Surfactant therapies for pediatric and neonatal ARDS

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Original article

Association between age at disease onset of anti-neutrophil cytoplasmic antibody–associated vasculitis and clinical presentation and short-term outcomes

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Abstract

Objectives. ANCA-associated vasculitis (AAV) can affect all age groups. We aimed to show that differences in disease presentation and 6 month outcome between younger- and older-onset patients are still incompletely understood.
Methods. We included patients enrolled in the Diagnostic and Classification Criteria for Primary Systemic Vasculitis (DCVAS) study between October 2010 and January 2017 with a diagnosis of AAV. We divided the population according to age at diagnosis: <65 years or ≥65 years. We adjusted associations for the type of AAV and the type of ANCA (anti-MPO, anti-PR3 or negative).
Results. A total of 1338 patients with AAV were included: 66% had disease onset at <65 years of age [female 50%; mean age 48.4 years (S.D. 12.6)] and 34% had disease onset at ≥65 years [female 54%; mean age 73.6 years (S.D. 6)]. ANCA (MPO) positivity was more frequent in the older group (48% *vs* 27%; $P = 0.001$). Younger patients had higher rates of musculoskeletal, cutaneous and ENT manifestations compared with older patients. Systemic, neurologic,cardiovascular involvement and worsening renal function were more frequent in the older-onset group. Damage accrual, measured with the Vasculitis Damage Index (VDI), was significantly higher in older patients, 12% of whom had a 6 month VDI ≥5, compared with 7% of younger patients ($P = 0.01$). Older age was an independent risk factor for early death within 6 months from diagnosis [hazard ratio 2.06 (95% CI 1.07, 3.97); $P = 0.03$].
Conclusion. Within 6 months of diagnosis of AAV, patients >65 years of age display a different pattern of organ involvement and an increased risk of significant damage and mortality compared with younger patients.

Key words: anti-neutrophil cytoplasmic antibody–associated vasculitis, age, outcome

Rheumatology key messages

- Age at disease onset is associated with a different clinical presentation in younger patients compared with older patients with AAV.
- Age at onset of AAV influences the short-term outcome.
- Damage accrual and increased mortality risk occur early after diagnosis, especially in patients >65 years of age.

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CLINICAL SCIENCE

Introduction

ANCA-associated vasculitis (AAV) can potentially affect all age groups, with a peak incidence in the 6th–7th decades [1, 2]. Disease onset at an older age has been reported to be associated with a higher frequency of renal involvement and worse outcome [3,4]. International recommendations suggest a tailored approach in the management of older patients, with dose adjustments of remission-induction treatment with cyclophosphamide according to age and glomerular filtration rate (GFR) [5]. Nevertheless, the impact of age on the management and outcome of AAV is still largely unknown. Several randomized controlled trials of AAV excluded patients >75 years of age [6, 7] and the available evidence comes mainly from retrospective observational studies [8, 9]. Nonetheless, an intriguing pathogenetic explanation that goes beyond expected epidemiologic data comes from an animal model of ANCA-associated glomerulonephritis. An age-dependent severity of renal damage was demonstrated in older mice injected with anti-MPO antibodies [10]. The concept of immunosenescence is gaining interest in rheumatic diseases [11, 12]. Ageing leads to a series of changes in the innate and adaptive immunity that promote persistent inflammation. Increased susceptibility to external pathogenic agents and impaired tissue-repairing capacity potentially also contribute to a worse course of disease in older patients [12]. A better understanding of the differences in the type of clinical presentation and outcome of AAV according to age will be informative to potentially lead to more rapid diagnosis and development of therapeutic or follow-up strategies to reduce damage and mortality. The aim of this study was to identify distinguishing characteristics of clinical presentations, short-term outcomes and accumulated damage for patients with AAV based on age of disease onset.

Methods

Data from patients recruited between October 2010 and January 2017 in the Diagnostic and Classification Criteria for Primary Systemic Vasculitis (DCVAS) study was used for this analysis. The DCVAS study is an international observational study of newly diagnosed patients with vasculitis or mimics that was created with the aim of producing new classification and diagnostic criteria for several forms of systemic vasculitides [13]. The University of Oxford is the sponsor of the DCVAS study, with overall ethical approval given by the UK Berkshire Research Ethics (10/H0505/19, 7 May 2010). The DCVAS study was performed in accordance with the 1964 Declaration of Helsinki and ethical approval was obtained by national and local ethics committees in accordance with national legislation. Participants consented to the study and access to their records was granted.

We selected records of patients from the DCVAS study who had a confirmed final diagnosis of AAV [granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) or microscopic polyangiitis (MPA)]. Confirmation of the diagnosis was agreed following review of each case by at least one independent expert using the DCVAS external expert review process.

We divided the population according to age at disease onset as <65 years or ≥65 years. We used the following data for the analysis, comparing differences between the younger and older groups: demographics (age, sex, disease duration, ethnicity), comorbid conditions, detailed description of organ systems involved at presentation and laboratory tests (acute phase reactants, full blood count data, creatinine, GFR values and ANCA test results). We assessed the Vasculitis Damage Index (VDI) at 6 months from diagnosis. We analysed mortality at up to 6 months of follow-up (which was the final visit in the DCVAS study).

Statistical analysis

We used Stata 15.1 (StataCorp, College Station, TX, USA) for all computations. We set statistical significance at a two-sided *P*-value <0.05. We described continuous data with the mean and SD. or the median and 25th–75th percentiles [interquartile range (IQR)] and categorical data as number and percent. We compared them between age groups with logistic and linear regression models, respectively. We used generalized ordinal logit models for ordinal outcome models (categories of VDI) and checked the proportional odds assumption for verification. To account for intracentre correlation of measures, we computed Huber–White robust standard errors. We further fitted the same models while adjusting for diagnosis (GPA, MPA or EGPA) and for ANCA status: PR3-ANCA, MPO-ANCA or negative. We computed the odds ratios (ORs) and 95% CIs. We computed the rate of death at 6 months per 100 person-years for each age group. We used the log-rank test and the Cox model for comparison. We adjusted the effect of age for a series of potential confounders identified a priori based on the available literature (e.g. renal function impairment, respiratory failure). We reported hazard ratios (HRs) and 95% CIs. We computed both the naïve Harrell's C statistic for model discrimination and the Harrell's C computed on 70% of the cohort and validated in 30% of the cohort, together with its 95% CI. For all models we tested for the interaction of age and confounders (diagnosis type and ANCA status) to exclude a modifying effect of the latter.

We reported detailed comparisons of signs and symptoms between groups as Supplementary tables, available at *Rheumatology* online, with a descriptive aim only.

Results

Demographics, diagnosis and baseline characteristics

We included data from 1338 patients with a 6 month final diagnosis of AAV [(GPA, 735 patients (55%); MPA, 334 patients (25%); EGPA, 255 patients (19%); general

diagnosis of AAV, 14 patients (1%)]. Among the 878 patients (66% of the total) with younger-onset disease (mean age 48.4 years (S.D. 12.6; range 18–64.96), 50% were female. In the older-onset group [≥65 years; mean age 73.6 years (S.D. 6; range 65.03–91)] there were 460 patients (34%), of whom 53.7% were female.

Diagnostic delay (defined by time from onset of symptoms to diagnosis) was greater in the younger group [median 3.90 months (IQR 1.64–11.02) *vs* 3.04 (1.22–8.29); $P = 0.036$].

The type of AAV according to age is presented in Table 1. Within each diagnostic group, 73% of patients with GPA and 74% of patients with EGPA belonged to the younger group, while 56% of the patients with MPA had an older onset ($P < 0.001$). ANCA-PR3 was more frequent in the younger group compared with the older-onset group (48% *vs* 35%; $P = 0.002$), while ANCA-MPO was more frequent in the older group (27% in younger patients *vs* 48% in older patients; $P < 0.001$).

As shown in Table 2, comorbidities were more frequent in the older-onset group, with 85% of patients having at least one comorbid condition at the time of diagnosis of AAV compared with 59% in the younger group ($P < 0.001$). Cardiovascular (CV) comorbidities (hypertension, diabetes mellitus, dyslipidaemia, CV or cerebrovascular ischaemic events) and malignancies were most frequently recorded for older patients (Table 2).

Clinical presentation

The clinical presentation at onset differed significantly between the two groups, as shown in Fig. 1A and B. Frequencies of specific organ system manifestations according to age groups are presented in Supplementary Table 1, available at *Rheumatology* online.

Patients from the younger-onset group had higher rates of musculoskeletal, cutaneous and ENT manifestations compared with older patients. Inflammatory arthritis was

Table 1 Distribution of diagnosis and ANCA according to age groups

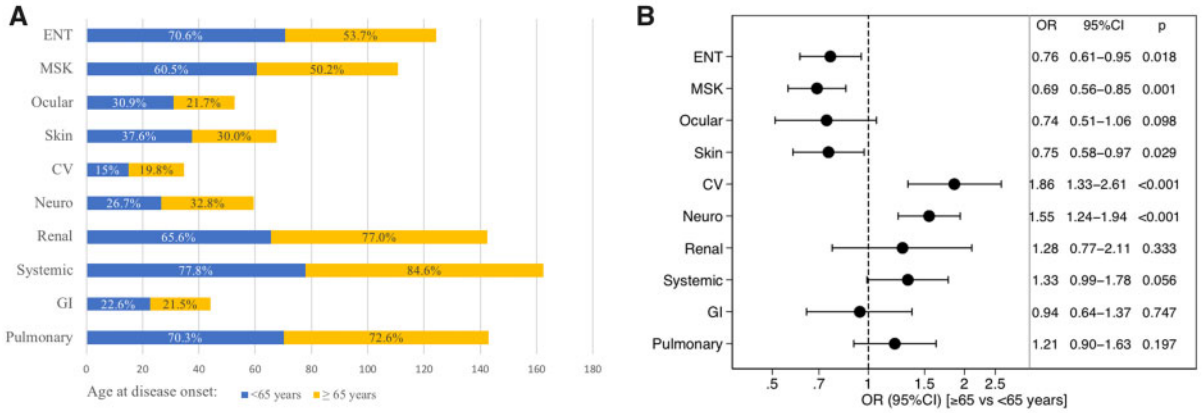
Diagnosis	Younger-onset AAV < 65 years old ($n = 878$)	Older-onset AAV ≥ 65 years old ($n = 460$)	*P*-value
Type of AAV			<0.001
GPA, *n* (%)	536 (61)	199 (44)	
MPA, *n* (%)	189 (22)	66 (15)	
EGPA, *n* (%)	148 (17)	186 (41)	
ANCA-PR3, *n* (%)	421 (48)	161 (35)	0.001
ANCA-MPO, *n* (%)	240 (27)	222 (48)	<0.001
ANCA negative, *n* (%)	160 (18)	59 (13)	0.02

Table 2 Demographic data and baseline comorbid conditions according to age groups

Outcome variable	Younger-onset AAV <65 years ($n = 878$)	Older-onset AAV ≥65 years ($n = 460$)	Univariable OR (95% CI) for age ≥65 *vs* <65 years	*P*-value	Multivariable OR (95% CI) for age ≥65 *vs* <65 years	Adjusted *P*-value[a]
Sex, *n* (%)						
Female	439 (50)	247 (53.7)				
Male	439 (50)	213 (46.3)	0.86 (0.69, 1.07)	0.545	0.92 (0.72, 1.19)	0.174
Smoker, *n* (%)						
Never	532 (60.6)	250 (54.3)				
Current/previous	346 (39.4)	210 (45.6)	1.29 (0.97, 1.72)	0.077	1.31 (0.99, 1.74)	0.062
Comorbidities, *n* (%)						
None	360 (41)	70 (15.2)	0.26 (0.19, 0.36)	<0.001	0.26 (0.20, 0.33)	<0.001
Hypertension	173 (19.7)	197 (42.8)	3.05 (2.24, 4.16)	<0.001	2.75 (1.98, 3.82)	<0.001
Diabetes mellitus	51 (5.9)	68 (14.8)	2.76 (2.01, 3.79)	<0.001	2.56 (1.74, 3.75)	<0.001
Dyslipidaemia	62 (7.1)	84 (18.3)	2.94 (2.29, 3.76)	<0.001	2.82 (2.01, 3.94)	<0.001
Coronary heart disease	30 (3.4)	53 (11.5)	3.68 (2.56, 5.29)	<0.001	3.59 (2.53, 5.08)	<0.001
Heart failure	5 (0.6)	10 (2.2)	3.88 (1.17, 12.84)	0.026	4.71 (1.24, 17.91)	0.023
Stroke	9 (1)	17 (3.7)	3.71 (1.82, 7.56)	<0.001	3.79 (1.90, 7.56)	<0.001
Peripheral vascular	7 (0.8)	14 (3)	3.91 (2.29, 6.64)	<0.001	3.40 (1.34, 5.05)	0.022
COPD	20 (2.3)	40 (8.7)	4.09 (2.58, 6.47)	<0.001	2.96 (1.92, 4.55)	<0.001
Asthma	161 (18.3)	56 (12.2)	0.62 (0.45, 0.84)	0.002	1.10 (0.79, 1.54)	0.057
Malignancy	27 (3.1)	55 (11.9)	4.28 (2.83, 6.48)	<0.001	4.25 (2.70, 6.67)	<0.001

[a]Adjusted for diagnosis and ANCA status.
COPD: chronic obstructive pulmonary disease.

FIG. 1 Age and clinical presentation[a]



(**A**) Frequency of involvement of various organ systems at clinical presentation according to age groups. (**B**) Effect of age at disease onset on clinical presentation. [a]Adjusted for diagnosis and ANCA status. MSK: musculoskeletal; Neuro: neurological; GI: gastrointestinal.

the most frequently reported musculoskeletal feature in the younger group (51.6% *vs* 33.7%; $P < 0.001$) while muscle weakness was more frequent in older patients (11.1% *vs* 7.6%; $P = 0.02$). Cutaneous involvement represented by papular lesions was mainly reported in younger patients. All types of ENT manifestations were more frequent in younger patients, even after adjusting for diagnosis type. Within subgroups, exploratory descriptive analyses revealed that ENT involvement was particularly more frequent in GPA and in PR3-ANCA-positive patients who were younger. Significant differences were reported for the frequency of bloody nasal discharge, nasal blockage, anosmia, ageusia, nasal ulcers, septal perforation, hoarse voice and subglottic stenosis (Supplementary Table 1, available at *Rheumatology* online).

Subgroup analyses of the effect of age adjusted for diagnosis and ANCA type on clinical manifestations, detailed for each subgroup, are presented in Supplementary Table 4, available at *Rheumatology* online. The effect of age was not modified by any confounder factor except for musculoskeletal involvement and neurological involvement, for which the effect of age was concomitantly modified by PR3-ANCA positivity and GPA diagnosis, respectively.

Systemic symptoms and neurologic and CV involvement were more frequent in the older-onset group (Fig. 1). In terms of systemic manifestations, fatigue was significantly more frequent in older-onset patients (68.3% *vs* 56.6%; $P = 0.01$). Night sweats occurred in 25.9% of younger-onset patients compared with 18.3% in older-onset patients ($P = 0.002$). The higher reported frequency of neurologic manifestations in the older group was mainly motor and sensory neuropathies, peripheral nerve involvement in general and, rarely, transient ischaemic attacks. (Supplementary Table 1, available at *Rheumatology* online). CV manifestations were prominent in the older group, with a higher frequency of congestive heart failure, arrhythmia and murmur. Renal involvement was predominant in older-onset patients in terms of impaired renal function, proteinuria and microscopic haematuria. However, after adjusting for diagnosis and ANCA status, only increased creatinine/reduced GFR remained significant: 57.7% of cases in the older group had an abnormally high creatinine/reduced GFR attributed to active vasculitis *vs* 35.3% of the younger group.

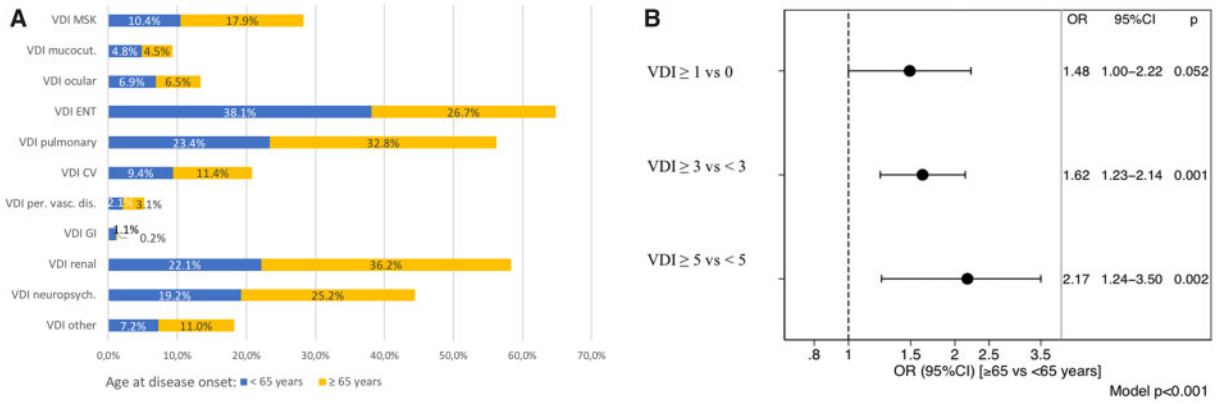
Overall, ocular, pulmonary and gastrointestinal disease manifestations were equally distributed between the two age groups (Supplementary Table 1, available at *Rheumatology* online). Ocular involvement within the PR3-ANCA subgroup was more frequent in the younger group, as was skin involvement in MPO-ANCA-positive patients. For pulmonary involvement, the only significant difference between groups was for minor haemoptysis (16.7% in the younger group *vs* 10.6% in the older group; $P < 0.001$). Pulmonary function test abnormalities did not differ between the two groups except for a reduced diffusion capacity of carbon monoxide (DLCO) being more frequent in older-onset patients (Supplementary Table 1, available at *Rheumatology* online). The only gastrointestinal manifestations that differed were abdominal pain and bloody diarrhoea, both more commonly reported in the younger-onset group.

Laboratory findings, after adjustment for diagnosis and ANCA status, were not significantly different according to age at diagnosis except for a higher rate of elevated inflammatory markers, ESR and/or CRP, mainly occurring in the older group (Supplementary Table 2, available at *Rheumatology* online).

Damage accrual

Damage accrual measured with the VDI was significantly higher in patients in the older group, of whom 12% had a 6 month VDI score ≥ 5, compared with 7% of patients in the younger-onset group ($P = 0.01$). Individual VDI

FIG. 2 Age and damage accrual[a]



(**A**) VDI items at the 6 month follow-up according to age groups. (**B**) Effect of age on increasing damage accrual (VDI scores categorized into 0, 1–2, 3–4 and ≥5). [a]Adjusted for diagnosis and ANCA status. MSK: musculoskeletal; mucocut: mucocutaneous; per.vasc.dis.: peripheral vascular disease; GI: gastrointestinal; neuropsych: neuropsychiatric.

TABLE 3 Multivariable analysis of the factors associated with increased mortality

Factors	Deaths, *n*	Rate per 100 person-years (95% CI)[a]	HR	95% CI	*P*-value
Age, years					
<65	13	4.01 (2.40, 7.23)	1		
≥65	22	12.49 (6.45, 24.68)	1.93	1.09, 3.44	0.030
Impaired renal function[b]					
No	8	2.83 (1.64, 5.09)	1		
Yes	26	12.56 (7.76, 20.88)	2.32	1.08, 4.99	0.024
Respiratory failure					
No	23	5.05 (3.03, 8.82)	1		
Yes	12	26.72 (14.37, 51.27)	4.66	1.74, 12.47	0.002
Diagnosis					<0.001
GPA	12	4.37 (2.92, 6.87)	1		
MPA	19	15.26 (7.99, 31.63)	3.85	2.24, 6.63	<0.001
EGPA	4	4.22 (1.67, 12.47)	2.96	0.84, 10.38	0.233
ANCA[c]					0.014
Negative	2	2.46 (0.59, 19.22)	1		
PR3-ANCA	11	5.06 (3.19, 8.99)	6.94	0.98, 49.63	0.053
MPO-ANCA	20	11.51 (5.64, 25.84)	3.31	0.37, 29.62	0.284

Model $P < 0.001$; naïve Harrell's C = 0.80; test validating Harrell's C = 0.68 (95% CI 0.50, 0.86).
[a]No significant interactions between age and diagnosis or ANCA type ($P < 0.05$ in all cases).
[b]Data missing in 1 patient.
[c]Data missing in 2 patients.

items according to age groups are presented in Fig. 2A and Supplementary Table 3, available at *Rheumatology* online. Older age is significantly associated with a 2-fold increased risk of higher VDI scores [OR 2.17 (95% CI 1.24, 3.50), $P = 0.002$; Fig. 2B]. Subgroup analyses of the effect of age adjusted for diagnosis and ANCA type on the VDI, detailed for each subgroup, are presented in Supplementary Table 5, available at *Rheumatology* online, confirming no modification of the effect of age on damage.

Mortality

There were 13 (1.49%) deaths recorded in the younger-onset group and 22 (4.8%) in the older-onset group within 6 months from diagnosis. In the multivariable analysis, older age conferred an independent risk of early mortality, even after adjusting for diagnosis, ANCA specificity, respiratory failure and impaired renal function at presentation [HR 2.06 (95% CI 1.07, 3.97), $P = 0.03$]. The apparent model discrimination was excellent (naïve Harrell's C = 0.80), although it decreased to 0.68 (95%

CI 0.50–0.86) with the testing validating approach (Table 3). Kaplan–Meier survival curves are presented in Supplementary Fig. 1, available at *Rheumatology* online. Subgroup analyses of the factors associated with increased mortality are shown in Supplementary Table 6. The causes of death were as follows: pulmonary haemorrhage (2 cases in each group), renal failure (3 in the younger group *vs* 1 in the older group), myocardial infarction (1 in the younger group *vs* 4 in the older group), malignancy (1 in the older group), infections (3 in the younger group *vs* 10 in the older patients) and unknown (4 in the younger group *vs* 4 in the older group).

Discussion

The effects of ageing on physiological and pathological processes are gaining increasing interest with the lengthening of life expectancy and the improved prognosis of several conditions, including AAV. This is the first large study demonstrating that age at disease onset appears to influence the clinical presentation and prognosis of AAV. We demonstrated that age >65 years is an independent risk factor for significant damage accrual and mortality in the early phases (the first 6 months) of the disease. Recently there has been a move to classify AAV based on clinical presentation or ANCA status rather than clinical diagnosis [14–16]. To fully capture the impact of age at disease onset on the clinical presentation and course of disease we adjusted all comparisons for the type of AAV (anti-PR3, anti-MPO or negative).

Consistent with previous epidemiologic data [17], we demonstrated that patients with MPA were more likely to be >65 years of age, while EGPA and GPA were more frequent in the younger group. AAV is generally considered a disease of older people, with a peak incidence in the 6th–7th decades of life [18]. However, in this large international cohort, 66% of patients had disease onset at <65 years of age. This finding does not seem to be related to increased disease awareness and earlier diagnosis, since the diagnostic delay was more frequent in the younger group. It is possible that following the onset of AAV, an older patient with pre-existing comorbidity might seek medical attention earlier than an otherwise previously healthy younger individual. The severity of clinical manifestations (with more prominent systemic, neurologic and renal symptoms in the older group) might also explain the difference in time to diagnosis. The management of a potentially life-threatening systemic disease in older patients poses a series of challenges [19]. We demonstrated that 85% of older patients have at least one comorbid condition, mainly CV disease. The CV burden is further increased in AAV beyond that associated with traditional risk factors [20, 21]. Older age has previously been identified as a risk factor for the development of CV events within 5 years from the diagnosis of GPA or MPA [22].

In this study, cardiovascular manifestations were significantly more frequent as the initial presentation of AAV in the older-onset group. The development of new CV risk factors, particularly the VDI item 'diabetes', was also significantly more common in older patients. Our data highlight the need for a personalized approach to implement a CV risk management approach at least in patients with a diagnosis of AAV at an older age.

This study demonstrated that older-onset patients experience severe manifestations of disease with predominant neurologic, CV, renal (in terms of worsening renal function) and systemic manifestations compared with the more common musculoskeletal, cutaneous and ENT manifestations in the younger group. Bomback *et al.* [9] reported on the benefit of immunosuppression in reducing the risk of death and end-stage renal disease (ESRD) even in the oldest patients (>80 years) with glomerulonephritis in AAV. Nevertheless, the results of the only randomized trial specifically addressing a tailored therapeutic approach to older patients (≥65 years) with AAV addressed the significantly higher risk of this group of patients to develop serious adverse events, particularly infections. The trial demonstrated that reduced glucocorticoid and cyclophosphamide regimens are safer in older patients without affecting the remission rates [23].

This study demonstrated a higher mortality rate in the very early stages of the disease (first 6 months from diagnosis) in patients with disease onset at ≥65 years. Although we did not perform an adjustment for expected age-related mortality rates, only three patients in the older group were ≥85 years of age and 87% of patients were <80 years of age. Therefore we can speculate that the excessive mortality rate due to age itself, independent of vasculitis- or treatment-related complications, was not the main determinant for reduced survival in our study population. In the multivariable analysis, older age conferred an increased risk of early mortality together with impaired renal function and respiratory failure at onset, as well as diagnosis and PR3-ANCA. Nevertheless, an analysis of four European Vasculitis Study Group trials reported that the majority (59%) of early deaths within 1 year from AAV diagnosis are attributable to adverse events rather than to disease complications [24]. In our cohort, infections represented the cause of death in 54% of older-onset patients compared with 23% in the younger group. Harper and Savage [25] retrospectively collected outcome data on 233 patients with AAV who were >65 years of age compared with a younger cohort and reported a significantly increased risk of infections in this age group associated with poor prognosis. Higher infection rates have been attributed to increased rates of pulmonary involvement in AAV patients with older onset [26]. We did not find an age-specific trend for lung involvement; however, we did demonstrate a correlation between respiratory failure at diagnosis and a 4-fold increased mortality risk. We observed that older patients are at higher risk of accumulating damage in the early phase of disease with significantly higher VDI scores (mainly due to renal and treatment-related complications components).

The results of the study highlight the importance of optimizing preventive strategies to reduce the risk of infections and damage accrual, especially in patients newly diagnosed with AAV at ≥65 years of age. A tighter follow-up might be warranted in these patients to detect these complications early and potentially prevent excessive death risk.

Our study has some limitations. We made use of data collected from the DCVAS study, which was not an epidemiological study to assess the prevalence of AAV by age. There is a potential recruitment bias based on disease severity that might have been unbalanced between age groups. We performed multiple exploratory analyses based on detailed presenting symptoms that might have an impact on the statistical significance of the results. Nevertheless, only a limited number of variables were assessed as correlated outcomes assessed in the study. Moreover, we could not analyse the presence of differences in therapeutic choices, effectiveness and safety between age groups. This does not allow us to consider unbalanced treatment choices as a potential confounding factor for the assessed outcomes. The relatively short follow-up does not allow assessment of the long-term influence of age at diagnosis. Previous reports have demonstrated significantly higher mortality rates, especially in the first year after diagnosis, with a reduction in the mortality risk thereafter [9]. Long-term studies are needed to address this aspect. The higher age-related mortality expected in the older group and a selection bias towards more patients with more severe disease need to be considered as potential sources of bias for these findings. Nevertheless, this is the largest prospective study conducted to date to assess the influence of age on the clinical presentation and outcome of AAV, demonstrating a series of age-specific characteristics and challenges that will be useful to improve a more personalized management of what it is now considered to be a disease of older patients.

Conclusion

In conclusion, this study describes age-related clinical differences in disease presentation and short-term outcomes among patients with newly diagnosed AAV, with worse damage accrual and increased risk of mortality in patients with older onset of disease. These findings raise interesting questions about the interplay between age and disease pathogenesis in this complex set of diseases.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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