Clinical Kidney Journal, 2018, 1–7

doi: 10.1093/ckj/sfy084
Original Article

ORIGINAL ARTICLE

Comparing outcomes of biopsy-proven anti-neutrophil cytoplasmic autoantibody–associated glomerulonephritis patients treated with cyclophosphamide in the 20th and 21st centuries: a 23-year study

Steven Whatmough[1], Sophie Fernandez[1], Niamh Sweeney[1], Laura Howell[2] and Ajay Dhaygude[1]

[1]Renal Department, Royal Preston Hospital, Preston, UK and [2]Faculty of Health and Wellbeing, University of Central Lancashire, Preston, UK

Correspondence and offprint requests to: Steven Whatmough; E-mail: steven.whatmough@nhs.net

ABSTRACT

Background. Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is a multisystem autoimmune disorder associated with significant morbidity and mortality. Approximately 80–90% of patients have circulating ANCAs. Long-term outcomes appear to be improving. This retrospective study analyses the incidence and patient outcomes over a period of 23 years at a single tertiary centre.

Methods. Outcomes of patients diagnosed with AAV between 1 January 1988 and 31 December 2010 were collected retrospectively. Data including patient demographics, age of diagnosis, dates of starting renal replacement therapy, death and biochemistry results were collected. Patients were divided into two cohorts (1988–99 and 2000–10) and analysed using Stata software (StataCorp, College Station, TX, USA).

Results. A complete dataset was obtained for 273 patients. Of these patients, 101 were diagnosed between 1988 and 1999 while 172 were diagnosed between 2000 and 2010. The number of patients diagnosed with AAV increased from 2.2/million in 1988 to 10.3/million in 2010. A higher proportion of patients (56.4%) in the earlier cohort presented with creatinine $>500\ \mu$mol/L compared with the later cohort (30.2%; $P < 0.001$). Overall patient survival improved significantly between the two cohorts. Cohort 1 had a median survival of 59 months compared with 125 months for Cohort 2 ($P = 0.003$).

Conclusions. This study shows that AAV is being diagnosed at an earlier stage, resulting in improved outcomes. This may be because of improvements in the management of AAV and chronic kidney disease.

Keywords: ANCA, epidemiology, survival, vasculitis

Received: 18.3.2018. Editorial decision: 31.7.2018

INTRODUCTION

Anti-neutrophil cytoplasmic autoantibody (ANCA)–associated vasculitis (AAV) is a multisystem disease associated with significant morbidity and mortality. Approximately 80–90% of patients demonstrate the presence of circulating ANCAs. Three major phenotypes are described: granulomatosis with polyangiitis (GPA), eosinophilic GPA and microscopic polyangiitis. Although AAV is usually considered a single entity, there remain significant differences in genetics, epidemiology, clinical presentations and outcomes in the major three phenotypes. Untreated systemic AAV has a mortality rate of 90% within the first 2 years [2]. Treatment with immunosuppression has made significant improvements in survival outcomes, with the 5-year survival rate reaching 75% [3]. Several factors are associated with outcomes in AAV: early diagnosis, organ involvement, presenting renal function, immunosuppression, ANCA serotype, clinical phenotype, renal histology and the number of relapses [4–8]. Recent advances in the understanding of the pathogenesis, increased awareness and advancements in treatment protocols may be associated with increased patient survival.

An increased tendency to optimize immunosuppression with reduced use of cyclophosphamide and prednisolone could be responsible for improvements in infection-related vasculitis outcomes. Furthermore, chronic kidney disease (CKD) management has changed with the widespread use of renin–angiotensin–aldosterone system blockers and statins and rigid blood pressure targets should reduce cardiovascular outcomes. Published data from Germany and Holland have confirmed this [9, 10].

In this study we analysed outcomes of 273 AAV patients diagnosed and treated in a single tertiary centre over a period of 23 years.

MATERIALS AND METHODS

A retrospective study was performed to analyse outcomes of all the patients diagnosed with AAV at a single centre between 1 January 1988 and 31 December 2010. Follow-up continued up to 1 January 2014. Our centre is a regional tertiary renal service provider for the population of Lancashire and South Cumbria. This includes East Lancashire Hospitals (Blackburn Hospital), West Lancashire Hospitals (Blackpool Victoria Infirmary) and North Lancashire Hospitals including Lancaster Royal Infirmary, Westmorland General Hospital and Furness General Hospital. Patients from North Cumbria are not part of our catchment area and were not included. Multiple databases were screened for complete information. Data were collected using the electronic records of kidney biopsies performed in patients diagnosed with AAV. All the biopsies confirming pauci-immune necrotizing glomerulonephritis with or without crescent formation were considered as evidence of small-vessel vasculitis. The Histopathology Department uses immunohistochemistry for diagnosing immune complex deposits. If non-specific immune complex staining was reported, then a lack of immune dense deposits on electron microscopy was essential for inclusion of the patient. All the biopsy reports were reviewed by two assessors (S.W. and A.D.). Electronic patient records were assessed to confirm if patients met the inclusion and exclusion criteria. The department also maintains an accurate cyclophosphamide database. This was reviewed along with the biopsy database to find all eligible patients. Patients were excluded if they were <16 years of age, had positive anti–glomerular basement membrane (anti–GBM) antibodies, were only treated with azathioprine and/or prednisolone or they were deemed unfit for renal biopsy and/or cyclophosphamide-based immunosuppression.

Electronic patient records were analysed in order to collect data regarding ANCA serology, patient demographics, renal survival and patient survival. ANCA testing took place by indirect immunofluorescence (IIF). IIF was introduced in the centre during the early 1990s, although the exact year is not known. Enzyme-linked immunosorbent assay (ELISA) for proteinase 3 (PR3) and myeloperoxidase (MPO) was introduced later. Our laboratory is a recognized regional centre for immunology work and currently used the Phadia assay for ANCA.

All patients were treated with intravenous pulse cyclophosphamide and tapering doses of glucocorticoids. Plasma exchange was used for severe presentations of AAV, defined as presenting creatinine $\geq 500\,\mu$mol/L and/or pulmonary haemorrhage. Our centre started using plasma exchange treatment for AAV around 2000. It became standard practice in 2003 for patients meeting the criteria set out by the European Vasculitis Study Group (EUVAS) trials. Maintenance of immunosuppression was a combination of azathioprine or mycophenolate mofetil with low-dose glucocorticoids. Data regarding immunosuppression treatments in two cohorts were not available and therefore comparisons of treatment could not be made. The CYCLOPS trial (Randomised Trial of Daily Oral versus Pulse Cyclophosphamide as Therapy for ANCA-associated Systemic Vasculitis) was published in 2009 and this protocol has been used since 2009 [11]. Prior to 2009, patients were treated with monthly pulses of intravenous cyclophosphamide for at least 6 months. Plasma exchange indications remained the same during the study period; however, exact details of patients receiving this treatment in each cohort were not available. Patients who had inadequate data were excluded ($n = 41$). The remaining 273 patients were followed up until the last appointment (1 January 2014) or death.

To compare the outcomes, patients were divided into two cohorts according to the year of diagnosis:

- Cohort 1: diagnosed between 1 January 1988 and 31 December 1999 (12 years)
- Cohort 2: diagnosed between 1 January 2000 and 31 December 2010 (11 years).

The chi-squared test or Fisher's exact test compared categorical patient characteristics between the two cohort groups. Kaplan–Meier curves and the log-rank test were used in an unadjusted univariate analysis to determine which variables should be included in a Cox regression model for predicting patient and renal survival, respectively. Variables were retained for Cox regression modelling if the P-value was ≤ 0.1. Cox regression modelling compared patient and renal survival times between the two cohorts after adjusting for other factors that were found to be significantly associated with patient and renal survival, respectively, in the univariate analyses. The proportionality assumption, which is needed for Cox regression, was assessed, including time covariates in the model and looking at the Schoenfeld residuals.

Statistical analyses were performed using Stata software (StataCorp, College Station, TX, USA) [1].

Ethical approval

This study protocol was reviewed by the Hospital Research and Development directorate and was approved as a service evaluation project without a need for formal ethics approval.

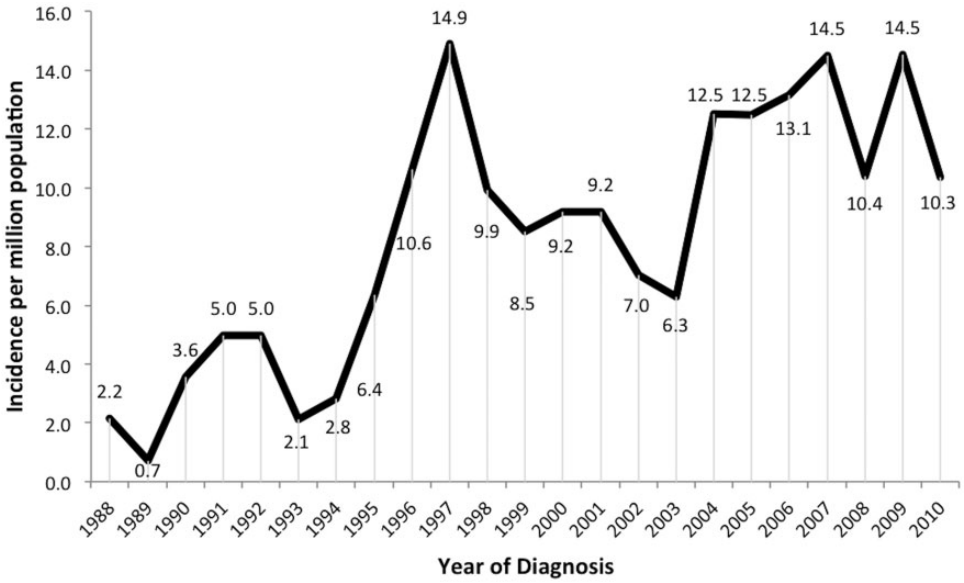

FIGURE 1: Patients diagnosed with AAV per million population by the year of diagnosis.

RESULTS

Diagnosis of small-vessel vasculitis

In the area of Lancashire and South Cumbria, the incidence of biopsy-proven renal involvement of AAV increased from 2.2/million in 1988 to 10.3/million in year 2010 (Figure 1). In this study, a total of 314 patients with AAV were identified.

Of the 314 patients, 41 had insufficient data and were excluded from the analysis. Of the remaining 273 patients, 101 were diagnosed between 1988 and 1999 (Cohort 1) and 172 patients were diagnosed between 2000 and 2010 (Cohort 2). The median age of patients was 62 years: Cohort 1 had a median age of 61 years and Cohort 2 had a median age of 63 years. The median regional annual incidence of biopsy-proven renal involvement of AAV was found to be 9.2/million population. This was highest between 75 and 79 years of age (Figure 2). The average age at diagnosis was 59 years [standard deviation (SD) 15.8]. The main characteristics of the cohorts are shown in Table 1.

The median follow-up of all patients was 57 months [interquartile range (IQR) 77.3] and that of still alive patients was 81 months (IQR 79.8).

There was a significantly higher proportion of patients with a creatinine concentration >500 μmol/L at the time of diagnosis ($P < 0.001$) in Cohort 1 compared with Cohort 2. For Cohort 1, the median creatinine at diagnosis was 705 μmol/L (IQR 585) and for Cohort 2 was 333 μmol/L (IQR 369.3). These remained true when only patients with known ANCA status were included. For those with known ANCA status, the median creatinine results for Cohorts 1 and 2 were 614 μmol/L (IQR 739.8) and 330 (362.5), respectively ($P \leq 0.001$). There was a significantly lower proportion of patients ≥75 years of age in Cohort 1 compared with Cohort 2 ($P = 0.02$). This result was not significant when only patients with known ANCA status were included ($P = 0.10$). In Cohort 1, the ANCA status was unknown in 42 of the 101 patients.

ANCAs were discovered in 1981 and the significance of their association was established 4 years later. Even after the association of ANCA and small-vessel vasculitis was established in 1985, it took many years for standardization of the assay and acceptance of it as a clinical tool. Furthermore, antigen-specific ELISA was discovered later. Overall, ANCAs were not used routinely until the early 1990s in most centres, including ours. This explains the high percentage of unknown ANCA status for patients in Cohort 1. ANCA measured by IIF and ELISA at the time of diagnosis or noted to be positive during any stage of follow-up were included for assessment. In Cohort 2, only three patients had an unknown ANCA status.

Patient survival using all patients

Overall, 1-, 5- and 10-year patient survival was 78.8, 49.5 and 19.1%, respectively. Overall, the median survival for all patients was 60 months. The Kaplan–Meier patient survival curves for the two cohorts ($n = 273$) are shown in Figure 3. Cohort 1 had a median patient survival of 59 months compared with 125 months for Cohort 2 ($P = 0.003$).

Unadjusted univariate analysis, using the log-rank test, found that patients diagnosed at ≥75 years of age ($P = 0.013$) and with creatinine ≥500 μmol/L ($P = 0.035$) were significantly associated with worse survival rates. Gender approached statistical significance ($P = 0.08$).

In the adjusted analysis, Cohort 1 and patients >75 years of age had a worse prognosis when compared with their counterparts ($P = 0.001$ and $P = 0.002$, respectively). The estimated hazard ratio for Cohort 2 was 0.55 when compared with Cohort 1. The estimated hazard ratio for patients ≥75 years of age was 2.03 (Table 2).

Renal survival using all patients

Overall, renal survival for 12 months was 54.2%. This dropped to 33.7% at 5 years and was 12.5% at 10 years. The median death-censored renal survival was only 25 months and death-uncensored renal survival was 65 months. The Kaplan–Meier renal survival curves for the two cohorts ($n = 273$) are shown in Figure 4. Cohort 1 had a median renal survival of 9 months compared with 43 months for Cohort 2 ($P = 0.003$). Of the patients who required initial renal replacement therapy, 17% experienced renal recovery.

Unadjusted univariate analyses, using the log-rank test, for male gender ($P = 0.033$) and diagnosis creatinine ≥500 μmol/L

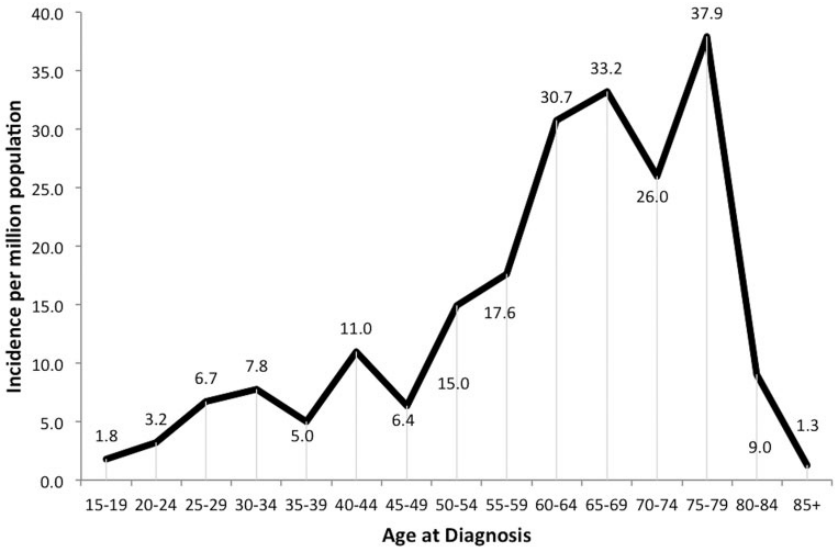

FIGURE 2: Patients diagnosed with AAV between 1988 and 2010 across different age groups.

Table 1. Patient characteristics for Cohort 1 (1988–99) and Cohort 2 (2000–10)

Variable	1988–99 ($n = 101$)	2000–10 ($n = 172$)	P-value
Gender, *n* (%)			
Male	62 (61.4)	96 (55.8)	0.38
Age, *n* (%)			
≥75 years	9 (8.9)	34 (19.8)	0.02
Creatinine, *n* (%)			
≥500 μmol/L	57 (56.4)	52 (30.2)	<0.001
Creatinine at diagnosis (μmol/L), median (IQR)	705 (585)	333 (369.3)	<0.001
Patients with known ANCA status ($n = 228$)	1988–99 ($n = 59$)	2000–10 ($n = 169$)	P-value
Gender, *n* (%)			
Male	36 (61.0)	94 (55.6)	0.54
Age, *n* (%)			
≥75 years	5 (8.5)	31 (18.3)	0.10
Creatinine, ≥500 μmol/L, *n* (%)	31 (52.5)	50 (29.6)	0.002
ANCA status, *n* (%)			
PR3-ANCA	27 (45.8)	61 (36.1)	
Negative	15 (25.4)	51 (30.2)	
MPO-ANCA	17 (28.8)	57 (33.7)	0.45
Creatinine at diagnosis (μmol/L), median (IQR)	614 (739.8)	330 (362.5)	<0.001

MPO, myeloperoxidase; PR3, proteinase 3.

($P < 0.001$) were significantly associated with worse renal survival for all patients and therefore were retained in the Cox regression in addition to age at diagnosis and cohort to provide an adjusted analysis (Table 3).

In the adjusted analysis, diagnosis creatinine ≥500 μmol/L ($P < 0.001$) was significantly associated with poorer renal survival. Gender ($P = 0.08$) was approaching statistical significance and age at diagnosis ($p = 0.11$) was not found to be significant. The estimated hazard ratio for Cohort 2 was 0.75, for males it was 1.32 and for patients with diagnosis creatinine ≥500 μmol/L it was 1.77.

DISCUSSION

Two large European studies have shown that outcomes of AAV are improving [9, 10]. Although 5-year outcome data from England have been published before, long-term outcome data remain limited [6]. Our study, while confirming these findings, has also demonstrated some new insights into long-term outcomes of AAV.

Increasing diagnosis of AAV

At our centre, annual diagnosis of AAV appears to be steadily increasing over a period of two decades, from 2.2/million in 1988 to 10.3/million in 2010. A significant increase in the diagnosis was noted after introduction of ANCA assays, with this reflecting improved diagnosis of AAV [8, 12, 13]. Our data are from 1988 and ANCAs were discovered in 1985. ANCA assays were introduced in the 1990s in our centre and widespread use was not until the late 1990s. Therefore it is possible that during

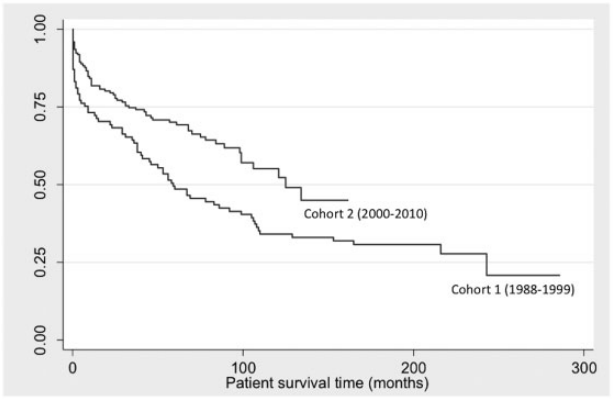

FIGURE 3: Kaplan–Meier curves showing patient survival by cohort for all patients ($n = 273$, P = 0.003). See Supplementary data, Appendix S1 for details of the number of patients at each time point.

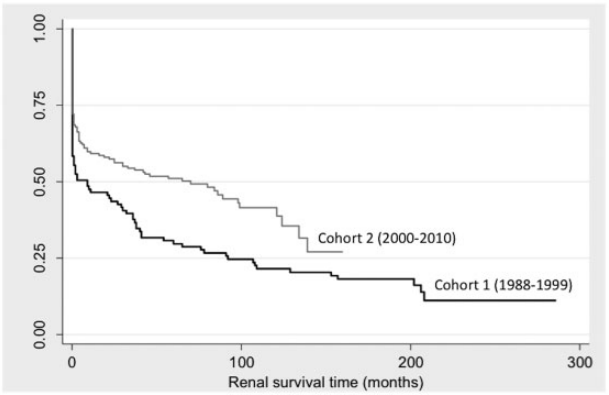

FIGURE 4: Kaplan–Meier curves showing renal survival by cohort for all patients ($n = 273$, P = 0.003). See Supplementary data, Appendix S2 for details of the number of patients at each time point.

Table 2. Hazard ratios from Cox regressions of patient survival for all patients (N = 273, deaths = 136)

Variable	Hazard ratio (95% CI)	P-value
Cohort		
2000–10	0.55 (0.39–0.79)	0.001
Age at diagnosis		
≥75 years	2.03 (1.30–3.19)	0.002
Gender		
Male	1.31 (0.92–1.86)	0.13

Table 3. Hazard ratios from Cox regressions of renal survival for all patients (N = 273, failures = 180)

Variable	Hazard ratio (95% CI)	P-value
Cohort		
2000–10	0.75 (0.55–1.03)	0.07
Age at diagnosis		
≥75 years	1.41 (0.93–2.13)	0.11
Gender		
Male	1.32 (0.97–1.78)	0.08
Creatinine ≥500 μmol/L	1.77 (1.30–2.40)	<0.001

the early years of our study, underdiagnosis of AAV occurred until the widespread use of ANCA assays became common practice. This also explains the very high number of patients with negative ANCA serology in the first cohort and the peak incidence in 1995. For the later cohort, our centre has been using the Phadia assay. Rather than a true increase in AAV incidence, we suspect that the increasing number of patients with AAV is due to these advancements in ANCA testing. These are highly sensitive and accepted assays, and although the percentage of seronegative patients decreased, it still remains higher than the published literature. Reasons behind this are unclear. Published European data suggest much greater rates of AAV diagnosis (~15–20/million population [14]. In our cohort, the number of patients diagnosed with AAV was significantly lower than expected. It is possible that a very small number of patients were hospitalized at nearby centres in earlier years and therefore were missed in the incidence calculation. As incidence was significantly low, even missing a few patients could influence the results. Furthermore, we used biopsy as a criterion for diagnosis of AAV and ~20% of patients do not have renal involvement with AAV and every patient with renal involvement may not undergo kidney biopsy. Our rate of diagnosis is higher than published UK data using similar criteria [15]. However, a recently published large histology study from the Southeast USA over the same period of time shows a similar rate of diagnosis of 7.9/million population using biopsy criteria [16].

A significantly higher proportion of patients >75 years of age were diagnosed with AAV in the later cohort (P = 0.02; Table 2). An increased acceptance of older patients undergoing invasive investigations and potentially harmful treatments may account for this. On the other hand, an increased number of patients >75 years of age being diagnosed with AAV may also explain the increased diagnosis in the later cohort. However, the increasing age in the second cohort may simply reflect the increasing age of the general population over this time period. Nonetheless, it is impossible to know if the true incidence of AAV is increasing and further epidemiological studies in the current era would be helpful to resolve this conundrum.

Our study also suggests improved diagnosis in the second cohort, similar to data found by Hilhorst *et al.* [10]. In their cohort, the average time to diagnosis had decreased over time. Although we do not have data to confirm these findings, in the later cohort, a significantly lower number of patients presented with serum creatinine ≥500 μmol/L. We postulate that this observation suggests earlier diagnosis in the later cohort of patients.

AAV survival

Overall, patient survival was better for Cohort 2. Data regarding treatment were not available, but this was expected to be a major factor influencing the survival difference in the two cohorts. However, this may not be limited to differences in treatment protocol alone. Survival benefit appears to be greatest during the early follow-up period; however, this benefit continues even during the later period. Meta-analysis of four EUVAS trials also showed very high mortality within the first 12 months, due to infections as well as active vasculitis. Clearly, improving management during this period remains crucial. Early improvement in survival is likely to be multifactorial. The EUVAS has performed several high-quality randomized controlled trials

focusing on treatment of AAV. This evidence has been pivotal in forming vasculitis treatment guidelines. These guidelines have assisted the vasculitis community in rationalizing the treatment of AAV and the possible reduction in early mortality due to infections and active vasculitis.

Regarding improved survival during long-term follow-up, again there are several reasons. With emerging evidence, it is likely that there is an increased awareness of cancer surveillance among the vasculitis community, which would reduce late mortality [17–19]. In addition to improved cancer surveillance, further reduction in late mortality in the later cohort probably reflects improved management of CKD. There were significantly more elderly patients in the second cohort. This suggests that many older patients with vasculitis would have not been included in the first cohort because they were not considered fit enough for an invasive procedure like kidney biopsy.

Recently Rhee *et al.* [20] published composite outcomes of death and end-stage renal disease (ESRD) for 544 AAV patients from the USA. They showed a significant reduction in the risk of death and ESRD over a period of 25 years. Interestingly, although they observed changes and variations in cyclophosphamide treatments over 25 years, this did not alter the outcome. There are other smaller studies with variable inclusion criteria and variable outcomes, e.g. Drooger *et al.* [21] and Caravaca *et al.* [22]. Nonetheless, it is worth noting that not all long-term epidemiology studies of AAV have shown improved outcomes.

Improved renal survival of patients with AAV, mainly GPA, in recent years has been reported in other studies [9]. In our cohort, we found a trend towards improvement of renal survival ($P = 0.07$). Serum creatinine $\geq$500 μmol/L at the time of diagnosis was significantly associated with poorer renal outcome. This finding has also been previously reported and would suggest a degree of severity of renal involvement when diagnosed with vasculitis [6, 23, 24]. Without immunosuppression, these patients would experience significant CKD and hence poor long-term outcomes. There was also a trend towards poor renal survival among male patients. Although of interest, this finding is less likely to have any impact on clinical practice. Overall, male gender is a well-known risk factor for progression of unspecified causes of CKD and some specific aetiologies such as immunoglobulin A nephropathy [25, 26].

Despite the improved renal survival, we found poor renal recovery for patients requiring initial renal replacement therapy at the time of diagnosis when compared with the published data. Although histology was essential for the diagnosis of small-vessel vasculitis, the Berden classification system was introduced in 2010 and our cohort lacks these details. An attempt was made to retrospectively classify the biopsies but was not accurate due to the lack of uniform reporting methods [27]. In a Dutch cohort, the number of patients requiring renal replacement therapy was much smaller than our cohort. Higher serum creatinine itself is associated with poor renal survival.

CONCLUSIONS

To our knowledge, this study presents the largest cohort of British AAV patients followed over 2 decades. There has been an increasing rate of diagnosis of AAV in Lancashire and South Cumbria over the last 20 years, with most patients diagnosed at 65–69 years of age. The study reassuringly shows improved overall and renal survival of AAV patients in recent decades. Although it shares all the limiting factors of a retrospective study conducted over a long period of time, it represents real clinical practice outcomes. The EUVAS trials have given the vasculitis community real insight into factors affecting survival; however, these patients are treated with a strict trial protocol designed by experts, are closely monitored and do not represent true clinical practice outcomes. We hope that this study will provide further insight to clinicians treating these complex vasculitis patients in their day-to-day practice.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

AUTHORS' CONTRIBUTIONS

S.W. was responsible for data collection and assisted with analysis and preparation of the manuscript. S.F. and N.S. were responsible for data collection. L.H. was responsible for statistics and data analysis and editing of the manuscript. A.D. was responsible for supervising, preparing and editing the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this article.

REFERENCES

1. StataCorp. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp, 2013
2. Walton E. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J* 1958; 2: 265–270
3. Flossmann O, Berden A, de Groot K *et al.* Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011; 70: 488–494
4. Hogan SL, Falk RJ, Chin H *et al.* Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med* 2005; 143: 621–631
5. Berden AE, Jones RB, Erasmus DD. Tubular lesions predict renal outcome in antineutrophil cytoplasmic antibody–associated glomerulonephritis after rituximab therapy. *J Am Soc Nephrol* 2012; 23: 313–321
6. Booth AD, Almond MK, Burns A *et al.* Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 2003; 41: 776–784
7. Hauer HA, Bajema IM, Van Houwelingen HC *et al.* Determinants of outcome in ANCA-associated glomerulonephritis: a prospective clinico-histopathological analysis of 96 patients. *Kidney Int* 2002; 62: 1732–1742
8. Cohen BA, Clark WF. Pauci-immune renal vasculitis: natural history, prognostic factors, and impact of therapy. *Am J Kidney Dis* 2000; 36: 914–924
9. Holle JU, Gross WL, Latza U *et al.* Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. *Arthritis Rheum* 2011; 63: 257–266
10. Hilhorst M, Wilde B, Van Paassen P *et al.* Improved outcome in anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis: a 30-year follow-up study. *Nephrol Dial Transplant* 2013; 28: 373–379
11. De Groot K, Harper L, Jayne DR *et al.* Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody–associated vasculitis: a randomized trial. *Ann Intern Med* 2009; 150: 670–680

12. Andrews M, Edmunds M, Campbell A *et al*. Systemic vasculitis in the 1980s—is there an increasing incidence of Wegener's granulomatosis and microscopic polyarteritis? *J R Coll Physicians Lond* 1990; 24: 284–288
13. Watts RA, Carruthers DM, Scott DG. Epidemiology of systemic vasculitis: changing incidence or definition? *Semin Arthritis Rheum* 1995; 25: 28–34
14. Watts RA, Lane SE, Bentham G *et al*. Epidemiology of systemic vasculitis. *Arthritis Rheum* 2000; 43: 414–419
15. Hedger N, Stevens J, Drey N *et al*. Incidence and outcome of pauci-immune rapidly progressive glomerulonephritis in Wessex, UK: a 10-year retrospective study. *Nephrol Dial Transplant* 2000; 15: 1593–1599
16. O'Shaughnessy MM, Hogan SL, Poulton CJ *et al*. Temporal and demographic trends in glomerular disease epidemiology in the southeastern United States, 1986–2015. *Clin J Am Soc Nephrol* 2017; 12: 614–623
17. Shang W, Ning Y, Xu X *et al*. Incidence of cancer in ANCA-associated vasculitis: a meta-analysis of observational studies. *PLoS One* 2015; 10: e0126016
18. Knight A, Askling J, Ekbom A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. *Int J Cancer* 2002; 100: 82–85
19. Rahmattulla C, Berden AE, Wakker SC *et al*. Incidence of malignancies in patients with antineutrophil cytoplasmic antibody–associated vasculitis diagnosed between 1991 and 2013. *Arthritis Rheumatol* 2015; 67: 3270–3278
20. Rhee RL, Hogan SL, Poulton CJ *et al*. Trends in long-term outcomes among patients with antineutrophil cytoplasmic antibody–associated vasculitis with renal disease. *Arthritis Rheumatol* 2016; 68: 1711–1720
21. Drooger J, Dees A, Swaak A. ANCA-positive patients: the influence of PR3 and MPO antibodies on survival rate and the association with clinical and laboratory characteristics. *Open Rheumatol J* 2009; 3: 14–17
22. Caravaca-Fontán F, Yerovi E, Delgado-Yagüe M *et al*. Antineutrophil cytoplasmic antibody-associated vasculitis with renal involvement: analysis of 89 cases. *Medicina Clínica (English Edition)* 2017; 148: 1–7
23. Aasarød K, Iversen BM, Hammerstrøm J *et al*. Wegener's granulomatosis: clinical course in 108 patients with renal involvement. *Nephrol Dial Transplant* 2000; 15: 611–618
24. Weiner M, Goh SM, Mohammad AJ *et al*. Outcome and treatment of elderly patients with ANCA-associated vasculitis. *Clin J Am Soc Nephrol* 2015; 10: 1128–1135
25. Chang WX, Arai S, Tamura Y *et al*. Time-dependent risk factors associated with the decline of estimated GFR in CKD patients. *Clin Exp Nephrol* 2016; 20: 58–70
26. O'Shaughnessy MM, Montez-Rath ME, Lafayette RA *et al*. Patient characteristics and outcomes by GN subtype in ESRD. *Clin J Am Soc Nephrol* 2015; 10: 1170–1178
27. Berden AE, Ferrario F, Hagen EC *et al*. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol* 2010; 21: 1628–1636