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Multimorbidity in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: Results From a Longitudinal, Multicenter Data Linkage Study

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Objective. Antineutrophil cytoplasmic antibody–associated vasculitis (AAV) is considered a chronic, relapsing condition. To date, no studies have investigated multimorbidity in AAV nationally. This study was undertaken to characterize temporal trends in multimorbidity and report excess health care expenditures associated with multimorbidities in a national AAV cohort from Scotland.

Methods. Eligible patients with AAV were diagnosed between 1997 and 2017. Each patient was matched with up to 5 general population controls. Linked morbidity and health care expenditure data were retrieved from a Scottish national hospitalization repository and from published national cost data. Multimorbidity was defined as the development of ≥2 disorders. Prespecified morbidities, individually and together, were analyzed for risks and associations over time using modified Poisson regression, discrete interval analysis, and chi-square test for trend. The relationship between multimorbidities and health care expenditure was investigated using multivariate linear regression.

Results. In total, 543 patients with AAV (median age 58.7 years [range 48.9–68.0 years]; 53.6% male) and 2,672 general population controls (median age 58.7 years [range 48.9–68.0 years]; 53.7% male) were matched and followed up for a median of 5.1 years. AAV patients were more likely to develop individual morbidities at all time points, but especially <2 years after diagnosis. The highest proportional risk observed was for osteoporosis (adjusted incidence rate ratio 8.0, 95% confidence interval [95% CI] 4.5–14.2). After 1 year, 23.0% of AAV patients and 9.3% of controls had developed multimorbidity ($P < 0.0001$). After 10 years, 37.0% of AAV patients and 17.3% of controls were reported to have multimorbidity ($P < 0.0001$). Multimorbidity was associated with disproportionate increases in health care expenditures in AAV patients. Health care expenditure was highest for AAV patients with ≥3 morbidities (3.89-fold increase in costs, 95% CI 2.83–5.31; $P < 0.001$ versus no morbidities).

Conclusion. These findings emphasize the importance of holistic care in patients with AAV, and may identify a potentially critical opportunity to consider early screening.

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INTRODUCTION

The antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAVs) are a set of systemic autoimmune diseases comprising granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (1). With modern immunosuppressive therapy, these previously fatal diseases have become chronic, relapsing conditions in which the mean 5-year survival rate is ~70% (2).

With improved survival, AAV patients are now at an increased risk of multimorbidity, defined as the presence of ≥2 concurrent long-term disorders (3). Multimorbidity is increasingly common in the general population (4) and has also been described in other chronic inflammatory conditions, including rheumatoid arthritis (5,6). It complicates chronic disease management and is associated with reduced functional status, decreased quality of life, and increased mortality (7,8). Multimorbidity also has important implications for the organization and delivery of health care, which is traditionally structured to optimize the management of individual diseases (9).

Previous studies have demonstrated an increased risk of several individual morbidities in AAV, including cardiovascular disease, diabetes mellitus, and venous thromboembolic disease (10–13). These associations are thought to be a consequence of chronic inflammation or the increasingly potent and toxic medications used to treat AAV (14). However, to our knowledge, no studies have yet investigated the frequency or burden of multimorbidity in AAV patients. In this Scottish national, multicenter data linkage study, we compare temporal trends in the incidence of a wide range of individual morbidities and multimorbidity between AAV patients and matched general population controls, and report the cost of excess resource consumption attributable to multimorbidity in AAV patients.

PATIENTS AND METHODS

Ethical considerations. This study was conducted in compliance with the Declaration of Helsinki. Approval was received from the Scotland Research Ethics Committee A (reference no. 15-SS-0152). Individual patient consent was not required as the research was approved by the Public Benefit and Privacy Panel for Health and Social Care, which oversees studies accessing anonymized health care data held by the NHS Scotland. Information governance, confidentiality, and data protection were undertaken according to the Data Protection Act of 1998. All study data were analyzed and held within a unique, secure national safe-haven environment (15) administered by the Electronic Data and Innovation Service, NHS Scotland.

Study design and data linkage. We performed a retrospective, matched-cohort, population-based data linkage study using routine health care data from multiple national registries in Scotland (see the flow diagram in Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41557/abstract). Record linkage was conducted by investigators at NHS Scotland, using a robust methodology that has previously been shown to produce highly accurate and complete data (16,17).

Study population. AAV patients were identified by clinicians using the European Medicines Agency criteria (18) in 7 secondary and tertiary care hospitals across Scotland. Patients were eligible for inclusion if they were diagnosed as having AAV after January 1, 1995 and were age ≥16 years at the time of data linkage. The date of AAV diagnosis was assigned as the index date. Each patient was matched with at least 1, but up to 5, general population controls based on age (±2 years), sex, and postal code of residence. General population controls were assigned the same index date as their matched AAV patient.

Study follow-up. Patients were followed up from the index date until their date of death or February 28, 2017, whichever came first. Information regarding cause of death was obtained via data linkage from the National Records of Scotland death registry, which records all deaths in Scotland (19).

Definition and identification of individual morbidities and multimorbidity. Morbidities were defined as clinically distinct diseases co-occurring with AAV, but which were not a direct complication of AAV itself (e.g., chronic kidney disease, neuropathy, arthritis, and sino-nasal disease). Our analysis focused a priori on a set of 12 individual morbidities of public health concern in elderly populations (as shown in Supplementary Figure 1 [http://onlinelibrary.wiley.com/doi/10.1002/art.41557/abstract]), which were identified following discussions between senior coauthors and an extensive review of the relevant literature describing multimorbidity in AAV (20,21). The majority of these morbidities have previously been shown to be identifiable from administrative data sets with moderate-to-high validity (21). Multimorbidity was defined as the presence of ≥2 disorders and was determined by summing each patient's individual morbidities at specific time points (years 1, 2, 5, and 10). Information regarding each patient's morbidities was obtained via data linkage with a Scottish national, population-based hospitalization repository. This registry holds information on the discharge codes of all hospitalizations in Scotland since the 1980s and details up to 6 diagnoses per admission (22). The first diagnosis corresponds to the primary reason for hospitalization, while the remaining diagnoses capture information regarding the patient's morbidities. All diagnostic codes recorded for each hospitalization were included in this analysis.

Morbidities were identified using previously validated International Classification of Diseases, Ninth Revision (ICD-9) codes (ICD-9 pre-1996; ICD-10 post-1996) (as listed in Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41557/abstract)

(21,23,24). The first date that a relevant diagnostic code appeared in a patient's record was assigned as the incident date for that specific morbidity. Individual morbidities identified during the 5 years prior to the patient's enrollment in the study (i.e., prior to the index date) were classified as preexisting morbidities and were thus excluded from the analysis. This duration of "look-back" period has previously been shown to allow incident morbidities to be distinguished from prevalent morbidities with accuracy and reliability (25).

Determination of health care expenditure. Count data regarding the number of outpatient encounters, number of inpatient hospitalizations, and overall length of inpatient stay (on both general medical wards and intensive care units) were obtained via data linkage with the Scottish outpatients and hospitalizations registries for each study year (see Supplementary Figure 1 [http://onlinelibrary.wiley.com/doi/10.1002/art.41557/abstract]). The NHS Scottish Health Service Costs Book was used to obtain annual tariffs for resource consumption (26). Tariffs were inflated to 2016 values using the Hospital and Community Health Service Index. Inaccessible data regarding tariffs from pre-2002 were estimated using the 2002 tariff as the reference for deflation.

Statistical analysis. Baseline characteristics of the AAV patients and matched general population controls were summarized. Incident morbidities were summed for each participant and used to derive an ordinal variable representing patients with 0, 1, 2, or ≥3 morbidities. Differences in the proportions of AAV patients and general population controls in each of these categories were compared using a chi-square test for trend.

The overall risk of individual morbidities in AAV patients and matched controls was compared using modified Poisson regression models, adjusted for age, sex, and local health board (27,28). Discrete-time analysis was conducted with follow-up at 1, 2, 5, and 10 years using Lexis expansions (29). These time points were selected a priori based on current treatment guidelines on the duration of induction and remission therapy in AAV (30), in order to provide sufficient granularity to observe potential temporal changes in the occurrence of morbidities. The incidence rates for individual morbidities at each interval were calculated by dividing the number of morbidities observed in each interval by person-years of follow-up included in each interval. Data are expressed as the adjusted incidence rate ratio (IRR) with 95% confidence interval (95% CI), computed using the Poisson assumption (31).

A multivariate linear regression model, adjusted for age, sex, and socioeconomic deprivation status (for further clarification, see Supplementary Methods, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41557/abstract), was created to determine the relationship between number of individual morbidities and health care expenditure. As the residuals were not normally distributed, the continuous dependent variable "health care expenditure" was log-transformed using the natural logarithm. Homoscedasticity was evaluated using the Breusch-Pagan test. All analyses were performed in Stata (version 14) (32) and R (version 3.6.1) (33).

RESULTS

Patient characteristics. In total, 543 patients with AAV (median age at index date 58.7 years [range 48.9–68.0 years]; 53.6% male) were matched with 2,672 general population controls (median age at index date 58.7 years [range 48.9–68.0 years]; 53.7% male) and followed up for a median of 5.1 years (range 2.5–9.4 years) (Table 1). Of the patients with AAV, 316 (58.2%) had GPA, 157 (28.9%) had MPA, and 68 (12.5%) had EGPA. ANCAs with the proteinase 3 specificity were present in 52.7% of patients (286 of 543) and ANCAs with the myeloperoxidase specificity were present in 34.6% of patients (188 of 543). A total of 12.0% of patients with AAV (65 of 543) were classified as ANCA negative.

Risk of developing individual morbidities in AAV. The risk of developing most individual morbidities was higher in AAV patients than in general population controls (Figure 1). The morbidity most frequently observed in AAV patients during study follow-up was hypertension (19.7% of AAV patients [92 of 466] versus 9.4% of general population controls [234 of 2,482]; $P < 0.0001$) (Table 2). However, the highest proportional risk difference between AAV patients and general population controls was observed for osteoporosis (adjusted IRR 8.0, 95% CI 4.5–14.2) (Figure 1).

Table 1. Baseline characteristics of the AAV patients and general population controls*

	AAV patients	General population controls
No. of participants	543	2,672
Male sex, no. (%)	291 (53.6)	1,434 (53.7)
Age at index, median (IQR) years	58.7 (48.9–68.0)	58.7 (48.9–68.0)
Follow-up, median (IQR) years	5.1 (2.5–9.4)	5.2 (2.5–9.5)
AAV type, no. (%)		NA
GPA	316 (58.2)	
MPA	157 (28.9)	
EGPA	68 (12.5)	
Missing	2 (0.4)	
ANCA seropositivity, no. (%)		NA
PR3-ANCA	286 (52.7)	
MPO-ANCA	188 (34.6)	
ANCA negative	65 (12.0)	
Missing	4 (0.7)	

* AAV = antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; EGPA = eosinophilic granulomatosis with polyangiitis; PR3 = proteinase 3; MPO = myeloperoxidase; NA = not applicable.

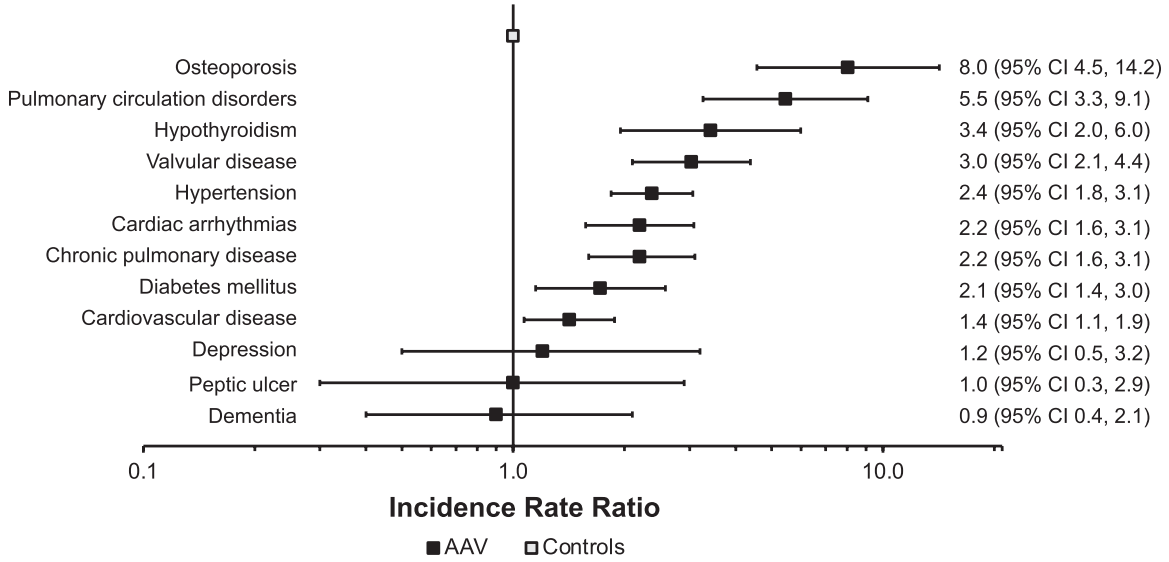

Figure 1. Comparison of the incidence of individual morbidities between patients with antineutrophil cytoplasmic antibody–associated vasculitis (AAV) and general population controls. Results are incidence rate ratios with 95% confidence intervals (95% CIs), adjusted for age, sex, and local health board. The rate of incident morbidity in the general population controls was set as the referent.

A sensitivity analysis exploring the proportional risk of hospital admissions due to hip fractures was performed to validate this finding. The risk of hip fractures in AAV patients was found to be twice that in general population controls (adjusted IRR 2.0, 95% CI 1.1–3.7).

To explore the influence of surveillance bias, a further sensitivity analysis was performed to evaluate the proportional risk of hypothyroidism and stroke in only those patients and controls with a record of at least 1 hospitalization during study follow-up (see Supplementary Results, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41557/abstract).

Table 2. Comparison of incident morbidities between AAV patients and general population controls during follow-up*

	AAV patients	General population controls	*P*
Cardiac arrhythmias	49 (9.6)	119 (5.0)	<0.0001
Cardiovascular disease	61 (12.6)	236 (9.5)	0.042
Chronic pulmonary disease	46 (9.7)	120 (4.7)	<0.0001
Depression	<5 (<0.9)	21 (0.8)	0.749
Diabetes mellitus	37 (7.2)	94 (3.6)	<0.0001
Dementia	6 (1.1)	32 (1.2)	0.846
Hypertension	92 (19.7)	234 (9.4)	<0.0001
Hypothyroidism	21 (4.0)	34 (1.3)	<0.0001
Osteoporosis	29 (5.4)	22 (0.8)	<0.0001
Peptic ulcer disease	<5 (<0.9)	21 (0.8)	0.918
Pulmonary circulation disorders†	31 (5.8)	30 (1.1)	<0.0001
Valvular disease	46 (8.7)	80 (3.0)	<0.0001

* Values are the number (%) of subjects. AAV = antineutrophil cytoplasmic antibody–associated vasculitis.
† A full list of conditions encompassed by this term is provided in the Supplementary materials.

Temporal trends in individual morbidities and multimorbidity in AAV. Figure 2 illustrates trends in the incidence of individual morbidities over time following the diagnosis of AAV. In general, the highest incidence for most morbidities was observed during the first 2 years of follow-up. This was especially marked for hypertension and hypothyroidism. However, a further increase in the incidence of several morbidities, including cardiovascular disease, diabetes mellitus, and chronic pulmonary disease, was also noted at 5–10 years after AAV diagnosis.

The proportion of study participants developing at least 1 incident morbidity increased over time in both AAV patients and general population controls (Figure 3). However, at every time point, AAV patients developed a significantly higher number of individual morbidities compared to general population controls ($P < 0.0001$ for all time points) (Figure 3).

Multimorbidity (defined as the presence of ≥2 disorders) was also more common in AAV patients than in general population controls at all time points. For example, after 1 year of follow-up, 23.0% of AAV patients (125 of 543) could be considered to have developed multimorbidity versus 9.3% of general population controls (248 of 2,672) ($P < 0.0001$). Ten years after diagnosis, a further 37.0% of AAV patients (101 of 273) had developed multimorbidity, compared with 17.3% of general population controls (235 of 1,362) ($P < 0.0001$).

Health care expenditure attributable to multimorbidity in AAV patients. Figure 4 illustrates the relationship between the number of individual incident morbidities and the total cost (in British pound sterling) of excess resource

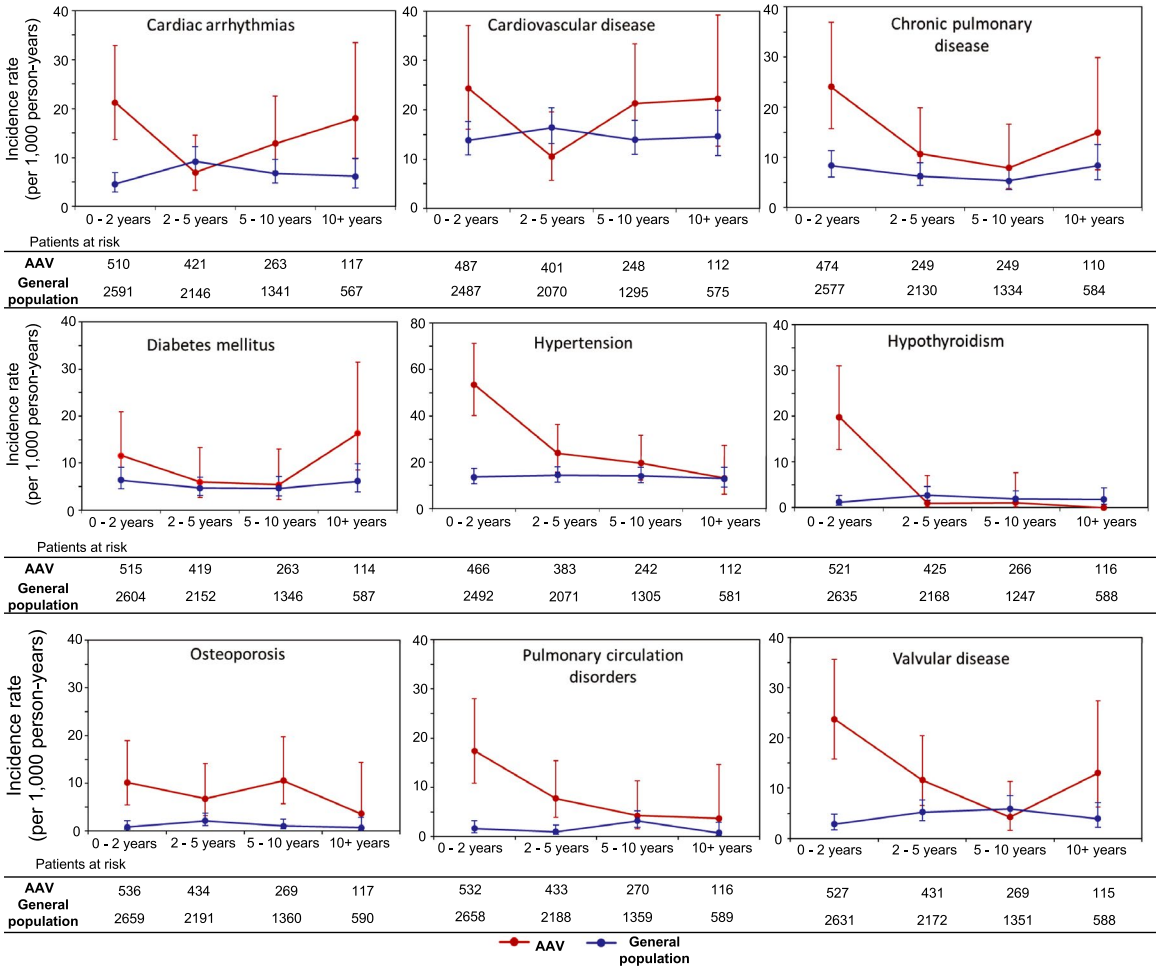

Figure 2. Temporal trends in the incidence of individual morbidities in patients with antineutrophil cytoplasmic antibody–associated vasculitis (AAV) and general population controls. Scale of the y-axis is different for hypertension. Numbers of subjects at each time point are shown below the graphs.

consumption due to outpatient encounters and inpatient hospitalizations (on both general medical wards and intensive care units) in 502 AAV patients during study follow-up. Multivariate linear regression modeling confirmed that the development of multimorbidity was associated with a proportionally higher cost of excess resource consumption in AAV patients (results shown in Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41557/abstract). Compared to the development of no morbidities during study follow-up, the development of 2 morbidities was associated with a 2.78-fold increase (95% CI 2.09–3.71) ($P < 0.0001$) in health care expenditure in AAV patients, while the development of ≥3 morbidities was associated with a 3.89-fold increase (95% CI 2.83–5.31; $P < 0.001$) in health care expenditure in AAV patients. The increases in total health care expenditure observed with the development of multimorbidity were predominantly related to increases in inpatient, rather than outpatient, health care expenditure (see Supplementary Results and Supplementary Tables 3 and 4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41557/abstract).

DISCUSSION

This is the first study to describe longitudinal trends in the incidence of multimorbidity and report the health care expenditure attributable to multimorbidity in a large national cohort of AAV patients from Scotland. We report a number of important observations.

First, AAV patients are at a significant risk of developing individual morbidities throughout their disease course, but especially in the first 2 years following diagnosis. Second, multimorbidity (the presence of ≥2 disorders) is common in AAV patients and significantly increases in frequency over time. Indeed, it affected almost one-quarter of the AAV patients in their first year after diagnosis, and affected more than one-third of patients by year 10 of follow-up. Third, multimorbidity is associated with an ~3-fold increase in excess health care expenditure in AAV patients.

Figure 3. Prevalence of morbidities at baseline and cumulative incidence of morbidities and multimorbidity at 1, 2, 5, and 10 years in patients with antineutrophil cytoplasmic antibody–associated vasculitis (AAV) and general population controls. $P < 0.0001$ by chi-square test for trend for all time points. Numbers of subjects at risk at each time point are shown below the graph.

Uniquely, our study demonstrates that AAV patients are at an increased risk of developing multimorbidity compared to general population controls. While the impact of multimorbidity has not been studied previously in AAV, we also found that multimorbidity is associated with a disproportionate increase in the cost of overall excess resource consumption. In comparison to AAV patients with no morbidities, the development of multimorbidity in AAV patients is associated with a 2–4-fold increase in total health care expenditure, but a 3–5-fold increase in inpatient health care expenditure. Relevant studies in other chronic disease populations, for example in patients with cardiovascular disease (34) or chronic kidney disease (35), have also demonstrated that multimorbidity is becoming the rule rather than the exception (9,36). The implications of this are significant, given the striking association of multimorbidity with polypharmacy, greater resource consumption, reduced quality of life, and poorer outcomes (7–9,37).

Our findings are also consistent with previous assessments of individual morbidities in AAV. In relation to the risk of cardiovascular disease, we demonstrate an increased risk in both early and late stages of AAV (10,11,38). Uniquely, our study extends these findings to other cardiovascular disorders, including valvular disease and arrhythmias, both of which demonstrate a similar bimodal risk pattern over time. Although primary cardiovascular disease is relatively uncommon in AAV, the observed risk may be due to a combination of chronic inflammation and glucocorticoid toxicity (39,40). It is possible that these findings are partly explained by surveillance bias. For example, valvular heart disease may have been diagnosed during routine echocardiography, an investigation that AAV patients are more likely to undergo than general population controls.

As general population controls were not selected from the time point of a new diagnosis, the increased risk observed for several morbidities early in the AAV disease course may also be explained by surveillance bias, due to the additional investigations performed in AAV patients following their index diagnosis. For example, AAV patients are commonly tested for hypothyroidism as part of their diagnostic evaluation. Nevertheless, an increased risk of hypothyroidism has previously been demonstrated in AAV patients prior to diagnosis, which aligns with accumulating evidence supporting shared mechanisms across the autoimmune disease spectrum (41). Similarly, the increased risk of osteoporosis in AAV patients observed in the present study may be related to current guideline recommendations for dual energy x-ray absorptiometry scans when patients commence treatment with glucocorticoids (30). Hip fractures are a reliable surrogate end point unlikely to be affected by surveillance bias and, as a result, we performed a sensitivity analysis to evaluate the risk of hip fractures during follow-up. Interestingly, we observed that the risk of hip fractures in AAV patients was twice that of general population controls—verifying our finding that osteoporosis risk is indeed increased in AAV patients.

Our findings have important implications for clinical practice. Specifically, the results of our temporal analysis highlight the importance of early screening for many common conditions in AAV patients, while also highlighting the significance of late-onset cardiovascular disease and diabetes mellitus. Our observation that peptic ulcer disease is no more likely in AAV patients than in general population controls, despite the frequent administration of high-dose glucocorticoids to patients with AAV, also appears to reflect the relative success of prophylactic therapies aimed at

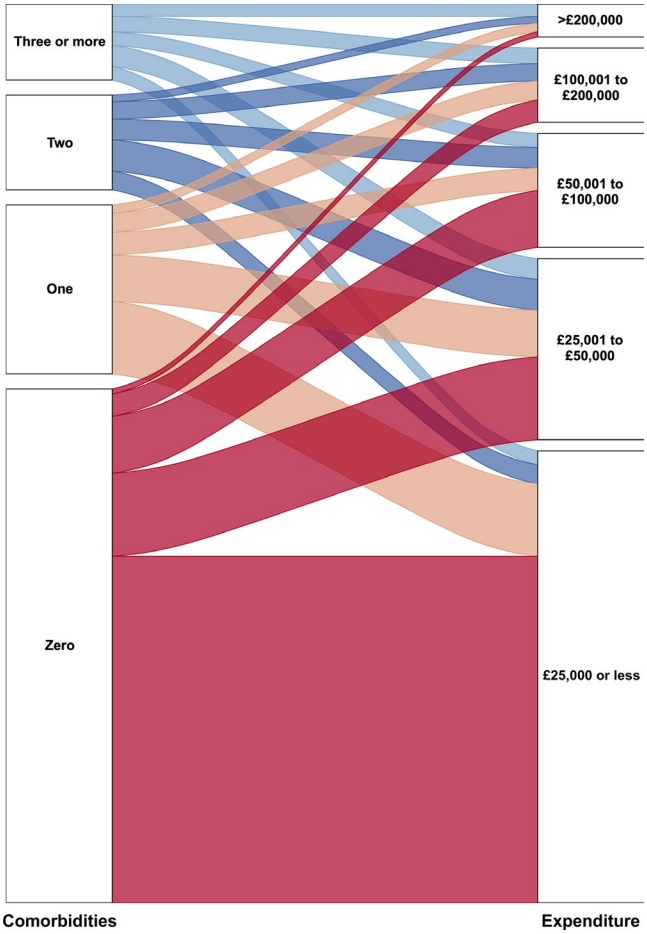

Figure 4. Alluvial plot illustrating the relationship between number of incident morbidities and total excess health care expenditure during the study follow-up in patients with antineutrophil cytoplasmic antibody–associated vasculitis (n = 502).

suppressing gastric acid secretion. Therefore, our data encourage similar preventative strategies for other morbidities.

Further research is required to understand what exact mechanisms underlie the increased risk of multimorbidity observed in AAV patients in the present study. Given the relationship between multimorbidity and adverse pharmacologic effects, such work could ultimately incentivize a shift toward a reduction in the use of pharmacologic therapies associated with numerous adverse effects, such as glucocorticoids. Indeed, with the transformation of AAV into a chronic disease, it is timely to prioritize a more holistic approach toward the management of AAV. This is analogous to the concept of "cancer survivorship," which has been established in oncology in response to improvements in cancer-related mortality. The overarching aim of cancer survivorship is to address the physical, psychological, and social health burden that arises as a consequence of cancer patients living longer (42). Clinicians must therefore consider how best to organize and deliver health care to AAV patients, in order to fully address both their multimorbidity and their primary disease. Greater collaboration with primary care providers is likely be critical to the potential success of any such move toward a more holistic approach to patient care in AAV.

Our study has several important strengths. Utilizing one of the largest cohorts of AAV patients, we adopted a comprehensive approach for improving our understanding of the burden associated with multimorbidity in AAV patients. Indeed, our method for identifying AAV patients suitable for inclusion in our cohort was also robust. In addition, we assessed prevalent morbidity burden using a validated length of "look-back" period (25) and previously verified ICD9/ICD-10 discharge coding (21,23,24), which has a reported accuracy of ~96% for common diagnoses recorded in the SMR01 data set (43).

However, a number of limitations must be considered. First, our study identified morbidities from secondary care records, which mostly capture major disorders. Despite including all available diagnostic codes, relatively minor disorders may have been overlooked by secondary care coders, and therefore our incidence estimates are likely to be conservative. However, this will have affected AAV patients and general population controls equally.

Second, given the higher hospitalization rate observed among AAV patients (98% versus 79% of general population controls), the IRRs for conditions managed in primary care are likely to be overestimates. To address this limitation, we performed a sensitivity analysis including only those patients and controls with a hospitalization record, and found that the degree of overestimation was small for hypothyroidism, stroke, and myocardial infarction (see Supplementary Results [http://onlinelibrary.wiley.com/doi/10.1002/art.41557/abstract]).

Third, patients not hospitalized in the 5 years prior to their index date were classified as having no preexisting morbidities. It is therefore difficult to be certain exactly when these patients developed "incident" morbidities. To limit the impact of this, we utilized a validated, fixed 5-year look-back period (25) to standardize the identification of baseline morbidities across all patients.

Fourth, study follow-up was limited to a median period of 5 years, which may partly explain why we failed to demonstrate an increased risk of depression or dementia in AAV patients. Although sufficient for identifying relatively acute-onset conditions, longer follow-up is required to reliably establish the occurrence of more gradual-onset disorders, such as depression and dementia.

Fifth, despite being one of the largest studies of its kind, we were unable to undertake stratified analysis by AAV type, due to a lack of statistical power.

In conclusion, this novel study is the most comprehensive and detailed analysis of multimorbidity in AAV patients to date. AAV patients are at a high risk of developing individual morbidities, especially early in their disease course. Multimorbidity is also common in AAV patients and is associated with disproportionate increases in health care expenditure. Our findings emphasize the importance of holistic care in AAV patients and the need to consider early screening for other conditions.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Basu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Sarica, Marks, Black, Basu.
Acquisition of data. Sarica, Gallacher, Dhaun, Sznajd, Harvie, McLaren, McGeoch, Kumar, Amft, Erwig, Marks, Bruno, Zöllner, Black, Basu.
Analysis and interpretation of data. Sarica, Gallacher, Amft, Black, Basu.

ADDITIONAL DISCLOSURE

Author Erwig is an employee of GlaxoSmithKline.

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