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Changing Phenotypes and Clinical Outcomes Over Time in Microscopic Polyangiitis

Martina Uzzo[1,2,8], Umberto Maggiore[3,8], Filippo Sala[1,4], Francesco Reggiani[2,5], Vincenzo L'Imperio[6], Federica Deliso[7], Marta Calatroni[2,5], Gabriella Moroni[2,5,9] and Renato A. Sinico[2,9]

[1]Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy; [2]Nephrology and Dialysis Unit, IRCCS Humanitas Research Hospital, Milano, Italy; [3]Department of Medicine and Surgery, University of Parma, Nephrology Unit, University Hospital of Parma, Parma, Italy; [4]Nephrology and Dialysis Unit, IRCCS Fondazione San Gerardo dei Tintori, Monza, Italy; [5]Department of Biomedical Sciences, IRCCS Humanitas Research Hospital, Milano, Italy; [6]Department of Medicine and Surgery, Pathology, University of Milano-Bicocca, IRCCS Fondazione San Gerardo dei Tintori, Monza, Italy; and [7]Clinical Pathology Unit, IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milano, Italy

Introduction: Diagnosis and management of microscopic polyangiitis (MPA) have evolved considerably over the past decades, but it is unknown whether clinical and histological presentation and patient and renal outcomes have changed accordingly.

Methods: We compared clinical and histopathological characteristic at diagnosis, risk of death, end-stage kidney disease (ESKD), and relapse rate in patients diagnosed with MPA between 1980 and 2022, after grouping them in 2 periods (p): p1980–2001 and p2002–2022. We compared the mortality rate between the 2 periods using Kaplan-Meier estimator and Cox-regression, and competing risks of ESKD and death using the Aalen–Johansen estimator, Fine-Gray multiple regression, and multistate models.

Results: Out of 187 patients, 77 were in p1980–2001 and 110 in p2002 to 2022. Patients in p2002 to 2022 were older (66.2 $\pm$ 14.0 SD vs. 57.7 $\pm$ 15.8; $P < 0.001$), had a better kidney function (estimated glomerular filtration rate [eGFR] 25.9 $\pm$ 24.8 vs. 21.5 $\pm$ 28.2 ml/min per 1.73 m^2; $P = 0.011$) and a lower prevalence of the Berden sclerotic class (5.9 vs. 20.9%; $P = 0.011$). Despite a similar crude and adjusted patient survival, the risk of ESKD decreased during p2002 to 2022 (subdistribution hazard ratio [HR] 0.30, 95% confidence interval [CI]: 0.16–0.57; $P < 0.001$). The results remained significant after accounting for death after ESKD and after adjusting for potential confounders (HR 0.33 [95% CI: 0.18–0.63; $P < 0.001$]). The risk of relapse was numerically higher during p2002 to 2022 (subdistribution-HR 1.64 [95% CI: 0.95–2.83; $P = 0.075$]).

Conclusion: MPA kidney involvement has become less severe over the past decades, leading to a reduced risk of ESKD and a higher relapse rate, despite a comparable risk of death.

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MPA is a small vessel antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) with no or few immune-deposits, in which necrotizing glomerulonephritis is very common and pulmonary capillaritis often occurs.[1,2] ANCA are usually directed against myeloperoxidase, giving rise to a perinuclear pattern by indirect immunofluorescence on neutrophils.[3,4]

Most of the MPA patients are usually >50 years old with a slight male prevalence.[5–7] Recent data seem to indicate an increasing age of patients; furthermore, despite being classified as a rare disease, incidence rates of MPA have risen with time.[8–10] If this is due to the wider availability of ANCA testing and to a greater awareness of the disease especially in the elderly, it is not known.[11]

The kidneys are the organs most frequently affected, up to 90% to 100% in some series.[8–14] The main clinical

Correspondence: Martina Uzzo, Department of Medicine and Surgery, Nephrology and Dialysis Unit, University of Milano-Bicocca, Monza, Italy. E-mail: m.uzzo@campus.unimib.it

[8]MZ and UM contributed equally.

[9]GM and RAS contributed equally as senior consultants.

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presentation is a rapidly progressive glomerulonephritis, characterized by a fast decrease in the glomerular filtration rate of at least 50% over a short period, an active urinary sediment (dysmorphic erythrocytes and red cells casts) and blood pressure in the normal range; histologically, rapidly progressive glomerulonephritis is characterized by extensive glomerular crescent formation.[3,15]

Untreated MPA has an unfavorable course with patient survival of less than 20% at 5 years.[5–7] Since the introduction of glucocorticoids (GCs) and cytotoxic agents in the 1960s, AAV prognosis has had a significant improvement; however, in a recent study there were 19.9% more deaths at 10 years and 36.3% at 20 years in a cohort of AAV patients compared to the general population. The main factors independently related to death are renal involvement and older age.[16–18]

Over the past decades, knowledge of AAV pathogenesis has evolved considerably, enabling the use of a greater range of therapeutic options. Furthermore, MPA recognition became easier and quicker after the introduction of ANCA testing in 1985; by the late 90s, ANCA were used all over the world as a diagnostic tool.[19–21]

To the best of our knowledge, this is the first analysis evaluating whether changes in demographic, clinical, and histological features have occurred over the past decades in a cohort of patients with an exclusive diagnosis of MPA and whether these changes have had any impact on clinical outcomes, namely death and ESKD.

The objective of our study was to examine the changes in demographic, clinical, and histological features at the time of MPA diagnosis in a large cohort of patients during a 42-year follow-up. We additionally verified whether changes in the competing risk of death and ESKD have occurred, before and after adjusting for the baseline prognostic factors differing between the two periods.

METHODS

Patients

We searched the medical records of patients followed at 4 AAV referral Italian centers: the Nephrology Unit of the San Gerardo Hospital (Monza), the Nephrology Unit of Fondazione IRCCS Ca'Granda Maggiore Policlinico (Milano), the Nephrology Unit of San Carlo Borromeo Hospital (Milano), and the Nephrology Unit of the Humanitas Research Hospital (Milano). Patients diagnosed with MPA between 1980 and January 31, 2022, were included in this multicenter retrospective cohort study.

First, we screened AAV cases classified as MPA using the European Medicines Agency algorithm,[22] with available ANCA serology (indirect immunofluorescence and enzyme-linked immunosorbent assay) and documented renal involvement at diagnosis, defined as an eGFR $\leq$60 ml/min per 1.73 m^2 and/or urinalysis disclosing proteinuria or microhematuria. The screened patients did not have AAV secondary to drugs, cancer, infections, or other systemic autoimmune disorders, nor they received immunosuppressive therapy during the 6 months before diagnosis.

The final cohort was divided into 4 decades (d) based on the year of MPA diagnosis: d1980 to 1990, d1991 to 2001, d2002 to 2011, and d2012 to 2022. The patients belonging to the first and the past 2 decades were grouped into 2 periods: p1980 to 2001 and p2002 to 2022. The 2 periods aim to reflect the change in the management of the disease that took place from the early 2000s, because of the wide distribution of ANCA testing and new therapeutic options.

The study was performed in accordance with the declaration of Helsinki and was approved by the Ethics Committee of the San Gerardo Hospital (protocol number 1922).

Data Collection

The patients' demographic and clinical data were recorded in a dedicated database. The assessment of clinical features was based on previous examinations by expert physicians.

Patients' characteristics were collected focusing on the following: (i) clinical/demographic characteristics and laboratory tests at the first detection of the disease; (ii) renal syndromes at presentation: rapidly progressive glomerulonephritis, urinary abnormalities, and chronic kidney disease; (iii) drugs and other treatments used; (iv) renal follow-up at the last available visit; (v) time of ESKD; (vi) time of death; and (vii) renal relapse.

Clinical features were reported according to the Birmingham Vasculitis Activity Score version 3. eGFR was calculated using the Modification of Diet in Renal Disease formula.[23] ANCA were tested using conventional immunofluorescence and enzyme-linked immunosorbent assays. In patients diagnosed before 1989, when ANCA testing was not available yet, it was performed retrospectively in stored serum samples.

The treatments used were divided into regimens based on GCs alone (pulse/oral or oral), or on GCs plus immunosuppressive drugs. In addition, some patients were treated with plasma exchange and/or hemodialysis. The number of patients treated with maintenance therapy, whether based on GCs, on other immunosuppressive therapies, or both, was recorded.

Outcome Measures

Our primary outcomes were overall survival, renal survival (ESKD), and renal relapse rate.

ESKD was defined as an eGFR <15 ml/min per 1.73 m^2 at 2 consecutive assessments or the need for chronic renal replacement therapy until the last available follow-up.

Any vasculitic manifestation occurring after remission, defined by at least 1 major item or 3 minor items of the Birmingham Vasculitis Activity Score was considered an MPA relapse. We defined AAV remission as Birmingham Vasculitis Activity Score version 3 for renal items equal to 0.[24] ESKD, death, and MPA relapse rates were evaluated both in the whole cohort and in the 2 periods previously described.

Renal Biopsies

The kidney biopsies were stained with routine light microscopy techniques and analyzed by experienced pathologists. Specimens with at least 10 glomeruli were included. According to Berden *et al.*,[25] the kidney biopsies were classified into 4 categories, purely based on glomerular lesions at light microscopy: the focal, the crescentic, the mixed, and the sclerotic class.

Data Analysis

We performed all the analyses with R 4.2.2 statistical package (https://www.R-project.org/). We regarded a 2-sided *P*-value < 0.05 as statistically significant. We tested the baseline pairwise differences using the Mann-Whitney test for continuous variables and the Fisher exact for categorical variables. Due to the small number of patients diagnosed in each decade, main analysis were focused on the comparison between 2 periods, p1980–2001 and p2002–2022. We compared crude patient survival using the Kaplan-Meier estimator and compared the adjusted rate ratio (hazard ratio) of death using Cox proportional-hazard multiple regression models. Hazard ratios were adjusted for potential confounders, that we regarded as the clinical characteristics that differed between the 2 periods at diagnosis. We did not adjust for rituximab and mycophenolate, because the distinction between the 2 periods p1980–2001 and p2002–2022 coincided with changes in the therapeutic approach, which therefore did not overlap between the 2 periods. For analyses on mortality, time started from MPA diagnosis and continued until death or January 31, 2022, irrespective of whether the patient had started dialysis or developed a relapse during the follow-up. We examined nonlinearity of continuous variables using cubic splines and tested proportional hazard assumption using Schoenfeld residuals. We estimated the crude cumulative incidence of death and ESKD between the 2 periods based on the Aalen–Johansen estimator. To this purpose, we analyzed the time from MPA diagnosis to death or ESKD, whichever came first, by regarding death and ESKD as 2 terminal states. We then compared the adjusted cumulative incidence of death and of relapse by calculating subdistribution hazard ratios via Fine-Gray multiple regression models.

Finally, we analyzed the differences in death rate and ESKD rate by estimating hazard ratios using a multistate model whereby each patient can have multiple transitions between different states. Because death is a terminal state, there were 3 possible transitions: from MPA diagnosis to ESKD, from MPA diagnosis to death, and from ESKD to death. Based on the model estimates we could calculate the probability of ESKD at each time point since MPA diagnosis, considering that patients on dialysis remain at risk of dying. The R code for the analyses is freely available at https://github.com/UMaggiore/MPA-onset-and-outcome-over-time.

RESULTS

Patient Selection and Follow-Up

Patient selection is reported in Figure 1. Out of 201 patients, 187 had nonmissing follow-up to ESKD and/or death and could be included in the study. There were

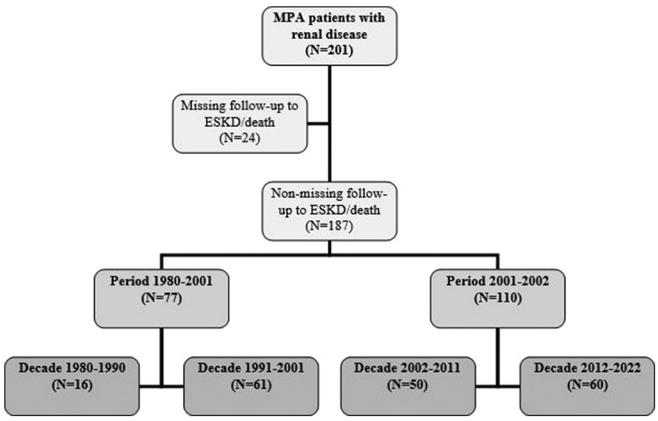

Figure 1. AAV cases with renal involvement were classified as MPA using the EMA algorithm,[22] with serology for ANCA available (indirect immunofluorescence and ELISA) and documented renal involvement at diagnosis, defined as an eGFR ≤60 ml/min per 1.73 m^2 and/or urinalysis disclosing proteinuria or microhematuria. Patients with other concomitant glomerulonephritis or secondary MPA were excluded. Of 201 patients, 24 were excluded due to the missing follow-up to ESKD or death. The remaining 187 patients were grouped into 2 periods (p) (p1980–2001, p2001–2002); each period included 2 decades (d) (d1980–1990, d1992–2001, d2002–2011, d2012–2022) according to the time of MPA diagnosis. The two 20-year periods identify a change in the approach of the disease that took place from the early 2000s, thanks to the wide distribution of ANCA testing and new therapeutic options. ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA associated vasculitis; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; ESKD, end-stage kidney disease; MPA, microscopic polyangiitis.

77 patients in p1980–2001 (16 in d1980–1990 plus 61 in d1991–2001), and 110 patients in p2002–2022 (50 in d2002–2011 and 60 in d2012–2022). The overall follow-up time was 6292 person-months (14 deaths, 0.22 per 100 person-months) during p1980–2001 and 5541 person-months (14 deaths, 0.25 per 100 person-months) during p2002–2022; median (range) follow-up time was 50 (1–294) and 40 (1–192) months, respectively. There were 34 patients who started chronic dialysis during p1980–2001 (0.64 per 100 person-months), and 14 patients who did so during p2002–2022 (0.26 per 100 person-months); 7 patients (20.5%) in p1980–2001 and 2 patients (14.3%) in p2002–2022 died after starting dialysis. At 12 months, 11 (7.1%) patients had died and 7 (4.5%) had ESKD in the overall cohort. Most of the patients were lost at follow-up after developing ESKD. At 60 months, 22 (24.2%) patients had died; at 120 months, 26 (44.1%) patients had died. Approximately 85% of the clinical outcomes (death and ESKD) occurred by month 96 (i.e., 8 years) of follow-up; approximately 85% of the patients in p2002–2022 had a follow-up of less than 96 months.

Characteristics of the Study Population

The characteristics of the study population are reported in Tables 1 and 2. Compared to p1980–2001, patients in p2002–2022 were older (66.2 ± 14.0 SD vs. 57.7 ± 15.8; $P < 0.001$) and had a better kidney function (eGFR 25.9 ± 24.8 vs. 21.5 ± 28.2 ml/min per 1.73 m^2; $P = 0.011$). The prevalence of the Berden sclerotic class was lower in p2002–2022 (5.9 vs. 20.9%; $P = 0.011$) and the Berden mixed class was higher (25.9 vs. 19.4%; $P = 0.040$). There were mild differences in the clinical presentation, the patients in p2002–2022 showing a slight lower prevalence of constitutional symptoms (83.6 vs. 94.8%; $P = 0.021$) and a higher prevalence of pulmonary disease (30.0 vs. 16.9%; $P = 0.040$) and peripheral neuropathy (17.3 vs. 5.2%; $P = 0.013$). Induction regimen consisted of GCs only (13% in p1980–2001 vs. 1.9% in p2002–2022; $P = 0.01$) or GCs plus cyclophosphamide, with or without plasmapheresis or dialytic treatment. As expected, no patient in the p1980–2001 was treated with rituximab. Maintenance therapy in the overall cohort consisted of low-dose GCs (42%) or low dose GCs plus other immunosuppressive regimens and lasted at least 18 months: mycophenolate mofetil only (6%), azathioprine only (30%), cyclophosphamide only (10%, intravenous or oral). Some patients used different immunosuppressive regimens in different periods.

We additionally examined differences across the 4 different decades. There was an increase of the mean age at diagnosis from d1980–1990 to d2002–2011 (Table 3). Furthermore, creatinine at diagnosis was significantly higher in d1980–1990 compared to all the subsequent decades, while a significant drop in the frequency of the Berden sclerotic class was confirmed between the second and the third decades ($P = 0.02$) (Table 3).

Patient Survival

Crude survival probability was similar between the 2 periods ($P = 0.93$) (Figure 2). After adjusting for baseline potential confounders (age, eGFR, constitutional symptoms, pulmonary disease, and peripheral neuropathy), the mortality rate was still similar (adjusted hazard ratio of death in the period 2002–2022 vs. period 1980–2001: 0.79, 95% CI: 0.29–1.66; $P = 0.41$).

Diverging Risk of ESKD Between the Two Periods

In Figure 3, the crude cumulative incidence of ESKD and death are shown as competing events and as terminal states (i.e., time is measured from MPA diagnosis to ESKD or death, whichever came first). The crude subdistribution hazard ratio of ESKD was 0.30 (95% CI: 0.16–0.57; $P < 0.001$) indicating that the crude risk of ending up in dialysis was approximately one-third in p2002–2022 compared to p1980–2001. After adjusting for baseline potential confounders (age, eGFR, constitutional symptoms, pulmonary disease, and peripheral neuropathy) the subdistribution hazard ratio was 0.51 (95% CI 0.24–1.09; $P = 0.081$).

The analysis of multiple state models, which allows patients starting dialysis to remain at risk of dying, confirmed the diverging risk of ESKD between the 2 periods. In fact, as shown in Figure 4, the probability of being on dialysis remained lower during p2002–2022 compared to p1980–2001, whereas the probability of death remained similar between the 2 periods. The crude and adjusted hazard ratios of ESKD since MPA diagnosis comparing p2002–2022 with p1980–2001 were 0.33 (95% CI: 0.18–0.63; $P < 0.001$) and 0.39 (95% CI: 0.19–0.80; $P = 0.010$), whereas the rate of death (either from MPA diagnosis or since dialysis start) did not differ between groups (data not shown).

Difference in Relapse Risk Between the Two Periods

Of the 187 patients selected, 172 had nonmissing follow-up to relapse. Twenty-three (30%) and 33 (30%) patients relapsed during p1980–2001 and p2002–2022, respectively. The analysis of ESKD, death, and relapse as terminal events, showed that the risk of relapse as first event (i.e., prior to ESKD) tended to be numerically higher during p2002–2022 (crude and adjusted subdistribution hazard ratios of

Table 1. Baseline characteristics of a cohort of MPA patients in 2 historical periods: clinical features

Patient characteristic	Historical period						*P*-value
	1980–2001			2002–2022			
Number of patients	77			110			
Age at kidney diagnosis, yrs	77	57.4	(15.8)	110	66.2	(14.1)	<0.001[a]
Age at diagnosis, yrs	77	57.7	(15.8)	110	66.2	(14.0)	<0.001[a]
Male sex	35		45.5%	54		49.1%	
ANCA type							
Negative	9		12.9%	8		7.3%	0.597
PR3	5		7.1%	6		5.5%	
MPO	55		78.6%	93		85.3%	
Clinical features							
Constitutional symptoms	73		94.8%	92		83.6%	0.021[a]
Pulmonary disease							0.040[a]
Lung infiltrates	13		16.9%	33		30.0%	
ILD/fibrosis	2		2.6%	8		7.3%	
Pleurisy	1		1.3%	3		2.7%	
Peripheral neuropathy	4		5.2%	19		17.3%	0.013[a]
Central nervous system	1		1.3%	3		2.7%	0.644
Ocular disease	3		3.9%	2		1.8%	0.404
Gastrointestinal disease	2		2.6%	5		4.5%	0.702
Cardiac disease							1.000
Pericarditis	0		0.0%	1		0.9%	
Myocardial infarction	0		0.0%	1		0.9%	
ENT	8		10.4%	9		8.2%	0.615
Skin involvement							
Purpura	8		10.4%	21		19.1%	
Ulcers	4		5.2%	1		0.9%	
No systemic manifestations	4		5.2%	12		10.9%	0.195
Disease features at diagnosis							
Renal syndrome							
RPGN	63		81.8%	89		80.9%	1.000
UA	7		9.1%	11		10.0%	
CKD	7		9.1%	10		9.1%	
Serum Creatinine, mg/dl	77	5.8	(4.5)	108	3.8	(2.3)	0.006[a]
GFR (MDRD), ml/min per 1.73 m^2	77	21.5	(28.2)	108	25.9	(24.8)	0.011[a]
Proteinuria, mg/d	71	1.9	(2.0)	100	1.5	(1.3)	0.634
Hb, g/dl	33	9.7	(2.0)	82	9.7	(1.9)	0.889
C-reactive protein, mg/l	13	6.5	(5.9)	77	7.7	(7.9)	0.948
C3, mg/dl	27	104.5	(29.0)	74	113.0	(22.8)	0.119
C4, mg/dl	27	30.0	(10.6)	74	29.4	(10.5)	0.659
Hypertension	23		59.0%	47		53.4%	0.699

ANCA, antineutrophil cytoplasmic autoantibody; CKD, chronic kidney disease; ENT, eyes/nose/throat involvement; GFR, glomerular filtration rate; Hb, hemoglobin; ILD, interstitial lung disease; MDRD, the Modification of Diet in Renal Disease formula; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase -3; RPGN, rapidly progressive glomerulonephritis; UA, urinary abnormalities.
[a]*P*-value < 0.05. Baseline patient characteristics. Baseline laboratory characteristics refer to time of diagnosis.
Continuous variables are reported as nonmissing data, mean (SD); categorical variables as number, percentage (%).

relapse comparing p2002–2022 with p1980–2001: 1.64 [95% CI: 0.95–2.83; $P = 0.075$] and 1.80 [95% CI: 1.00–3.24; $P = 0.048$]).

DISCUSSION

In this retrospective cohort study of 187 MPA patients, we showed that MPA demographic, clinical and histological presentation have changed over the past 4 decades, and the risk of ESKD has markedly reduced. Compared to the first ones, the past 2 decades showed less severe kidney disease at diagnosis with more active features at renal biopsy. Those differences were associated with a sharp reduction in the risk of ESKD, whereas mortality risk did not differ.

Several studies have evaluated AAV outcomes and risk factors so far, but only a few analyzed how they have changed over time[26–30]: 2 studies screened patients with granulomatosis with polyangiitis only,[28,29] whereas the others investigated AAV in general.[26,27,30] In the latter case, only 2 studies investigated AAV with renal involvement:[27,30] particularly, Rhee *et al.*[27] evaluated death and

Table 2. Baseline characteristics of a cohort of MPA patients in 2 historical periods: histopathological-features and treatments

Patient characteristics	Historical period 1980–2001		2002–2022		*P*-value
Number of patients	77		110		
Histophatologic parameters					
Number of patients with renal biopsy	67	87.0%	85	81.0%	0.375
Berden classification[b]					
Focal	20	29.9%	29	34.1%	0.700
Crescentic	20	29.9%	29	34.1%	0.700
Mixed	13	19.4%	22	25.9%	0.040[a]
Sclerotic	14	20.9%	5	5.9%	0.011[a]
Induction therapy					
Steroids					
None	2	2.7%	2	1.9%	0.628
Pulses/oral	67	89.3%	93	86.1%	
Oral	6	8.0%	13	12.0%	
Steroids alone	10	13.0%	2	1.9%	0.010[a]
Cyclophosphamide	44	58.7%	56	51.9%	0.370
Plasma exchange	14	18.7%	16	14.8%	0.545
Dialysis	21	28.0%	14	13.0%	0.013[a]
Rituximab	0		15	21.4%	<0.001[a]
Maintenance therapy	48	84.2%	102	96.2%	0.012[a]

MPA, microscopic polyangiitis.
[a]*P*-value <0.05.
[b]Berden AE, *et al.*[25] *J Am Soc Nephrol* 2010.
Baseline patient characteristics. Baseline laboratory characteristics refer to time of diagnosis.
Categorical variables as number, percentage (%).

ESKD as competitive risks over 25 years in a cohort of 554 general AAV patients (56% MPA). Although a multistate model was not used in this study, they concluded that both the risk of death and ESKD have decreased over time; on the contrary, the relapse rate did not change.[27]

This is the first analysis of changing patterns and risk factors over time in a cohort of patients with an exclusive diagnosis of MPA; furthermore, we had the most extensive time frame and length of follow-up.

We analyzed changes in demographic, clinical, and histological features. In line with previous studies, we showed a progressive increase in the mean age at diagnosis over time.[8–10] This can be due to both a new awareness of AAV as a potential disease in elderly patients with renal failure and to the presence of induction and maintenance treatments suitable for old patients. The leading causes of death in AAV patients are known to be infections, followed by cardiovascular disease and malignancies.[16] Considering that age at disease diagnosis has increased over the past decades, we would have expected a concomitant increased mortality, regardless of clinical pattern an treatments: however, mortality was similar between the 2 periods.

In p2002–2022, patients also had a significant higher eGFR at diagnosis and a more active histopathological counterpart, with a higher prevalence of the Berden mixed class ($P = 0.040$) and a lower prevalence of the Berden sclerotic one ($P = 0.011$).[25] Despite a better kidney function, no differences in renal syndromes were found between groups. We believe that older age and better renal function in p2002–2022 may not be explained by a higher frequency of slowly progressive AAV phenotype[31]; rather, they might reflect increased awareness of the disease, especially in the elderly, leading to an earlier referral to the nephrologist and an earlier diagnosis. ANCA was discovered in 1985 and

Table 3. Baseline clinical and histopathological features of a cohort of MPA patients divided in 4 decades

Patient characteristic	d1980–1990 (*N* = 16)	d1991–2001 (*N* = 61)	d2002–2011 (*N* = 50)	d2012–2022 (*N* = 60)
Age at kidney diagnosis (yr)	57.0 (44.0-69.3)[a]	61.0 (49.0-70.0)	66.0 (53.3-75.8)	71.5 (63.0-78.0)
Male sex	6 (37.5%)	29 (48%)	21 (42%)	33 (55%)
Disease features at diagnosis				
Renal syndrome				
RPGN	15 (93.8%)	48 (78.6%)	39 (78.0%)	50 (83.4%)
UA	0	7 (11.7%)	6 (12.0%)	5 (8.3%)
CKD	1 (6.2%)	6 (9.7%)	5 (10.0%)	5 (8.3%)
Renal function				
Creatinine (mg/dl)	9.4 (6.0-12.1)[b]	3.4 (2.2-6.6)	3.4 (1.8-5.0)	3.3 (2.03-4.9)
Proteinuria (mg/d)	2.0 (1.1-3.6)	1.1 (0.4-2.5)	1.3 (0.9-2.0)	1.0 (0.5-1.8)
Histophatologic parameters				
Patients with renal biopsy	13	54	42	43
Berden classification				
Focal	4 (30.8%)	16 (29.7%)	14 (33.3%)	15 (34.9%)
Crescentic	5 (38.6%)	15 (27.9%)	16 (38.0%)	13 (30.2%)
Mixed	2 (15.3%)	11 (20.1%)	10 (23.9%)	12 (27.9%)
Sclerotic	2 (15.3%)	12 (22.3%)[c]	2 (4.8)	3 (7.0%)

CKD, chronic kidney disease; MPA, microscopic polyangiitis; RPGN, rapidly progressive glomerulonephritis; UA, urinary abnormalities.
[a]$P < 0.05$, d1980–1990 vs. all d2012–2022.
[b]$P < 0.05$, d1980–1990 vs. all other decades.
[c]$P < 0.05$, d1991–2001 vs. d2002–2011 and d1991–2001 vs. d2012–2022
Baseline laboratory characteristics refer to time of diagnosis.
Continuous variables are reported as median (interquartile range); categorical variables as number, percentage (%).

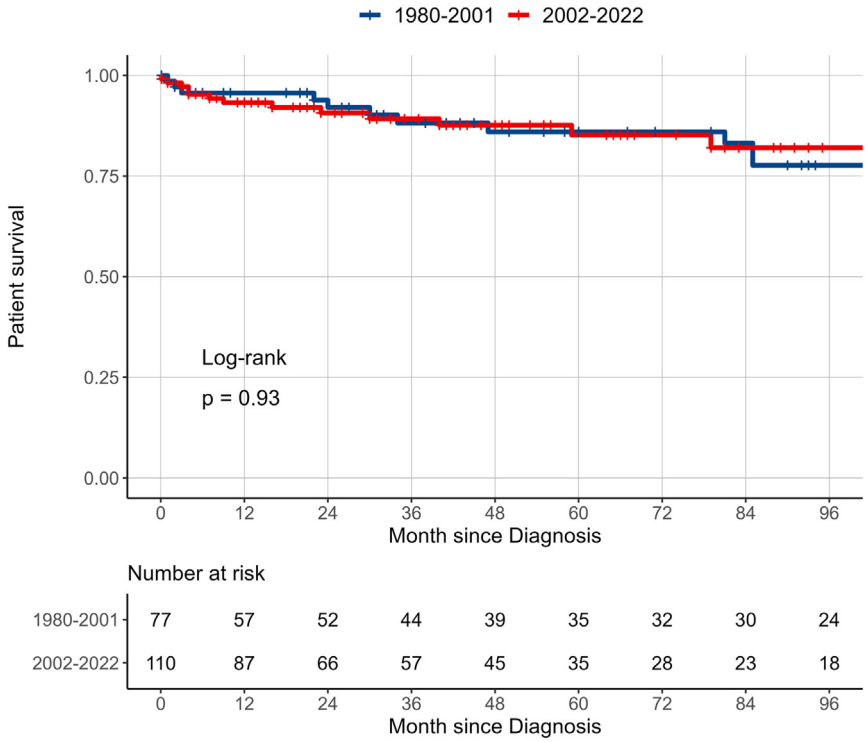

Figure 2. Crude patient's survival (Kaplan-Meier estimator) during the period 1980–2001 (blue line) and 2002–2022 (red line). *P*-value refers to Log-rank test, which is based on the time to the latest available follow-up, though the plot refers to the first 96 months (8 years). The difference remained nonstatistically significant after adjustment for potential confounders. MPA, microscopic polyangiitis.

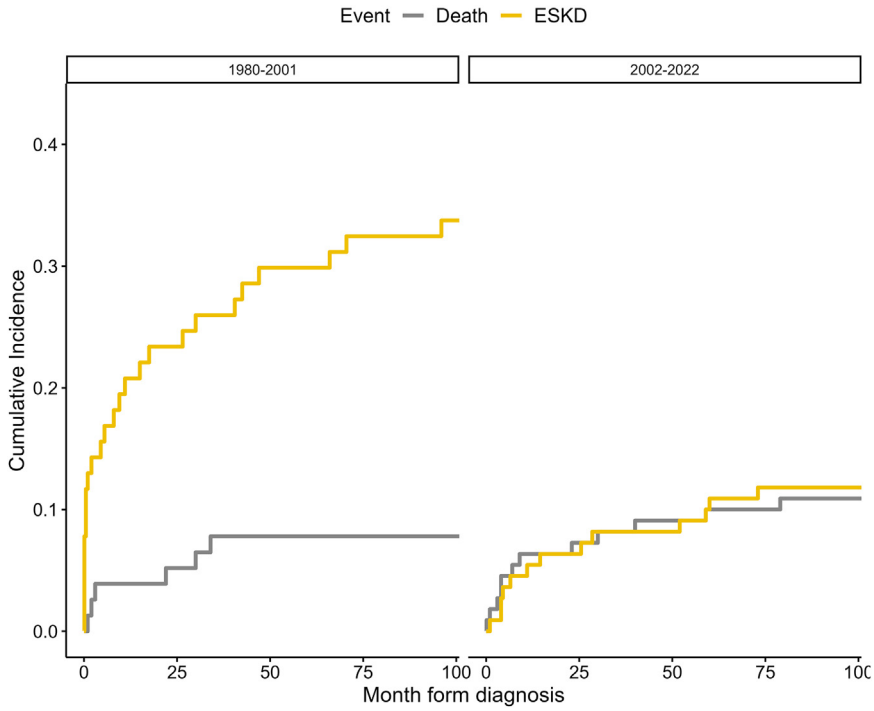

Figure 3. Crude cumulative incidence curves (Aalen–Johansen estimator) computed with the time from MPA diagnosis to the first event as terminal state (ESKD or death), whichever came first: cumulative incidence estimates can be interpreted as the actual probability of developing ESKD or death as first event following diagnosis. However, death occurring after ESKD is not accounted for. The crude subdistribution hazard ratio of ESKD was 0.30 (95% CI: 0.16–0.57; $P < 0.001$) indicating that, at the time of diagnosis the crude risk of ending up in dialysis was approximately one-third in the period 2002–2022 compared to the period 1980–2001. However, after adjusting for baseline potential confounders (age, eGFR, constitutional symptoms, pulmonary disease, and peripheral neuropathy) the subdistribution hazard ratio was 0.51 (95% confidence interval 0.24 to 1.09; $P = 0.081$). eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; MPA, microscopic polyangiitis.

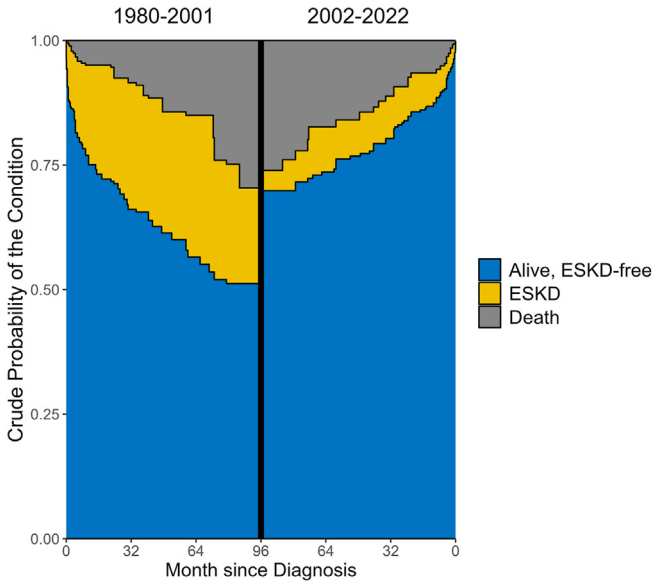

Figure 4. Crude probability of each outcome at each time-point since MPA diagnosis, that results from fitting the multiple state model. Unlike the model in which ESKD is a terminal state (Figure 3), the multistate model allows that patients starting dialysis remain at risk of dying. Therefore, multistate models consider that the larger the proportion of patients dying on dialysis, the lower the probability of being alive on dialysis at each time point: the plot can be interpreted as the cross-sectional proportion of patients who are dead, on ESKD, or alive ESKD-free at each time point on the x-axes. Even after taking this into account, the probability of being on dialysis (yellow area) remained lower during the period 2002–2022 compared to the period 1990–2001, whereas the probability of death (gray area) remained similar between the 2 periods. In fact, the hazard ratio of ESKD since MPA diagnosis was 0.39 (95% confidence interval: 0.19–0.80; $P = 0.010$), whereas the rate of death (either from MPA diagnosis or since dialysis start in patients who developed ESKD) did not differ between the 2 periods (data not shown). ESKD, end-stage kidney disease; MPA, microscopic polyangiitis.

ANCA testing progressively spread over the 1990s, becoming a worldwide recognized diagnostic tool at the beginning of 2000s and leading to an easier identification of the disease. This seems to be reflected by the considerable decrease of patients presenting with sclerotic class after 2001 and justify our main division into 2 periods. Importantly, renoprotective therapy improved over the years and better management of other non-AAV related factors such as hypertension, diabetes mellitus, and chronic kidney disease may have contributed to a better renal outcome.

Many negative prognostic factors of AAV survival have been reported in the literature.[17,32–37] On this basis, we adjusted the risk of death and ESKD for potential confounders.

In contrast to previous studies reporting an improvement in the mortality rate over time, both crude and adjusted overall survival were similar between the 2 periods.[17,26–28,38] Previous studies accounted for AAV in general, whereby MPA subanalysis was missing; in contrast, the effect of older age of patients in p2002–2022 may be offset by an earlier diagnosis of kidney disease.

By accounting for competing risk of death, the crude risk of ESKD was approximately 3 times lower in p2002–2022 compared to p1980–2001. This justifies the relatively short difference of follow-up between the 2 periods (10 months): ESKD patients are usually followed-up with in the referral hemodialysis or transplant hospital, which can be different and far from the place where they were originally diagnosed. Confounding factors did not fully explain the difference in ESKD risk between the 2 periods.

ANCA testing was essential for an earlier and easier diagnosis, contributing to improve clinicians' awareness of the disease; furthermore, deeper insights into the pathogenesis of AAV dramatically changed the therapeutic approach: the optimal dose of cyclophosphamide was investigated only in 2009 and rituximab was firstly approved for AAV induction therapy in 2011.[20,21,39] Subsequently, none of the patients belonging to p1980–2001 was treated with rituximab or with mycophenolate mofetil, and drug dosages and duration were not available in our data. We believe that the disparity in diagnosis and treatment may account for the adjusted difference in the risk of ESKD between the 2 periods

We acknowledge that our study has limitations. First, we could not directly assess the independent effect of treatment between the 2 periods. Thirteen percent of patients in p1980–2001 and 1.9% in p2002–2022 took steroids alone, without any other immunosuppressive therapy, and a meaningful number of patients in p1980–2001 were not treated with maintenance therapy (15.8%).[11] Second, histopathological data were deduced from previous reports, without central revision, and data regarding the causes of death were not available: changing patterns of mortality might help explain why mortality had not changed. Third, during the p2002–2022 there was an increase in the risk of relapse, which may be related to the reduced ESKD risk, as MPA relapses are infrequent in dialysis patients.[40,41] Lastly, most of our patients were Caucasian: our results may not be applied to other ethnic groups.

In conclusion, MPA kidney involvement at diagnosis has become less severe in the past decades, showing a higher proportion of active histological features at disease diagnosis, which is reflected by a reduced risk of ESKD. However, risk of death has not been reduced. Changing clinical and demographic patterns and better kidney function at the time of diagnosis do not fully account for the reduction in ESKD, which may instead be the result of improved diagnosis and management of MPA.

DISCLOSURE

RAS has received Consulting fees from Roche, GSK, Vifor and Otsuka. All other authors have declared no conflicting interests.

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Data Availability Statement

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

AUTHOR CONTRIBUTIONS

RAS and GM conceived the study. RAS, GM, FS, FR, MC, VL'I, and MU selected the eligible MPA patients and recorded histological data in a dedicated database. UM and MU conceived and conducted the statistical analysis. RAS, GM, UM, and MU drafted the manuscript. RAS, GM, UM, and MU reviewed and edited the manuscript and supported the study. All authors checked the final version of the manuscript.

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