Granulomatosis with polyangiitis: Study of 795 patients from the French Vasculitis Study Group registry

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†Other investigators are listed in the Appendix. We propose to list and designate all the site investigators and key personnel as “collaborators” as per Medline designation. This means their names are searchable on Medline. This is an important method to appropriately recognize the work of the many co-investigators of this study and is consistent with approaches taken by major journals for such work.

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Abbreviations

AAV. ANCA-associated vasculitis

EGPA. Eosinophilic granulomatosis with polyangiitis

GPA. Granulomatosis with polyangiitis

MPA. Microscopic polyangiitis

BVAS. Birmingham Vasculitis Activity Score

Abstract

Objective. To describe the characteristics and long-term outcomes of patients with granulomatosis with polyangiitis (GPA) from the French Vasculitis Study Group database.

Methods. Patients' clinical and laboratory characteristics, Birmingham Vasculitis Activity Score (BVAS)-assessed disease activity, malignancies, opportunistic infections, and vital status were collected at diagnosis and each visit. Estimated probabilities and predictors of overall (OS) and relapse-free survival (RFS) were analyzed by Cox regression.

Results. We enrolled 795 newly diagnosed patients, followed for a median of 3.5 years. Initial clinical manifestations involved ear, nose & throat (ENT; 80%), lungs (68%) and kidneys (56%). Among the 728 available ELISA results, 75.0% were PR3-ANCA–positive, 16.5% MPO-ANCA–positive and 62 (8.5%) ANCA-negative. Relapses occurred in 394 (50%) patients, involving ≥1 organ(s) affected at onset in 179 (46%), mainly ENT, lungs and kidneys, with mean BVAS 10.2 points below that at diagnosis ($p<0.001$). Five- and 10-year RFS rates were 37% and 17%, respectively. PR3-ANCA-positivity independently predicted relapse ($p=0.05$) and prolonged survival ($p=0.034$). OS—but not RFS—improved significantly over time ($p<0.001$); 10-year OS reached 88.2% (95% CI 83.9 to 92.7) for the 660 patients diagnosed after 2000. Infections were the main causes of death. Malignancy or opportunistic infection each occurred in ≤5% of the patients.

Conclusion. Survival has improved dramatically over the last decades but the high relapse rate remains a major concern for GPA patients, once again stressing the need for therapeutic strategy optimization to lower it. PR3-ANCA-positivity was associated with increased probability of relapse and survival.

1. Introduction

Granulomatosis with polyangiitis (GPA) is a severe, multisystemic, antineutrophil cytoplasm antibody (ANCA)-associated granulomatous vasculitis [1] whose prevalence has been estimated in France [2], and the US [3], respectively, at ~25 and ~32 cases/million inhabitants. Clinical GPA manifestations are heterogeneous, affecting mainly the upper and lower respiratory tract, and the kidneys [1]. Most of our knowledge on GPA clinical presentation and evolution came mainly from observational studies, which represent the best tools to characterize a disease in a real-world setting [4], rather than from limited numbers of trials, most of which included patients with several distinct vasculitides, low morbidity and short follow-up [5].

Defining long-term outcomes of rare diseases, with a sufficient level of evidence, is difficult. That rarity makes collection of sufficiently robust and extensive information a challenge, as they are often underdiagnosed and seen in different clinical settings not necessarily linked by shared research interests. To obtain larger samples, analyses often included more than one disease or newly diagnosed and prevalent patients but obtained estimates could potentially be biased [6,7].

Availability of the French Vasculitis Study Group (FVSG) Registry, a large national database of prospectively entered longitudinal clinical and laboratory data from ANCA-associated vasculitis (AAV) patients since 1983, enabled some of these difficulties to be overcome. Investigators from >60 French centers regularly contribute those data. The data from 795 newly diagnosed GPA patients entered in that database were analyzed to obtain descriptions of their main initial clinical features and outcomes, particularly relapses, morbidity and mortality.

2. Methods

2.1 Patients

We studied newly diagnosed patients with GPA, satisfying the American College of

Rheumatology (ACR) 1990 classification criteria [8] and/or revised Chapel Hill nomenclature [1], entered into the FVSG database from May 1983 to April 2018. For the patients to be classified as fulfilling those criteria, their entire clinical histories were considered. All FVSG-Registry patients gave their written informed consent. Only newly diagnosed patients, entered in the Registry at diagnosis, and followed-up for ≥6 months or who died within 6 months of entry, were included. Patients with insufficient data (no clinical details at diagnosis) were excluded.

2.2 Demographic and GPA features collected from diagnosis onwards

For the complete list of demographic and clinical items recorded at onset and each follow-up visit, see the online supplement. The database collects patient's information at baseline, thereafter every 6 months, or in case of refractory/relapsing disease requiring treatment escalation. Electronic records were the source of information on demographics; clinical, laboratory, radiological and histological findings; opportunistic infections and malignancies. We defined opportunistic infections as known to occur more often in immunocompromised patients and included in the list provided by Winthrop *et al* [9]; vital status at last known date was obtained from clinical charts, contacting patients, or their family members or general practitioners; and congestive heart failure exclusively by clinical symptoms (eg, pulmonary edema), thereby corresponding to the 2009 revised Five-Factor Score (FFS) definition [10]. Severe gastrointestinal manifestations (including bowel perforation, bleeding and/or pancreatitis) met FFS definitions.

The laboratory parameters included: serum creatinine level; proteinuria on dipstick (≥1+); hematuria (>10 red blood cells/mm^3); C-reactive protein (CRP) level; immunofluorescence- and/or enzyme-linked immunosorbent assay (ELISA)-determined ANCA status (anti-myeloperoxidase (MPO); anti-proteinase-3 (PR3)) in serum at diagnosis or thereafter when positive or had not been available initially. Biopsy findings were recorded as normal, or as showing evidence of vasculitis, granulomatous and/or other lesions.

2.3 Disease activity and scores

Disease activity was assessed at diagnosis and each visit using the original 1994 Birmingham Vasculitis Activity Score (BVAS) [11]. For patients enrolled before its publication, BVAS was calculated retrospectively. The 2009 FFS score at diagnosis was calculated retrospectively for each patient [10]. This prognostic tool is composed by the following 5 items: severe gastrointestinal involvement, cardiac insufficiency, serum creatinine level >150 µmol/L, age older >65, and absence of ENT involvement, with each item accorded one point, for a maximum score of 5.

2.4 Treatment procedures

Patients were enrolled in randomized–controlled trials [12-18] or received standard-of-care therapy. Agents used to induce and maintain disease remission, glucocorticoids (GC) use and dose, initially and for relapse(s), were recorded.

2.5 Outcomes

According to the European League Against Rheumatism (EULAR) recommendations [19] relapse was defined as the re-occurrence or new onset of disease attributable to active vasculitis; remission as the absence of disease activity attributable to GPA manifestations for >3 consecutive months, corresponding to BVAS=0. According to that definition, patients in remission could still be taking immunosuppressant or prednisone. The term active disease was not restricted to vasculitic manifestations; it also included other clinical signs, like granulomatous manifestations, eg retro-orbital tumors or lung nodules [19]. Refractory AAV was defined as failure to fully control vasculitis-related disease activity by 6 months or progressive disease within the first 3 months.

2.6 Statistical analyses

Patient characteristics are reported as the number (percentage) for categorical variables and as mean±SD or median [interquartile range; IQR] for continuous variables. Continuous

variables were compared with Student's t-test or Mann–Whitney test, and categorical variables with chi-square test or Fisher's exact test, as appropriate. Kaplan–Meier curves estimating relapse-free and overall survival were compared using log-rank tests. Relapse-free survival was calculated from GPA diagnosis to relapse, death or end of follow-up, whichever occurred first. Survival was calculated from GPA diagnosis to death or the last follow-up visit. To identify independent predictors of relapse-free or overall survival, univariable and multivariable Cox-regression analyses assessed potential associations with patient demographics, clinical, laboratory and therapeutic parameters. Because few deaths or relapses occurred, only variables with $p \leq 0.05$ in univariable models were tested in the multivariable Cox proportional hazards model. Results are expressed as hazard ratios (HR) and 95% confidence intervals (95% CI). Linear mixed models were used to compare BVAS between baseline values and at relapse, while accounting for the repeated measures for each patient. All statistical analyses were computed with R v3.6.1; $p \leq 0.05$ was considered significant. The Ethics Committee of Cochin University Hospitals approved this study (CLEP AAA-2019-08019).

3. Results

3.1 Patient characteristics at diagnosis

The study included 795 GPA FVSG-Registry patients (mean age, 53±16.3 years), mostly males (n=445; 56%). Their main demographic characteristics and clinical manifestations are reported in table 1. Among the 513 with available ethnicity information, 476 (93%) were white/Caucasian, 14 (3%) African/Caribbean descent, 11 (2%) Asian ancestry, and 12 (2%) others.

The main initial clinical manifestations were ENT (80.4%) and lung (67.7%) involvement; 56% had renal involvement: 193 (24%) experienced worsening of glomerular filtration (eg, >25% vs pre-diagnosis), and 46 (6%) required hemodialysis. Fifty-five (7%) patients had localized GPA limited to ENT tract and/or lungs. Mean BVAS was 17.4±8.8.

Among the 728/795 patients with available ELISA results (table 2), 75.0% were PR3-

ANCA–positive, 16.5% MPO-ANCA–positive and 8.5% ANCA-negative. Among the 389 biopsies taken from 381/795 (48%) patients, 345/389 (89%) yielded histological findings supporting the GPA diagnosis: 41% vasculitis, 29% necrosis, 24% granuloma or 5% not specified.

3.2 Treatments

Two hundred and fifty-nine (32.6%) patients were included in clinical trials (12-18). The most frequently prescribed induction agents were oral GC (n=772; 97%), intravenous (n=602; 76%) or oral (n=53; 6.7%) cyclophosphamide, rituximab (n=52; 6.5%) or methotrexate (n=36; 4.5%). Among the 59 patients undergoing plasma exchange at diagnosis, 53 had renal involvement (associated with alveolar hemorrhages for 25), and 6 had isolated alveolar hemorrhages. After post-diagnosis induction treatment, 583 (73.3%) patients achieved remission. The median follow-up duration was 3.5 [1.7–6.6] years and exceeded 1 year from study entry for 687 (86.4%) with a median of 6 visits (range 2-16) per patient. After induction-remission, patients received ≥1 dose(s) of the following maintenance agents: oral GC (n=744; 93.6%), azathioprine (n=382; 48.1%), rituximab (n=269; 33.8%), methotrexate (n=206; 25.9%) or mycophenolate mofetil (n=59; 7.4%).

3.3 Relapses and main damage-related clinical manifestations at last visit.

Patients (n=394, 50%) relapsed a mean±SD of 2.7±2.2 years post-diagnosis. Overall, with a median follow-up duration of 3.5 years, we observed 652 relapses in the whole sample of patients. One-hundred forty-seven (23.5%) patients experienced more than one relapse. The cohort's Kaplan–Meier-estimated 5- and 10-year relapse-free–survival rates, respectively, were 37% and 17% (figure 1A): 35% and 14% ANCA-PR3–positive, 46% and 25% ANCA-MPO–positive (p=0.11); they did not differ according to diagnosis before or after 2000.

Mean BVAS at relapse was 10.2 (95% CI 9.39 to 10.8) points below diagnosis value (p<0.001). Relapses affected mainly ENT (n=456), lungs (n=244), kidneys (n=186), eyes (n=145), central or peripheral nervous system (n=134) and/or skin (n=99). Throughout GPA evolution, about 60% of patients experienced relapse involving ≤2 organs: single organ in

117 (29.6%) patients: ENT (n=36; 9%), lungs (n=28; 7%) or kidneys (n=14; 3.5%) the main targets; or two-organs in 131 (33.2%): with most frequent being ENT and systemic (n=20), lung (n=14), kidneys (n=12) or eyes (n=10). The relapse patterns and numbers of affected organs are schematized in figure 2. Three or more organ involvement were recorded in the remaining 146 (37.2%) relapsing patients. Overall, isolated ENT (n=36), or lung (n=28), or ENT relapse with systemic signs (n=20), were the main observed patterns. Relapses in ≥1 organs(s) initially affected were observed in 179/394 (46%) patients; those involving previously uninvolved systems mostly affected the nervous system (n=53), eyes (n=41), kidneys (n=37), skin (n=35), ENT (n=32), lungs (n=24) or cardiovascular (n=13) or gastrointestinal (n=5) systems. New systemic signs and/or musculoskeletal symptoms appeared in 83 patients.

A variety of disease sequelae were recorded in 433 (54%) patients. The main disabling GPA-related manifestations were chronic renal insufficiency (n=114; 26.3%), hearing loss (n=73; 16.8%), peripheral neuropathy (n=55; 12.7%), saddle nose/nasal septum perforation/ENT bone destruction (n=40; 9.2%), dialysis (n=29; 6.7%).

3.4 Overall survival and causes of death

Eighty-two (10.3%) patients died after a median 3.5 [7–6.6] years post-diagnosis and 33 (4%) within 6 months of diagnosis. The main causes of deaths (available for 72/82 patients; supplementary table 1) were infections (36%), refractory disease (20%), malignancies (17%), cardiovascular events (15%), suicide (4%) or others (8%). Five-year overall survival rates (95% CI) for all patients and those diagnosed before or after 2000, respectively, were: 90.7% (88.3 to 93.2), 72.5% (64.2 to 81.9) and 94.6% (92.5 to 96.8) (figure 1B), with respective 10-year rates of 85.5% (81.8 to 89.4), 71.0% (62.4 to 80.7) and 88.2% (83.9 to 92.7).

3.5 Malignancies

Forty-one (5%) patients developed malignancies; 13 died (5 lung, 2 bladder, and 1 each: hepatic, colorectal, ovary, pancreas, bladder or non-Hodgkin lymphoma). There were solid

tumors (14 non-melanoma skin cancer, 6 bladder, 5 lung, 3 colorectal, 2 bile duct, 2 urothelial, and 1 each: breast, endometrium, ovary, liver, pancreas, prostate or unspecified) and 1 each mucosa-associated lymphoid tissue-lymphoma of the intestinal tract or non-Hodgkin lymphoma. Thirty-six of them had received CYC, 2 another immunosuppressant and 3 received only GC.

3.6 Opportunistic infections

Thirty-six opportunistic infections [38.9 (95% CI 20.1 to 68.0) vs 14.6 (95% CI 9.2 to 22.2) events/100 patient-years before or after 2000, respectively; p=0.004] were diagnosed in 30 (4%) patients after a median 17.5 [5.5-42.5] months post-diagnosis. Fourteen (38.8%) and 20 (55.5%) infections, respectively, occurred within year 1 or 2 post-diagnosis. Infection-causing pathogens were: *Aspergillus* (n=12), *Pneumocystis jirovecii* (n=11; 1/7 patient taking trimethoprim–sulfamethoxazole 400 mg/day; unknown for the other 4), cytomegalovirus (n=6), Herpes zoster virus (n=5), *Nocardia* (n=3), *Mycobacterium tuberculosis* (n=2) *Listeria monocytogenes* (n=1), *Legionella* (n=1) and non-tuberculous-mycobacterium (n=1). Eight patients, who had received GC and intravenous (n=4) or oral (n=4) CYC, died a median of 5.5 [4–14] months post-GPA diagnosis.

3.7 Univariable and multivariable predictors of relapse or death

Univariable analyses (table 3) selected PR3-ANCA–positivity (p=0.042) as being associated with higher probability of relapse and oral CYC induction (p=0.05) with a lower probability of relapse. Multivariable analysis retained only PR3-ANCA–positivity as an independent predictor of relapse (p=0.05).

Multivariable analysis retained date of diagnosis, age and congestive heart failure as significant and independent predictors of death, while PR3-ANCA–positivity was protective. The predictive power of the baseline 2009 FFS was confirmed for this large GPA sample (supplementary table 2).

4. Discussion

Herein, we described the main GPA characteristics at diagnosis and during evolution of 795 patients with long-term follow-up. This large population enabled better evaluation of the initial prevalences of less frequently observed manifestations, and characterization of evolution and relapse patterns throughout follow-up. GPA carries a high risk of relapse, especially for PR3-ANCA–positive patients, with a stable incidence rate over time. Overall, the clinical picture at relapse was milder than that observed at diagnosis. Moreover, disease reactivation affected organs involved initially for half the patients, mainly ENT, lungs and kidneys. Notably, mortality, mostly due to infections, has gradually decreased over the last 35 years to approach that of the general population.

Our analysis confirmed relapses in at least half of patients, a rate that has remained frustratingly high and stable over time. Most previous studies grouped patients with GPA, microscopic polyangiitis, kidney-limited disease or eosinophilic granulomatosis with polyangiitis [20-22]. Although PR3-ANCA–positivity was found to best predict vasculitis relapse [21], it remains controversial whether that parameter is specifically associated with GPA relapses [23-25]. In keeping with the Glomerular Disease Collaborative Network findings [21], our results further confirmed, based on more patients, that PR3-ANCA–positivity was also independently associated with a higher risk of GPA relapse. Rituximab has been shown to be more effective at preventing relapses than conventional treatments, like azathioprine [14], but, despite having been given to more than a third of our patients, its efficacy for the entire cohort could have been diluted by its more recent introduction. The persistently high relapse rate, despite effective therapies, suggests that novel implementation strategies aimed at better preventing relapses should be further prioritized.

GPA relapses have been quantified in many studies conducted in different settings [21-28], but less is known about disease-reactivation patterns over time. First, we found that, like at diagnosis, almost half the relapses affected ENT, lungs and kidneys, and that disease extended to previously unaffected organs in the remaining half of patients, with frequent involvement of the nervous system, eyes, and kidneys. Improving patient's awareness of this

disease behavior is crucial to allow patients an early recognition of flares and a prompt introduction of treatment. Second, ~60% of relapsing patients had a maximum of 2 organs affected during follow-up, most often combining ENT and lung, renal or systemic features. Moreover, mean BVAS at relapse was lower than at GPA diagnosis in a real-life setting, as observed in trials when patients have easier access to their physicians [29]. That lower disease activity can be explained by several factors, eg, patients better educated about GPA-related relapse manifestations and how to recognize them, leading to earlier consultation, or the influence of concomitant medications attenuating relapse severity. The rarity of renal relapses and the predominantly nonsevere relapses might also explain why, despite relapsing more frequently, our PR3-ANCA–positive GPA patients' survival was not poorer. Taken together, those observations enabled better recognition of relapse patterns that can be expected in daily practice; they also further inform physicians, inciting them to educate patients not to delay consultation, so treatment intensification can be initiated rapidly. They also highlight the need for careful follow-up of patients with milder initial GPA.

Our data confirmed previous observations of improved survival over time [20-22] and contribute to better estimating GPA-mortality rates. They also highlighted that improvement was progressive, with a ≥15% gain of 10-year survival rates (from 71% to 88%) for patients diagnosed before or after 2000, which roughly corresponds to the first rituximab use. In accordance with a cluster analysis of 482 renal AAV patients [30], PR3-ANCA–positivity also predicted longer survival. That finding further strengthens the concept that anti-MPO–positivity might define a distinct GPA subset with the worst survival. Better GPA recognition leading to earlier diagnosis, ANCA testing, the availability of effective and less toxic treatments, together with improved management of cardiovascular and infectious risk factors, could help explain the lowered mortality [31]. Patients now diagnosed with GPA should be told that their life expectancy approaches that of the general population.

As reported previously [32, 33], infections were the main causes of death. Despite newer agents having emerged as potential first-line therapies, their safety profiles are quite similar to those of older approaches, like CYC-based regimens. Hence, even though survival

has improved, the percentage of patients developing severe infections has remained substantial. Herein, we focused our attention only on opportunistic infections, because severe infection rates were analyzed previously [34]. About 4% of our patients developed opportunistic infections, with half occurring within the first 2 years post-diagnosis; when fatal, patients succumbed rapidly (median 5 months post-diagnosis). Pertinently, their incidence after 2000 was less than half of that recorded before. Different factors could explain that observation, eg, less use of oral CYC, lower cumulative CYC exposure or the wider use of trimethoprim–sulfamethoxazole prophylaxis over time. Those findings emphasize the need to identify patients at high-risk of infection and constitute a strong incentive for using GC-sparing strategies, less toxic immunosuppressants [17, 35] and/or trimethoprim–sulfamethoxazole prophylaxis to prevent severe or life-threatening infections [36].

This study has several strengths including its large population, coming from different specialties across France, enabling thorough qualitative descriptions of a wide range of characteristics, long-term follow-up and relapse patterns.

However, some limitations should be acknowledged. Therapeutic strategies have evolved over the 35 years of enrollment. Although patients derived from different specialties, bias resulting from the inclusion of those with more severe disease consulting at tertiary referral centers cannot be excluded. Furthermore, we were unable to better appraise to what extent trimethoprim–sulfamethoxazole prophylaxis for CYC- or rituximab-treated patients might have influenced the observed lower risk of severe infections.

In conclusion, GPA is a severe, relapsing, rare disease involving—at onset and at relapse—mainly ENT, lungs and kidneys. Better disease-specific management over the last few decades could be among the leading factors contributing to the improved survival of these patients, whose life expectancy now approaches that of the general population, even though the risk of relapse remains high for predominantly nonsevere events. PR3-ANCA–positivity is a weak albeit still the best predictor of GPA relapse and was associated with better survival. GPA monitoring over time should be driven by patient education about the high risk of disease reactivation, potentially involving organs affected at diagnosis for half of

them.

APPENDIX

In addition to the authors, the following investigators and FVSG members participated in the study (all in France): Benjamin Chaigne, Pierre Charles, Jonathan London, Yoann Crabol, Romain Paule, Bertrand Dunogué, Véronique Le Guern, Nathalie Costedoat-Chalumeau, Claire Le Jeunne, Department of Internal Medicine, Hôpital Cochin, Paris; Christophe Deligny, Médecine Interne, CHU Fort-de-France, Martinique, France; Arsène Mékinian, Olivier Fain, CHU Saint-Antoine, Paris; Thomas Papo, Hôpital Bichat, Paris; Vincent Cottin, CHU Louis-Pradel and UMR754, Université Claude-Bernard Lyon 1, Lyon; Philippe Delaval, CHU Pontchaillou, Rennes; Hélène Desmurs-Clavel, CHU Edouard-Herriot, Lyon; Elisabeth Diot, CHU Bretonneau, Tours; Laura Frederici, Hôpital Louis-Mourier, Colombes; Eric Liozon, Guillaume Gondran, Holy Bezanahary, Elisabeth Vidal, CHU Dupuytren, CHU Limoges; Isabelle de Lacroix-Szmania, Centre Hospitalier Intercommunal de Créteil, Créteil; Marc Lambert, CHRU Lille, Lille; Jean-Christophe Lega, CHU Lyon-Sud, Lyon; Grégory Pugnet, CHU Purpan, Toulouse; Alice Bérezné, CH Annecy Genevois, Annecy; Audrey de Parisot de Bernecourt, Hôpital de la Croix-Rousse, Lyon; Stéphane Durupt, CHU-Sud, Lyon; Helder Gil, CHU Jean-Minjoz, Besançon; Nicolas Limal, CHU Henri-Mondor, Créteil; Edouard Pertuiset, CH René-Dubos, Pontoise; Sophie Rivière, CHU Saint-Eloi, Montpellier; Amar Smail, CHU-Nord, Amiens; Jean-François Subra, CHU d'Angers, Angers.

Author contributions. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Puéchal had full access to all the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. MI, LG and XP.

Acquisition of data. MI, CP, PC, MH, AA, FL, MR, OA, BB, FM, OD, EH, AK, CK, NJ-C, J-FV, CB-D, PG, ALQ, TQ, CdD, AR, BT, LM, LG and XP.

Analysis and/or interpretation of data. MI, CP, DSC, LG and XP.

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567

Table 1 Main clinical characteristics and treatment at diagnosis of 795 FVSG-Registry GPA patients

Characteristic	Value
Demographic	
Sex, female	350 (44.0)
Age at diagnosis, years, mean (SD)	53 (16.3)
Age >65 years*	209 (26.3)
Year of diagnosis	
<2000	135 (17.0)
2000–2009	415 (52.2)
2010-April 2018	245 (30.8)
Smoker	207/625 (33.1)
General	628 (78.9)
Fever >38.5°C	342 (43.0)
Weight loss >3 kg within 3 months	355 (44.7)
Arthralgias	410 (51.6)
Myalgias	218 (27.4)
Ear, nose & throat	639 (80.4)
Sinusitis	331 (41.6)
Rhinitis	426 (53.6)
Nasal crusts	299 (37.6)
Epistaxis	156 (19.6)
Saddle nose	10 (1.3)
Nasal obstruction	204 (25.7)
Otitis	185 (23.3)
Lung	538 (67.7)
Alveolar hemorrhage	142 (17.9)
Massive alveolar hemorrhage and/or Hb <9 g/dL	36 (4.5)
Lung nodules	328 (41.3)
Lung infiltrate	150 (18.9)
Subglottic stenosis	13 (1.6)
Wheezing	8 (1.0)
Renal	447 (56.2)
Serum creatinine worsened >30%	193 (24.3%)
Biopsy-proven glomerulonephritis	147 (18.5)
Proteinuria	279 (35.1)
Hematuria	301 (37.9) ()
Need for dialysis	46 (5.8)
Mucocutaneous	263 (33.1)

Purpura	127 (16)
Livedo reticularis	30 (3.8)
Gangrene	17 (2.1)
Gingivitis	6 (0.8)
Eye	212 (26.7)
Exophthalmos	29 (3.6)
Episcleritis	73 (9.2)
Scleritis	30 (3.8)
Cardiovascular	119 (15)
Pericarditis	33 (4.2)
Myocarditis	11 (1.4)
Congestive heart failure*	15 (1.9)
Gastrointestinal	87 (10.9)
Abdominal pain	49 (6.2)
Perforation	2 (0.3)
Neurological	191 (24.0)
Central nervous system involvement	24 (3.0)
Peripheral neuropathy	151 (19)
Induction therapy†	
Intravenous cyclophosphamide	602 (75.7)
Oral cyclophosphamide	53 (6.7)
Rituximab	52 (6.5)
Methotrexate	36 (4.5)
Mycophenolate mofetil	1 (0.1)
Glucocorticoids	772 (97.1)
Glucocorticoid dose, mg/day, median [IQR]	60 [50–70]
Methylprednisolone pulse	215 (27.0)
Plasma exchanges	59 (7.4)
2009 FFS at diagnosis	
0	381/692 (55.1)
1	169/692 (24.4)
≥2	142/692 (20.5)
BVAS at diagnosis, mean (SD)	17.5(8.8)

Values are expressed as n (%) unless stated otherwise.

*2009 Five Factor Score item.

†In addition, trimethoprim–sulfamethoxazole was given to 249/674 (36.9) patients.

Table 2 Main laboratory findings at GPA diagnosis for FVSG-Registry patients

Parameter	Value
Serum creatinine level, median [IQR] µmol/L*	93 [74–146]
Serum creatinine level >150 µmol/L	177/609 (29.1%)
ANCA-positivity by immunofluorescence	700/788 (88.8%)
c-ANCA	568/788 (72.1%)
p-ANCA	132/788 (16.8%)
ANCA-positivity by ELISA	666/728 (91.5%)
PR3 specificity	546/728 (75%)
MPO specificity	120/728 (16.5%)
Histology	
Patients with ≥1 biopsies	381 (48%)
Biopsies supporting GPA diagnosis	345/389 (89%)
Vasculitis	142 (41%)
Necrosis	101 (29%)
Granuloma	84 (24%)
Not specified	18 (6%)

*Serum creatinine levels at diagnosis were available for 609 patients. c/p-ANCA, cytoplasmic or perinuclear labeling pattern of antineutrophil cytoplasm antibodies; ELISA, enzyme-linked immunosorbent assay; PR", p 3, MPO, myeloperoxidase.

Table 3 Hazard ratios (95% CI) for the risk of death or relapse for FVSG-Registry GPA patients.

	Death				**Relapse**			
	Univariable analysis		**Multivariable analysis**		**Univariable analysis**		**Multivariable analysis**	
Factor	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age	1.06 (1.04-1.08)	<0.001	1.07 (1.04-1.10)	<0.001	0.95 (0.78-1.16)	0.669		
Female	0.56 (0.35-0.90)	0.017			1.00 (0.99-1.00)	0.806		
Lung	1.91 (1.10-3.30)	0.02			0.96 (0.84-1.28)	0.710		
Alveolar hemorrhage	2.19 (1.36-3.54)	0.001			0.86 (0.88-1.49)	0.289		
Renal	3.53 (2.06-6.03)	<0.001			0.97(0.83-1.24)	0.837		
Serum creatinine >150 µmol/L*	2.51 (1.56-4.02)	<0.001			0.92 (0.70-1.19)	0.538		
Hemodialysis	3.12 (1.54-6.28)	0.001			1.27 (0.81-1.97)	0.287		
Skin	2.21 (1.21-4.03)	0.009			0.97 (0.83-1.26)	0.814		
Ear, nose & throat*	0.74 (0.44-1.24)	0.26			0.91 (0.84-1.41)	0.490		
Eye	0.79 (0.48-1.31)	0.36			0.95 (0.84- 1.30)	0.648		
Cardiovascular	1.94 (1.17-3.22)	<0.01			0.98 (0.76-1.34)	0.916		
Congestive heart failure*	9.28 (4.20-20.24)	<0.0001	3.15 (1.04-9.05)	0.041	0.65 (0.20-2.03)	0.463		
Gastrointestinal*	2.24 (1.22-4.05)	0.009			0.97 (0.72-1.44)	0.906		
Neurological	1.40 (0.88-2.20)	0.146			1.02 (0.82-1.27)	0.826		
BVAS	1.06 (1.04-1.09)	<0.001			0.99 (0.98-1.00)	0.48		
Anti-myeloperoxidase°	2.05 (1.18-3.54)	0.010			0.81 (0.61-1.09)	0.173		
Anti-proteinase-3°	0.48 (0.29-0.79)	0.004	0.42 (0.18-0.95)	0.038	1.30 (1.01-1.68)	0.042	1.29 (0.99-1.67)	0.05
Date of diagnosis								
before 2000			Ref.					

2000-2004	0.39 (0.20 - 0.77)	0.006		
2005-2009	0.19 (0.08 - 0.44)	<0.001		
since 2010	0.17 (0.06 - 0.49)	0.001		
IV CYC			0.88 (0.69-1.12)	0.313
Oral CYC			0.60 (0.36-1.00)	0.05
Rituximab			0.77 (0.44-1.35)	0.375
Methotrexate			0.96 (0.61-1.51)	0.885

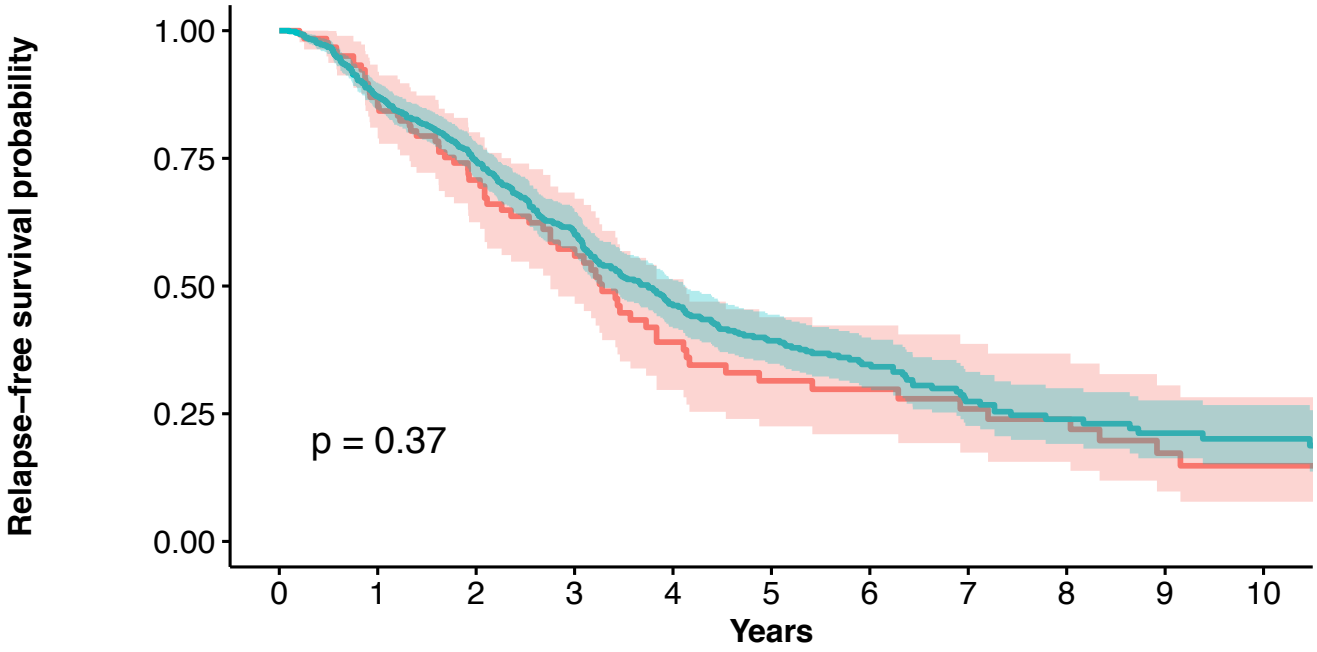
Survival was calculated from the time of GPA diagnosis to death, relapse or the last follow-up visit. ° As single variable within ANCA status.

*2009 Five Factor Score item. IV CYC, intravenous cyclophosphamide; BVAS, Birmingham Vasculitis Activity Score.

Figure 1 Kaplan–Meier curves of (A) relapse-free survival and (B) overall survival for 795 FVSG-Registry GPA patients, according to year of diagnosis (before or after 2000).

Figure 2 Number of relapsing patients (A) according to the most frequently observed relapse patterns or (B) ordered by the number of relapse-involved organs. Each patient's pattern over time after diagnosis is illustrated by "connecting the dots" (affecting 1 or several organ(s)). For each patient, one pattern is recorded over time as the cumulative combination of involvements (eg, affecting one or several of organs) observed after diagnosis. In panel A, for example, reading from left to right, you can see that the majority of patients experienced isolated ENT (n=36), or lung (n=28) relapses, followed by a combination of lung, ENT relapses with systemic signs (n=24) (connected dots at the bottom of the graph). The number of patients with each relapse pattern is expressed in a decreasing order from left to right. In panel B, from left to right, we show the number of patients with relapses involving a single organ (gastrointestinal, cardiovascular, cutaneous, ocular, neurologic, etc), or a combination of 2 or more organs. The 'combination' pattern can be identified by connecting the dots on the bottom of the figure. GI, gastrointestinal; CV, cardiovascular; ENT, ear, nose & throat.

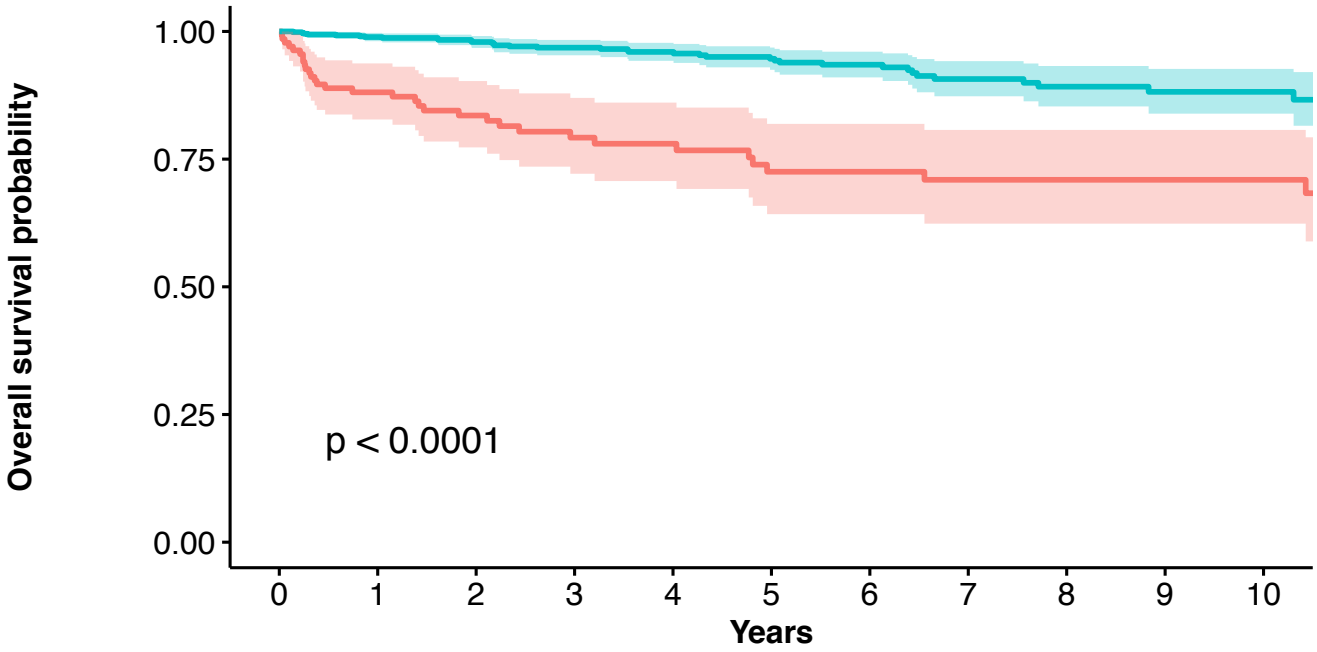
A



N at risk

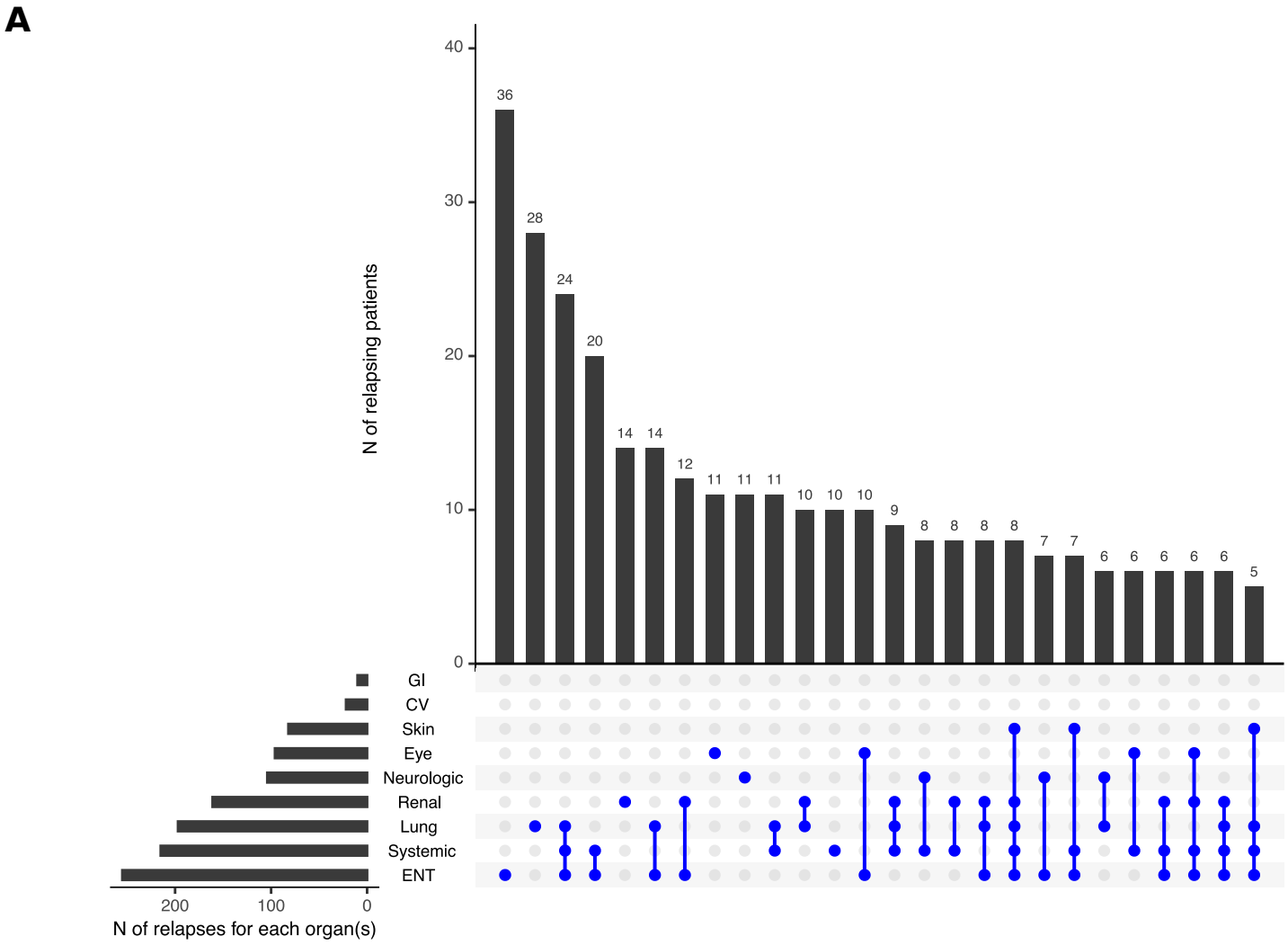
before 2000	135	95	60	42	27	19	16	13	12	7	6
after 2000	660	514	366	240	155	118	74	43	29	22	17

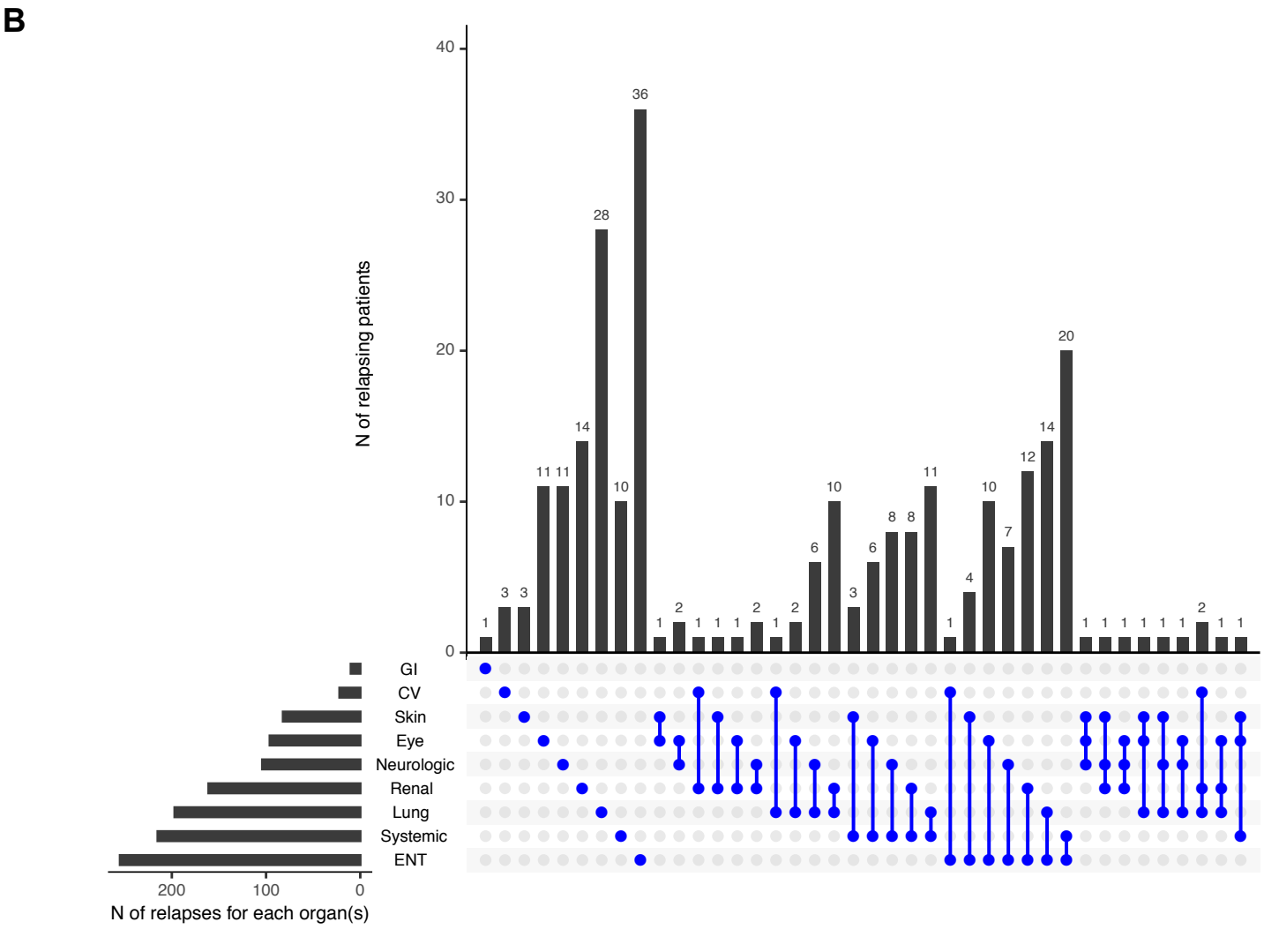
B



N at risk

before 2000	135	108	82	68	61	52	48	43	37	28	27
after 2000	660	579	474	377	307	258	185	140	109	84	65


A
N of relapsing patients
40
30
20
10
0
36
28
24
20
14 14
12
11 11 11
10 10 10
9
8 8 8 8
7 7
6 6 6 6 6
5
GI
CV
Skin
Eye
Neurologic
Renal
Lung
Systemic
ENT
200
100
0
N of relapses for each organ(s)


B
N of relapsing patients
40
30
20
10
0
1 3 3 11 11 14 28 10 36 1 2 1 1 1 2 1 2 6 10 3 6 8 8 11 1 4 10 7 12 14 20 1 1 1 1 1 2 1 1
GI
CV
Skin
Eye
Neurologic
Renal
Lung
Systemic
ENT
200
100
0
N of relapses for each organ(s)