Outcome and Prognostic Factors During the Course of Primary Small-Vessel Vasculitides

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ABSTRACT. ***Objective.*** To identify the prognostic factors of relapse and/or death during the course of primary small-vessel vasculitides (PSVV), and to differentiate their prognostic relevance by the type of vasculitis.

Methods. Seventy-five patients were retrospectively followed up after diagnosis: 36 with Wegener's granulomatosis (WG), 23 with Churg-Strauss syndrome (CSS), and 16 with microscopic polyangiitis. Cox regression analysis was used to identify the significant predictors of relapse and death.

Results. Gastrointestinal (GI) involvement was associated with an increased risk of relapse, mainly in the patients with CSS, whereas renal disease and perinuclear antineutrophil cytoplasmic antibody positivity were correlated with a lower risk of relapse. Presence of nasal *Staphylococcus aureus* tended to increase the risk of relapse in CSS [hazard ratio (HR) 4.45, p = 0.087], but to decrease it in WG (HR 0.12, p = 0.066). Older age, renal and hepatic involvement, erythrocyte sedimentation rate ≥ 100 mm/h, and serum creatinine level ≥ 1.5 mg/dl were all related to higher risk of death in univariate analysis; however, only cerebral (HR 8.52, p = 0.021) and hepatic involvement (HR 4.40, p = 0.028) and serum creatinine level ≥ 1.5 mg/dl (HR 5.72, p = 0.044) were independently correlated with an unfavorable prognosis for survival. The risk of death associated with each of these indicators did not depend on the form of PSVV.

Conclusion. GI involvement increases the risk of relapse in CSS, whereas the prognostic significance of nasal *S. aureus* in terms of relapse seems to be opposite in patients with CSS and those with WG. Patients with cerebral, hepatic, and renal involvement have the poorest prognosis for survival. Our data do not show that the prognostic relevance of these factors depends on the form of PSVV. (First Release June 15 2006; J Rheumatol 2006;33:1299–306)

Key Indexing Terms:
PAUCI-IMMUNE SMALL-VESSEL VASCULITIS
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CHURG-STRAUSS SYNDROME
ONSET SEASON

Systemic necrotizing vasculitides make up a heterogeneous group of diseases characterized by a primary process of inflammation and damage to the vessel wall. Primary small-vessel vasculitides (PSVV) are a subgroup of these vasculitides and include Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS), the common histological hallmarks of which are inflammation and fibrinoid necrosis of small-vessel walls (arterioles, capillaries, or venules), with few or no immune deposits. Their etiology is unknown, but they are also called ANCA-associated systemic vasculitides because of their frequent association with antineutrophil cytoplasmic antibodies (ANCA).

PSVV are considered rare diseases, but there has been an overall increase in their prevalence and annual incidence over the last 10 years[1], probably because of greater physician awareness and better case identification. In addition to epidemiological changes, greater knowledge has led to improvements in treatment, such as the introduction of corticosteroids at the beginning of the 1950s[2] and cyclophosphamide later[3], both of which have dramatically improved disease outcomes.

Various immunosuppressive drugs and schedules are now used depending on disease activity and the presence of unfavorable prognostic factors. However, it is possible that the same clinical manifestation may have different prognostic significance in the different forms of PSVV, because most studies identifying prognostic factors did not distinguish one from

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the other[4,5]. Further, although there are some reports concerning the predictors of survival in patients with WG[6-8], there are still no reliable studies of CSS and MPA because of their lower prevalence.

The aim of our retrospective followup study was to identify the factors at the time of diagnosis that are predictive of relapse or death, and differentiate their prognostic relevance on the basis of the type of vasculitis.

MATERIALS AND METHODS

Patients. We reviewed the clinical charts of 75 patients with PSVV collected by the interdisciplinary Secondary and Primary Vasculitides study group between 1985 and 2003. The patients were classified as having CSS[9] or WG[10] on the basis of the American College of Rheumatology criteria (ACR); MPA cases were diagnosed on the basis of the Chapel Hill Consensus Conference definitions[11] and recommendations for the differential diagnosis of MPA and polyarteritis nodosa (PAN) proposed by other authors[12,13]. We excluded patients with fewer than 2 involved organs, as in the case of renal limited vasculitis. Patients' case histories were documented in detail up to December 31, 2003, and the relevant data were retrospectively recorded in a computer database for statistical analysis.

The demographic, clinical, and laboratory characteristics recorded at diagnosis were sex, age, organ involvement, the Birmingham Vasculitis Activity Score (BVAS), the first-hour erythrocyte sedimentation rate (ESR; Westergren method), serum C-reactive protein (CRP), creatinine and ANCA pattern (perinuclear, pANCA; cytoplasmic, cANCA), and the results of nasal swab cultures for *Staphylococcus aureus*.

The season of disease onset, time from disease onset to diagnosis, and time from diagnosis to first remission were also recorded.

Impaired renal function was defined as serum creatinine levels $\geq$ 1.5 mg/dl or a 30% increase in comparison with baseline, and endstage renal disease as a chronic need for replacement therapy (dialysis or transplant).

Disease activity was evaluated using the modified BVAS (BVAS 3), which includes a specialist opinion[14,15]; the maximum total score is 66.

Indirect immunofluorescence (IIF) for ANCA became available for clinical use in our hospital in 1991; in order to confirm the possible presence of pANCA, the IIF test for antinuclear antibodies (ANA) on HEp-2 cells should be negative. Every ANCA-positive serum sample detected by IIF has been routinely investigated since 1995 using an ELISA for the detection of anti-proteinase-3 (PR3) or anti-myeloperoxidase (MPO) antibodies. Patients who were examined only during the remission phase and who were ANCA-negative were considered not evaluable for ANCA, as were those who died before 1991.

Nasal testing for *S. aureus* has been carried out in every patient with a diagnosis of PSVV since 1999.

Treatment and followup. Patients with active disease were treated with a 1 g intravenous methylprednisolone bolus for 3 consecutive days, followed by oral prednisone (1 mg/kg/day) and cyclophosphamide (1.5–2 mg/kg/day)[3]; patients experiencing remission were subsequently given oral prednisone combined with cyclophosphamide, methotrexate, or azathioprine for at least one year after remission.

Patients with WG with nasal *S. aureus* infection were also given sulfamethoxazole (160 mg) and trimethoprim (800 mg) twice a day for 3 days (subsequently reduced to once daily), and topical antibiotic treatment (mupurocine) for 1–2 months until periodically-assessed swab cultures became negative.

We reviewed the clinical charts for any clinical or laboratory signs of remission or relapse at every visit in order to record a global clinical evaluation in the database.

Remission was defined as the absence of any clinical signs/symptoms of active vasculitis, supported by laboratory evidence of normal CRP and ESR. Three patients were considered to be in remission because, although they had slightly abnormal ESR values (but 50% less than those observed in the acute phase), they had no clinical symptoms of active disease; we always considered clinical factors as preeminent.

Relapse was defined as the recurrence of clinical signs/symptoms, or the occurrence of new symptoms after an initial remission, requiring the resumption of immunosuppressive therapy or an increased dose.

Asthma or an isolated rise of eosinophilia were not considered signs of persistent CSS disease activity or relapse.

Statistical analysis. All statistical analysis were performed using SPSS 11.0 (SPSS Inc., Chicago, IL, USA) and Stata Release 9.0 (Stata Corp., College Station, TX, USA); a 2-sided p value < 0.05 was considered statistically significant. Between-group differences in categorical variables were examined using Fisher's exact test, and those relating to continuous variables were examined using the Kruskal-Wallis test and Mann-Whitney test, as appropriate. Bonferroni's adjustment was used for pairwise comparisons.

To investigate the prognostic significance of each demographic, clinical, and laboratory characteristic, we computed the hazard ratio (HR) of death and relapse in the study population as a whole, using log-rank test and Cox's regression analysis, with the time at risk starting from the time of diagnosis in the case of the prognostic indicators of death, and from the time of the first remission in the case of the prognostic indicators of relapse (the outcome being the time to relapse after having censored the followup for deaths unrelated to the vasculitic process). Additionally, we performed the same tests after adjusting for the type of vasculitis.

To test departure from the proportional assumption, we used the procedure proposed by Grambsch and Therneau based on Shoenfeld residuals[16].

We also verified whether the prognostic significance of each variable differed in relation to the type of vasculitis by applying the likelihood ratio test to the interaction term between each prognostic indicator and the variable indicating the type of vasculitis.

In order to identify the independent predictors of relapse and death, all variables with p values < 0.10 in the univariate analyses were entered into multiple regression models. For the predictors of relapse, the analysis was performed using only 62 of the original 67 patients, since ANCA data were missing in 5 patients. For analysis on the predictors of death, we did not include CRP and ESR data, which were missing in 32 and 23 patients, respectively. Since there were no missing values in any other univariate predictors, this analysis was performed on the entire set of 75 patients.

We additionally performed multiple imputation analysis using the Stata program ice* (imputation by chained equations) to verify whether CRP and ESR were significant multivariate predictors, but the results did not change substantially[17].

Using a stepwise backward elimination procedure we selected the variables that predicted the outcome with a p value < 0.05 by the Wald test. No interaction term was included. All the multiple regression models were refitted after inclusion of the type of vasculitis, which can potentially behave as a strong confounder in the relation between each predictor and the outcome.

RESULTS

Patient characteristics. We enrolled 75 patients with PSVV: 36 (48%) with WG, 23 (31%) with CSS, and 16 (21%) with MPA. Their demographic and clinical characteristics at diagnosis are shown in Table 1.

The patients with MPA were significantly older than the others ($p < 0.001$ vs both WG and CSS). The most frequently involved organs were the lower airways, ear-nose-throat (ENT), and kidney. Lower airway involvement consisted of pulmonary hemorrhage, which was prevalent in the patients with MPA ($p = 0.048$ vs WG and $p = 0.002$ vs CSS); radiographic infiltrates or nodules, the prevalence of which was not different in the 3 groups ($p = 0.15$); and asthma, which was obviously typical in the patients with CSS ($p < 0.001$ vs both WG and MPA). ENT symptoms were significantly more common in the patients with WG ($p < 0.001$) and CSS ($p = 0.004$) than in those with MPA.

Table 1. Demographic and clinical characteristics at the time of diagnosis.

	Total, n = 75	WG, n = 36	CSS, n = 23	MPA, n = 16	p
Males	37 (49)	20 (56)	11 (48)	6 (38)	0.36
Females	38 (51)	16 (44)	12 (52)	10 (62)	
Age, yrs	57 (14–82)	53 (14–75)	49 (18–70)	68 (53–82)	< 0.001[b,c]
Onset to diagnosis, mo	5 (0–160)	6.5 (0–160)	4 (0–151)	4.5 (0–140)	0.73
Diagnosis to remission, mo	4 (1–118)	4 (1–118)	6 (1–25)	1 (1–14)	0.21
Constitutional symptoms	56 (75)	29 (81)	16 (70)	11 (69)	0.54
Organ involvement					
Lower airways	56 (75)	24 (67)	22 (96)	10 (63)	0.012[a]
Pulmonary hemorrhage	9 (12)	3 (11)	0	6 (38)	
Infiltrates/nodules or cavities	42 (56)	23 (64)	9 (39)	10 (63)	
Asthma	21 (28)	0	21 (91)	0	
Ear-nose-throat	51 (68)	30 (83)	17 (74)	4 (25)	< 0.001[b,c]
Nasal obstruction	34 (45)	16 (44)	16 (69)	2 (13)	
Nasal polyposis	14 (19)	2 (6)	12 (52)	0	
Crusting rhinitis	19 (25)	16 (44)	3 (13)	0	
Sinus involvement	27 (36)	16 (44)	11 (48)	0	
Deafness	19 (25)	11 (31)	5 (22)	3 (19)	
Conductive	6 (8)	3 (8)	1 (4)	2 (13)	
Sensorineural	9 (12)	4 (11)	4 (17)	1 (6)	
Mixed	4 (5)	4 (11)	0	0	
Subglottic involvement	4 (5)	4 (11)	0	0	
Kidney	39 (52)	22 (61)	3 (13)	14 (88)	< 0.001[a,c]
Isolated urinary abnormalities	5 (7)	4 (11)	1 (4)	0	
Impaired renal function	34 (45)	18 (50)	2 (9)	14 (88)	
Endstage renal disease	13 (17)	7 (19)	0	6 (37)	
Peripheral nervous system	18 (24)	3 (8)	11 (48)	4 (25)	0.007[a]
Cranial nerve palsy	2 (3)	1 (3)	0	1 (3)	
Polyneuropathy	10 (13)	2 (6)	4 (17)	4 (25)	
Multiple mononeuropathy	5 (7)	0	4 (17)	1 (3)	
Mixed peripheral neuropathy	3 (4)	0	3 (13)	0	
Central nervous system	4 (5)	0	2 (9)	2 (13)	0.13
Skin	16 (21)	4 (11)	9 (39)	3 (19)	0.038
Gastrointestinal tract	11 (15)	3 (8)	8 (35)	0	0.004[a,c]
Abnormal pain/diarrhea	8 (11)	3 (8)	5 (22)	0	
Other	3 (4)	0	3 (13)	0	
Liver	9 (12)	4 (11)	1 (4)	4 (25)	0.15
Abnormal ALT	9 (12)	4 (11)	1 (4)	4 (25)	
Abnormal AST	6 (8)	2 (6)	1 (4)	3 (19)	
Abnormal γ-GT/AP	7 (9)	3 (8)	0	4 (25)	
Cardiovascular system	5 (7)	3 (8)	2 (9)	0	0.49
Pericardial effusion	3 (4)	2 (6)	1 (4)	0	
ECG changes	3 (4)	2 (6)	1 (4)	0	
Other	2 (3)	2 (6)	0	0	
BVAS	18 (0–37)	15 (0–37)	17 (4–30)	20 (14–27)	0.36

WG: Wegener's granulomatosis; CSS: Churg-Strauss syndrome; MPA: microscopic polyangiitis; BVAS: Birmingham Vasculitis Activity Score (0–66); ALT: alanine aminotransferase; AST: aspartate aminotransferase; γ-GT: γ-glutamyl transferase; AP: alkaline phosphatase. Onset to diagnosis: time from onset disease to diagnosis (mo); Diagnosis to remission: time from diagnosis to first remission (mo). p values refer to the global test for differences between the 3 groups. The letters indicate the significant ($p < 0.05$) pairwise comparisons as follows: [a] WG vs CSS; [b] WG vs MPA: [c] CSS vs MPA. Categorical variables are shown as number (%) and continuous variables as median values (ranges).

Thirty-nine patients showed kidney involvement, which was significantly less frequent in the patients with CSS ($p < 0.001$ vs both WG and MPA). Of the 34 patients with impaired renal function, 21 underwent renal biopsy: 2 patients showed a nondiagnostic histological pattern, 18 had pauci-immune necrotizing crescentic glomerulonephritis, and one CSS patient showed a pattern of eosinophilic tubulo-interstitial nephritis.

Peripheral neuropathy was significantly more frequent in the patients with CSS than in those with WG ($p = 0.002$). Gastrointestinal (GI) symptoms were mainly present in the CSS patients ($p = 0.017$ vs WG; $p = 0.012$ vs MPA).

In terms of laboratory indicators, ESR was lowest in the CSS patients ($p = 0.016$ vs WG; $p = 0.003$ vs MPA), and CRP levels were significantly lower in the CSS patients than in

those with MPA (p = 0.023). The median serum creatinine level at diagnosis was 1.2 mg/dl (range 0.7–21 mg/dl); patients with CSS had significantly lower levels than those with WG (p = 0.001) or MPA (p < 0.001), and the MPA patients had significantly higher levels than those with WG (p = 0.009). The ANCA distribution pattern was disease-typical in the 70 evaluable patients: most of the WG patients (76%) were cANCA-positive, and most of the MPA patients (93%) were pANCA-positive; only 45% of the CSS patients were ANCA-positive, and most of them (80%) showed a perinuclear pattern (Table 2).

The season of onset of WG and MPA was significantly different (p = 0.036), with WG symptoms beginning mainly in the autumn and winter (74%), and MPA symptoms in the spring and summer (69%); CSS showed only a slight tendency to onset in autumn and winter (62%).

Prognostic factors for relapse. Four patients died without ever achieving remission after a median followup of 3.5 months (range 1–10.5 mo); 4 had not yet achieved first remission at the time of the study termination after a median followup of 3.8 months (range 1.3–30 mo). Of the 67 patients available for this analysis, 33 had WG, 21 CSS, and 13 MPA.

The median time of relapse-free survival was 73 months (95% CI 10.33–135.67). The one, 2, and 5-year risk of relapse in the population as a whole was, respectively, 18%, 27%, and 44%. The risk of relapse one and 2 years after first remission was, respectively, 27% and 35% in CSS, 16% and 26% in WG, and 10% and 19% in MPA (Figure 1). The only difference, of borderline statistical significance, was the higher risk of relapse in CSS compared to MPA (HR 4.52, 95% CI 0.98–20.89, p = 0.052).

We analyzed time to relapse (since remission) using time from diagnosis to remission as a baseline covariate. There was a trend showing that the longer the time to remission the lower was the risk of subsequent relapse; however, this was not statistically significant (HR 0.70, 95% CI 0.43–1.12, p = 0.14).

In terms of clinical features, kidney disease was related to a lower risk of relapse (HR 0.39, 95% CI 0.18–0.87, p = 0.026), whereas GI involvement was related to a 3-fold higher risk (HR 3.26, 95% CI 1.28–8.33, p = 0.013). As for laboratory indicators, the pANCA positivity was associated with a significantly lower risk of relapse (HR 0.32, 95% CI 0.11–0.95, p = 0.039) than cANCA positivity and ANCA negativity considered together (Table 3).

Results were not substantially different after adjusting for the type of vasculitis (Table 3).

The interaction test showed that the risk of relapse associated with GI involvement and nasal *S. aureus* depended significantly on the type of vasculitis (p = 0.046, p = 0.001, respectively). Indeed, GI involvement (which was observed only in the WG and CSS patients) appeared to have little or no effect on the prognosis of WG (HR 0.76, 95% CI 0.10–5.87, p = 0.80), but had a strong negative influence on the prognosis of CSS (HR 6.75, 95% CI 1.55–29.52, p = 0.011); nasal *S. aureus* tended to increase the risk of relapse in CSS (HR 4.45, 95% CI 0.80–25.12, p = 0.087), but tended to decrease the risk of relapse in WG (HR 0.12, 95% CI 0.01–1.15, p = 0.066). The prognostic value of the other demographic, clinical, and laboratory indicators was similar in all 3 groups.

Multiple regression analysis selected only GI involvement as an independent prognostic factor for relapse in the entire population (HR 2.83, 95% CI 1.08–7.42, p = 0.034); pANCA-positive vasculitides tended to relapse less frequently than the others, although the difference was not statistically significant (HR 0.39, 95% CI 0.13–1.16, p = 0.091).

Prognostic factors for death. After a median followup of 42

Table 2. Laboratory indicators at the time of diagnosis.

	Total, n = 75	WG, n = 36	CSS, n = 23	MPA, n = 16	p
ESR, mm/1st h	65 (8–138)	90 (8–138)	50 (9–99)	88 (16–116)	0.010[a,c]
CRP, mg/l	54 (0–400)	67 (1–400)	27 (0–103)	67 (21–242)	0.079[c]
Serum creatinine, mg/dl	1.2 (0.7–21)	1.2 (0.7–14.6)	0.9 (0.7–2)	7.4 (0.7–21)	< 0.001[a,b,c]
ANCA					< 0.001[a,b,c]
Evaluable patients, no.	70	34	22	14	
Negative	16 (23)	4 (12)	12 (55)	0	
cANCA	29 (41)	26 (76)	2 (9)	1 (7)	
Anti-PR3	18 (26)	16 (47)	1 (5)	1 (7)	
pANCA	25 (36)	4 (12)	8 (36)	13 (93)	
Anti-MPO	16 (21)	0	7 (32)	9 (64)	
Nasal swab culture					0.37
Evaluable patients, no.	40	19	17	4	
S. aureus-negative	24 (60)	9 (47)	12 (71)	3 (75)	
S. aureus-positive	16 (40)	10 (53)	5 (29)	1 (25)	

Abbreviations as in Table 1. MPO: myeloperoxidase. P values refer to the global test for differences between the 3 groups. Letters indicate the significant (p < 0.05) pairwise comparisons as follows: [a] WG vs CSS; [b] WG vs MPA; [c] CSS vs MPA. Categorical variables are shown as number (%) and continuous variables as median values (ranges).

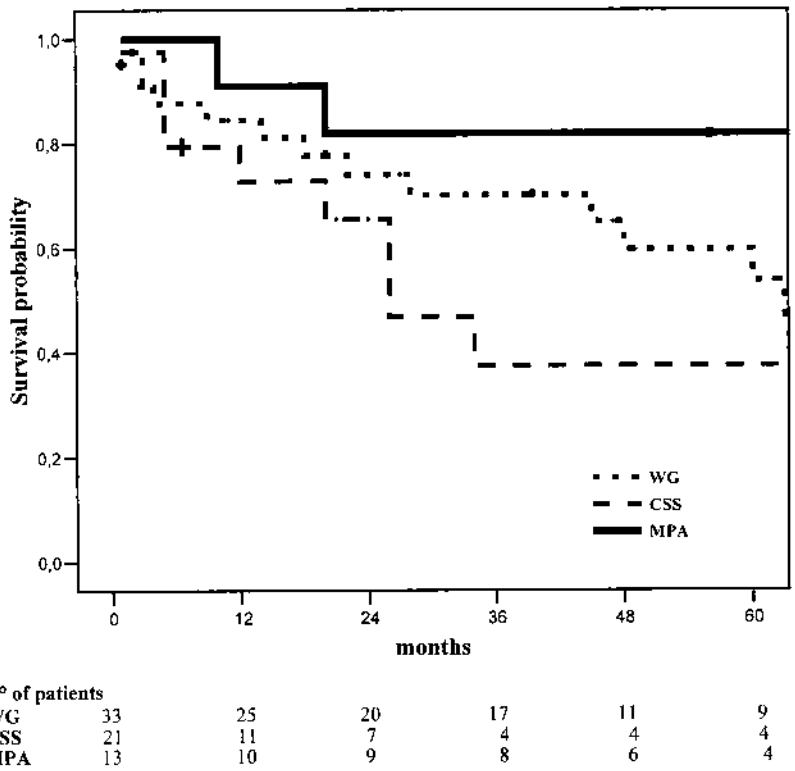


Figure 1. Probability of relapse-free survival according to type of vasculitis.

Table 3. Association between clinical and laboratory characteristics and risk of relapse. The analyses refer to 67 patients; however, only 47 were evaluable for ESR, 39 for CRP, 62 for ANCA, and 35 for nasal swab culture.

	Total	Crude HR	95% CI	Adjusted HR	95% CI
Males	34 (51)	2.12	0.94–4.77	2.12	0.94–4.77
Age ≥ 57 yrs	29 (43)	0.67	0.29–1.55	0.94	0.38–2.37
Onset to diagnosis ≥ 5 mo	33 (49)	1.07	0.49–2.33	0.95	0.43–2.12
Diagnosis to remission ≥ 3 mo	34 (51)	1.38	0.63–3.01	1.38	0.63–3.01
Pulmonary infiltrates/nodules	40 (60)	1.48	0.64–3.43	1.98	0.83–4.76
Pulmonary hemorrhage	9 (13)	0.23	0.03–1.69	0.42	0.05–3.89
Kidney involvement	35 (52)	0.39	0.18–0.87	0.39	0.18–0.87
Endstage renal disease	12 (18)	0.38	0.11–1.26	0.55	0.15–2.02
Ear-nose-throat involvement	45 (67)	1.56	0.66–3.70	1.36	0.53–3.50
Nervous system involvement	17 (25)	0.41	0.05–3.24	0.52	0.16–1.63
Skin involvement	16 (24)	0.80	0.30–2.13	0.70	0.26–1.91
Gastrointestinal involvement	10 (15)	3.26*	1.28–8.33	3.26*	1.28–8.33
Liver involvement	8 (11)	1.21	0.36–4.10	1.47	0.42–5.19
Cardiovascular involvement	5 (7)	2.20	0.65–7.49	2.01	0.58–7.01
ESR ≥ 100mm/1st h	13 (28)	0.91	0.29–2.88	1.52	0.40–5.79
CRP ≥ 100 mg/l	11 (28)	0.18	0.12–1.40	0.18	0.02–1.40
Serum creatinine ≥ 1.5 mg/dl	28 (42)	0.53	0.23-1.23	0.78	0.31-1.97
ANCA-negative	14 (33)	1.36	0.32–1.69	0.65	0.37–1.17
cANCA	28 (45)	1.81	0.82–4.00	0.82	0.60–1.11
pANCA	20 (32)	0.32	0.11–0.95	0.56	0.34–0.94
Positive nasal swab culture	14 (40)	1.20*	0.43–3.37	0.96*	0.88–1.05

First column shows number (%) of patients with the characteristic; second column shows crude hazard ratio (HR) and 95% confidence interval, computed by Cox regression analysis; third column shows the same analysis after adjustment for type of vasculitis. Onset to diagnosis: time from onset of disease to diagnosis; diagnosis to remission: time from diagnosis to first remission. * Hazard ratio differed significantly ($p < 0.05$) depending on the type of vasculitis (interaction test).

months (range 1–274 mo), 16 patients had died: the cumulative 5-year risk of death was 22%. Of the 16 deaths, 4 (25%) were judged to be disease-related: 3 patients died before achieving a first remission (one with WG suffered pulmonary hemorrhage; one died of systemic cytomegalovirus infection; and one, with impaired renal function and severe peripheral neuropathy of the 4 limbs due to active MPA, died of unknown causes at home) and the fourth died of cerebral hemorrhage during a severe WG relapse. Another patient with severe clinical symptoms of MPA (endstage renal disease, seizures, and pulmonary infiltrates) died of congestive heart failure before achieving remission. Death was treatment-related in 3 cases (19%; one case of cyclophosphamide-related pneumonia, one methotrexate-related pneumonia, and one systemic cryptococcosis). Nine patients died when their disease was in a remission phase: 4 of cardiovascular disease, one pneumonia, one peritonitis due to biliary tract perforation, one sudden death, and 2 of unknown causes.

There was a nonsignificant trend showing that the type of vasculitis influenced survival (p = 0.086); this was due to the borderline statistically significant difference between MPA and CSS patients (HR 0.14, 95% CI 0.02–1.22, p = 0.076; Figure 2).

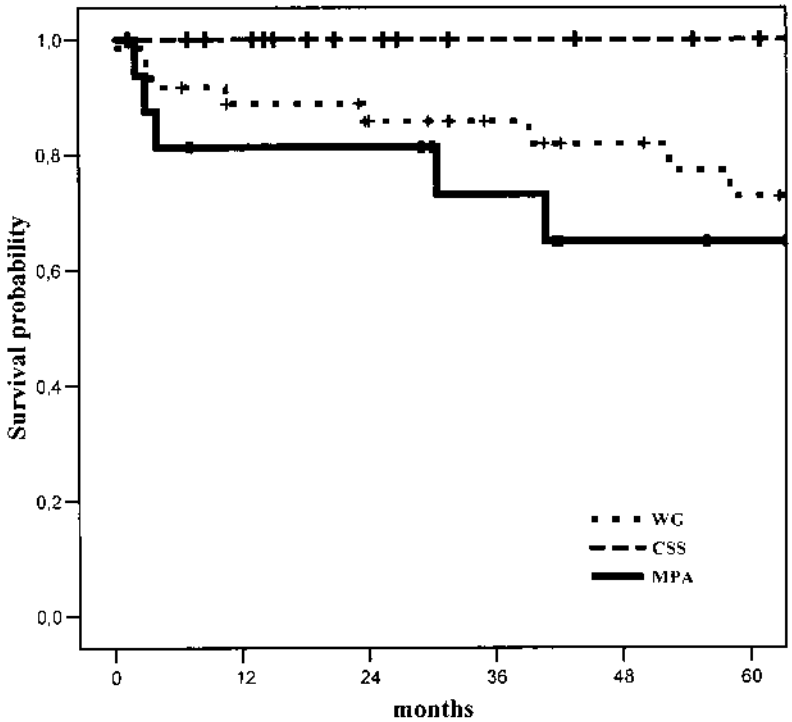
We analyzed mortality since diagnosis using time to the first remission as a time-dependent covariate. After adjustment for type of vasculitis and age, being in remission tended to be associated with reduced risk of death, although this was not statistically significant (HR 0.64, 95% CI 0.17–2.44, p = 0.51).

In the population as a whole, older age was associated with an increased risk of death (HR 4.05, 95% CI 1.29–12.73, p = 0.017), as was renal (HR 5.16, 95% CI 1.16–22.95, p = 0.031) and hepatic involvement (HR 4.29, 95% CI 1.44–12.84, p = 0.009), ESR ≥ 100 mm/h (HR 4.12, 95% CI 1.28–13.28, p = 0.018), and serum creatinine levels ≥ 1.5 mg/dl (HR 6.02, 95% CI 1.70–21.27, p = 0.005). It is notable that the patients with ENT symptoms tended to survive longer than those without (HR 0.39, 95% CI 0.14–1.11, p = 0.078), while patients with cerebral involvement (HR 4.49, 95% CI 0.97–20.82, p = 0.055) or with CRP levels ≥ 100 mg/l (HR 3.52, 95% CI 0.99–12. 54, p = 0.052) had a shorter (but statistically nonsignificant) survival time (Table 4).

Results were not substantially different after adjusting for the type of vasculitis (Table 4).

There was no statistical difference in the prognostic significance of any patient characteristic that depended on the type of vasculitis.

Multiple regression analysis selected 3 predictors of unfavorable outcome: cerebral involvement (HR 8.52, 95% CI 1.47–49.25, p = 0.021), hepatic involvement (HR 4.40, 95% CI 1.17–16.52, p = 0.028), and serum creatinine level ≥ 1.5 mg/dl (HR 5.72, 95% CI 1.05–31.12, p = 0.044).



N° of patients						
WG	36	30	26	22	19	16
CSS	23	19	14	11	10	9
MPA	16	12	12	9	6	5

Figure 2. Probability of patient survival according to type of vasculitis.

Table 4. Association between clinical and laboratory characteristics and risk of death. The analyses refer to 75 patients; however, only 67 were evaluable for diagnosis to remission, 52 for ESR, 43 for CRP, 70 for ANCA, and 35 for nasal swab culture.

	Total	Crude HR	95% CI	Adjusted HR	95% CI
Males	37 (49)	0.56	0.20–1.53	0.55	0.19–1.60
Age ≥ 57 yrs	34 (45)	4.05	1.29–12.73	4.05	1.29–12.73
Onset to diagnosis ≥ 5 mo	36 (48)	2.10	0.71–6.15	2.10	0.71–6.15
Diagnosis to remission ≥ 3 mo	34 (51)	2.47	0.75–8.12	2.47	0.75–8.12
Pulmonary infiltrates/nodules	42 (56)	1.47	0.50–4.31	1.16	0.39–3.45
Pulmonary hemorrhage	10 (13)	2.63	0.84–8.27	1.94	0.47–7.95
Ear-nose-throat involvement	51 (68)	0.39	0.14–1.11	0.39	0.14–1.11
Renal involvement	39 (52)	5.16	1.16–22.95	5.16	1.16–22.95
Endstage renal disease	13 (17)	1.91	0.67–5.38	1.28	0.43–3.84
Peripheral neuropathy	20 (27)	0.99	0.28–3.53	1.46	0.40–5.41
Cerebral involvement	4 (5)	4.49	0.97–20.82	4.49	0.97–20.82
Skin involvement	16 (21)	1.08	0.34–3.41	1.48	0.46–4.79
Gastrointestinal involvement	11 (15)	0.57	0.07–4.40	1.12	0.13–9.30
Liver involvement	9 (12)	4.30	1.44–12.84	4.30	1.44–12.84
Cardiovascular involvement	5 (7)	0.96	0.13–7.29	0.97	0.12–7.71
ESR ≥ 100 mm/1st h	14 (27)	4.12	1.28–13.28	4.12	1.28–13.28
CRP ≥ 100 mg/l	12 (28)	3.52	0.99–12.54	3.52	0.99–12.54
Serum creatinine ≥ 1.5 mg/dl	31 (41)	6.02	1.70–21.27	6.02	1.70–21.27
ANCA-negative	16 (23)	3.75	0.49–28.72	1.02	0.86–1.20
cANCA	29 (41)	1.55	0.52–4.53	1.07	0.92–1.25
pANCA	25 (36)	1.27	0.41–3.88	1.01	0.85–1.20
Positive nasal swab culture	16 (40)	0.35	0.04–3.41	1.06	0.94–1.20

First column shows number (%) of patients with the characteristic; second column shows crude hazard ratio (HR) and 95% confidence interval, computed by Cox regression analysis; third column shows the same analysis after adjustment for type of vasculitis. Onset to diagnosis: time from onset of disease to diagnosis; diagnosis to remission: time from diagnosis to first remission. Hazard ratio differed significantly ($p < 0.05$) depending on the type of vasculitis (interaction test).

DISCUSSION

The 5-year risk of relapse in this cohort of 75 patients with PSVV was similar to that observed in other series[18,19]; serum pANCA positivity and kidney involvement were associated with lower risk of relapse, as reported in large renal vasculitis series[20,21], whereas GI tract involvement was related to higher risk of relapse.

Our patients with MPA, in whom the frequencies of pANCA and renal disease were very high (93% and 88%, respectively), had the lowest risk of relapse (19%) 2 years after first remission; the highest 2-year risk of relapse (35%) was observed in the patients with CSS, and this increased in the presence of nasal *S. aureus* infection (up to 50%) or GI tract involvement (up to 75%). Of the 36 patients with WG, those with nasal *S. aureus* infection showed prolonged disease remission. The different effect of this parameter on the clinical course of WG and CSS may have emerged because all our WG patients with positive nasal swab cultures for *S. aureus* were treated with cotrimoxazole, as it has been reported that daily treatment with cotrimoxazole for 24 months reduces the incidence of WG relapse[22]. If confirmed in a larger series of patients with CSS, this could justify eradication of the bacterium as prophylaxis for relapse in this form of vasculitis also.

In our series of patients with PSVV, the immunosuppression related to endstage renal disease[23] did not reduce the risk of relapse (Table 3), as observed in the case of systemic lupus erythematosus[24]. Thus, relapses in dialyzed patients should not be considered uncommon, and such patients should undergo longterm immunosuppressive therapy and close clinical/immunological followup[25].

We acknowledge that the analysis of relapse since remission might be biased due to the unavoidable exclusion of patients who either did not achieve remission or died before remission.

An older age at diagnosis and severe systemic inflammation (ESR ≥ 100 mm/h) were unfavorable prognostic factors for survival during the course of PSVV, and similar results have been reported in patients with WG[6].

Of the main clinical features, kidney disease (particularly serum creatinine levels ≥ 1.5 mg/dl) and cerebral and liver involvement were the most relevant predictors of death in our study population as a whole. However, although the unfavorable prognostic value of renal and cerebral involvement has been reported by others[4,5], one study found that increased transaminase concentration was a good prognostic factor for survival in a series of patients with systemic necrotizing vasculitides; these conflicting data are probably due to the good prognosis of the patients with hepatitis B virus-related PAN enrolled in this series[5].

Due to the retrospective design of our study, we preferred not to evaluate the BVAS as a prognostic factor for relapse or death, but other investigators have shown that death rates reflect disease severity as assessed by the Five Factor Score and BVAS[26].

The older age at diagnosis of our MPA patients, together with the high frequency of severe renal involvement, explains the trend toward a higher 5-year risk of death in comparison with the other 2 forms of vasculitides.

As described in other series[27,28], symptoms of WG in our patients started mainly during the autumn and winter, probably because of the more frequent upper airway infections that can trigger its immunopathological course. The onset of MPA in our series occurred mainly during the spring and summer; no other data are reported in the literature, except for epidemiological evidence of a considerably lower prevalence of MPA in cold countries such as Norway (2.4/million inhabitants) than in hot countries such as Spain (11.4/million)[29]. However, if confirmed in larger series, this trend may indicate that the 2 diseases have a different etiopathogenesis.

In conclusion, the main predictor of relapse in our series was GI involvement (particularly in the case of CSS patients), whereas nasal *S. aureus* seemed to have an opposite prognostic significance in patients with CSS and WG. The main predictors of death were cerebral and hepatic involvement, and serum creatinine concentrations; our data do not show that these clinical characteristics may have different prognostic relevance for survival in each form of PSVV.

The most adequate treatment schedule should therefore be chosen on the basis of the presence of the main clinical and laboratory indicators with prognostic significance, regardless of the type of PSVV; the difficulty of classifying the disease according to the Chapel Hill Consensus Conference nomenclature and/or ACR criteria should therefore not delay the start of immunosuppressive therapy. Nonetheless, we recognize that the limited sample size in our study did not allow firm conclusions; therefore these findings need to be confirmed in larger series.

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