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Microscopic polyangiitis: clinical characteristics and long-term outcomes of 378 patients from the French Vasculitis Study Group Registry

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ABSTRACT (241/250 words)

Objective. To describe characteristics and long-term outcomes of patients with microscopic polyangiitis (MPA), an antineutrophil cytoplasm antibody (ANCA)-associated small-vessel necrotizing vasculitis.

Methods. MPA patients from the French Vasculitis Study Group Registry satisfying the European Medicines Agency algorithm were analyzed retrospectively. Characteristics at diagnosis, treatments, relapses and deaths were analyzed to identify factors predictive of death or relapse.

Results. Between 1966 and 2017, 378 MPA patients (median age 63.7 years) were diagnosed and followed for a mean of 5.5 years. At diagnosis, the main clinical manifestations included renal involvement (74%), arthralgias (45%), skin (41%), lung (40%) and mononeuritis multiplex (32%), with less frequent alveolar hemorrhage (16%), cardiomyopathy (5%) and severe gastrointestinal signs (4%); mean serum creatinine was 217 $\mu\text{mol/L}$. ANCA were detected in 298/347 (86%) patients by immunofluorescence and/or enzyme-linked immunosorbent assay (ELISA). Among the 293 patients with available ELISA specificities, 272 (92.8%) recognized myeloperoxidase and 13 (4.4%) proteinase-3. During follow-up, 131 (34.7%) patients relapsed and 78 (20.6%) died, mainly from infections. Respective 5-year overall and relapse-free survival rates were 84.2% and 60.4%. Multivariable analyses retained age >65 years, creatinine >130 $\mu\text{mol/L}$, severe gastrointestinal involvement and mononeuritis multiplex as independent risk factors for death. Renal impairment was associated with a lower risk of relapse.

Conclusion: Non-renal manifestations and several risk factors for death or relapse were frequent in this nationwide cohort. While mortality was low, and mainly due to treatment-related complications, relapses remained frequent, suggesting that MPA management can be further improved.

1. INTRODUCTION

Microscopic polyangiitis (MPA) is a systemic small-vessel necrotizing vasculitis belonging to the group of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAVs). The 2012 revised Chapel Hill Consensus Conference nomenclature defined MPA as clinical and histopathological criteria (mainly general symptoms, visceral manifestations, including rapidly progressive glomerulonephritis and alveolar hemorrhage, and the absence of granulomatous inflammation, unlike granulomatosis with polyangiitis (GPA, Wegener's) or eosinophilic granulomatosis with polyangiitis (Churg–Strauss)), and ANCA, predominantly of anti-myeloperoxidase (MPO) specificity, which are present in ~80% of MPA patients.[1]

MPA has often been studied with other AAVs, mostly GPA. However, the two diseases differ in their genetic backgrounds, clinical picture at onset, prognoses and ANCA specificities, with anti-proteinase 3 (PR3) antibody-negativity being associated with a lower relapse risk.[2,3] Most epidemiological studies or clinical trials analyzed MPA and GPA patients together,[4–6] and only a few studies focused on MPA as a distinct entity.[7–10] Moreover, because renal involvement is frequent in MPA, many series concerned nephrology patients.

The aim of this study was to describe MPA characteristics, prognoses and outcomes.

2. PATIENTS AND METHODS

2.1. Patients

In this retrospective multicenter study, we analyzed data from patients enrolled between 1966 and September 2017 in the French Vasculitis Study Group (FVSG) computerized database, which includes all systemic vasculitis patients referred to the members of the FVSG, and/or enrolled in randomized trials conducted by the FVSG.[6, 11–17]

Patients satisfying the criteria of the European Medicines Agency (EMA) consensus

algorithm to identify MPA in epidemiological studies[18] were included. According to that algorithm, patients with PR3- or MPO-ANCA without biopsy-proven vasculitis were also included if they had at least one surrogate marker of renal vasculitis and no evidence of surrogate markers of granulomatous disease. MPA diagnoses were reassessed by the investigators (YN, LG and XP), considering the entire follow-up period, so that those patients who were initially misdiagnosed as GPA or polyarteritis nodosa were excluded. Patients with insufficient data (<6 months of follow-up, unless they died within the first 6 months, and/or no initial clinical details) or with other systemic diseases were not included.

2.2.Characteristics at diagnosis

Baseline characteristics, including age at diagnosis, sex, clinical, biological, radiological and histological findings, were extracted from the standardized FSVG-registry record form. Fever was defined as temperature >38.5°C, weight loss as >2 kg lost over the 3 months preceding diagnosis. Heart manifestations included pericarditis and congestive heart failure, defined only by clinical symptoms (for example, pulmonary edema), thereby corresponding to the 2009 revised Five-Factor Score (FFS) definition.[19] Severe gastrointestinal manifestations, defined according to the FFS definition, included bowel perforation, bleeding and/or pancreatitis.[19] Only gastrointestinal manifestations considered to be directly attributable to active vasculitis were considered an FFS item. Alveolar hemorrhage was deemed massive when mechanical respiratory support, including all methods of artificial ventilation with an artificial airway or without, was required.

Laboratory findings included hemogram, serum creatinine level, proteinuria, C-reactive protein (CRP) and ANCA status. ANCA detection in serum, at diagnosis or later during follow-up when they had not been tested initially, by immunofluorescence (IF) and/or enzyme-linked immunosorbent assay (ELISA) defined positivity for most patients. Biopsies

showing vasculitis and/or necrotizing glomerulonephritis were considered abnormal.

2.3.Disease activity and scores

Disease activity was assessed at diagnosis using the Birmingham Vasculitis Activity Score (BVAS) version 3.[20] If missing, BVAS was calculated retrospectively. The five items included in the original 1996 FFS (central nervous system involvement, cardiomyopathy, serum creatinine >140 µmol/L, proteinuria >1 g/24 hours and/or severe gastrointestinal involvement),[15] and the revised 2009 FFS (severe gastrointestinal involvement, cardiac insufficiency, serum creatinine >150 µmol/L, ≥65 years old, and absence of ear, nose & throat symptoms) were collected from the FSVG database.[19]

2.4.Treatment

Patients included in clinical trials were treated according the protocols, evaluating induction azathioprine or glucocorticoids alone,[12, 15] and mycophenolate mofetil, methotrexate, azathioprine or rituximab as maintenance therapy.[6, 12, 13, 17, 21] Others received the standard-of-care at the time diagnosed, mainly based on the FFS. Remission-induction, maintenance and post-relapse–induction treatments were collected.

2.5.Outcomes

Studied outcomes included mortality and relapses, with major and minor relapses defined according to the European League Against Rheumatism (EULAR) recommendations.[22]

2.6.Statistical analyses

Continuous variables are expressed as mean±standard derivation (SD) or median (interquartile range [IQR]) and categorical variables as number (percentage). Overall survival

(OS) was calculated from MPA diagnosis to death or the last follow-up visit and relapse-free survival (RFS) from MPA diagnosis to relapse, death or end of follow-up, whichever occurred first. Patients' OS and RFS rates 1- and 5-years post-diagnosis were estimated with the Kaplan–Meier method. For OS and RFS, baseline clinical and biological parameters were compared using log-rank tests. Continuous variables (age, creatinine level, BVAS) were dichotomized based on the median value. Variables achieving $p < 0.10$ in univariable analyses were candidates for the multivariable Cox proportional hazard models. Variable selection for the final model was based on 1,000 bootstrapped samples from the original one with replacement. For each sample, a backward-stepwise selection was used, and the final model was defined as the most frequently selected model among the 1,000 bootstrapped samples.[23] FFS and BVAS were not included in the multivariable model because their composite items were already analyzed separately. Results are expressed as hazard ratios (HRs) [95% confidence intervals (95% CIs)]. All p-values were two-tailed, with $p < 0.05$ defining significance. Analyses were computed with R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.7.Ethics

The FSVG database was approved by the French National Computer-Watchdog Commission (CNIL). Patients enrolled in prospective therapeutic trials gave written informed consent at enrollment for the prospective collection and further analysis of their data. All other patients received oral and written information attesting to their unrestricted rights to request deletion of their data. This study was conducted in compliance with the Good Clinical Practices and principles of the Declaration of Helsinki. It was approved by the Cochin Hospital Ethics Committee (AAA-2019-08016).

3. RESULTS

3.1. Study population

The FSVG registry contained 557 patients diagnosed with MPA. After excluding 175 patients with insufficient information recorded at diagnosis and/or <6 months of follow-up, unless they died within the 6 months post-diagnosis, and four others strongly suspected of having MPO-ANCA-positive MPA but without histologically proven vasculitis and no renal involvement, thereby not satisfying EMA criteria, 378 patients satisfied the inclusion criteria.

Among them, 23 patients were enrolled in the database at the time of relapse but had complete initial data available at MPA diagnosis, which were fulfilled retrospectively.

Patients were followed for a mean±SD of 5.5±4.6 years.

3.2. Baseline clinical characteristics

Main baseline clinical and demographic characteristics patients diagnosed between 1966 and 2017 are reported in table 1. Patients' median age was 63.7 years and 52.6% were women. At least one-third initially had the following clinical manifestations in decreasing order: renal, weight loss, fever, arthralgias, myalgias, lung, skin manifestations and/or mononeuritis multiplex. Alveolar hemorrhage, congestive heart failure and severe gastrointestinal signs were less frequent. At MPA diagnosis, original 1996 FFSs were 0 for 41.3%, 1 for 36.2% and ≥2 for 22.5% of the patients, whereas 2009 FFSs were 0 for 23.3%, 1 for 44.7% and ≥2 for 32.0%. Median (IQR) BVAS was 16 (12–23).

3.3. Laboratory findings

The main biological characteristics at diagnosis are summarized in table 2. Mean±SD creatinine values were 217±223 µmol/L; they rose >30% in 154 (40.7%) patients and 158 (42%) had levels >150 µmol/L.

ANCA status (IF and/or ELISA) was available for 347 (92%) patients either at diagnosis or determined later for those recruited before ANCA results became routinely available. Among them, 86.1% were ANCA-positive (230 with ELISA and IF, 51 with only ELISA and 17 with only IF). Only three patients were ELISA and IF ANCA-negative, and 46 were IF ANCA-negative without available high-quality ELISA results. IF ANCA results were available for 346 (91.5%) patients, among whom 72.5% were positive, predominantly with a perinuclear-labeling pattern, (with five patients' sera recognized both specificities) and 95 (27.5%) were ANCA-negative. ELISA-determined ANCA results were available for 293 (77.5%) patients, among whom 95.9% were positive; among them, 272 recognized MPO specificity and 13 PR3;4 had both MPO and PR3-ANCA. None of the PR3-positive patients had any signs or symptoms suggestive of granulomatous disease affecting the upper and/or lower respiratory tract (e.g. fixed pulmonary infiltrates, pulmonary nodules, bloody nasal discharge and/or crusting) or any biopsies containing granulomas at diagnosis or during median follow-up of 5.6 years.

3.4.Histological findings

One or more histological findings were available for 297 (78.6%) patients, with vasculitis and/or necrotizing glomerulonephritis found in 254 (85.5%) patients: 158/164 (96.3%) kidney biopsies revealed necrotizing glomerulonephritis, and 78/109 (71.6%) neuromuscular and/or 33/39 (84.6%) skin samples showed necrotizing vasculitis predominantly affecting small vessels.

3.5.Treatments

One hundred thirty-nine (36.8%) patients had been included in prospective clinical trials. Induction therapy consisted of glucocorticoids alone for 90 patients (23.8%) and combined

with immunosuppressants for 278 (73.5%): cyclophosphamide for 237 (62.6%) and rituximab for 20 (5.3%). Forty-six (12.2%) patients underwent plasma exchanges for severe renal involvement (n=28), alveolar hemorrhage (n=3), both (n=5) or severe mononeuritis multiplex (n=6). Azathioprine was prescribed as first line and/or maintenance therapy for 95 (25.1%) patients, and 43 (11.4%) received low-dose preemptive rituximab-maintenance therapy.

3.6.Disease outcomes

During follow-up, 131 (34.7%) patients relapsed after a mean±SD of 3.0±2.9 years post-diagnosis. Among them, 105 relapsed with at least one clinical manifestation that had been present at diagnosis. Relapses were major, i.e. involving potentially organ- or life-threatening disease, for 56/131 (42.7%), and minor for 75/131 (57.3%) patients. Relapses were treated with intensified glucocorticoids alone (n=40), or combined with cyclophosphamide (n=52), rituximab (n=20), azathioprine (n=10) or mycophenolate mofetil (n=4), or plasma exchanges and cyclophosphamide (n=3) or rituximab (n=2).

Estimated 1- and 5-year RFS rates (95% CI) were 88.6% (85.3–92.0) and 60.3% (54.4–66.8), respectively. According to univariable analyses (table 3), mononeuritis multiplex was significantly associated with a higher risk of relapse, while creatinine >130 µmol/L and an immunosuppressive drug in the remission-induction regimen were significantly associated with a lower risk of relapse. Multivariable analyses retained only creatinine >130 µmol/L as an independent factor protective against relapse. RFS curves for the 378 patients according to their initial creatinine level are shown in figure 1.

Seventy-eight (20.6%) patients died during follow-up after a median [IQR] of 34.4 [6.5–83.6] months post-diagnosis. Causes of death are reported in Supplementary table S1, with the main causes being infections (18; 23%), cardiovascular disease (14; 18%) and malignancies (14; 18%). Death was directly attributable to MPA for 11 (14%). Sixty-one (78.2%) of those

78 patients who died had received glucocorticoid and immunosuppressant induction regimens.

Estimated 1- and 5-year OS rates (95% CI) were 93.3% (90.8–95.9) and 84.1% (80.0–88.3), respectively. According to univariable analyses, age >65 years, creatinine >130 $\mu\text{mol/L}$, severe gastrointestinal manifestations and mononeuritis multiplex were significantly associated with an increased risk of death (table 3). 2009 revised FFS ≥ 1 (HR 2.7 for FFS=1 and HR 7.1 for FFS ≥ 2 vs FFS=0) and for BVAS ≥ 16 vs <16 (HR 2.1) were also significantly associated with death. Multivariable analyses retained age >65 years, creatinine level >130 $\mu\text{mol/L}$, severe gastrointestinal manifestations and mononeuritis multiplex as independent risk factors for death (table 3). OS curves for the 378 patients and as a function of the 2009 FFS, or age, creatinine level, mononeuritis multiplex or severe gastrointestinal manifestations are shown in figures 2 and 3, respectively.

4. DISCUSSION

In this retrospective multicenter study based on 378 MPA patients recruited from internal medicine, rheumatology, nephrology, and pulmonary medicine departments, and entered in the FVSG database, respective 5-year OS and RFS rates were 84.1% and 60.3%.

Multivariable analyses retained age >65 years, renal impairment, severe gastrointestinal involvement and mononeuritis multiplex as independent risk factors for death, while renal impairment was also associated with a lower relapse risk.

This analysis of characteristics and long-term outcomes provided a better characterization of the whole MPA spectrum. Compared with other cohorts focusing only on MPA, mainly from nephrology departments, one-quarter of our patients did not have renal involvement and extrarenal manifestations were more frequent.[10, 24, 25]

In our cohort, >85% of the 347 MPA patients with available ANCA status were ANCA-

positive. Despite MPA patients being predominantly anti-MPO-ANCA-positive, 13 had anti-PR3 specificity. Although anti-PR3-ANCA are more common in GPA, they are not considered an exclusion criterion for MPA,[18] and account for 0–26% of patients in the different MPA series.[7,26–31] Because our 13 anti-PR3-positive patients had no surrogate markers for granulomatous disease, they should be considered as having MPA. No apparent clinical discrepancies were seen between anti-PR3- and anti-MPO-positive MPA patients, but the number of the former was too small to allow meaningful comparisons.

Three-quarters of our patients were prescribed glucocorticoids combined with immunosuppressants. Most of them received cyclophosphamide as induction therapy, but only 43 patients were given first-line rituximab. Because rituximab was demonstrated to be effective as induction and maintenance therapies against severe MPA only after 2010, our results must be contextualized with the standard-of-care at diagnosis during each period.

Our 5-year OS rate of 84% was better than the 74% our group reported for an MPA series in 1999.[7] However, it is close to the 89.6% Shirmer *et al* recently reported, based on a German series of 144 MPA patients.[8] The considerable progress in managing AAV patients over the past few decades could explain our and their findings.

Our results confirm that the FFS is useful for assessing MPA survival probability at diagnosis and could be one of the tools applied to adapt the therapeutic regimen. Mortality varied widely according to the FFS but it remains to be demonstrated whether therapeutic adaptation according to this score could improve the prognoses of patients with a poor-prognosis factor at diagnosis, as was shown for eosinophilic granulomatosis with polyangiitis.[32]

In our series, age >65 years, renal impairment, gastrointestinal manifestations and mononeuritis multiplex were independently associated with death. The first three of those parameters are 2009 FFS items, and already known as poor-prognosis factors for AAV

patients, especially those with MPA.[19] Herein, mononeuritis multiplex was shown to be an independent poor-prognosis factor. To our knowledge, only Schimer *et al* [8] also identified peripheral nervous system involvement at MPA diagnosis as being strongly associated with mortality (HR 5.26 [1.10–25.14]). In the 2009 FFS study, when focusing on MPA patients, neurological signs were not significantly associated with an increased risk of death (HR 1.8 [0.7–4]), perhaps because of the smaller number of patients. It could be hypothesized that patients with mononeuritis multiplex involving the lower limbs might have more difficulties walking, longer hospitalizations and, thus, be more susceptible to complications, like infections.

In our cohort, mortality was more frequently caused by infections, malignancies or cardiovascular disease than directly attributable to vasculitis progression. While the drugs prescribed seemed to effectively prevent mortality due to MPA, those causes of death make us wonder whether the patients had been overtreated and their treatments could be better adapted to prevent some complications. However, with the dramatic advances in AAV management, particularly increased rituximab use for induction and maintenance, those observations will most likely change.[12, 30]

Multivariate analyses retained only creatinine >130 $\mu\text{mol/L}$ as independently associated with a lower relapse risk. As found previously when studying MPA and GPA together,[3] based on five clinical trials assessing 535 AAV patients including 251 with MPA, Walsh *et al* described creatinine >200 $\mu\text{mol/L}$ as being strongly associated with a lower relapse risk, compared to creatinine <100 $\mu\text{mol/L}$ (HR 0.39; $p<0.001$). However, it is still unclear whether these patients need a shorter and/or less intense maintenance therapy, once remission has been obtained. Our univariate analysis identified an immunosuppressant in the induction regimen as significantly associated with a lower relapse risk but multivariate analyses did not retain it. While the risk of relapse remains high for patients with FFS=0 treated with glucocorticoids

alone, adding azathioprine for those patients did not lower the relapse risk, as previously demonstrated by the results of an FVSG randomized clinical trial.[17]

We acknowledge some limitations in our study. First, our analysis was conducted retrospectively. **Notably, a minority of patients has not been enrolled at MPA diagnosis, but at the time of relapse, provided their initial data was available. Thus, their evaluation of clinical MPA characteristics at diagnosis had been fulfilled retrospectively. However, this small number of patients is unlikely to have biased our findings.** Moreover, patients with renal-limited vasculitis might be underrepresented in our cohort, and we have limited data concerning the renal prognosis of our population. Finally, standard-of-care and ANCA findings have changed markedly over the last decades, which might have affected outcome assessment.

A strength of this study is the long-term follow-up of one of the largest MPA-patient cohorts, followed in multiple centers (by internal medicine specialists, rheumatologists, nephrologists and pulmonary medicine specialists), thereby enabling us to establish a clearer real-life picture of the entire MPA spectrum. Because we focused exclusively on MPA patients and had access to the data of a large cohort, we were able to more accurately evaluate the risk factors associated with this vasculitis.

In conclusion, the results obtained for this large MPA-patient cohort indicated a high prevalence of non-renal manifestations, and poorer prognoses for patients >65 years old, or with renal impairment, severe gastrointestinal involvement and/or mononeuritis multiplex. While mortality was low and mainly attributable to treatment-related complications, relapses remained too frequent. Further studies are needed to optimize management of these patients.

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FIGURE LEGENDS

Figure 1. Kaplan–Meier curves of (A) estimated probability of relapse-free survival of the 378 microscopic polyangiitis patients and (B) according to their creatinine levels at diagnosis.

Figure 2. Kaplan–Meier curves (A) of the estimated probability of survival of the 378 microscopic polyangiitis patients and (B) according to their 2009 Five-Factor scores (FFS).

Figure 3. Kaplan–Meier curves of the estimated probability of survival of the 378 microscopic polyangiitis patients according to (A) age category, (B) serum creatinine level, (C) mononeuritis multiplex status and (D) severe gastrointestinal manifestations at diagnosis.

TABLES

Table 1. Main clinical characteristics of 378 microscopic polyangiitis patients at diagnosis

Clinical characteristic	Value
Sex, male/female	179/199
Age at diagnosis, median [IQR]	63.7 [53.2–72.2]
Age >65 years (2009 FFS item)	180 (47.6)
Year of diagnosis	
<1990	30 (7.9)
1990–2000	101 (26.7)
2000–2010	152 (40.2)
>2010	95 (25.1)
Smoker	103 (27.2)
Fever >38.5°C	171 (45.2)
Weight loss >2 kg within 3 months	152 (40.2)
Arthralgias	171 (45.2)
Myalgias	152 (40.2)
Lung manifestations	152 (40.2)
Alveolar hemorrhage	59 (15.6)
Massive alveolar hemorrhage and/or Hb <9 g/dL	17 (4.5)
Dyspnea	72 (19.0)
Lung infiltrate	52 (13.8)
Interstitial lung disease	55 (14.6)
Pleural effusion	20 (5.3)
Renal manifestations	281 (74.3)

Serum creatinine >150 µmol/L (2009 FFS item)	158/353 (44.8)
Need for dialysis	40 (10.6)
Cutaneous manifestations	155 (41.0)
Purpura	71 (18.8)
Livedo reticularis	42 (11.1)
Ear, nose & throat manifestations	50 (13.2)
Eye involvement	18 (4.8)
Cardiovascular manifestations	79 (20.9)
Pericarditis	24 (6.3)
Congestive heart failure (2009 FFS item)	20 (5.3)
Gastrointestinal involvement	62 (16.4)
Severe gastrointestinal manifestations	15 (4)
Neurological involvement	191 (50.5)
Central nervous system involvement	10 (2.6)
Mononeuritis multiplex	119 (31.5)

Immunosuppressant in the induction regimen	277 (73.3)
1996 FFS at diagnosis	
0	156 (41.3)
1	137 (36.2)
≥2	85 (22.5)
2009 FFS at diagnosis	
0	88 (23.3)
1	169 (44.7)
≥2	121 (32.0)
BVAS at diagnosis	16 [12–23]

Results are expressed as n (%) or median [interquartile range, IQR]. MPA, microscopic polyangiitis; FFS, Five-Factor Score; BVAS, Birmingham Vasculitis Activity Score (version 3).

Table 2. Main biological characteristics at diagnosis of 378 microscopic polyangiitis patients

Biological parameter	Value
Creatinine, $\mu\text{mol/L}^*$, median [IQR]	130 [80–265]
Cockroft and Gault eGFR, mL/min/1.73 m ²	46 \pm 37
Estimated proteinuria, g/day [†]	1.4 \pm 1.7
Antineutrophil cytoplasm antibodies, n (%)§	298/347 (86.1%)
Immunofluorescence-positivity	251/346 (72.5%)
c-ANCA	34/346 (9.8%)
p-ANCA	222/346 (64.2%)
ELISA-positivity	281/293 (95.9%)
Anti-MPO + / Anti-PR3 –	268/293 (91.5%)
Anti-MPO – / Anti-PR3 +	9/293 (3.1%)
Anti-MPO + / Anti-PR3 +	4/293 (1.4%)
Anti-MPO – / Anti-PR3 –	12/293 (4.1%)

Results are expressed as mean \pm SD for continuous variables or n (%) for categorical variables, unless specified otherwise.

*Serum creatinine levels at diagnosis were available for 353 patients.

[†]Proteinuria estimates were available for 103 patients.

[‡]C-reactive protein (CRP) levels were available for 218 patients, and white blood cell and platelets counts were available for 283 patients.

§ANCA status was available for 347 patients, immunofluorescence for 346 patients and enzyme-linked immunosorbent assay for 293 patients. Cytoplasmic (c-) or perinuclear (p-)–labeling pattern.

Data are expressed as mean \pm standard deviation, unless stated otherwise, or as n (%).

eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay;

IQR, interquartile range; PR3, proteinase-3; MPO, myeloperoxidase.

Table 3 Hazard ratios (HR) and 95% confidence intervals (CI) for the risk of death or relapse for the 378 microscopic polyangiitis patients

Parameter	Risk of death				Risk of relapse			
	Univariable analysis*		Multivariable analysis†		Univariable analysis*		Multivariable analysis†	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age >65 years‡	3.52 (2.17–5.70)	<0.001	3.93 (2.39–6.46)	<0.001	0.74 (0.51–1.06)	0.10	0.71 (0.49–1.04)	0.08
Female	0.78 (0.50–1.21)	0.26			1.03 (0.73–1.46)	0.86		
Lung manifestations								
Interstitial lung disease	1.64 (0.93–2.90)	0.09			1.19 (0.74–1.92)	0.47		
Alveolar hemorrhage	1.11 (0.60–2.06)	0.74			1.27 (0.81–1.99)	0.30		
Pleural effusion	2.10 (0.96–4.58)	0.06			0.92 (0.40–2.09)	0.84		
Renal manifestations								
Serum creatinine >130 µmol/L	2.38 (1.49–3.79)	<0.001	2.81 (1.71–4.60)	<0.001	0.64 (0.44–0.92)	0.015	0.68 (0.47–0.98)	0.04
Cutaneous manifestations								
Purpura	1.29 (0.78–2.14)	0.32			1.23 (0.82–1.87)	0.32		
Livedo reticularis	1.19 (0.59–2.39)	0.63			1.29 (0.77–2.15)	0.33		
Ear, nose & throat manifestations	1.20 (0.63–2.27)	0.58			0.95 (0.56–1.59)	0.83		
Eye involvement	1.00 (0.40–2.50)	0.99			1.29 (0.63–2.65)	0.49		
Cardiovascular manifestations								
Pericarditis	1.12 (0.48–2.60)	0.79			1.26 (0.68–2.34)	0.46		

Cardiac insufficiency‡	2.15 (1.06–4.38)	0.034	1.99 (0.97–4.10)	0.06	1.68 (0.82–3.44)	0.16		
Gastrointestinal involvement								
Severe manifestations‡	4.18 (2.08–8.42)	<0.001	2.29 (1.10–4.77)	0.03	1.36 (0.56–3.33)	0.50		
Neurological involvement								
Central nervous system involvement	1.12 (0.35–3.66)	0.85			0.51 (0.13–2.07)	0.35		
Mononeuritis multiplex	2.17 (1.38–3.42)	0.001	2.70 (1.66–4.39)	<0.001	1.46 (1.03–2.08)	0.04	1.24 (0.85–1.81)	0.26
ANCA-positivity	0.96 (0.51–1.81)	0.89			1.05 (0.64–1.73)	0.84		
Immunosuppressant as initial treatment	1.49 (0.96–2.59)	0.16			0.66 (0.45–0.95)	0.03		
BVAS								
<16	1 (reference)				1 (reference)			
≥16	2.12 [1.29–3.48]	0.003			0.99 [0.68–1.44]	0.96		
1996 FFS at diagnosis								
0	1 (reference)				1 (reference)			
1	1.49 [0.84–2.62]	0.169			0.62 [0.41–0.92]	0.019		
≥2	3.13 [1.81–5.41]	<0.001			0.92 [0.59–1.43]	0.698		
2009 FFS at diagnosis								
0	1 (reference)				1 (reference)			
1	2.65 [1.19–5.89]	0.017			0.75 [0.50–1.12]	0.163		
≥2	7.12 [3.30–15.34]	<0.001			0.66 [0.42–1.04]	0.075		

*Univariable analyses were computed with the log-rank test. Survival was calculated from the time of diagnosis to death, relapse or the last follow-up visit.

†Variables included in the final model were those associated with the outcomes in univariable analyses at $p=0.10$ and which were the most frequently selected in a backward-stepwise selection algorithm based on 1,000 bootstrapped samples with replacement. The 1996 Five-Factor Score (FFS), 2009 revised FFS and Birmingham Vasculitis Activity Score (version 3) (BVAS) were not included in the multivariable model because their composite items were already analyzed separately.

‡2009 FFS items.

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CONTRIBUTORS

YN, LG and XP designed the study. All authors acquired data. YN, LG and XP were involved in data interpretation. YN, LG and XP prepared the manuscript. All authors participated in the revision of the manuscript and approved the final version.

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COMPETING INTERESTS

Dr. Pagnoux reports grants and personal fees from Roche, personal fees from ChemoCentryx, grants and personal fees from GSK, personal fees from Sanofi, outside the submitted work;

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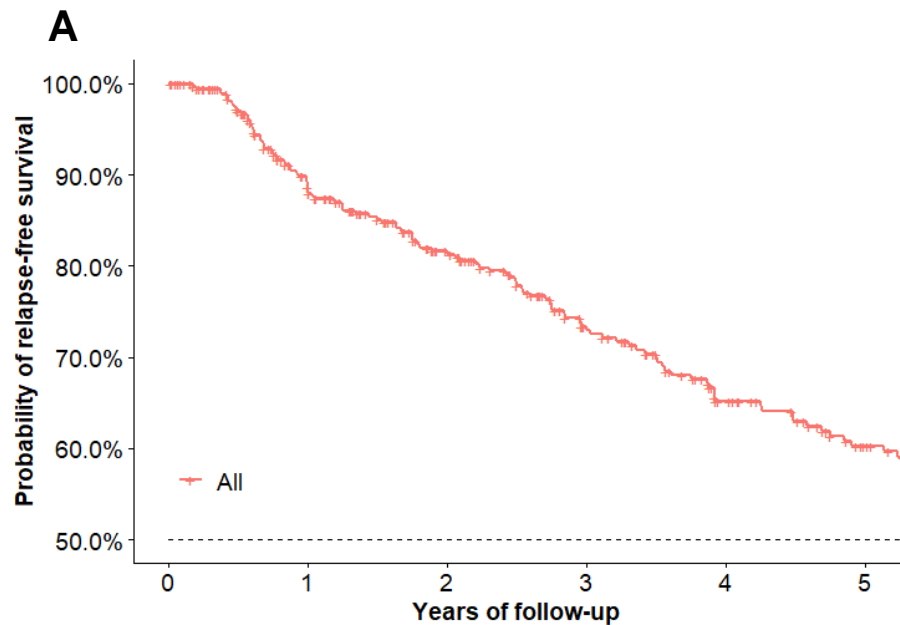
All other authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

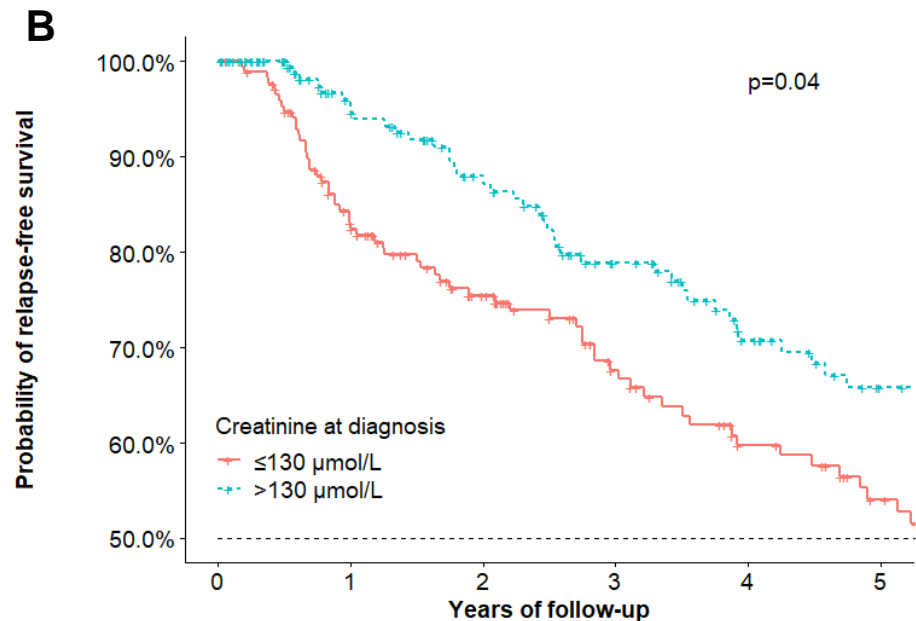
Data are available on reasonable request.

APPENDIX. List of FSVG investigators.

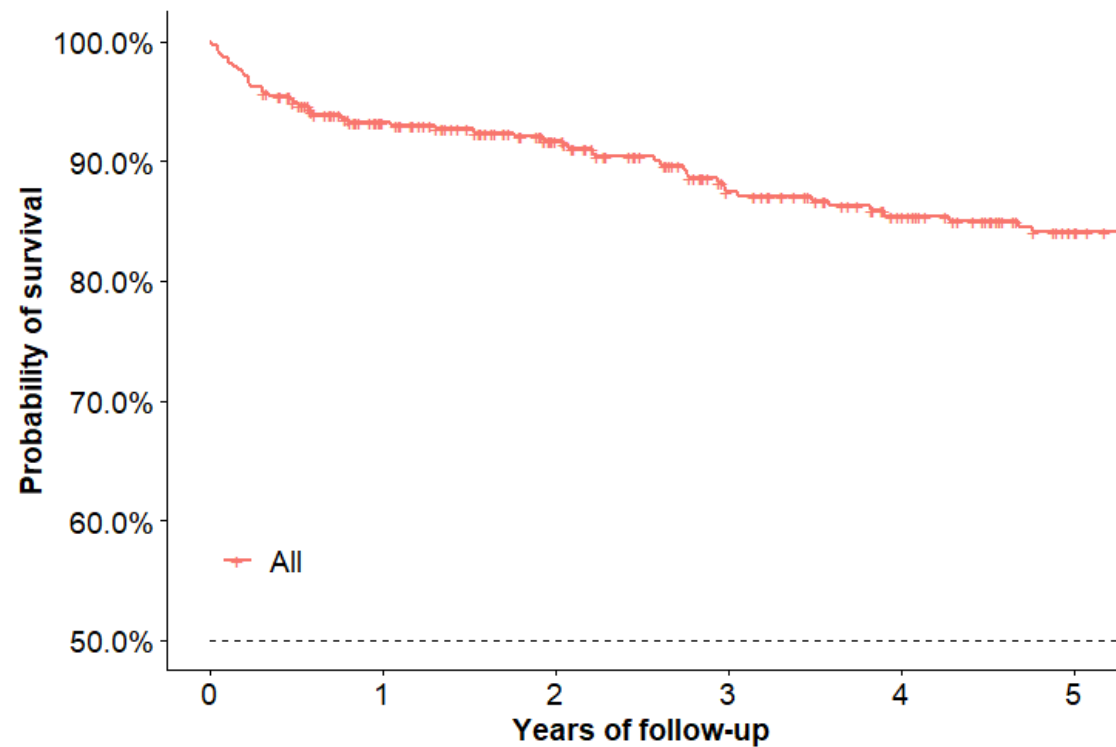
The investigators' full names in alphabetical order are as follows: Christian Agard, Elisabeth Aslangul, Olivier Aumaître, Claude Bachmeyer, Alice Bérezné, Sophie Besnard, Boris Bienvenu, Claire Blanchard-Delaunay, Bernard Bonnotte, Anne Bourgarit, Pierre-Louis Carron, Marie-Paule Chauveheid, Olivier Decaux, Xavier Delbrel, Hélène Desmurs-Clavel, Elisabeth Diot, Bertrand Dunogué, Anne-Laure Fauchais, Renato Fior, Elena Foïs, Brigitte Gilson, Pierre Gobert, Bertrand Godeau, Matthieu Groh, Philippe Guilpain, Catherine Hanrotel-Saliou, Gilles Hayem, Xavier Kyndt, Marc Lambert, Cédric Landron, Pierre-Yves Le Berruyer, Claire Le Jeunne, Jean-Christophe Lega, Philippe Letellier, Olivier Lidove, Nicolas Limal, Jonathan London, Kim Ly, Julie Magnant, Alfred Mahr, Romain Paule, Grégory Pugnet, Viviane Queyrel, Maxime Samson, Amar Smail, Benoit Vendrely, Christine Vinter, Stéphane Vinzio, Denis Wahl, Abdelkader Zoulim.



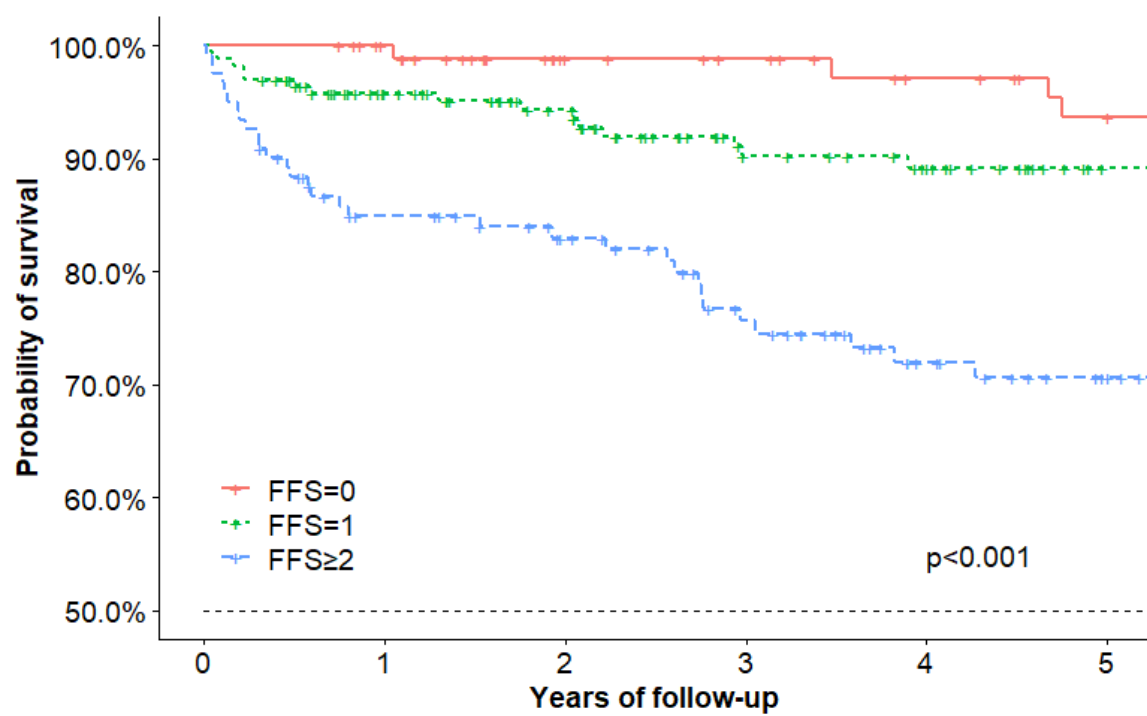
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number at risk						
All	378	287	227	171	130	103



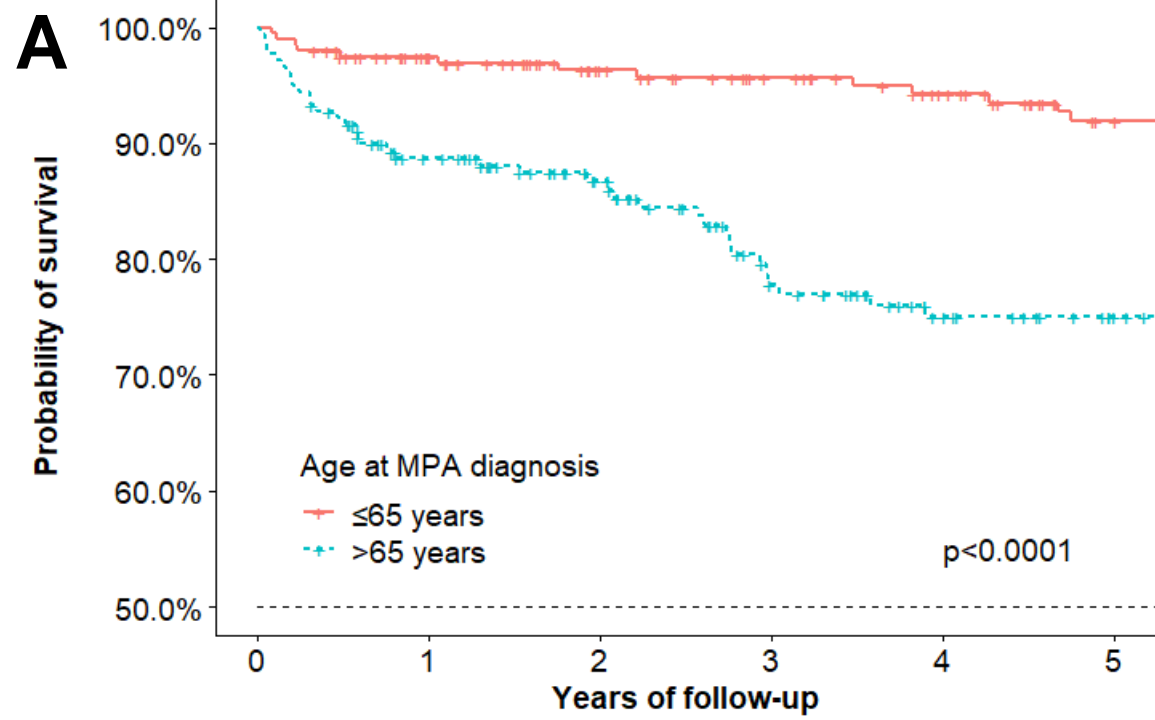
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number at risk						
≤130 $\mu\text{mol/L}$	173	131	100	72	56	44
>130 $\mu\text{mol/L}$	180	136	111	85	64	50

A

	number at risk					
	0	1	2	3	4	5
All	378	321	276	231	202	173

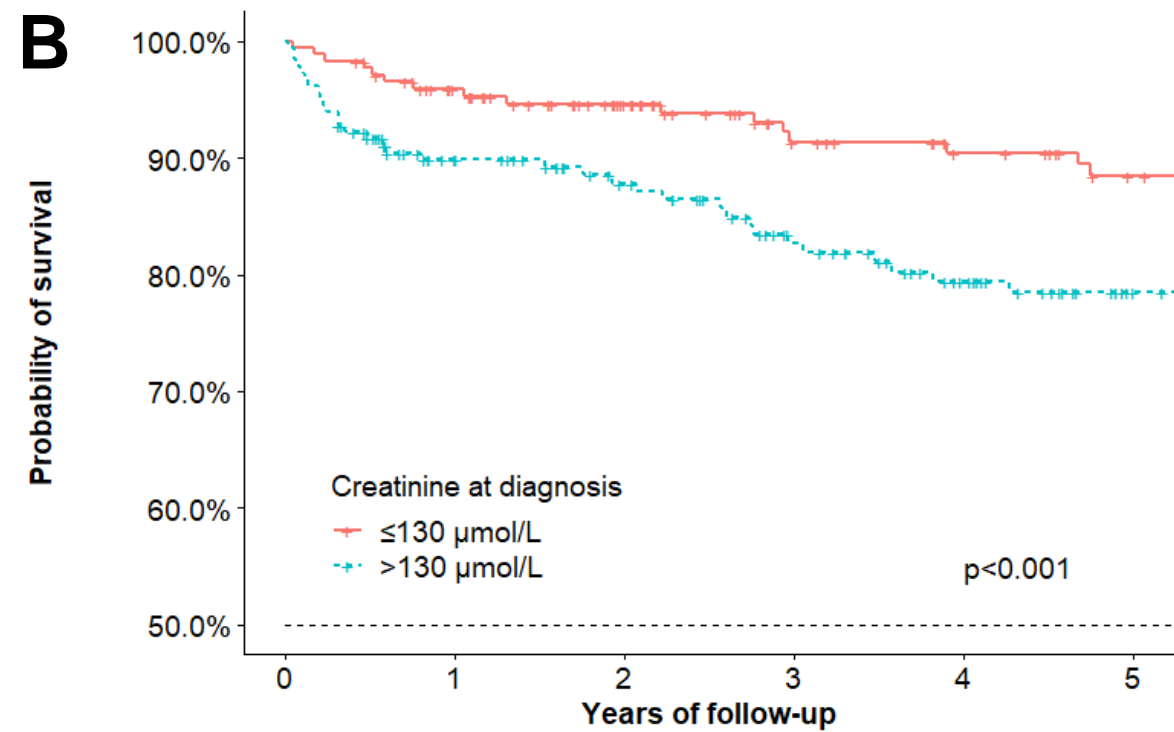
B

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FFS=0	88	83	68	64	58	53
FFS=1	169	144	124	98	91	76
FFS \geq 2	121	94	84	69	53	44



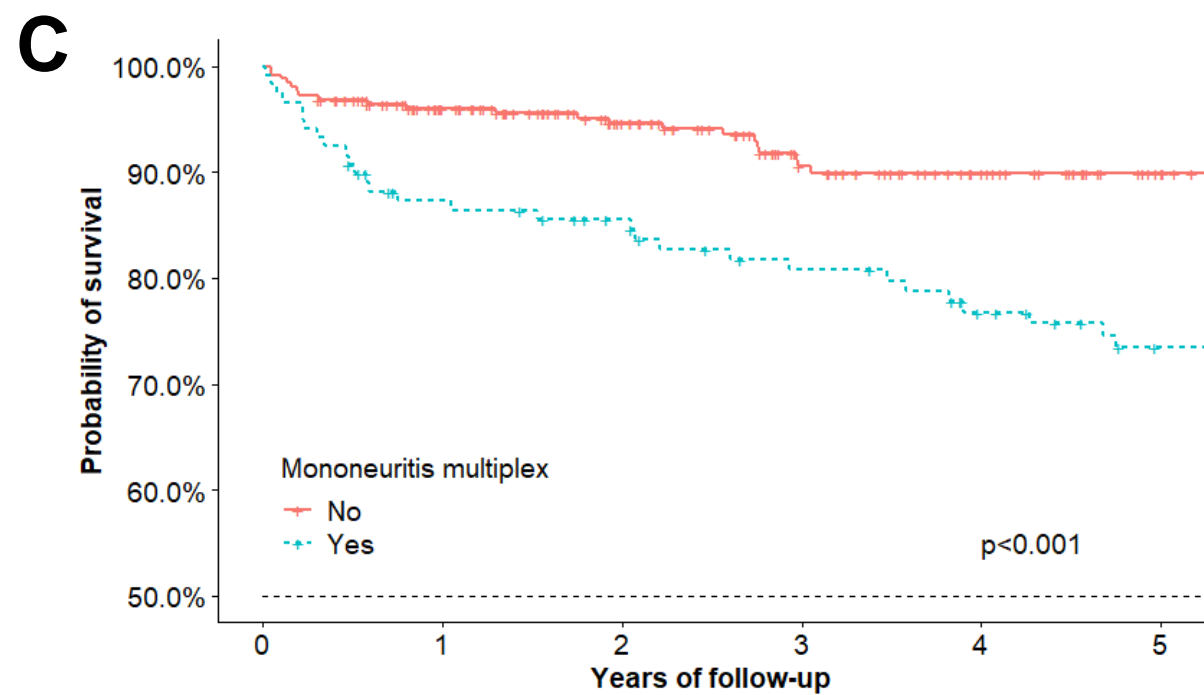
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≤65 years	198	176	155	141	129	111
>65 years	180	145	121	90	73	62
	0	1	2	3	4	5



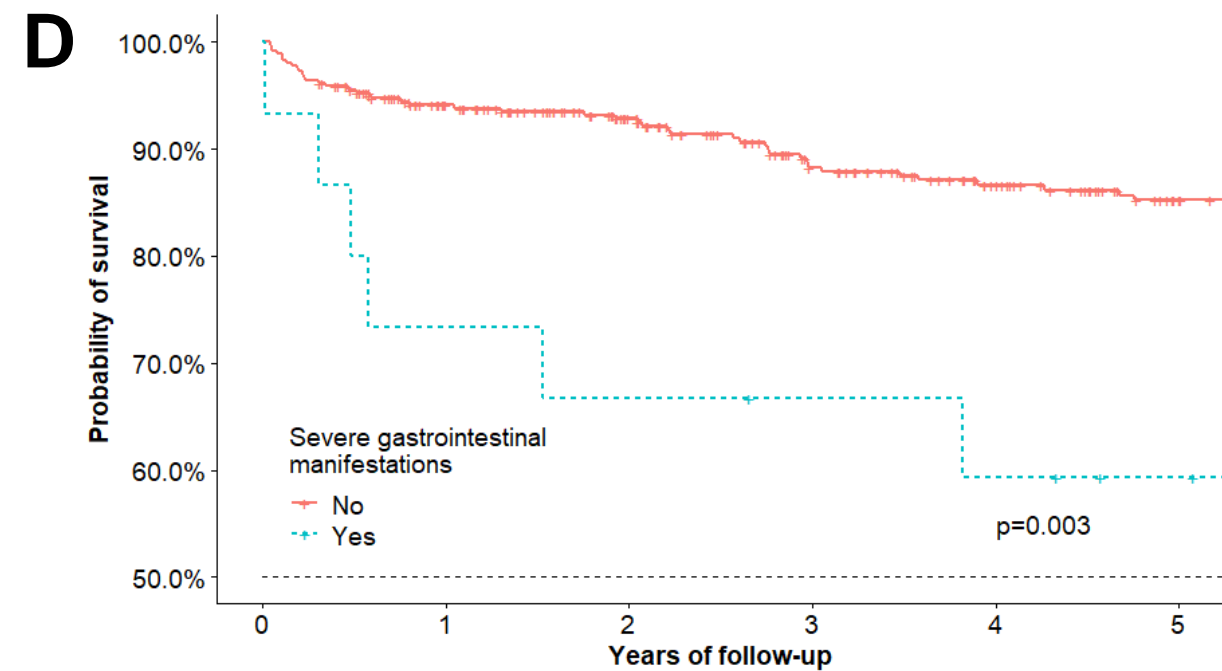
number at risk

≤130 μmol/L	173	155	131	107	98	89
>130 μmol/L	180	142	126	106	89	72
	0	1	2	3	4	5



number at risk

No	259	222	184	148	128	108
Yes	119	99	92	83	74	65
	0	1	2	3	4	5



number at risk

No	363	310	266	222	194	167
Yes	15	11	10	9	8	6
	0	1	2	3	4	5