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# Treatment outcomes of ANCA-associated vasculitis in patients over age 75 years: a meta-analysis

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**Short title:** Treatment outcomes of AAV in patients  $\geq$  75 years

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1 **Background:** The benefits of treating ANCA-associated vasculitis (AAV) in advancing age remains unclear with  
2 most published studies defining elderly as  $\geq 65$  years. This study aims to determine outcomes of induction  
3 immunosuppression in patients aged  $\geq 75$  years.

4 **Method:** A cohort of patients aged  $\geq 75$  years with a diagnosis of AAV between 2006-2018 was constructed from  
5 two centres. Follow up was to two years or death. Analysis included multivariable Cox regression to compare  
6 mortality and ESRD based on receipt of induction immunosuppression therapy with either cyclophosphamide or  
7 rituximab. A systematic review of outcome studies was subsequently undertaken amongst this patient group  
8 through Pubmed, Cochrane and Embase databases from inception until 16/10/19.

9 **Results:** 67 patients were identified. Mean age was  $79 \pm 2.9$  years and 82% (n=55) received induction  
10 immunosuppression. Following systematic review, four studies were eligible for inclusion, yielding a combined  
11 total of 290 patients inclusive of our cohort. The aggregated one year mortality irrespective of treatment was 31%  
12 (CI 25% - 36%). Within our cohort, induction immunosuppression therapy was associated with a significantly lower  
13 two-year mortality risk [HR 0.29 (95% CI 0.09 – 0.93)]. The pooled HR by meta-analysis confirmed this with a  
14 significant risk reduction for death [HR 0.31 (95% CI 0.16 - 0.57),  $I^2=0\%$ ]. Treated patients had a lower pooled rate  
15 of ESRD, but was not statistically significant [HR 0.71 (95% CI 0.15 – 3.35)].

16 **Conclusion:** This meta-analysis suggests that patients  $\geq 75$  years with AAV do benefit from induction  
17 immunosuppression with a significant survival benefit. Age alone should not be a limiting factor when  
18 considering treatment.

## 19 **Introduction**

20 ANCA-associated vasculitis (AAV) tends to present with rapidly progressive renal disease, carrying a significant risk  
21 of morbidity and mortality with a poorer survival probability in those patients requiring renal replacement therapy  
22 at presentation (1). Current established immunosuppressive therapies are effective with improved patient and  
23 renal survival (2, 3), but their use requires careful patient selection when balanced against the potential risks,  
24 with up to 60% of deaths in the first year resulting from adverse effects of treatment (3, 4).

25 Advancing age is often considered to be a negative predictor for death and end stage renal disease (ESRD) when  
26 considering treatment in patients with AAV (5, 6). This is based on the outcomes of previously published  
27 observational studies and randomised control trials, most of which tended to categorise older age as greater than  
28 65 years and may not provide an accurate representation of those with advancing age (4, 6-8). Subsequently,  
29 despite being a disease that predominantly effects the elderly, as well as the most common cause of biopsy  
30 proven acute kidney injury in patients over the age of 80 years, the benefit of treating AAV in older age groups  
31 remains unclear (9-12). This study attempts to address this by evaluating treatment outcomes in patients  $\geq 75$   
32 years with AAV from two centres with subsequent systematic review and meta-analysis of the published  
33 literature.

## 34 **Materials & Method**

### 35 **Participants & Study design**

36 A cohort of consecutive patients aged  $\geq 75$  years with a diagnosis of AAV between 2006-2018 was constructed  
37 from two centres; one in the United Kingdom (UK) and one in the United States of America. All participants had  
38 renal impairment secondary to AAV at the time of diagnosis. Those with missing data or dual positivity for both  
39 ANCA and anti-GBM antibodies were excluded. For the remaining patients, the following data was retrospectively  
40 collected from the time of diagnosis; demographics, clinical presentation, modified Charlson comorbidity index  
41 (CCI) (13, 14), histopathology, immunosuppression therapy, patient outcomes and laboratory values including  
42 ANCA specificity, serum creatinine and estimated glomerular filtration rate (eGFR). As renal and connective tissue  
43 disease were the conditions of interest in our cohort, a modified CCI that did not include these in its calculation  
44 was used. Total score could range from 0 to 32. eGFR was calculated using the Modified Diet in Renal Disease  
45 equation (15). Cause of death was attained from review of medical records and categorised as follows; infection,  
46 active vasculitis, cardiovascular disease, respiratory disease, peripheral vascular disease, cerebrovascular disease,  
47 malignancy and unknown cause.

48 Patients were categorised into two groups; those who received induction therapy and those who did not.  
49 Induction therapy was defined as regimes utilising either cyclophosphamide or rituximab. The dosing regimen of  
50 intravenous cyclophosphamide adopted in both centres adjusted for renal function and patient age in accordance  
51 with recommendations made by the European vasculitis study group (16, 17). Depending on local practice,

52 rituximab was administered at a dose of 375mg per square meter of body surface area per week for four weeks  
53 or as 1g every two weeks for two doses. Pulsed intravenous methylprednisolone and plasma exchange were  
54 administered according to local physician discretion. The cumulative dose range of methylprednisolone was 0.5-  
55 3g. Considerations for plasma exchange included dialysis dependence, serum creatinine >500 µmol/L or  
56 pulmonary haemorrhage. This retrospective cohort study received ethical approval from the UK Health Research  
57 Authority and Confidentiality Advisory Group and institutional review board at Johns Hopkins Hospital.

## 58 **Outcomes**

59 The primary outcomes were risk of ESRD, death and the composite outcome of death or ESRD within two years  
60 of follow up. ESRD was defined by continued use of renal replacement therapy at follow up. Secondary outcomes  
61 included serious adverse events and renal recovery. Serious adverse events of therapy were defined as infection  
62 requiring hospitalisation, new onset malignancy, thrombocytopenia, leukopenia, bone marrow suppression and  
63 complications of glucocorticoid therapy including new onset diabetes mellitus, osteoporosis and osteoporotic  
64 fractures. Renal recovery was defined as sufficient improvement in renal function to achieve dialysis  
65 independence. Renal histopathology was categorised according to the Berden histopathological classification  
66 system (18).

## 67 **Systematic review & study selection for meta-analysis**

68 A systematic review was undertaken to identify any studies evaluating outcomes in patients aged  $\geq 75$  years with  
69 AAV. Pubmed, Cochrane and Embase databases were each searched independently by two reviewers (AM & ME)  
70 from inception until 16.10.2019 using the following search strategy; "ANCA" OR "anti-neutrophil cytoplasmic  
71 antibody" OR "vasculitis" OR "PR3" OR "MPO" OR "ANCA-associated" AND "elderly" OR "old" OR "75 years" OR  
72 "geriatric" AND "ESRD" OR "end stage renal disease" OR "dialysis" OR "death" OR "survival" OR "mortality" OR  
73 "renal replacement therapy" OR "outcome". All outcome studies on patients  $\geq 75$  years with AAV, inclusive of those  
74 presenting data as a subgroup analysis, were included. Case reports, editorials, letters to the editor, review  
75 articles, conference abstracts and studies not published in English were excluded from review. Eligible studies  
76 were independently screened and reviewed by two authors. In instances of disagreement, resolution by  
77 consensus was sought. The methodological quality and risk of bias of eligible studies was assessed using the  
78 Newcastle-Ottawa scale for observational studies. The protocol for this review was registered and published on  
79 PROSPERO ([http://www.crd.york.ac.uk/PROSPERO/display\\_record.php?ID=CRD42019123279](http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019123279)).

80 Two investigators independently undertook data extraction using a predefined criterion. The study characteristics  
81 extracted for inclusion in meta-analysis were as follows; year of publication, study type, sample size of participants  
82 aged  $\geq 75$  years, male percentage, the number of participants who received induction immunosuppression, follow  
83 up period, the rate of death and ESRD at one and two years, the rate of serious adverse events and the hazard  
84 ratios for death and ESRD in treated and untreated participants.

## 85 **Statistical analysis**

86 Patient characteristics were presented as mean  $\pm$  SD or median for continuous variables and proportions for  
87 categorical variables. A comparison between treated and untreated groups were analysed utilising t-Tests, Mann-  
88 Whitney, chi- squared or Fisher exact tests where appropriate. Patient survival times were calculated from the  
89 point of diagnosis until death, two years, loss to follow up or end of study (01/12/2018). Renal survival was  
90 calculated similarly with the addition of censor for death. The risk of death, ESRD and death or ESRD were studied  
91 using univariate and multivariable cox regression models, presented as hazard ratios (HR) with 95% confidence  
92 intervals (CI). The following parameters were adjusted for in the final model; use of induction  
93 immunosuppression, gender, CCI, eGFR at the time of diagnosis and the presence of renal limited disease. Gender  
94 and co-morbidity index were selected to reflect patient characteristics. eGFR was selected an indicator of disease  
95 severity and predictor of renal outcome. Renal limited disease was selected as a predictor variable as the absence  
96 of multi-system disease may confer a survival advantage. Univariate Kaplan-Meier curves were constructed to  
97 complement the cox regression hazard models for death, ESRD and death or ESRD. The rate of serious adverse  
98 events and impact of intravenous methylprednisolone were analysed utilising t-tests, Mann-Whitney, chi-squared  
99 or Fisher exact tests where appropriate.

100 The systematic review was conducted in accordance with PRISMA guidelines. A random effects meta-analysis  
101 model was used to calculate pooled HR for ESRD and death by treatment status. Study heterogeneity was  
102 evaluated using chi- square with a significance level of  $P < 0.10$  and  $I^2$  statistics. Thresholds for  $I^2$  statistics were as  
103 follows; low (25-49%), moderate (50-74%) and high (>75%).

## 104 **Results**

### 105 **Study Population**

106 Follow up data was completed in 67 patients aged  $\geq 75$  years, of which 98.5% (n=66) had disease confirmed on  
107 renal biopsy. Descriptive baseline characteristics for this cohort according to treatment status are shown in Table  
108 1. Mean age was  $79 \pm 2.9$  years with a mean follow up period of  $1.7 \pm 0.62$  years. Renal biopsy data was available  
109 in 94% of patients (n=63) with focal disease as the most common histological subtype as defined by the Berden  
110 classification (18). Just under half of patients had renal limited disease and ANCA serology was positive in 86.6%  
111 of patients (n=58) with a predominance for MPO serotype.

112 Induction immunosuppression with cyclophosphamide or Rituximab was given to the majority of patients (82%).  
113 All received concomitant oral steroids and cyclophosphamide was the most commonly used agent with a median  
114 cumulative dose of 2.73g (interquartile range 7.14–1). 3 patients failed treatment with cyclophosphamide and  
115 warranted continued therapy with rituximab. The non-induction cohort consisted solely of patients from the UK  
116 centre. Amongst this group, three patients received alternative oral immunosuppression at the time of diagnosis;  
117 two with azathioprine and steroids, one with steroids alone. From the induction and non-induction cohorts, 44

118 and 9 patients were alive and dialysis independent at 6 months, respectively. Maintenance therapy amongst these  
119 patients is shown in Table 1.

120

121 A total of thirty-three patients received intravenous methylprednisolone; 56.4% (n=31) vs. 16.7% (n=2) in the  
122 induction and non-induction therapy cohorts respectively. Dosing data was available in twenty-nine patients with  
123 mean dose of  $2.24 \pm 0.8$  grams across both groups. Twelve (21.8%) patients in the induction therapy cohort  
124 received plasma exchange with treatment data available in ten cases. The median number of sessions  
125 administered was five. No patients in the non-induction therapy cohort received plasma exchange. Of the 67  
126 patients in our cohort, 26 were aged  $\geq 80$  years with 88.5% (n=23) receiving induction immunosuppression.

### 127 **Outcomes of study population**

128 Clinical outcomes according to treatment status are outlined in Table 2. Three patients (4.5%) died within the first  
129 three months of diagnosis, of which only one received induction therapy. The overall one and two-year survival  
130 rates irrespective of treatment were 79.1% (n=53) and 76.1% (n=51) respectively. The use of induction  
131 immunosuppression was associated with a significant reduction in the risk of death [HR 0.29 (95% CI 0.09–0.93)]  
132 (Table 3). Of the 16 deaths at the end of the two-year follow up period, one confirmed case was attributable to  
133 underlying vasculitic disease. The leading cause of death in the non-induction cohort cannot be commented on  
134 due to incomplete data with an unknown cause of death in 80% (n=4) of cases. Amongst those receiving induction  
135 therapy, infection was the leading cause of death.

136 Eighteen patients (26.9%) required dialysis within thirty days of their initial presentation, with no new cases of  
137 dialysis dependence beyond this point throughout the follow up period. Of these patients, 15 received induction  
138 immunosuppression, with four recovering renal function by twelve months. At the end of the two year follow up  
139 period the rate of ESRD was 20% (n=11) and 16.7% (n=2) in the induction and non-induction cohorts respectively.  
140 In multivariable cox regression analysis, renal survival was similar between the two groups [HR 1.17 (95% CI 0.25–  
141 5.54)] (Table 3). A higher eGFR at the time of initial diagnosis was associated better renal survival [HR 0.75 (95%  
142 CI 0.63–0.89)] (Table 3).

143

144 The therapeutic benefit of induction immunosuppression was maintained on assessing the composite outcome  
145 of death or ESRD ([HR 0.33 (95% CI 0.12–0.86)] (Table 3). Supplementary figures 1-3 depicts univariate Kaplan-  
146 Meier survival curves for death, ESRD and death or ESRD by induction immunosuppression.

147 On subgroup evaluation of patients  $\geq 80$  years, 88% (n=23) received induction immunosuppression with a  
148 mortality rate of 21.7% (n=5) and all deaths occurring within 12 months of diagnosis. Acknowledging that analysis  
149 may be limited the small sample size, use of induction immunosuppression did not confer a higher risk of death  
150 in this group upon restricting the multivariable cox regression model to those aged  $>80$  years [HR 0.01 (95% CI 0–  
151 0.84)] (supplementary Table1). No deaths or episodes of ESRD occurred within the first year in untreated patients  
152  $\geq 80$  years.

153 No instances of death or ESRD occurred in those patients receiving rituximab. Meaningful analysis of  
154 cyclophosphamide versus rituximab as outcome predictors was limited. Twenty-eight patients (41.8%)  
155 experienced serious adverse events, comprising of 22 patients from the induction cohort and 6 from the non-  
156 induction cohort. Overall, infection accounted for the majority of cases. The use of induction immunosuppression  
157 did not confer a higher risk of serious adverse events ( $p=0.54$ ). Similarly, the rate of adverse events did not  
158 significantly differ between those patients who received intravenous methylprednisolone and those who did not;  
159 42.9% ( $n=12$ ) vs. 57.1% ( $n=16$ ) respectively ( $p=0.46$ ).

## 160 **Systematic Review & Study Selection**

161 The process of study selection is outlined in supplementary Figure 4. Thirteen citations qualified for full text  
162 review. Nine were published as abstracts only and subsequently excluded. Characteristics of the four remaining  
163 eligible studies are summarised in supplementary Table 2.

164 Only three studies categorised patients according to the use of immunosuppressive therapy; Bomback *et al*,  
165 Weiner *et al* and Sato *et al*, with an aggregated total of 175 patients receiving induction immunosuppression (19-  
166 21). The most commonly used agent was cyclophosphamide (72.6%) with the majority receiving oral therapy  
167 (59%). Statistical analysis with stratification according to the use of induction immunosuppression was  
168 undertaken by two studies; Weiner *et al* and Bomback *et al* (19, 20). The control group in Weiner *et al* consisted  
169 of untreated patients as well as those receiving alternative regimes such as azathioprine, methotrexate or  
170 mycophenolate. The control group in Bomback *et al* consisted of untreated patients only.

## 171 **Meta-analysis results**

172 With the addition of our cohort, a sample size of 290 patients aged  $\geq 75$  years with AAV were available for review.  
173 The one year mortality rate irrespective of treatment was 31% (CI 25%-36%). Weiner *et al* and Bomback *et al* both  
174 used multivariable cox models to analyse the hazard of death and ESRD with induction therapy. Their results in  
175 conjunction with the findings from our presented cohort were used to present the pooled HR for death and ESRD  
176 by meta-analysis in 258 patients. The use of induction immunosuppression demonstrated a significant benefit for  
177 patient survival with a pooled hazard ratio for death of 0.31 (95% CI 0.16-0.57) [ $I^2 = 0\%$ ] (Figure 1). Induction  
178 therapy was also associated with a lower pooled rate of ESRD, although not statistically significant [HR 0.71 (95%  
179 CI 0.15–3.35)] (supplementary Figure 5). Serious adverse events were available for two studies with a combined  
180 cohort of 105 treated patients and an incident rate of 38.1% ( $n = 40$ ).

## 181 **Discussion**

182 To date there has been limited published data guiding treatment outcomes of AAV in older populations and the  
183 potential benefit of utilising established induction immunosuppression in those aged  $\geq 75$  remains poorly defined.



184 This represents an area of increasing clinical need owing to an overall rise in the both the incident and prevalence  
185 of disease, with the former rising from 8-10/million to 13-20/million over recent years (9, 10, 22). The present  
186 study addresses this by reporting the experiences of two centres followed by a meta-analysis of published studies.  
187 In doing so we identified a clear survival benefit in patients  $\geq 75$  years treated with induction immunosuppression  
188 with either Cyclophosphamide or Rituximab.

189 Within the first twelve months of treatment, the greatest risk to patient survival is adverse effects of therapy  
190 rather than active vasculitis, with up to 60% of deaths resulting from infection (4, 8). It is considered that with  
191 increasing age, a patient's ability to tolerate any significant immunosuppression is reduced with a higher  
192 propensity to succumb to such adverse effects. Although not by study design, recent landmark trials in the  
193 management of AAV have tended to only include patients under the age of 75 years (17, 23-25) and to date the  
194 majority of observational studies reviewing the outcome of patients with AAV have often considered older age as  
195 being greater than 65 years (2, 5-7, 26, 27). These have identified age  $\geq 65$  years as a poor prognostic marker for  
196 patient outcomes and in view of this, it would be anticipated that patients older than 75 years would fare even  
197 worse.

198 In a retrospective single centre study evaluating one-year outcomes in patients over the age of 80 years, Bomback  
199 *et al* demonstrated that treatment can prolong dialysis free survival with a remission rate of 49% and up to 37%  
200 fewer patients reaching ESRD at one year compared to the untreated cohort (19). Although the cumulative  
201 mortality rate was 49%, with most patients dying from infection rather than underlying disease, the risk of death  
202 at one year was 17% lower in treated patients (19). While this difference was not statistically significant, follow  
203 up beyond one year identified a significantly lower risk for both ESRD and death. In a similar study, Weiner *et al*  
204 evaluated the two-year survival in patients over the age of 75 years in a multi-centre retrospective study (20).  
205 Their survival analysis supported that of Bomback *et al*, identifying superior patient survival in those given  
206 induction therapy with 36% fewer deaths and a significantly lower hazard ratio for death on multivariable analysis  
207 (20). This remained unchanged on subgroup analysis of patients who received a lower cumulative dose of  
208 cyclophosphamide.

209 Within our cohort analysis, we exhibited comparable findings to previous studies with a significantly lower hazard  
210 ratio for death in treated patients. The survival benefit of induction immunosuppression persisted despite  
211 advancing age following subgroup analysis of those aged  $\geq 80$  years. There was no demonstrable benefit for renal  
212 survival. The burden of co-morbidity was similar between the two groups and parallel to the findings of Bomback  
213 *et al*, renal function at the time of diagnosis was predictive of outcomes. When considered in light of the findings  
214 of Bomback *et al*, the current evidence suggests that on its own advancing age  $\geq 80$  years should not discount  
215 patients from treatment and that despite a higher potential risk of adverse effects, certain selected elderly  
216 patients may benefit from induction immunosuppression in AAV.

217 The present meta-analysis of these observational studies confirmed a clear survival advantage of induction  
218 immunosuppression over no/other oral immunosuppression in patients  $\geq 75$  years with AAV. Similarly, a lower

219 rate of ESRD with treatment was shown, although this did not reach statistical significance. In view of these  
220 findings, the safe use a reduced dose of cyclophosphamide applied in both our cohort and Wiener *et al* suggests  
221 that the dosing regimen described by previous studies can safely be adopted in older patients, with sufficient  
222 mitigation of risk without compromising therapeutic benefit (4, 6, 7).

223 The remaining two studies of Hoganson *et al* and Sato *et al* identified on systematic review were not included in  
224 meta-analysis (21, 28). Sato *et al* was a comparative study evaluating treatment outcomes of AAV in patients aged  
225  $\geq 75$  years against those  $< 75$  years. In the cohort described, patients  $\geq 75$  years numbered ten, of which 80% did  
226 not receive induction therapy with either Cyclophosphamide or Rituximab (21). This was despite presenting with  
227 more severe vasculitic disease due to the presumption that they were more susceptible to adverse events. The  
228 implication of this selection bias is acknowledged by the authors when concluding a poorer survival rate in elderly  
229 patients. The limitation of this study design could have affected our presented pooled one year survival rate,  
230 however it did not have any implication on our subsequent meta-analysis with no stratification of outcomes by  
231 treatment status. Similarly, data from Hoganson *et al* was excluded from meta-analysis on the same basis.

232 Despite improved patient survival with induction immunosuppression, the question remains, at what cost is this  
233 achieved. Amongst other factors, advancing age has previously been associated with a higher degree of long term  
234 damage and this patient group are potentially more frail with increased susceptibility to any potential treatment  
235 related morbidity (29). In a follow-up study of their previously reported cohort, Weiner *et al* set out to address  
236 this by evaluating the potential association between end organ damage and hospitalisation rates with therapy at  
237 one and two years (30). In doing so, they identified that amongst patients  $\geq 75$  years the use of cyclophosphamide  
238 or rituximab was actually associated with a lower rate of damage (30). As disease severity at presentation is known  
239 risk factor for permanent organ damage (29), this finding likely reflects the benefit of attenuated disease activity  
240 achieved with therapy. There was no increased rate of hospitalisation or length of stay within 12 months of  
241 treatment (30).

242 The potential for treatment related damage secondary to glucocorticoids is widely accepted and reported (29,  
243 31). Although our study showed no increased risk of adverse event secondary to methylprednisolone exposure,  
244 this is likely limited by our relatively small sample size. In their more recent study, Weiner *et al* did identify an  
245 association between treatment related damage and fatal infections with a higher cumulative steroid exposure  
246 within the first three months of therapy. Taking this into account in conjunction with the findings of our study, it  
247 may be that future treatment strategies of AAV in advancing age would benefit more from minimising steroid  
248 exposure, as opposed to avoidance or further modification of current therapy with rituximab or reduced dose  
249 cyclophosphamide.

250 The findings of our study should be considered in context of its limitations. Firstly, the lack of randomised control  
251 trials and the retrospective design of all included studies limits the level of evidence that could be derived from  
252 them. Secondly, we acknowledge that the modified CCI scores observed in our cohort were seemingly low. In a

253 previous small study applying a similar modified CCI to ours at diagnosis, with the exception of weighted score for  
254 age, a higher score was associated with reduced patient and renal survival. In this study, patient age ranged from  
255 18-76 years with a mean age of  $53.2 \pm 15.63$  years and mean CCI at diagnosis of  $4.9 \pm 2.49$  (14). The lower mean  
256 CCI scores observed in our cohort would indicate a less comorbid and potentially less frail population, which would  
257 favour better outcomes and should be taken into account when interpreting our cohort results. Thirdly, allocation  
258 of treatment varied in each centre based on local expertise and clinical assessment which may have imposed a  
259 significant selection bias: a factor evident by the imbalance of untreated patients between our two centres which  
260 restricted adjustment for centre effect in the final models. This likely reflects individualisation of care based on  
261 recognition of frailty and suitability of immunosuppressive therapy; an aspect of clinical assessment which is not  
262 captured by measures such as the modified Charlson comorbidity index. A potential tool that could account for  
263 this is the Clinical Frailty Scale, a frailty screening method that has recently been validated in patients with chronic  
264 kidney disease. Its incorporation in future prospective studies could help stratify this crucial aspect of clinical  
265 judgement, further guiding future immunosuppressive therapy in renal vasculitis (32). Fourthly, statistical analysis  
266 to adjust treatment outcome according to the histological pattern of disease could not be undertaken due to  
267 limited variability and small sample size. This is a factor which may have influenced treatment decisions. These  
268 limitations should be weighed the rigorous and systematic approach of this study, as well as the previously limited  
269 data guiding treatment in our defined population.

270 The question of whether or not induction immunosuppression is of more harm than benefit in patients with AAV  
271 and advancing age is of increasing importance. The data presented here from our centres and pooled results from  
272 meta-analysis suggests that patients  $\geq 75$  years with AAV do benefit from induction immunosuppression, with a  
273 significant survival advantage within the first two years of therapy. Age alone should not be a limiting factor when  
274 considering treatment. Future trials in AAV may benefit from increasing the upper age limit at which patients are  
275 considered elderly to 75 years in order to attain more representative data.

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280 conducted in accordance with the declaration of Helsinki.

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286 **Author contributions:** Authors A.M, M.E, A.P and A.D were responsible for conception, design and oversight  
287 of the study. A.M and D.G undertook data collection. A.M and M.E undertook systematic review, data analysis  
288 and interpretation. A.M and M.E prepared the manuscript with critical review, contributions and approval from  
289 all authors prior to final submission.

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**Figure Legends:**

**Figure 1** – Forest plot of mortality risk in patients with ANCA-associated vasculitis aged  $\geq 75$  years based on the use of induction immunosuppression

**Supplementary Figure 1** – Kaplan-Meier survival curves for the outcome of death according to the use of induction immunosuppression therapy. Curves reflect univariate analysis

**Supplementary Figure 2** – Kaplan-Meier survival curves for the outcome of end stage renal disease (ESRD) according to the use of induction immunosuppression therapy. Curves reflect univariate analysis

**Supplementary Figure 3** – Kaplan-Meier survival curves for the composite outcome of death or end stage renal disease (ESRD) according to the use of induction immunosuppression therapy. Curves reflect univariate analysis

**Supplementary Figure 4** – Flow diagram of systematic review and study selection for meta-analysis

**Supplementary Figure 5** – Forest plot of ESRD risk in patients with ANCA-associated vasculitis  $\geq 75$  years based on the use of induction immunosuppression