

Clinical Burden and Costs of Anti-Neutrophil Cytoplasmic Antibody-ANCA-Associated Vasculitis: Main Findings from REDCap Registry of a University Hospital in Spain

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Purpose: Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) are rare chronic autoimmune diseases, potentially fatal, with frequent relapses. They are associated with vital organ damage, especially renal, often resulting in end-stage renal disease. While current standard of care with immunosuppressants has improved renal function and survival, the main risks for patients under life-long immunosuppression are infections and other concomitant diseases. This study evaluated the burden of AAV using patient-level data from a disease-specific registry.

Patients and Methods: The cohort of incident AAV patients (2013–2022) in the REDCap registry in a university hospital in Spain was studied. Patients with Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA) with at least one year of follow-up (or deceased during the period) were included. Clinical outcomes, including Birmingham Vasculitis Activity Score (BVAS) and healthcare resource consumption were analysed for the first year after diagnosis. Mean annual costs were calculated using unitary costs from the hospital accounting department.

Results: Seventy-five patients (12% EGPA, 32% GPA, and 56% MPA) were included. Fifty-two percent were women. Mean age at diagnosis was 65.20±14.70 years. At baseline, mean BVAS was 17.35±5.70, 93.33% of patients showed renal affection, mean estimated glomerular filtration rate was 33.32±29.93mL/min/1.73m². As induction treatment, 62.67% received methylprednisolone, 37.33% rituximab, 25.33% cyclophosphamide, 14.67% rituximab plus cyclophosphamide, 34.67% plasmapheresis. During the first year after diagnosis, 17.33% relapsed and 78.67% had at least 1 hospitalisation; 97.33% received steroids; 13.33% were on dialysis at some point; one patient received a kidney transplant; 46.67% presented infections and 28% suffered corticosteroid-associated complications; 4 patients died, being 50% of deaths treatment-related. The highest observed mean cost per patient for the first year was €11,647.95 for hospital care.

Conclusion: This study revealed a considerable burden of AAV, as evidenced by high rates of hospitalisation, relapses, and the need for intensive medical interventions.

Keywords: anti-neutrophil cytoplasmic antibody-associated vasculitis, vasculitis, disease burden, registry, treatment outcome

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) comprises 3 different clinical phenotypes: Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA), a group of systemic diseases characterized by pauci-immune necrotizing inflammation of small to medium vessels.¹ In this condition, attachment of neutrophils to endothelial cells, extravascular migration, and release of

components constitute distinctive early ultrastructural lesions,² which contribute to vascular injury and necrosis, typical features of AAV.³

The immunofluorescence pattern of ANCA distinguishes cytoplasmic ANCA (c-ANCA), targeting proteinase 3 (PR3) in most cases, and perinuclear ANCA (p-ANCA), usually targeting myeloperoxidase (MPO). Inflammation of small-sized vessels is responsible for organ damage with granulomatous involvement of the upper and lower respiratory tract in GPA and EGPA,⁴ and glomerulonephritis, intra-alveolar haemorrhage, and/or peripheral neuropathy in GPA, MPA, and EGPA.⁵

AAV is defined as a rare autoimmune disease with a current annual incidence of 20 per million,⁶ however, an increasing incidence has been reported in the past years.⁷ The incidence of PR3-AAV and MPO-AAV varies worldwide. In general, MPO-AAV is more frequent in southern Europe, Asia, and the Pacific (except in New Zealand and Australia) and PR3-AAV is more common in the north of the world.^{4,8–10} This distribution is possibly a result of a combination of genetic and environmental factors.^{5,10–13}

The prognosis of AAV in the absence of treatment is unfavourable. However, the facilitation of early diagnosis through ANCA testing and the introduction of immunosuppressant therapies have contributed to better survival rates.^{14–17} Standard of care encompasses an induction phase, intending to achieve remission, and a maintenance phase with less intensive medication aiming at preventing relapse, minimizing the risk of comorbidities and treatment toxicity. The combination of glucocorticoids with cyclophosphamide or rituximab is the current induction standard of care for severe disease, associated, in some cases, with plasma exchange.^{18–20} Treatment in AAV particularly with glucocorticoids is associated with toxicity and important complications, such as infections and other comorbid events, limiting its overall benefit for patients and impacting health-related quality of life.^{21–23} Infections and adverse events are the most frequent serious complications in the first year of treatment for AAV.²⁴

Published data on the clinical outcomes during the course of AAV and its management costs is scarce since data availability is limited due to a relatively low incidence and the need to take into account disease-specific parameters for its assessment. As a rare and severe disease in which patients are impacted both by the illness itself and potentially by the treatment themselves, characterization of the burden to patients and the health system is key to strive for potential improvements in its management.

The current study focused on the clinical characterization of AAV patients as well as the quantification of the current burden of disease of AAV patients during the first year after diagnosis, using high-quality data from the AAV registry of a university hospital.

Materials and methods

The cohort of patients diagnosed with GPA, MPA and EGPA in the University Hospital of Bellvitge, in Barcelona, Spain, between 2013 and 2022 and with one year of follow-up (or deceased during the period) was studied during the first year after diagnosis. Informed consent for the inclusion in this registry as well as approval by the local Ethics Committee Board (Comité de ética de la investigación del Hospital Universitario de Bellvitge) were requested and granted. The study followed the principles of the Helsinki Declaration of 1964 and its later amendments.

The REDCap registry is structured according to the following specific sections and sub-sections considered in this study:

- At enrolment Demographics, including demographic information such as date of birth, gender, employment status and ethnicity.
- At enrolment Clinical history, including detailed information about the patient's general medical history, smoking history, comorbidities prior to diagnosis and specific details related to the diagnosis as date of diagnosis, ANCA specificity and titre, systems involved at any point, renal function, presence of haematuria, proteinuria (g/L) and hemogram, PCR and ESR.
- Annual follow-up section capturing longitudinal information collected annually, including disease activity, defined by BVAS score, treatment, relapse, complications, and healthcare resource consumption.

BVAS dataset²⁵ was collected at baseline, representing the initial assessment upon entering the study, and at the time of each relapse event.²⁶

Other sections, such as medications, complications, dialysis, ESKD outcomes and death outcomes were used to obtain complementary information.

Sociodemographic and clinical characteristics, including comorbidities and BVAS and its features, were described at baseline, for the cohort and each diagnostic group: GPA, MPA, EGPA. Clinical outcomes including relapses according to BVAS, corticosteroid-associated complications, renal replacement therapy, renal transplant, and death were analysed during the first year after diagnosis. Estimated glomerular filtration rate (eGFR) was described at baseline and at one year of follow-up and changes in eGFR categories between the two periods were analysed.

Resource utilization was assessed in terms of hospitalisations, visits to specialists, visits to day hospital, and to emergency department, pulse and continuing medications, plasma exchange, haemodialysis, and transplant.

The accumulated dose of medications was calculated to assess the total exposure to specific medications for each subject in the study, considering dose and posology of administration.

Mean annual costs for hospital care (visits to specialists, day hospital, emergency department visits and hospitalisations), dialysis, renal transplant, plasma exchange, medications, and testing were calculated using unitary costs from the Hospital accounting services, using 2022 as reference year. When not available, the regional average tariff for hospital care or testing, and for medications, the real ex-factory price plus VAT after the Royal Decrees 08/2010 was used as a reference.

The statistical software used for the analysis was R v.4.²⁶ Descriptive statistics, including frequencies and proportions for categorical variables, and mean and standard deviation for continuous variables were calculated. Given the limited number of subjects in the study, missing dates were not imputed or replaced. Queries on missing data/outliers were reported to the corresponding principal investigators, and data were completed/corrected using electronic health records when possible.

Ethical Compliance Sstatement

This study involved the analysis of existing data and did not involve the participation of human subjects. The use of data was conducted in accordance with ethical standards and regulations, ensuring confidentiality and privacy. All data were anonymised prior to analysis to protect the privacy of individuals.

Results

Out of the 86 patients included in the registry, 75 had completed the first follow-up and were thus included in the present analysis; of them, 12% were EGPA, 32% GPA, and 56% MPA patients, respectively. Sixty-four percent of patients were ANCA-MPO, 32% were ANCA-PR3 and 2.67% were ANCA-MPO-PR3. [Table 1](#) and [Figure 1](#) show the main socio-demographic and clinical characteristics at baseline. Fifty-two percent of the included patients were female, and patients were mainly of Caucasian ethnicity, and most were retired. Mean age at diagnosis was 65.20 years. The mean BVAS score at baseline was 17.35. According to BVAS, the most frequent ANCA-associated affectation at baseline, was renal (93.33%), followed by general features (63.89%) and chest (50.70%). The indicator of eGFR at baseline was 33.32/min/1.73m², 18.67% of patients presented eGFR<15mL/min/1.73m² and 13.33% of patients were under renal replacement therapy. The most common comorbidities were hypertension requiring treatment, hyperlipidaemia, malignancy/neoplasm, and chronic obstructive pulmonary disease (COPD): 45.33%, 29.33%, 12% and 10.67% of patients, respectively. Regarding induction treatment, 62.67% received methylprednisolone, 37.33% rituximab, 25.33% cyclophosphamide, 14.67% rituximab plus cyclophosphamide and 34.67% underwent plasmapheresis. In the course of follow-up, 97.33% of patients received corticosteroids.

[Figure 2](#) shows main clinical outcomes and complications during the first year of follow-up. 17.33% of the patients relapsed during the first year, and all of them presented only one relapse. According to BVAS at relapse, the most common affectation was renal, followed by general features and chest. Concerning other clinical complications, 46.67% of the patients presented infection(s), being the most frequent pneumonia, followed by pyelonephritis ([Figure 3a](#)). Regarding severity, 48.58% of infections required hospitalisation, and 5.71% caused death.

Table 1 Main Sociodemographic and Clinical Characteristics at Baseline

		Overall (n=75)	EGPA (n=9)	GPA (n=24)	MPA (n=42)
ANCA (%)	MPO	64.00	88.89	8.33	90.48
	MPO-PR3	2.67	0.00	0.00	4.76
	PR3	32.00	0.00	91.67	4.76
Age at diagnosis (mean $\pm$ SD)		65.20 $\pm$ 14.70	64.11 $\pm$ 16.10	60.33 $\pm$ 15.35	68.21 $\pm$ 13.57
Ethnicity (%)	Caucasian	89.33	100.00	91.67	85.71
	Latin	9.33	0.00	4.17	14.29
	White/Black African	1.33	0.00	4.17	0.00
Occupation (%)	Retired	62.67	66.67	58.33	64.29
	Not Working	2.67	0.00	4.17	2.38
	Employed Full Time	20.00	11.11	20.83	21.43
	Homemaker	1.33	0.00	0.00	2.38
BMI (mean $\pm$ SD) Kg/m²		27.45 $\pm$ 4.87	23.82 $\pm$ 3.84	27.22 $\pm$ 5.39	28.30 $\pm$ 4.48
eGFR Calculated (mean $\pm$ SD) mL/min/1.73m²		33.32 $\pm$ 29.93	58.62 $\pm$ 32.53	46.46 $\pm$ 39.11	21.00 $\pm$ 13.21
Baseline BVAS Score (mean $\pm$ SD)		17.35 $\pm$ 5.70	13.44 $\pm$ 4.16	17.50 $\pm$ 6.67	18.10 $\pm$ 5.14
Affectation (%)	General	63.89	71.43	79.17	53.66
	Cutaneous	12.31	33.33	14.29	7.89
	Mucous Membranes/Eyes	13.43	0.00	28.57	7.50
	Ear, nose, and throat	22.86	57.14	27.27	14.63
	Chest	50.70	75.00	61.90	40.48
	Renal	93.33	66.67	91.67	100.00
	Cardiovascular	4.69	0.00	5.26	5.13
	Nervous System	18.46	14.29	14.29	21.62

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; SD, standard deviation.

In addition, 28% of patients presented corticosteroid-associated complications, being the most frequent secondary hyperlipidaemia, followed by weight gain, induced hyperglycaemia and peptic ulcer disease (Figure 3b). Notably, 23.81% of corticosteroid-associated complications required hospitalisation.

The mean eGFR at one year of follow-up was 46.53mL/min/1.73m² and 6.67% of patients had an eGFR<15mL/min/1.73m². 13.33% of the patients were on dialysis at some point during the first year of follow-up (mean duration of dialysis 209.90 $\pm$ 164.92 days), and half of them were on ongoing dialysis at follow-up. One patient received a kidney transplant. Most patients (54%) improved their renal status according to the eGFR category during the first year after diagnosis, while 19% showed deterioration of renal function. Figure 4 shows distribution of patients according to renal function at diagnosis and at 1 year of FU and depicts flow of patients among the categories in this period.

Four patients died during the period, with 50% of the deaths reported to be treatment-related (Table 2).

Figure 5 and Table 3 show the main resource consumption items during the first year of follow-up, including accumulated doses for medications. About 78.67% of the patients were hospitalised at some point during the first year of

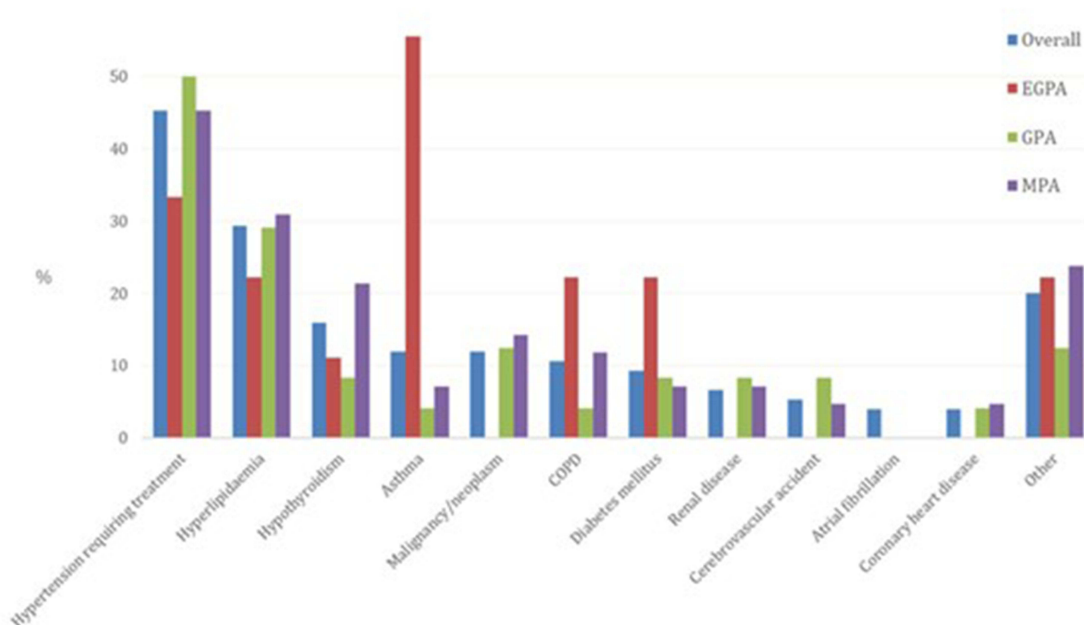


Figure 1 Main comorbidities at baseline.

Abbreviations: COPD, Chronic obstructive pulmonary disease; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

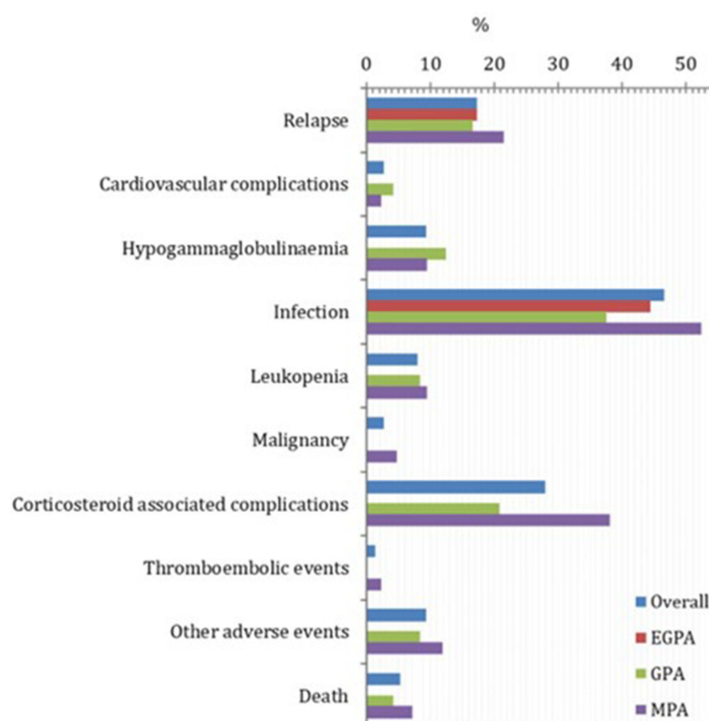


Figure 2 Main clinical outcomes at one year of follow-up (% of patients).

Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

follow-up, and the same percentage had visits to specialists. The mean number of hospitalisations per patient was 1.24 ± 1.16 , and the mean length of stay was 17.79 ± 21.73 days (23.76 ± 24.10 days for patients with hospitalisations). About 33.33% of the patients had at least one emergency department visit.

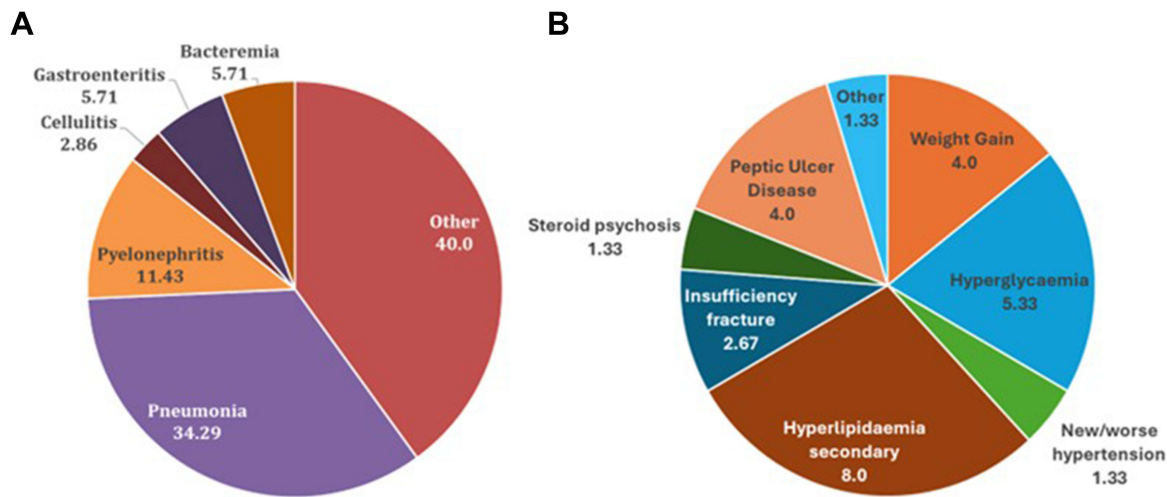


Figure 3 (a) Main types of infections (%) at one-year follow-up (n=35); (b) Main types of clinical Steroid-associated complications (%) at one-year follow-up (n=21).

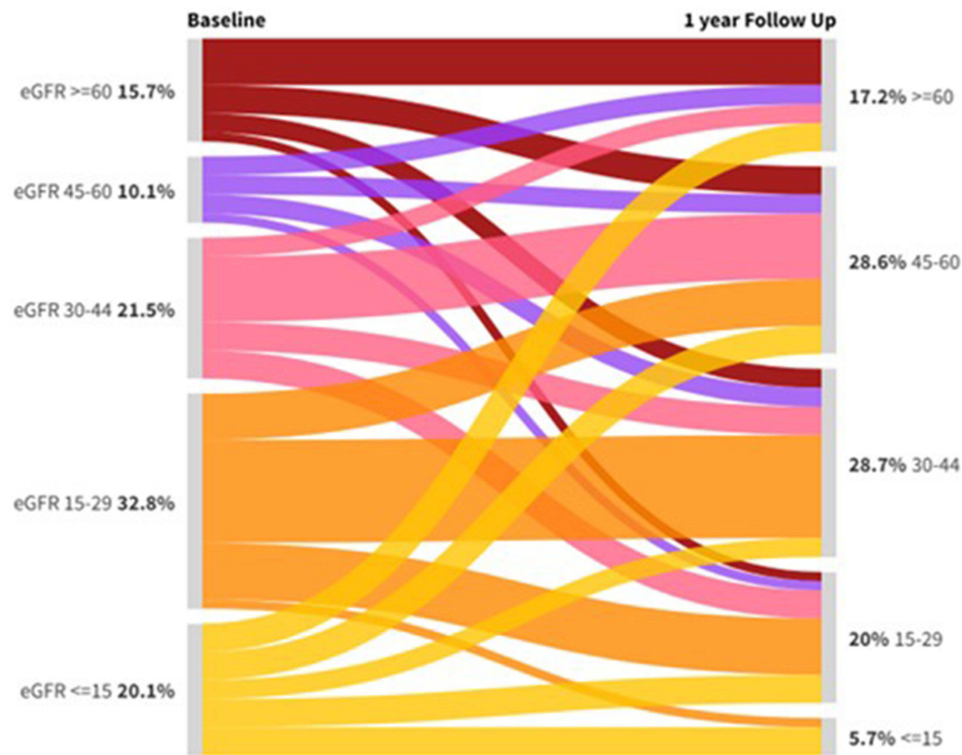


Figure 4 Change in eGFR according to categories, from baseline to 1 year of follow-up (%).
Abbreviation: eGFR, estimated glomerular filtration rate.

Mean costs per patient for the first year after diagnosis were €11,647.95 for hospital care (89% attributable to hospitalisations, 6% to visits to specialists, 3% to emergency department visits, 2% to day hospital); €1579.16 for dialysis; €834.53 for medication costs (91% attributable to pulse medications); €462.04 for renal transplant; €104.89 for tests; €41.44 for plasma exchange. All mean costs estimated led to the conclusion that GPA patients exhibited the highest hospital care cost and EGPA patients the lowest (€13,487.46 and €6356, respectively).

Table 2 Death Outcomes at One Year of Follow-Up

Level		Overall	EGPA	GPA	MPA
Days to Death (mean (SD))		145.00 (85.21)	–	79.00 (NA)	167.00 (89.37)
Cause of Death (%)	Not Vasculitis related	1 (25.00)	–	0 (0.00)	1 (33.33)
	Treatment-Related	2 (50.00)	–	1 (100.00)	1 (33.33)
	Vasculitis Related	1 (25.00)	–	0 (0.00)	1 (33.33)

Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; SD, standard deviation.

Discussion

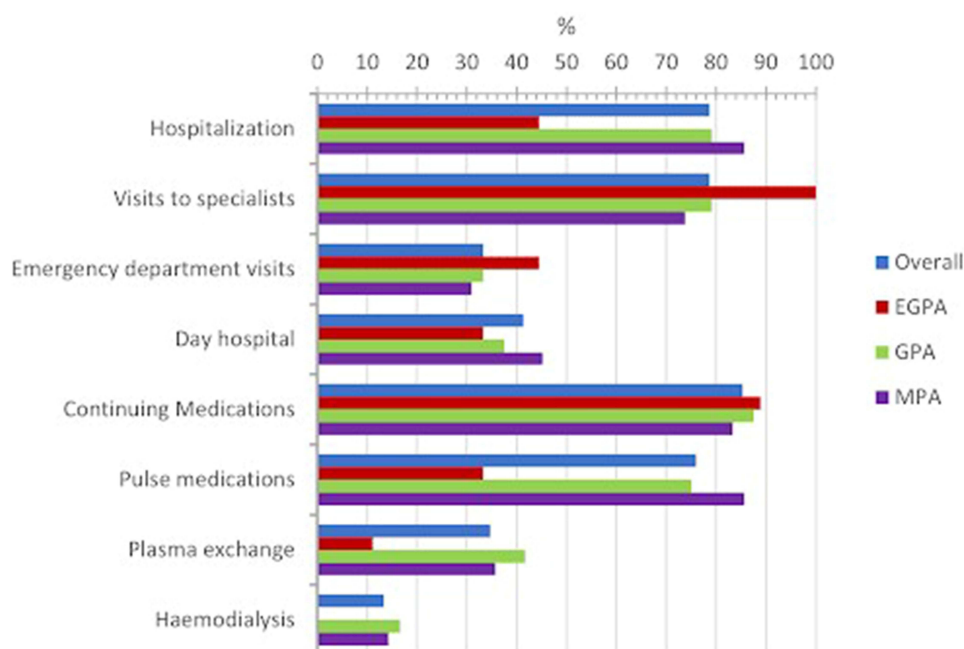
The present study focused on clinical outcomes and management costs of AAV patients during the first year after diagnosis, using a highly detailed registry of all incident patients managed at the nephrology service of a university hospital in Barcelona (Spain), based on the structure of the REDCap database.

The study revealed a considerable burden of AAV, with a high proportion of patients hospitalised during the first year, considerable rates of relapse, and complications, mainly corticosteroid-associated and infections.

Consistent with the results of two Italian studies,^{27,28} the highest observed costs were hospitalisations, and higher costs were found for GPA, followed by MPA, with considerable difference with EGPA management costs.

In the present study, mortality during the first year after diagnosis was 6%, with half of the deaths reported to be treatment related. This proportion was similar to the one reported in a meta-analysis of AAV clinical trials, which found that 59% of deaths were due to therapy-associated adverse events, whereas only 14% were due to active vasculitis.²⁴ These data suggest that the greatest threat of death for patients with AAV during the first year after diagnosis lies in the therapy rather than in the active disease itself.

Corticosteroids are generally associated with a range of complications, including avascular necrosis, gastrointestinal bleeding, myocardial infection, heart failure, cerebrovascular events, and infections, among others. Increased daily and

**Figure 5** Main resource consumption items during the first year of follow-up.

Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; FU, follow-up; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

Table 3 Specific Resource Consumption Items During the First Year of FU

		Overall (n=75)	EGPA (n=9)	GPA (n=24)	MPA (n=42)
Induction treatment (%)	Rituximab	37.33	22.22	45.83	35.71
	Cyclophosphamide (oral or IV)	25.33	11.11	20.83	30.95
	Rituximab + cyclophosphamide	14.67	0.00	16.67	16.67
	Methylprednisolone	62.67	22.22	66.67	69.05
	Plasmapheresis	34.67	11.11	41.67	35.71
Maintenance treatment (%)	Rituximab	30.67	11.11	54.17	21.43
	Oral mycophenolate	30.67	11.11	25.00	38.10
	Azathioprine	25.33	44.44	25.00	21.43
	Methotrexate	2.67	0.00	8.33	0.00
Length of stay (hospitalisation) in days (mean $\pm$ SD)		17.79 $\pm$ 21.73	8.89 $\pm$ 13.24	20.96 $\pm$ 21.84	17.88 $\pm$ 22.96
Number of visits to specialists (mean $\pm$ SD)		7.71 $\pm$ 6.28	6.89 $\pm$ 3.69	7.29 $\pm$ 6.50	8.12 $\pm$ 6.67
Number of day hospital visits (mean $\pm$ SD)		1.40 $\pm$ 2.29	1.67 $\pm$ 3.94	1.21 $\pm$ 2.00	1.45 $\pm$ 2.04
Number of emergency department visits (mean $\pm$ SD)		0.87 $\pm$ 1.58	0.78 $\pm$ 1.09	1.12 $\pm$ 1.83	0.74 $\pm$ 1.53
Plasma exchange sessions (mean $\pm$ SD)		7.15 $\pm$ 2.72	7.00 $\pm$ NA	7.40 $\pm$ 2.76	7.00 $\pm$ 2.88
Rituximab accumulated dose mg (mean $\pm$ SD)		1201.18 $\pm$ 1113.16	444.44 $\pm$ 881.92	1414.10 $\pm$ 1095.30	1241.67 $\pm$ 1121.51
Cyclophosphamide accumulated dose mg (mean $\pm$ SD)		905.00 $\pm$ 1646.92	433.33 $\pm$ 1300.00	629.17 $\pm$ 1367.47	1163.69 $\pm$ 1831.60
Methylprednisolone accumulated dose mg (mean $\pm$ SD)		677.33 $\pm$ 933.44	211.11 $\pm$ 562.24	756.25 $\pm$ 909.05	732.14 $\pm$ 996.45
Azathioprine accumulated dose mg (mean $\pm$ SD)		1735.67 $\pm$ 5309.56	3811.11 $\pm$ 6893.86	2834.38 $\pm$ 7157.95	663.10 $\pm$ 3167.94
Daily oral Cyclophosphamide accumulated dose mg (mean $\pm$ SD)		1179.21 $\pm$ 4228.86	0.00 $\pm$ 0.00	711.46 $\pm$ 2192.08	1699.19 $\pm$ 5373.19
Methotrexate accumulated dose mg (mean $\pm$ SD)		1020.06 $\pm$ 8833.45	0.00 $\pm$ 0.00	0.18 $\pm$ 0.87	1821.43 $\pm$ 11,804.21
Mycophenolate mofetil accumulated dose mg (mean $\pm$ SD)		13,048.90 $\pm$ 25,724.41	7201.39 $\pm$ 21,604.17	10,895.83 $\pm$ 23,569.07	15,532.26 $\pm$ 27,841.31
Prednisolone accumulated dose mg (mean $\pm$ SD)		4954.50 $\pm$ 3265.80	5304.17 $\pm$ 3140.87	5506.56 $\pm$ 3379.17	4564.11 $\pm$ 3249.29
Avacopan accumulated dose mg (mean $\pm$ SD)		122.00 $\pm$ 753.45	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	217.86 $\pm$ 1001.61

Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; SD, standard deviation.

cumulative doses of corticosteroids are associated with increased excess risk of complications in a number of conditions.^{29–32} In the present study, over 97% of the patients received corticosteroids. Consistently, in addition to the relationship between treatment and death, a considerable percentage of patients, particularly in the MPA group, presented corticosteroid-associated complications during the first year of follow-up, which in over one-fourth of occasions required hospitalisation. This is consistent with the increased healthcare resource use, in terms of inpatient visits, observed for patients with use of medium and high-dose corticosteroids in chronic conditions like asthma.^{31,32}

Furthermore, in the present study, nearly half of the patients experienced infections, which in nearly half of the times required hospitalizations and, in some cases, caused death. The incidence of serious infections in the present study is higher than that reported in other studies, like Vassilopoulos et al³³ who found in patients treated with rituximab and azathioprine an overall cumulative incidence of serious infections of 16%. In line with other studies,²⁸ the burden of chest affection was relevant in relapses, and also in terms of infections, being pneumonia the most frequent.

The main strength of the current study lies in the richness and reliability of data, collected by a single service of a university hospital following the structure of the European registry for this specific disease. In terms of limitations, the study is based on a database managed by the nephrology service of a tertiary hospital, therefore cases are biased

towards those with significant renal involvement (94% of patients with renal affectation in baseline BVAS). Consequently, the proportion of MPA patients is higher, and the proportion of EGPA patients is considerably lower than in other studies.²⁸

Conclusion

In conclusion, in this study the clinical and economic burden of AAV has been assessed for the first time in a Spanish setting, focusing on the first year after diagnosis. It has shown, despite remission and stabilization of renal function in many cases, a high burden in terms of complications, particularly infections and corticosteroid-associated events, with most patients being hospitalised during the period and half of the deaths related to treatment. As a single-centre analysis with a reliable and standardized database, this analysis sets the scene for broader analyses, and to monitor management of the disease as the treatment landscape evolves.

Data Sharing Statement

The datasets generated during and/or analysed during the current study are not publicly available due to privacy regulations and institutional policies regarding patient data confidentiality.

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Disclosure

ARA is an employee of CSL Vifor and may hold shares and/or stock options in the company. HDC, CC and JC are consultants of Axentiva Solutions, which received consultancy fees from CSL Vifor, Spain and, during the conduct of this study, from other pharmaceutical companies (Amgen, Pfizer, and Biogen) in unrelated projects. JD, FGP and LMV report having received a consulting fee from Axentiva Solutions for collaboration in this study and, during the conduct of this study, from other CSL Vifor-funded projects. The authors report no other conflicts of interest in this work.

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