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ORIGINAL ARTICLE

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Long-term outcomes and prognostic factors for survival of patients with ANCA-associated vasculitis

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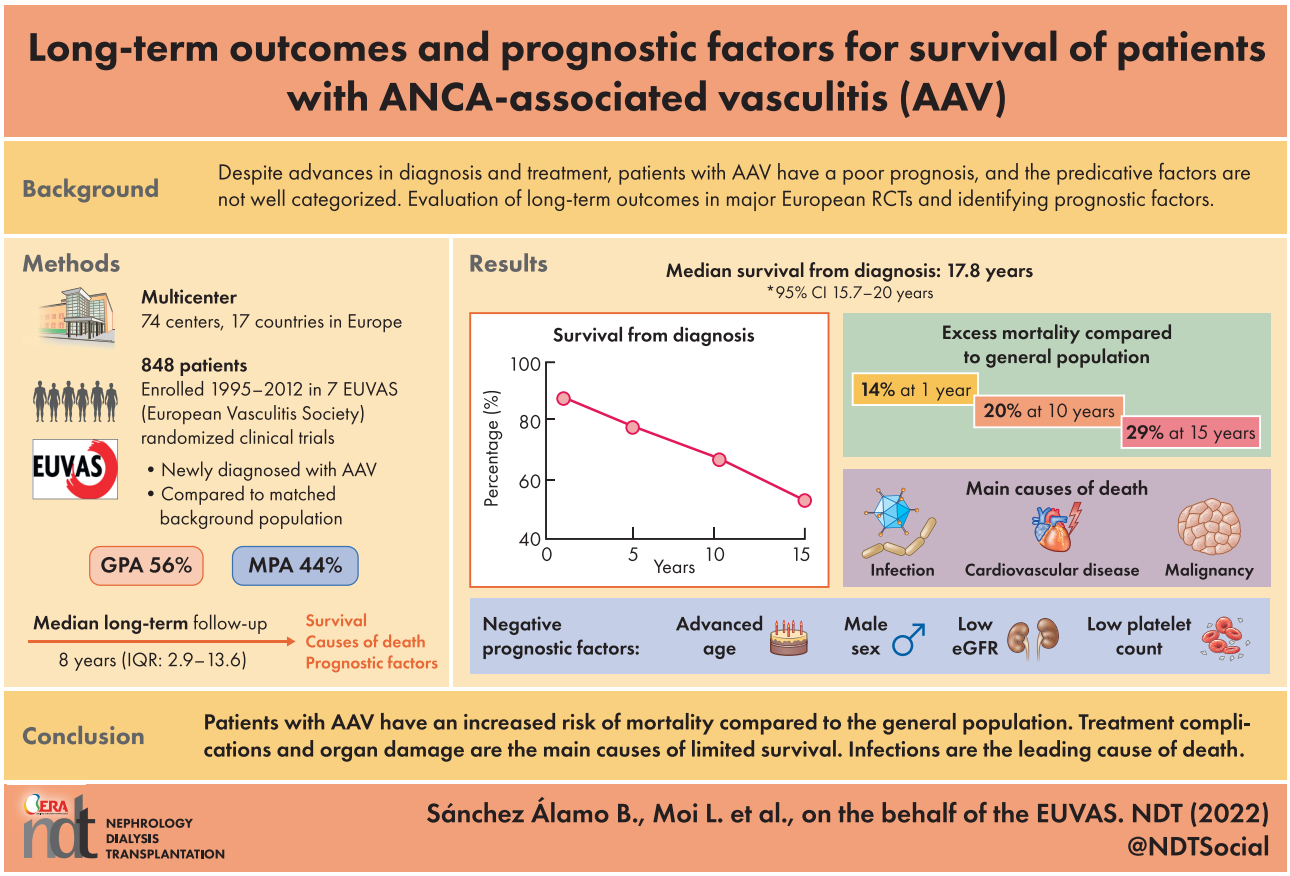
GRAPHICAL ABSTRACT



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KEY LEARNING POINTS

What is already known about this subject?

- Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare and heterogeneous group of diseases. Despite advances in diagnosis and the introduction of immunosuppressive therapy, patients with AAV suffer a poor prognosis and the predicative factors are not well categorized.

What this study adds?

- This study included a unique cohort of 848 patients from seven EUVAS RCTs (1995–2012): MEPEX, NORAM, CYCAZAREM, CYCLOPS, IMPROVE, RITUXVAS and MYCYC, all newly diagnosed with AAV, well characterized at inclusion in the trials respectively, as was the type and duration of induction therapy.
- Despite all the improvements in the treatment strategies of AAV patients, it has been shown that the long-term mortality as well as morbidity in AAV remains high, even among younger patients. The cumulative excess mortality compared with that matched general population was 7.9% at 1 year, 14.2% after 5 years, 19.9% after 10 years, 28.8% after 15 years and 36.3% after 20 years.
- Advanced age, male sex, low estimated glomerular filtration rate and baseline platelet count $<250 \times 10^9$/l were found to be strong baseline predictors of death in the multivariate Cox regression model.

What impact this may have on practice or policy?

- The conclusions of the study will raise concern about the need for a systematic follow-up of patients with AAV in the long term and will also have impact on improved design of future RCTs, tailoring therapy to the individual patient with respect to risk factors to prevent eventual side effects such as infections and malignancies.

ABSTRACT

Background. Despite newer treatments with immunosuppressive agents, there still exists a considerable morbidity and mortality risk among patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Since 1994 the European Vasculitis Society (EUVAS) has aimed for an improved outcome for patients with AAV, conducting several prospective randomized controlled trials (RCTs). The aim for the present study was to further evaluate the long-term survival of patients with AAV included in seven RCTs conducted by the EUVAS as well as to identify potential prognostic factors.

Methods. Long-term follow-up data were collected from questionnaires sent to the principal investigators of the original RCTs (1995–2012): MEPEX, NORAM, CYCAZAREM, CYCLOPS, IMPROVE, RITUXVAS and MYCYC, comprising 848 patients, all newly diagnosed with AAV. Relative survival estimates are presented for the study cohorts. Demographic, clinical and laboratory characteristics at trial entry were studied as potential prognostic factors in multivariable models.

Results. A total of 478 (56%) patients had granulomatosis with polyangiitis (GPA) and 370 (44%) had microscopic polyangiitis (MPA) with a mean age at diagnosis of 58 ± 14 years. The median follow-up time was 8 years (interquartile range 2.9–13.6). During the observation period there were 305 deaths and the main causes were infections (26%), cardiovascular disease (14%) and malignancies (13%). When compared with a matched cohort (regarding country, age group and sex) from the background population there were 14.2% more deaths among our cohort of AAV patients at 5 years, 19.9% at 10 years, 28.8% at 15 years and 36.3% at 20 years. The excess mortality occurred in all age groups. The estimated median survival time (from diagnosis) was 17.8 years (95% confidence interval 15.7–20). Among variables measured at baseline, advanced age, male sex, low estimated glomerular filtration rate and low platelet count were identified as predictors of death in a multivariate Cox model.

Conclusions. Patients with AAV still have an increased risk of mortality compared with the general population despite newer therapeutic regimens. Treatment complications and organ damage are the main causes of limited survival and infections remain the leading cause of mortality among patients with AAV.

Keywords: ANCA-associated vasculitis, autoimmune diseases, granulomatosis with polyangiitis, microscopic polyangiitis, prognostic factors, survival

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA), has a heterogeneous clinical presentation.

The prognosis for patients with AAV was extremely poor before the advent of immunosuppressive induction treatment. In the 1950s, the survival of patients with untreated GPA averaged 5 months and the 1-year mortality was extremely high, at 82% [1]. After the introduction of corticosteroids and cytotoxic agents, the prognosis improved dramatically. A remission rate of 93% and a mean duration of remission of ≈4 years were observed in a long-term follow-up study of 85 GPA patients treated with glucocorticoids and cyclophosphamide from the 1960s onwards [2].

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Table 1: Trials information.

Characteristics	NORAM ($N = 95$)	CYCAZAREM ($N = 155$)	CYCLOPS ($N = 148$)	MEPEX ($N = 137$)	RITUXVAS ($N = 44$)	IMPROVE ($N = 156$)	MYCYC ($N = 140$)
Disease stage	Early systemic	Mild–moderate	Mild–moderate	Severe	Mild–moderate	Mild–moderate	Mild–moderate
Age (years), median (IQR)	53 (18–78)	58 (20–77)	57 (18–86)	66 (27–81)	63 (20–84)	55 (19–74)	56 (9–87)
Induction	MTX versus CYC po	CYC po	CYC IV versus po	MEP versus PE	RTX + CYC versus CYC	CYC po	CYC po versus MMF
Maintenance	MTX or CYC po	CYC po versus AZA	AZA	AZA	AZA	AZA versus MMF	AZA
Duration (months)	18	18	18	12	24	48	18
Inclusion period	1995–2000	1995–1997	1998–2001	1995–2001	2006–2007	2002–2005	2008–2011

AZA: azathioprine; CYC: cyclophosphamide; iv: intravenous; MEP: pulse methylprednisolone; MMF: mycophenolate mofetil; MTX: methotrexate; OCS: oral corticosteroids; po: oral.

The patient survival described in subsequent studies including patients diagnosed between 1982 and 2010 appeared to improve over time, with 1-year survival ranging from 80 to 88% and 5-year survival from 70 to 78% [3–6].

Long-term survival data are limited and vary considerably depending on the population studied, as poor 10-year outcome is reported for patients requiring renal replacement therapy at entry [7], while series including GPA patients only show a better prognosis [8]. The European Vasculitis Society (EUVAS) has conducted several prospective randomized controlled trials (RCTs) since 1995 in an attempt to improve the outcome for patients with AAV with diverse disease extent and disease severity, aiming to harmonize and improve therapy and minimize the side effects of immunosuppressive and cytotoxic agents. As the follow-up within the individual RCTs was mostly limited to <18 months, we aimed for a longer follow-up of the first RCTs conducted by EUVAS. Thus a 5-year follow-up of the patients included in the first four EUVAS trials [Non-Renal Wegener's granulomatosis treated Alternatively with Methotrexate (NORAM), Randomised trial of cyclophosphamide versus azathioprine during remission in ANCA positive Systemic Vasculitis (CYCAZAREM), Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis (MEPEX) and Randomised trial of daily oral versus pulse Cyclophosphamide as therapy for ANCA-associated Systemic Vasculitis (CYCLOPS); Table 1] comprising 535 patients enrolled during the period 1995–2002 was published in 2011 [6]. This study [6], as well as other studies [5, 9, 10], showed a substantially higher mortality of patients with AAV compared with a matched general population. AAV patients from the first four EUVAS trials had a 2.6-fold [95% confidence interval (CI) 2.2–3.1] increased risk of death compared with the general population. A meta-analysis published in 2017 comprising 3338 patients with AAV enrolled from 1966 to 2009 showed a similar mortality excess [10].

Regarding prognostic factors, the EUVAS 5-year follow-up [6], as well as other studies, revealed that older age [3–5, 11–17] and decreased renal function at the time of diagnosis [3–5, 12–14, 16–18] were associated with an increased risk of death.

The present study is a continuation of the previous EUVAS 5-year follow-up study of patients with newly diagnosed AAV (GPA or MPA) recruited into the first four EUVAS clinical trials, with the addition of patients enrolled in the later Mycophenolate mofetil vs Azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis (IMPROVE), Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis (RITUXVAS) and Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis (MYCYC) trials.

The aim of the present study was to assess the long-term patient survival of this unique cohort of patients previously included in EUVAS RCTs and to identify possible prognostic factors. Secondary outcomes were to establish the cumulative survival, to compare the mortality of patients with AAV with that of the general population and to establish the different causes of death.

MATERIALS AND METHODS

Study population

We included patients with a diagnosis of AAV who participated in EUVAS RCTs (NORAM, CYCAZAREM, CYCLOPS, MEPEX, IMPROVE, RITUXVAS and MYCYC), recruited from 74 centres in 17 European countries. Patients <18 years of age and EGPA patients were excluded. Diagnosis of GPA and MPA were made according to the criteria adapted from the Chapel Hill Consensus Conference 1994 [19]. The diagnosis was based on clinical presentation compatible with AAV together with positive ANCA or histology. All studies were approved by the local ethics committees and all patients gave written informed consent.

All patients were well characterized at inclusion in the trials, as was the type and duration of induction and subsequent remission-sustaining therapy. All EUVAS studies used uniform diagnostic and disease stage criteria and demographic, clinical and laboratory data were entered into a central dataset for each trial.

Questionnaires

Data on long-term outcomes were collected by means of questionnaires sent to the principal investigators of the original RCTs.

Long-term follow-up data regarding cumulative duration and type of immunosuppressive therapy, end-stage renal failure (ESRF), renal transplantation, patient survival, selected comorbidities (cardiovascular events, malignancies, infections

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requiring hospital stay) and an optional Vasculitis Damage Index at the last follow-up were recorded. If the patient had died, the cause of death was sought. The questionnaires were available on a webpage belonging to a platform at the University of Oxford and data collection was finalized in 2020.

The information in the previous datasets on the patients included in the earlier trials was updated and corresponding information regarding patients from the IMPROVE, RITUXVAS and MYCYC studies was added.

The study was performed in accordance with the principles laid down in the 1964 Declaration of Helsinki and subsequent amendments and ethical approval was obtained from local and national ethics committees in accordance with national legislation, prior to sending out questionnaires.

Baseline evaluation

Data recorded at trial entry included ANCA type [proteinase 3 (PR3) and myeloperoxidase (MPO), respectively), full blood count and serum creatinine. Disease activity was assessed by the Birmingham Vasculitis Score (BVAS) [20]. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [21].

Statistical analyses

Comparisons were made with the *t*-test for normally distributed continuous variables and the Mann–Whitney *U* test for non-normally distributed continuous variables. The Kolmogorov–Smirnov test was used to assess for normality. The study population was divided into age group tertiles to study the different causes of death.

Analysis of variance and chi-squared tests were used to compare variables among groups. Estimation of survival rates were presented as Kaplan–Meier graphs.

Study baseline was defined as the date of trial entry. The main outcome was assessed using time-to-event analyses. In order to identify the factors that were associated with mortality we employed a multivariate Cox regression model. The following parameters were included: age, gender, clinical diagnosis (GPA, MPA), ANCA type (PR3, MPO), eGFR, BVAS, baseline haemoglobin, baseline white blood cell (WBC) count and baseline platelet count. The assumptions of the Cox proportional hazards model were tested using Schoenfeld residuals.

The Ederer II method was employed to estimate the relative survival rates for the study cohorts. Relative survival means that the excess mortality rate is estimated as the difference between the total (all-cause) mortality rate among the patients and the expected mortality rate of a comparable group from the general population, matched to the patients with respect to the main factors affecting patient survival (e.g. age, sex and calendar year) [22]. Data on the expected survival for the general population was obtained from nationwide population life tables stratified by age, sex and calendar time hosted by the Human Mortality Database (HMD) [23]. The life tables from the HMD contain general population survival probabilities (conditional probabilities of surviving 1 year) stratified by those variables that uniquely determine the records and on which it is assumed that expected survival depends, in this case calendar year, age, sex and country.

For comparisons regarding countries, patients were divided according to United Nations area codes for statistical use (M49) into two groups: North Europe (Denmark, Finland, Sweden, Ireland and the UK) and West and South Europe (pooled together; Austria, Belgium, Czech Republic, France, Germany, Greece, Holland, Italy, Poland, Portugal and Spain) [24].

All estimations were performed using the statistical analysis software SPSS Statistics 26 (IBM, Armonk, NY, USA), except relative survival analysis, which was done with Stata 16 (StataCorp, College Station, TX, USA). The remaining graphs were designed with GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA).

RESULTS

Baseline characteristics

A total of 848 patients were eligible for the study. Before the start of this study, 150 of the 848 patients had died. Thus questionnaires were sought from the remaining 698, of which we received questionnaires from 490 (70%). Table 2 summarizes the clinical baseline characteristics.

The median duration of follow-up for the whole cohort was 8 years [range 0–24.5, interquartile range (IQR) 2.9–13.6]. Including all patients, 38.6% were followed up during >10 years, and if we only consider those alive at the end of follow-up, 62.2% were followed up during >10 years.

The mean age was 57.5 ± 14.2 years at the time of the diagnosis of AAV; MPA was diagnosed in 370 patients (43.6%) and GPA in 478 patients (56.4%). PR3-ANCA was more frequent (59.5%) than MPO-ANCA (40.5%). Regarding ANCA type, there were 44 (5%) patients with negative ANCA; as they were very few, they were excluded in the statistical analyses. The median eGFR at baseline was 42.1 ml/min/1.73 m^2 (IQR 16.2–88.6) and 23.5% of the patients presented with an eGFR <15 ml/min/1.73 m^2 (Table 2).

A total of 638 patients received cyclophosphamide as induction therapy, of which 402 (63%) received cyclophosphamide orally and 236 (37%) intravenously. Patients who received intravenous cyclophosphamide seemed to have a better survival compared with oral (log rank 11.0, $P = .001$).

Of the studied patients, 58.8% had at least one relapse during the whole follow-up from the start of the RCT to the end of the long-term follow-up. The median time to the first relapse after start in the RCTs was 3.6 years (IQR 2.1–5.9).

Patient survival

During the observational period there were 305 deaths. Our cohort exhibited a higher mortality compared with the matched background population (matched for country, age group and sex) (Fig. 1). The cumulative observed survival of the patients at 1, 5, 10 and 15 years was 88.2% (95% CI 85.8–90.2), 78.2% (95% CI 75.1–81), 66.7% (95% CI 63–70.2) and

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Table 2: Baseline characteristics for the cohort comparing patients with GPA and MPA.

Characteristics		Entire cohort ($N = 848$)	GPA [$n = 478$ (56%)]	MPA [$n = 370$ (44%)]	*P*-value
Male sex (n, %)		474 (56)	283 (59)	191 (52)	**.03**
Age (years), mean ± SD		57.5 ± 14.2	54.7 ± 14.5	61.2 ± 12.8	**<.001**
Weight (kg), mean ± SD		71.7 ± 13	71 ± 13	72 ± 13	0.5
ANCAs, *n* (%)	MPO	326 (40.5)	51 (11.3)	275 (78.3)	**<.001**
	PR3	478 (59.5)	402 (88.7)	76 (21.7)	
Trial, *n* (%)	CYCAZAREM	155 (18.3)	94 (19.7)	61 (16.5)	**<.001**
	CYCLOPS	143 (16.9)	54 (11.3)	89 (24.1)	
	IMPROVE	167 (19.7)	107 (22.4)	60 (16.2)	
	MEPEX	137 (16.2)	42 (8.8)	95 (25.7)	
	MYCYC	116 (13.7)	74 (15.5)	42 (11.4)	
	NORAM	94 (11.1)	89 (18.6)	5 (1.4)	
	RITUXVAS	36 (4.2)	18 (3.8)	18 (4.9)	
BVAS score, mean ± SD		18 ± 8	19 ± 9	16 ± 7	**<.001**
Creatinine (µmol/l), median (IQR)		137.5 (75.8–303.8)	92.6 (63.9–214.1)	221.2 (118–430.6)	**<.001**
eGFR (ml/min/1.73 m^2), median (IQR)		42.1 (16.2–88.6)	73.1 (27.1–102)	23.7 (11.1–47.7)	**<.001**
eGFR (ml/min/1.73 m^2), *n* (%)	>90	203 (24)	184 (38.5)	19 (5.1)	**<.001**
	60–90	118 (13.9)	76 (15.9)	42 (11.4)	
	30–60	183 (21.6)	85 (17.8)	98 (26.6)	
	15–30	144 (17)	66 (13.8)	78 (21.1)	
	<15	199 (23.5)	67 (14)	132 (35.8)	
Hb (g/dl), median (IQR)		10 (8.8–11.6)	10.4 (8.9–12)	9.6 (8.7–11)	.9
WBC ($\times 10^9$/l), mean ± SD		11.8 ± 4.7	12.4 ± 5	11.1 ± 4.2	**<.001**
Platelets ($\times 10^9$/l), mean ± SD		397.4 ± 168.8	399 (305–531)	332 (253–440)	**<.001**
CRP (mg/l), median (IQR)		49 (14–114)	59 (17.2–132)	34.8 (11–89)	**<.001**
Follow-up (years), median (IQR)		8 (2.9–13.6)	8.6 (4–14.1)	6.6 (1.5–12.9)	**<.001**

The glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.
Hb: haemoglobin; MPA-RLV: microscopic polyangiitis including renal-limited vasculitis.
Significant values in bold.

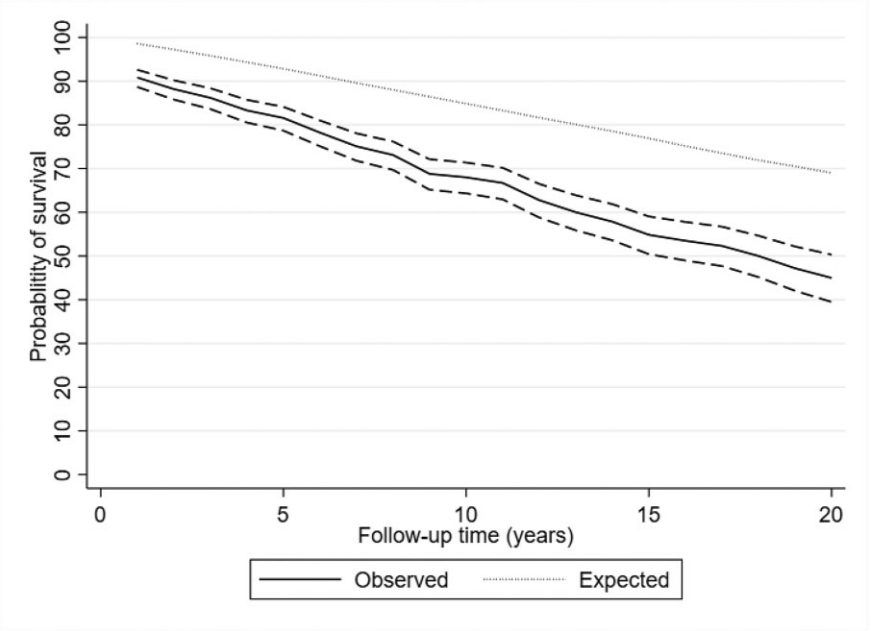

Figure 1: Patient survival in our cohort and in the matched cohort from the background population by age, sex and country (Ederer II method).

53.5% (95% CI 49–57.8), respectively (Fig. 1). When compared with a matched cohort, patients with AAV had 14.2% more deaths at 5 years, 19.9% at 10 years, 28.8% at 15 years and 36.3% at 20 years (Supplementary Table 1).

The excess mortality occurred in all age groups, even in those patients <50 years of age (Fig. 2).

According to Kaplan–Meier estimations, the median survival time for the whole cohort was 17.8 years (95% CI 15.7–20) and the survival rate at 5, 10 and 15 years was 81.2%, 67.6% and 54.2%, respectively.

Our study included a cohort of patients who participated in the EUVAS clinical trials during 17 years (1995–2012).

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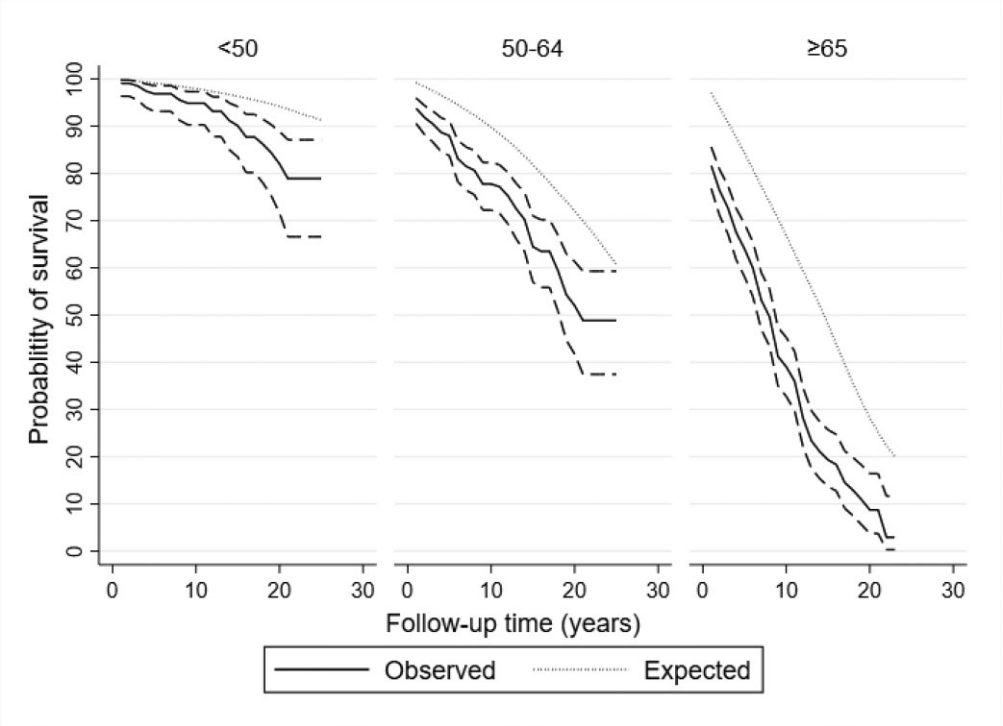

Figure 2: Patient survival grouped by age in our cohort and in the matched cohort from the background population by age, sex and country (Ederer II method).

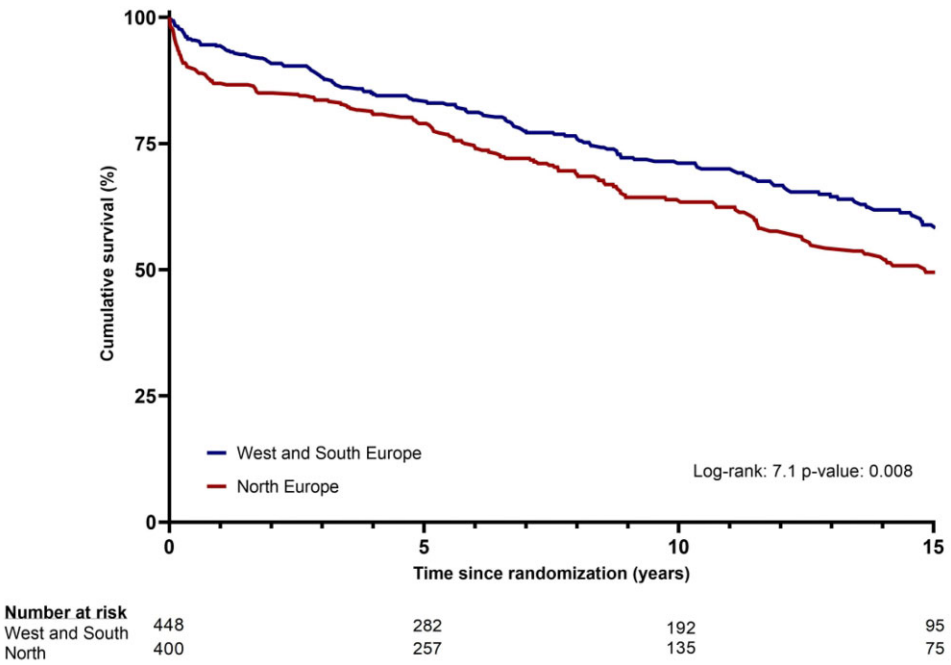

Figure 3: Kaplan–Meier curves grouped by country of origin.

A total of 394 patients (46.5%) were enrolled before 2000 and 53.5% in 2000 or later. Patients included later (after 2000) seemed to have a trend for better survival than those included earlier; however, it was not statistically significant ($P = .25$) (Supplementary Fig. 1).

Patients from northern European countries had lower eGFR values at the time of trial entry than patients from western and southern European countries [35.2 ml/min/1.73 m^2 (IQR 11.4–85.9) versus 46.5 (IQR 21.2–89.8)] and lower survival rates during follow-up ($P = .008$) (Fig. 3).

Looking at individual RCTs, patients from MEPEX had the worst survival, followed by patients included in the RITUXVAS and CYCLOPS studies (Fig. 4).

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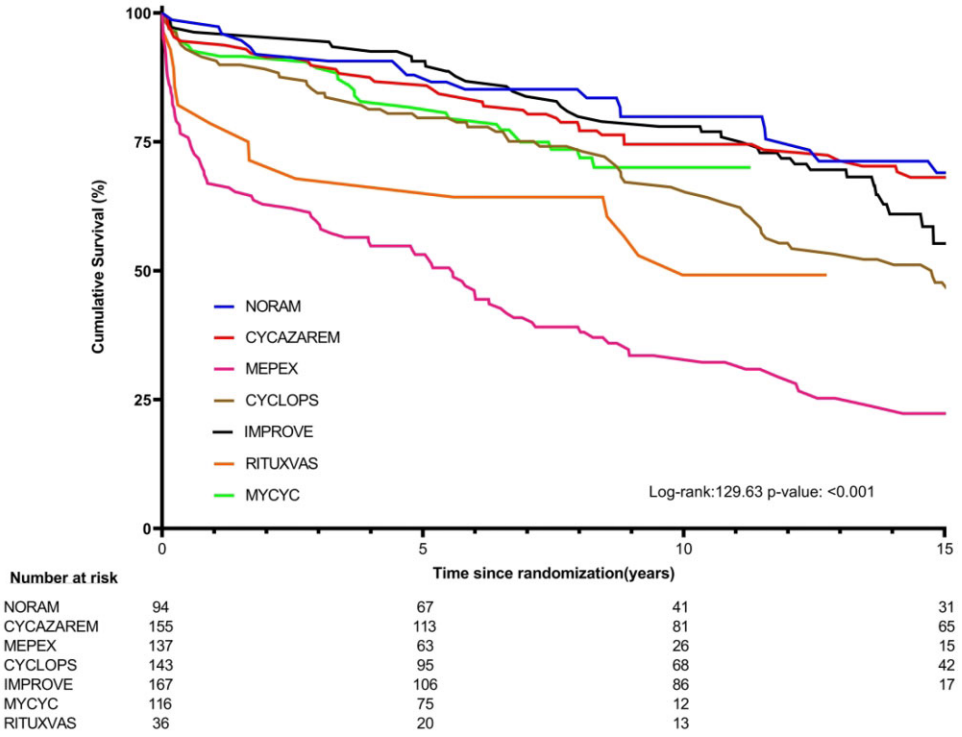

Figure 4: Kaplan–Meier curves grouped by RCTs.

Causes of death

The main causes of death were infections (26%), cardiovascular disease (14%) and malignancies (13%), followed by pulmonary diseases, vasculitis, kidney disease and gastrointestinal disease. The cause of death could not be assessed in 95 patients (Supplementary Table 2).

While infection was the dominant cause of death among the entire cohort, the most common cause of death among the youngest patients was malignancies (22.6%) (Supplementary Table 3).

The main causes of death within the first year were infections (36 patients) and cardiovascular disease (8 patients). Within years two to five of follow-up, the main cause of death was cancer (15 patients), followed by cardiovascular diseases (13 patients). Later during the follow-up, the main causes of death were infections, malignancies and cardiovascular diseases. Of all deaths, 110 occurred in patients with ESRF and the main cause of death in this group was infections (Supplementary Table 4).

Vasculitis and immunosuppression were considered as major contributors to the causes of death in 18.4% and 17.4% of the cases, respectively.

In our cohort, 175 patients (20.6%) reached ESRF. When we categorized the deaths according to eGFR at trial entry, the highest number of deaths was found in the group of patients with low eGFR, i.e. an initial eGFR <15 ml/min/1.73 m^2 (40%).

Predictors of death

The results from the univariate and multivariate Cox regression analysis predicting patient survival are presented in Supplementary Table 5. In the multivariate Cox regression model, advanced age [hazard ratio (HR) 9.9 (95% CI 6.2–15.8), $P < .001$], male sex [HR 1.3 (95% CI 1.1–1.7), $P = .02$], low eGFR [HR 2.63 (95% CI 1.77–3.91), $P = .00$] and low platelet count [HR 1.7 (95% CI 1.2–2.4), $P = .004$] were negative prognostic factors for patient survival (Fig. 5).

Patient survival according to age tertiles, sex, renal function and platelet count is presented in Fig. 6 as Kaplan–Meier curves.

DISCUSSION

This study assessed the long-term survival and factors predicting mortality in patients with AAV from seven different EUVAS RCTs. This cohort represents the broad spectrum of the systemic AAV manifestations, from milder forms with predominantly upper respiratory involvement only to generalized forms and even life-threating organ dysfunction with severe renal insufficiency. The strengths of this study are the well-documented data and the very long period of follow-up. To our knowledge, this is the largest and most extensive long-term follow-up of patients with AAV. A Finnish study documented a 20-year follow-up, however, it was restricted to 85 patients, all with renal involvement [25].

The cumulative observed survival at 1, 5, 10 and 15 years was 88.2%, 78.2%, 66.7% and 53.5%, respectively. This information is complementary to our previous follow-up in which the 1- and 5-year survival was 88% and 78%, respectively [6]. Compared with the southern Swedish cohort, the survival in our study seemed to be higher at 5 and 10 years, even

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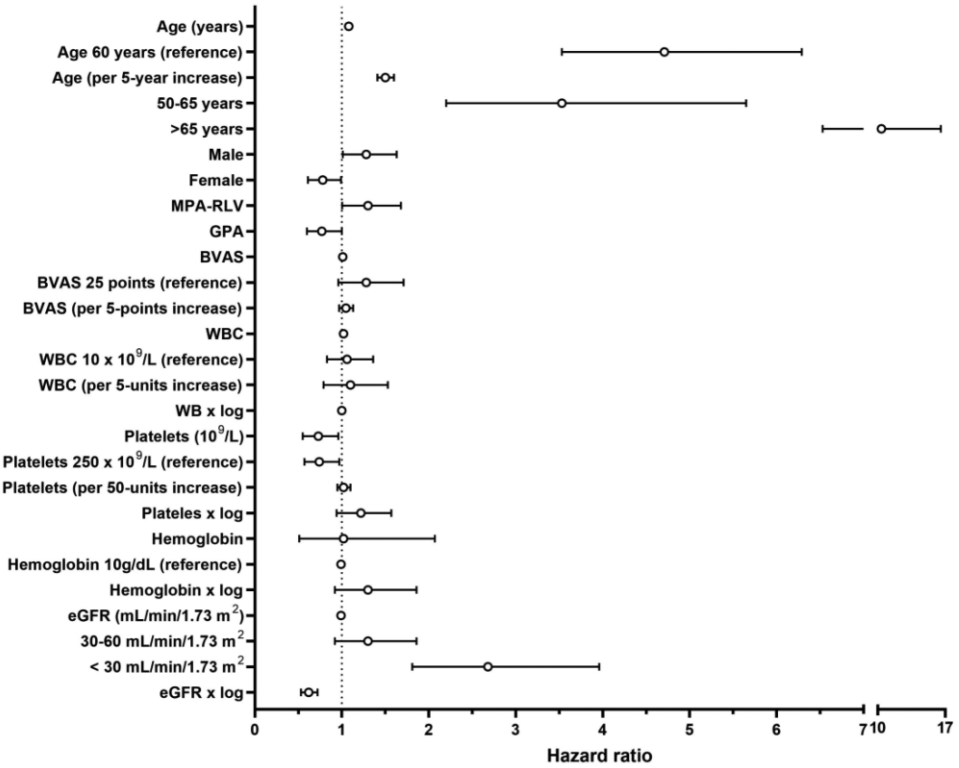

Figure 5: Cox proportional hazards model analysis (forest plot).

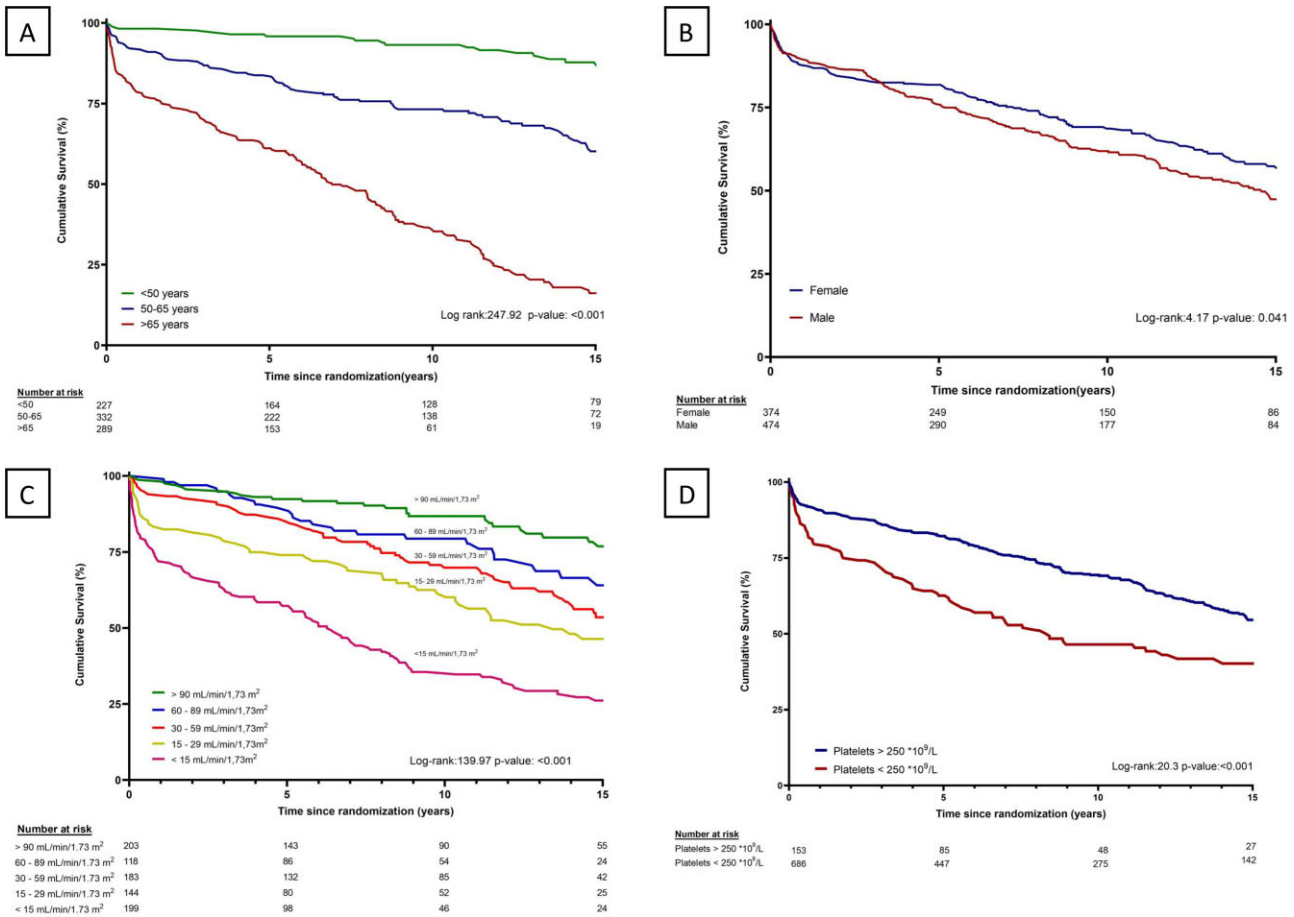

Figure 6: Kaplan–Meier curves grouped by **(A)** age, **(B)** sex, **(C)** baseline eGFR and **(D)** baseline platelet count.

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if there seemed to be no obvious differences in the baseline characteristics of the patients [5].

Patient survival in our study was comparable to that in smaller previous studies, which have reported survivals of 65% and 78% at 5 years and 50% and 62% at 10 years for patients with GPA and MPA [5, 26]. Our results seem to indicate an improved patient survival during the later decades, as has been shown by some other studies [27–29]. The explanation for this may be better awareness of the disease after introduction of the ANCA test, and possibly a better and more individual tailoring of therapy. However, we also documented that active vasculitis as well as infections, the latter probably reflecting side effects of immunosuppressive therapy, contributed to almost 20% of the deaths.

Despite the trend of improved patient survival in recent decades, survival rates are lower than for the general population, with a cumulative excess mortality at 10 years of 19.9%. A recent meta-analysis on patient outcome reported a 2.7 times increased mortality risk of patients with AAV [9]. Interestingly, patients from Southern Europe have a better survival than patients from the northern regions (Fig. 3). This is probably the effect of a better eGFR for patients in Southern and Western Europe but may have been influenced by recruitment bias between trials. Further studies are needed to clarify this. As far as we know, this finding has not been presented previously.

Excess mortality rate increases with time, which highlights the importance of clinical follow-ups in AAV to monitor disease activity and potential complications.

Older age and low eGFR were found to be strong baseline predictors of death, as has been shown by others [3, 7, 12, 13, 30]. Other negative prognostic factors for survival have been identified, including low serum albumin [11], low haemoglobin, leucocytosis [6], a high level of anti-PR3-ANCA [15, 16] and anti-MPO-ANCA positivity [6, 30]. Moreover, a worse outcome for patients with AAV was found in association with clinical features of the disease at presentation, including cardiovascular or gastrointestinal cluster affiliation [5], lung involvement [12], lack of ear, nose and throat involvement [17] and higher BVAS [6]. In our present study there seemed to be an association with higher BVAS at entry and worse outcome; however, the impact of disease activity may be considered more accurate in the short-term follow-up than for the long-term.

We also found that male sex was an independent mortality risk factor. Male sex has been associated with increased mortality in some reports, although not in others [5, 6, 31, 32]. This may be due to the fact that most of the previous follow-up studies did not have a sufficiently long follow-up period [17]. It has been shown that male patients have a better survival in the immediate follow-up, however, their prognosis is worse after 3 years of follow up, which can be also found in the general population [33].

Although AAV patients have a high mortality, it seems that there is a trend towards better survival for those treated in the later decade. It can be speculated that it could be due to an increased awareness of the disease among clinicians and possibly because of changes in the dosing and duration of cyclophosphamide and glucocorticoids. Furthermore, more rapid diagnosis and treatment initiation is also likely to improve outcomes.

We could not prove that either low WBC count or low haemoglobin count were risk factors for mortality, as has been documented by Flossmann *et al.* [6], Little *et al.* [34] and Crnogorac *et al.* [35]. An explanation for this could be that these variables are prognostic factors for the short term but not for the long term. However, in the multivariable Cox model, a platelet count $>250 \times 10^9$/l was found to be a protective factor for survival. In a previous report on a Swedish cohort, it was shown that patients who presented with higher levels of platelets at baseline had better patient survival [17]. We are not aware that this finding has previously been documented by any other authors. It has been hypothesized that the lower platelet count may be due to consumption, immune complex formation, less bone marrow activity, the formation of microparticles or the development of secondary thrombotic microangiopathy caused by endothelial damage. Indeed, glomerular thrombosis has been shown to be an early, initial finding in renal biopsies [36, 37].

The leading causes of death in our cohort were infections, cardiovascular disease and malignancies, but infection was the most common cause of death overall. This finding has been confirmed in previous studies [27]. However, malignancies were the most common cause of death among the young. This fact might be explained by the longer time of follow-up with longer exposure to immunosuppressive treatments in younger individuals. This statement must be confirmed in further studies. Further analyses regarding the cumulative incidence of malignancies with respect to the severity and extent of AAV as well as the cumulative dose and type of immunosuppressants are needed, although the use of rituximab as an alternative to cyclophosphamide appears to be reducing the excess malignancy risk [37].

Regarding the individual RCTs, patients in the MEPEX trial showed the worst survival, followed by those in RITUXVAS and CYCLOPS. Probably this reflects the more severe renal involvement that patients in the MEPEX trial suffered at baseline. Thus we should not compare outcomes from the various RCTs without taking into consideration eGFR and age at inclusion.

In our cohort, those patients who received pulse intravenous cyclophosphamide as induction treatment seemed to have a better survival when compared with low-dose oral cyclophosphamide. It has been reported in a previous RCT that pulse cyclophosphamide induced remission of AAV as effectively as the daily oral regimen at a reduced cumulative cyclophosphamide dose and caused fewer cases of leukopenia [38]. Greater use of intravenous cyclophosphamide in more recent studies with better baseline renal function may have explained the difference in survival.

One of the main limitations of this study is that the patients included in the study were part of different clinical trials and therefore they do not necessarily represent real-world data, as shown by Pagnoux *et al.* [39]. As our present study was a follow-up of RCTs and included several patients with severe kidney disease [almost 24% of the studied cohort (199/848)], this may have resulted in a possible overestimation of the

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mortality overall for patients with AAV. Another point to consider is that almost all patients received cyclophosphamide. As this study comprised patients entered into RCTs in 1995–2011, all studies except RITUXVAS did not include rituximab as induction therapy. It took considerable time to design even the later RCTs, which explains the absence of rituximab as an alternative. Although it would have been excellent to have included a larger RCT with this therapy, we think it is valuable and important to present the results from these earlier RCTs. However, due to the coronavirus disease 2019 pandemic and the abrogated vaccine response, the risk of viral infection and difficulties in clearing the virus after rituximab treatment, cyclophosphamide may still be an option for induction and thus the information and results of our study are important and valuable [40]. Patients with extremely life-threatening disease may not be included in an RCT, resulting in bias when analysing patients' outcomes. However, as has been shown, our cohort comprised patients with severe renal involvement and even dialysis dependency. We have not included histological data analysis in our study. Nevertheless, this cohort included only European patients and may not necessarily cover the whole spectrum of the different AAV phenotypes from different racial and ethnic groups.

In conclusion, in a series of >800 patients with AAV, 10-year mortality was predominantly associated with impaired renal function at onset, older age, male gender and lower platelet counts rather than the subtype of disease or ANCA type. The main strength of this study is a well-defined cohort of patients with AAV, all with well-defined induction treatments and with a long period of follow-up with the possibility to analyse prognostic factors regarding outcomes. The data support efforts to diagnose these patients at an earlier stage, when they have a higher eGFR. Furthermore, we need to tailor therapy for the individual patient. Even if patients are at high risk of mortality at the onset of the disease, there is still an increased mortality risk in the long-term follow-up. Although newer treatment modalities are available, there is still considerable morbidity and mortality in the long-term.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

K.W. and D.W. were responsible for conceptualization. K.W., B.S.A. and A.Å. were responsible for methodology. B.S.A. and A.Å. were responsible for formal analysis and software. L.M. and B.S.A. were responsible for data retrieval. B.S.A. was responsible for data curation. K.W., L.M. and B.S.A. wrote the original draft. K.W. was responsible for supervision. D.J. and K.W. were responsible for funding acquisition. All authors were responsible for review and editing and visualization.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript. The results presented in this article have not been published previously in whole or part, except in abstract format.

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