Clinical and Histologic Determinants of Renal Outcome in ANCA-Associated Vasculitis: A Prospective Analysis of 100 Patients with Severe Renal Involvement

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This study aimed to identify clinical and histologic prognostic indicators of renal outcome in patients with ANCA-associated
vasculitis and severe renal involvement (serum creatinine >500 μmol/L). One hundred patients who were enrolled in an interna-
tional, randomized, clinical trial to compare plasma exchange with intravenous methylprednisolone as an additional initial
therapy were analyzed prospectively. Diagnostic renal biopsies were performed upon entry into the study. Thirty-nine histologic
and nine clinical parameters were determined as candidate predictors of renal outcome. The end points were renal function at the
time of diagnosis (GFR0) and 12 mo after diagnosis (GFR12), dialysis at entry and 12 mo after diagnosis, and death. Multivariate
analyses were performed. Predictive of GFR0 were age (r = -0.40, P = 0.04), arteriosclerosis (r = -0.53, P = 0.01), segmental
crescents (r = 0.35, P = 0.07), and eosinophilic infiltrate (r = -0.41, P = 0.04). Prognostic indicators for GFR12 were age (r = -0.32,
P = 0.01), normal glomeruli (r = 0.24, P = 0.04), tubular atrophy (r = -0.28, P = 0.02), intraepithelial infiltrate (r = -0.26, P = 0.03),
and GFR0 (r = 0.29, P = 0.01). Fibrous crescents (r = 0.22, P = 0.03) were predictive of dialysis at entry. Normal glomeruli (r = -0.30,
P = 0.01) and treatment arm (r = -0.28, P = 0.02) were predictive of dialysis after 12 mo. No parameter predicted death. Both chronic
and acute tubulointerstitial lesions predicted GFR12 in severe ANCA-associated glomerulonephritis, whereas plasma exchange was
a positive predictor of dialysis independence after 12 mo for the entire patient group. Plasma exchange remained a positive predictor
when patients who were dialysis dependent at presentation were analyzed separately (r = -0.36, P = 0.01). Normal glomeruli were
a positive predictor of dialysis independence and improved renal function after 12 mo, indicating that the unaffected part of the
kidney is vital in determining renal outcome.

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Rapidly progressive deterioration of renal function is a
common and usually severe clinical feature of ANCA-
associated vasculitis, which may lead to end-stage re-
nal failure or death (1). Histopathology of renal biopsies shows
pauci-immune crescentic glomerulonephritis (2) with variable
amounts of extracapillary proliferation, fibrinoid necrosis, and
glomerulosclerosis (3). The most frequently occurring forms of
ANCA-associated vasculitis are microscopic polyangiitis and
Wegener’s granulomatosis, whereas renal limited vasculitis oc-
curs less frequently (4). Despite the existence of clear definitions
(5), the diagnosis for individual patients may be difficult. Pa-
tients with ANCA-associated glomerulonephritis are treated
similarly regardless of which form is diagnosed. European
trials are aimed at developing treatment that corresponds to
disease severity (6).

Therapy is associated with severe and potentially lethal ad-
verse effects for a substantial number of patients (7–9); nearly
90% of patients experience persistent morbidity despite ade-
quate treatment (10). Therefore, there is a need for prognostic
markers of renal outcome to help to modify therapy for patients
who have ANCA-associated vasculitis (11). Several studies that
searched for clinical and histologic predictors of renal outcome
provided contradictory results (11–19). Meta-analyses are dif-
cult to conduct because there is substantial heterogeneity with
regard to study designs, inclusion criteria, scoring methods,
treatment strategies, and end points (11–19). We previously
studied patients who had ANCA-associated vasculitis and mild
to moderate renal involvement (serum creatinine <500 μmol/L) and received standardized treatment in an attempt to identify clear clinical and histologic predictors (20). We demonstrated that renal function at diagnosis, in combination with chronic renal lesions identified by histology, is predictive of renal function after 18 mo, and active lesions are associated with renal function recovery. In this study, performed within the framework of the European Vasculitis Study (EUVAS) group (21), we investigated the distribution of acute and chronic lesions in renal biopsies and evaluated clinical and histologic predictors of outcome in patients with severe renal involvement (serum creatinine >500 μmol/L).

Materials and Methods

Patients

Patients were derived from 29 hospitals located in 11 European countries. Patients were enrolled in the Methylprednisolone versus Plasma Exchange (MEPEX) trial, which is a randomized trial to evaluate adjunctive therapy for severe glomerulonephritis in ANCA-associated systemic vasculitis (21). Patients who had a serum creatinine of 500 μmol/L or more were included. The local ethics committees approved the study, and all patients gave written informed consent for participation. Inclusion criteria for MEPEX are listed in Table 1. Exclusion criteria of this study are described extensively elsewhere (21). All patients followed a standard treatment regimen. For adjunctive therapy, they were randomly assigned either to receive intravenous methylprednisolone or to undergo plasma exchange. Standard therapy consisted of oral corticosteroids, which started at 1.0 mg/kg per d and was tapered down within the first 6 mo, and cyclophosphamide 2.5 mg/kg per d, which at 3 mo was replaced by the less toxic azathioprine. Patients who were randomly assigned to receive intravenous methylprednisolone were administered 1000 mg/d for 3 consecutive days, starting directly after diagnosis. The patients in the plasma exchange arm received seven plasma exchanges of 60 ml/kg during the first 14 d after diagnosis. Patients were included in this analysis only when both histologic 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 (5) and a previous European Union study (22). The diseases were distinguished on the basis of criteria that were published previously (21), and determinations were made by local physicians.

ANCA Testing

Indirect immunofluorescence (IIF) and ELISA for ANCA testing were performed locally at all participating centers. The staining pattern in the IIF test was scored as perinuclear (P-ANCA), cytoplasmic (C-ANCA), atypical, or negative. Positive sera for ANCA directed against myeloperoxidase (MPO) or proteinase-3 (PR3) were reported as MPO-ANCA and PR3-ANCA, respectively.

Candidate Predictors of Renal Outcome

Candidate parameters for clinical predictors of renal outcome in this study were renal function at entry (GFR0), dialysis status at entry, age, gender, quantitatively assessed proteinuria at entry, diagnosis (Wege- ner’s granulomatosis, microscopic polyangiitis, or renal limited vasculitis), ANCA-antigen specificity (PR3-ANCA or MPO-ANCA), IIF pattern (C-ANCA or P-ANCA), and treatment arm (intravenous methylprednisolone or plasma exchange). Candidate parameters for histologic predictors were determined from paraffin sections of renal biopsies that were stained with silver, periodic acid-Schiff, hematoxylin and eosin, and trichrome. Sections were reviewed by two of five participating pathologists (I.M.B., F.F., L.H.N., R.W., or J.A.B.). Both pathologists, blinded to patient data and the other observer’s results, scored the biopsies separately and according to a previously standardized protocol (23,24). 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 semiquantitatively. Granulomas were scored quantitatively. In total, 39 histologic parameters were examined. Discrepancies between observers were resolved by conference during central reviews to achieve a consensus for each biopsy.

Clinical Outcome Parameters

Clinical outcome parameters were renal function at diagnosis (GFR0), renal function at 12 mo (GFR12), dialysis dependence at diagnosis, dialysis dependence at 12 mo, relapse, and death. Renal function was defined as the GFR, which was determined using the equation developed by Cockcroft and Gault (25). Renal function at entry has been shown to be a major predictor of renal outcome for a number of renal diseases (11,26,27). Therefore, we also investigated the correlation between clinical and histologic parameters and GFR12 after correction for GFR0. The latter value was expressed as the corrected GFR12 (CORGFR12), defined as the difference between the observed GFR12 and its linear prediction on the basis of GFR0. This correction created a corrected value that was statistically independent of the starting value (28).

Table 1. Inclusion criteria for MEPEX (1, 2, and 3 are required)a

1. New diagnosis of WG or MPA or its renal-limited variant, in accordance with the Chapel Hill consensus criteria (7), with active vasculitis, as indicated by the presence of active necrotizing glomerulonephritis on renal biopsy.
2. ANCA positivity for one of the following:
   a. C-ANCA pattern by IIF
   b. in the PR3 ELISA
   c. in the MPO ELISA, with or without P-ANCA ANCA negative is allowed if the disease is confirmed histologically
3. Biopsy-proven necrotizing and/or crescentic glomerulonephritis, in the absence of another defined glomerulopathy, with severe renal impairment defined by:
   a. oliguria (<400 ml/24 h) or
   b. intention to commence dialysis within 48 h of admission
   c. creatinine >500 μmol/L

aC-ANCA, cytoplasmic ANCA; IIF, indirect immunofluorescence; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA; PR3, proteinase-3; WG, Wegener’s granulomatosis.
Statistical Analyses

The software used for statistical analyses was the SPSS 10.0 standard version for Windows (SPSS, Inc., Chicago, IL). Correlation of the quantitative and dichotomous candidate predictors with GFR₀, GFR₁₂, and CORGFR₁₂ was determined by using Pearson correlation test. The Spearman rank correlation test was used to correlate categorical variables with GFR₀, GFR₁₂, and CORGFR₁₂. Correlations of quantitative candidate predictors with the occurrence of dialysis and death were assessed by the Pearson correlation test. Phi values were used to correlate dichotomous and categorical candidate predictors with the occurrence of dialysis and death at 12 mo. A model for the estimation of GFR₀, GFR₁₂, and CORGFR₁₂ was designed using a stepwise linear multiple regression analysis. An estimation model that was based on a binary logistic regression analysis was used for dialysis dependence and death at 12 mo. Each parameter that correlated with \( P \leq 0.10 \) was entered in the model as a possible predictor of renal outcome. The group was analyzed as a whole, and subgroup analyses were made for patients who were dialysis dependent at entry and those who were not. The values of exponent \( \beta \) were used for the expression of odds ratios. Correlation coefficients were noted as \( r \) and predictive values as \( r^2 \).

Results

Patients

Patients were enrolled in the MEPEX trial between March 25, 1995, and October 29, 2001. Four of the 151 patients who entered the trial declined further participation, nine were found to have circulating anti–glomerular basement membrane antibodies, and one had already received \( >500 \) µg of intravenous methylprednisolone; these patients were excluded. None of the remaining 137 patients was lost to follow-up or withdrawn from the study. Renal biopsies were obtained from 102 patients for reevaluation. Two biopsies were excluded because of the absence of cortical tissue, meaning that 100 biopsies were available for the final analysis. Clinical characteristics of the patients are depicted in Table 2.

The average cumulative dose of cyclophosphamide was 18 g. On average, 4.8 L was exchanged during every plasma exchange; this was performed seven times. A total of 1000 mg of intravenous methylprednisolone was administered intravenously three times to patients who were assigned to this treatment arm.

Focusing on the 69 patients who were on dialysis at entry, 51% received plasma exchange; of these, 54% became dialysis independent, 17% were on dialysis, and 29% were dead at 12 mo. Of the 69 patients who were on dialysis at entry, 49% received intravenous methylprednisolone; of these, 32% became dialysis independent, 47% were on dialysis, and 21% were dead at 12 mo. These data show that patients who were on dialysis at entry were equally distributed over the two additional therapy arms and that in both groups, a similar percentage of patients died. However, patients who received plasma exchange had a better prognosis than those who received intravenous methylprednisolone, in terms of dialysis independence.

An overview of patient courses, from study entry to outcome, is shown in Figure 1. Only three patients experienced a relapse. Correlations with patient relapse were not calculated because they were of low statistical value.

Histologic Features

The occurrence of the main histologic lesions was analyzed to explore the extent found at the entry period in this group of patients with clinical severe renal impairment. The frequencies of the glomerular and tubulointerstitial lesions are presented in Table 3. The majority of the nonsclerotic glomeruli contained crescents; only very few were unaffected, irrespective of the presence of focal or diffuse glomerulosclerosis. In other words, severe and extensive acute lesions were characteristic of the renal biopsies from this patient group, whereas the extent of chronic changes in the form of global glomerulosclerosis was mild to moderate.

Predictors of Outcome

Correlation coefficients of the variables in relation to the outcome parameters are presented in Table 4. A poor correlation was obtained for the histologic parameters that were excluded from Table 4. Models for the estimation of outcome parameters were designed using binary logistic and stepwise linear multiple regression analyses and are reported in Table 5. These models showed that a combination of parameters predicted the outcome parameter best. The univariate correlation of these predictors with the outcome parameters is shown in Figure 1.

Table 2. Clinical characteristics of the whole patient group (n = 100)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr; range)</td>
<td>64.1 (26.8 to 80.7)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>63/37</td>
</tr>
<tr>
<td>Diagnosis (WG/MPA/RLV)</td>
<td>33/57/10</td>
</tr>
<tr>
<td>GFR₀ (ml/min; mean ± SD)</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>GFR₁₂ (ml/min; mean ± SD)</td>
<td>32 ± 13</td>
</tr>
<tr>
<td>Proteinuria (mg/24 h)</td>
<td>30 ± 6</td>
</tr>
<tr>
<td>Adjunctive treatment</td>
<td>49/51</td>
</tr>
</tbody>
</table>

*IVMeP, intravenous methylprednisolone; PE, plasma exchange; RLV, renal-limited vasculitis.

Figure 1. Flow chart of the clinical courses of patients. □, Patients who were on dialysis at entry; □, patients who were dialysis independent at entry. Numbers and percentages are listed. Black dots represent patients who experienced a relapse.
Table 3. Average distribution of most characteristic glomerular and tubulointerstitial lesions

<table>
<thead>
<tr>
<th>Histologic Lesion</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glomeruli</td>
<td>12.8 ± 15.3</td>
</tr>
<tr>
<td>Fibrinoid necrosis</td>
<td>25.5 ± 25.2</td>
</tr>
<tr>
<td>Crescents a</td>
<td>56.0 ± 28.8</td>
</tr>
<tr>
<td>segmental crescents</td>
<td>25.9 ± 27.3</td>
</tr>
<tr>
<td>circumferential crescents</td>
<td>74.1 ± 49.5</td>
</tr>
<tr>
<td>cellular crescents</td>
<td>90.6 ± 26.1</td>
</tr>
<tr>
<td>fibrous crescents</td>
<td>9.4 ± 2.7</td>
</tr>
<tr>
<td>Global sclerosis</td>
<td>26.4 ± 25.7</td>
</tr>
<tr>
<td>Interstitial edema (0/1)</td>
<td>0.5 ± 0.5</td>
</tr>
<tr>
<td>Interstitial infiltrates (0/1/2/3)</td>
<td>1.8 ± 0.7</td>
</tr>
<tr>
<td>neutrophils (0/1/2)</td>
<td>0.7 ± 0.5</td>
</tr>
<tr>
<td>monocytes (0/1/2)</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>eosinophils (0/1/2)</td>
<td>0.4 ± 0.5</td>
</tr>
<tr>
<td>Interstitial fibrosis (0/1/2)</td>
<td>1.2 ± 0.6</td>
</tr>
<tr>
<td>Tubular casts (0/1)</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>Tubular necrosis (0/1)</td>
<td>0.8 ± 0.4</td>
</tr>
<tr>
<td>Tubular atrophy (0/1/2)</td>
<td>1.1 ± 0.6</td>
</tr>
<tr>
<td>Intraepithelial infiltrates (0/1)</td>
<td>0.8 ± 0.4</td>
</tr>
<tr>
<td>Small-vessel vasculitis (0/1)</td>
<td>0.1 ± 0.3</td>
</tr>
<tr>
<td>Arteriosclerosis (0/1)</td>
<td>0.8 ± 0.4</td>
</tr>
<tr>
<td>Arteriolosclerosis (0/1)</td>
<td>0.5 ± 0.5</td>
</tr>
</tbody>
</table>

aGlomerular lesions are expressed as a mean percentage of the total number of glomeruli per patient together with the SD. Numbers after tubulointerstitial lesions indicate the categorical scoring system.

bAll crescents were scored as either segmental or circumferential and as either cellular or fibrous and are expressed as percentage of total number of crescents.

Figures 2 and 4. When the number of variables is high (48 in this study) and the number of cases is relatively low (100 in this study), inclusion of all variables in the regression analysis is not statistically relevant. The number of variables should be lower than one 10th of the number of cases to prevent “over fitting.” Therefore, the number of variables that were 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 5.

Predictors of GFR0 for Patients Not on Dialysis

Patients who were on dialysis at entry (n = 69) were excluded from this analysis because their GFR was not measurable. Arteriosclerosis was the best predictor of GFR0 (r = −0.53, P = 0.01). Other clinical and histologic parameters that showed relationships to GFR0 were gender (r = −0.45, P = 0.02), age (r = −0.40, P = 0.04), tubular casts (r = −0.47, P = 0.01), and eosinophilic infiltrates (r = −0.41, P = 0.04; Table 4). Women had a significantly worse GFR0 than men. Higher patient age, the presence of tubular casts and arteriosclerosis, and a predominant eosinophilic infiltrate correlated with a worse GFR0. It seemed from the regression analysis that arteriosclerosis in combination with age, segmental crescents, and eosinophilic infiltrates was predictive for GFR0 (Table 5). The univariate relationship of these variables with GFR0 is shown in Figure 2, A through D.

Predictors of GFR12 and CORGFR12

Age (r = −0.32, P = 0.01), GFR0 (r = 0.29, P = 0.01), dialysis at entry (r = −0.27, P = 0.02), tubular atrophy (r = −0.28, P = 0.02), normal glomeruli (r = 0.24, P = 0.04), interstitial fibrosis (r = −0.24, P = 0.04), and intraepithelial infiltrate (r = −0.26, P = 0.03) showed a relationship with GFR12 (Table 4). Although the univariate correlation of some predictive variables with GFR12 is weak (Figure 2, E through I), the combination of age, normal glomeruli, tubular atrophy, intraepithelial infiltrate, and GFR0 showed a reasonable correlation with GFR12 (r² = 0.491, r = 0.701) as shown in Figure 3 and Table 5.

An analysis was performed to determine which parameters independent of GFR0 correlated with GFR12 (the so-called CORGFR12), which could be regarded as renal function recovery. The same parameters that were predictive of GFR12, except for dialysis at entry and GFR0 as defined, also were predictive of CORGFR12 (Table 5). The univariate correlation of these variables with CORGFR12 is shown in Figure 2, J through M.

Predictors of Dialysis Dependence at Entry and at 12 Mo

A prognostic indicator of dialysis dependence at entry was the percentage of fibrous crescents (r = 0.22, P = 0.03). There was an increased chance for being dialysis dependent with an increased percentage of fibrous crescents, although the predictive value was moderate (Table 5). The percentage of normal glomeruli (r = −0.30, P = 0.01), dialysis dependence at entry (r = 0.25, P = 0.03), intraepithelial infiltrates (r = 0.31, P = 0.03), and treatment arm (r = −0.28, P = 0.02) showed a relationship with dialysis dependence at 12 mo (Table 5). In the logistic regression analysis, the combination of normal glomeruli and treatment arm was predictive of dialysis at 12 mo. Univariate relationships of these predictors are shown in Figure 4. In clinical terms, the higher the percentage of normal glomeruli, the lower the chance for developing dialysis dependence. Plasma exchange for treatment arm was clinically favorable over intravenous methylprednisolone as adjunctive therapy.

Analyzing the subgroups, only for 69 patients who were dialysis dependent could statistical significance be reached. For this subgroup, the same parameters correlated with dialysis dependence at 12 mo: The percentage of normal glomeruli (r = −0.31, P = 0.03), treatment arm (r = −0.36, P = 0.01), and intraepithelial infiltrates (r = 0.32, P = 0.07). In addition, more glomerulosclerosis (r = 0.27, P = 0.05) and the presence of arteriosclerosis (r = 0.32, P = 0.03) correlated with a higher chance for dialysis dependence at 12 mo.

Predictors of Death

Only two parameters correlated with death: ANCA directed against MPO (r = 0.24, P = 0.04) and the amount of neutrophils in the interstitial infiltrate (r = 0.37, P = 0.01; Table 4). However, there were no parameters that were predictive of death as determined by regression analysis. Twenty-four patients died within the first year of follow-up. Two deaths clearly were
Table 4. Correlation of clinical and histologic parameters with GFR0, GFR12, CORGFR12, dialysis at entry, dialysis at 12 mo, and deatha

<table>
<thead>
<tr>
<th></th>
<th>GFR0 of Patients Not on Dialysis</th>
<th>GFR12</th>
<th>CORGFR12</th>
<th>Dialysis at Entryb</th>
<th>Dialysis at 12 Moa</th>
<th>Deathc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>GFR0 of patients not on</td>
<td>—</td>
<td>—</td>
<td>0.255</td>
<td>0.230</td>
<td>0.048</td>
<td>0.824</td>
</tr>
<tr>
<td>dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR0 of all patients</td>
<td>—</td>
<td>—</td>
<td>0.290</td>
<td>0.013</td>
<td>0.000</td>
<td>1.000</td>
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<tr>
<td>genderd</td>
<td>—0.454</td>
<td>0.015</td>
<td>—0.137</td>
<td>0.248</td>
<td>—0.070</td>
<td>0.526</td>
</tr>
<tr>
<td>age</td>
<td>—0.399</td>
<td>0.035</td>
<td>—0.321</td>
<td>0.006</td>
<td>—0.319</td>
<td>0.006</td>
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<tr>
<td>MPA (—/+)</td>
<td>—0.105</td>
<td>0.595</td>
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<td>0.276</td>
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<td>0.199</td>
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<td>0.808</td>
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<td>0.116</td>
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<td>0.019</td>
<td>—0.002</td>
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<td>0.245</td>
<td>0.125</td>
<td>0.291</td>
<td>0.121</td>
<td>0.309</td>
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<tr>
<td>Glomerular lesions</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no abnormalities</td>
<td>—0.094</td>
<td>0.635</td>
<td>0.239</td>
<td>0.042</td>
<td>0.245</td>
<td>0.038</td>
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<tr>
<td>fibrinoid necrosis</td>
<td>0.126</td>
<td>0.523</td>
<td>0.152</td>
<td>0.199</td>
<td>0.081</td>
<td>0.498</td>
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<td>crescents</td>
<td>—0.069</td>
<td>0.729</td>
<td>0.072</td>
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<td>0.049</td>
<td>0.681</td>
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<td>0.794</td>
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<td>0.187</td>
<td>—0.106</td>
<td>0.376</td>
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<td>0.813</td>
<td>—0.274</td>
<td>0.019</td>
<td>—0.269</td>
<td>0.022</td>
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<tr>
<td>global sclerosis</td>
<td>0.044</td>
<td>0.826</td>
<td>—0.282</td>
<td>0.016</td>
<td>—0.273</td>
<td>0.020</td>
</tr>
<tr>
<td>Interstitial lesions</td>
<td></td>
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</tr>
<tr>
<td>neutrophilic infiltrate</td>
<td>0.114</td>
<td>0.579</td>
<td>—0.037</td>
<td>0.758</td>
<td>—0.010</td>
<td>0.931</td>
</tr>
<tr>
<td>eosinophilic infiltrate</td>
<td>—0.412</td>
<td>0.037</td>
<td>0.169</td>
<td>0.155</td>
<td>0.157</td>
<td>0.190</td>
</tr>
<tr>
<td>interstitial fibrosis</td>
<td>—0.007</td>
<td>0.971</td>
<td>—0.244</td>
<td>0.037</td>
<td>—0.233</td>
<td>0.049</td>
</tr>
<tr>
<td>tubular atrophy</td>
<td>0.035</td>
<td>0.858</td>
<td>—0.279</td>
<td>0.017</td>
<td>—0.311</td>
<td>0.008</td>
</tr>
<tr>
<td>intraepithelial infiltrates</td>
<td>—0.105</td>
<td>0.597</td>
<td>—0.260</td>
<td>0.026</td>
<td>—0.310</td>
<td>0.008</td>
</tr>
<tr>
<td>Vascular lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small-vessel vasculitis</td>
<td>—0.256</td>
<td>0.189</td>
<td>—0.047</td>
<td>0.695</td>
<td>—0.045</td>
<td>0.707</td>
</tr>
<tr>
<td>arterosclerosis</td>
<td>—0.531</td>
<td>0.009</td>
<td>—0.131</td>
<td>0.310</td>
<td>—0.142</td>
<td>0.275</td>
</tr>
</tbody>
</table>

aCORGFR12, corrected GFR at 12 mo; GFR0, renal function at time of diagnosis; GFR12, renal function at 12 mo.
bDialysis independence was coded 0, and dialysis dependence was coded 1.
cBeing alive was coded as 0, and being dead was coded as 1.
dMale was coded as 0, and female was coded as 1.
ePlasma exchange treatment was coded 0, and intravenous methylprednisolone was coded as 1.
fCorrelation with P < 0.05.

disease related. These deaths were due to pulmonary vasculitis and to vasculitic gastrointestinal bleeding with pulmonary capillaryitis and myocardial infarction. Three deaths probably were disease related: These patients died from pulmonary hemorrhage, which was not specified further. Eleven deaths were therapy related. These were due to infections, such as Pneumocystis carinii pneumoniae and cytomegalovirus. One patient died of a cerebral abscess; whether this death was due to therapy or disease is unclear. Furthermore, three patients died of vascular causes, such as myocardial infarction and stroke. Finally, four patients died of unknown causes.

**Discussion**

In this study, clinical and histologic prognostic indicators of outcome for patients with ANCA-associated vasculitis and severe renal involvement (serum creatinine > 500 μmol/L) were determined. This was a prospective study in which patients were treated uniformly, investigating for the first time the subgroup of patients who have ANCA-associated glomerulonephritis and present with acute severe renal dysfunction. It is widely assumed that patients who present with severe renal dysfunction must have an extensive amount of chronic lesions for which treatment would not likely to be successful. This study shows that the majority of patients have extensive acute lesions and that a significant number of patients benefit from treatment, in particular when plasmapheresis is given. The combination of normal glomeruli, acute and chronic tubulointerstitial damage, age, and treatment was predictive of renal outcome at 12 mo. A worse outcome in patients with a low percentage of normal glomeruli, more acute and chronic tubulointerstitial lesions, and intravenous methylprednisolone as adjunctive treatment was observed. A greater extent of acute and chronic glomerular and interstitial lesions predicted a worse renal function and higher chance for dialysis dependence at entry.

Most biopsies at entry showed extensive acute lesions in these patients, who had serum creatinine levels >500 μmol/L, whereas the number of globally sclerosed glomeruli was relatively low. This indicated that the severely disturbed renal function that was observed at entry was not due to a low-level disease that led to extensive chronic damage but rather to an acute onset of disease that was characterized by extensive acute lesions in the form of crescents and fibrinoid necrosis. The acute
lesions did not correlate with GFR₀ or with dialysis at entry. We also found this in a previous study (29), and we think that this phenomenon may be because although, histologically, acute lesions seem to be similar to each other, they are in fact a heterogeneous group of lesions of which some are in a healing process and others are on their way to irreversible damage. This could explain their lack of predictive value for renal function at time of biopsy.

A relationship existed between GFR₀ and age, gender, arteriosclerosis, tubular casts, and interstitial infiltrates (in particular of eosinophilic granulocytes) for patients who were not on dialysis at entry. Three of these variables, age, tubular casts, and interstitial infiltrates, also showed a relationship with GFR₀ in a previous study of patients with mild to moderate renal involvement (serum creatinine < 500 μmol/L) (20). This indicated that these parameters are important for renal impairment in ANCA-associated glomerulonephritis, both at a high and a low range of renal dysfunction. Age and gender were already known to have a high impact on renal function in ANCA-associated renal disease, worse renal function in elderly patients with acute disease and a relative benefit for men was observed (30–32).

Arteriosclerosis was not associated with age and had prognostic value for determining renal outcome in this analysis. This possibly reflects a component of chronic renal vascular disease (11). It is interesting that the severity of tubular casts and interstitial infiltrates reflected the level of renal dysfunction at entry in this patient group, as well as in our previously described patient group with ANCA-associated glomerulonephritis with moderate renal involvement. The amount of tubular casts may reflect the degree of obstruction (33). The interstitial infiltrate, in part consisting of eosinophilic granulocytes, may be indicative of ongoing chronic interstitial fibrosis and could account for the increased intrarenal collagen synthesis as has been shown for lupus nephritis (34) and renal allograft fibrosis (35).

The percentage of fibrous crescents was the only parameter that was predictive of dialysis at entry. It is tempting to hypothesize that patients who are in need of dialysis at the time of diagnosis have had the disease for some time, which is reflected by the fibrous crescents. However, approximately half of the patients who were on dialysis at entry were no longer on dialysis at 12 mo. This suggests that fibrous crescents should not be a contraindication to start therapy. One parameter that predicted dialysis at 12 mo was the treatment arm. The adjunctive treatment of preference was plasma exchange, which had a favorable effect on dialysis independence after 1 yr. Therefore, plasma exchange seems to be the preferred additional form of therapy for patients who have ANCA-associated glomerulonephritis and present with severe renal failure. The trial report on the MEPEX data revealed that the addition of plasma exchange to oral cyclophosphamide led to an increased chance of renal recovery compared with the addition of intravenous methylprednisolone (unpublished data). This beneficial effect was sustained throughout the 12-mo study period. The mortality rate was comparable between the two treatment groups.

Age, the percentage of normal glomeruli, intraepithelial infiltrates, tubular atrophy, and GFR₀ predicted GFR₁₂. Age has been shown to be important for renal outcome before (11,36). We reported on the importance of normal glomeruli for renal recovery in patients with ANCA-associated glomerulonephritis in 1999 (23) and in 2002 (20). Also in several other studies,

### Table 5. Formulas for estimated outcomes<sup>a</sup>

<table>
<thead>
<tr>
<th>Formulas</th>
<th>Label of Values</th>
<th>( r^2 )</th>
<th>Exponent ( \beta )</th>
<th>Chance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated GFR₀&lt;sup&gt;b&lt;/sup&gt; (ml/min) = 23.0 − 4.9 \times arteriosclerosis − 0.15 \times age + 0.13 \times segmental crescents − 3.1 \times eosinophilic infiltrate</td>
<td>Arteriosclerosis: −/+</td>
<td>0.678</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated GFR₁₂ (ml/min) = 79.1 − 0.63 \times age + 0.58 \times normal glomeruli − 14.4 \times tubular atrophy − 14.2 \times intraepithelial infiltrate + 0.95 \times GFR₀</td>
<td>Age: years</td>
<td>0.491</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated CORGFR₁₂ (ml/min) = 62.1 − 0.63 \times age + 0.58 \times normal glomeruli − 14.5 \times tubular atrophy − 14.1 \times intraepithelial infiltrate</td>
<td>See box above</td>
<td>0.443</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated dialysis at entry: ( \beta = 0.081 )</td>
<td>Fibrous crescents: %</td>
<td>0.212</td>
<td>1.09</td>
<td>OR = Exp (( \beta \times \Delta \text{fibrous crescents} )) = (Exp ( \beta ))^\Delta \text{fibrous crescents}</td>
</tr>
<tr>
<td>Probability dialysis at 12 months: ( y = -0.64 - 0.070 \times \text{normal glomeruli} + 1.3 \times \text{arm} )</td>
<td>Normal glomeruli: % Arm: 0 = plasma exchange, 1 = intravenous methylprednisolone</td>
<td>0.309</td>
<td>0.93</td>
<td>p = Exp (y)/[1 + Exp (y)]</td>
</tr>
</tbody>
</table>

<sup>a</sup>Odds ratios (OR) expressed as exponent \( \beta \). Values in formulas are \( \beta \). Predictive values of the models are expressed as \( r^2 \).

<sup>b</sup>Estimated GFR₀ applies only to patients who were not on dialysis.
Figure 2. Correlation figures for predictive variables of renal function and renal function recovery. Predictors of renal function at the time of diagnosis (GFR₀) for only patients who were not on dialysis at entry: Arteriosclerosis (r = -0.531, P = 0.009; A), age (r = -0.399, P = 0.035; B), segmental crescents (r = 0.348, P = 0.069; C), and eosinophilic infiltrate (r = -0.412, P = 0.037; D). Predictors of renal function at 12 mo (GFR₁₂): GFR₀ (r = 0.290, P = 0.013; E), age (r = -0.321, P = 0.006; F), percentage of normal glomeruli (r = 0.239, P = 0.042; G), tubular atrophy (r = -0.279, P = 0.017; H), and intraepithelial infiltrate (r = -0.260, P = 0.026; I). Predictors of corrected GFR₁₂ (CORGFR₁₂): Age (r = -0.319, P = 0.006; J), percentage of normal glomeruli (r = 0.245, P = 0.038; K), tubular atrophy (r = -0.311, P = 0.008; L), and intraepithelial infiltrate (r = -0.310, P = 0.008; M). All correlations are visualized either as scatter plots (continuous variables) or as box plots (categorical or dichotomous variables).
normal glomeruli were shown to predict renal outcome over time (36–40). In follow-up biopsies of patients with ANCA-associated glomerulonephritis, the percentage of normal glomeruli did not change over time (29). Therefore, apart from reflecting the functioning part of the kidney, normal glomeruli also are a relatively constant parameter, the combination of which may explain their strength as a predictive parameter. Also intraepithelial tubular infiltrates are predictive of GFR$_{12}$, and their presence may well be related to the development of tubular atrophy, a widely known parameter of chronic renal failure in general and associated with worse renal outcome in ANCA-associated vasculitis (11,18).

No parameters predicted death; however, one of the parameters that correlated with death was the amount of neutrophils in the interstitial infiltrate. It is interesting that leucocytosis was demonstrated previously as a predictor of death in patients with idiopathic renal vasculitis (41), although a causal relationship between leukocyte count and progression of injury could not be established. We think that a possible link could be leucocytosis as one of the first signs of an infection, which, in combination with immunosuppressive treatment, would be a high-risk factor for death. Our study shows that the most important cause of death of patients who died between 3 and 12 mo of follow-up was therapy-related infection. Recent studies also showed that the main cause of death in ANCA-associated glomerulonephritis is treatment-related infectious complication (42,43).

Baseline renal function was found previously to be a predictor of renal outcome in retrospective studies (11,36,44). In addition, our previous study of patients with mild to moderate renal involvement in ANCA-associated vasculitis showed that GFR$_0$ is important for predicting GFR$_{12}$ (20). CORGFR$_{12}$ was used to determine the influence of the GFR$_0$-independent variables. This measure for renal function recovery enabled us to study the difference between the measured GFR$_{12}$ and the expected GFR$_{12}$ on the basis of GFR$_0$. However, the same parameters, except for GFR$_0$ and dialysis at entry, as expected, predicted GFR$_{12}$ and CORGFR$_{12}$. This means that age, the percentage of normal glomeruli, tubular atrophy, and intraepithelial infiltrates indeed are important predictors of renal function recovery and are independent of renal function at entry.

The reason that some of the parameters that correlated univariately with GFR$_{12}$ were not predictive of GFR$_{12}$, as resulting from the regression model, could be that some of the parameters correlated with each other. For instance, glomerulosclerosis and interstitial fibrosis were strong correlators with GFR$_{12}$ in the univariate analysis, but because of their positive relationship with tubular atrophy, they did not turn out to be predictors of GFR$_{12}$ in the regression model.

The models that were obtained from regression analysis are useful to the clinician for estimating renal status after 12 mo. In addition, the maximum chance for dialysis could be deducted from one of these models. If patients have the worst phenotype possible in this model—that is, no normal glomeruli in the renal biopsy and intravenous methylprednisolone as adjunctive treatment—then their chance for being on dialysis after 12 mo is 50%. Taking into account the chance of 24% for dying, this means that even in the worst case, there is still a 26% chance for recovery. Despite that the predictive values of the models postulated are limited ($r^2$ for GFR$_{12}$ = 0.491; $r^2$ for dialysis at 12 mo = 0.309), these models clearly showed that consideration of several clinical and histologic parameters results in a better prediction of renal outcome after 12 mo than evaluation of GFR$_0$ ($r^2$ for GFR$_{12}$ = 0.084; $r^2$ for dialysis at 12 mo = 0.073) or dialysis dependence at entry ($r^2$ for GFR$_{12}$ = 0.075; $r^2$ for dialysis at 12 mo = 0.091) alone.

Predictive parameters in this study were defined for different outcome parameters in patients with ANCA-associated glomerulonephritis and severe renal involvement. All patients who participated in the study presented with severe renal
Figure 4. Correlation figures for predictive variables of dialysis status. Predictor of dialysis status at entry: Percentage of fibrous crescents ($r = 0.220, P = 0.028$; A), Predictors of dialysis status at 12 mo: Percentage of normal glomeruli ($r = -0.303, P = 0.008$; B) and treatment arm ($r = -0.277, P = 0.016$; C). All correlations are visualized either as box plots or as bar diagrams.

Conclusion

This study identified determinants of renal outcome in patients with ANCA-associated vasculitis and severe renal involvement. The prospective design, the homogeneity of the population, the population size, the standardization of patient treatment, and the detailed scoring system provided optimal conditions for this analysis. Our data suggest that in severe ANCA-associated glomerulonephritis, the combination of renal function at diagnosis, the percentage of normal glomeruli, age, and acute and chronic tubulointerstitial lesions predict GFR_{12}. The prediction was much more accurate than that based on GFR at entry alone. The percentage of normal glomeruli at diagnosis combined with adjuvant treatment predicted dialysis dependence at 12 mo. The regression model provides a tool to the clinician for estimating the chances for a favorable outcome for patients.

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