Title

The Association Between Age at Diagnosis and Disease Characteristics and Damage in Patients With ANCA-Associated Vasculitis.

Journal

Arthritis and Rheumatology, 75(12)

Authors

Corbridge, Thomas

Khalidi, Nader

Koening, Curry

et al.

Publication Date

2023-12-01

DOI

10.1002/art.42651

Peer reviewed

HHS Public Access

Author manuscript

Arthritis Rheumatol. Author manuscript; available in PMC 2024 February 16.

Published in final edited form as:

Arthritis Rheumatol. 2023 December ; 75(12): 2216–2227. doi:10.1002/art.42651.

The Association Between Age at Diagnosis and Disease Characteristics and Damage in Patients with ANCA-Associated Vasculitis

Jessica L. Bloom, MD MSCS[1], **Kaci Pickett, MS**[1], **Lori Silveira, PhD**[1], **Robert C. Fuhlbrigge, MD PhD**[1], **David Cuthbertson, MS**[2], **Praveen Akuthota, MD**[3], **Thomas C. Corbridge, MD**[4], **Nader A. Khalidi, MD FRCPC**[5], **Curry L. Koening, MD MS**[6], **Carol A. Langford, MD MHS FACP**[7], **Carol A. McAlear, MA**[8], **Paul A. Monach, MD PhD**[9], **Larry W. Moreland, MD**[1], **Christian Pagnoux, MD MPH MSc**[10], **Rennie L. Rhee, MD MSCE**[8], **Philip Seo, MD MHS**[11], **Jared Silver, MD**[4], **Ulrich Specks, MD**[12], **Kenneth J. Warrington, MD**[13], **Michael E. Wechsler, MD MMSc**[14], **Peter A. Merkel, MD MPH**[8] **Vasculitis Clinical Research Consortium**

[1.]University of Colorado, Denver, CO, USA

[2.]University of South Florida, South Florida, Florida, USA

[3.]University of California San Diego, La Jolla, CA, USA

[4.]US Medical Affairs - Respiratory GSK, Durham, NC, USA

[5.]St. Joseph's Healthcare Hamilton, McMaster University, Ontario, Canada

[6.]University of Utah, Salt Lake City, UT, USA

[7.]Cleveland Clinic, Cleveland, OH, USA

[8.]University of Pennsylvania, Philadelphia, PA, USA

[9.]Brigham and Women's Hospital, Boston, MA, USA

[10.]Mount Sinai Hospital, Toronto, Canada

[11.]Johns Hopkins University, Baltimore, MD, USA

[12.]Mayo Clinic, Rochester, MN, USA

[13.]Mayo Clinic, Rochester, MN, USA

[14.]National Jewish Health, Denver, CO, USA

Abstract

Objective: This study examined the relationship between age at diagnosis and disease characteristics and damage in patients with ANCA-associated vasculitis (AAV).

Methods: Analysis of a prospective longitudinal cohort of patients with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA) in the

Corresponding Author: Jessica L. Bloom, MD, MSCS, Department of Pediatrics, Section of Pediatric Rheumatology, University of Colorado Anschutz Medical Campus, 12123 East 16th Avenue B-311, Aurora, CO 80045, T: 720-777-6132, F: 720-777-7341, Jessica.Bloom@childrenscolorado.org.

Vasculitis Clinical Research Consortium (2013-2021). Disease cohorts were divided by age at diagnosis (years): children (< 18), young adults (18-40), middle-aged adults (> 40-65), and older adults (> 65). Data included demographics, ANCA type, clinical characteristics, Vasculitis Damage Index (VDI) scores, ANCA Vasculitis Index of Damage (AVID) scores, and novel disease-specific and non-disease-specific damage scores built from VDI and AVID items.

Results: Analysis included data from 1020 patients with GPA/MPA and 357 with EGPA. Female predominance in GPA/MPA decreased with age at diagnosis. AAV in childhood was more often GPA and PR3-ANCA positive. Children with GPA/MPA experienced more subglottic stenosis and alveolar hemorrhage, Children/young adults with EGPA experienced more alveolar hemorrhage, need for intubation, and gastrointestinal involvement. Older adults (GPA/MPA) had more neurologic manifestations. After adjusting for disease duration, medications, tobacco, and ANCA, all damage scores increased with age at diagnosis for GPA/MPA ($p < 0.001$) except the disease-specific damage score which did not differ ($p = 0.44$). For EGPA, VDI scores increased with age at diagnosis ($p < 0.009$) while all other scores were not significantly different.

Conclusion: Age at diagnosis is associated with clinical characteristics in AAV. While VDI and AVID scores increase with age at diagnosis, this is driven by non-disease-specific damage items.

Keywords

ANCA; ANCA-Associated Vasculitis; Damage Index; Outcome Measures; Pediatric Rheumatology

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) represents a group of systemic autoimmune diseases that cause inflammation of small- to medium-sized arteries and may be diagnosed in any decade of life. The 3 AAV subtypes include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (1).

While AAV in children is rare, with an estimated incidence of 0.45 to 6.4 cases per million children per year, most children with AAV present at onset with life- or organ-threatening disease (2-4). Incidence in adults is higher at 17.2 per million adult person-years (95% CI: 13.3,21.6) and the spectrum of disease at presentation is much broader (5).

Clinical characteristics and outcomes of rheumatic disease often differ for patients diagnosed with the same condition across the lifespan. This is well-documented in systemic lupus erythematosus: those diagnosed in childhood have more neurologic and renal manifestations and a higher standardized mortality ratio than those diagnosed as adults (18.3 vs 3.1 respectively) (6). However, such comparative data is limited in AAV as children are often excluded from studies, with most work arising from the Pediatric Vasculitis Initiative in Canada and the French Vasculitis Study Group Registry (3,4,7).

As a chronic condition, AAV is measured by both disease activity and accumulated damage, with damage usually defined as irreversible consequences of the disease or treatment. The instruments used to assess damage in AAV include items that are not specific to AAV itself,

such as damage specific to other forms of vasculitis, medication toxicity, and comorbidities, limiting the ability to understand the impact of disease as it relates to age (8). Prior studies showed increased overall damage with age; however, this was based solely on the Vasculitis Damage Index (VDI) and a binary age cut-off of 65 years. Additionally, the investigators used age at enrollment rather than age at diagnosis and combined data from several vasculitides (9,10).

The objective of this study was to examine the relationship between age at diagnosis and disease characteristics and damage in patients with AAV. Through an innovative approach, patients diagnosed with AAV were captured during childhood in an adult-based registry and both disease-specific and non-disease-specific damage scores were developed to further assess damage across age in disease groups. The hypothesis was that there would be differences in disease characteristics and non-disease-specific damage across age at diagnosis groups but that disease-specific damage would be similar.

MATERIALS AND METHODS

Study Design and Population

This was an analysis of data from a prospective longitudinal cohort of adults with GPA, MPA, or EGPA, as classified by the 1990 American College of Rheumatology Classification Criteria or the 2012 Chapel Hill Consensus Conference, enrolled in the Vasculitis Clinical Research Consortium (VCRC) Longitudinal Studies from 2013 to 2021 (NCT00315380). The VCRC Longitudinal Studies are observational cohorts consisting of physician- and patient-reported data collected prospectively on patients enrolled at expert centers in the United States and Canada.

Study Variables

Data collected included demographics, ANCA type, and clinical characteristics at diagnosis and ever up until a patient's last study visit. “Ever” was defined as the presence of a characteristic at any time over the course of the patient’s disease, regardless of whether it was present at diagnosis or the patient’s most recent visit. “Unknown” responses were considered missing for each variable. This study concentrated on the more severe disease characteristics and those for which there were a priori insights into possible age-related differences. Use of rituximab (RTX) and cyclophosphamide (CYC) was assessed before and after 2012, the year following approval of RTX by the Food and Drug Association for adults with severe GPA and MPA.

Damage was assessed through the Vasculitis Damage Index (VDI), a 64-item validated damage index created for use in systemic vasculitides with a maximum score of 64, and the ANCA Vasculitis Index of Damage (AVID), an index created specifically for AAV with a maximum score of 112 (Supplementary Figures 1 and 2) (8,11). Additional scores were created using input from experts in the field to further explore the relationship between damage and age at diagnosis. To create the novel scores, all damage items from VDI and AVID were divided into items specific to AAV (e.g., bony erosions of sinuses, subglottic stenosis, and motor neuropathy) and items not-specific to AAV (e.g. osteoporosis,

drug-induced cystitis, striae, and malignancy) that are specific to other forms of vasculitis, medication toxicity, and comorbidities. These items were aggregated to create the AAV-Disease-Specific Damage Score (AAV-DSDS, Figure 1) and the AAV-Non-Disease-Specific Damage Score (AAV-Non-DSDS, Supplementary Figure 3). Items were grouped together within each new score so that similar items from both VDI and AVID would only count for one point. When VDI and AVID are scored, all damage items are weighted equally. The VDI hearing loss item was removed in order to avoid matching it with both the conductive and sensorineural hearing loss items in AVID, as only 14 registry participants had the VDI hearing loss item without either AVID hearing loss item. In an effort to make the AAV-DSDS as highly disease-specific as possible, any item only occasionally specific to AAV (such as visual impairment and angina) was allocated to the AAV-Non-DSDS. An AAV-Total Damage Score (AAV-TDS) was also created to combine all VDI and AVID items into one score with point groupings similar to the AAV-DSDS and AAV-Non-DSDS (Supplementary Figure 4). The maximum scores for the AAV-DSDS, AAV-Non-DSDS, and AAV-TDS were 19, 47, and 60 for GPA/MPA and 21, 45, and 60 for EGPA, respectively.

Patients were divided by age at diagnosis into four cohorts: children (diagnosed at < 18 years old), young adults (diagnosed from 18-40 years old), middle-aged adults (diagnosed at > 40 to 65 years old), and older adults (diagnosed at > 65 years old). The primary analytic cohorts were GPA or MPA (GPA/MPA), and EGPA. GPA and MPA are routinely studied together in cohorts and clinical trials, while EGPA is most frequently studied separately from GPA/MPA. For cohorts with EGPA, all patients diagnosed at 40 years old or younger were combined into one “children/young adults” age at diagnosis group due to smaller sample sizes. Sub-analyses further stratified within disease-types by ANCA status: PR3-ANCA, MPO-ANCA, and ANCA-negative.

Statistical Analysis

Descriptive statistics were summarized by means and standard deviation (sd) or median and interquartile range [IQR] for normally and non-normally distributed continuous variables, respectively. Categorical variables were presented as frequencies and proportions. Differences among age at diagnosis groups were tested via t-test or Kruskal-Wallis test for continuous variables dependent on distribution and Chi Squared test or Fisher’s Exact test for categorical variables dependent on cell size. Associations between age at onset of symptoms, age at diagnosis, and disease duration at last follow-up were assessed with Pearson’s correlations. Statistical significance was set at 0.05.

Multivariable linear regression was used to estimate differences (with 95% Confidence Intervals) in damage scores between age categories. These models adjusted for disease duration at time of the most recently-updated damage score (measured from symptom onset), medication use (RTX, CYC, neither, or both), tobacco use, and ANCA type (MPO, PR3, or neither). A sensitivity analysis also assessed the effects of continuous age on the damage scores, using the same adjustment variables. Due to the multiple comparisons with the five damage scores, significance level for the linear regressions was set at 0.01. R version 4.1.2 software (R Foundation for Statistical Computing, Vienna, Austria, http://

www.R-project.org/) and SAS, version 9.4 (SAS Institute, Cary, NC) were utilized for statistical analyses.

RESULTS

Manifestations of disease based on age at diagnosis of ANCA-associated vasculitis

Granulomatosis with Polyangiitis/Microscopic Polyangiitis—Data from 1020 patients with GPA/MPA were analyzed by age at diagnosis: 61 children (diagnosed at < 18 years old), 240 young adults (diagnosed from 18-40 years old), 560 middle-aged adults (diagnosed at > 40 to 65 years old), and 159 older adults (diagnosed at > 65 years old). The demographic and clinical characteristics of those with GPA or MPA stratified by age at diagnosis are listed in Table 1. Fifty-five percent of patients were female, with a female predominance in all age at diagnosis groups that decreased with age: 75% of children, 62% of young adults, 51% of middle age, and 52% of older adults ($p < 0.001$). Eighty-four percent of patients had GPA and 16% had MPA. GPA was more common in children and young adults (90% and 94% respectively vs 64% of older adults), while MPA was more common in older adults (34% vs 10% of children and 6% of young adults). Ninety-two percent of patients with ANCA testing results were ANCA-positive: 65% had PR3-ANCA, 25% had MPO-ANCA, and 1% had both PR3- and MPO-ANCA, with significantly different ANCA type proportions by age ($p < 0.001$). Seventy-seven percent of children and young adults were PR3-ANCA, which decreased to 64% in middle age and 50% in older adults. MPO-ANCA-positivity was more common in older adults (45% vs 18% of children).

Those diagnosed in childhood experienced more subglottic stenosis (21% at diagnosis, 31% ever), alveolar hemorrhage (38% at diagnosis, 39% ever), and gastrointestinal disease (8% at diagnosis, 10% ever) than older age at diagnosis groups, especially older adults (2% with subglottic stenosis at diagnosis and ever, 26% with alveolar hemorrhage at diagnosis, 28% with alveolar hemorrhage ever, 2% with gastrointestinal disease at diagnosis and ever) (all p-values < 0.05). Those diagnosed as older adults had less ocular, nasal septal perforation, sinus disease, and musculoskeletal disease at diagnosis and ever and more nervous system manifestations (28% at diagnosis, 30% ever) than younger age at diagnosis groups (i.e., 17% of children at diagnosis and ever, 16% of young adults at diagnosis and ever) (all p-values < 0.05). With the exception of sinus disease, these results remained statistically significant when assessed in patients with GPA only, as well (Supplementary Table 1). Notably, only musculoskeletal disease at diagnosis and ever, cutaneous disease ever, and nervous system disease ever remained statistically significant when assessed in patients with MPA only. Cutaneous disease at diagnosis was newly significant in this population, with increased cutaneous findings in children and young adults (Supplementary Table 2).

Results for patients with PR3-ANCA, MPO-ANCA, and ANCA-negative GPA/MPA were similar to the overall GPA/MPA cohort (Supplementary Table 3). All age at diagnosis groups had female predominance that waned with age, though the MPO-ANCA cohort was not statistically significant (PR3: $p < 0.001$, ANCA negative: $p = 0.048$, MPO: $p = 0.110$). Similar to the GPA/MPA overall cohort, patients with MPO-ANCA had fewer ocular manifestations when diagnosed as older adults ($p = 0.018$). PR3-ANCA patients had more alveolar hemorrhage ($p < 0.001$) and gastrointestinal disease ($p = 0.007$) when diagnosed in

childhood and less musculoskeletal ($p < 0.001$), and more neurologic disease ($p = 0.031$) when diagnosed as older adults. Children and young adults had more subglottic stenosis at diagnosis in the MPO- and PR3-ANCA cohorts, and ever in all 3 ANCA cohorts. Unlike the GPA/MPA overall cohort, there were differences in constitutional symptoms at diagnosis across PR3-ANCA age at diagnosis groups (85% of children, 77% of young adults, 88% of middle-aged adults, 76% older adults) ($p = 0.006$) and cardiac disease at diagnosis across ANCA-negative cohorts (0% of children and middle-aged adults, 6% of young adults, 25% of older adults) ($p = 0.017$).

Eosinophilic Granulomatosis with Polyangiitis—Data from 357 adult patients with EGPA were analyzed by age at diagnosis: 87 children or young adults, 207 middle-aged adults, and 63 older adults. The demographic and clinical characteristics of those with EGPA, stratified by age at diagnosis are listed in Table 2. There was no significant difference in sex between age at diagnosis groups ($p = 0.180$), although each age at diagnosis group had a female predominance with 56% female patients overall. Forty percent of patients with ANCA results were ANCA positive: 2% had PR3-ANCA, 38% had MPO-ANCA, and < 1% had both PR3- and MPO-ANCA, with differences in ANCA type by age ($p = 0.002$). Forty-seven percent of older adults were MPO-ANCA, which decreased to 42% in middle age and 18% in children and young adults. Seventy-eight percent of children and young adults, 56% of middle-aged adults, and 51% of older adults with EGPA were ANCA-negative.

Those diagnosed as children or young adults experienced more alveolar hemorrhage (12% at diagnosis and ever), need for intubation (10% at diagnosis and ever), and gastrointestinal involvement (26% at diagnosis, 29% ever) than older age at diagnosis groups at diagnosis and ever, especially older adults (3% with alveolar hemorrhage, 2% with need for intubation, 10% with gastrointestinal involvement) (all p-values < 0.05). Those diagnosed as older adults had a lower rate of cutaneous findings (38% at diagnosis, 40% ever) than younger age at diagnosis groups, particularly children/young adults (61% at diagnosis, 64% ever) (all p-values < 0.05). No other manifestations were different across age at diagnosis groups. Approximately one third of patients had cardiac manifestations at diagnosis and/or ever.

Results for patients with MPO-ANCA and ANCA-negative EGPA were similar to the overall EGPA cohort (Supplementary Table 4). Similar to the overall EGPA cohort, patients with MPO-ANCA had less cutaneous findings at diagnosis ($p = 0.006$) and ever ($p = 0.003$) when diagnosed as older adults while patients who were ANCA-negative had a greater need for intubation at diagnosis ($p = 0.023$) when diagnosed as children/young adults.

Medications ever received for the treatment of ANCA-associated vasculitis, based on age at diagnosis

Granulomatosis with Polyangiitis (GPA)/Microscopic Polyangiitis (MPA)—Over half of patients with GPA/MPA diagnosed in childhood received both CYC and RTX, a rate that decreased with older age at diagnosis (52% of children, 37% young adults, 27% middle-aged adults, and 14% of older adults) (Supplementary Figure 5A). There was a significant difference in the distribution of CYC and/or RTX ever received by patients with

GPA/MPA stratified by age at diagnosis before and after 2012 in children/young adults and middle-aged groups ($p < 0.0001$) but not older adults ($p = 0.07$) (Figure 2A). By pairwise comparisons, these proportions were significantly different before and after 2012 for all medication levels except the neither RTX nor CYC group ($p < 0.01$).

Eosinophilic Granulomatosis with Polyangiitis—Five percent of children/young adults, 5% of middle-aged, and 5% of older adults with EGPA received both CYC and RTX. Twenty-six percent of children/young adults received CYC only versus 41% of older adults; 59% of children/young adults received neither CYC nor RTX versus 46% of older adults (Supplementary Figure 5B). The only age at diagnosis group with a significant difference in proportions of medications ever received stratified by age at diagnosis before and after 2012 was the middle-aged group ($p = 0.007$). By pairwise comparison, the proportions of patients treated with RTX only were significantly different between the time periods ($p < 0.01$), but there were no significant differences in the rates of CYC only, both RTX and CYC, or neither RTX nor CYC (Figure 2B).

Damage scores based on age at diagnosis of ANCA-associated vasculitis

Granulomatosis with Polyangiitis/Microscopic Polyangiitis—Nine hundred seventy-two and 1019 patients with GPA/MPA had VDI and AVID scores documented, respectively, and were included in the models. After adjusting for disease duration, medication use, tobacco use, and ANCA type, the VDI score of those diagnosed with GPA/MPA was associated with age at diagnosis ($p < 0.001$). The VDI score of those diagnosed as children was estimated to be 1.67 points lower than those diagnosed as older adults (95%CI: [−2.38, −0.96], $p < 0.001$) (Figure 3A). The AVID score of those diagnosed with GPA/MPA was also associated with age at diagnosis ($p < 0.001$). The AVID score of those diagnosed as children was estimated to be 2.46 points lower than those diagnosed as older adults (95%CI: [−3.72, −1.20], $p < 0.001$) (Figure 3B). The AAV-non-DSDS and AAV-TDS results were similar to that of the VDI and AVID, with higher damage scores with increased age at diagnosis (Figure 3D). However, there were no longer significant differences in damage scores based on age at diagnosis when assessing the AAV-DSDS ($p = 0.44$) (Figure 3C).

For patients with PR3-ANCA GPA/MPA, the VDI, AVID, AAV-Non-DSDS, and AAV-TDS scores increased with age at diagnosis for the majority of age at diagnosis group comparisons, all of these differences were no longer significantly different when utilizing the AAV-DSDS (Supplementary Figure 5). There were no significant differences in any scores for patients with MPO-ANCA GPA/MPA or ANCA-negative GPA/MPA (Supplementary Figures 6 and 7).

When assessing the average change in damage score for every year increase in age at diagnosis of GPA/MPA using the multivariate model, the VDI score increased by 0.024 for every year increase in age at diagnosis (95%CI: [0.015,0.033], $p < 0.001$). The AVID score increased by 0.031 (95%CI: [0.014, 0.047], $p<0.001$), the AAV-non-DSDS increased by 0.028 (95%CI: [0.019,0.037], $p<0.001$), and the AAV-TDS increased by 0.032 (95%CI:

[0.019,0.046], p<0.001). The AAV-DSDS did not significantly change for every year increase in age at diagnosis (p = 0.223).

Eosinophilic Granulomatosis with Polyangiitis—Two hundred seventy-five patients with EGPA had VDI and AVID scores documented and were included in the models. After adjusting for disease duration, medication use, tobacco use, and ANCA type, the VDI score of those diagnosed with EGPA was associated with age at diagnosis (p < 0.009). The VDI score of those diagnosed as children/young adults was estimated to be 1.01 points lower than those diagnosed as older adults (95%CI: [−1.78, −0.25], p < 0.01) (Figure 4A). Any significant differences in damage scores were no longer significantly different when assessed with the AAV-DSDS (p = 0.28) (Figure 4C). The AVID and AAV-Non-DSDS scores of those diagnosed with EGPA were not associated with age at diagnosis (p = 0.13 and p = 0.28) (Figure 4B). Similar results were also seen for patients with MPO-ANCA EGPA and ANCA-negative EGPA (Supplementary Figures 8 and 9). There were not enough PR3-ANCA EGPA patients for analysis.

When assessing the average change in damage score for every year increase in age at diagnosis of EGPA using the multivariate model, the VDI score increased by 0.025 for every year increase in age at diagnosis (95%CI: [0.007,0.042], p = 0.006). The AVID (p = 0.062), AAV-DSDS (p = 0.125), AAV-Non-DSDS (p = 0.409), and AAV-TDS (p = 0.071) scores did not significantly change for every year increase in age at diagnosis.

DISCUSSION

This analysis of a large cohort of patients with EPGA, GPA, and MPA found that age at diagnosis of AAV is associated with disease characteristics and damage. Female predominance in patients with GPA/MPA decreases with age at diagnosis while MPO-ANCA positivity in patients with GPA/MPA and EGPA increases with age at diagnosis. Compared to those diagnosed as adults, children with GPA/MPA experience certain severe manifestations more frequently, such as subglottic stenosis, alveolar hemorrhage, and gastrointestinal disease. These signs of severity occur in EGPA as well with children more likely to have alveolar hemorrhage, need for intubation, cutaneous manifestations, and gastrointestinal involvement. Those diagnosed with GPA/MPA in older adulthood experience more neurologic disease and less musculoskeletal and sinus disease.

This study also found that patients diagnosed with GPA/MPA at older ages have higher amount of accumulated damage than those diagnosed at younger ages, but that these differences are no longer significant when measuring disease-specific items. Thus, the differences in VDI and AVID scores between age at diagnosis groups are driven by non-disease-specific damage, such as damage specific to other forms of vasculitis, medication toxicity, and comorbidities. The significant differences between each pairwise age group comparison (apart from children versus young adults) and the continuous age analysis further emphasize the relevance of these findings across the lifespan. The results for patients with EGPA demonstrate a similar trend in which any scores that were significantly different between age at diagnosis groups (all of which increased with increasing age) were no longer different when non-disease-specific damage items were removed. Similar results for

the PR3-ANCA GPA/MPA cohort, MPO-ANCA EGPA cohort, and ANCA-negative EGPA cohort further reinforce the findings.

The novel reorganization of damage scores for this study uncovered the ways in which both disease-specific and non-disease-specific damage influence assessment of damage. The performance characteristics of damage assessment in AAV have not been well studied, including what constitutes meaningful differences or to what extent differential weighting of items would be appropriate. However, adopting a disease-specific approach to the measurement of damage is expected to provide greater specificity and responsiveness when utilized in research involving response to treatment. While both types of damage certainly negatively impact patients with AAV, clinicians and researchers must recognize the varying impact of non-disease-specific damage on damage scores across age at diagnosis groups when designing studies and interpreting data. There has long been an interest in incorporating such attribution to vasculitis and non-vasculitis for clinical trials in vasculitis and these data may offer evidence of the feasibility of doing so, even utilizing current outcome tools (12).

The results of the current study are consistent with, and expand on, the limited prior studies on the variation of characteristics in GPA and MPA across age at diagnosis groups, particularly those diagnosed in childhood (7,13). Differences in organ involvement, damage, and mortality risk have also been demonstrated between adults diagnosed before and after age 65 years (9,10). However, no prior studies have assessed characteristics and damage across the lifespan nor separated out the impact of disease-specific and non-disease-specific items on damage scores. Prior data on how EGPA differs across the lifespan is even more limited. It is interesting that such a large proportion of children and young adults diagnosed with EGPA were ANCA-negative. Confirmation in an independent cohort would be useful.

This study also demonstrated a difference in prescribing practices for AAV based on age at diagnosis, with younger age at diagnosis groups receiving both CYC and RTX more often than older age at diagnosis groups in GPA/MPA. A recent survey of pediatric rheumatologists across the United States reported a strong desire for age-specific management guidelines. However, without data comparing AAV in children to other age at diagnosis groups, it is challenging to know whether to adopt results from trials in older patients when treating children (14). A 2016 study assessing medication trends in children with AAV (primarily those with GPA/MPA) across the United States found an increase in use of RTX and decrease in use of CYC from 2004 to 2014 (15). The United States Food and Drug Administration approved RTX for use in adults with GPA/MPA in 2011. Not surprisingly, RTX use increased for all age at diagnosis groups diagnosed after 2012. RTX was ultimately approved for use in children 2 years and older with GPA/MPA in 2019, which has likely impacted the management practices observed for patients diagnosed as children and young adults (16).

This large, comprehensively characterized cohort provided the ability to longitudinally study patients diagnosed in childhood using an adult registry. This is critical as AAV in children is significantly understudied despite how age at disease onset could indicate varying genetic or environmental influences and have unique physical and psychosocial impact on patients,

particularly during puberty. Similarly, patients diagnosed in older age may also have a unique burden of comorbidities and/or physical or cognitive limitations, including risk of osteoporosis and dementia. While not based on age at diagnosis, a study by Thietart et al found that patients 75 years and older with GPA/MPA had a lower risk of relapse than those who were 65-75 years old, despite a lower probability of receiving maintenance therapy (17).

This study has several strengths. The use of adult registry data to analyze patients diagnosed with rare conditions in both childhood and adulthood provided insights into unique aspects of disease across the lifespan, for which data are otherwise limited. The large sample size also allowed for detailed analyses of disease subtypes. Additionally, data were collected prospectively using a protocol-based comprehensive data collection system at expert centers allowing for consistent longitudinal data collection and the ability to assess outcomes over time.

There are also limitations to this study to consider. The study population included fewer patients in the younger age at diagnosis groups, particularly for EGPA, as well as fewer MPA patients than GPA patients in the GPA/MPA cohort. Additionally, this analysis did not assess other maintenance therapies used to treat AAV (such as azathioprine, methotrexate, and mycophenolate mofetil in GPA/MPA or anti-interleukin-5 therapies in EGPA) and the data on damage do not reflect whether a younger age at diagnosis would allow for more time to accumulate damage following the end point of this study than an older age at diagnosis. The scores also do not account for the impact of AAV on growth and development, which may affect age at diagnosis groups differently.

As approaches to management of AAV based on age at diagnosis are developed and implemented, future studies will be vital to determine whether and how these differences, along with the continually shifting treatment paradigms, impact management decisions and clinical outcomes. For now, providers should consider these differences when evaluating and following patients with AAV. Further research could explore which non-disease-specific damage items primarily drive the age-related differences in VDI and AVID. Additionally, continued study and validation of a more disease-specific damage score for both children and adults with AAV may advance research methodology and address some of the limitations of the instruments currently used in clinical trials (8,11,18). The results from this study and future work will help develop a more targeted approach to studying and managing AAV in different age groups and ultimately lead to improved outcomes for patients across the lifespan.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial support:

The Vasculitis Clinical Research Consortium (VCRC) has received support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (U54 AR057319), the National Center for Research Resources (U54 RR019497), the Office of Rare Diseases Research (ORDR), and the National Center for Advancing Translational

Science (NCATS). The VCRC also receives funding from GlaxoSmithKline. Dr. Bloom is supported in part by a Vasculitis Clinical Research Consortium-Vasculitis Foundation Vasculitis Fellowship.

REFERENCES:

1. Jennette J. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Clin Exp Nephrol. 2013;17(5):603–606. [PubMed: 24072416]
2. Jariwala MP, Laxer RM. Primary Vasculitis in Childhood: GPA and MPA in Childhood. Front Pediatr. 2018;6:226. doi:10.3389/fped.2018.00226 [PubMed: 30167431]
3. Cabral DA, Canter DL, Muscal E, et al. Comparing Presenting Clinical Features in 48 Children With Microscopic Polyangiitis to 183 Children Who Have Granulomatosis With Polyangiitis (Wegener's): An ARChiVe Cohort Study. Arthritis & Rheumatology. 2016;68(10):2514–2526. doi:10.1002/art.39729 [PubMed: 27111558]
4. Cabral DA, Uribe ARG, Benseler S, et al. Classification, presentation, and initial treatment of Wegener's granulomatosis in childhood. Arthritis & Rheumatism. 2009;60(11):3413–3424. doi:10.1002/art.24876 [PubMed: 19877069]
5. Redondo-Rodriguez R M-V N, Cabezas-Lucena AM, Manrique-Arija S, Mucientes A, Fernández-Nebro A. Systematic Review and Metaanalysis of Worldwide Incidence and Prevalence of Antineutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis. J Clin Med. May 4 2022;11(9):2573. [PubMed: 35566698]
6. Ambrose N, Morgan T, Galloway J, Ionnoau Y, Beresford M, Isenberg D. Differences in disease phenotype and severity in SLE across age groups. Lupus. 2016;25:1542–1550. [PubMed: 27147622]
7. Iudici M, Pagnoux C, Quartier P, et al. Childhood- versus adult-onset ANCA-associated vasculitides: A nested, matched case-control study from the French Vasculitis Study Group Registry. Autoimmun Rev. Feb 2018;17(2):108–114. doi:10.1016/j.autrev.2017.11.014 [PubMed: 29180123]
8. Seo SR FO, Bernhard H, Herlyn K, Hoffman GS, Kallenberg C, Langford CA, Mahr A, Matteson EL, Neogi T, Rutgers A, Specks U, Stone JH, Merkel PA. The Future of Damage Assessment in Vasculitis. The Journal of Rheumatology. 2007;34(6):1357–1371. [PubMed: 17552062]
9. Mohammad AJ, Bakoush O, Sturfelt G, Segelmark M. The extent and pattern of organ damage in small vessel vasculitis measured by the Vasculitis Damage Index (VDI). Scand J Rheumatol. 2009;38(4):268–75. doi:10.1080/03009740802668554 [PubMed: 19296401]
10. Monti S CA, Klersy C, Montecucco C, Caporali R, Watts R, Merkel PA, Luqmani R; on behalf of DCVAS Collaborators. Association between age at disease onset of anti-neutrophil cytoplasmic antibody–associated vasculitis and clinical presentation and short-term outcomes. Rheumatology. 2021;60:617–628. [PubMed: 32447389]
11. Exley AR BP, Luqmani RA, et al. Development and initial validation of the vasculitis damage index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum. 1997;40:371–80. [PubMed: 9041949]
12. Merkel PA AS, Boers M, Direskeneli H, Herlyn K, Seo P, Suppiah R, Tomasson G, Luqmani RA. T. The OMERACT core set of outcome measures for use in clinical trials of ANCA-associated vasculitis. J Rheumatol. July 2011;38(7):1480–6. [PubMed: 21724720]
13. Rottem M, Fauci AS, Hallahan CW, et al. Wegener granulomatosis ini children and adolescents: Clinical presentation and outcome. The Journal of Pediatrics. 1993;122(1):26–31. [PubMed: 8419611]
14. Westwell-Roper C, Lubieniecka JM, Brown KL, et al. Clinical practice variation and need for pediatric-specific treatment guidelines among rheumatologists caring for children with ANCA-associated vasculitis: an international clinician survey. Pediatr Rheumatol Online J. Aug 7 2017;15(1):61. doi:10.1186/s12969-017-0191-z [PubMed: 28784150]
15. James KE, Xiao R, Merkel PA, Weiss PF. Variation in the Treatment of Children Hospitalized With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis in the US. Arthritis Care Res (Hoboken). Sep 2017;69(9):1377–1383. doi:10.1002/acr.23142 [PubMed: 27813340]
16. Brogan P YR, Cleary G, Rangaraj S, Kasapcopur O, Hersh AO, Li S, Paripovic D, Schikler K, Zeft A, Bracaglia C, Eleftheriou D, Pordeli P, Melega S, Jamois C, Gaudreault J, Michalska M, Brunetta P, Cooper JC, Lehane PB, and the PePRS Study Group. Phase IIa Global

Study Evaluating Rituximab for the Treatment of Pediatric Patients With Granulomatosis With Polyangiitis or Microscopic Polyangiitis. January 2022;74(1):124–133.

17. Thietart S BG, Smets P, Karras A, Philipponnet C, Augusto JF, El Karoui K, Mesbah R, Titeca-Beauport D, Hamidou M, Carron PL, Maurier F, Sacre K, Cohen P, Liozon E, Blanchard-Delaunay C, Kostianovsky A, Pagnoux C, Mouthon L, Guillevin L, Terrier B, Puéchal X; French Vasculitis Study Group. Patients of 75 years and over with ANCA-associated vasculitis have a lower relapse risk than younger patients: A multicentre cohort study. J Intern Med. March 2022;291(3):350–363. [PubMed: 34755398]
18. Flossmann O BP, de Groot K, et al. Development of comprehensive disease assessment in systemic vasculitis. . Ann Rheum Dis. 2007;66:283–292. [PubMed: 16728460]

Significance:

- Reveals associations between age at diagnosis and disease characteristics for patients with ANCA-associated vasculitis (granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis)
- Demonstrates that increases in damage scores with age at diagnosis of AAV are driven by non-disease-specific damage items

Innovations:

- Use of adult registry data to analyze patients diagnosed with rare diseases in childhood
- Novel approach to studying damage scores in vasculitis by differentiating between disease-specific and non-disease-specific features

Category	Group Number	GROUP NAME	Vasculitis Damage Index Criteria	ANCA-Associated Vasculitis Index of Damage Criteria
Cutaneous	1	ULCERS	Cutaneous ulcers	Cutaneous ulcers
	2	GANGRENE		Gangrene with permanent tissue loss
Ocular	3	ORBIT	Orbital wall destruction	Proptosis
	4	SCLERA		Scleral Disease
Ear Nose and Throat	5	SINUSITIS	Chronic sinusitis/Radiological damage	Chronic sinusitis
	6	BONY DESTRUCTION		Bony erosion of sinuses Neo-ossification of the sinuses
	7	NASAL PASSAGE	Nasal blockage/chronic discharge/crusting	Chronic rhinitis/crusting Nasolacrimal gland obstruction Anosmia Ageusia
	8	NASAL DEFORMITY	Nasal bridge collapse/septal perforation	Nasal bridge collapse/saddle nose deformity Nasal septal perforation
	9	SENSORINEURAL		Sensorineural hearing loss
	10	OTOLOGIC		Eustachian tube dysfunction Tympanic membrane perforation or scarring Conductive hearing loss
	11	SUBGLOTTIC STENOSIS	Subglottic stenosis (no surgery) Subglottic stenosis (with surgery)	Subglottic stenosis
Pulmonary	12	PULMONARY	Chronic breathlessness Impaired lung function	Irreversible loss of lung function Fixed large airway obstruction Continuous oxygen dependency
Cardiovascular	13	TISSUE LOSS	Major tissue loss due to peripheral vascular disease	
	14	VENOUS THROMBOSIS		Pulmonary embolism Deep venous thrombosis
	15	ARTERIAL THROMBOSIS		Renal artery stenosis Arterial thrombosis or occlusion
Gastrointestinal	16	GASTROINTESTINAL	Gut infarction/resection Mesenteric insufficiency/pancreatitis	Gut infarction
Renal	17	RENAL	End stage renal disease Estimated/measured GFR ≤ 50% Proteinuria ≥ 0.5g/24hr	Chronic kidney disease Dialysis Renal transplant Proteinuria
Neurologic	18	CENTRAL NERVOUS SYSTEM	Cranial nerve lesion	Cranial nerve lesion Chronic pachymeningitis
	19	PERIPHERAL NERVOUS SYSTEM	Peripheral neuropathy	Sensory polyneuropathy Motor neuropathy Neuropathic pain
EGPA only	20	ASTHMA	Chronic asthma	
	21	CARDIAC	Cardiomyopathy	Left ventricular dysfunction Third degree AV block
Total Score				**GPA/MPA ___ / 19 points** **EGPA ___ / 21 points**

Figure 1. ANCA-Associated Vasculitis Disease-Specific Damage Score (AAV-DSDS).

Scoring system for the ANCA-Associated Vasculitis Disease-Specific Damage Score (AAV-DSDS) for patients with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Each group is worth 1 point regardless of the number of items met within each group. Group numbers 20 and 21 are only applicable to patients with EGPA. Maximum possible scores are 19 points for patients with GPA/MPA and 21 points for patients with EGPA.

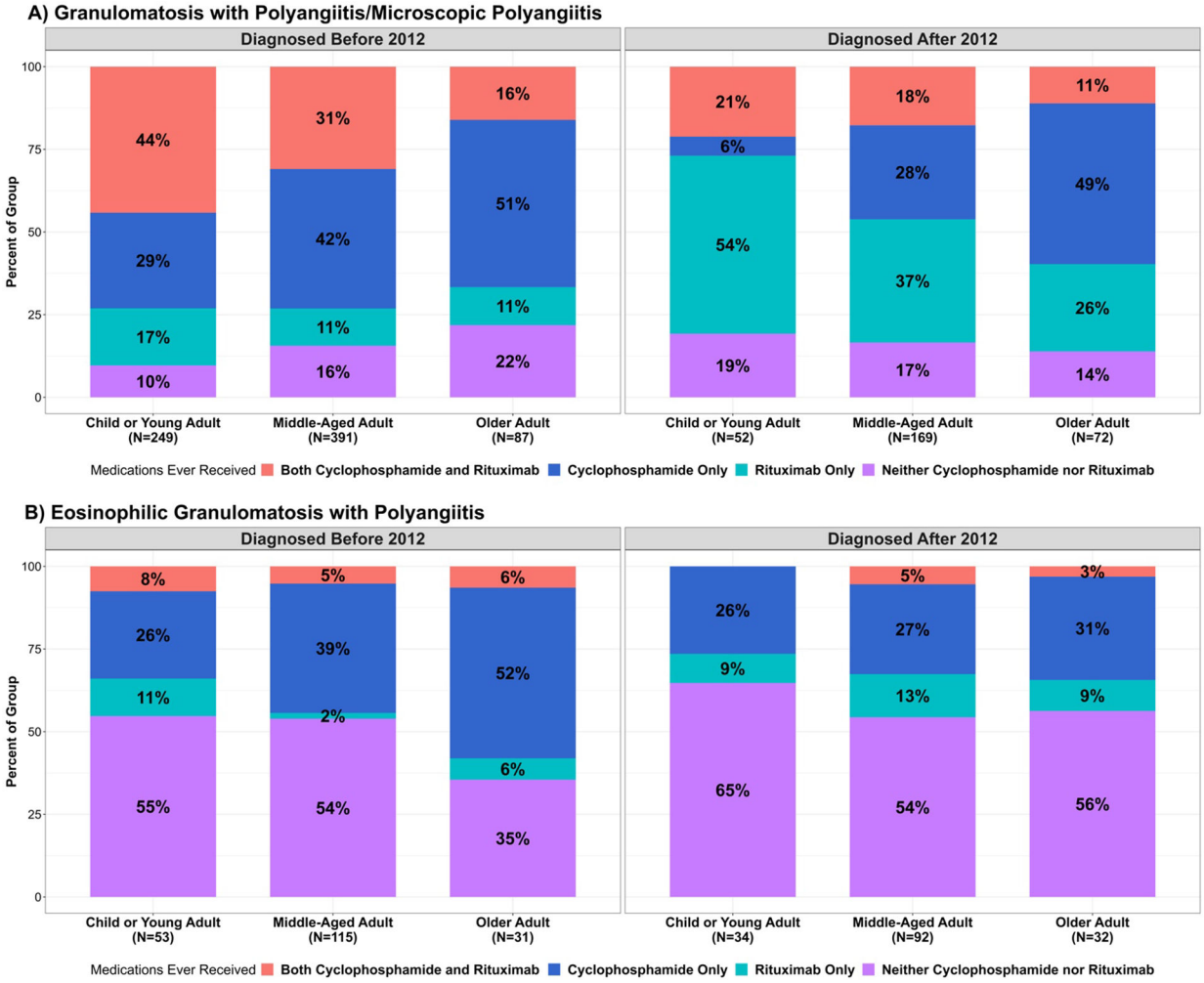

Figure 2. Medications ever received by patients with granulomatosis with polyangiitis and microscopic polyangiitis (GPA/MPA, A) and eosinophilic granulomatosis with polyangiitis (EGPA, B) stratified by age at diagnosis before and after 2012.

Patients diagnosed during the year 2012 are included in the “Diagnosed Before 2012” category.

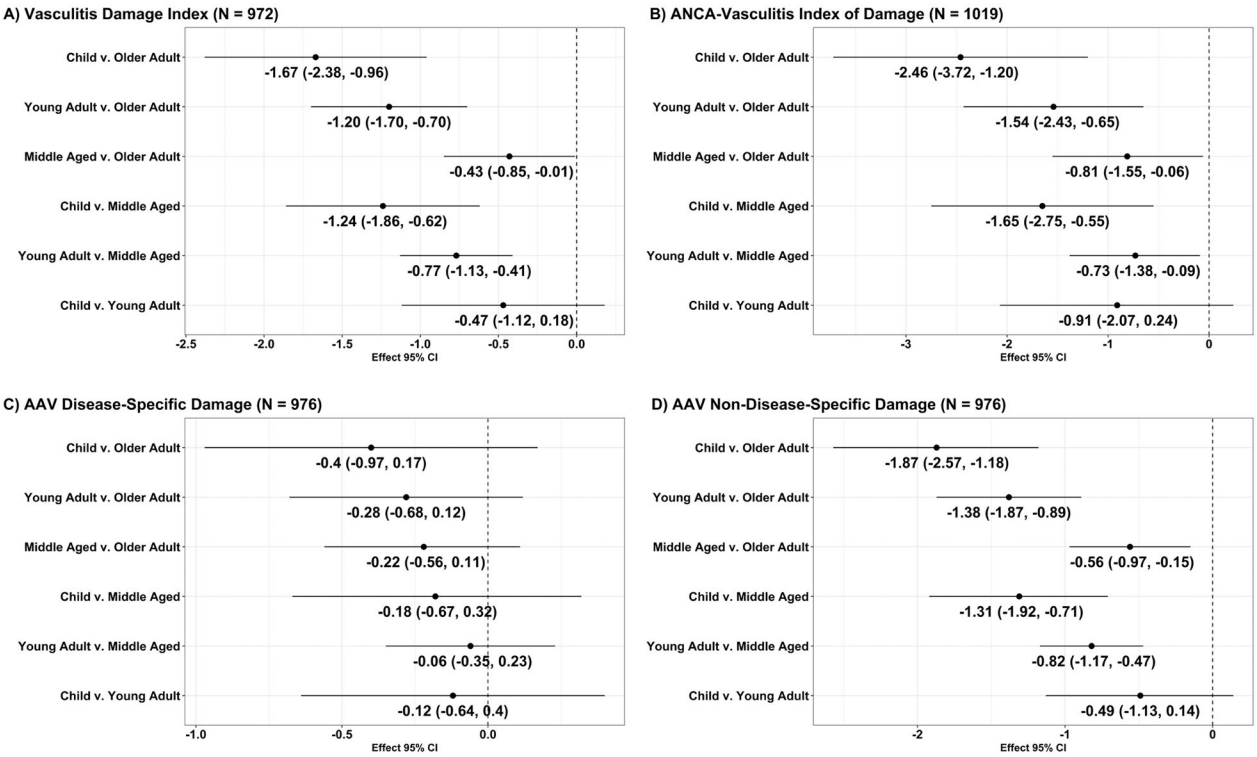

Figure 3. Differences in damage scores based on age at diagnosis among patients with granulomatosis with polyangiitis and microscopic polyangiitis.

Differences in damage scores between age at diagnosis groups were assessed among patients with granulomatosis with polyangiitis and microscopic polyangiitis after adjusting for disease duration, medication use, tobacco use, and ANCA type. Cohorts were divided by age at diagnosis (years): children (< 18), young adults (18-40), middle-aged adults (> 40-65), and older adults (> 65). Younger age at diagnosis groups were compared to older age at diagnosis groups. A negative estimated difference (i.e., to the left of zero) in damage scores between age at diagnosis groups represents a lower score, or less damage. If a horizontal line crosses zero, the difference in damage scores between those two age at diagnosis groups is not significant.

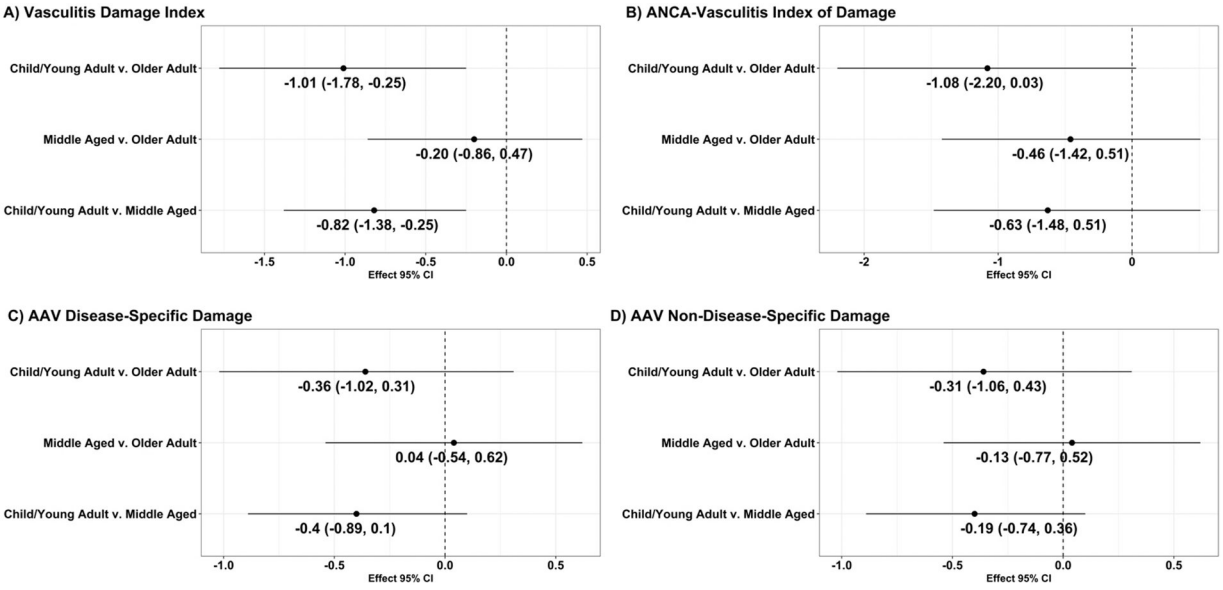

Figure 4. Differences in damage scores based on age at diagnosis among patients with eosinophilic granulomatosis with polyangiitis.

Differences in damage scores between age at diagnosis groups were assessed among patients with eosinophilic granulomatosis with polyangiitis after adjusting for disease duration, medication use, tobacco use, and ANCA type. Cohorts were divided by age at diagnosis (years): children (< 18), young adults (18-40), middle-aged adults (> 40-65), and older adults (> 65). Younger age at diagnosis groups were compared to older age at diagnosis groups. A negative estimated difference (i.e., to the left of zero) in damage scores between age at diagnosis groups represents a lower score, or less damage. If a horizontal line crosses zero, the difference in damage scores between those two age at diagnosis groups is not significant.

Table 1.

Characteristics of patients with granulomatosis with polyangiitis and microscopic polyangiitis stratified by age at diagnosis

Characteristic	Age at Diagnosis: Child *< 18 years old* N = 61	Young Adult *18-40 years old* N = 240	Middle-Aged *> 40-65 years old* N = 560	Older Adult *> 65 years old* N = 159	All N = 1020	*p*-value*
	Mean (standard deviation) or n (percentage)					
Age at Diagnosis (years)	14.8 (2.5)	29.1 (6.5)	53.3 (6.9)	71.4 (5.4)	48.2 (17.0)	< 0.001
Sex (female)	46 (75.4%)	149 (62.1%)	283 (50.5%)	82 (51.6%)	560 (54.9%)	< 0.001
Race						0.397
Asian	2 (3.3%)	14 (6.0%)	21 (3.8%)	6 (3.8%)	43 (4.3%)	
Black/African American	0 (0.0%)	8 (3.4%)	10 (1.8%)	1 (0.6%)	19 (1.9%)	
White	58 (96.7%)	208 (88.9%)	516 (93.5%)	147 (93.6%)	929 (92.6%)	
Other Race	0 (0.0%)	4 (1.7%)	5 (0.9%)	3 (1.9%)	12 (1.2%)	
Missing (N)	1	6	8	2	17	
Ethnicity						0.738
Hispanic	0 (0.0%)	5 (2.3%)	14 (2.7%)	2 (1.4%)	21 (2.2%)	
Not Hispanic	56 (100.0%)	216 (97.7%)	513 (97.3%)	143 (98.6%)	928 (97.8%)	
Missing (N)	5	19	33	14	71	
Follow Up Time (years)	4.6 (3.9)	4.6 (3.6)	4.6 (3.6)	3.3 (2.8)	4.4 (3.5)	< 0.001
Missing (N)	2	8	29	7	46	
Disease Category						< 0.001
GPA	55 (90.2%)	226 (94.2%)	468 (83.6%)	103 (64.8%)	852 (83.5%)	
GPA and MPA	0 (0.0%)	0 (0.0%)	1 (0.2%)	2 (1.3%)	3 (0.3%)	
MPA	6 (9.8%)	14 (5.8%)	91 (16.2%)	54 (34.0%)	165 (16.2%)	
ANCA Type (ELISA)						< 0.001
PR3-ANCA	46 (76.7%)	173 (76.9%)	340 (63.6%)	78 (50.3%)	637 (65.3%)	
MPO-ANCA	11 (18.3%)	35 (15.6%)	132 (24.7%)	69 (44.5%)	247 (25.3%)	
PR3- and MPO- ANCA	0 (0.0%)	1 (0.4%)	8 (1.5%)	0 (0.0%)	9 (0.9%)	
ANCA-negative	3 (5.0%)	16 (7.1%)	55 (10.3%)	8 (5.2%)	82 (8.4%)	
Missing (N)	1	15	25	4	45	
Clinical Manifestations at Diagnosis (DX) and Ever Identified Over the Course of the Disease (EV)						
Constitutional DX	46 (75.4%)	177 (73.8%)	456 (81.4%)	123 (77.4%)	802 (78.6%)	0.088
Constitutional EV	50 (82.0%)	193 (80.4%)	469 (83.8%)	127 (79.9%)	839 (82.3%)	0.565
Fever DX	15 (24.6%)	57 (23.8%)	119 (21.2%)	36 (22.6%)	227 (22.3%)	0.839
Fever EV	18 (29.5%)	65 (27.1%)	143 (25.5%)	41 (25.8%)	267 (26.2%)	0.90
Musculoskeletal DX	38 (62.3%)	155 (64.6%)	367 (65.5%)	60 (37.7%)	620 (60.8%)	< 0.001
Musculoskeletal EV	40 (65.6%)	169 (70.4%)	396 (70.7%)	73 (45.9%)	678 (66.5%)	< 0.001
Cutaneous DX	20 (32.8%)	81 (33.8%)	154 (27.5%)	35 (22.0%)	290 (28.4%)	0.062
Cutaneous EV	21 (34.4%)	90 (37.5%)	170 (30.4%)	39 (24.5%)	320 (31.4%)	0.042
Mucous Membranes DX	4 (6.6%)	30 (12.5%)	55 (9.8%)	14 (8.8%)	103 (10.1%)	0.478

Characteristic	Age at Diagnosis: Child < 18 years old N = 61	Young Adult 18-40 years old N = 240	Middle-Aged > 40-65 years old N = 560	Older Adult > 65 years old N = 159	All N = 1020	*p*-value*
	Mean (standard deviation) or n (percentage)					
Mucous Membranes EV	7 (11.5%)	34 (14.2%)	64 (11.4%)	14 (8.8%)	119 (11.7%)	0.431
Ocular DX	17 (27.9%)	89 (37.1%)	148 (26.4%)	21 (13.2%)	275 (27.0%)	< 0.001
Ocular EV	21 (34.4%)	95 (39.6%)	167 (29.8%)	25 (15.7%)	308 (30.2%)	< 0.001
Ear, Nose, and Throat DX	51 (83.6%)	203 (84.6%)	421 (75.2%)	102 (64.2%)	777 (76.2%)	< 0.001
Ear, Nose, and Throat EV	53 (86.9%)	208 (86.7%)	436 (77.9%)	107 (67.3%)	804 (78.8%)	< 0.001
Nasal Septal Perforation DX	4 (6.6%)	38 (15.8%)	50 (8.9%)	7 (4.4%)	99 (9.7%)	0.002
Nasal Septal Perforation EV	7 (11.5%)	43 (17.9%)	53 (9.5%)	7 (4.4%)	110 (10.8%)	< 0.001
Sinus Involvement DX	40 (65.6%)	157 (65.4%)	310 (55.4%)	73 (45.9%)	580 (56.9%)	< 0.001
Sinus Involvement EV	44 (72.1%)	172 (71.7%)	337 (60.2%)	76 (47.8%)	629 (61.7%)	< 0.001
Subglottic Stenosis DX	13 (21.3%)	44 (18.3%)	35 (6.2%)	3 (1.9%)	95 (9.3%)	< 0.001
Subglottic Stenosis EV	19 (31.1%)	55 (22.9%)	42 (7.5%)	3 (1.9%)	119 (11.7%)	< 0.001
Cardiac DX	1 (1.6%)	6 (2.5%)	24 (4.3%)	7 (4.4%)	38 (3.7%)	0.560
Cardiac EV	2 (3.3%)	7 (2.9%)	29 (5.2%)	7 (4.4%)	45 (4.4%)	0.576
Gastrointestinal Tract DX	5 (8.2%)	12 (5.0%)	10 (1.8%)	3 (1.9%)	30 (2.9%)	0.011
Gastrointestinal Tract EV	6 (9.8%)	13 (5.4%)	14 (2.5%)	3 (1.9%)	36 (3.5%)	0.012
Pulmonary DX	43 (70.5%)	167 (69.6%)	370 (66.1%)	113 (71.1%)	693 (67.9%)	0.553
Pulmonary EV	45 (73.8%)	172 (71.7%)	388 (69.3%)	117 (73.6%)	722 (70.8%)	0.667
Alveolar Hemorrhage DX	23 (37.7%)	63 (26.2%)	115 (20.5%)	42 (26.4%)	243 (23.8%)	0.011
Alveolar Hemorrhage EV	24 (39.3%)	69 (28.8%)	130 (23.2%)	45 (28.3%)	268 (26.3%)	0.027
Intubation DX	3 (4.9%)	13 (5.4%)	30 (5.4%)	9 (5.7%)	55 (5.4%)	0.992
Intubation EV	3 (4.9%)	13 (5.4%)	31 (5.5%)	9 (5.7%)	56 (5.5%)	1.000
Renal Disease DX	41 (67.2%)	119 (49.6%)	353 (63.0%)	109 (68.6%)	622 (61.0%)	< 0.001
Renal Disease EV	42 (68.9%)	126 (52.5%)	370 (66.1%)	111 (69.8%)	649 (63.6%)	< 0.001
Dialysis DX	3 (4.9%)	13 (5.4%)	48 (8.6%)	13 (8.2%)	77 (7.5%)	0.432
Dialysis EV	3 (4.9%)	13 (5.4%)	49 (8.8%)	14 (8.8%)	79 (7.7%)	0.344
Nervous System DX	10 (16.4%)	37 (15.4%)	138 (24.6%)	44 (27.7%)	229 (22.5%)	0.007
Nervous System EV	10 (16.4%)	39 (16.2%)	152 (27.1%)	48 (30.2%)	249 (24.4%)	0.001
Venous Thrombosis DX	6 (9.8%)	19 (7.9%)	63 (11.2%)	17 (10.7%)	105 (10.3%)	0.559
Venous Thrombosis EV	6 (9.8%)	21 (8.8%)	71 (12.7%)	17 (10.7%)	115 (11.3%)	0.421

*Differences were tested via t-test or Kruskal-Wallis test for continuous variables and Chi Squared test or Fisher's Exact test for categorical variables. Statistical significance was set at 0.05. Abbreviations: GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; ANCA, anti-neutrophil cytoplasmic antibody; PR3, protease 3; MPO, myeloperoxidase. Unknown or Missing responses for each characteristic were not included.

Table 2.

Characteristics of patients with eosinophilic granulomatosis with polyangiitis stratified by age at diagnosis

Characteristic	Age at Diagnosis: Child or Young Adult, < *40 years old* N = 87	Middle-Aged > *40-65 years old* N = 207	Older Adult > *65 years old* N = 63	All N = 357	*p*-value
	Mean (standard deviation) or n (percentage)				
Age at Diagnosis (years)	30.3 (6.7)	52.7 (6.4)	70.6 (4.5)	50.4 (14.6)	< 0.001
Sex (female)	56 (64.4%)	1909 (52.7%)	35 (55.6%)	200 (56.0%)	0.180
Race					0.136
Asian	5 (6.2%)	12 (6.0%)	2 (3.2%)	19 (5.5%)	
Black/African American	2 (2.5%)	4 (2.0%)	0 (0.0%)	6 (1.7%)	
White	70 (86.4%)	183 (91.5%)	60 (96.8%)	313 (91.3%)	
Other Race	4 (4.9%)	1 (0.5%)	0 (0.0%)	5 (1.5%)	
Missing (N)	6	7	1	14	
Ethnicity	0.218				0.218
Hispanic	4 (5.1%)	10 (5.2%)	0 (0.0%)	14 (4.3%)	
Not Hispanic	75 (94.9%)	183 (94.8%)	56 (100.0%)	314 (95.7%)	
Missing (N)	8	14	7	29	
Follow Up Time (years)	4.6 (4.1)	4.3 (3.7)	3.7 (3.3)	4.3 (3.7)	0.433
Missing (N)	20	44	17	81	
ANCA Type (ELISA)					0.002
MPO-ANCA	11 (18.3%)	64 (42.1%)	24 (47.1%)	99 (37.6%)	
PR3-ANCA	2 (3.3%)	1 (0.7%)	1 (2.0%)	4 (1.5%)	
MPO- and PR3- ANCA	0 (0.0%)	2 (1.3%)	0 (0.0%)	2 (0.8%)	
ANCA-negative	47 (78.3%)	85 (55.9%)	26 (51.0%)	158 (60.1%)	
Missing (N)	27	55	12	94	
Clinical Manifestations at Diagnosis (DX) and Ever Identified Over the Course of the Disease (EV)					
Active Asthma DX	73 (83.9%)	182 (87.9%)	54 (85.7%)	309 (86.6%)	0.661
Active Asthma EV	79 (90.8%)	199 (96.1%)	57 (90.5%)	335 (93.8%)	0.092
Constitutional DX	67 (77.0%)	147 (71.0%)	48 (76.2%)	262 (73.4%)	0.492
Constitutional EV	70 (80.5%)	156 (75.4%)	48 (76.2%)	274 (76.8%)	0.650
Fever DX	19 (21.8%)	39 (18.8%)	12 (19.0%)	70 (19.6%)	0.861
Fever EV	22 (25.3%)	40 (19.3%)	13 (20.6%)	75 (21.0%)	0.516
Musculoskeletal DX	47 (54.0%)	96 (46.4%)	24 (38.1%)	167 (46.8%)	0.169
Musculoskeletal EV	52 (59.8%)	105 (50.7%)	30 (47.6%)	187 (52.4%)	0.272
Cutaneous DX	53 (60.9%)	109 (52.7%)	24 (38.1%)	186 (52.1%)	0.019
Cutaneous EV	56 (64.4%)	113 (54.6%)	25 (39.7%)	194 (54.3%)	0.013
Mucous Membranes DX	5 (5.7%)	5 (2.4%)	3 (4.8%)	13 (3.6%)	0.300
Mucous Membranes EV	5 (5.7%)	5 (2.4%)	3 (4.8%)	13 (3.6%)	0.322
Ocular DX	9 (10.3%)	20 (9.7%)	3 (4.8%)	32 (9.0%)	0.442
Ocular EV	10 (11.5%)	23 (11.1%)	4 (6.3%)	37 (10.4%)	0.589

Characteristic	Age at Diagnosis: Child or Young Adult, < *40 years old* N = 87	Middle-Aged > *40-65 years old* N = 207	Older Adult > *65 years old* N = 63	All N = 357	*p*-value
	Mean (standard deviation) or n (percentage)				
Ear, Nose, and Throat DX	78 (89.7%)	186 (89.9%)	55 (87.3%)	319 (89.4%)	0.863
Ear, Nose, and Throat EV	78 (89.7%)	188 (90.8%)	55 (87.3%)	321 (89.9%)	0.688
Nasal Septal Perforation DX	2 (2.3%)	4 (1.9%)	2 (3.2%)	8 (2.2%)	0.782
Nasal Septal Perforation EV	2 (2.3%)	6 (2.9%)	2 (3.2%)	10 (2.8%)	1.000
Sinus Involvement DX	70 (80.5%)	169 (81.6%)	46 (73.0%)	285 (79.8%)	0.323
Sinus Involvement EV	71 (81.6%)	173 (83.6%)	46 (73.0%)	290 (81.2%)	0.166
Subglottic Stenosis DX	0 (0.0%)	1 (0.5%)	2 (3.2%)	3 (0.8%)	0.130
Subglottic Stenosis EV	0 (0.0%)	2 (1.0%)	2 (3.2%)	4 (1.1%)	0.190
Cardiac DX	31 (35.6%)	51 (24.6%)	22 (34.9%)	104 (29.1%)	0.089
Cardiac EV	31 (35.6%)	55 (26.6%)	22 (34.9%)	108 (30.3%)	0.194
Gastrointestinal Tract DX	23 (26.4%)	31 (15.0%)	6 (9.5%)	60 (16.8%)	0.013
Gastrointestinal Tract EV	25 (28.7%)	34 (16.4%)	6 (9.5%)	65 (18.2%)	0.007
Pulmonary DX	84 (96.6%)	199 (96.1%)	57 (90.5%)	340 (95.2%)	0.181
Pulmonary EV	84 (96.6%)	201 (97.1%)	57 (90.5%)	342 (95.8%)	0.079
Alveolar Hemorrhage DX	10 (11.5%)	8 (3.9%)	2 (3.2%)	20 (5.6%)	0.033
Alveolar Hemorrhage EV	10 (11.5%)	8 (3.9%)	2 (3.2%)	20 (5.6%)	0.038
Intubation DX	9 (10.3%)	3 (1.4%)	1 (1.6%)	13 (3.6%)	< 0.001
Intubation EV	9 (10.3%)	4 (1.9%)	1 (1.6%)	14 (3.9%)	0.004
Renal Disease DX	11 (12.6%)	28 (13.5%)	9 (14.3%)	48 (13.4%)	0.957
Renal Disease EV	11 (12.6%)	31 (15.0%)	10 (15.9%)	52 (14.6%)	0.831
Dialysis DX	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.3%)	1.000
Dialysis EV	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.3%)	1.000
Nervous System DX	50 (57.5%)	136 (65.7%)	47 (74.6%)	233 (65.3%)	0.096
Nervous System EV	51 (58.6%)	138 (66.7%)	47 (74.6%)	236 (66.1%)	0.130
Venous Thrombosis DX	4 (4.6%)	18 (8.7%)	6 (9.5%)	28 (7.8%)	0.432
Venous Thrombosis EV	4 (4.6%)	18 (8.7%)	6 (9.5%)	28 (7.8%)	0.437

*Differences were tested via t-test or Kruskal-Wallis test for continuous variables and Chi Squared test or Fisher's Exact test for categorical variables. Statistical significance was set at 0.05. Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; PR3, protease 3; MPO, myeloperoxidase. Unknown or Missing responses for each characteristic were not included.