmonary

infections; 12 patients with immune-mediated DAH unrelated to ANCA-associated vasculitis, most frequently systemic lupus erythematosus; and 8 patients with incomplete medical records. After application of the inclusion and exclusion criteria, 50 patients with ANCA-associated DAH were identified. Of these, 10 patients were lost to follow-up after hospital discharge and were excluded from the final analysis due to unavailable one-year outcome data. The final study cohort therefore consisted of 40 patients with ANCA-associated DAH (Figure 1).

The mean age of the study population was 50 years (SD ±14), and 55% of the patients were female. Only one patient (2.5%) had a history of diffuse alveolar hemorrhage. The initial presentation of ANCA-associated vasculitis was DAH in 75% of cases. The classical triad of anemia, hemoptysis, and pulmonary infiltrates was present in 75% of patients. In terms of ANCA specificity, 26 patients (65%) were PR3-ANCA positive, while 14 patients (35%) were MPO-ANCA positive (Table 1).

On chest computed tomography (CT), the most frequent finding was bilateral diffuse ground-glass opacities with subpleural sparing (57%). Other patterns included bilateral patchy ground-glass opacities, consolidations, and, less commonly, unilateral infiltrates.

Figure 1 | Flow diagram of patient selection



A total of 103 medical records of hospitalized patients were screened. Fifty-three patients were excluded, including 33 with non-immune diffuse alveolar hemorrhage, 12 with immune-mediated diffuse alveolar hemorrhage unrelated to ANCA-associated vasculitis, and 8 with incomplete medical records. Fifty patients met eligibility criteria for ANCA-associated diffuse alveolar hemorrhage. After excluding 10 patients lost to follow-up after hospital discharge, 40 patients were included in the final analysis.

Laboratory results and clinical presentation

Dyspnea was the most prevalent clinical manifestation at presentation in 87.5% of patients, followed by hemoptysis (85%) and cough (70%). Fever was detected in 37.5% of cases. Additional laboratory data are presented in Table 2.

Bronchoscopy with bronchoalveolar lavage (BAL) was performed in 65% of patients. In all cases in which BAL was conducted, the presence of hemosiderin-laden macrophages (siderophages) was confirmed, as this constituted a diagnostic inclusion criterion.

Active urinary sediment was detected in 87.5% of patients, and acute kidney injury was diagnosed in 65% of patients. Hemodialysis was required in 47.5% of patients. The mean serum creatinine level was 3.8 mg/dL (SD ±3.7).

Among the total patients examined, 15 patients (37.5%) required invasive mechanical ventilation. Among ventilated patients, the median duration of mechanical ventilation was 4 days (IQR 2-7; range 1-14 days). Prolonged mechanical ventilation (>10 days) occurred in a small proportion of patients.

In-hospital mortality occurred in 9 patients (22.5%), while cumulative one-year mortality reached 12/40 (30.0%).

In bivariate analysis, invasive mechanical ventilation was significantly associated with in-hospital mortality (60.0% vs 0%, Fisher's exact test, $p < 0.001$). Hemodialysis was also significantly associated with in-hospital mortality (88.9% among non-survivors vs. 35.5% among survivors; OR 14.55, Fisher's exact test, $p = 0.007$). No significant differences in hospital mortality or duration of mechanical ventilation were ob-

Table 1 | Baseline characteristics of the study population

Characteristic	Value
Age, years (mean ± SD)	50 ± 14
Female sex, n (%)	22 (55)
Former smoker, n (%)	9 (23)
Previous history of DAH, n (%)	1 (2.5)
DAH as initial presentation, n (%)	30 (75)
Hemoptysis, n (%)	34 (85)
Dyspnea, n (%)	35 (87.5)
Cough, n (%)	28 (70)
Fever, n (%)	15 (37.5)

DAH: diffuse alveolar hemorrhage
Data are presented as mean ± standard deviation (SD) or number (%)

Table 2 | Laboratory, immunological and renal findings

Parameter	Value
Hemoglobin (mean ± SD), g/dL	8.4 ± 2.5
Hematocrit (mean ± SD), %	28 ± 6.5
Anemia, n (%)	34 (85)
ESR (mean ± SD), mm/h	80 ± 37
Elevated ESR, n (%)	34 (85)
CRP (mean ± SD), mg/L	112 ± 79
Elevated CRP, n (%)	28 (70)
Active urinary sediment, n (%)	35 (88)
Acute kidney injury (KDIGO), n (%)	26 (65)
Serum creatinine (mean ± SD), mg/dL	3.8 ± 3.7

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein
Data are presented as mean ± standard deviation (SD) or number (%)

served between patients who received rituximab or cyclophosphamide as induction therapy.

Comparative analysis: demographic and clinical characteristics of MPO-ANCA and PR3-ANCA groups

When stratified by ANCA specificity, the MPO-ANCA group consisted of 14 patients (35%), whereas the PR3-ANCA group consisted of 26 patients (65%). Mean age was significantly higher in the MPO-ANCA group compared with the PR3-ANCA group (55.9 ± 14.3 vs 46.5 ± 13.5 years, 95% CI for the mean difference: 0.2–18.5, p = 0.045). Smoking history and overall clinical presentation were comparable between groups at diagnosis.

Rates of hemoptysis, dyspnea, and fever were similar between groups, as was the proportion of patients presenting with DAH as the initial manifestation of vasculitis (Table 3).

Laboratory findings

No significant differences in laboratory parameters were observed between groups. The MPO-ANCA and PR3-ANCA groups had mean hematocrit levels of 26.5 ± 4.8% and 29.2 ± 6.8%, respectively (difference –2.7%, 95% CI –6.9 to 1.4, p = 0.19). Erythrocyte sedimentation rate values were also comparable between groups (MPO 74.9 ± 36.8 mm/h vs PR3 84.6 ± 35.5 mm/h, difference –9.7 mm/h, 95% CI –33.8 to 14.4, p = 0.40).

Renal involvement

Renal involvement differed between groups. Acute kidney injury occurred in 92.9% of MPO-ANCA patients compared with 50.0% of PR3-ANCA patients (p = 0.013). Active urinary sediment was present in all MPO-ANCA patients (100%) and in 80.8% of PR3-ANCA patients, although this difference was not statistically significant (p = 0.14).

Hemodialysis was more frequent in MPO-ANCA patients than in PR3-ANCA patients (57.1% vs 42.3%), although this difference did not reach statistical significance (p = 0.51) (Table 4).

Treatment

Analysis of therapeutic interventions did not reveal statistically significant differences between groups (Table 5). Corticosteroid pulse therapy was administered to all patients (100%). Cyclophosphamide was the most frequently used induction agent, administered to 71.4% of MPO-ANCA patients and 76.9% of PR3-ANCA patients (p = 0.72). Plasmapheresis was performed in 50.0% of MPO-ANCA patients and 42.3% of PR3-ANCA patients (p = 0.74). Rituximab was administered to 28.6% of MPO-ANCA patients and 11.5% of PR3-ANCA patients (p = 0.21).

Table 3 | Clinical and laboratory features according to ANCA specificity

Variable	MPO-ANCA (n=14)	PR3-ANCA (n=26)	p-value
Hemoptysis	12 (85.7%)	22 (84.6%)	0.92
Dyspnea	13 (92.9%)	22 (84.6%)	0.45
Fever	6 (42.9%)	9 (34.6%)	0.61
DAH as initial manifestation	12 (85.7%)	18 (69.2%)	0.25
Anemia	13 (92.9%)	21 (80.8%)	0.31
Elevated ESR	11 (78.6%)	23 (88.5%)	0.40

MPO: myeloperoxidase; PR3: proteinase-3; DAH: diffuse alveolar hemorrhage; ESR: erythrocyte sedimentation rate
Values are presented as number (%). Comparisons between groups were performed using chi-square or Fisher's exact test, as appropriate.

Table 4 | Renal involvement in patients with diffuse alveolar hemorrhage according to ANCA specificity

Variable	MPO-ANCA (n=14)	PR3-ANCA (n=26)	p-value
Acute kidney injury (KDIGO), n (%)	13 (92.9)	13 (50.0)	0.013
Active urinary sediment, n (%)	14 (100)	21 (80.8)	0.14
Hemodialysis requirement, n (%)	8 (57.1)	11 (42.3)	0.51

MPO: myeloperoxidase; PR3: proteinase-3; DAH: diffuse alveolar hemorrhage; ESR: erythrocyte sedimentation rate
Values are presented as number (%). Comparisons between groups were performed using chi-square or Fisher's exact test, as appropriate.

Table 5 | Treatment according to ANCA specificity

Variable	MPO-ANCA (n=14)	PR3-ANCA (n=26)	p-value
Steroid pulses	14 (100%)	26 (100%)	NA
Cyclophosphamide	10 (71.4%)	20 (76.9%)	0.72
Plasmapheresis	7 (50.0%)	11 (42.3%)	0.74
Rituximab	4 (28.6%)	3 (11.5%)	0.21

MPO: myeloperoxidase; PR3: proteinase-3; NA: not applicable
Values are presented as n (%). Comparisons between groups were performed using chi-square or Fisher's exact test, as appropriate.

Clinical outcomes

Intensive care support requirements were similar between groups. Mechanical ventilation was required in 35.7% of MPO-ANCA patients and 38.5% of PR3-ANCA patients (p = 1.00). Prolonged ventilation (>10 days) occurred infrequently and was comparable between groups (MPO 7.1% vs PR3 7.7%, p = 1.00) (Table 6).

In-hospital mortality was 28.6% in the MPO-ANCA group and 19.2% in the PR3-ANCA group (p = 0.69). Cumulative one-year mortality, including deaths occurring during hospitalization and after discharge within 12 months, was 28.6% in the MPO group and 30.8% in the PR3 group, with no statistically significant difference between groups (p = 1.00) (Table 6).

Discussion

In this cohort of patients with ANCA-associated diffuse alveolar hemorrhage, MPO-ANCA positivity was associated with older age and a higher frequency of acute kidney injury, whereas short-term mortality and organ support requirements were similar between MPO-ANCA and PR3-ANCA patients. The clinical presentation of DAH in our cohort was consistent with international experience (Table 7). The mean age of our population (50 years) was lower than that reported by Fussner et al.[3] (61.1 years) and Quartuccio et al.[9] (median age, 55 years), but similar to that reported by Yadavalli et al.[7] (49.4 years).

Hemoptysis was more frequent in our cohort (85%) than in previously published series.

Table 6 | Comparison of clinical outcomes between myeloperoxidase and proteinase-3 groups

Variable	MPO-ANCA (n=14)	PR3-ANCA (n=26)	p-value
Invasive mechanical ventilation	5 (35.7%)	10 (38.5%)	1.00
Prolonged mechanical ventilation (>10 days)	1 (7.1%)	2 (7.7%)	1.00
In-hospital mortality	4 (28.6%)	5 (19.2%)	0.69
Cumulative one-year mortality*	4 (28.6%)	8 (30.8%)	1.00

IMV: invasive mechanical ventilation; MPO: myeloperoxidase; PR3: proteinase-3
Values are presented as n (%). Comparisons between groups were performed using chi-square or Fisher's exact test, as appropriate.
*Cumulative one-year mortality includes in-hospital deaths and deaths occurring within 12 months after admission.

Table 7 | Comparative analysis of diffuse alveolar hemorrhage in ANCA-associated vasculitis

Variable	Fussner et al. (2024) n=191	Quartuccio et al. (2020) n=106	Yadavalli et al. (2024) n=42	Güemes cohort (2015–2023) n=40
Hemoptysis %	74.3	51.9	61.9	85
Renal involvement / acute kidney injury (%)*	NR	72.6	83.3	65
Mechanical ventilation %	15.2	NR	23.8	38
DAH as initial manifestation %	NR	71.7	NR	75
Age (years) **	61.1± 15.4	55 (42-67)	49.4 ± 18.9	50± 14
Overall mortality % ***	12	17.9	16.6	30
ANCA phenotype (PR3:MPO)	99:92	56:33	33:9	26:14

DAH: diffuse alveolar hemorrhage; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; AAV: ANCA-associated vasculitis; NR: not reported
Data are presented as reported by the original authors or calculated as percentages.
* Renal involvement was defined according to the criteria used in each original study. In the Güemes cohort, the reported percentage corresponds to acute kidney injury defined according to KDIGO criteria.
**Age is presented as mean ± standard deviation, except for Quartuccio et al., for whom age is reported as median (interquartile range).
***Mortality rates were assessed over different follow-up periods: 1 year for Fussner et al. and the Güemes cohort, a median follow-up of 37 months for Quartuccio et al., and a median follow-up of 10 months for Yadavalli et al. Therefore, mortality rates are not directly comparable across studies.

Quartuccio et al.[9] reported hemoptysis in 51.9% of patients and Yadavalli et al.[7] in 61.9%. These findings suggest that although hemoptysis is a common manifestation of DAH, its absence does not exclude the diagnosis and should not reduce clinical suspicion in the appropriate clinical context.

Chest CT abnormalities were present in nearly all patients, with bilateral ground-glass opacities and consolidation being the most frequent patterns. These findings are consistent with prior studies demonstrating the high diagnostic sensitivity of CT imaging in DAH[3]. BAL was required in patients who did not meet the full diagnostic triad of DAH. In these cases, bronchoalveolar lavage confirmed the diagnosis through the presence of hemosiderin-laden macrophages, consistent with previously established diagnostic criteria[10].

All patients received corticosteroids as part of induction therapy, with most receiving high-dose intravenous methylprednisolone. Cyclophosphamide was used in the majority of patients, either alone or in combination with rituximab, in accordance with current international treatment recommendations[1,11]. The use of rituximab in approximately 17.5% of patients reflects evolving clinical practice following randomized trials demonstrating comparable efficacy to cyclophosphamide.

Acute kidney injury was observed in 65% of patients, while active urinary sediment was present in 87.5%. Previous studies have also reported frequent renal involvement, although definitions may differ across cohorts. Quartuccio et al.[9] reported renal involvement in 72.6% of patients. More recent studies have emphasized the prognostic importance of concurrent glomerulonephritis in patients presenting with diffuse alveolar hemorrhage secondary to ANCA-associated vasculitis[12]. The coexistence of pulmonary and renal involvement reflects the well-described pulmonary–renal syndrome in ANCA-associated vasculitis and has been associated with worse outcomes in several cohorts[13].

In our cohort, 37.5% of patients required invasive mechanical ventilation. Previous studies have reported variable rates of mechanical ventilation, including 15.2% in Fussner et al.[3] and 23.8% in Yadavalli et al.[7]. However, differences in the timing of assessment and definitions of ventilatory support limit direct comparisons between cohorts.

Previous studies have identified respiratory failure and the need for mechanical ventilation as major predictors of mortality in these patients[14,15]. Consistent with these observations, invasive mechanical ventilation was strongly associated with in-hospital mortality in our cohort. Hemodialysis was also significantly associated with in-hospital mortality, suggesting that the severity of renal dysfunction may contribute to poor clinical outcomes.

Similarly, in a large Italian multicenter study including 106 patients, Quartuccio et al.[9] reported respiratory failure in 66.7% of cases, with ventilatory support required in a substantial proportion of patients. Differences between studies likely reflect variations in referral patterns, disease severity at presentation, and healthcare system factors.

In our cohort, DAH represented the initial manifestation of ANCA-associated vasculitis in 75% of patients, consistent with the 71.7% reported by Quartuccio et al.[9].

The in-hospital mortality rate in our cohort was 22.5%, while cumulative one-year mortality reached 30%. Previous studies have reported mortality rates ranging from approximately 12% to 18%[3,7,9], although follow-up periods differed across cohorts (Table 7), limiting direct comparisons.

The substantial mortality observed in our cohort highlights the importance of early recognition and aggressive management of this life-threatening complication.

In our cohort, PR3-ANCA positivity predominated (65%), whereas MPO-ANCA accounted for 35% of cases. This distribution differs from that observed in several Asian cohorts, such as the study by Qi et al., which reported MPO predominance[5], but is consistent with many European and North American series.

The most notable difference between groups in our study was the higher rate of acute kidney injury among MPO-ANCA patients (92.9% vs 50.0%). Similar findings have been described in population-based studies. Mohammad et al. demonstrated that patients with MPO-ANCA have a higher risk of progression to end-stage renal disease compared with PR3-ANCA patients[16].

These observations have been supported by subsequent studies and may reflect underlying biological differences between ANCA subtypes[17].

Genetic studies have further reinforced the concept that MPO-ANCA and PR3-ANCA vasculitis represent biologically distinct disease entities. Lyons et al. demonstrated different genetic associations for MPO-ANCA and PR3-ANCA vasculitis, suggesting that ANCA specificity may represent a more meaningful classification than clinical phenotype alone[18].

Previous studies have also shown that PR3-ANCA is associated with higher relapse rates, whereas MPO-ANCA is more frequently associated with renal involvement[5]. However, several studies have reported similar overall survival between ANCA subtypes, particularly during early disease follow-up[19]. In our cohort, no significant differences were observed in in-hospital or one-year mortality between MPO-ANCA and PR3-ANCA patients.

These findings suggest that although ANCA specificity may influence patterns of organ involvement, the severity of organ dysfunction may play a more important role in determining short-term outcomes. In our cohort, both invasive mechanical ventilation and hemodialysis were significantly associated with in-hospital mortality. Wallace et al. similarly observed comparable overall survival between ANCA subtypes but reported differences in cause-specific mortality patterns[20].

This study has several limitations. Its retrospective single-center design and modest sample size may have limited statistical power and reduced the ability to detect differences between groups. Standardized disease activity scores were not systematically available, and residual confounding cannot be excluded. Additionally, the exclusion of 10 patients due to unavailable one-year follow-up data may have introduced selection bias.

Vasculitis subtype classification (GPA, MPA, or EGPA) was not consistently available and therefore could not be incorporated into the analysis.

In conclusion, diffuse alveolar hemorrhage secondary to ANCA-associated vasculitis remains a severe clinical condition associated with substantial early mortality. In this cohort, MPO-ANCA positivity was associated with older age and more frequent acute kidney injury, whereas short-term mortality was similar between MPO-ANCA and PR3-ANCA patients.

Conflict of Interest: None to declare

Declaration of AI use: During the preparation of this work, ChatGPT (OpenAI) was used to improve language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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