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ANCA-associated glomerulonephritis : insights into etiology, pathogenesis, and prognosis

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Prediction is very difficult, especially about the future.
Niels Bohr





Chapter 4

Histological and clinical determinants of long term outcome in ANCA-associated renal vasculitis

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Abstract

The objective of this study was to investigate which histological and clinical variables predicted outcome of patients with ANCA-associated glomerulonephritis at long term follow up (5 years). From two prospective, multi-center European trials, 175 patients with mild to severe ANCA-associated glomerulonephritis (serum creatinine > 200 $\mu\text{mol/L}$) were prospectively analyzed. Diagnostic renal biopsies were performed. 39 histological and 12 clinical variables at diagnosis were candidate predictors of long term outcome. After 5 years, 60% of patients were in recovery, 11% had end-stage renal failure (ESRF), and 29% had died. Recovery at 5 years was predicted by GFR ($r = 0.31$, $p = 0.002$) and the percentage of fibrous crescents at diagnosis ($r = -0.16$, $p = 0.04$). The percentage of normal glomeruli ($r = -0.24$, $p = 0.002$) and fibrous crescents ($r = 0.22$, $p = 0.004$), and the presence of tubular necrosis ($r = 0.26$, $p = 0.001$) predicted for a higher risk of ESRF at 5 years. There was a strong relationship between dialysis dependency at 1 year and having ESRF ($r = 0.41$; $p < 0.001$) at 5 years.

In patients with newly diagnosed mild to severe ANCA-associated glomerulonephritis, renal function at diagnosis, the percentage of normal glomeruli and fibrous crescents, and tubular necrosis are predictive of renal outcome at 5 years. The clinical status at 1 year is highly predictive of clinical status at 5 years.

Introduction

In anti-neutrophil cytoplasm autoantibody (ANCA)-associated vasculitides, such as microscopic polyangiitis (MPA), Wegener's granulomatosis (WG), and renal limited vasculitis (RLV), involvement of the kidney is a common and clinically unfavourable feature ¹. The histological pattern of these diseases is that of a pauci-immune crescentic glomerulonephritis ², with two important histological hallmarks: extracapillary proliferation and fibrinoid necrosis ³. The degree of histological damage in the renal biopsy can vary widely, but whether this is also important for long term outcome is relatively unknown. Several studies searching for clinical and histologic predictors of renal outcome have provided contradictory results ⁴⁻¹². Recently, light has been shed on which clinical and histological parameters are important in short term outcome ^{13,14}, but it was unclear until now which parameters are important for long term outcome. This is an important issue with respect to the evaluation of the effect of immunosuppressive therapeutic regimens, and to the selection of patients on their likelihood of favourable and unfavourable outcomes. Finally, identification of determinants of outcome may render insight into the pathogenesis of the disease process, especially with regard to which renal lesions are likely to recover with therapy and which are likely to progress.

In the present study, initiated by the European Vasculitis Study (EUVAS) group, we investigated which diagnostic clinical and histological parameters are important in long term outcome in patients with ANCA-associated vasculitis with primary renal involvement.

Materials and Methods

Patients

Patients with ANCA-associated vasculitis who were analyzed in this study were newly diagnosed and had either mild to moderate, or severe renal involvement (serum creatinine > 200 µmol/L) at diagnosis. Patients were derived from two trials of the EUVAS: the MEPEX trial, a randomized trial evaluating adjunctive therapy of intravenous methyl prednisolone and plasma exchange for severe glomerulonephritis in ANCA-associated systemic vasculitis ¹⁵, and the CYCAZAREM trial, a randomized trial of cyclophosphamide versus azathioprine during remission of generalized ANCA-positive systemic vasculitis without renal failure ¹⁶. Inclusion criteria for both trials are described elsewhere, but were, in short: newly diagnosed clinical WG, MPA, or RLV,

preferably with histological confirmation (mandatory in MEPEX), with ANCA-positivity and/or evidence of renal involvement. Exclusion criteria of this study are described extensively elsewhere ¹⁵⁻¹⁸. All patients followed standard treatment regimens.

In MEPEX, for adjunctive therapy, patients were randomized to either receive intravenous methyl prednisolone or undergo plasma exchanges. Standard therapy consisted of oral corticosteroids, which started at 1.0 mg/kg daily and was tapered down within the first six months, and cyclophosphamide 2.5 mg/kg daily, which at three months was replaced by the less toxic azathioprine. Those patients that were randomized to receive intravenous methyl prednisolone, were administered three times 1,000 mg daily for three consecutive days, starting directly after diagnosis. The patients in the plasma exchange limb, received seven plasma exchanges of 60 mL/kg during the first 14 days after diagnosis. The treatment protocol continued until 12 months after diagnosis.

In CYCAZAREM, patients in both treatment limbs received oral cyclophosphamide (2 mg/kg/day) and prednisolone (initially 1 mg/kg/day, with the dose tapered to 0.25 mg/kg/day by 12 weeks) ¹⁸. The dose of cyclophosphamide was reduced by 25 mg for patients older than 60 years of age, and cyclophosphamide therapy was discontinued if the patient had a white-cell count of less than 4000 per cubic millimeter. After randomization, patients received either continued cyclophosphamide therapy (1.5 mg/kg/day) or azathioprine (2 mg/kg/day), with the same dose of prednisolone (10 mg/day). From 12 months on, both groups received azathioprine (1.5 mg/kg/day) and prednisolone (7.5 mg/day). In this trial, the therapeutic regimen ended 18 months after diagnosis. After the treatment protocol ended, patients were treated according to their local physician's standards.

The local ethics committees approved the studies, and all patients gave written informed consent for participation. Patients were only included in this analysis if both histological data, obtained from renal biopsy at the time of study entry, and clinical data were available.

Disease definitions were adopted from the 1992 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis ¹⁹ and a previous European Union Study ²⁰. The diseases were distinguished based on criteria previously published ¹⁵ and determinations were made by local physicians.

Clinical and histological parameters

Candidate parameters for clinical predictors of renal outcome in this study were renal function at entry (GFR_0), dialysis status at entry, age, gender, quantitatively assessed proteinuria at entry, diagnosis (WG, MPA, or RLV), ANCA-antigen specificity (PR3-ANCA or MPO-ANCA), and treatment limb of the patients from MEPEX (intravenous methyl prednisolone or plasma exchange) and CYCAZAREM (cyclophosphamide or azathioprine). Candidate parameters for histological predictors were determined from paraffin sections of renal biopsies stained with silver, periodic acid-Schiff, haematoxylin and eosin, and trichrome. Sections were reviewed by two of five participating pathologists (IMB, FF, LHN, RW, or JAB). Both pathologists, blinded to patient data and the other observer's results, scored the biopsies separately and according to a previously standardized protocol^{21,22}. Briefly, each glomerulus had to be scored separately for the presence of fibrinoid necrosis, crescents (cellular/fibrous and segmental/circumferential), sclerosis (local, segmental, or global), periglomerular infiltrates, granulomatous reactions, and other lesions. The number of glomerular lesions was reported as the percentage of glomeruli in a biopsy. Most interstitial, tubular, and vascular lesions were scored dichotomously, except for interstitial infiltrates, type of cellular infiltrates (neutrophils, mononuclear cells, and eosinophils), interstitial fibrosis, and tubular atrophy, which were scored semi-quantitatively. Granulomas were scored quantitatively. In total, thirty-nine histologic parameters were examined. Discrepancies between observers were resolved by conference during central reviews to achieve a consensus for each biopsy.

Clinical Outcomes

The primary clinical outcome parameters were recovery at 5 years, defined as dialysis-independent survival, end-stage renal failure (ESRF) at 5 years – including those who received a renal transplant-, and death at 5 years. The secondary outcome parameter was GFR at 5 years (GFR_5) within the group of patients that were in recovery by that time. An analysis was performed to determine which parameters independent of GFR_0 correlated with GFR at 5 years (the so-called corrected GFR_5 or $CORGFR_5$), which could be regarded as renal function recovery. Renal function was defined as the glomerular filtration rate, which was determined using the equation developed by Cockcroft and Gault²³.

Statistical Analyses

The software used for statistical analyses was the SPSS 14.0 standard version for Windows (SPSS Inc., Chicago, IL, USA). Correlation of the quantitative candidate predictors with recovery, ESRF, and being alive was determined by using Pearson correlation test. Phi-values were used to correlate dichotomous and Cramér's V values were used to correlate categorical candidate predictors with the outcome parameters of recovery, ESRF, and being alive. Correlations of quantitative and dichotomous candidate predictors with GFR_5 and $CORGFR_5$ were determined by using Pearson correlation test. Spearman's rank correlation test was used to correlate categorical variables with GFR_5 and $CORGFR_5$. A model for the estimation of GFR_5 and $CORGFR_5$ was designed using a stepwise backward linear multiple regression analysis. An estimation model based on a binary logistic regression analysis was constructed for recovery, ESRF, and being alive at 5 years. Each parameter that correlated with a P value of 0.10 or less was entered into the model as possible predictor of renal outcome. Both univariate and multivariate analyses were also performed for each trial alone (data not shown). The values of exponent β were used for the expression of odds ratios. Correlation coefficients were noted as r and predictive values as r^2 .

Results

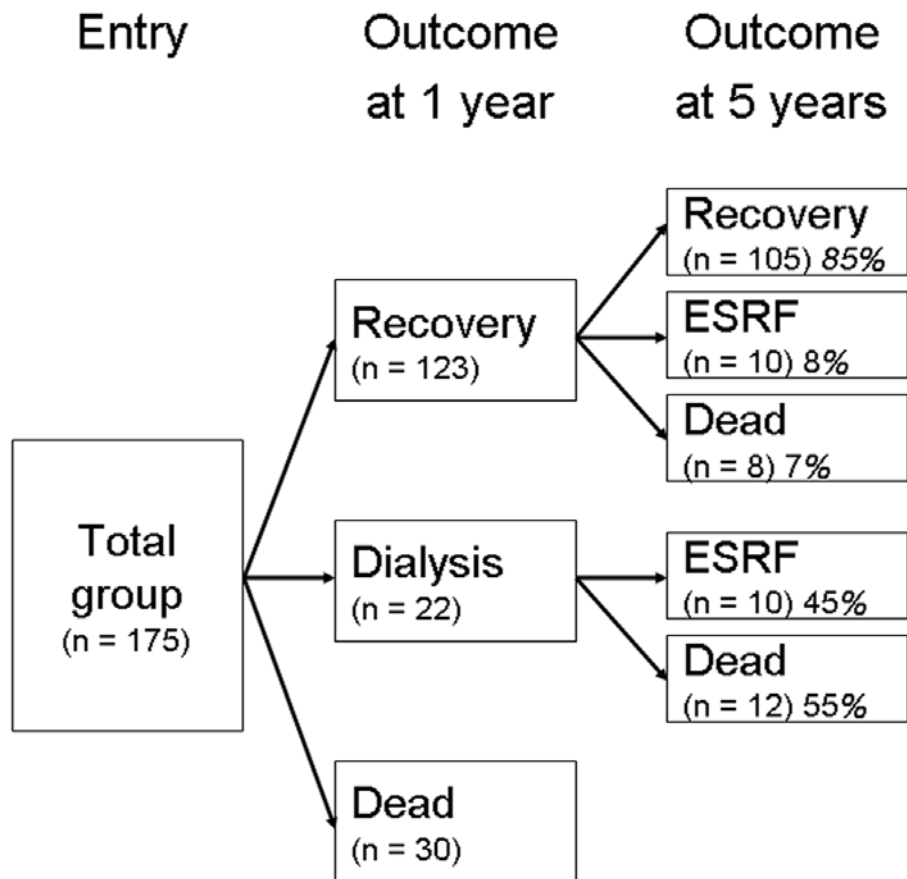
Patients

Of 203 out of the 303 patients who entered the trials, renal biopsies were obtained for re-evaluation. Fifteen patients were lost to follow-up. Biopsies from seven other patients were excluded because of the absence of cortical tissue. During follow-up, six patients were withdrawn (own wish, ischaemic cerebrovascular accident, therapy intolerance, hepatitis B, diabetes mellitus, and dialysis dependency in the first trial week). For final analysis, data were available of 175 patients. Clinical characteristics of the patients are depicted in Table 1. An overview of the patients' clinical courses is shown in Figure 1.

Histological Features

Analysis of the occurrence of the main histologic lesions yielded a low frequency of unaffected glomeruli (28%), while almost half of the glomeruli contained crescentic lesions, and 23% glomerulosclerosis. Accordingly, there was an abundance of acute and chronic damage in the tubulointerstitium. We refer to Table 1 for a detailed overview of the frequencies of the glomerular and tubulo-interstitial lesions.

Figure 1. Flow chart of the clinical courses of all patients in this analysis. Numbers and percentages are listed. Percentages at 5 years reflect the fraction of patients with outcome at 1 year as reference. ESRF = end-stage renal failure.



Predictors of Outcome

Correlation coefficients and P values of the variables in relation to the outcome parameters are presented in Table 2. A poor correlation was obtained for the histological parameters that were excluded from these tables. Models for the estimation of outcome parameters were designed using binary logistic and stepwise linear multiple regression analyses. These models showed that a combination of parameters predicted the outcome parameter best. When the number of variables is high (48 in this study) and the number of cases relatively low (175 in this study) inclusion of all variables in the regression analysis is not statistically relevant. The number of variables should be limited to a fraction

Table 1. Baseline characteristics

No. of patients	175
Age (yr) [mean $\pm$ SD]	60 $\pm$ 13
Gender (male/female/NR)	90 / 81 / 4
Diagnosis (WG/MPA/RLV)	84 / 76 / 15
ANCA antigen (PR3/MPO/double negative/NR)	81 / 56 / 17 / 21
GFR ₀ (mL/min)* [mean $\pm$ SD]	35 $\pm$ 28
Normal glomeruli (%)	28 $\pm$ 29
Fibrinoid necrosis (%)	22 $\pm$ 24
Total crescents (%)	47 $\pm$ 30
Segmental crescents (%)	18 $\pm$ 18
Circumferential crescents (%)	30 $\pm$ 27
Cellular crescents (%)	42 $\pm$ 30
Fibrous crescents (%)	5 $\pm$ 9
Glomerulosclerosis (%)	23 $\pm$ 26
Interstitial infiltrates (-/+ /++ /+++ /NR)	11 / 68 / 69 / 25 / 2
Interstitial fibrosis (-/+ /++)	26 / 83 / 86
Tubular necrosis (-/+)	59 / 116
Tubular atrophy (-/+ /++)	22 / 98 / 55
Intra-epithelial infiltrates (-/+)	55 / 120
Arteriosclerosis (-/+ /NR)**	48 / 105 / 22

* Of patients who were dialysis-independent at entry. ** In the biopsies of seven patients no arteries were detected. NR stands for not recorded. The fraction of glomerular lesions and normal glomeruli is expressed as % of total number of glomeruli.

of the number of cases to prevent “over fitting”. Therefore, the number of variables taken into account was limited to only those that exhibited reasonable correlations with the outcome parameter and with $P < 0.10$. The formulas for the predictive variables with the odds ratios are reported in Table 3.

Recovery at 5 years

Variables were analyzed that differentiated between recovery at 5 years and non-recovery: ESRF or death. Variables that showed a relationship to recovery are depicted in Table 2. The combination of a higher GFR₀ and a lower percentage of fibrous crescents predicted best for recovery at 5 years ($r^2 = 0.305$). The most striking finding when analyzing each of the two trials alone (data not shown), was that in patients with severe renal involvement, a higher percentage of arteriosclerosis and the presence of large-vessel sclerosis predicted a higher chance of recovery ($r^2 = 0.376$).

Table 2. Correlation of clinical and histological parameters with with recovery, ESRF, being alive at 5 years, and GFR at 5 years (GFR5) of those patients that were in recovery. All patients are included (n=175)

Clinical variables	Recovery (a)		ESRF (b)		Alive (c)		GFR5 of patients not on dialysis	
	r	p	r	p	r	p	r	p
GFR0 of patients not on dialysis	0.305	0.002*	-0.179	0.073	0.223	0.025	0.564	<0.001*
Gender (d)	0.077	0.315	-0.037	0.626	0.057	0.454	-0.085	0.414
Age	-0.266	<0.001*	-0.100	0.189	-0.358	<0.001*	-0.556	<0.001*
Microscopic polyangiitis (+/+)	-0.249	0.001*	0.120	0.112	-0.186	0.014*	-0.273	0.007*
Renal limited vasculitis (+/+)	-0.042	0.581	0.082	0.275	0.013	0.864	-0.066	0.521
Wegener's granulomatosis (+/+)	0.271	<0.001*	-0.165	0.029*	0.177	0.019*	0.295	0.003*
PR3-ANCA (+/+)	0.242	0.003*	-0.083	0.304	0.209	0.010*	0.110	0.287
MPO-ANCA (+/+)	-0.282	<0.001*	0.070	0.383	-0.260	0.001*	-0.064	0.540
Dialysis at entry (e)	-0.431	<0.001*	0.152	0.045*	-0.360	<0.001*	-0.294	0.003*
Glomerular lesions								
No abnormalities	0.348	<0.001*	-0.239	0.002*	0.209	0.006*	0.356	<0.001*
Fibrinoid necrosis	-0.097	0.201	0.023	0.763	-0.089	0.241	0.212	0.038*
Crescents	-0.192	0.011*	0.184	0.015*	-0.078	0.307	0.887	<0.001*
Circumferential crescents	-0.287	<0.001*	0.162	0.033*	-0.197	0.009*	-0.140	0.175
Segmental crescents	0.118	0.122	0.061	0.427	0.170	0.025*	0.155	0.133
Cellular crescents	-0.144	0.057	0.119	0.116	-0.072	0.343	0.038	0.714
Fibrous crescents	-0.157	0.038*	0.215	0.004*	-0.019	0.805	-0.199	0.051
Glomerulosclerosis	-0.204	0.007*	0.071	0.349	-0.170	0.025*	-0.438	<0.001*
Interstitial lesions								
Interstitial edema	-0.168	0.084	0.059	0.736	0.166	0.089	0.034	0.742
Interstitial infiltrates	-0.308	0.012*	0.143	0.739	0.314	0.009*	0.356	<0.001*
Neutrophilic infiltrate	0.157	0.430	0.144	0.519	0.205	0.160	0.017	0.876
Mononuclear cell infiltrate	0.173	0.230	0.062	0.963	0.202	0.169	-0.042	0.705
Eosinophilic infiltrate	0.073	0.842	0.194	0.119	0.179	0.175	-0.033	0.766
Interstitial fibrosis	-0.291	0.005*	0.126	0.599	0.242	0.036*	-0.442	<0.001*
Tubular lesions								
Tubular casts	-0.099	0.193	0.028	0.712	-0.087	0.249	-0.187	0.066
Tubular necrosis	-0.237	0.002*	0.256	0.001*	-0.076	0.312	-0.182	0.074
Tubular atrophy	-0.290	0.005*	0.095	0.812	-0.260	0.019*	-0.303	0.003*
Intra-epithelial infiltrates	-0.240	0.006*	0.287	0.001*	0.114	0.319	-0.204	0.045*
Vascular lesions								
Small-vessel vasculitis	-0.066	0.384	-0.005	0.950	-0.075	0.323	-0.064	0.541
Arteriosclerosis	-0.145	0.073	-0.002	0.983	-0.158	0.050	-0.094	0.402
Arteriolosclerosis	-0.191	0.012*	-0.036	0.640	-0.232	0.002*	0.005	0.961
Arteriothrombosis	-0.139	0.068	0.153	0.044*	-0.042	0.579	-0.103	0.322
Large-vessel vasculitis	-0.070	0.516	-0.080	0.458	-0.140	0.195	-0.184	0.179
Large-vessel sclerosis	-0.247	0.022*	0.025	0.814	-0.259	0.016*	-0.012	0.933

* correlation with a *P* value < 0.05

(a) non-recovery was coded '0' and recovery '1'

(b) no end-stage renal failure (ESRF) was coded '0' and ESRF '1'

(c) being dead at 5 years was coded '0' and being alive was coded '1'

(d) male was coded '0' and female '1' in this analysis

(e) dialysis-independency was coded '0' and dialysis-dependency '1' in this analysis

Table 3. Formulas for estimated outcomes

Formulas	Label of values	Exp β	r^2	Chance
Probability recovery at 5 yrs: $y = -0.164 + 0.07 \times \text{GFR}_0 - 0.09 \times \text{fibrous crescents}$	GFR ₀ : mL/min fibrous crescents: %	1.07 0.92	0.305	$p = \text{Exp}(y) / (1 + \text{Exp}(y))$
Probability ESRF at 5 yrs: $y = -20.9 + 0.07 \times \text{fibrous crescents} - 0.05 \times \text{normal glomeruli} + 19.6 \times \text{tubular necrosis}$	fibrous crescents: % normal glomeruli: % tubular necrosis: 0/1	1.07 0.95 ∞	0.334	$p = \text{Exp}(y) / (1 + \text{Exp}(y))$
Probability being alive at 5 yrs: $y = 21.4 - 0.01 \times \text{age} - 3.7 \times \text{MPO-ANCA} - 0.10 \times \text{circumferential crescents} - 0.07 \times \text{glomerulosclerosis} - 4.3 \times \text{tubular atrophy} - 2.8 \times \text{arteriolosclerosis}$	age: years MPO-ANCA: 0/1 circumferential crescents: % glomerulosclerosis: % tubular atrophy: 0/1/2 arteriolosclerosis: 0/1	0.91 0.02 0.91 0.94 0.01 0.06	0.494	$p = \text{Exp}(y) / (1 + \text{Exp}(y))$
Estimated GFR ₅ (mL/min) = $60.1 + 0.45 \times \text{GFR}_0 - 0.36 \times \text{age} + 0.37 \times \text{fibrinoid necrosis} - 0.26 \times \text{glomerulosclerosis}$	age: years fibrinoid necrosis: % glomerulosclerosis: %		0.574	

Odds ratios (OR) are expressed as exponent Beta (exp β). Values in the formulas are β s. Predictive values of the models are expressed as r^2 . * Estimated GFR₀ only goes for patient not on dialysis. Recovery, ESRF, and being alive are coded as no (0) or yes (1). GFR₀ and GFR₅ are expressed as mL/min. ESRF = end-stage renal failure.

End-stage renal failure at 5 years

There was an increased chance of having end-stage renal failure in patients with a lower percentage of normal glomeruli, a higher percentage of fibrous crescents, and the presence of tubular necrosis ($r^2 = 0.334$).

Being alive at 5 years

Younger age, the absence of MPO-ANCA, a lower percentage of circumferential crescents and glomerulosclerosis, less tubular atrophy, and the absence of arteriolosclerosis were predictive of being alive at 5 years ($r^2 = 0.494$).

GFR₅

The combination of younger age, more fibrinoid necrosis, less glomerulosclerosis, and a higher GFR₀ was reasonably well predictive of GFR₅ ($r^2 = 0.574$) as shown in Table 3. Younger age, a lower percentage of total crescents and glomerulosclerosis, and a higher percentage of cellular crescents predicted for a GFR₀ independent GFR₅ (CORGFR₅; $r^2 = 0.320$).

“Clinical courses”

The status of a patient at 5 years was highly defined by the clinical status at 1 year. There was a strong relationship between dialysis dependency at 1 year and having ESRF ($r = 0.41$; $p < 0.001$) at 5 years. The clinical courses of the patients after 1 and 5 years are visualized in Figure 1.

Discussion

In this study, we prospectively investigated which clinical and histological parameters are important in long term outcome in patients with ANCA-associated vasculitis with primary renal involvement. In particular, we investigated whether the renal histology findings at diagnosis had implications for long term follow-up. To study this question in detail, 175 patients with mild to severe renal involvement at diagnosis were analyzed.

In this cohort, patients were more likely to be in recovery at 5 years if they had a higher GFR and a lower percentage of fibrous crescents at diagnosis. In those patients who had recovered at 5 years, a higher GFR₅ was predicted by a higher GFR at diagnosis, a higher percentage of glomeruli with fibrinoid necrosis, a lower percentage of glomerulosclerosis, and younger age. Patients were more likely to have ESRF at 5 years if the percentage of fibrous crescents was higher, the percentage of normal glomeruli was lower, and tubular necrosis was present. Predictors of death at 5 years were: older age, the presence of MPO-ANCA, a higher percentage of circumferential crescents and glomerulosclerosis, more tubular atrophy, and the presence of arteriolosclerosis. In summary, acute glomerular injury (fibrinoid necrosis) was related to good outcome. Chronic glomerular injury (fibrous crescents and glomerulosclerosis) was related to adverse outcome. Acute and chronic tubular lesions (tubular necrosis and tubular atrophy) were both related to adverse renal and patient outcome.

Studies on transplant biopsies have shown that tubular necrosis is important in the follow up of renal transplants, showing a positive correlation between tubular necrosis and delayed, or no graft function²⁴. Tubular necrosis has also been related to a shorter graft survival²⁵. The importance of acute tubular necrosis in the prognosis of renal transplants is an enigma: histopathologically, acute tubular necrosis is rapidly restored, as can be seen in protocol biopsies. It does not lead to rapid interstitial damage such as tubular atrophy or interstitial fibrosis. Therefore, it is difficult to understand why it has such a close relationship to unfavourable long term outcome²⁶. Data from the current study demonstrate that acute tubular necrosis is also an important predictor of long term outcome in ANCA-associated glomerulonephritis. Also in this field, the mechanisms responsible for this phenomenon are incompletely understood. Another point of interest is the predictive value of atherosclerosis for survival at 5 years and recovery at 5 years in the group with severe renal involvement, as well as the relation between large-vessel sclerosis and recovery and survival.

A link between ANCA-associated vasculitis and a higher incidence of cardiovascular disease was first reported in 2002²⁷. Although ANCA may not play a major role in premature atherosclerosis²⁸, and a direct link has never been described, there is epidemiological evidence strongly supporting an increased risk of premature atherosclerosis and cardiovascular disease in ANCA-associated vasculitis^{29,30}. Inflammatory mediators and shear stress alterations may trigger or perpetuate atheromatous lesions in vasculitis²⁹. Endothelial dysfunction and arterial stiffness in vasculitis patients may predispose them to atherosclerosis²⁹. We hypothesize that when atherosclerotic lesions are already present at diagnosis, under the influence of ANCA and the vasculitic disease process these lesions will aggravate, making patients with atherosclerosis less likely to recover in the long run.

In an earlier study, we analyzed variables that were predictive of GFR at 1.5 years for patients with mild to moderate renal disease¹³. It was shown that a higher GFR at diagnosis and a higher percentage of fibrinoid necrosis and segmental crescents (both acute glomerular lesions) were predictive of GFR at 1.5 years. Interestingly, our current study shows that fibrinoid necrosis and GFR at diagnosis remained predictive of GFR at 5 years. In another study, analyzing variables predictive of dialysis at 1 year for patients with severe renal disease, it was shown that normal glomeruli and the type of adjunctive treatment were predictive parameters¹⁴. In patients who were dialysis dependent at diagnosis, normal glomeruli were also found to be predictive of recovery at 1 year³¹. In the current study, the percentage of normal glomeruli was also a predictive parameter of ESRF at 5 years. This result shows once again that the percentage of glomeruli unaffected by the disease is important in renal outcome, and that under treatment, this proportion of glomeruli remains unaffected by the disease during a long period of time.

The similarities between predictors of short and long term outcome might be due to the stability in clinical status between 1 and 5 years. In this patient cohort, 123 out of 175 patients were in recovery at 1 year (70%). Of these recovered patients, 85% was still in recovery at 5 years. Additionally, none of the patients on dialysis at 1 year showed recovery at 5 years: about half of these patients had ESRF at 5 years, whereas the other half had died.

All patients in this prospective study were treated according to protocol. The size of the population and the detailed scoring system provided optimal conditions to perform this study. However, one must be cautious when interpreting the results of this study. These observations only apply to patients

that meet the entry criteria, and extrapolation of these results to patients who do not meet the entry criteria should be avoided. Another point of consideration is that the r-values of the univariate analyses could raise some doubt on the clinical applicability of the findings. A possible explanation for the relatively low r-values may be that at long term follow up, also other factors than only those at entry can influence patient outcome. Therefore, it was necessary not only to analyze the data in a univariate manner, but also in a multivariate manner, since the combination of parameters predicts much better for outcome than single parameters alone.

Since this study shows that patient outcome at 5 years is strongly determined by outcome at 1 year, future research should focus in particular on how to optimize the clinical status of the patient at 1 year. It would also be of great interest to analyze patients' status with a follow up of longer than 5 years.

In conclusion, this study identified determinants of outcome in ANCA-associated vasculitis patients with mild to severe renal involvement. Clinical status at 1 year is highly predictive of clinical status at 5 years. Our data suggest that in ANCA-associated glomerulonephritis, renal function at diagnosis, the percentage of normal glomeruli and fibrous crescents, and the presence of tubular necrosis are predictive of renal outcome at 5 years.

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