Prognostic Markers in Patients with Antineutrophil Cytoplasmic Autoantibody-Associated Microscopic Polyangiitis and Glomerulonephritis[1,2]

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ABSTRACT

The purpose of this study was to determine the prognostic value of clinical, laboratory, and pathologic features at the time of presentation on patient and renal survival in patients with antineutrophil cytoplasmic autoantibody (ANCA)-associated microscopic polyangiitis and glomerulonephritis (excluding Wegener's granulomatosis). One hundred seven ANCA-positive patients with necrotizing and crescentic glomerulonephritis, including 69 with evidence for microscopic polyangiitis, were evaluated for this study. The relative risk of death was calculated for the following potential prognostic indicators: (*1*) ANCA pattern; (*2*) pulmonary hemorrhage at onset; (*3*) presence of extrarenal manifestations *versus* renal limited disease; and (*4*) treatment with corticosteroids and cyclophosphamide (intravenous or oral), compared with corticosteroids alone. Cox's proportional hazard model was used to assess the predictive value of the following variables on renal survival: (*1*) age; (*2*) race; (*3*) pulmonary symptoms at onset of disease; (*4*) renal pathology; (*5*) ANCA pattern; and (*6*) peak serum creatinine values obtained near the time of renal biopsy. Patients were followed prospectively for 2.5 yr (range, 5 days to 12 yr 2 months). There were 12 disease-related deaths and 46 patients who reached ESRD. The relative risk (and 95% confidence interval) of patient death was 8.65 (3.36, 22.2) times greater in patients who presented with pulmonary hemorrhage, and 3.78 (1.22, 11.70) times greater in patients with cytoplasmic ANCA compared to those with perinuclear ANCA. The relative risk of pulmonary hemorrhage was no different by ANCA pattern. The risk of death was 5.56 times lower in the cyclophosphamide-treated patients *versus* those treated with corticosteroids alone. The predictors of renal survival were entry serum creatinine value ($P = 0.0002$), race (African Americans having a worse outcome compared with Caucasians, $P = 0.0008$), and the presence of arterial sclerosis on kidney biopsy ($P = 0.0076$) when controlling for age, ANCA pattern, microscopic polyangiitis *versus* glomerulonephritis alone, and pulmonary involvement. Pathology indices such as glomerular necrosis, glomerular crescents, glomerular sclerosis, and interstitial sclerosis were not predictive of renal survival when controlling for entry serum creatinine value, race, and arterial sclerosis. However, in the subgroup of patients with a peak creatinine value of ≤ 3.0 mg/dL ($N = 29$), increased interstitial sclerosis was a predictor of a poor renal outcome ($P = 0.04$).

Key Words: *Vasculitis, prospective cohort, renal survival, patient survival*

The question of prognosis in patients with glomerulonephritis is one of the most common questions that patients ask clinicians. Prognosis is an especially important issue when the disease process is aggressive and the therapeutic options are inherently dangerous. Such is the case with antineutrophil cytoplasmic autoantibody (ANCA)-associated systemic vasculitis and necrotizing and crescentic glomerulonephritis (1–5). At the time of disease presentation, clinicians are faced with several factors that may influence prognosis, including patient age, renal function, renal pathology, ANCA specificity, and vasculitis in extrarenal organ systems (6–13).

The treatment options that have been reported in

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the literature are toxic. Corticosteroids, immunosuppressive agents (such as cyclophosphamide and methotrexate), plasma exchange, and pooled intravenous γ-globulin, carry the potential risk of life-threatening infection (3,14–18). Additionally, cytotoxic agents are associated with carcinogenesis, mutagenesis, infertility, and interstitial cystitis.

In the ANCA-associated diseases, the complexity of ascertaining the long-term prognosis has been further complicated by the difficulty in categorizing patients according to specific types of systemic vasculitis. The terms for ANCA-associated vasculitides have been used differently across the globe, among diverse practice specialties, and even among colleagues. As a result, rendering a specific diagnosis for a given patient, then determining their prognosis on the basis of existing patient series with systemic vasculitis, is difficult. Recently, the nomenclature of systemic vasculitis was agreed upon by an international consensus conference (19). By using this nomenclature system, the ANCA-associated vasculitides are categorized as Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis (MPA). The patients that we have evaluated in this series all have necrotizing crescentic glomerulonephritis alone (NCGN) or as a constituent feature of MPA. Patients with Wegener's granulomatosis, as defined by this nomenclature system, which requires the presence of granulomatous inflammation for diagnosis, were excluded from evaluation in this study. Therefore, the patients in this study who had pulmonary involvement had evidence for nongranulomatous disease, such as hemorrhagic alveolar capillaritis.

Our goal was to determine the prognostic factors that affect patient survival and renal survival in individuals with ANCA-associated MPA and NCGN.

METHODS

Entry Criteria and Definitions

Patients diagnosed with ANCA-associated MPA and NCGN by the University of North Carolina Nephropathology Laboratory were eligible for entry. Of these, only patients followed by members of the Glomerular Disease Collaborative Network were available for follow-up. The Glomerular Disease Collaborative Network is a group of 150 nephrologists from 40 private community offices and 3 medical schools, primarily located in North Carolina and the southeast region of the United States (3,20). Review of all renal biopsy specimens and ANCA assays was performed by a single nephropathologist (Dr. J.C. Jennette). These studies were approved by the University of North Carolina Committee on the Protection of Human Rights.

Renal biopsy evaluation and a positive ANCA determination were required for all patients. All renal biopsy specimens revealed a pauci-immune necrotizing glomerulonephritis with or without the presence of crescents (21). A minimum of five glomeruli for diffuse or ten glomeruli for focal glomerular lesions was considered adequate tissue for pathologic evaluation. A paucity of the immune deposits was defined as less than 2+ (out of 0 to 4+) immunoglobulin deposits on immunofluorescence microscopy. A semiquantitative grading system from 0 to 4 was designed to assess the degree of glomerular necrosis, glomerular crescents, glomerular sclerosis, interstitial fibrosis, and tubular atrophy. Thirteen patients had more than one renal biopsy. The first renal biopsy was used for evaluation in predicting outcome.

The ANCA pattern was defined as either perinuclear ANCA (P-ANCA) or cytoplasmic ANCA (C-ANCA) as determined by indirect immunofluorescence microscopy (2,22). P-ANCA were further characterized as being myeloperoxidase-specific by using a previously described ELISA (2). One hundred percent of P-ANCA were MPO-specific in this case series. All C-ANCA were evaluated for proteinase-3 reactivity by using the ANTI-PR3 ELISA Kit (Progen Biotechnik Gmbh, Heidelberg, Germany). Eighty-seven percent of C-ANCA reacted to proteinase 3 in this case series.

Patient Population

All patients had biopsy-proven pauci-immune necrotizing glomerulonephritis. Microscopic polyangiitis was considered to be present in any patient with biopsy-proven small-vessel vasculitis. Patients with granulomatous inflammation discovered in any organ (*i.e.*, Wegener's granulomatosis) were excluded from this study. Patients with well-defined nodules or cavitary pulmonary lesions were also excluded because of the likelihood of Wegener's granulomatosis. In the absence of pathologic confirmation of extrarenal vasculitis, the presence of vascular inflammation was inferred on the basis of the following clinical findings. Lower respiratory tract vasculitis was considered likely in the presence of hemoptysis (*e.g.*, blood-tinged sputum), pulmonary hemorrhage (*e.g.*, multilobular infiltrates from blood emanating from the lung), respiratory failure, or radiographic proof of infiltrates without evidence of infection.

Upper-respiratory tract disease was considered likely when radiographic studies revealed sinusitis or when there was clear evidence for otitis media. Patients with upper respiratory disease were considered to have Wegener's granulomatosis and were excluded from this study if there was evidence of invasive bony disease or granulomatous inflammation. Skin disease was defined by a characteristic palpable purpuric rash with or without ulcerations, and/or pathologically confirmed leukocytoclastic angiitis. Gastrointestinal vasculitis was presumed when abdominal pain and/or gastrointestinal bleeding were present and not concluded to be secondary to corticosteroid treatment. Neurological involvement included seizures or focal neural deficits characteristic of mononeuritis multiplex with abnormal nerve conduction velocities.

Start and Stop Points

Patients were prospectively followed from the time of diagnosis. The start date for entry into the study was the date of renal biopsy. Medical records from before the time of renal biopsy were reviewed to estimate the onset of symptoms and laboratory values before the time of diagnosis. Stop points for renal survival analysis were loss of renal function requiring dialysis or renal transplantation (if before dialysis). Treatment of disease-related deaths was examined in a separate analysis. Patients not reaching an end point were followed until the date of their most recent office visit or hospital discharge.

Description of Treatment

The treating physicians used one of three therapeutic options in this case series: (*1*) corticosteroids alone; (2) oral cyclophosphamide therapy with concurrent therapy with

corticosteroids; or (3) intravenous cyclophosphamide therapy with concurrent therapy with corticosteroids (3). Therapy was not randomly assigned. A total of ten patients were not treated: four were considered to have unrecoverable renal damage, one died before receiving treatment, one because of advanced age (92 years), one was lost to follow-up, and three for unknown reasons.

Induction therapy with 3 days of intravenous methylprednisolone was administered at a dose of 7 mg/kg, to a maximum single dose of 1 g. Ninety percent (N = 87) of the 97 treated patients received this induction therapy.

All treated patients were begun on oral corticosteroids at a dose of 1 mg/kg per day (not exceeding 80 mg per single dose) for 3 wk, 2 mg/kg (not exceeding 120 mg every other day for 3 months), then tapered off 25% over 4 wk until completely off. Twenty-five patients were treated with corticosteroids alone.

Patients receiving oral cyclophosphamide (N = 29) were administered at a dose of 2 mg/kg per day and titrated on the basis of the white blood count in accordance with the treatment protocol described by Fauci *et al.* (14). Patients treated with intravenous cyclophosphamide (N = 43) were given six monthly treatments, starting with a dose of 0.5 g/m^2. This dose was adjusted in order to maintain leukocyte counts no lower than 3000 cells/mm^3. Plasma exchange was added in four patients with massive pulmonary hemorrhage.

Statistical Methods

The relative risk of death and 95% confidence intervals was calculated for each variable of interest to evaluate their impact on disease-related death. A continuity-adjusted chi-square test was used to evaluate the statistical significance of the relative risks. Multivariate modeling of prognostic variables for death was not possible because there were only 12 deaths.

The Kaplan-Meier lifetable analysis was used to estimate cumulative renal survival without controlling for multiple variables. Cox's proportional hazard model was used to assess the predictive value of selected variables on renal survival. The log of the negative log for survival by each covariate was viewed to determine if the proportional hazard assumption was valid (23). On the basis of the sample size (N = 107) and number of renal end points (N = 42), the statistical model was limited to no more than eight prognostic variables. Interaction terms were not tested because of the limited sample size. The prognostic indicators to be tested were selected before evaluation of the statistical models (see "Selection of Prognostic Variables" below).

The pathology variables were not preselected for use in the model. Each pathology variable was tested individually to assess its impact on outcome. Each pathology variable was ranked by a single pathologist (Dr. J.C. Jennette) with a score ranging from 0 to 4 with 0.5 intervals. These variables were explored in the statistical analysis by using a cut-off of score 1.0 or less *versus* greater than 1.0, by using the median for each as a cut-point, and also as continuous scores. For the variables that predicted outcome by univariate or multivariate analysis, a linear trend was consistently seen with increasing levels of the pathology score. Therefore, all pathology outcomes are presented as continuous scores (0 to 4) unless otherwise noted. All pathology variables that met the criteria of an estimated hazards ratio of greater than or equal to 1.25 and a P value less than or equal to 0.10 in individual models were then tested together in one model. Finally, the pathology variables that were selected from individual models were added one at a time to the preselected model. These models were compared with the log likelihood chi-square goodness of fit test to determine if the pathology variable added to the prediction of outcome (24).

The distribution of the serum creatinine values (mg/dL) was strongly skewed, therefore, the natural log of the serum creatinine value (mg/dL) was used to transform this variable to a Gaussian (normal) distribution. Transformations of other variables used in the models were not needed. Residuals of all models were plotted to assess if there was indication of a lack of fit.

Subgroup analysis was done using subjects with serum creatinine values equal to or below 3.0 mg/dL and 4.5 mg/dL (the median of the overall group). The slope of the serum creatinine value from entry to 1 month post-entry was calculated by using the reciprocal of each value.

The three-dimensional plot was made with SAS/Graph software (25). The plot was made after analysis of the model, with a selected range of entry creatinine values (1.0 to 10.0 mg/dL). The log of creatinine was used in the model, and then transformed back to the original units of mg/dL for the plot, because this is a more familiar unit of measure. All other variables in the model were held constant at their mean value for the prediction curves.

Selection of Prognostic Variables

It was not possible to control for all possible clinical manifestations of the disease. Pulmonary hemorrhage has been considered to be a potential prognostic indicator of death, especially early in the disease (1). We sought to substantiate this claim by examining whether pulmonary hemorrhage carried an independent prognostic risk for patient or renal survival. Additionally, we determined whether or not each patient presented with or without any pulmonary symptoms and evaluated the prognostic implications of this more general category on death and renal survival. We explored whether patients with MPA *versus* those with NCGN alone had a higher risk of death or differences in renal survival.

A different ANCA pattern, P-ANCA or C-ANCA, was considered to be a potential predictor of both death and renal survival and was therefore evaluated as a prognostic variable for both outcomes.

The peak entry serum creatinine value, defined as the highest value closest to diagnosis and before initiation of therapy, was used in statistical models for renal survival.

Patients ranged in age from 2 to 92 yr of age, therefore, age was controlled for in the multivariate model for renal survival. Age was explored by different age groups and as a continuous variable. Grouping age in three categories—less than 25, 25 to 75, and greather than 75 yr—appeared to best fit the risk of renal failure. Therefore, these categories were used for statistical modeling.

Race was categorized as African American or Caucasian. Races other than these were were not represented in this sample. Sex was not included in the models because it was not related to survival when using univariate lifetable analysis.

Each pathology measure was tested individually (as described above). Pathology variables included increased glomerular cellularity, glomerular polymorphonuclear leukocytes, interstitial leukocytes, sclerotic or fibrotic crescents, glomerular necrosis, glomerular crescents, glomerular sclerosis, interstitial sclerosis, arterial sclerosis, and tubular atrophy. We also designated two renal biopsy combination

scores (indices) for testing in the models: (*1*) an index for active disease, calculated as the sum of the scores for glomerular necrosis and glomerular crescents (0 to 8); and (*2*) an index for chronicity, calculated as the sum of the scores for glomerular sclerosis, interstitial sclerosis, and tubular atrophy (0 to 12).

Treatment modality was not compared in the analysis of renal survival because during the varying course of the disease (relapses), patients were treated with different combinations of therapy. The impact of treatment on relapse in these patients is evaluated by Nachman *et al.* (26).

RESULTS

Demographics and Entry Characteristics

Prospective follow-up was obtained on 107 patients who met the serological and pathologic entry criteria. All patients were followed by physicians in the Glomerular Disease Collaborative Network. The patients had a mean age at diagnosis of 57 ± 18 yr, with a range of 2 to 92 yr. The cohort included 58 men (54%) and 49 women (46%). There were 94 Caucasians (88%) and 13 African Americans (12%), corresponding to a ratio of 7 to 1. The ratio of Caucasians to African Americans in the region of our renal biopsy population is 2:1, and the overall region population ratio is 3.5 to 1.

By definition, all patients had NCGN. Thirty-eight patients (35.5%) presented with NCGN alone. The remaining 69 patients (64.5%) had MPA with renal and extrarenal organ system vasculitis. Thirty-eight patients (35.5%) had a pulmonary-renal vasculitic syndrome without evidence for granulomatous inflammation, whereas 31 patients (30.0%) manifested extrarenal organ system vasculitis that did not involve the lungs. The spectrum of disease manifestations for the total group and for the subgroup of patients with MPA are displayed in Table 1.

The duration of symptoms from the estimated time of disease onset to the time of renal biopsy (with ANCA specificity confirmed within the next few days), was 2.5 ± 3.0 months, with a range of 0.8 to 21.9 months. Sixty-eight patients (65%) had P-ANCA whereas 37 patients (35%) had C-ANCA (Table 2). This predominance of P-ANCA patients would be expected in a population from which Wegener's granulomatosis patients have been excluded. The median entry serum creatinine value of the cohort was 4.5 mg/dL (mean ± SD, 5.9 ± 4.0 mg/dL), ranging from 0.8 to 21.6 mg/dL. Ninety percent of the entry serum creatinine values were less than 10.0 mg/dL. Hematuria of 1+ or greater was present at onset in 95% of patients, and 3+ or greater in 86% of patients. The mean proteinuria at onset was 2.7 ± 2.8 g/24 h, with a range of 0.1 to 12.0 g/24 h.

A detailed discussion of the pathology of a representative portion of this population has been described in a previous publication (21). The mean activity score (glomerular necrosis + glomerular crescents) was 3.7 ± 2.0, with a range of 0 to 8. The mean pathology score for chronicity (glomerular sclerosis + interstitial sclerosis + tubular atrophy or injury) was 5.0 ± 2.5, ranging from 0 to 11, with a maximum possible value of 12. The mean arterial sclerosis score was 1.58 ± 0.87, ranging from 0 to 4 in 0.5 increments (Table 2).

TABLE 1. Distribution of disease manifestations by organ system

Organ System	*N*	%
Renal	107	100
Pulmonary	38	36
Upper respiratory[a]	14	13
Cutaneous	13	12
Musculoskeletal	10	9
Gastrointestinal	9	8
Neurologic	9	8
Ocular	2	2

[a] This category includes patients with otitis media or radiographic proof of sinusitis.

TABLE 2. Characteristics of patients at the time of renal biopsy (*N* = 107)[a]

Characteristic	*N* (%)	Mean ± SD
Diagnosis		
MPA		
Pulmonary involvement	38 (36)	
Other Organ involvement	31 (29)	
Glomerulonephritis Alone	38 (36)	
ANCA pattern		
P-ANCA	68 (64)	
C-ANCA	39 (36)	
African American Race	13 (12)	
Age (yr)		57.8 ± 17.0
Creatinine (mg/dL)		5.9 ± 4.0
Pathology Indices		
Activity (0–8)		4.9 ± 2.3
Chronicity (0–12)		3.7 ± 2.0
Arterial Sclerosis (0–4)		1.6 ± 0.9

[a] MPA, microscopic polyangiitis; ANCA, antineutrophil cytoplasmic autoantibody-associated; P-ANCA, perinuclear ANCA; C-ANCA, cytoplasmic ANCA.

Follow-Up

The mean follow-up for the entire cohort was 2.5 yr, with a range of 5 days to 12 yr 2 months. Overall, 88 (82.2%) of patients were followed until the occurrence of an end point or to within 6 months of the end of the study. One patient was lost to follow-up after 12 months. The remaining 18 patients were stable and seen by their physician within 12 months of the end of the study. Forty-five patients were followed without reaching either end point for a mean of 3 yr 9 months (median, 3 yr 2 months), ranging from 2 months to 12 yr 2 months. Forty-six patients reached ESRD (45 began dialysis and 1 was transplanted before dialysis)

in a mean of 1 yr 7 months (median, 1 yr 3 months), ranging from 5 days to 6 yr 5 months. Sixteen of the patients died during the course of the study. Four of the deaths were considered unrelated to disease onset or relapse (two with carcinoma, neither of whom received cyclophosphamide, and two with myocardial infarction). These deaths were not considered as end points in the statistical analysis (*i.e.*, they were censored at the time of death) and their time to death is included above in the mean and range of time for patients who did not reach an end point. The remaining 12 deaths were considered disease related: five from sepsis, three from pulmonary hemorrhage at or near the onset of disease, three from a myocardial infarction associated with complications at disease onset (pulmonary edema in two, bleeding during surgery in one), and one from multi-system failure (specific cause unknown, but at disease onset). Ten of these patients died within 3 months, 1 at 11 months, and 1 at 18 months from diagnosis.

Seventeen patients had a serum creatinine value that indicated advanced renal failure, and required dialysis at the onset of their disease. Nine of these recovered renal function. Four of these nine progressed to ESRD in a mean of 2 yr, despite their initial recovery of renal function. Results on the outcomes of these patients are further discussed by Nachman *et al.* (26).

Predictors of Patient Survival

Several variables were associated with an increased risk of patient death (see Table 3). Patients experiencing pulmonary hemorrhage have 8.65 times the risk of death as compared to those without pulmonary hemorrhage. The risk of death was no greater in patients with any form of pulmonary symptoms compared with those without pulmonary symptoms.

Patients with C-ANCA have 3.78 times the risk of death as compared to P-ANCA patients. The relative risk of pulmonary hemorrhage was not associated with ANCA pattern (relative risk, 1.01; 95% confidence interval, 0.45 to 2.37, $P = 0.99$).

The risk of death was equivalent in patients with multi-system manifestations of MPA *versus* those with renal limited disease. There was also no difference in the risk of death by race.

Patients treated with corticosteroids and cyclophosphamide (oral and intravenous combined) had 5.56 (reciprocal of 0.18) times less the risk of death compared with those treated with corticosteroids alone.

Predictors of Renal Survival

Unadjusted renal survival rates (censoring all deaths) for the entire cohort were 0.78 at 12 months, 0.66 at 24 months, 0.58 at 36 months, and 0.44 at 48 months.

Each potential prognostic variable for renal survival was shown not to violate the proportional hazards assumption for use in the proportional hazards model.

Evaluation of the prognostic value of entry information indicates that entry serum creatinine value is a strong predictor of renal outcome ($P = 0.0002$), when controlling for age, race, ANCA specificity, disease category, and pulmonary involvement (Table 4). The higher the entry serum creatinine value, the higher the probability of renal failure or death. The conditional risk ratio of the serum creatinine value corresponds to a 2.93-fold increase in risk per unit of the log of the serum creatinine value. For example, a patient with a log serum creatinine value of 1 is 2.93 times more likely to reach an end point than a patient with a log serum creatinine value of 0 (equivalent to serum creatinine units in mg/dL of 2.72 [equal to e^1] and 1.0 [equal to e^0]). The conditional risk ratio is calculated independent of time, since Cox's proportional hazards model assumes a proportional relationship over time.

The impact of the entry serum creatinine value can be seen in a three-dimensional plot of the probability

TABLE 3. Predictors of disease-related death[a]

Predictor	Relative Risk of Death[b]	95% Confidence Interval	*P* value
Pulmonary Hemorrhage (present *versus* absent)	8.64	(3.36, 22.19)	0.0002
Any Pulmonary Symptoms (present *versus* absent)	2.36	(0.80, 6.95)	0.16
Disease Category (MPA *versus* NCGN alone)	1.68	(0.48, 5.82)	0.61
ANCA Pattern (C-ANCA *versus* P-ANCA)	3.78	(1.22, 11.70)	0.031
Race (African American *versus* Caucasian)	2.41	(0.75, 7.77)	0.34
Treatment (cyclophosphamide *versus* corticosteroids alone)	0.18	(0.05, 0.66)	0.012

[a] NCGN, necrotizing crescentic glomerulonephritis. All other abbreviations as in Table 2.
[b] Each relative risk was evaluated without controlling for other variables in the Table.

TABLE 4. Predictors of reaching a renal end point

Predictor	Conditional Risk Ratio[a]	95% Confidence Interval	*P* value[b]
Log of Serum Creatinine	2.93	(1.67, 5.19)	0.0002
Age			
<25 years	2.91	(0.74, 12.51)	0.14
25 to 75 years	Reference	NA	NA
>75 years	2.15	(0.96, 4.80)	0.06
Race (0 = Caucasian, 1 = African American)	4.57	(1.87, 11.13)	0.0008
ANCA Pattern (0 = P-ANCA, 1 = C-ANCA)	0.55	(0.25, 1.23)	0.14
Disease Category (0 = NCGN, 1 = MPA)	1.04	(0.48, 2.28)	0.93
Any Pulmonary Symptoms (0 = no, 1 = yes)	0.98	(0.43, 2.27)	0.97
Arterial Sclerosis (0–4)	1.67	(1.07, 2.60)	0.03

[a] Each conditional risk ratio was calculated while controlling for all other variables in the Table.
[b] From the Wald chi-square test, testing if the conditional risk ratio is equivalent to 1.00.
[c] NA, not applicable.

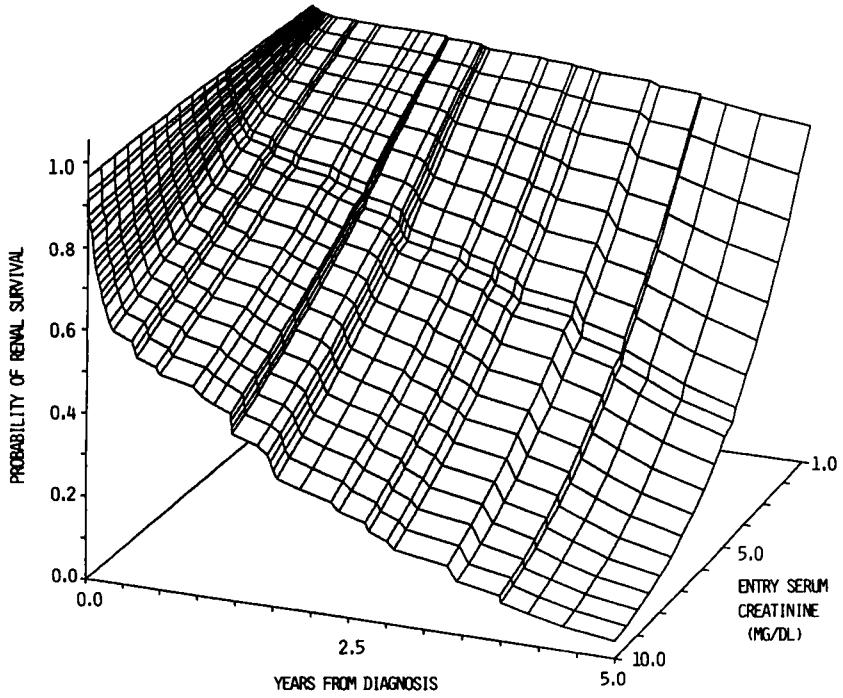

Figure 1. Predicted probabilities of renal survival based on a set range of entry serum creatinine values (1.0 to 10.0 mg/dL), demonstrate the impact of incremental increases in the entry serum creatinine on renal survival.

of renal survival over time by entry serum creatinine value (as shown in Figure 1). One of 14 (7%) patients with a peak entry serum creatinine value of 2.0 mg/dL or below reached an endpoint, five of 29 (17%) with an entry serum creatinine value of 3.0 mg/dL or below, and 17 of 53 (32%) with a serum creatinine value of 4.5 or below.

In view of the fluctuating nature of the entry serum

creatinine value, the serum creatinine value at 1 month post-renal biopsy was evaluated. The median serum creatinine value at 1 month post-biopsy was 2.75 mg/dL (mean ± SD, 2.9 ± 1.5 mg/dL). One-month serum creatinine values were a strong predictor of long-term renal outcome (risk ratio, 12.9; 95% CI [1.50, 37.17], $P = 0.0001$) when controlling for age, race, ANCA-specificity, disease category, and pulmonary involvement. Additionally, the slope of the reciprocal serum creatinine value, representing the change from entry to 1 month, had a statistically significant impact on renal outcome (risk ratio, 0.055; 95% CI [0.01, 0.76], $P = 0.03$), when controlling for the same variables.

African Americans were 4.6 times more likely to reach a renal endpoint compared with Caucasians ($P = 0.0008$) when controlling for the peak entry serum creatinine value, age, ANCA-specificity, disease category, and pulmonary involvement. Nine of 13 African Americans (69%) and 37 of 94 Caucasians (39%) reached a renal end point. There were no statistical differences in entry serum creatinine value, renal pathology scores, or duration of disease before renal biopsy between African Americans and Caucasians.

Surprisingly, the selection of pathology variables indicated that only arterial sclerosis added to the prediction of renal survival in the entire cohort. Other variables, such as glomerular crescents, increased glomerular cellularity, glomerular polymorphonuclear leukocytes, interstitial leukocytes, interstitial sclerosis and tubular atrophy, appeared to be predictors when tested univariately, but did not add to the prediction of renal survival when controlling for arterial sclerosis and the other selected variables (Table 5). Therefore, only arterial sclerosis was added to the overall model for evaluation of other prognostic variables for renal survival.

Arterial sclerosis on renal biopsy is a strong predictor of a poor renal survival ($P = 0.03$) when controlling for the other variables in the model (Table 4). For each 1-unit increase in arterial sclerosis on the renal biopsy evaluation, patients are 1.67 times more likely to reach an end point, when controlling for the log of the entry serum creatinine value, age, race, ANCA-specificity, disease category, and pulmonary involvement. Although the crude rates of reaching a renal endpoint increase as arterial sclerosis scores increase, the largest jump in risk appears to be between no arterial sclerosis (6 out of 16 [37.5%] with scores of 0 and 0.5) *versus* higher values of arterial sclerosis (48 out of 95 [50.5%] with scores of 1.0 or greater).

Other variables in the model did not reach statistical significance in predicting renal survival (Table 4), when controlling for entry serum creatinine value and arterial sclerosis. The impact of using either a continuous or categorical form of age did not have an impact on the model for renal survival (data not shown). The categorical form of age was used for presentation of the data because the younger (less than 25 yr of age) and older (greater than 75 yr of age) age groups tended to have an increased risk over the middle age group (25 to 75 yr of age), although these risks did not reach statistical significance.

When the patients who received no treatment were dropped from the model ($N = 10$), the results remained virtually the same for all prognostic variables (data not shown). Since the number of untreated patients was small, the model including all patients was selected for presentation of the data in Table 4.

TABLE 5. Selection of predictive pathology variables

Pathology Variables (Range of Possible Values)	Univariate Conditional Risk Ratio (P value)[a]	Multivariate Conditional Risk Ratio[b] (P value)	Multivariate Conditional Risk Ratio[c] (P value)
Arterial Sclerosis (0–4)	1.56 (0.01)	1.46 (0.03)	1.67 (0.03)
Glomerular Necrosis (0–4)	1.22 (0.20)		
Glomerular Crescents (0–4)	1.26 (0.07)	1.04 (0.83)	1.14 (0.38)
Increased Glomerular Cellularity (0–4)	2.57 (0.02)	2.01 (0.14)	1.17 (0.19)
Sclerotic Crescents (0–4)	1.01 (0.85)		
Glomerular Polymorphonuclear Leukocytes (0–4)	2.56 (0.001)	2.17 (0.10)	1.38 (0.12)
Interstitial Leukocytes (0–4)	1.50 (0.02)	1.20 (0.45)	1.34 (0.14)
Glomerular Sclerosis (0–4)	0.98 (0.98)		
Interstitial Sclerosis (0–4)	1.41 (0.16)	2.00 (0.11)	1.37 (0.10)
Tubular Atrophy (0–4)	1.32 (0.09)	0.07 (0.23)	1.21 (0.31)
Combined Glomerular Necrosis + Glomerular Crescents (0–8)	1.13 (0.16)		
Combined Glomerular Sclerosis + Interstitial Sclerosis + Tubular Atrophy (0–12)	1.07 (0.24)		

[a] From the Wald chi-square test, testing if the conditional risk ratio is equivalent to 1.00.
[b] Each pathology variable tested while controlling for other pathology variables selected from univariate modeling.
[c] Each pathology variable tested separately while controlling for the log of the peak entry creatinine value, age, race, ANCA pattern, disease type, and presence of lung symptoms.

In view of the lack of prognostic impact of the pathology indices, we reexamined the predictive value of these variables in the subgroup of patients with lower serum creatinine values. When the study group was limited to those with peak entry serum creatinine values of 3.0 mg/dL or less, interstitial sclerosis was a strong univariate predictor of a poor renal outcome (risk ratio, 2.73; 95% CI [1.04, 7.13], $P = 0.04$). Because this group was small ($N = 29$), with only 5 reaching a renal end-point, multivariate analysis was not possible. Univariate analysis of serum creatinine values in this subgroup did not reach statistical significance.

When using the median value of the peak entry serum creatinine value (4.5 mg/dL) as the cutpoint for subgroup analysis ($N = 53$, 17 of whom reached a renal endpoint), the serum creatinine value became a strong predictor of renal survival (risk ratio, 9.79; 95% CI [1.33, 72.3], $P = 0.03$). There were no pathology variables that reached statistical significance in this subgroup when controlling for the peak entry serum creatinine value.

DISCUSSION

In this cohort of patients with a spectrum of ANCA-associated microscopic polyangiitis and glomerulonephritis, pulmonary hemorrhage is a strong independent risk factor for patient death. Although many of our patients with massive pulmonary hemorrhage do well on our current treatment protocols, massive pulmonary hemorrhage remains a substantial life-threatening and devastating complication of ANCA-associated disease. Pulmonary hemorrhage is also an ominous feature of Wegener's granulomatosis, which was not included in this study.

C-ANCA pattern is not a prognostic aid in determining the risk associated with the development of pulmonary hemorrhage but is independently associated with the risk of death. The implications of this latter finding cannot be fully appreciated because we were limited to univariate analysis because of the few deaths that occurred. The lack of correlation between C-ANCA and pulmonary hemorrhage supports the concept that hemorrhagic alveolar capillaritis occurs in patients with either C-ANCA or P-ANCA.

Microscopic polyangiitis with manifestations of extra-renal organ involvement can lead to serious complications of the disease. For example, one of our patients died with a perforated abdominal viscus as a consequence of vasculitis. However, the majority of other patients with gastrointestinal or other organ manifestations of the disease have done well. Because of the small numbers, we could not evaluate the risk of death associated with each organ's involvement; however, as a group, patients with manifestations of vasculitis in other organs in addition to the kidney have a similar risk of death as those with renal limited disease. A marked increase in risk of death appears to be related only to pulmonary hemorrhage, and not to the vasculitic process in other organs.

The strongest predictors of long-term renal outcome in patients with ANCA-associated microscopic polyangiitis and necrotizing glomerulonephritis were the entry serum creatinine value, race, and arterial sclerosis on renal biopsy. It was not possible to determine a specific serum creatinine value beyond which there was no chance for any individual patient to have long-term recovery of their renal function. This is most likely a consequence of the fact that half of the patients requiring dialysis at the time of their onset of disease had recovery of kidney function.

There are several important issues that stem from these observations. The diagnosis and initiation of therapy of this disease must begin as early in the course of disease as possible to decrease glomerular inflammation and renal insufficiency. We recommend that during the process of evaluation, in the presence of a nephritic urine sediment and a positive ANCA, some form of anti-inflammatory therapy (*e.g.*, pulse methylprednisolone) be instituted during the time that the kidney biopsy is performed and pathological diagnosis reported.

With the observation that an elevated serum creatinine concentration portends a poor long-term renal prognosis, the dilemma that confronts clinicians is the relative benefit of treating patients with an elevated serum creatinine value at the time of diagnosis. While it is impossible to delineate recommendations for a specific patient, physicians must be aware that the higher the serum creatinine value, the worse the long-term renal prognosis. However, patients may recover sufficient renal function to permit the cessation of dialysis, at least for a while. This issue is further evaluated in this cohort of patients by Nachman *et al.* (26).

The importance of the entry serum creatinine value as a long-term prognostic marker of renal survival is a phenomenon found in two other forms of aggressive glomerulonephritis: Goodpasture's syndrome and lupus nephritis. In a study by Peters *et al.* (27), a serum creatinine value of over 600 μmol (6.8 mg/dL) was associated with poor long-term prognosis, although a serum creatinine value of less than 600 μmol was associated with recovery of renal function. Additionally, in the recent lupus nephritis plasmapheresis trial, the entry serum creatinine value was the most important long-term prognostic variable for renal function in patients with lupus nephritis (28). This similarity with ANCA-associated glomerulonephritis should come as no surprise because glomerular damage by either immune complexes, anti-glomerular basement membrane antibodies, or ANCA-associated mechanisms all result in a final common pathway of injury (1).

African Americans with ANCA-associated microscopic polyangiitis or glomerulonephritis have a poorer renal prognosis than Caucasians. It is unknown if African Americans are less likely to have biopsies performed, and therefore are less likely to be diagnosed with ANCA-associated microscopic polyangiitis and glomerulone-

phritis than Caucasians, or if they are less likely to acquire the disease. Only 13 patients in our cohort of 107 were African Americans. It is possible that hypertensive changes in the kidneys of African Americans result in an increase in susceptibility to damage from active glomerulonephritis, as in other glomerular diseases.

Arterial sclerosis on renal biopsy proved to be a strong independent predictor of poor renal outcome for the cohort as a whole. The predictive value of this, however, did not alter the predictive value of the entry serum creatinine value. We had anticipated that active glomerular necrosis and inflammation, or advanced glomerular sclerosis, might be prognostic indicators, but they were not. This may be because most patients had such severe glomerular disease that there was not enough variability in the severity of glomerular injury to predict outcome. The basis for the predictive value of arterial sclerosis is unknown. The pattern of sclerosis was not suggestive of healing vasculitis, but was rather the typical arterial sclerosis seen associated with hypertension and older age. Although greater age was not a statistically significant predictor of renal outcome, the expected correlation of arterial sclerosis and hypertension may explain the impact of increased arterial sclerosis on the renal outcome in this cohort. Another possible explanation for the relationship between arterial sclerosis and renal outcome is that patients with a background of chronic renal vascular disease had less renal reserve to tolerate additional injury to nephrons caused by the necrotizing glomerulonephritis.

In a subgroup analysis, interstitial sclerosis proved to be an important predictor in those patients with entry serum creatinine values less than 3.0 mg/dL. Tubulointerstitial damage has been shown to be an important predictor of long-term outcome in many renal diseases (29).

Several previous studies have described the prognosis of patients with rapidly progressive glomerulonephritis and systemic vasculitis. All of these studies have a mixture of disease entities in their patient population and the statistical analysis was limited to univariate evaluation. Keller *et al.* examined 46 patients with idiopathic rapidly progressive glomerulonephritis (6). In this study, factors indicating poor prognosis were an initial high serum creatinine value, a high percentage of crescents and glomeruli, and glomerulosclerosis. This study combined patients with rapidly progressive glomerulonephritis who had idiopathic rapidly progressive glomerulonephritis, Goodpasture's syndrome, anti-glomerular basement membrane disease, systemic lupus erythematosis, immunoglobulin-A nephropathy, and what more than likely are ANCA-associated diseases, including Wegener's granulomatosis and "AN arteritis." Both the Keller study and the study presented here reflect the importance of the entry serum creatinine value as a long-term predictor of renal survival. Gans *et al.* suggested that a kidney biopsy score was predictive of which patients with ANCA-associated glomerulonephritis would have a favorable response to immunosuppressive therapy (7). In their study, the percentage of sclerosed glomeruli and the degree of tubular atrophy were of prognostic importance. In our multivariate analysis, multiple pathology scores other than arterial sclerosis did not have an impact on survival when controlling for the entry serum creatinine value. In an interesting study of patients with Wegener's granulomatosis by Briedigkeit *et al.*, several prognostic factors, including renal disease, initial serum creatinine value, serum albumin value, erythrocyturia, and leukocyte count were predictive variables (13). These results are not surprising, because aggressive glomerulonephritis has been considered a predictor of poor outcome in other studies of patients with Wegener's granulomatosis (30,31). Whether any of these variables, most of which reflect activity of the glomerulonephritis, would remain independent risk factors in multivariate analysis is not certain. Nonetheless, progressive glomerulonephritis and interstitial scarring should eventually result in a poor long-term renal prognosis.

Despite a greater awareness of ANCA-associated microscopic polyangiitis and glomerulonephritis, patients often present with advanced and/or aggressive disease. Therapy with cyclophosphamide and corticosteroids have a beneficial effect in reducing the risk of death, but progressive renal damage occurs in many patients. Until a clear understanding of the pathogenesis of ANCA-associated microscopic polyangiitis and glomerulonephritis results in disease prevention, clinicians will struggle with a disease process that often causes irreversible renal damage before therapy has been instituted.

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