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Impact of treatment on damage and hospitalization in elderly patients with microscopic polyangiitis and granulomatosis with polyangiitis

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Title page

Full title

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Conflict of interest

The authors declare no conflicts of interest.

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Running head

Damage in ANCA-associated vasculitis

Abstract

Objective

Age is a risk factor for organ damage, adverse events, and mortality in microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA). However, the relationship between treatment and damage, hospitalizations, and causes of death in elderly patients is largely unknown.

Methods

Consecutive patients from Sweden, England, and the Czech Republic diagnosed between 1997 and 2013 were included. Inclusion criteria were a diagnosis of MPA or GPA and age 75 years or more at diagnosis. Treatment with cyclophosphamide, rituximab, and corticosteroids the first three months was registered. Outcomes up to two years from diagnosis included vasculitis damage index (VDI), hospitalization, and cause of death.

Results

Treatment data was available for 167 of 202 patients. At two years, 4% had no items of damage. There was a positive association between VDI score at two years and Birmingham Vasculitis Activity Score at onset, and a negative association with treatment using cyclophosphamide or rituximab. Intravenous methylprednisolone dose was associated with treatment-related damage. During the first year, 69% of patients were readmitted to hospital. MPO-ANCA positivity and lower creatinine levels decreased the odds for readmission. The most common cause of death was infection, and this was associated with cumulative oral prednisolone dose.

Conclusion

Immunosuppressive treatment with cyclophosphamide or rituximab in elderly patients with MPA and GPA was associated with development of less permanent organ damage and was

not associated with hospitalization. However, higher doses of corticosteroids during the first three months was associated with treatment-related damage and fatal infections.

Introduction

Microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis) are part of the disease spectrum called anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which also includes the clinically different and less common eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome)(1, 2). Patients with AAV are often of older age, peak incidence is found in patients aged above 65-75 years(3, 4).

Treating vasculitis patients is a delicate balance between the need for immunosuppression to attenuate the vasculitic activity, and the risk of adverse effects of treatment(5, 6). In the general AAV-population, therapy-related adverse events are more commonly the cause of death than active vasculitis. Since the risk of adverse events increases with age and decreased renal function, elderly patients can be expected to be at high risk for both treatment-related damage, and mortality(7).

Morbidity in AAV is assessed using the vasculitis damage index (VDI), a clinical tool recording all permanent damage occurring after the onset of vasculitis. The damage items are scored regardless of their attribution, and can thus reflect both the accumulated long-term effects of the vasculitic disease, and of therapy(8). Over time, most vasculitis patients develop some degree of permanent organ damage(9). Previous studies have shown an association between higher age, lower estimated glomerular filtration rate (eGFR) and the total number of damage items at follow-up(10). Both total damage and treatment-related damage is more common in older patients(11). There is also an association between use of glucocorticoids and development of permanent organ damage(10, 12).

We have previously reported that elderly patients with MPA and GPA who had received immunosuppressive treatment with cyclophosphamide or rituximab had significantly better survival compared to patients who had not been given such treatment(13). However, it is not

known if this survival benefit is at the expense of increased morbidity and need for longer and more frequent hospitalizations. Neither is it known if the mortality pattern seen in younger patients with AAV also applies to elderly patients. Older patients in general utilize more health care resources than younger patients(14), but the need for in-hospital care during the early period after diagnosis has not previously been described for elderly patients with MPA and GPA.

The aim of this study was to investigate the presence of permanent organ damage, hospitalization patterns, and causes of death, and to assess the potential association with the initial treatment regimens, in patients aged 75 years or more with MPA or GPA.

Materials and Methods

Case retrieval and classification

Consecutive patients presenting at seven centers in Sweden, the United Kingdom, and the Czech Republic between 1997 and 2013 were included if having an age 75 years or more at diagnosis, and a clinical diagnosis of MPA or GPA according to the European Medicines Agency (EMA) algorithm(15). Exclusion criteria were EGPA, polyarteritis nodosa, secondary vasculitis, drug-induced vasculitis and anti-glomerular basement membrane disease(15).

The Swedish cohort was recruited from Linköping University Hospital, Skåne University Hospital in Lund and Malmö, and Karolinska University Hospital in Stockholm. The English cohort was recruited from Imperial College Renal and Transplant Centre and Royal Free Hospital in London, and Queen Elizabeth Hospital in Birmingham. The Czech cohort was recruited from General University Hospital in Prague. The participating centers have been described in detail previously(13). The study was approved by the Ethical Review Board in Lund, Sweden (registration numbers 2010/517; 2012/252).

Data collection

Data were collected retrospectively from databases and medical records. End of follow-up was at two years from diagnosis, death, or loss to follow-up. Data collected from time of diagnosis included diagnosis date, age, sex, disease phenotype (MPA/GPA), ANCA-specificity, C-reactive protein (CRP), creatinine (at diagnosis or before start of dialysis in patients dialysis dependent at diagnosis), disease activity according to Birmingham Vasculitis Activity Score (BVAS)(16), and major comorbidities.

Data on outcome included accumulated organ damage according to VDI at one and two years, hospitalization (for any reason) during the first year, and causes of death during the first two years. Treatment with rituximab and cumulative doses of cyclophosphamide and glucocorticoids (pulsed intravenous methylprednisolone and oral prednisolone) during the first three months after diagnosis were recorded.

Date of diagnosis was defined as: start of treatment with prednisolone ≥30 mg/day, plasma exchange or cyclophosphamide; if not treated, the day of biopsy; if no biopsy, the day of the first positive ANCA test. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation(17). In assessing VDI an estimated GFR of <50 ml/min/1.73 m^2 was considered as GFR <50% irrespective of age and a dipstick value of ≥2 was considered representative of 24-h proteinuria of >0.5 g. A dipstick value of >2 was considered as representative of hematuria equal to 10 RBCs/hpf when assessing BVAS. Indirect immunofluorescence (IIF) or antigen-specific enzyme-linked immunosorbent assay (ELISA) was used to detect ANCA. Treatment-related VDI items were defined as described by Exley et al. (18) and included osteoporosis, avascular necrosis, osteomyelitis, cataract, gonadal failure, marrow failure, chemical cystitis, diabetes mellitus and malignancy.

A comorbidity score was assessed using a modified version of the Davies score(19) with one

point each given for malignancy, ischemic heart disease, peripheral vascular disease, heart failure, diabetes, systemic inflammatory disease (excluding AAV), pulmonary disease and cirrhosis. Relapses were defined as an increase in BVAS to ≥1 and increased immunosuppressive therapy.

Statistical analyses

Statistical analysis was performed using SPSS Statistics for Windows software (version 24.0; IBM Corp., Armonk, NY). P-values <0.05 were considered significant. Differences between groups were analyzed using the Mann-Whitney test or Kruskal-Wallis test for non-parametric data. Categorical data were analyzed using the Chi-square test or Fisher's exact test. All analyses exclude missing data.

In analysis of outcome, patients who died within the first 30 days after diagnosis and patients without complete treatment data were excluded. Patients were divided into three treatment groups: RTX group (any dose of rituximab), CYC group (≥2000 mg oral/≥1500 mg intravenous cyclophosphamide during first three months) and No/other group (<2000 mg oral/<1500 mg intravenous cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, steroids only, no treatment).

Binary logistic regression analysis was utilized to analyze hospital readmission and treatment-related damage (binary variables), linear regression analysis to analyze total hospital stay and VDI score (continuous variables), and Cox regression analysis to analyze mortality (time-dependent variable). The variables used in multivariable analyses were chosen to reflect patient characteristics (age, sex and comorbidity score), disease severity (BVAS, CRP and creatinine), clinical phenotype (ANCA serotype) and treatment (cyclophosphamide/rituximab, oral prednisolone dose and pulsed intravenous methylprednisolone dose). In analysis of VDI at two years, year of diagnosis as a continuous

variable (from 1997 and onward) was also included. In analyses using ANCA serotype as a binary variable, double-positive patients were designated as having either myeloperoxidase-ANCA (MPO-ANCA)/perinuclear ANCA (P-ANCA) or proteinase-3-ANCA (PR3-ANCA)/cytoplasmic ANCA (C-ANCA) depending on the highest titer.

Results

Baseline patient characteristics

A total of 202 patients were included. For the outcome analyses, only patients alive after 30 days with complete treatment data were included (N=167). The flow of patients is shown in Figure 1 and detailed patient characteristics in Table 1. Median age at diagnosis was 79 years (interquartile range [IQR] 77-82). MPA was diagnosed in 69.8%, and GPA in 30.2% of patients. MPO/P-ANCA was seen in 62%, PR3/C-ANCA in 33.5%, double-positivity in 1%, and ANCA-negativity in 3.5%. Renal involvement was seen in 90.7% of the patients (Sweden 89.2%, United Kingdom 93.9% and Czech Republic 92.1%; P=0.67). Median creatinine at diagnosis was 278 µmol/L (IQR141-439). In MPO/P-ANCA positive patients it was 315 (IQR 171-491) and in PR3/C-ANCA positive patients 217 (IQR 95-386) (P=0.04). Median BVAS was 15 (IQR 12-19).

Treatment

Patients were divided into three different treatment groups, CYC (n=112), RTX (n=24) and No/other (n=31). Methylprednisolone was given in 45.5% of the patients during the first three months after diagnosis (48.2% in CYC group, 62.5% in RTX group and 22.6% in No/other group). Median cumulative doses of oral prednisolone, cyclophosphamide and intravenous methylprednisolone during the first three months are shown in Table 2. In the No/other group, seven patients received no treatment, three patients steroids only, nine patients low

doses of cyclophosphamide, eight patients azathioprine, three patients methotrexate and one patient mycophenolate mofetil.

Vasculitis damage index

Median VDI score was 2 (IQR 1-3) both at one and two years. At one year, 5.0% (6/121) of the patients had no items of damage and 5.0% had five or more items. The corresponding figures at two years were 3.7% (4/108) and 6.5% (7/108). Damage in the renal domain was most common, followed by cardiovascular and neuropsychiatric damage (Figure 2). End stage renal disease (ESRD) constituted 20.5% (18/88) and 18.3% (15/82) of the damage in the renal domain at one and two years respectively.

Treatment-related VDI items were present in 21.4% (25/117) of the patients at one year and in 26.9% (28/104) at two years. The most common items were osteoporosis, diabetes, and cataract (Figure 2). There were no cases of osteomyelitis, avascular necrosis or gonadal failure.

In multivariable linear regression analysis, BVAS score was positively associated with VDI score at two years, while treatment with cyclophosphamide or rituximab was negatively associated with VDI score (Table 3). Patients treated with cyclophosphamide or rituximab had a median VDI of 2 (IQR 1-3) at two years compared to 3 (IQR 2-4) in patients not given such treatment (P=0.09). Year of diagnosis was negatively associated with VDI score in univariable, but not multivariable analysis. The results of the analysis of VDI score at one year were similar to the results at two years.

During the first two years, relapses were seen in 9.6% (14/146) of patients who reached remission after induction therapy. Relapse (as a dichotomous variable) was not associated with VDI score at two years in univariable analysis (β 0.31 95% CI -0.61-1.23; P=0.50).

In multivariable binary logistic regression analysis of treatment-related items at two years cumulative methylprednisolone dose was associated with increased odds for treatment-related damage (OR 1.25 95% CI 1.01-1.55; P=0.043; Supplementary table 1). Similar results were seen at one year.

There were significant differences in total VDI score, but not the frequency of treatment-related damage between countries, with more damage in patients from the Czech Republic (Supplementary table 2).

Hospitalization

The median initial hospital period was 18 days (IQR 11-29), and during the first year 69.1% (114/165) of the patients were readmitted to hospital, with a median stay of 12 days (IQR 6-31). Median total hospital stay (including initial stay) during the first year was 31 days (IQR 17-50). During the first year 24.2% of the patients experienced two or more readmissions to the hospital. Data on causes of readmission to hospital was available for 156 of 187 readmissions in 98 of 114 patients during the first year. The most common cause was infections (N=58), followed by dialysis-related events (N=18), cardiovascular events (N=15), adverse drug reactions (N=11), thromboembolic events (N=9), relapses/active vasculitis (N=8), fractures (N=6), gastrointestinal bleeding/perforation (N=4), diabetes (N=4) and other causes (N=23).

In multivariable binary logistic regression analysis of readmission there was a significant association with MPO-ANCA positivity and creatinine level at diagnosis. MPO-ANCA positivity decreased the odds of being readmitted, while higher creatinine levels increased the odds (Table 4).

In multivariable linear regression analysis of total time spent in hospital during the first year, there was a significant association with creatinine level at diagnosis (β 5.04 95 % CI 0.67-9.41, P=0.024; Supplementary Table 3).

More patients were readmitted to hospital in the Czech Republic, compared to Sweden and the United Kingdom (Supplementary Table 2).

Cause of death

A total of 69 patients (34.2% of 202 patients) died during the first two years after diagnosis. In 55 patients the cause of death was known. The most common causes of death among these were infection (34.5%), myocardial infarction (16.4%) and active vasculitis (14.5%). Less common causes were gastrointestinal bleeding (7.3%), heart failure (7.3%), and malignancy (7.3%). Nine patients died within 30 days from diagnosis. Of these, five died of vasculitis, one of myocardial infarction and one of gastrointestinal bleeding. In two patients, the cause of death was unknown. Among the 19 patients who died from infection, there were no deaths within 30 days of diagnosis and five deaths within 90 days of diagnosis.

Analysis of death caused by infections was performed on 146 patients alive at three months with complete data on glucocorticoid use. In multivariable Cox regression analysis only cumulative oral prednisolone dose was predictive of death caused by infection (OR per percentile 1.57 95% CI 1.06-2.32; P=0.024.) The results were similar in analysis of the 167 patients alive at one month. Median oral prednisolone dose in patients who died from infection was 3480 mg (IQR 2760-4000), in patients who died from other/unknown causes 2280 mg (IQR 1500-2730) and in patients alive after two years 2290 mg (IQR 1800-3190). There was no significant difference between countries regarding the frequency of deaths caused by infections (Supplementary Table 2).

Discussion

The aim of this study was to investigate associations between permanent organ damage, hospital admissions, causes of death, and the treatment given during the first months after diagnosis in elderly patients with MPA and GPA. The most important finding is that elderly patients treated with adequate doses of cyclophosphamide or rituximab developed less permanent organ damage as compared to patients who were treated with less aggressive regimens and patients who received no treatment. The most probable cause for this is that the immunosuppressive treatment halts the inflammatory process and that damage accrued over time is mainly caused by the disease and not the treatment. There was no association between treatment and rehospitalization or total hospital stay during the first year after diagnosis.

In a previous study by our group, largely based on the same cohort, we found that the patients who had received treatment with rituximab or cyclophosphamide had better survival at two years(13). The concern that this increased survival would be at the expense of increased morbidity and health care utilization was thus not confirmed in the current study.

A selected number of VDI items are considered as being treatment-related(18), and these were seen in about one fourth of the patients. When limiting the analysis to these items, there was no association between damage and treatment with cyclophosphamide or rituximab, or the total oral prednisolone dose. However, there was a positive association between treatment-related damage and cumulative methylprednisolone dose. Previous studies in younger patients have shown an association between organ damage and higher cumulative doses and longer duration of glucocorticoid use(10, 12). A recently published retrospective study of patients with severe AAV with renal involvement found an association between treatment with intravenous methylprednisolone and higher incidence of diabetes mellitus(20), one of the damage items considered as treatment-related.

Another important finding in this study is that the patients who died from infections had received higher doses of oral glucocorticoids compared to patients who died from other causes or who survived the first two years, and this was the only significant factor associated with death caused by infections in multivariable analysis. Infections were the most common cause of death in this elderly population, as previously shown in younger patients(7), and in smaller studies of elderly patients(21, 22). Patients with AAV have high rates of severe infections compared to the general population, and the risk increases with advancing age(23). Most of the deaths caused by infections occurred after the first three months of treatment. As we did not have data on glucocorticoid use beyond three months, we are not able to discern if this observed association was due to a continued trend of longer or higher cumulative dose of corticosteroids during the first year. Further studies are needed before any firm conclusions can be made on whether oral or intravenous glucocorticoids are associated with the greatest risks in elderly patients. However, our results do raise concerns regarding the use of high doses of glucocorticoids with respect to treatment-related damage and severe infections. A regimen with lower cyclophosphamide dose and faster tapering of glucocorticoids was associated with lower risk for serious adverse events, while deaths, remission and relapse rates did not differ significantly, in a cohort of AAV-patients aged 65 years or more(24).

We found high readmission numbers among the patients included in this study; 69 % were readmitted to the hospital during the first year after diagnosis. This can be compared to readmission rates of 71% in advanced cancer patients(25) and 58% in older patients on chronic hemodialysis(26). There are few studies of hospitalization patterns in AAV. Wallace et al(27) studied patients in all age groups and found that the median length of stay in hospital with a primary diagnosis of GPA was 6.2 days. This can be compared to the total median hospital stay of 31 days and the median stay during readmission of 12 days found in the present study. In the general population in Sweden aged 75 years or more, the mean hospital

stay during 2013 was 6.3 days(14). In a Danish population-based study, the risk of infection-related hospitalization was 9.5 times higher among GPA-patients compared to population controls during the first year of follow-up(28). In line with those results, infections were most common among known causes of rehospitalization in our cohort.

In multivariable analysis, MPO-ANCA positivity decreased the odds for readmission to hospital during the first year, while poorer renal function at diagnosis was associated with increased odds for readmission. The negative association between MPO-ANCA positivity and readmission was not seen in the univariable analysis, but in the multivariable analysis after adjusting for creatinine. The most probable reason for this finding is that the MPO-ANCA positive patients had less extra-renal involvement causing readmission. Creatinine level at diagnosis was also associated with total time spent in hospital during the first year, showing the importance and severity of renal impairment in these elderly patients.

A great majority of the patients had some item of permanent damage at two years of follow-up, although multiple items of damage were only seen in a minority of the patients. Higher BVAS at diagnosis was associated with higher VDI score at follow-up, reflecting the impact of disease activity on subsequent damage. This is in line with the results from the EUVAS trials(10).

We found damage to be most common in the renal domain, which is similar to previous published studies(9, 11, 18). However, ENT damage was seen less frequently, a result of the fact that GPA with ENT involvement was less common in our cohort. This is expected given the older age of the patients in this study. MPA is more common than GPA in older patients(6, 22, 29, 30), and older patients have more renal and less ENT involvement(21, 31). Of the centers participating in the present study, a majority mainly recruits nephrology patients. However, referral bias is not the only explanation for the predominance of renal

involvement since it did not differ between countries, and was high also in the countries recruiting from rheumatology units(13).

The main limitation of this study is that data are retrospective and that the patients have not been randomized to treatment. Due to the retrospective collection of data, information on treatment, causes of death and causes of rehospitalization was not complete for all patients included. There is a risk of confounding by indication in the treatment data, since the motive for treatment decisions is not known. When analyzing and interpreting the data, it was presumed that the therapy given during the first 30 days was intended to continue in accordance with current guidelines(32, 33). However, we cannot exclude the possibility that patients who were perceived as having a poorer prognosis due to comorbidities or frailty were not treated according to guidelines and that these patients also developed more permanent damage. Neither can we rule out the possibility that patients who were perceived as having an aggressive disease received more intensive treatment, including higher doses of glucocorticoids. These severely ill patients were likely to be at higher risk for adverse events and damage.

The risk of survival bias also needs to be acknowledged. Patients with more damage have an increased mortality risk (18) and patients with severe damage resulting in death are thus not included in the analyses of VDI. However, the starting point for this study was to investigate damage in just surviving patients. Our previous study in elderly patients showed reduced mortality in treated patients, making survival bias an unlikely cause for the negative association between treatment and damage.

In conclusion, we found that a majority of elderly patients with MPA and GPA developed permanent organ damage over time and that the frequency of readmission during the first year after diagnosis was high. Treatment with cyclophosphamide and rituximab was associated with development of less permanent organ damage and was not associated with

readmission to hospital or total time spent in hospital during the first year after diagnosis. However, intravenous glucocorticoids were associated with treatment-related damage and oral corticosteroids given during the first three months with increased risk of fatal infections.

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Figure legends

Figure 1. Flow of patients in the study.

Figure 2. Vasculitis damage index (VDI) items.

A. Frequency of damage items at one and two years in patients surviving two years (N=108).

B. Frequency of treatment-related damage items at one and two years in patients surviving two years (N=104).

Figure 1. Flow of patients in the study

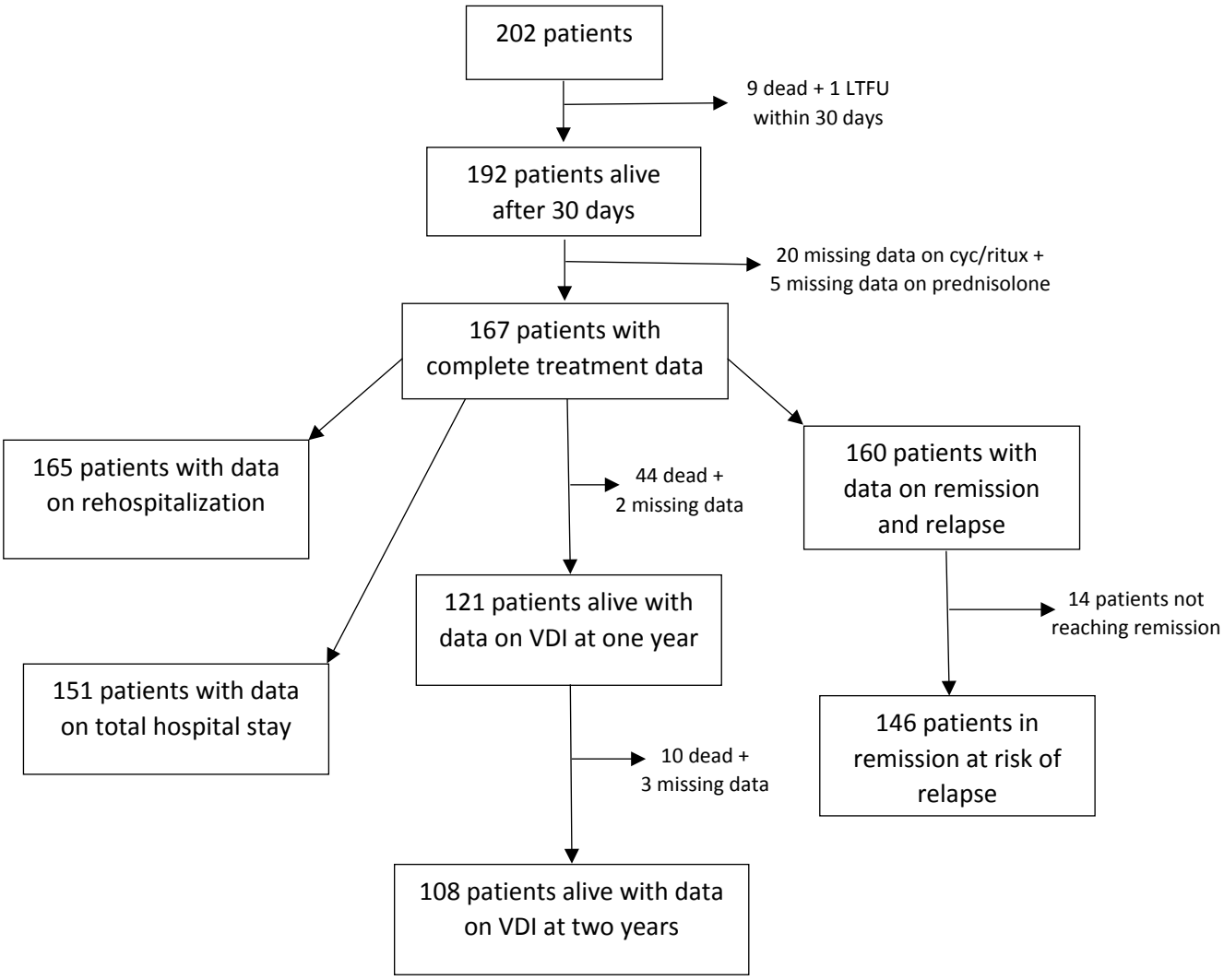

Figure 2. Vasculitis damage index (VDI) items.

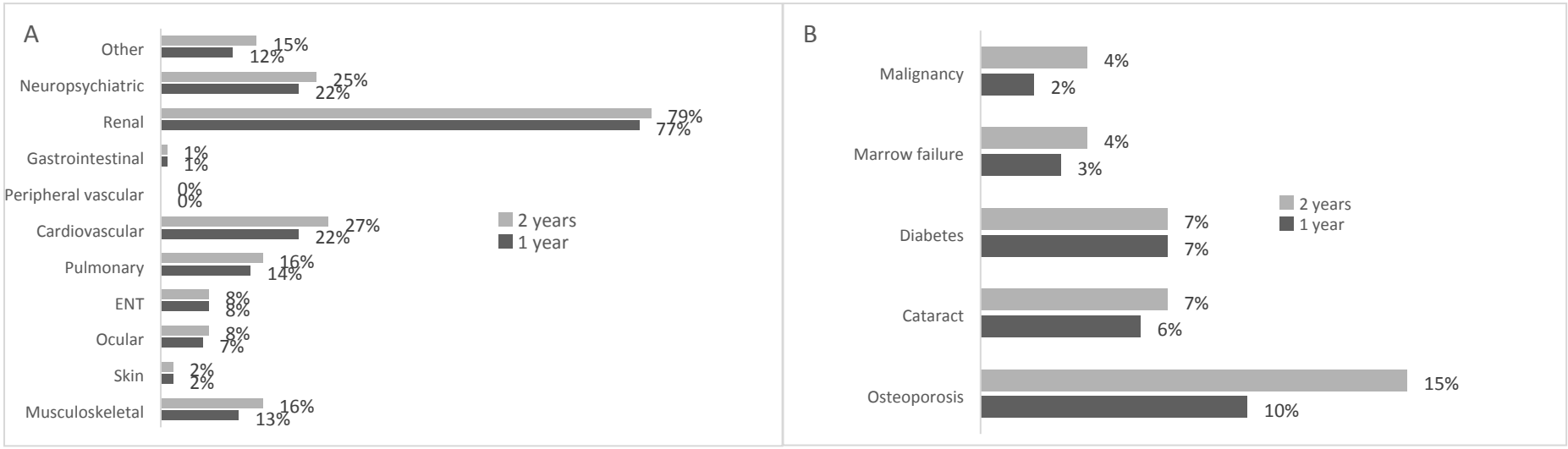

Table 1. Demographic and clinical factors. Demographic and clinical factors at time of diagnosis.

		Patients alive after 30 days and with complete treatment data		
Variables	All patients N=202	Yes N=167	No N=35	P value
Sex				
Female	53.5% (108)	54.5% (91)	48.6% (17)	0.52
Male	46.5% (94)	45.5% (76)	51.4% (18)	
Diagnosis				
MPA	69.8% (141)	70.1% (117)	68.6% (24)	0.862
GPA	30.2% (61)	29.9% (50)	31.4% (11)	
Median age (years)	79 (77-82)	79 (77-82)	80 (77-85)	0.25
ANCA[1]				
MPO/P-ANCA	62.0% (124)	64.5% (107)	50.0% (17)	<0.001
PR3/C-ANCA	33.5% (67)	33.7% (56)	32.4% (11)	
Double-positive	1.0% (2)	1.2% (2)	0% (0)	

Negative	3.5% (7)	0.6% (1)	17.6% (6)	
Creatinine (µmol/L)[2]	278 (141-439)	268 (137-429)	287 (178-493)	0.33
CRP (mg/L)[3]	73 (20-131)	81 (23-135)	48 (8-112)	0.035
BVAS[4]	15 (12-19)	15 (13-19)	13 (10-16)	0.014
Dialysis dependency[5]	26.8% (53)	23.5% (39)	43.8% (14)	0.018
Renal involvement[6]	90.7% (165)	90.3% (139)	96.4% (27)	0.47
ENT involvement[7]	17.0% (31)	16.2% (27)	14.3% (4)	0.79
Country				
Sweden	55.0% (111)	61.7% (103)	22.9% (8)	<0.001
United Kingdom	26.2% (53)	16.8% (28)	71.4% (25)	
Czech Republic	18.8% (38)	21.6% (36)	5.7% (2)	

Demographic and clinical variables shown for all 202 patients. Comparison of demographic and clinical data between patients alive at 30 days with complete treatment data (N=167) and patients who died or did not have data on treatment (N=35).

Values are presented as % (n) or median (interquartile range) and exclude missing data. MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; ANCA, anti-neutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase-3; P, perinuclear; C, cytoplasmic; CRP, C-reactive protein; BVAS, Birmingham Vasculitis Activity Score; ENT, ear nose and throat

[1]Data missing in two patients [2]Data missing in 11 patients [3]Data missing in six patients [4]Data missing in 11 patients [5]Data missing in four patients [6]Data missing in 20 patients

Table 2. Treatment groups. Median dose of oral prednisolone, cyclophosphamide and intravenous methylprednisolone the first three months in the different treatment groups.

	CYC[1]	RTX[2]	No/other[3]	P value
N (%)	112 (67.1%)	24 (14.4%)	31 (18.6%)	
Prednisolone (mg)	2570 (1920-3480)	1920 (1300-2770)	1800 (670-2320)	<0.001
Cyclophosphamide (mg)	3630 (3000-6000)	1000 (0-2380)	0 (0-1040)	<0.001
Methylprednisolone (mg)	0 (0-750)	500 (0-1500)	0 (0-0)	0.007

Values are presented as medians (interquartile range).

[1]Cumulative cyclophosphamide dose ≥2000 mg oral cyclophosphamide/≥1500 mg intravenous cyclophosphamide during the first three months [2]Any dose of rituximab [3]No treatment, steroids only, other cytotoxic agents

Table 3. Vasculitis damage index (VDI). Univariable and multivariable linear regression analysis of VDI score at two years.

	Univariable analysis		Multivariable analysis[1]	
Variable	β (95% CI)	P value	β (95% CI)	P value
Age (per year)	0.008 (-0.08-0.095)	0.86	0.026 (-0.065-0.12)	0.57
Male sex	-0.29 (-0.85-0.27)	0.31	-0.32 (-0.89-0.25)	0.26
BVAS (per point)[2]	0.076 (0.027-0.13)	0.002	0.096 (0.037-0.16)	0.002
MPO/P-ANCA	-0.45 (-1.03-0.13)	0.13	-0.072 (-0.72-0.57)	0.82
CRP (per percentile)[3]	-0.038 (-0.21-0.13)	0.66	-0.18 (-0.34-0.007)	0.059
Creatinine (per percentile)[4]	0.023 (-0.16-0.21)	0.81	-0.068 (-0.26-0.12)	0.48
Comorbidity score (per point)	0.19 (-0.17-0.55)	0.29	0.12 (-0.24-0.48)	0.52
CYC/RTX	-0.82 (-1.66-0.022)	0.056	-1.16 (-2.09- -0.23)	0.015
Prednisolone dose (per percentile)	-0.002 (-0.18-0.17)	0.98	0.005 (-0.19-0.20)	0.96
Methylprednisolone dose (per 250 mg)	-0.004 (-0.11-0.11)	0.95	0.059 (-0.064-0.18)	0.34

Year of diagnosis (per year from 1997)	-0.09 (-0.15--0.025)	0.007	-0.046 (-0.12-0.025)	0.20

Analysis of 108 patients with complete treatment data and data on VDI at two years.

CI, confidence interval; BVAS, Birmingham Vasculitis Activity Score; MPO, myeloperoxidase; P-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; CRP, C-reactive protein; CYC/RTX, ≥2000 mg oral cyclophosphamide/≥1500 mg intravenous cyclophosphamide or rituximab

[1]Multivariable analysis performed on 100 patients [2]Data missing in two patients [3]Data missing in five patients [4]Data missing in two patients

Table 4. Rehospitalization. Univariable and multivariable binary logistic regression analysis of rehospitalization during the first year.

	Univariable analysis		Multivariable analysis[1]	
Variable	OR (95% CI)	P value	OR (95% CI)	P value
Age (per year)	0.99 (0.91-1.09)	0.89	0.99 (0.89-1.10)	0.82
Male sex	0.73 (0.37-1.41)	0.34	0.50 (0.24-1.06)	0.072
BVAS (per point)[2]	1.05 (0.98-1.11)	0.16	1.02 (0.95-1.10)	0.63
MPO/P-ANCA	0.56 (0.27-1.16)	0.12	0.36 (0.15-0.87)	0.024
CRP (per percentile)[3]	1.02 (0.82-1.26)	0.89	1.02 (0.78-1.34)	0.87
Creatinine (per percentile)[4]	1.22 (0.98-1.52)	0.072	1.34 (1.02-1.78)	0.039
Comorbidity score (per point)	1.18 (0.78-1.80)	0.43	1.23 (0.77-1.96)	0.39
CYC/RTX	1.83 (0.82-4.09)	0.14	2.21 (0.82-5.94)	0.12
Prednisolone dose (per percentile)	1.05 (0.86-1.29)	0.62	0.99 (0.76-1.30)	0.96
Methylprednisolone dose (per 250 mg)	1.07 (0.93-1.23)	0.37	1.02 (0.86-1.20)	0.85

Analysis of 165 patients with complete treatment data and data on rehospitalization.

OR, odds ratio; CI, confidence interval; BVAS, Birmingham Vasculitis Activity Score; MPO, myeloperoxidase; P-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; CRP, C-reactive protein; CYC/RTX, ≥2000 mg oral cyclophosphamide/≥1500 mg intravenous cyclophosphamide or rituximab

[1]Multivariable analysis performed on 148 patients [2]Data missing in five patients [3]Data missing in five patients [4]Data missing in seven patients