

Chances of Renal Recovery for Dialysis-Dependent ANCA-Associated Glomerulonephritis

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ABSTRACT

In patients who have anti-neutrophil cytoplasm autoantibody (ANCA)-associated glomerulonephritis and are on dialysis at time of diagnosis, renal function is sometimes insufficiently restored by immunosuppressive treatment, which often coincides with potentially lethal adverse effects. This study investigated the clinical and histologic variables that determine the chances of dialysis independence, dialysis dependence, or death after 12 mo in these patients. Sixty-nine patients who had ANCA-associated glomerulonephritis and were dialysis dependent at diagnosis received uniform, standard immunosuppressive therapy plus either intravenous methylprednisolone or plasma exchange. Eleven clinical and histologic variables were assessed. Univariate and binary logistic regression analyses were performed. Predictive parameters were entered into a two-step binary logistic regression analysis to differentiate among the outcomes of dialysis independence, dialysis dependence, or death. The point at which the chance of therapy-related death exceeded the chance of dialysis independence was determined. The chance of recovery exceeded the chance of dying in most cases. Intravenous methylprednisolone as adjunctive therapy plus <18% normal glomeruli and severe tubular atrophy increased the chance of therapy-related death over the chance of dialysis independence. Plasma exchange treatment plus severe tubular atrophy and <2% normal glomeruli increased the chance of therapy-related death over that of dialysis independence. Even with ominous histologic findings, the chance of renal recovery exceeds the chance of therapy-related death when these patients are treated with plasma exchange as adjunctive therapy.

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In anti-neutrophil cytoplasm autoantibody (ANCA)-associated vasculitides, such as microscopic polyangiitis, Wegener's granulomatosis, and renal-limited vasculitis, a characteristic clinical feature is rapidly progressive deterioration of renal function. This deterioration may result in end-stage renal failure or death,¹ especially when patients are dialysis dependent at diagnosis^{2–5} or have high initial serum creatinine levels.^{6,7} Histopathologically, pauci-immune crescentic glomerulonephritis appears, with variable amounts of extracapillary pro-

liferation, fibrinoid necrosis, and glomerulosclerosis in the renal biopsy.⁸

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Table 2. Binary logistic regression models differentiating between dialysis independence and dialysis at 1 yr^a

Compared Outcomes	Models	% Correct	r ²	Variables	P	Exp β	95% CI of Exp β
Dialysis independence (0) versus dialysis (1)	$y = -1.3 - 2.5 \times \text{arm} + 2.8 \times \text{tubular atrophy} - 0.09 \times \text{normal glomeruli}$	77.8	0.531	Arm	0.008	0.08	0.01 to 0.52
				Tubular atrophy	0.005	17.2	2.4 to 122.7
				Normal glomeruli	0.025	0.91	0.84 to 0.99
				Constant	0.189	0.27	
Dialysis (0) versus death (1)	$y = 0.18 + 1.4 \times \text{arm} - 0.04 \times \text{glomerulosclerosis}$	66.7	0.256	Arm	0.056	4.1	0.97 to 17.4
				Glomerulosclerosis	0.061	0.03	0.001 to 1.2
				Constant	0.783	1.2	
Dialysis independence (0) versus death (1)	$y = -1.4 + 1.5 \times \text{arteriosclerosis}$	63.4	0.147	Arteriosclerosis	0.042	4.7	1.1 to 20.5
				Constant	0.032	0.25	

^aThe chance of a certain outcome can be calculated by the formula $p = \text{Exp}(y)/[1 + \text{Exp}(y)]$. For treatment arm, IVMeP = 0, PE = 1. Tubular atrophy was scored as -/+ and arteriosclerosis as -/+. Glomerulosclerosis and normal glomeruli are continuous parameters and expressed as percentage of total number of glomeruli. Odds ratios are expressed as exponent β (Exp β); the 95% confidence intervals (95% CI) are also listed.

model as candidate predictors. Because there were three pairs of two outcome parameters, this resulted in three binary logistic regression models (Table 2).

Two-Step Binary Logistic Regression Analysis

Type of adjunctive treatment, the percentage of normal glomeruli, the extent of tubular atrophy, the percentage of glomerulosclerosis, and the presence of arteriosclerosis were predictive in at least one of the three models that differentiated between two outcomes (Table 2). On the basis of their predictive value, these parameters were selected to be used in the two-step binary logistic regression analysis. This analysis was performed to design a prediction model. Values for sensitivity and predictive values of the two-step binary logistic regression analysis are given in Table 3.

Worst- and Best-Case Scenarios According to the Two-Step Binary Logistic Regression Analysis

A patient with the lowest chance on dialysis independence and the highest chance on dialysis dependence would have the maximum of unfavorable factors within these study observations: Intravenous methylprednisolone as adjunctive treatment, 0% normal glomeruli, 88% glomerulosclerosis, severe tubular atrophy, and arteriosclerosis. This patient has a 6% chance of recovery, a 93% chance of dialysis dependence, and a 1% chance of death.

A patient with the highest chance of dialysis independence and the lowest of dialysis dependence would have the minimum of unfavorable factors within these study observations: Plasma exchange as adjunctive treatment, 89% normal glomeruli, no glomerulosclerosis, no tubular atrophy, and no arteriosclerosis. This patient has a 94% chance of recovery, a 0% chance of dialysis dependence, and a 6% chance of death.

Chances of Dying

In this study, 17 patients died within the first year of follow-up. Two deaths were disease related, two patients died of vascular causes (myocardial infarction and gastrointestinal bleeding), one patient died of respiratory failure, and two patients died of unknown causes. Ten deaths were clearly therapy related; these were the result of infections, such as *Pneumocystis carinii* pneumonia and cytomegalovirus. Of the 10 patients who died of therapy-related causes, seven came from the plasma exchange group (seven [20%] of 35) and three came from the intravenous methylprednisolone group (three [8.8%] of 34). Differences between the two groups were not statistically significant, as determined by the Fisher exact test ($P = 0.306$).

From these analyses, it became clear that the clinical and histologic parameters studied could not distinguish very well between death, irrespective of the cause, and the other outcomes (dialysis dependence and independence; data not shown). This observation was confirmed by logistic regression

Table 3. Classification of the two-step logistic regression model

Observed	Predicted			Total ^a	Predicted/ Observed (Sensitivity; %)
	Dialysis Independent	On Dialysis	Dead		
Dialysis independent	13	4	7	24	54.2
On dialysis	4	14	3	21	66.7
Dead	5	4	8	17	47.1
Total	22	22	18	62	56.5
Observed/predicted (predictive value; %)	59.1	63.6	44.4		

^aSeven patients were unclassifiable for arteriosclerosis because of the absence of arteries in their biopsies.

analysis in which there were no predictive parameters for death or for therapy-related death (data not shown).

The chance of recovery can be calculated by using the logistic regression model of dialysis dependence *versus* dialysis independence at 1 yr (Table 2), also taking into account the outcome of death. Analysis of the predictive values of the binary logistic regression model that differentiate best between dialysis dependence and independence after 12 mo shows that predictive values are reasonably high, namely 80.0% for dialysis independence and 72.7% for dialysis dependence.

A total of 17 of 69 patients died, resulting in a 25% chance of dying in this patient group. Considering the chances of dying in each treatment arm, the point at which the chance of dialysis independence is lower than the chance of dying can be determined from the number of normal glomeruli in combination with the severity of tubular atrophy. This relationship is illustrated in Table 4, which shows that in patients who were treated with intravenous methylprednisolone, the chance of dying from therapy was higher than the chance of dialysis independence in the case of severe tubular atrophy and <18% normal glomeruli. For patients who were on plasma exchange, the chance of dying from therapy was higher than the chance of dialysis independence in the case of severe tubular atrophy and <2% of normal glomeruli (Figure 1).

Time from Disease Onset to Death

Figure 2 shows data for all patients in this study who died within 1 yr after disease onset, including the time point at which they died and the cause of death. A pattern emerged that distinguished between therapy-related deaths and deaths that were attributable to other causes. All of the patients who died from causes other than therapy-related causes (*n* = 7) did so within 3 mo after diagnosis with a mean of 1.5 mo; vascular causes were responsible for the first two deaths. In contrast, all patients who died after 3 mo died from therapy-related causes, with a mean from diagnosis to death of 5.6 mo.

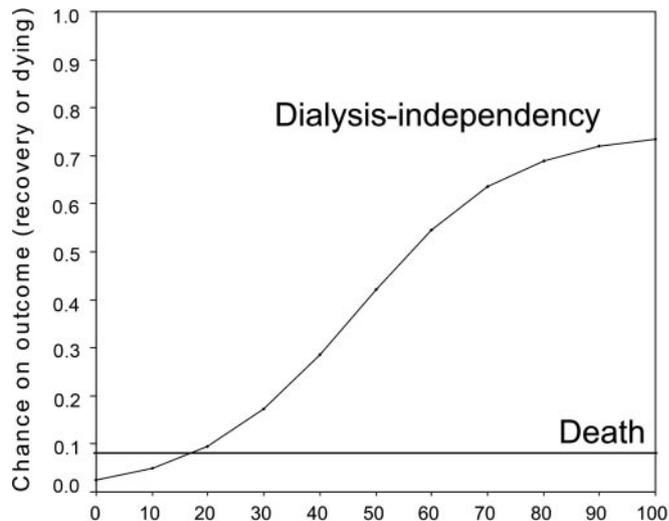
DISCUSSION

ANCA-associated glomerulonephritis is a rare entity. Patients who are affected by this disease and present with acute renal

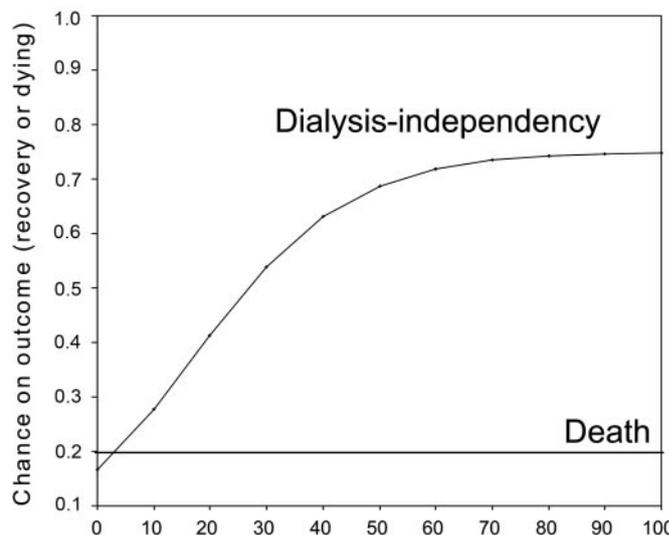
Table 4. Points at which the chance of dying from therapy exceeds the chance of recovery^a

Adjunctive Treatment	Tubular Atrophy	Normal Glomeruli (%)
IVMeP	No	<0
IVMeP	Moderate	<0
IVMeP	Severe	18.1
PE	No	<0
PE	Moderate	<0
PE	Severe	2.1

^aWhen the percentage of normal glomeruli is less than the number in the column, the chance of dying from therapy exceeds the chance of becoming dialysis independent.



A % Normal glomeruli



B % Normal glomeruli

Figure 1. Chances of therapy-related death and dialysis independence after 1 yr related to the percentage of normal glomeruli in a diagnostic biopsy. Figures are shown for the patients who received IVMeP as adjunctive treatment and showed severe tubular atrophy in their biopsies (A) and for the patients who received PE as adjunctive treatment and showed severe tubular atrophy in their biopsies (B). Left of the point where the lines cross, the chance of dialysis independence drops below the chance of therapy-related death. For the patients with IVMeP, this point is at 18% of normal glomeruli, whereas for the patients who were on PE, this point is at 2% of normal glomeruli.

failure that requires dialysis are even more rare. In this prospective study, clinical and histologic determinants of outcome in patients with dialysis-dependent ANCA-associated vasculitis at diagnosis were identified. In this patient group, the outcome after 1 yr was as follows: 43% were dialysis independent,

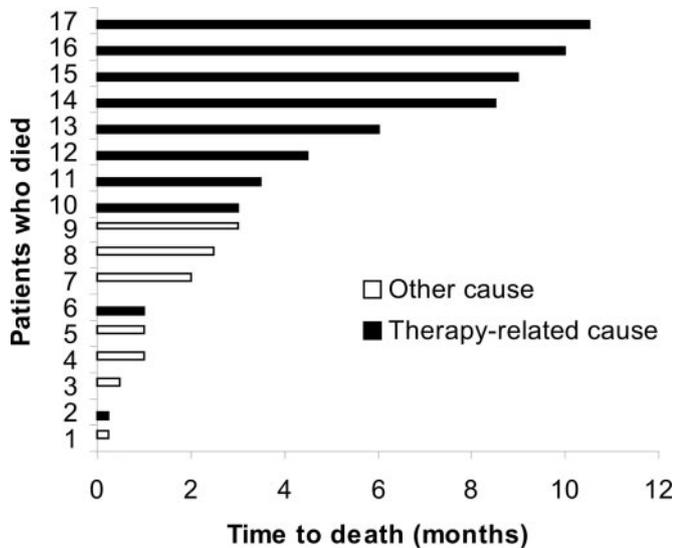


Figure 2. Causes of death divided by therapy-related causes and other causes.

32% were dialysis dependent, and 25% had died. On the basis of a two-step binary logistic regression analysis, estimated chances of recovery after 1 yr in this patient group seemed to vary widely. This variability in outcome was mainly determined by type of adjunctive treatment, percentage of normal glomeruli and glomerulosclerosis, the extent of tubular atrophy, and the presence of arteriosclerosis.

Models that resulted from a two-step binary logistic regression analysis provided insight into the chances that an individual patient has to become dialysis dependent or independent or to die within 1 yr after diagnosis. The models also gave insight into which histologic and clinical variables predict outcome. Chronic lesions, in both the glomerular and the interstitial compartments, showed an inverse relationship with recovery. Glomerulosclerosis and arteriosclerosis also correlated with dialysis dependence at 1 yr; this is a specific feature of patients who have ANCA-associated glomerulonephritis and are dialysis dependent at diagnosis, because these parameters did not play a role in a previous analysis.²¹ Apparently, when patients receive a diagnosis of ANCA-associated vasculitis and are dialysis dependent, preexisting vascular lesions have a high impact on renal outcome. This could be explained by the irreversibility of glomerulosclerosis and arteriosclerosis despite therapy. Type of adjunctive therapy was shown to be a predictor of dialysis independence at 12 mo with plasma exchange as the adjunctive treatment of choice.

Outweighing the benefits against the hazards of treatment and making subsequent decisions on the basis of clinical information is a difficult task for the physician. This study shows that histopathologic lesions may be of help in this decision-making process. The point at which the chance of therapy-related death became higher than the chance of dialysis independence could be calculated by taking into account the type of adjunctive treatment, the degree of tubular atrophy, and the

number of normal glomeruli. However, when evaluating the percentages of normal glomeruli, the total number of glomeruli in a biopsy is of utmost importance. When tubular atrophy was severe and patients were treated with intravenous methylprednisolone as adjunctive treatment and had <18% normal glomeruli, the chance of therapy-related death exceeded the chance of renal recovery. For patients with severe tubular atrophy who were treated with plasma exchange, when they had <2% normal glomeruli, their chance of therapy-related death would exceed their chance of renal recovery. Because the total number of glomeruli in the biopsies varied between two and 49, 2% normal glomeruli is negligibly small. When tubular atrophy was absent or moderate, the chance of renal recovery exceeded the chance of therapy-related death. From these data, the important conclusion can be drawn that even in patients who showed an ominous histologic picture in their biopsies at diagnosis, the chance of renal recovery almost always exceeded the chance of therapy-related death when the patient was treated with plasma exchange as adjunctive therapy.

In an examination of the causes of death within the 12 mo of the study, a subdivision emerges for the first 3 mo of the disease and the period after 3 mo. In the first 3-mo period, death most often resulted from causes that were not therapy related, such as the disease itself and vascular factors. Between 3 and 12 mo, death was exclusively caused by therapy. Considering earlier reports that the addition of plasma exchange and intravenous methylprednisolone facilitates the improvement of renal function within the first 3 mo after disease onset,^{22–24} it is most striking that death as a result of therapy almost exclusively occurs in the period after 3 mo. This phenomenon may be ascribed to the cumulative dosage of immunosuppressive treatment, when combining standard treatment with adjunctive treatment, according to the regimen used in this study. Moreover, this finding suggests that improved and safer treatment regimens are required for patients with ANCA-associated glomerulonephritis and dialysis dependence at diagnosis.

For this study, the treatment regimen with aggressive adjunctive treatment was aimed at restoring renal function within a short period of time; therefore, follow-up was limited to 12 mo. Results indeed showed that when recovery took place, the patient's renal function stabilized within 3 mo, which justified the duration of follow-up within the scope of this study. Although this is the largest study of a homogeneously treated cohort of dialysis-dependent ANCA-associated vasculitis patients to date, the number of patients could be expanded for firmer predictions. The sample size of this patient group may seem relatively limited but can be explained by the very low incidence of this particular disease. Only through a collaborative study in which many European centers have joined efforts to contribute patient data were we able to gather this group, which is extremely homogeneous in terms of clinical status (dialysis dependence at diagnosis) and treatment. The number of patients is also the reason that a two-step binary logistic regression analysis was performed instead of a multinomial logistic regression analysis; they are essentially the

same, but using the two-step analysis provided more insight into the process of how predictive models are constructed. The predictive value of the two-step binary logistic regression model is somewhat limited, but it illustrates the factors that are associated with and predictors of certain outcomes. An important cause of this limited predictive value is probably the inability to predict death. Because death can be considered as a given chance, factors that could differentiate between dialysis dependence and dialysis independence were distinguished. Because many patients die as a result of adverse effects of therapy, there should be careful consideration about exposing them to an aggressive immunosuppressive treatment in case of renal failure. If it were possible to predict which patients would not recover from renal insufficiency, then treatment in those patients could target suppressing disease activity in other involved organs and the achievement and maintenance of remission. Bearing in mind that most patients are affected not only by renal involvement but also by systemic disease, stopping immunosuppressive treatment completely is usually not an option.

Recently, we published an article in which predictive parameters of outcome were investigated in a group of patients who had ANCA-associated vasculitis and presented with acute deterioration of renal function.²¹ In this study, we focused on patients who required dialysis at presentation, identifying factors that are important in determining renal function recovery and associating these factors with therapy-related deaths. Moreover, this study provides insight into factors that are important in treatment decision-making.

CONCLUSION

In patients with dialysis-dependent, ANCA-associated vasculitis, the chances of recovery differ depending on the type of adjunctive treatment, the percentage of normal glomeruli and glomerulosclerosis, the extent of tubular atrophy, and the presence of arteriosclerosis. Even with an ominous biopsy at diagnosis in combination with dialysis dependence, the chance of renal recovery exceeds the chance of therapy-related death when the patient is treated with plasma exchange as adjunctive treatment. Therapy-related death usually occurs between 3 and 12 mo after diagnosis. Prevention of therapy-related death requires safer treatment regimens for patients who have ANCA-associated glomerulonephritis and are already dialysis dependent at diagnosis.

CONCISE METHODS

Patients

Within the framework of the EUVAS, 29 hospitals in 11 European countries enrolled patients in the MEPEX trial, a randomized trial that evaluated adjunctive therapy for severe glomerulonephritis in ANCA-associated systemic vasculitis.²⁵ In this study, we included patients from this trial who were dialysis dependent at entry. The local ethics committees approved the study, and all patients gave

written informed consent for participation. Inclusion and exclusion criteria for MEPEX are described extensively elsewhere.^{21,25} All patients followed a standard treatment regimen, which consisted of oral corticosteroids, started at 1.0 mg/kg per d and tapered down within the first 6 mo, and 2.5 mg/kg per d cyclophosphamide, which at 3 mo was replaced by the less toxic azathioprine. For adjunctive therapy, patients were randomly assigned to either receive intravenous methylprednisolone or undergo plasma exchanges. Patients who were randomly assigned to receive intravenous methylprednisolone were administered 1000 mg three times daily 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 they were on dialysis at diagnosis and when both histologic data, obtained from renal biopsy at the time of study entry, and clinical data were available.

Disease definitions were adapted from the 1992 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis²⁶ and a previous European Union Study.²⁷ They were distinguished by criteria previously published²⁵ and as such determined by local physicians.

Clinical Outcome Variables and Their Clinical and Histologic Candidate Predictors

In this study, clinical outcome variables were dialysis dependence and dialysis independence at 12 mo and death. Because the number of variables was high and the number of cases relatively low in this study, inclusion of all variables in the regression analysis would not have been statistically relevant.^{21,28} To prevent "overfitting," only the most promising variables were selected as candidate predictors of renal outcome on the basis of earlier findings.^{17,21,28,29} Eleven clinical and histologic variables were examined. Age and type of adjunctive treatment (intravenous methylprednisolone or plasma exchange) were candidates for clinical predictors of renal outcome.

Paraffin sections of renal biopsies were stained with silver, periodic acid-Schiff, and hematoxylin and eosin. These sections were reviewed by two of five participating pathologists (L.H.N., F.F., R.W., J.A.B., and I.M.B.). Both pathologists scored the biopsies separately and according to a previously standardized protocol for scoring renal biopsies of patients with ANCA-associated vasculitis.^{30,31} They were blinded to patient data and the scores of the other observer. Briefly, each glomerulus had to be scored separately for the presence of fibrinoid necrosis, crescents (cellular/fibrous and segmental/circumferential), and glomerulosclerosis. The presence of glomerular lesions was calculated as the percentage of the total number of glomeruli in a biopsy. Interstitial, tubular, and vascular lesions were scored dichotomously or semiquantitatively. Discrepancies between the observers were resolved by conference during central reviews, achieving consensus for each biopsy.

Statistical Analyses

The computer program that was used to perform statistical analyses was the SPSS 12.0 standard version for Windows (SPSS, Chicago, IL). For each test, the statistical methods used are outlined in the next paragraphs.

Univariate Analysis and Logistic Regression Analysis, Distinguishing between Two Outcome Variables

Univariate correlation tests were performed to determine which of the 11 variables distinguished between two outcome variables, namely dialysis at 1 yr *versus* death, dialysis independence at 1 yr *versus* death, and dialysis independence *versus* dialysis dependence at 1 yr. Quantitative variables were correlated using Pearson correlation test; for correlation with dichotomous or categorical variables, Phi-values were used. Each variable that showed a correlation with a $P \leq 0.10$ was entered into a binary logistic regression model as a potential predictor. This approach led to three formulas expressing the histologic and clinical parameters that were predictive of differences between dialysis at 1 yr and death, dialysis independence at 1 yr and death, and dialysis independence and dialysis dependence at 1 yr. Parameters that were shown to be predictors in any of the three formulas were used to construct the formulas of the two-step binary logistic regression analysis.

Two-Step Binary Logistic Regression Analysis

Consequently, to calculate the chance of a certain outcome for each patient, we performed a two-step binary logistic regression analysis, mimicking a multinomial logistic regression model but providing more insight into the construction of the predictive models. In each step, a binary logistic regression model reflects the chance of a previously defined outcome. The first model differentiated between recovery—dialysis independence after 12 mo—and unfavorable outcome: Either dialysis dependence or death after 12 mo. The second model distinguished between dialysis dependence and death after 12 mo.

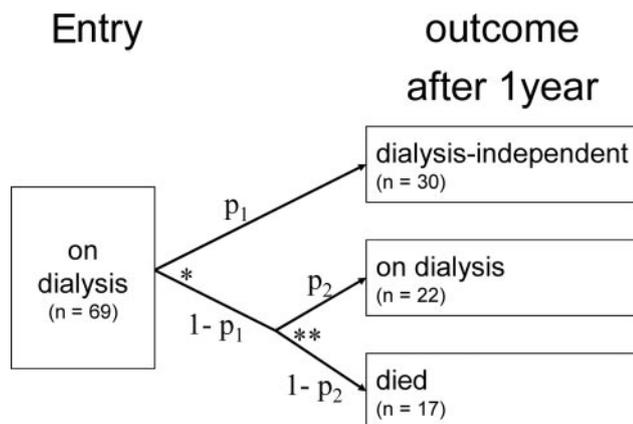


Figure 3. Two-step binary logistic regression model. The chance of becoming dialysis-independent is p_1 , the chance of being on dialysis is $(1 - p_1) \times p_2$, and the chance of dying is $(1 - p_1) \times (1 - p_2)$. *Model 1: recovery (1) *versus* nonrecovery (0) = $0.2 + 1.1 \times \text{arm} [\text{IVMeP} = 0, \text{PE} = 1] + 0.02 \times \text{normal glomeruli} - 0.01 \times \text{glomerulosclerosis} - 0.2 \times \text{tubular atrophy} - 1.4 \times \text{arteriosclerosis}$. **Model 2: Death (1) *versus* dialysis (0) = $0.2 + 2.4 \text{ arm} + 0.04 \times \text{normal glomeruli} - 0.03 \times \text{glomerulosclerosis} - 2.3 \times \text{tubular atrophy} + 1.8 \times \text{arteriosclerosis}$. In these equations, arm and arteriosclerosis are dichotomous variables, tubular atrophy is categorical (−/+), and normal glomeruli and glomerulosclerosis are continuous variables (0 to 100%). IVMeP, intravenous methylprednisolone; PE, plasma exchange.

These models are visualized in Figure 3. All parameters that were predictive in one of the binary logistic regression models that differentiated between two outcomes, as described above, were entered into and forced to stay in the two binary logistic regression models of the two-step analysis. With the help of these models, the chances of a certain outcome could be calculated for each patient (Figure 1).

Sensitivity values and predictive values for the outcomes were identified by creating classification tables. Chances of different outcomes for the phenotypically best and worst cases for this patient cohort were calculated to determine the range of chances of a certain outcome.

Comparing the Chance of Therapy-Related Death with the Chance of Recovery

We determined how many patients died how long after disease onset and from what cause. Patients who had died because of infection or sepsis were considered to have died of therapy-related causes. By setting out the values of parameters that determined the chances of therapy-related death and dialysis independence, the point at which the chance of therapy-related death exceeded the chance of recovery (*i.e.* dialysis independence) could be estimated.

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DISCLOSURES

None.

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- See the related editorial, “Removing Antibody and Preserving Glomeruli in ANCA Small-Vessel Vasculitis,” on pages 1987–1989.