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Trends in Long-Term Outcomes Among Patients with ANCA-Associated Vasculitis with Renal Disease

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Abstract

Objective—How advances in the management of ANCA (anti-neutrophil cytoplasmic antibody)-associated vasculitis (AAV) have impacted long-term outcomes is still unclear. We examined temporal changes over 25 years in long-term clinical outcomes, including the impact of renal function at diagnosis (a potential marker of time to disease detection) and duration of cyclophosphamide use in AAV patients with renal involvement.

Methods—ANCA-positive, biopsy-proven patients with AAV diagnosed in 1985–2009 followed in the Glomerular Disease Collaborative Network inception cohort were included. Outcomes included the composite outcome of end-stage renal disease (ESRD) or death as well as relapse. Cox proportional hazard or competing risk regression models were adjusted for potential baseline confounders.

Results—Data from 544 patients were included in the analysis. There was a decreasing 5-year risk of ESRD or death over time (log rank test for trend: $p < 0.001$). After adjustment for baseline characteristics, the risk of relapse was similar across the time periods (test for trend: $p = 0.45$). Serum creatinine at baseline was the only significant predictor of an increased risk of ESRD or death (HR 1.11 per 1 mg/dL of serum creatinine [95% CI 1.04–1.18], $p = 0.002$).

Conclusion—In patients with renal disease secondary to AAV, over 25 years the risk of ESRD or death has decreased but the risk of relapse has not changed. A higher serum creatinine at diagnosis is associated with a higher risk of ESRD or death, suggesting that earlier disease detection is potentially an important measure to improve outcomes in AAV.

Keywords

vasculitis; glomerulonephritis; outcomes; survival; end-stage renal disease; relapse

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Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of diseases characterized by inflammation of blood vessels often leading to tissue destruction and organ failure. Renal involvement, in the form of glomerulonephritis, is a common complication of AAV and indicates a poor prognosis[1–4]. Significant morbidities such as end-stage renal disease (ESRD) and frequent relapses lead to poorer survival and quality of life[5–7]. Over the past several decades patients with AAV have survived longer but whether morbidity has improved in terms of preservation of kidney function is unclear[8–10]. Examining changes in relapse rates over time was previously hindered by poorly standardized definitions of disease and relapse and lack of appropriate longitudinal data.

Significant progress has been made in the diagnosis and treatment of AAV over the past three decades. ANCA testing was introduced in the late 1980s and by the early 1990s became widely used, leading to a dramatic improvement in detection of AAV[11, 12]. Clinical trials focused on refining the use of cyclophosphamide, a primary induction agent for severe AAV, to minimize toxicity without losing efficacy[13–16]. These trials used a shorter duration of cyclophosphamide and found no difference in short-term remission rates; however, extension studies suggest there may be a higher rate of relapse in patients receiving less cumulative cyclophosphamide[17–19]. Additionally, the effect of a shorter duration of cyclophosphamide on long-term outcomes, such as survival and preservation of kidney function, is not known[4, 18, 20].

To better understand the impact of diagnostic and therapeutic changes on long-term outcomes in AAV, this study utilized a large, multi-center inception cohort of patients with AAV and renal involvement to examine changes in long-term outcomes over the past few decades.

PATIENTS AND METHODS

Study Population

Patients enrolled in the Glomerular Disease Collaborative Network (GDCN) AAV registry were eligible for this study. The GDCN began in 1985 and is a collaborative venture between academic and private practice nephrologists that now includes over 600 physicians. Centered at the University of North Carolina (UNC) at Chapel Hill, this registry consists of patients diagnosed with AAV who are primarily located in the Southeastern United States.

Patients were included in this study if they met all of the following 3 criteria: (1) had a native kidney biopsy showing pauci-immune glomerulonephritis or had kidney involvement as determined by the nephrologist based on active urine sediment with or without worsening renal impairment along with a diagnostic biopsy of extra-renal tissue (lung, nerve, or gastrointestinal tract) consistent with small-vessel vasculitis; (2) had a positive test for ANCA, defined as detection of ANCA specific to proteinase 3 (PR3) or myeloperoxidase (MPO) by enzyme-linked immunosorbent assay (ELISA) and/or cytoplasmic ANCA (C-ANCA) or perinuclear ANCA (P-ANCA) staining pattern on indirect immunofluorescence; and (3) were diagnosed between 1985 to 2009. Patients were excluded if they had no renal involvement. Four patients diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA; Churg-Strauss) were excluded from the study since EGPA is considered to have a

different clinical outcome than the other AAV diseases[21, 22]. Four patients who received cyclophosphamide more than 1 year prior to enrollment were also excluded. The 21 patients (4, 4, 8, and 5 in time period 1985–1989, 1990–1994, 1995–1999, and 2000–2004, respectively) who were dialysis dependent at time of diagnosis were also excluded.

Patients were enrolled in the registry at the time of diagnosis and followed prospectively until the occurrence of ESRD, defined as the onset of dialysis or transplantation, or death. Patients who did not reach an endpoint were followed until the date of their most recent office visit or hospital discharge.

Outcomes

The primary outcome was a composite endpoint of either ESRD or death within 5 years of diagnosis (henceforth referred to as ESRD-free survival). Secondary outcomes included ESRD and death separately, occurrence of any relapse, and occurrence of renal relapse (relapse involving the kidneys). The record of death was obtained either through medical records or the Social Security Death Index. Relapse was defined as the occurrence of at least one of the following: (1) a rise in serum creatinine accompanied by an active urine sediment, (2) a renal biopsy demonstrating active necrosis or crescent formation, (3) hemoptysis, pulmonary hemorrhage, or new or expanding pulmonary nodules without evidence for infection, (4) active vasculitis of the respiratory or gastrointestinal (GI) tract as demonstrated by endoscopy with biopsy, (5) inflammatory eye disease, (6) new mononeuritis multiplex, (7) clinical signs or symptoms of upper airway involvement, or (8) necrotizing vasculitis identified by biopsy in any tissue[23]. The definition of a renal relapse was limited to the first 2 options listed above.

Exposure

The primary exposure of interest was the time period in which the patient was diagnosed, determined by the date of first renal biopsy or a non-renal biopsy demonstrating active vasculitis. Patients were categorized into 5-year time intervals: 1985–1989, 1990–1994, 1995–1999, 2000–2004, and 2005–2009.

Definitions and Clinical Features

The specific AAV subtypes of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) were defined by the Chapel Hill Consensus Criteria[24]. Renal-limited vasculitis (RLV) was defined as the presence of renal vasculitis with no other organ involvement including constitutional symptoms. Diagnostic testing to exclude other organ involvement (e.g. pulmonary or upper airway) was up to the discretion of the treating physician and was not required. RLV was categorized as a separate subtype since its onset tends to be more insidious and is associated with a delay in diagnosis[25]. A small proportion of patients (10%) had a diagnosis of AAV prior to their renal biopsy and were started on an alternative immunosuppressive therapy (e.g. methotrexate) prior to induction therapy with cyclophosphamide; this duration of disease was accounted for in the analysis. Organ involvement of AAV at baseline was determined by biopsy or previously described criteria[3, 23, 26].

Peak serum creatinine at diagnosis was determined by selecting the highest serum creatinine during the period spanning the month before to the month after the date of the diagnostic biopsy. The estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease (MDRD) formula[27]. Serum creatinine, rather than eGFR, was used as a measure of renal function in the multivariable models in order to examine the influence of age, sex, and race separately (as these are incorporated in the MDRD formula). Duration of cyclophosphamide was examined as a proxy for cumulative cyclophosphamide dose since dose adjustments are frequently made in the setting of renal impairment.

Statistical Analysis

Kaplan-Meier estimators were used to plot the univariable probability of outcomes. Cox proportional hazards models estimated the effect of time period on composite ESRD or death as well as death alone with hazards ratios (HRs) and 95% confidence intervals (CI) presented. The assumption of proportionality was tested using Schoenfeld residuals. A secondary analysis was performed evaluating changes in ESRD-free survival among patients with severe renal disease at diagnosis (a priori chosen as an eGFR ≤ 45 ml/min/1.73 m^2) to determine if length-biased sampling, a form of selection bias, was occurring due to increasing detection of more indolent, slowly-progressing disease over time.

Competing risks regression was used to estimate the effect of time period on relapse with ESRD and death considered competing events. An analysis accounting for competing risks was used because the competing events (ESRD and death) are likely not independent from relapse and may informatively censor patients; for example, patients censored for death may have developed a higher rate of relapses if they had lived. Similarly, for the outcome of ESRD, death was treated as a competing event. Competing risks models were presented with subdistribution hazards ratios (SHRs) and 95% CI. Cumulative incidence graphs censoring ESRD and death were compared to those not censoring for ESRD and death to determine if improving survival could account for increasing relapse rates.

To evaluate the effect of duration of cyclophosphamide use on long-term outcomes, the subgroup of patients who received cyclophosphamide and had dates of cyclophosphamide use available was examined (N = 340). Because there were only 5 such patients in the first time period (1985–1989), these patients were combined with the next time period (1990–1994). Univariate models were performed using age, sex, race, ANCA type (C/PR3 or P/MPO), AAV disease type (GPA, MPA, or RLV), duration of disease prior to biopsy (if previously diagnosed), organ involvement (pulmonary, upper respiratory, joint, muscle, skin, GI, or neurological), use of plasma exchange for induction, and site where patient was primarily treated (tertiary care vs community practice). The proportion of patients managed at a tertiary care center likely increased over time stemming from changes in enrollment by the GDCN registry which began placing more emphasis on enrolling patients from UNC during the later time periods. Predictors of interest were peak serum creatinine at diagnosis and duration of cyclophosphamide use. Select interactions between duration of cyclophosphamide and ANCA type as well as disease subtype were evaluated to determine if the effect of the duration of cyclophosphamide differed between ANCA or disease groups.

All variables associated with the outcome with a p-value < 0.10 were included in a final multivariable model, except for age, ANCA type, serum creatinine, and duration of cyclophosphamide which were forced into all final models due to clinical relevance. Since inclusion of the duration of cyclophosphamide limited the analysis to only patients who received and had available data on cyclophosphamide use, we performed a sensitivity analysis excluding duration of cyclophosphamide from the multivariable analysis, therefore utilizing the entire cohort. Additional sensitivity analysis was performed including route of administration of cyclophosphamide (oral vs intravenous) in the multivariable analysis.

Duration of cyclophosphamide use was analyzed as a time-varying covariate since this variable was not constant throughout follow-up. In the analysis of ESRD-free survival, relapse was also treated as a time-varying covariate as determined by the start and end date of each relapse (if end date of relapse was not available, then the duration of relapse was assumed to be 3 months). All other variables were kept constant.

A two-tailed *P* value < 0.05 was considered significant for all analyses. All analyses were conducted using Stata (Version 12.1, StataCorp, College Station, TX).

The study was approved by the institutional review boards of the University of North Carolina at Chapel Hill and the University of Pennsylvania.

RESULTS

Patient characteristics

A total of 554 patients were included in the study with a median follow-up of 31 months (interquartile range [IQR] 11–67). Baseline characteristics by time period are presented in Table 1. The median age of this population was 60 years and 47% of the patients were female; mean age and sex ratios were similar across the time periods. Sixty percent of patients were anti-MPO-positive and more than 80% had MPA or RLV. ANCA type and disease type were similar across the time periods. Approximately half of the patients had lung involvement. 542 (98%) patients had a diagnostic renal biopsy while the remaining 12 (2%) patients were diagnosed by their nephrologist based on active urine sediment (with or without rising serum creatinine). Renal function at diagnosis significantly improved over time with a median eGFR of 11 ml/min/1.73 m^2 in the earliest time period and 23 ml/min/1.73 m^2 in the latest period. There was also a significant increase over time in the proportion of patients who used cyclophosphamide and a significant decline in the duration of cyclophosphamide used per patient.

Primary outcome: ESRD-free survival

Within the entire cohort, there were 260 (47%) patients who developed ESRD and/or died during the follow-up period and by 5 years from diagnosis, 180 patients (32%) were lost to follow-up. The incidence of first occurrence of ESRD and/or death was 12.9 events per 100 person-years. Overall, the 1-year ESRD-free survival rate was 75% and the 5-year rate was 54%. Comparing the 5 time periods, the ESRD-free survival rates improved over time both in the Kaplan-Meier curve (log rank test for trend: p < 0.001; Figure 1A) and the adjusted curve (log rank test for trend: p < 0.001; Figure 1B). Secondary analysis of patients

presenting with severe renal disease defined as eGFR ≤ 45 ml/min/1.73 m^2 also demonstrated that ESRD-free survival significantly improved over time (log rank test for trend: $p < 0.001$).

Of the 494 patients who received cyclophosphamide, 388 (79%) had available data on duration of cyclophosphamide use; among these patients, 48 (12%) were missing additional baseline data (e.g. serum creatinine or extra-renal manifestations). Thus, 340 patients were included in this subgroup analysis. There were no major differences between patients with or without available data on cyclophosphamide use (data not shown). In the multivariable Cox regression analysis, after adjustment for potential confounders, an elevated serum creatinine at diagnosis was the only significant factor associated with a higher risk of ESRD or death (HR 1.11 per 1 mg/dL of serum creatinine [95% CI 1.04–1.18], $p = 0.002$) while ANCA type, age, and duration of cyclophosphamide use were not significantly associated with the outcome (Table 3). Adjustment for route of administration of cyclophosphamide (oral vs intravenous) led to similar results (data not shown). Furthermore, the ANCA-by-cyclophosphamide duration and disease subtype-by-cyclophosphamide duration interactions were not significant (p for interaction 0.72 and 0.49, respectively), indicating that the effect of cyclophosphamide did not differ between ANCA and disease groups.

After removing duration of cyclophosphamide from the model and utilizing the entire cohort for a sensitivity analysis, a significant trend in improvement in outcome across the time periods was still observed (test for trend: $p < 0.001$).

Patient survival and renal survival

Among the 554 patients, 160 (29%) deaths were observed during the follow-up period with an incidence rate of 7.0 deaths per 100 patient-years. The 1-year patient survival for the entire cohort was 91% and 5-year survival was 72%. Survival significantly improved over time even after adjusting for age, ANCA type, baseline serum creatinine, and duration of cyclophosphamide use (log rank test for trend: $p = 0.03$).

There were 181 (33%) patients who developed ESRD during the observational period. At 1 year from diagnosis, 20% developed ESRD while 5% had died without developing ESRD; and at 5 years, 65% had developed ESRD while 23% had died without developing ESRD. Renal survival significantly improved across the 5 time periods even after adjusting for age, ANCA type, baseline serum creatinine, and duration of cyclophosphamide use (test for trend: $p = 0.03$) and the highest yearly incidence of ESRD occurred within the first year.

Relapse

Of the 554 patients, 185 (33%) patients experienced a relapse after diagnosis for an incidence rate of relapse of 13.9 events per 100 patient-years. The cumulative occurrence of relapse at 1 year, 3 years, and 5 years was 11%, 29%, and 35%, respectively. Among the 185 patients who experienced a relapse, 136 (74%) had kidney involvement at the time of relapse and 112 (61%) used cyclophosphamide to treat the relapse.

The unadjusted occurrence of relapse increased over time as shown in the cumulative incidence curves in Figure 2A (test for trend: $p < 0.001$). However, in the subgroup of

patients with data on cyclophosphamide use (n = 340), after adjusting for potential confounders in a multivariable competing risk regression, this trend was no longer significant (p for trend = 0.45; Figure 2B). When examining predictors of relapse, there were no studied factors associated with relapse. Notably, ANCA type and duration of cyclophosphamide use were not associated with the occurrence of relapse (Table 4). Adjustment for route of administration of cyclophosphamide (oral vs intravenous) led to similar results (data not shown). The ANCA-by-cyclophosphamide interaction and the disease subtype-by-cyclophosphamide interaction were not significant (p for both interactions = 0.41) indicating that the effect of the duration of cyclophosphamide is not modified by ANCA or disease type.

In a sensitivity analysis, the duration of cyclophosphamide was removed from the model (to allow for analysis of entire cohort) along with variables that correlate with ANCA type (disease subtype and upper respiratory involvement); there continued to be no significant change in occurrence of relapse over the time periods (test for trend: p = 0.24).

To determine whether the increasing hazard rates for relapse were the result of better ESRD-free survival (i.e. more patients developed relapse because patients were living longer), cumulative incidence graphs with and without censoring ESRD and death were compared (data not shown). The unadjusted cumulative incidence of relapse increases over time whether or not ESRD and death were censored (test for trend: $p < 0.001$) or not censored (i.e. treated as competing event; test for trend: $p < 0.001$), suggesting that the higher rate of relapses in the unadjusted analysis is not simply due to longer ESRD-free survival.

A total of 136 (25%) patients experienced a renal relapse and 74% of patients who experienced at least one relapse had relapse of their kidney disease. There was no significant difference in the occurrence of renal relapses over time (proportion of patients with renal relapse was 23%, 26%, 18%, 24%, 32% in 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009 respectively, test for trend: p = 0.13).

DISCUSSION

Both patient and renal survival significantly improved between 1985 and 2009 in this cohort of patients with AAV and renal disease. Serum creatinine at diagnosis was the only predictor associated with this better outcome, suggesting that early detection is fundamental to improving ESRD-free survival in AAV. After adjusting for potential confounders, the risk of relapse did not significantly change over time.

While many studies have examined predictors of outcome in AAV, to our knowledge only 5 studies have addressed how outcomes have temporally changed over the time span of several decades[8–10, 28, 29]. This study was the largest study examining long-term changes over time and the largest study to evaluate the impact of the duration of cyclophosphamide on long-term outcomes. Hilhorst et. al. examined 181 patients in The Netherlands who were diagnosed with ANCA-associated glomerulonephritis between 1979 and 2009 and found significant improvement in patient and renal survival over time[9]. Holle et. al. studied 290 patients diagnosed with AAV (specifically GPA) in Germany between 1994 and 2002 and

compared them to a historical cohort of 155 patients diagnosed between 1966 and1993. They found a significant reduction in mortality but, unlike the results found in this study, a lower rate of relapses was seen in their study over time[28]. Differences in the population studied may explain the contradictory results since only about half the patients in the German cohort had renal disease and most patients were PR3-ANCA positive. In addition, competing risks analysis was not used in their study and, therefore, the rate of relapse may have appeared higher in the earlier time periods as more patients were being censored for death.

Compared to prior studies determining predictors of outcomes, our study showed consistent results indicating that better renal function at diagnosis is associated with improved survival and renal outcomes[30–32]. Lung involvement, age, and upper respiratory involvement have also been shown to be associated with outcome, although these factors were not associated with events in this study[32, 33]. Similar to previous studies, better renal function at diagnosis was associated with a higher risk of relapse[34, 35].

Neither changes in the definition of relapse nor severity of relapse likely explains the lack of improvement in the risk of relapse seen in the current study. A standard definition of relapse was implemented throughout the entire cohort. A large majority of patients experienced a relapse involving the kidneys and this rate did not change over time. It is notable that ANCA type was not associated with the occurrence of relapse in this study. A prior study by Hogan et. al. using this cohort did show that patients with PR3-positive ANCA are more likely to relapse compared to patients with MPO-positive ANCA and similar findings have been shown in other cohorts[26, 36, 37]. When the same inclusion and exclusion criteria and analytic approach as described in Hogan et. al. was used, similar results were obtained including a significant association between ANCA type and relapse. Therefore, it is likely this relationship was attenuated in the current analysis due to the enrichment of the cohort with patients with renal disease (excluding patients with primarily upper airway disease who are more prone to relapse) and censoring all patients after 5 years of follow-up. Additionally, since one of the aims of this study was to examine the effect of duration of cyclophosphamide use on relapse, only patients who received cyclophosphamide were included in the multivariable models; this subgroup of patients were more likely to be on longer periods of maintenance therapy after cyclophosphamide resulting in lower occurrence of relapse.

The current study also found no association between duration of cyclophosphamide use and ESRD-free survival or relapse. The lack of effect of cyclophosphamide use on relapse seen in this study contradicts prior studies, including several long-term follow-up studies of clinical trials examining maintenance therapies in AAV[17–19]. Several possible reasons may explain why no association between duration of cyclophosphamide and long-term outcomes was seen in this study. First, the extension studies of the clinical trials compared results based on initial randomization but most did not account for repeated uses of cyclophosphamide in their analysis. It is possible that if overall use of cyclophosphamide was included in the prior studies no difference in outcomes would be seen. Second, the cohort used in the current study had a different overall clinical phenotype compared to the patients in the trials, including ANCA and disease type. This is further reflected by the large

proportion of patients who had a renal relapse. It is possible that a longer duration of cyclophosphamide use does not affect renal relapses; this contention is further supported by findings in the CYCAZAREM extension study which found no difference in renal relapses between patients on shorter versus longer durations of cyclophosphamide.

The current study has several strengths in the data source and methodology that enhanced its ability to address research questions of interest. The GDCN inception cohort is an optimal source to study renal disease in this rare disease. This cohort is unique in the U.S. and one of the largest cohorts of patients with ANCA-associated renal disease. All patients in this cohort had kidney involvement, a biopsy-proven diagnosis, and were closely followed by a nephrologist. Although the patients were confined to a particular geographic region (the Southeastern US), the GDCN provides uniformity and standardization, both of which are difficult to achieve in a multi-centered cohort. Patients were enrolled at diagnosis and followed prospectively, allowing examination of time-to-event without being prone to recall bias. Lastly, disease severity at diagnosis, an important confounder when examining long-term outcomes, was accounted for and the examination of cyclophosphamide as a time-varying covariate enabled a more real-world depiction of cyclophosphamide use in clinical practice.

There were some limitations to this study. There are several unmeasured confounders that may influence the interpretation of the findings. The dose and duration of use of glucocorticoids and other immunosuppressive therapies were not accounted for in the analysis. However, the results of this study are still noteworthy because they demonstrate continued improvement in outcomes in the setting of routine clinical care. Furthermore, a prior study using the same cohort found no association with duration of glucocorticoid therapy and risk of relapse[38]. Improvements in healthcare were not captured in the analysis and were likely affecting the long-term outcomes, particularly patient and renal survival. Frequency in follow-up was determined by individual clinicians and, therefore, was not standardized; this may have affected the ability to detect relapses. Lead-time bias is unlikely to be an issue due to the rapidly progressive nature of the disease that becomes clinically apparent in weeks to months. Therefore, improvements in long-term outcomes are expected to be a much higher magnitude (e.g. years) than any lead time in diagnosis based on our understanding of the disease (e.g. weeks to months). Similarly, length-biased sampling may have potentially occurred (e.g. ANCA testing could have led to greater detection of indolent disease, thereby giving the false appearance of improved outcomes). However, when the sample was restricted to patients with an eGFR $\leq$ 45 ml/min/1.73 m^2, a significant improvement in ESRD-free survival was still seen. Therefore, length-biased sampling was not likely an issue in this study. Additionally, there were 32% lost to follow-up by 5 years from diagnosis which, as in any observational cohort, may have affected results. Lastly, generalizability may be limited to other populations of AAV.

In conclusion, this analysis of a multi-centered inception cohort demonstrates that for patients with AAV and renal disease, ESRD-free survival has improved over the past several decades. The finding that a lower serum creatinine at diagnosis was the only significant predictor associated with a lower risk of ESRD or death underscores the importance of early disease detection and the need for diagnostic tools to identify patients with AAV before the

onset of irreversible renal damage. Nonetheless, despite advances in disease detection and therapeutic management, relapses continue to be an important clinical problem in AAV. Further studies are needed to address the problem of relapse, including better identification of at-risk populations and refining the use of current therapies to maintain better disease control without losing what has been gained in patient and renal survival.

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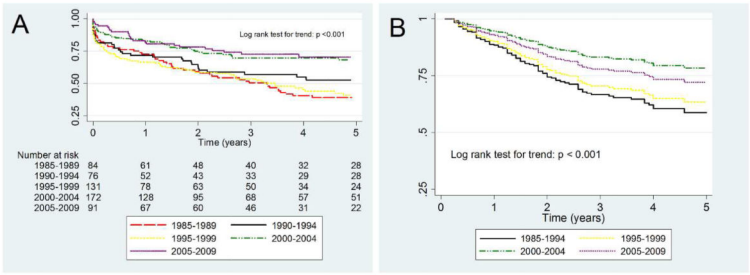

Figure 1.

Risk of developing ESRD or death in 5 years stratified by year of diagnosis, shown as Kaplan-Meier curve (1A) and multivariable Cox proportional hazards curve (1B). Patients diagnosed in earlier time periods have poorer ESRD-free survival. Multivariable analysis adjusted for age, race, ANCA type, site, baseline serum creatinine, duration of cyclophosphamide use, and occurrence of relapse. Time period 1985–1989 combined with time period 1990–1994 due to missing cyclophosphamide data in the 1985–1989 group.

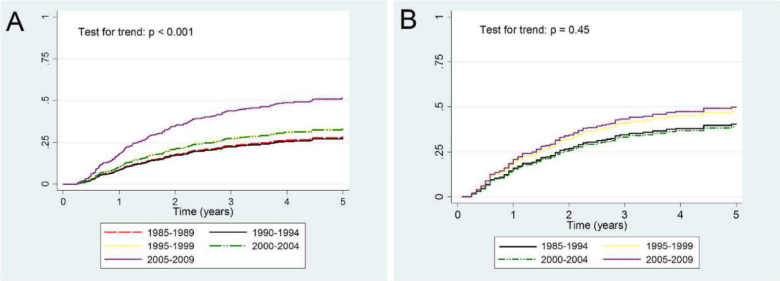

Figure 2.

Cumulative incidence of relapse stratified by year of diagnosis. Unadjusted incidence (2A) shows more relapses occur in patients diagnosed in later time periods, but no difference is seen after adjusting for baseline variables (2B). Adjusted for age, diagnosis, ANCA type, site, baseline serum creatinine, joint/upper respiratory/skin involvement, and duration of cyclophosphamide use. Time period 1985–1989 combined with time period 1990–1994 due to missing cyclophosphamide data in the 1985–1989 group.

Table 1

Baseline characteristics of cohort by time period

Characteristic	All	Time Period					*P*-value for trend
		85–89	90–94	95–99	00–04	05–09	
N	554	84	76	131	172	91	--
Median age, years (IQR)	60 (47–71)	62 (45–70)	61 (43–68)	64 (49–72)	58 (47–71)	58 (46–68)	0.98
Female, %	47%	46%	54%	45%	49%	42%	0.42
Race, %							
White	85%	87%	86%	91%	83%	79%	0.15
Black	9%	12%	8%	8%	9%	9%	0.61
Other	6%	1%	7%	2%	8%	12%	0.02
Diagnosis, %							
GPA	19%	15%	18%	18%	20%	24%	0.15
MPA	56%	58%	51%	56%	55%	58%	0.82
RLV	25%	26%	30%	26%	24%	18%	0.10
ANCA ELISA, %							
PR3/C	40%	44%	33%	43%	41%	37%	0.78
MPO/P	60%	56%	67%	57%	59%	63%	
Organ Involvement, %							
Lung	49%	50%	38%	49%	52%	53%	0.23
Joint	41%	36%	36%	40%	44%	48%	0.05
Upper respiratory	35%	36%	29%	34%	33%	44%	0.28
Skin	23%	21%	26%	25%	19%	19%	0.37
Gastrointestinal	11%	15%	16%	12%	8%	4%	0.005
Neurologic	10%	14%	8%	15%	8%	7%	0.13
Muscle	3%	6%	7%	2%	3%	0%	0.06
Pre-existing AAV prior to diagnostic biopsy, %	10%	7%	11%	10%	10%	11%	0.45

Characteristic	All	Time Period					*P*-value for trend
		85–89	90–94	95–99	00–04	05–09	
Median duration of follow-up, months (IQR)	31 (11–67)	35 (11–68)	32 (7–72)	23 (7–49)	29 (14–91)	38 (11–59)	0.98
Tertiary care, % (vs community practice)	48%	30%	26%	40%	55%	82%	< 0.001
Median serum creatinine, mg/dL (IQR)	3.6 (2–5.9)	4.8 (3–8.6)	3.7 (2.1–6.4)	4.1 (2.3–6.1)	3.2 (1.8–5.1)	2.8 (1.6–4.8)	< 0.001
Median Glomerular Filtration Rate, ml/min/1.73 m^2 (IQR) *	16 (9–32)	11 (7–20)	16 (8–30)	14 (8–29)	17 (11–37)	23 (12–37)	< 0.001
Used plasma exchange, %	16%	2%	4%	10%	22%	40%	< 0.001
Cyclophosphamide							
Ever used, %	89%	73%	80%	90%	95%	99%	< 0.001
Dates of use available, %	79%	8%	72%	88%	91%	96%	< 0.001
Median duration of cyclophosphamide, months (IQR)	7 (4–13)	17 (14–20)	8 (5–21)	7 (5–15)	7 (6–13)	6 (4–8)	0.009

* Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) formula. AAV, ANCA-associated vasculitis. ANCA, anti-neutrophil cytoplasmic antibody. GPA, granulomatosis with polyangiitis. IQR, interquartile range. MPA, microscopic polyangiitis. MPO/P, myeloperoxidase antibody and/or perinuclear pattern. PR3/C, proteinase 3 antibody and/or cytoplasmic pattern. RLV, renal-limited vasculitis.

Table 2

Cumulative incidence of study outcomes by time period

Outcome		All	Time Period					*P*-value for trend
			85–89	90–94	95–99	00–04	05–09	
ESRD-free survival	1-year	75%	73%	72%	66%	82%	82%	0.02
	3-year	61%	51%	57%	53%	69%	72%	< 0.001
	5-year	54%	39%	53%	40%	68%	70%	< 0.001
Patient survival	1-year	91%	89%	89%	89%	93%	90%	0.36
	3-year	81%	74%	84%	73%	87%	83%	0.15
	5-year	72%	64%	71%	58%	84%	83%	< 0.001
Renal survival	1-year	80%	77%	77%	70%	86%	89%	0.005
	3-year	69%	60%	61%	60%	76%	84%	< 0.001
	5-year	65%	51%	61%	53%	76%	82%	< 0.001
Relapse	1-year	11%	5%	7%	12%	14%	15%	0.008
	3-year	29%	22%	25%	28%	28%	40%	0.01
	5-year	35%	28%	27%	33%	30%	57%	< 0.001

ESRD, end-stage renal disease

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Table 3

Risk factors for the occurrence of ESRD or death in 5 years

Variable	Univariate model		Multivariable model*	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Time Period				
85–94†	1 (reference)	--	1 (reference)	--
95–99	0.94 (0.51–1.73)	0.84	1.03 (0.53–2.01)	0.94
00–04	0.51 (0.27–0.95)	0.03	0.58 (0.29–1.16)	0.13
05–09	0.66 (34–1.28)	0.22	0.80 (0.38–1.71)	0.57
Age, years	1.00 (0.99–1.01)	0.60	1.00 (0.99–1.01)	0.99
Sex (female vs male)	0.96 (0.62–1.46)	0.84		
Race				
White	1 (reference)	--	1 (reference)	--
Black	1.06 (0.51–2.20)	0.88	0.97 (0.45–2.08)	0.95
Other	0.29 (0.07–1.20)	0.09	0.15 (0.02–1.07)	0.07
Diagnosis				
GPA	1 (reference)	--		
MPA	1.43 (0.84–2.45)	0.20		
RLV	1.21 (0.61–2.41)	0.58		
ANCA (MPO/P vs PR3/C)	0.95 (0.62–1.45)	0.80	0.92 (0.57–1.47)	0.71
Organ Involvement				
Lung	1.23 (0.80–1.89)	0.34		
Joint	0.83 (0.54–1.27)	0.39		
Upper respiratory	0.81 (0.52–1.26)	0.34		
Skin	1.06 (0.65–1.72)	0.81		
Gastrointestinal	0.91 (0.44–1.89)	0.81		
Neurologic	1.10 (0.55–2.19)	0.79		
Muscle	0.70 (0.17–2.83)	0.61		
Duration of disease prior to biopsy, months	1.00 (0.99–1.00)	0.47		
Serum creatinine, mg/dL	1.12 (1.06–1.19)	< 0.001	1.11 (1.04–1.18)	0.002
Site (community vs tertiary)	1.46 (0.96–2.24)	0.087	1.01 (0.60–1.70)	0.96
Used plasma exchange	1.17 (0.71–1.92)	0.54		
Duration of cyclophosphamide, months	0.98 (0.93–1.02)	0.27	0.96 (0.92–1.01)	0.14
Occurrence of relapse	0.93 (0.44–1.94)	0.84	0.92 (0.42–2.05)	0.84

The effects are expressed as hazards ratio (HR) for ESRD or death in 5 years.

[*] Multivariable model included variables with $p < 0.10$ in univariate analysis along with pre-specified variables of interest (time period, age, ANCA type, serum creatinine, cyclophosphamide, and relapse).

[†] There were only 5 patients in 85–89 group so these patients were combined with 90–94 group.

ANCA, anti-neutrophil cytoplasmic antibody. GPA, granulomatosis with polyangiitis. MPA, microscopic polyangiitis. MPO/P, myeloperoxidase antibody and/or perinuclear pattern. PR3/C, proteinase 3 antibody and/or cytoplasmic pattern. RLV, renal-limited vasculitis.

Table 4

Risk factors for disease relapse

	Univariate model		Multivariable model*	
Variable	**SHR (95% CI)**	***P*-value**	**SHR (95% CI)**	***P*-value**
Time Period				
85–94†	1 (reference)	--	1 (reference)	--
95–99	1.47 (0.83–2.61)	0.20	1.26 (0.68–2.33)	0.47
00–04	1.21 (0.69–2.12)	0.50	0.96 (0.53–1.77)	0.91
05–09	1.72 (0.99–3.01)	0.06	1.35 (0.71–2.55)	0.35
Age, years	0.99 (0.99–1.00)	0.17	1.00 (0.99–1.01)	0.92
Sex (female vs male)	0.99 (0.70–1.39)	0.94		
Race				
White	1 (reference)	--		
Black	0.63 (0.30–1.30)	0.21		
Other	0.99 (0.48–2.04)	0.98		
Diagnosis				
GPA	1 (reference)	--	1 (reference)	--
MPA	0.65 (0.45–0.94)	0.02	0.75 (0.48–1.18)	0.21
RLV	0.39 (0.22–0.68)	0.001	0.59 (0.29–1.18)	0.14
ANCA (MPO/P vs PR3/C)	0.74 (0.52–1.04)	0.08	0.91 (0.62–1.34)	0.63
Organ Involvement				
Lung	1.14 (0.81–1.61)	0.45		
Joint	1.58 (1.12–2.22)	0.008	1.21 (0.82–1.79)	0.33
Upper respiratory	1.53 (1.09–2.15)	0.015	1.08 (0.70–1.65)	0.74
Skin	1.46 (1.00–2.11)	0.46	1.25 (0.82–1.90)	0.30
Gastrointestinal	0.97 (0.54–1.74)	0.92		
Neurologic	1.34 (0.79–2.29)	0.28		
Muscle	1.00 (0.34–2.91)	0.99		
Duration of disease prior to biopsy, months	1.00 (1.00–1.00)	0.92		
Serum creatinine, mg/dL	0.89 (0.81–0.97)	0.011	0.92 (0.84–1.01)	0.07
Site (community vs tertiary)	0.71 (0.50–1.00)	0.055	0.81 (0.52–1.25)	0.34
Used plasma exchange	1.30 (0.87–1.94)	0.20		
Duration of cyclophosphamide, months	1.02 (0.99–1.05)	0.176	1.01 (0.98–1.04)	0.55

The effects are expressed as hazards ratio (HR) for relapse in 5 years.

* Multivariable model included variables with $p < 0.10$ in univariate analysis along with pre-specified variables of interest (time period, age, ANCA type, serum creatinine, and cyclophosphamide).

† There were only 5 patients in 85–89 group so these patients were combined with 90–94 group.

ANCA, anti-neutrophil cytoplasmic antibody. GPA, granulomatosis with polyangiitis. MPA, microscopic polyangiitis. MPO/P, myeloperoxidase antibody and/or perinuclear pattern. PR3/C, proteinase 3 antibody and/or cytoplasmic pattern. RLV, renal-limited vasculitis. SHR, subdistribution hazard ratio.