Mortality in ANCA-Associated Vasculitis: A Meta-Analysis of Observational Studies

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ABSTRACT

Objective

To determine the magnitude of all-cause mortality risk in patients with ANCA-associated vasculitis (AAV) compared with the general population through a meta-analysis of observational studies.

Methods

We searched Medline and EMBase databases from their inception to April 2015. Observational studies that met the following criteria were assessed by two

researchers: 1) clearly defined AAV identified by either the American College of Rheumatology 1990 classification criteria or the 2012 Chapel Hill Consensus Conference disease definitions, and 2) reported standardized mortality ratios (SMR) and 95% confidence intervals (95% CI). We calculated weighted-pooled summary estimates of SMRs (meta-SMRs) for all cause mortality using random effects model, tested for publication bias and heterogeneity.

Results

Ten studies met the inclusion criteria, comprising 3,338 AAV patients enrolled from 1966-2009 and a total of 1,091 observed deaths. Overall, we found a 2.7-fold increased risk of death in AAV patients when compared to the general population (meta-SMR 2.71 [95% CI 2.26-3.24]). Analysis on studies that included only granulomatosis with polyangiitis (GPA) cases also indicated a similar mortality risk (meta-SMR 2.63, [95% CI 2.02-3.43]). There was no significant publication bias or small-study effect. Subgroup analyses showed that mortality risks were higher in older cohorts with a trend towards improvement over time (i.e., those with their midpoint of enrolment periods that were between 1980-1993 and 1994-1999, versus 2000-2005).

Conclusion

Published data indicate there is a 2.7-fold increase in mortality amongst AAV patients compared to the general population.

Keywords: ANCA, vasculitis, mortality, meta-analysis, observational studies

INTRODUCTION

Primary systemic vasculitides are a heterogeneous group of rare diseases characterized by the presence of necrotizing inflammation of the blood vessel wall. Amongst the various hypotheses on the immunologic mechanisms seeking to explain the nature of these diseases, the antineutrophil cytoplasmic antibodies (ANCA) appear to play a prominent role in the pathologic pathways of a group of predominantly small vessel vasculitis, otherwise known as ANCA-associated vasculitis (AAV).[1, 2] This distinctly pauci-immune form of vasculitis includes granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome).

The spectrum of AAV ranges from isolated organ involvement to life threatening fulminant disease. The prognosis in untreated systemic GPA was initially poor, with mortality rates of 80% within one year with a mean survival time of 5 months.[3] With the introduction of glucocorticoids and cyclophosphamide in management of AAV in the 1960s, significant advances have been made in survival.[4] The 1, 5, and 10-year survival rates in GPA patients are now reported to range between 81-95%, 73-83%, and 55-75%, respectively.[5-13] Similar improvements were also noted in MPA and EGPA studies. With treatment, MPA survival rate at 1 year is 80%, 5 years 45-85%, 10 years ~74%.[14-17] Recent EGPA studies have estimated 5-year survival rates at 89-97%.[18, 19]

Despite improving survival, patients with AAV still remain at a higher risk of death relative to the general population.[10] Standardized mortality ratio

(SMR) provides an estimate of the true death risk, as it compares the number of observed patient deaths to the number of expected deaths of age- and sex-matched individuals from the general population. Several studies have reported an elevated SMR for AAV patients, ranging from 1.6 to 4.8,[9, 13, 16, 20-23] although others have found that contemporary mortality risks were not significantly different from the general population.[19, 22, 24, 25] The conflicting results from these reports may be due to biases from small sample sizes and cohort types (e.g., community based versus clinic based).

The purpose of our study was to estimate all cause mortality risk of patients with AAV through a systematic review and meta-analysis from observational studies.

METHODS

Search strategies. A search was performed by an experienced research librarian (MDW) to identify primary studies and review literature using Medline and EMbase databases on the OVID platform. Records were captured for the full date range for each database through April 2015 (Medline from 1948, EMbase from 1980) in any language. Database specific indexing was used (Medline MeSH and EMbase subject headings), along with text words in titles and abstracts. Two search concepts were combined with the Boolean operator "AND": 1) ANCA-associated vasculitis (AAV) or vasculitis, and 2) mortality or survival. Conference abstracts were captured with this approach, as they were not specifically excluded as a publication type. The exact search strategy is available as an online supplementary material (or available upon request from the corresponding author).

Abstracts for all articles of interest were reviewed for relevance, that is those that reported mortality or survival data in AAV. Full papers of selected abstracts were retrieved and assessed for eligibility based on the inclusion criteria listed below. We also searched the reference lists of identified papers and conference abstracts for additional relevant publications.

All English-language peer-reviewed articles that met the following inclusion criteria were considered eligible: 1) clearly defined AAV identified by either the American College of Rheumatology (ACR) 1990 classification criteria [26, 27] or the 2012 Chapel Hill Consensus Conference (CHCC) on disease definitions,[28] 2) reported SMRs and 95% confidence intervals (95%CI), or available data to calculate SMRs. In cases of duplicate data used in more than one study, the sample with the most up to date data was selected for review.

Data extraction. Two authors (JA-T and ND) independently reviewed and assessed the selected articles for eligibility. From eligible studies, JAT and ND extracted data on year of publication, enrolment period, study design, country, population setting, definition of AAV, sample size and demographics, proportion of ANCA positivity, proportion of renal involvement at diagnosis, and survival or mortality data. Gender-specific SMR was also noted, where available. In two studies, we calculated the 95% confidence intervals (95% CI) for SMR from available information.[9, 20] In studies where the overall cohort was divided into time cohorts (by year of enrolment), each time cohort was computed as an individual cohort during meta-analysis.[22, 24] One study provided 1-year and 5-year SMRs and the latter was selected for the meta-analyses,[24] as the median or mean follow-up times for all studies were greater than 1 year. Any differences

between the two authors (JA-T and ND) were resolved by consensus together with a third author (JAA-Z).

Quality scores of included studies. We assessed study quality based on a 12-point scale that was adapted from previously published scales for observational studies.[29, 30] We used a similar scoring system in our previously published meta-analyses on the risk of mortality in rheumatoid arthritis[31, 32] and systemic lupus erythematosus.[33] Points were allocated on an ordinal scale for each of the 6 items recorded; source of the study population (population based = 2 points, clinic/hospital based = 1 point, and undefined = 0); cohort type (inception cohort = 2, non-inception cohort = 1, undefined = 0); definition of AAV (ACR or CHCC classification criteria = 2, other validated classification criteria = 1, other pre-defined but non-validated classification criteria = 0); ascertainment of death outcome (validated criteria = 2, non-validated, but clearly defined criteria [e.g., death certificates] = 1, not mentioned = 0); AAV exposure (≥10 years = 2, ≥5years and <10years = 1, <5years = 0); and loss to follow up (≤20% = 2, >20% and ≤40% = 1, >40% or not mentioned = 0). Studies with scores ≥7points were considered higher quality and those with ≤6 points were lower quality studies. Two authors (JA-T and ND) performed quality scoring independently, with differences resolved by consensus together with a third author (JAA-Z).

Statistical analysis. We calculated the meta-SMR for all-cause mortality in AAV, which is a weighted-pooled summary estimate of SMRs (weighted by the sample size of each study) using HEpiMA statistical software, version 2.1.2.0.[34] A GPA meta-SMR was determined from study cohorts that included only GPA cases, excluding MPA and EGPA. Separate meta-SMRs were also calculated for males

and females. Initial calculations were performed using SMRs from the individual studies on a log scale to approximate a normal sampling distribution. The resulting pooled values were then transformed back to the SMR scale. Results from the pooled statistics were based on the random-effects model. Statistical heterogeneity was assessed using the I^2 statistic, which indicates the proportion of variation in effect size due to heterogeneity.[35] Source of heterogeneity was determined by subgroup analysis. To do so, all included studies were stratified accordingly; population setting (population-based versus hospital/clinic-based samples), cohort type (inception versus non-inception), midpoint of enrolment periods (1980-1993, 1994-1999 and 2000-2005), and center (single center versus multi-center). Furthermore, a univariate meta-regression analysis was then used to study and interpret the difference in meta-SMRs between the subgroups.[36] The time cut-offs for our enrolment period analysis were chosen as such because of the increased usage of ANCA testing in the mid-1990s and because in the early 2000s, there was a paradigm shift in treatment strategies, with an emphasis on improving the safety profile of induction therapy.[37]

We evaluated the robustness of the results using jack-knife sensitivity analysis, by repeated meta-SMR analyses with removal of a single study in succession each time.[38]

Assessment of publication bias/small-study effect. We constructed a funnel plot in which a measure of the study size is plotted as a function of the measure of interest.[39] We used the log of the SMRs from individual studies as well as the log of precision (1/variance). This was done to detect publication bias (i.e., bias resulting from the greater likelihood of studies with positive results to be

published compared to negative results), or the small-study effect (i.e., a tendency for treatment effect estimates in small studies to differ from those in larger studies).[40] In the absence of publication bias and small-study effect, the distribution of the data points will be symmetric. Furthermore, we used Egger's regression as an objective, quantitative test statistic to test for presence of asymmetry in the data.[41]

RESULTS

We screened 570 abstracts published over the last 38 years (324 Medline and 238 EMbase and 8 from reference lists). A total of 58 studies were retrieved for detailed evaluation and 10 studies met the inclusion criteria (**Figure 1** and **Table 1**). Forty-eight studies were excluded: 43 did not provide SMRs or data to calculate them, 3 were review papers, and 2 included only patients with renal vasculitis. The complete list of references reviewed is available upon request from the corresponding author.

The ten studies included 3,338 AAV patients (2,619 with GPA, 501 with MPA, 185 with EGPA, and 33 with renal limited vasculitis) enrolled from 1966-2009 and a total of 1,091 observed deaths.[9, 13, 16, 19-25] Three were population-based studies (n=1,691), whereas 7 were hospital/clinic-based studies (n=1,647). Four of these studies included only GPA patients (n=1,987).

There were 14 unique cohorts available for the meta-analysis. Overall, the mortality risk in AAV patients was significantly increased when compared with the general population (meta-SMR 2.71 [95% CI 2.26-3.24]). See **Figure 2**. Analysis on GPA patients alone also showed a similar increase in risk of mortality

(GPA meta-SMR 2.63, [95% CI 2.02-3.43]). Five studies reported sex-specific mortality estimates with no differences in mortality risks between sexes (meta-SMR 3.36 [95% CI 2.10-5.38] and 3.11 [95% CI 2.21-4.36] for females and males, respectively).

There was significant heterogeneity among the studies (I^2 = 84.4%, 95% CI 72.6-96.3). Subgroup analyses showed that a number of factors might have influenced the mortality risk. Meta-SMRs were higher in population-based

Table 1: Summary of studies included in meta-analysis

Author/ Year published	Country (single/ multi-center)	Study design	Enrolment period	Mean follow-up, years	No. patients	Female (%)	Setting	Cohort type	AAV classification criteria	Mean age at study entry, years	No. death events (%)	Survival rate	Standardized mortality ratio, SMR (95% CI)	Quality score
Matteson/ 1996	Canada, Mexico, USA (multi-center)	Retrospective cohort	1978-1987	7.1	77 GPA	29 (37.7)	Tertiary hospital/clinic	Inception	ACR	N/A	28 (36)	5-year survival 75%	4.69 (3.41-5.96) Female 6.81 (3.73-9.89) Male 4.00 (2.72-5.27)	10
Knight/ 2002	Sweden (multi-center)	Retrospective cohort	1969-1994	Up to 31, Dec 1995	1065 GPA	502 (47.1)	Population based	Non- inception	ICD 8 and 9	N/A	516 (48.5)	N/A	4.0 (3.6-4.3) All Cancer 2.2 (1.7-2.8)	10
Booth/2003	UK (multi-center)	Retrospective cohort	1995-2000	3.1 (median)	246 AAV - 82 GPA - 120 MPA - 33 RLV - 11 EGPA	106 (43)	Tertiary hospital/clinic	Non- inception	CHCC	66 (median)	59 (24)	1-year survival 84% 5-year survival 76%	2.84 (2.53-3.18)	5
Lane/2005	UK (single center)	Retrospective cohort	1988-2000	3.3	99 AAV - 57 GPA - 24 MPA - 18 EGPA	38 (38.4)	Secondary district general hospital/clinic	Non- inception	ACR, CHCC and Lanham, plus case note reviews	62.6	31 (31.3)	1-year survival GPA 85.5% MPA 82.7% EGPA 83.2% 5-year survival GPA 75.9% MPA 45.1% EGPA 68.1%	4.8 (2.9-6.6) Female 3.05 (1.2-4.9) Male 5.9 (3.1-8.8)	8
Mohammad /2009	Sweden (multi-center)	Retrospective cohort	1997-2006	4.9 (median)	140 AAV - 63 GPA - 65 MPA - 6 EGPA - 6 PAN (excluded from analysis)	73 (52.1)	Population based	Inception	EMEA algorithm, plus case note reviews	67.6 (median)	GPA 14 (22.2) MPA 29 (44.6) EGPA 1 (16.7)	1-year survival GPA 95% MPA 80% 5-year survival GPA 83% MPA 55%	GPA 1.77 (0.84-2.70)* MPA 3.95 (2.51-5.38)* Female 3.27 (1.99-5.04) Male 2.48 (1.60-3.65) Renal SMR 3.22 (2.21-4.23)	7

Eriksson/ 2009	Sweden (single center)	Retrospective cohort	1978-2005 **Old cohort** 1978-1996 **Recent cohort** 1997-2005	**-** **Old cohort** 11.1 **Recent cohort** 4.4	95 AAV **Old cohort** 32 AAV (24 GPA, 8 MPA) **Recent cohort** 63 AAV (33 GPA, 30 MPA)	43 (45.3) **Old cohort** 15 (46.9) **Recent cohort** 28 (44.4)	Tertiary hospital/clinic	Inception	CHCC	**-** **Old cohort** 57.7 **Recent cohort** 61.4	22 (23.2) **Old cohort** 15 (46.9) **Recent cohort** 7 (11.1)	**-** **Old cohort** 1-year survival 91% 5-year survival 81% **Recent cohort** 1-year survival 95% 5-year survival 87%	**-** **Old cohort** 1 year SMR 5.2 (1.07-15.14) 5 year SMR 2.5 (0.93-5.52)^ **Recent cohort** 1 year SMR 2.1 (0.43-6.09) 5 year SMR 1.6(0.6-3.2)^	7
Takala/ 2010	Finland (multi-center)	Retrospective cohort	1981-2000 **Old cohort** 1981-1990 **Recent cohort** 1991-2000	Up to 30 July 2005	492 GPA **Old cohort** 126 GPA **Recent cohort** 366 GPA	249 (50.6) **Old cohort** 67 (53.2) **Recent cohort** 182 (49.7)	Population based	Non- inception	ICD 8,9 and 10 plus case note reviews with ACR criteria	**-** **Old cohort** 49.3 **Recent cohort** 54.5	203 (41.3) **Old cohort** 67 (53.2) **Recent cohort** 136 (37.2)	1-year survival 83% 5-year survival 74% **Old cohort** 1-year survival 4.9% 5-year survival 6.2% **Recent cohort** 1-year survival 82% 5-year survival 74%	3.43 (2.98-3.94) Female 4.38 (3.59-5.61) Male 2.80 (2.28-3.41)	8
Flossmann/ 2011	15 European countries (multi-center)	Prospective cohort	1995-2002	5.2 (median)	535 AAV - 281 GPA - 254 MPA	247 (46.2)	Tertiary hospital	Inception	CHCC	61 (median)	133 (24.9)	1-year survival 88% 5-year survival 78%	2.6 (2.2-3.1)	8
Holle/2011	Germany (single center)	Retrospective cohort	1994-2002 **Cohort 1** 1966-1993 **Cohort 2** 1994-1998 **Cohort 3** 1999-2002	**- (median)** **Cohort 1** 6.6 **Cohort 2** 7.3 **Cohort 3** 3.9	445 GPA **Cohort 1** 155 GPA **Cohort 2** 123 GPA **Cohort 3** 167 GPA	222 (49.9) **Cohort 1** 79 (51) **Cohort 2** 61 (49.6) **Cohort 3** 82 (49.1)	Tertiary hospital	Inception	ACR	**- (median)** **Cohort 1** 48 **Cohort 2** 52 **Cohort 3** 55	43 (9.6) **Cohort 1** 22 (14.2) **Cohort 2** 13 (10.6) **Cohort 3** 8 (4.8)	N/A	1.58 (1.14-2.13) **Cohort 1** 2.1 (1.34-3.25)# **Cohort 2** 1.41 (0.75-2.42)# **Cohort 3** 1.03(0.44-2.03)# Female 1.23 (0.66-2.11) Male 1.8 (1.22-2.58) Young patients 5.77 (2.6-10.95) Young males 8.87 (4.05-16.8)	9

													Cancer mortality 0.65 (0.24-1.43)	
Moosig/ 2013	Germany (single center)	Retrospective cohort	1990-2009	5.2	150 EGPA	74 (49.3)	Tertiary hospital	Non- inception	ACR	49.1	12/142 (8.5)	5-year survival 97% 10-year survival 89%	1.29 (0.66-2.12) EGPA-associated heart failure SMR 3.06 (1.10-6.00)	10

Abbreviations: RLV, renal limited vasculitis; PAN, polyarteritis nodosa; EMEA, European Medicines Evaluation Agency; ICD, International Classification of Diseases (8, 9 and 10 denotes 8th, 9th and 10th revision respectively)
^ 5-year SMRs computed into meta-SMR as 2 cohorts
* Computed into meta-SMR as 2 cohorts
# Computed into meta-SMR as 3 cohorts

studies, in non-inception cohorts, in multicenter studies, and in cohorts enrolled prior to 2000 (**Table 2**). All subgroups showed significantly increased mortality risk compared to the general population, although we observed a decreasing mortality trend in newer cohorts. Despite the differences in mortality within subgroups, only "center" was significantly associated with the observed heterogeneity using meta–regression analysis (p=0.05).

The results of the jack-knife sensitivity analysis are shown in **Table 3**. The meta-SMR remained significantly increased with every sequential study exclusion, with the point estimates ranging from 2.6 to 2.9 and the corresponding 95% CI remaining >1 in all analyses. This suggested that the meta-SMR result was robust and not skewed by a single dominant study.

The funnel plot is shown in **Figure 3.** Each plot represents individual cohorts and the solid line is the log of the meta-SMR. The distribution of our data points was symmetrical; therefore, we concluded that there was no significant publication bias or small-study effect. The Egger's test for presence of asymmetry in the data was not significant (p=0.308).

Table 2: Overall mortality and sensitivity analyses for the 10 studies (14 unique cohorts) in patients with AAV

Study subset	No. cohorts	No. patients	No. death events	Random-effects meta-SMR (95% CI)	p
All studies	14	3338	1091	2.71 (2.26-3.24)	
Disease definition					
GPA only (homogeneous)	7	1987	804	2.63 (2.02-3.43)	NS
AAV mixed (heterogeneous)	6	1125	257	2.59 (1.99-3.37)	
Sex					
Females	5	611	147	3.36 (2.10-5.38)	NS
Males	5	636	172	3.11 (2.21-4.36)	
Study population					
Population-based	4	1691	763	3.37 (2.73-4.17)	NS
Hospital/clinic-based	10	1647	328	2.39 (1.86-3.09)	
Cohort type					
Inception	9	1286	270	2.30 (1.69-3.13)	NS
Non-inception	5	2052	821	3.22 (2.57-4.05)	
Midpoint of enrolment period					
1980-1993	5	1821	784	3.43 (2.79-4.21)	NS
1994-1999	4	1003	236	2.82 (2.14-3.72)	
2000-2005	5	514	71	1.92 (1.12-3.29)	
Center					
Multi-center	7	2549	983	3.27 (2.73-3.91)	0.05
Single center	7	789	108	1.89 (1.17-3.07)	

Table 3: Sensitivity analysis using the jack-knife approach

Author/Year published	**All-cause mortality SMR (95% CI)**	**Study excluded, meta-SMR (95% CI)**
All studies	2.7 (2.3-3.2)	Not applicable
Matteson 1996	4.7 (3.4-6.0)	2.6 (2.1-3.1)
Knight 2002	4.0 (3.6-4.3)	2.6 (2.1-3.1)
Booth 2003	2.8 (2.5-3.2)	2.7 (2.2-3.3)
Lane 2003	4.8 (2.9-6.6)	2.6 (2.1-3.1)
Mohammad 2009 (GPA cohort)	1.8 (0.8-2.7)	2.8 (2.3-3.4)
Mohammad 2009 (MPA cohort)	4.0 (2.5-5.4)	2.6 (2.2-3.2)
Eriksson 2009 (Old cohort)	2.5 (0.9-5.5)	2.7 (2.3-3.3)
Eriksson 2009 (New cohort)	1.6 (0.6-3.2)	2.8 (2.3-3.3)
Takala 2010	3.4 (3.0-3.9)	2.6 (2.1-3.2)
Flossmann 2010	2.6 (2.2-3.1)	2.7 (2.2-3.3)
Holle 2011 (Cohort 1)	2.1 (1.3-3.3)	2.8 (2.3-3.3)
Holle 2011 (Cohort 2)	1.4 (0.8-2.4)	2.8 (2.4-3.4)
Holle 2011 (Cohort 3)	1.0 (0.4-2.0)	2.8 (2.4-3.4)
Moosig 2013	1.3 (0.7-2.1)	2.9 (2.4-3.4)

DISCUSSION

This is the first systematic review and meta-analysis of observational studies assessing the mortality risk in patients with AAV. We found a 2.7-fold increased risk of death in AAV patients when compared to the general population with no differences between sexes. Analysis on studies that included only GPA cases also indicated a similar mortality risk. Of interest, mortality risks were higher in earlier cohorts i.e., those with their midpoint of enrolment periods that were between 1980-1993 and 1994-1999, relative to those between 2000-2005 with a trend towards improvement over time.

Our meta-analyses did not show any significant difference in mortality between females and males. Individual studies have reported contrasting mortality risks between genders, with some favoring females [16, 22] and others favoring males.[9, 13, 25] It was interesting to note that in the study by Holle et al., young AAV patients (median age 31.7 years) were almost 6-times more likely to die than the age-matched general population with the entire risk contributed by young males (SMR 8.87 [95% CI 4.05-16.8) as there were no deaths amongst the 80 females within the same cohort.[22] The authors postulated that the higher mortality risk in young males were due to a higher frequency of renal involvement at diagnosis.

The secular decline in mortality risks was an interesting observation. Although the overall comparison between the cohorts was non-significant, there was a trend towards significance when we compared the earliest to the most recent cohorts (1980-1993 vs. 2000-2005, p=0.06). A similar finding was reported in a

recent mortality study in GPA patients.[42] In that study, 465 GPA patients were followed over a 20-year period and the authors found significantly improved hazard ratios for mortality between an early cohort (1992-2002) and a late cohort (2003-2013) (4.34 [95% CI 2.72-6.92] vs 2.41 [95% CI 1.74-3.34], respectively, p=0.04). We hypothesize that this observation may have resulted from therapeutic improvements, earlier diagnosis with increased availability of ANCA testing and increased physician awareness, as well as improved overall patient care in terms of CVD risk modification, drug toxicity prevention strategies, and cancer surveillance. Significant changes in the past decade on the way we treat AAV patients include the use of pulsed cyclophosphamide and rituximab, as less toxic therapeutic options.[43-45] There were insufficient data to directly assess impact of treatment strategies on mortality in this meta-analysis. Future studies will be needed to confirm the improvement in mortality.

We found a significant difference in reported mortality risks from multi-center studies compared to single center studies. In fact, single center studies had the lowest meta-SMR of 1.89 (95% CI 1.17-3.07). The observed mortality difference between single and multi-center studies were likely due to clinical differences in the respective patient populations, particularly in terms of the proportion and severity of renal involvement. Unfortunately, we were unable to test this hypothesis given that not all of the primary studies adequately described this type of data.

Unexpectedly, there was a trend towards higher mortality in the non-inception cohorts when compared to inception cohorts, although this did not reach

statistical significance. One might expect higher mortality to be associated with inception cohorts as they capture the entire natural history up until the end of follow up. However, inception cohorts may not follow patients for sufficiently long periods of time to capture late mortality risks, i.e., deaths due to long term disease or treatment-related complications such as cancer, cardiovascular disease, or chronic renal failure. Non-inception cohorts by design would include prevalent as well as incident cases and late mortality may be captured as the observation time begins at any point of the natural history. Unfortunately, we were unable to compare mean disease duration for the inception vs non-inception cohorts given that some reported mean times (n=5), some median times (n=6) and others none provided (n=2).

It was also interesting to note the trend for increased risk of death in studies that were population-based compared to those that were hospital/clinic-based. The risk estimates from population-based studies were more consistent, whereas there was wider variability in the estimates from hospital/clinic based studies. The variability in the latter subgroup was not unexpected, given the likelihood of biases inherent in selected or referral cohorts. We suggest that further research in population-based cohorts is necessary to add to the current pool of knowledge.

Our study has several limitations. A common issue with meta-analyses is the comparability of the cohorts and the appropriateness of the comparison. We included cohorts that were clinically different in terms of enrolment period, AAV subgroups, classification criteria, follow up, disease severity, and study design. We

adopted the random-effects model to incorporate the between-study heterogeneity into the analysis and provided an objective measure of the heterogeneity in the form of I^2. Significant heterogeneity was detected, as expected in meta-analyses of observational studies.[40] From the univariable meta-regression analysis, "center" and "enrolment period" were possible explanations for the heterogeneity (p=0.05 and p=0.06[cohorts 1980-1993 vs. 2000-2005], respectively). Furthermore, we performed a limited multivariable meta-regression analysis using these two variables. However, both variables were not significant predictors in the multivariable model. For this reason, our findings suggest that study center is associated with between-study heterogeneity, but its effects may be confounded by enrolment period.

The remaining between-study heterogeneity may be partially explained by the variability of renal involvement in the study cohorts. However, the lack of uniformity in the definition of "renal involvement" in the studies did not allow for grouping into a categorical "renal characteristic", which would be necessary for meta-regression analysis. In addition, we were also unable to include "quality score" in our meta-regression analysis as we only had one study scored as a lower quality study (≤6).

Current available data allowed us to report a meta-SMR on GPA, but not MPA or EGPA. A report on SMRs for each disease subcategory would be more clinically relevant than an overall SMR for AAV as they are clinically distinct diseases.

However, the SMR for AAV may serve as a reference point for future studies seeking to compare mortality risk differences over time.

In our meta-analysis, the SMR evaluated the mortality risk adjusted only for age and gender but did not account for other confounders. However, there is no method for adjusting the results of meta-analyses using SMRs. Meta-analyses on studies assessing risk factors or predictors of mortality in AAV is required to address these issues.

In summary, our meta-analysis indicated that there was a 2.7-fold increase in mortality amongst AAV patients compared to the general population. The pooled SMR for only GPA patients was elevated at 2.6 times the general population. The risk of death was elevated for both male and female AAV patients, with no significant difference between the genders. Furthermore, there was a trend towards improvement in mortality risks over time, which warrants further investigation. There is a need for longitudinal studies in contemporary cohorts to evaluate mortality benefits of modern therapies.

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COMPETING INTERESTS

None declared.

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