Development and validation of a renal risk score in ANCA-associated glomerulonephritis

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Predicting renal outcome in antineutrophil cytoplasmic antibody (ANCA)–associated glomerulonephritis (GN) remains a major challenge. We aimed to identify reliable predictors of end-stage renal disease (ESRD) and to develop and validate a clinicopathologic score to predict renal outcome in ANCA-associated GN. In a prospective training cohort of 115 patients, the percentage of normal glomeruli (without scarring, crescents, or necrosis within the tuft) was the strongest independent predictor of death-censored ESRD. Regression tree analysis identified predictive cutoff values for three parameters: percentage normal glomeruli (N0 >25%, N1 10 to 25%, N2 <10%), percentage tubular atrophy and interstitial fibrosis (T0 ≤25%, T1 >25%), and estimated glomerular filtration rate at the time of diagnosis (G0 >15 ml/min/1.73 m^2, G1 ≤15 ml/min/1.73 m^2). Cox regression analysis was used to assign points to each parameter (N1 = 4, N2 = 6, T1 = 2, G1 = 3 points), and the resulting risk score was used to classify predicted ESRD risk as low (0), intermediate (2 to 7), or high (8 to 11 points). The risk score accurately predicted ESRD at 36 months in the training cohort (0%, 26%, and 68%, respectively) and in an independent validation cohort of 90 patients (0%, 27%, and 78%, respectively). Here, we propose a clinically applicable renal risk score for ANCA-associated GN that highlights the importance of unaffected glomeruli as a predictor of renal outcome and allows early risk prediction of ESRD.

Kidney International (2018) **94,** 1177–1188; https://doi.org/10.1016/j.kint.2018.07.020

KEYWORDS: ANCA-associated vasculitis; glomerulonephritis; renal ANCA score; risk factors

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Received 19 February 2018; revised 14 June 2018; accepted 5 July 2018; published online 29 October 2018

Renal involvement in ANCA–associated vasculitis varies in the degree of its severity. The diversity of the histopathologic findings ranges from fresh fibrinoid necrosis to global sclerosis. Despite intensive therapies, a significant percentage of patients still reach ESRD or die of infectious complications.[1–4]

Clinicopathologic studies of the European Vasculitis Study Group have demonstrated that the percentage of normal glomeruli and glomerulosclerosis as well as the degree of tubular atrophy and interstitial fibrosis (TA/IF) are important parameters related to renal outcome in ANCA-associated necrotizing GN.[5–8] A histopathologic classification derived from these studies separates biopsies into 4 categories: focal, crescentic, mixed, and sclerotic, and it was initially shown that these categories predicted renal outcome.[9] Over the last years, several studies have tested these results.[10–26] Most studies found that 1 of the 4 classes was differently associated with renal outcome.[10,12,14,19,21–25,27,28] Most multivariable analyses demonstrated that using the histologic classes unfortunately did not improve outcome prediction.[22–25] A recent meta-analysis considered >1500 patients and could not detect different outcomes in the crescentic and mixed classes.[29] We therefore analyzed renal tissues in detail and tested different glomerular damage scores to address the following questions: Do all glomerular lesions lead to the loss of the nephron? and What percentage of glomeruli needs to be damaged to have differing renal outcomes?

RESULTS

Patients

Two hundred five patients with a new diagnosis of ANCA-associated GN were included in the present study. Table 1 summarizes their baseline clinical characteristics. The prospective training cohort (n = 115) and the retrospective validation cohort (n = 90) did not differ in their clinical characteristics. In the training cohort, the median follow-up period was 34 months (31 months in the validation cohort). Twenty-four patients (20.9%) developed ESRD in

Table 1 | Clinical baseline characteristics

Patient cohorts	Total (N = 205)	Training (n = 115)	Validation (n = 90)	P
Age (yr)	66 (54–73)	66 (54.5–72)	67.5 (55.3–74)	0.35
Male sex	143 (69.8)	84 (73)	59 (65.6)	0.23
ANCA type				
Proteinase 3	101 (49.3)	58 (50.4)	43 (47.8)	0.59
Myeloperoxidase	104 (50.7)	57 (49.6)	47 (52.2)	0.59
Renal function at the time of diagnosis				
eGFR[a] (ml/min per 1.73 m^2)	28 (20–45.8)	27.5 (18–47)	29.5 (20–44)	0.35
Dialysis dependence	39 (19)	24 (20.9)	15 (16.7)	0.20

ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate.
Data are median (interquartile range) or n (%).
[a]Patients not on dialysis.

this cohort (25 patients [27.8%] in the validation cohort). Eleven of these patients already needed renal replacement therapy at the time of diagnosis and remained dialysis dependent during follow-up (8 patients in the validation cohort). There was no difference in renal recovery between the training and the validation cohort. In the training cohort, 13 patients (11.3%) recovered renal function with a recovery rate of 54.2%. In the validation cohort, 7 patients (7.8%) recovered renal function with a recovery rate of 46.7% (Table 2). In the training cohort, 23 patients (20%) died during follow-up, and 10 of these were dialysis dependent at the end. Seven patients (6.1%) died during the first 6 months of induction therapy. There were no deaths in the validation cohort as patients needed to provide consent to participate in the study and only surviving patients were included in the retrospective validation cohort.

Treatment

In the prospective training cohort, patients received immunosuppressive therapy according to the guidelines of the European Renal Association–European Dialysis and Transplant Association.[30,31] In this cohort, 101 of 115 patients received steroids and i.v. cyclophosphamide pulses (median dosage, 4.5 g; interquartile range [IQR], 3–6 g) and 13 patients were treated with steroids and rituximab (median dosage, 2.1 g; IQR, 2–2.8 g). Among the rituximab-treated patients, 7 patients also received cyclophosphamide (median dosage, 1.5 g; IQR, 1.5–1.8 g).[2] Thirty-two patients (27.8%) in the prospective training cohort underwent additional treatment with plasma exchange. In 1 patient, induction therapy with cyclophosphamide and/or rituximab was withheld because of severe infectious complications. This patient received steroids and plasma exchange only, and the patient died after 5 weeks. In the retrospective validation cohort, patients were treated according to the European guidelines after 2009.[30,31] Before 2009, patients received steroids and oral cyclophosphamide.

Table 2 | Clinical outcome

Patient cohorts	Total (N = 205)	Training (n = 115)	Validation (n = 90)	P
Follow-up (mo)	33 (21–57)	34 (22–57)	31 (20.3–54)	0.83
Renal recovery	20 (9.8)	13 (11.3)	7 (7.8)	0.40
ESRD	49 (23.9)	24 (20.9)	25 (27.8)	0.20
Mortality	23 (11.2)	23 (20)	0 (0)	<0.05

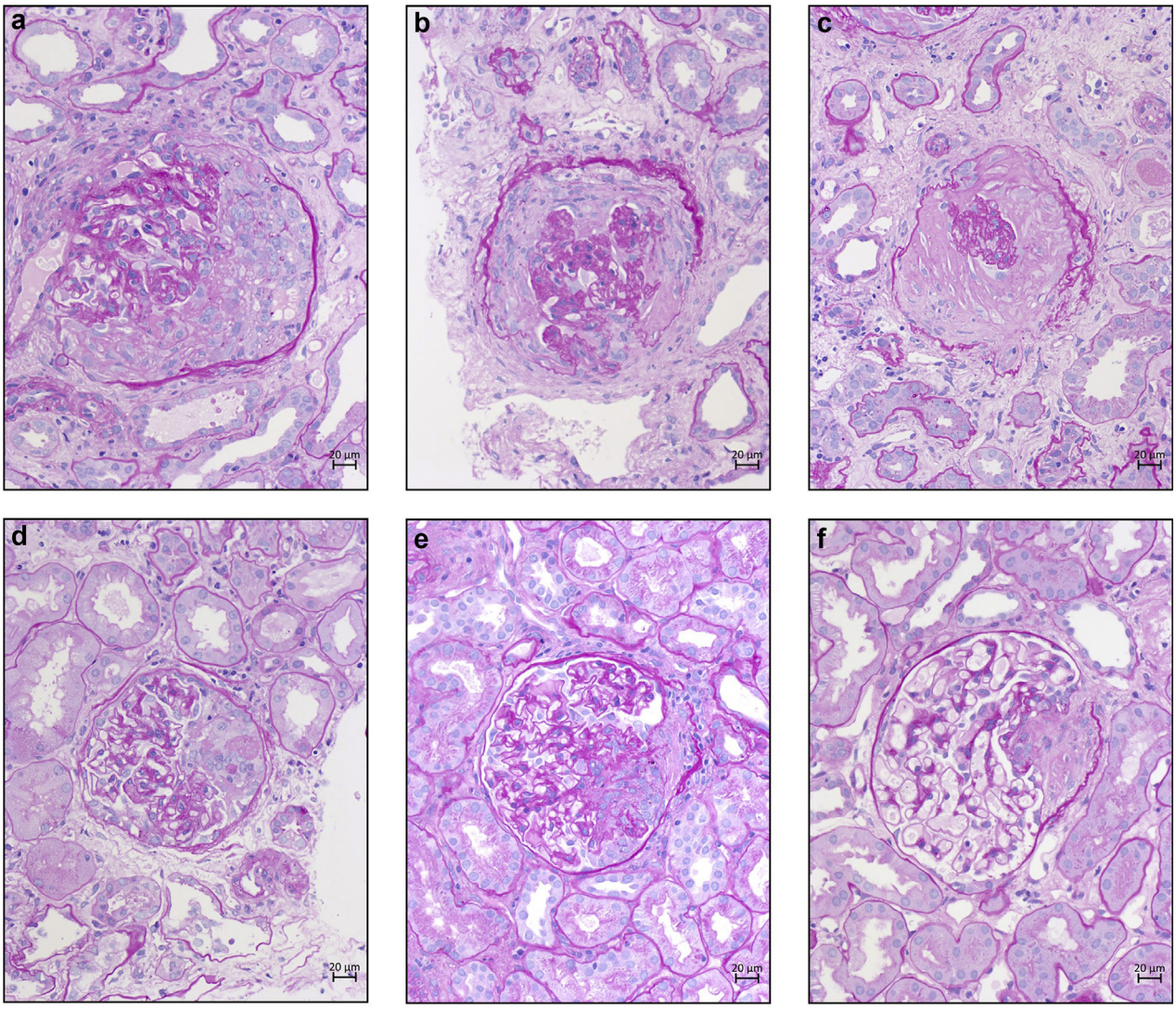
ESRD, end-stage renal disease.
Data are median (interquartile range) or n (%).

Histologic findings

In the training cohort, patients had a median of 13 glomeruli per biopsy (IQR, 9–17.5 glomeruli per biopsy). In the validation cohort, patients' renal biopsies showed a similar amount of glomeruli (median, 14; IQR, 9.3–21; $P = 0.11$). A detailed histologic analysis of biopsies from the training cohort was performed, and Figure 1 illustrates different glomerular lesions. Supplementary Table S1 presents findings of glomerular, tubulointerstitial, and vascular lesions. The findings of different glomerular lesions were combined into glomerular damage scores, and the median score results are also summarized in this table.

Correlations with renal function

Univariate analysis and concordance. In the training cohort, we used the univariate Cox regression model to test the ability of potential baseline risk factors to predict ESRD. The results of the analyses of all glomerular, interstitial, and vascular lesions, clinical parameters, and different scores are presented in Supplementary Table S2. Among all glomerular lesions, the fraction of normal glomeruli, as well as global fibrocellular and fibrous crescents, and the percentage of capsular rupture were significant predictors of ESRD ($P < 0.001$, $P = 0.001$, $P = 0.013$, and $P = 0.003$, respectively). Of the different glomerular damage scores, the score including necrosis and all crescentic and sclerotic lesions (consequently the percentage of normal glomeruli) showed the best predictive accuracy for ESRD (hazard ratio [HR], 1.06; 95% confidence interval [CI], 1.03–1.10; $P < 0.001$; concordance, 0.789) (Figure 1g). Preglomerular and peritubular vascular lesions did not predict ESRD. However, the degree of TA/IF was significant (HR, 1.04; 95% CI, 1.01–1.06; $P = 0.001$). Applying the Berden classification revealed that the crescentic class relative to the focal class showed an increased risk of ESRD but the mixed and sclerotic classes did not (HR, 3.78; 95% CI, 1.25–11.4; $P = 0.0184$). The estimated glomerular filtration rate (eGFR) at the time of biopsy was the only clinical variable that reached statistical significance to predict



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Glomerular damage scores

Score	HR	95% CI	*P* value	Concordance
All lesions	1.06	1.03–1.10	<0.001	0.789
All lesions excl. necrosis	1.05	1.02–1.07	<0.001	0.766
All lesions excl. necrosis + cellular crescents	1.02	1.00–1.03	0.011	0.654
Global lesions only	1.04	1.02–1.05	<0.001	0.745
Global lesions only excl. cellular crescents	1.02	1.01–1.04	0.003	0.668
All lesions with seg. lesions counting as half a lesion	1.05	1.03–1.07	<0.001	0.783
All lesions with seg. lesions as half excl. necrosis	1.04	1.02–1.07	0.002	0.760
All lesions with seg. lesions as half excl. necrosis + cellular crescents	1.02	1.01–1.04	0.005	0.665

Figure 1 | Crescentic lesions in antineutrophil cytoplasmic antibody–associated glomerulonephritis (GN). Development of glomerular damage in necrotizing GN with extracapillary proliferation of different extent (periodic acid–Schiff–stained sections). (**a–c**) Representative examples of global crescents over time. (**d–f**) Representative examples of segmental (seg.) crescentic lesions. Time course: examples for (**a,d**) cellular crescents, (**b,e**) fibrocellular crescents, and (**c,f**) fibrous crescents. (**g**) Different glomerular damage scores. Concordance and hazard ratios (HRs) with their corresponding 95% confidence intervals (95% CIs) and *P* values were calculated using univariate Cox regression to predict end-stage renal disease. excl., excluding. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

renal failure (HR, 0.95; 95% CI, 0.93–0.98; $P < 0.001$). Any of the other predictor variables were of histopathologic origin. An extract of the univariate analyses is presented in Table 3.

Multivariable analysis. To identify independent predictor variables in the training cohort, we performed multivariable analysis using Cox proportional hazards regression models. The predictors in the univariate analysis, for example, eGFR, TA/IF, and percentage of normal glomeruli, which inversely equals the damage score of all glomerular lesions, as well as the Berden classes were investigated (Table 4). The first model (model 1) included eGFR, TA/IF, and age. In the analysis of model 1, tubular atrophy and eGFR at the time of biopsy were still significant variables predicting outcome ($P = 0.03$ and $P = 0.01$). In the second model (model 2), the amount of normal glomeruli was added. In the analysis of model 2, the percentage of normal glomeruli remained the only independent predictor of ESRD ($P = 0.01$). In the third model (model 3), the Berden classes were added instead of the fraction of normal glomeruli. In the analysis of model 3, multivariable analysis showed that the Berden classes were not predictive while in this model the percentage of TA/IF remained as the significant predictor ($P < 0.001$). The forest plot of clinicopathologic parameters used in the multivariable Cox regression analysis of model 2 in Table 4 demonstrates the significance of the percentage of normal glomeruli (Figure 2a). The proportional hazards assumption of the multiple Cox regression model was tested using the Schoenfeld residuals test.[32] No evidence of violation was found.

Regression tree analysis. A tree analysis was performed to identify statistically relevant cutoff values in the training cohort, which influence ESRD. Cutoff values were detected for the amount of normal glomeruli (<5% and <23.3%). The regression tree analysis also detected cutoff values for the additional parameters eGFR and TA/IF (eGFR <15.5 ml/min per 1.73 m^2; TA/IF ≥27.5%). In the group of patients with normal glomeruli >23.3% and TA/IF <27.5%, none of the patients developed ESRD with a patient-year follow-up of >100 years. In the group of patients with eGFR <15.5 ml/min per 1.73 m^2 and normal glomeruli <5%, all patients developed ESRD in 11.8 patient-years (Figure 2b). Using an applicable cutoff value for normal glomeruli at 25%, the cohorts and analysis did not change statistically and the cutoff remained significant (HR, 6.7; 95% CI, 1.9–23.7; $P = 0.003$). Patients with normal glomeruli <25% had a 6.7 times higher risk of developing ESRD than did patients with normal glomeruli ≥25% in their biopsy. Choosing a higher cutoff at 50% normal glomeruli did not discriminate the cohort ($P = 0.88$).

Renal survival. Patients in the training cohort were divided according to the cutoff values for the percentage of normal glomeruli, the percentage of TA/IF, and the initial eGFR. These patient clusters differed in renal outcome. Kaplan-Meier survival curves demonstrate the discriminatory power of the individual components (Figure 3a–c). Applying the Berden classification revealed that the mixed, sclerotic, and focal classes did not differ from each other. The only differing classes were the focal versus the crescentic class. In our cohort, the crescentic class had the worst renal outcome (Figure 3d). To determine the reliability of biopsy specimens, only biopsies with at least 7 glomeruli were investigated. Univariate analyses revealed similar results (Supplementary Table S3). Upon applying the cutoff values for the individual components of the clinicopathologic score of patients with at least 7 glomeruli in their biopsy, Kaplan-Meier survival curves showed similar results (Supplementary Figure S1).

Table 3 | Univariate Cox regression in the training cohort

Parameter	Median (IQR)	HR	95% CI	*P*
eGFR at the time of diagnosis	27.5 (18–47)	0.95	0.93–0.98	<0.001
Tubular atrophy and interstitial fibrosis	25 (15–40)	1.04	1.01–1.06	0.001
Age	66 (54.4–72)	1.02	0.99–1.06	0.189
Normal glomeruli	27.3 (16.8–50)	0.93	0.90–0.96	<0.001
Histologic class				
Focal	39 (33.9)	Reference		
Crescentic	40 (34.8)	3.78	1.25–11.4	0.018
Mixed/sclerotic	31/5 (31.3)	1.30	0.34–4.70	0.730

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IQR, interquartile range.

Risk score proposal

Three risk groups. For the training cohort, a scoring system was developed using parameters that influence outcome: normal glomeruli (N0 >25%, N1 10%–25%, and N2 <10%), TA/IF (T0 ≤25% and T1 >25%), and eGFR (G0 >15 ml/min per 1.73 m^2; G1 ≤15 ml/min per 1.73 m^2) (Figure 4a). Relevant risk factors were assigned score points to calculate a risk score. Points were calculated by dividing the coefficient of each variable by 0.80 (the lowest β coefficient value, corresponding to TA/IF >25%), multiplied by a constant (2), and rounded to the nearest integer. The sum of score points ranged from 0 (no risk factors) to 11 (normal glomeruli <10%, TA/IF >25%, and eGFR ≤15 ml/min per 1.73 m^2). Renal survival estimates were used to define 3 differing risk groups with significantly different prognoses depending on their sum score: low, 0 points; medium, 2–7 points; high, 8–11 points (Figure 4b).

Independence of the risk score from immunosuppressive therapy

Additional analyses were performed to test whether the predictive value of the scoring system did apply independently of immunosuppressive therapy. To accurately investigate a potential influence of treatment on the scoring variables, age and weight of patients needed to be taken into consideration. Therefore, we performed multiple linear regression models using the initial and cumulative cyclophosphamide dosages to determine interactions between the description of immunotherapy with patient characteristics (age and weight) and the

Table 4 | Multivariable Cox regression in the training cohort

	Model 1			Model 2			Model 3		
Parameter	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
eGFR at the time of diagnosis	0.96	0.93–0.98	0.01	0.98	0.94–1.01	0.15	0.96	0.93–0.99	0.04
Tubular atrophy and interstitial fibrosis	1.03	1.00–1.05	0.03	1.01	0.99–1.04	0.28	1.04	1.01–1.06	0.003
Age	0.99	0.95–1.03	0.49	1.01	0.97–1.05	0.78	0.99	0.95–1.03	0.60
Normal glomeruli	–	–	–	0.96	0.93–0.99	0.01	–	–	–
Histologic class									
Focal							Reference		
Crescentic	–	–	–	–	–	–	1.43	0.40–5.21	0.58
Mixed/sclerotic		–	–	–	–	–	0.37	0.09–1.54	0.17

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

scoring system (eGFR, percentage of normal glomeruli, and TA/IF).

Initial cyclophosphamide treatment. All patients in the training cohort receiving i.v. cyclophosphamide treatment (n = 101) were included in these analyses. Supplementary Figure S2 demonstrates the cyclophosphamide dosages of each patient in correlation with other variables. We used interactions between risk groups and other variables to test for differences in prescriptions among risk groups. No significant differences were detected (weight by risk group, $P = 0.154$; age by risk group, $P = 0.817$; eGFR by risk group, $P = 0.329$; TA/IF by risk group, $P = 0.478$; percentage of normal glomeruli by risk group, $P = 0.103$) (Supplementary Figure S2). The regression coefficient β, 95% CI, and P value calculated using the multiple linear regression of the first cyclophosphamide pulse in correlation with weight, age, eGFR, and risk groups are listed in Supplementary Table S4. The intercept is the initial dosage of a patient in the low-risk group in correlation with mean age, eGFR, and weight. Overall, there were no significant changes in dosage. Dosages of cyclophosphamide increased nonsignificantly with higher risk, weight, and eGFR, and they decreased nonsignificantly with older age.

Cumulative cyclophosphamide treatment. Next, we investigated whether the cumulative cyclophosphamide induction dosages differed in our risk groups. All patients in the training cohort receiving i.v. cyclophosphamide induction therapy and with a survival of at least 3 months were included in this analysis (n = 96). Correlations of cumulative cyclophosphamide dosages with weight, age, eGFR, TA/IF, and percentage of normal glomeruli in the renal biopsy are depicted in Supplementary Figure S3. Cumulative dosages of cyclophosphamide increased with weight. Dosages increased nonsignificantly with higher risk and eGFR and decreased nonsignificantly with older age. The regression coefficient β, 95% CI, and P value calculated using the multiple regression of the cumulative cyclophosphamide dosage in correlation with weight, age, eGFR, and risk groups are listed in Supplementary Table S5. There was no significant difference in the administered cumulative dosage of cyclophosphamide between risk groups.

All patients were treated with steroids; 32 patients (27.8%) also received plasma exchange. Of these 32 patients, more patients were in the high- and medium-risk groups than in the low-risk group (Supplementary Table S6).

Validation analysis

Distribution of the sum score and the prognostic index. For validation, a second cohort of 90 patients with ANCA-associated GN was investigated. Validation detected a good concordance of our model in the 2 cohorts, with a comparable distribution of the sum score between the 2 cohorts using the methodology described by Royston and Altman (Supplementary Figure S4).[33] The distribution of the sum score was comparable between the initial and the validation cohort. The estimated slope of the back-transformed sum score in a Cox regression model in the validation cohort was 0.824 (95% CI, 0.536–1.112; $P = 0.232$). As it was close to 1 and did not differ statistically from 1, the discrimination of the sum score was preserved in the validation cohort.

Measure of discrimination. Renal survival did not differ in the training and validation cohorts, which were divided into 3 risk groups. The Kaplan-Meier curve demonstrates the renal survival of the risk groups (Figure 5a). Figure 5b depicts the estimates of the renal survival rates at 36 months of follow-up, emphasizing the similar behavior of the risk groups in the training and the validation cohort. The individual components of the clinicopathologic score discriminated the validation cohort in a similar manner as in the training cohort (Supplementary Figure S5). The Harrell's c concordance was used to measure the conformity of the 2 cohorts, where a perfect match would result in a concordance level of 1 and a random pairing would result in a concordance level of 0.5. Concordance was comparable between, and reasonably high within, the initial cohort (0.832) and the validation cohort (0.855).

Regression tree analyses of the validation and combined cohorts and their accuracy. Furthermore, we performed regression tree analyses of the validation and combined cohorts (Supplementary Figure S6). In the validation cohort, similar cutoff values were detected for the percentage of normal glomeruli (3.5% and 7.5%), percentage of TA/IF (17.5%), and eGFR (24 ml/min per 1.73 m^2). By combining the cohorts, an additional cutoff for age (71.5 years) was determined. Then, we evaluated the error rate characteristics of our regression trees. The inaccuracy of the renal survival trees was assessed using the integrated Brier score (IBS) (Supplementary Table S7).[34] The null model for our training cohort without predictors had an IBS of 0.169. The

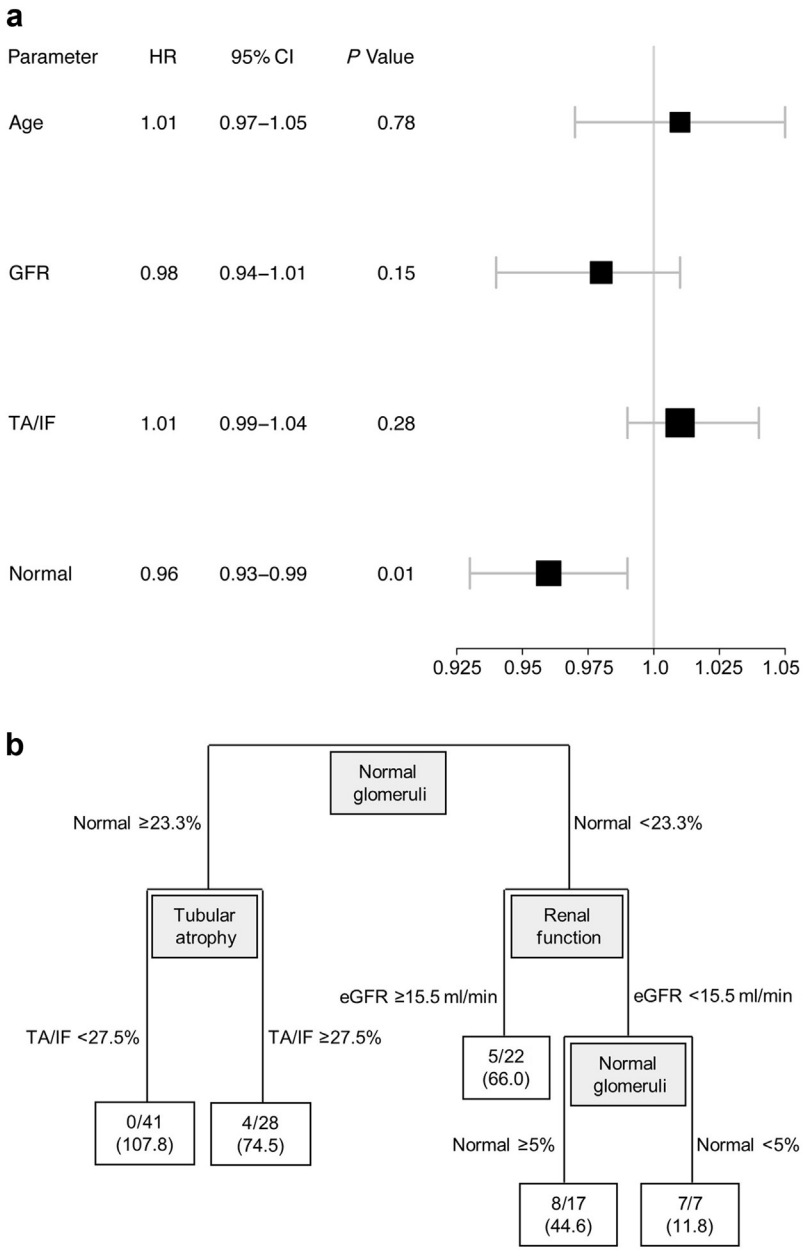


Figure 2 | Forest plot of clinicopathologic parameters and regression tree analysis. (**a**) Forest plot of clinicopathologic parameters age (per year), estimated glomerular filtration rate (eGFR, per 1-ml/min per 1.73 m^2 change), tubular atrophy and interstitial fibrosis (TA/IF, per 1% change), and percentage of normal glomeruli (per 1% change) in biopsies from patients in the training cohort. Hazard ratios (HRs) with their corresponding confidence intervals (95% CIs) and *P* values were calculated using multivariable Cox regression to predict end-stage renal disease (ESRD). (**b**) Regression tree analysis for the end point ESRD. Patients in the training cohort are grouped according to the cutoff values for the percentage of normal glomeruli, percentage of TA/IF, and eGFR at the time of biopsy. Each group has the number of patients developing ESRD, the number of all patients in the group, and the patient-year follow-up period.

prognostic value of our tree model was shown by a substantial reduction in IBS to 0.101. This reduction was maintained in the validation set (IBS 0.119).

Application of the risk score for mobile devices

For practicability, the risk score and its risk groups were implemented into an application for mobile devices. Supplementary Figure S7 shows a screenshot with the link to download the application.

Extrarenal ANCA-associated vasculitis

To determine whether a discussion about the reduction of the induction immunosuppression for renal survival purposes would be feasible at all, extrarenal vasculitic manifestations of patients in the training cohort, and particularly in the high-risk group, were investigated. Supplementary Table S8 lists patients' extrarenal ANCA-associated disease. Depending on risk groups, ~90% of patients suffered from systemic vasculitis. In the high-risk group (n = 21), 7 patients suffered

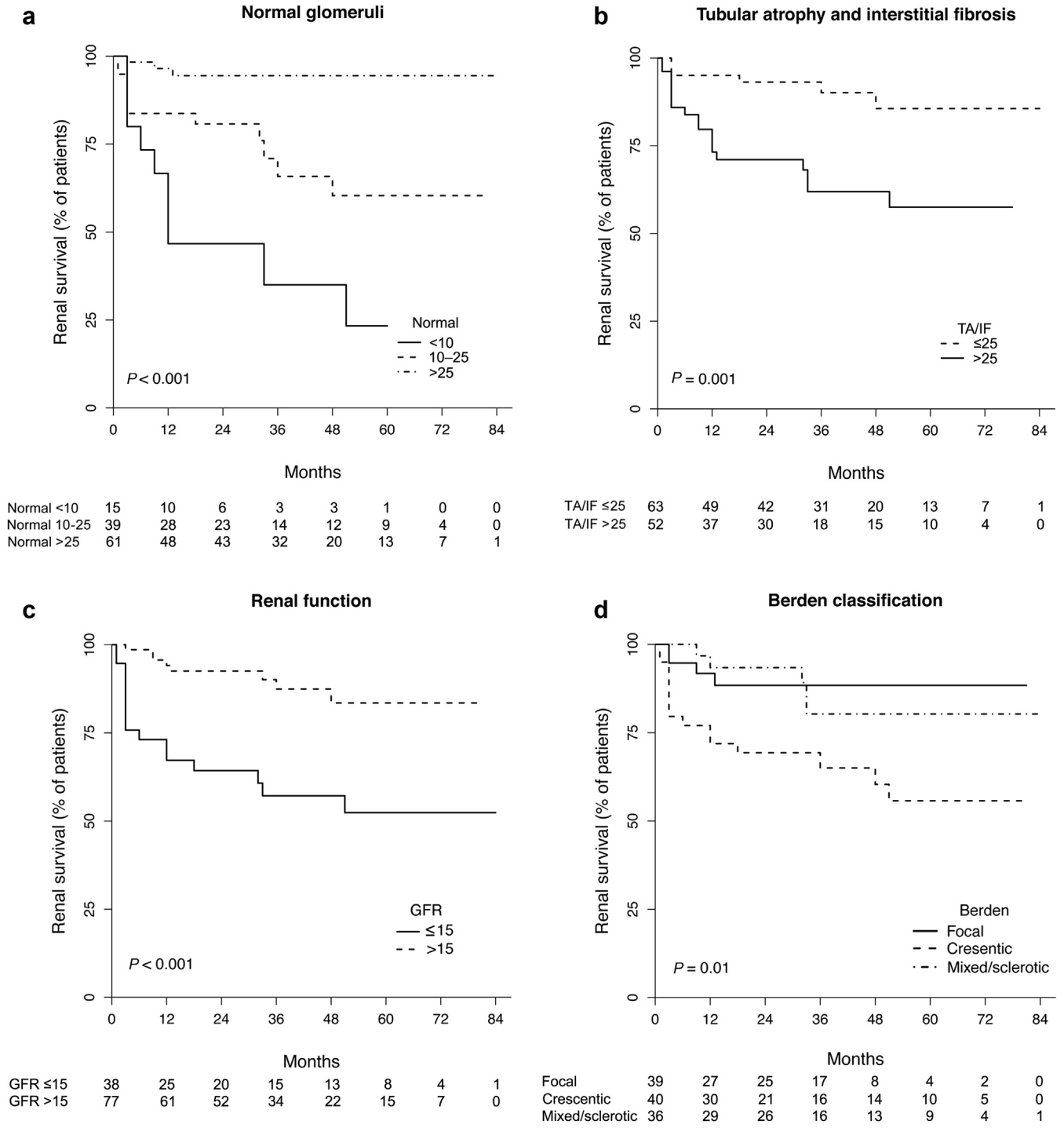


Figure 3 | Renal survival according to clinicopathologic parameters. Kaplan-Meier curves demonstrating renal survival of patients with antineutrophil cytoplasmic antibody–associated glomerulonephritis in the training cohort according to the Cox regression analysis using (**a**) the percentage of normal glomeruli. (**b**) Patients are divided into groups according to the cutoff values for the percentage of tubular atrophy and interstitial fibrosis (TA/IF) and (**c**) the estimated glomerular filtration rate (eGFR) at the time of biopsy. (**d**) Renal survival according to the Berden classification.

from diffuse alveolar hemorrhage (33.3%) and 4 patients required immunosuppression for organ-threatening disease other than kidney affection (19%). Nine patients with ANCA-associated GN (42.9%) had general and ear, nose, and throat symptoms as extrarenal manifestations only, and 1 patient (4.8%) suffered from renal-limited disease. In these last 10 patients, the kidney disease dictated the immunosuppressive induction load.

Observer agreement

Finally, interobserver variability was assessed in the training cohort of 115 patients. The descriptive agreement is depicted

a

Risk factor		N (%)	β Coefficient	HR	95% CI	*P* value	Points
Percentage of normal glomeruli (N)							
N0	>25%	61 (53)	Ref.				0
N1	10%–25%	39 (33.9)	1.49	4.42	1.18–16.5	0.027	4
N2	<10%	15 (13)	2.39	10.9	2.77–42.6	<0.001	6
Tubular atrophy + interstitial fibrosis (T)							
T0	≤25%	63 (54.8)	Ref.				0
T1	>25%	52 (45.2)	0.80	2.22	0.82–6	0.117	2
Renal function at time of diagnosis (GFR)							
G0	>15 ml/min	77 (67)	Ref.				0
G1	≤15 ml/min	38 (33)	1.06	2.89	1.19–7.02	0.019	3

b

Risk group	Points
Low	0
Medium	2–7
High	8–11

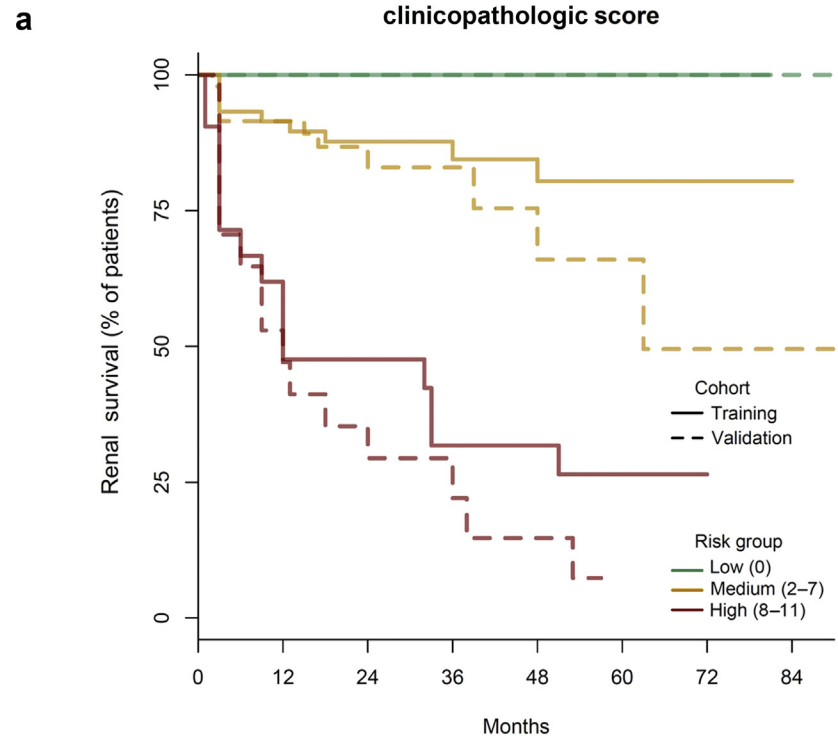
Figure 4 | Risk score proposal. (**a**) Clinicopathologic scoring system in antineutrophil cytoplasmic antibody–associated glomerulonephritis with parameters normal glomeruli (N), tubular atrophy and interstitial fibrosis (T), and estimated glomerular filtration rate (eGFR; G) at the time of biopsy. Proposal of a risk score with points for certain events (row 7). The sum of score points ranges from 0 (no risk factors) to 11 (N2 <10%, T1 >25%, and G1 ≤15 ml/min). (**b**) Risk score dividing patients into 3 risk groups: low, 0 points; medium, 2–7 points; and high, 8–11 points. CI, confidence interval; HR, hazard ratio.

in Supplementary Figure S8 showing all 1550 glomeruli assessed as normal (green), crescentic (yellow), or sclerosed (red) in 3 consecutive periodic acid–Schiff–stained sections by 2 pathologists. The intersecting lines emphasize the differences in rating the individual glomerulus. *Normal glomeruli* were defined as glomeruli that did not exhibit any vasculitic lesions or glomerulosclerosis. The analytical agreement using Cohen's κ showed sufficient agreement between the pathologists in the detection of normal glomeruli, crescents, and glomerulosclerosis (κ=0.912, κ=0.791, and κ=0.795, respectively) (Supplementary Table S9). Necrosis showed an interobserver variability as previously described (κ=0.467) (Supplementary Table S9).[8,14]

DISCUSSION

ANCA-associated necrotizing vasculitis is a heterogeneous entity with a wide variation in clinical course and prognosis. Patient survival has improved, but renal involvement is still associated with substantial morbidity and mortality.[35,36] The histopathologic analysis of renal biopsy has the potential to provide a status of the activity and chronicity of the disease and to predict response to treatment and renal prognosis.[37] Because the inflammatory lesions in ANCA-associated GN are diverse, a classification was proposed to categorize them.[38] Over the last years, the results of several studies using multivariable approaches have suggested that the proposed histopathologic classes alone might not be sufficient to predict renal outcome.[27] In many of these studies, the number of normal glomeruli and the degree of TA/IF remained important factors affecting renal outcome.[6,10,22,26] Therefore, we investigated renal biopsies in detail to evaluate which type of glomerular lesion affects the clinical outcome.

It was previously proposed that a damaged glomerulus has the potential of recovering and a fresh lesion may be reversible at least to a certain extent.[6,39] We aimed to find the cutoff where glomerular injury becomes relevant as it results in scarring and is not reversible under treatment. In our study, we provide evidence that all lesions need to be considered, emphasizing the importance of normal glomeruli and an early diagnosis. Studies of repeat biopsies strengthen this hypothesis, as they have demonstrated the progression of chronic lesions in necrotizing GN over time.[39,40] This could explain the variable outcomes of patients that are labeled as crescentic and mixed in the validation of the classification.[11,22,24,26] Hilhorst *et al.* demonstrated how the distinction between the 2 categories became apparent by adding the percentage of normal glomeruli.[10] In the past, several studies have already suggested that the percentage of normal glomeruli is a reliable predictor.[7,10,26,27,39] Our multivariable regression confirmed these results and identified the percentage of normal glomeruli as the only independent predictor of renal outcome. Repeatedly, factors such as the initial eGFR and the degree of TA/IF have been shown to predict renal outcome in ANCA-associated GN.[6,7,41] Our statistical models showed that these parameters have an influence on patients' outcome, but not an independent one. Adding the eGFR at the time of diagnosis and the degree of TA/IF to the amount of normal glomeruli, however, did improve the statistical power; and in



b

Renal survival 36 months

Risk group	**Training** (95% CI)	**Validation** (95% CI)
Low	100% (100)	100% (100)
Medium	84% (75–95)	83% (72–96)
High	32% (17–60)	22% (9–56)

Figure 5 | Validation of the risk score. (**a**) Kaplan-Meier curve demonstrating renal survival of patients in the training and the validation cohort according to their risk group (low, 0 points; medium, 2–7 points; high, 8–11 points). (**b**) Renal survival rates of patients in both cohorts at 36 months of follow-up. CI, confidence interval; HR, hazard ratio.

a regression tree, cutoff values for these parameters were detected. We performed a subanalysis to ensure that small-sized biopsies did not affect our results. We suggest to be cautious interpreting biopsies with only a few glomeruli (<7 glomeruli per biopsy) because of a potential sampling error, but our findings did not differ when excluding small-sized biopsies and thus did not demand a minimum size for tissue adequacy. Using stepwise multiple regression, we developed a scoring system combining statistically relevant histopathologic and clinical variables. We created a risk score with 3 differing risk groups that were independent of immunosuppressive treatment. In our prospective training cohort, patients received similarly aggressive immunotherapy and the treatment did not influence our scoring system. Our risk model was then validated in an independent patient cohort and showed comparable results with a reasonably high concordance.

There are limitations to our study. The study was observational, and it was restricted to German patients with a new diagnosis of ANCA-associated GN in the years 2000 to 2015. The risk score, however, defined 3 renal risk groups and determined patients at high risk of ESRD. Patients in the

high-risk group who needed dialysis at the time of diagnosis were unlikely to recover renal function. Over the last decades, immediate patient survival has improved and the longer-term outcome has become more important. Studies have demonstrated stabilization and improvement of renal function under aggressive immunosuppressive therapy.[42,43] Disease- and immunotherapy-related complications, in particular infections, now account for the majority of deaths during the first year. There is a need to find the right balance between gaining rapid control of the disease without exposing patients to undue risks of heavy immunosuppression. All our patients with the maximum score (N2T1G1, 11 points) developed ESRD, revealing a potential point where treatment attempts for renal survival purposes seem futile. We believe that a discussion about the reduction of the immunosuppressive load is feasible in patients who remain dialysis dependent after, for example, 4 weeks' time. Using our scoring system in the future may help to depict those patients who might be spared from aggressive immunosuppression. These results will need to be confirmed in a prospective interventional study to advocate a timely reevaluation of the induction treatment for renal survival purposes.

In conclusion, we developed a risk scoring system on the basis of 3 clinicopathologic features to predict ESRD in ANCA-associated GN. It includes the parameters normal glomeruli, TA/IF, and eGFR highlighting the importance of an early diagnosis. The risk score was validated in an independent patient cohort. In the future, the renal risk score for ANCA-associated GN may be useful to clinicians in predicting individual renal survival probabilities and directing therapy and to researchers in designing and interpreting clinical studies.

METHODS

Patients

A total of 205 patients with ANCA-associated GN with a diagnosis of granulomatosis with polyangiitis (n = 93) and microscopic polyangiitis (n = 112) were included in this observational study (101 proteinase 3–positive patients and 104 myeloperoxidase-positive patients). Patients with an eosinophilic granulomatosis with polyangiitis were not included. Patients with coexisting glomerular diseases, for example, concomitant IgA, antiglomerular basement membrane, or lupus nephritis, were also excluded. For the prospective training cohort, 115 patients were recruited at the time of disease onset between August 1, 2010 and October 31, 2013 from 10 centers in Germany. From November 1, 2016 through January 31, 2017, a second cohort of 90 patients with ANCA-associated GN in the years 2000 to 2015 was recruited from a separate single center in Germany for the retrospective validation cohort. The established inclusion criteria were as follows: (i) ANCA detected in the sera, (ii) necrotizing and/or crescentic GN in the renal biopsy, and (iii) patient follow-up for at least 12 months (including patients who died within these 12 months but excluding patients who were lost to follow-up). The trial was performed in accordance with the Declaration of Helsinki.

Data

After informed consent was obtained, patient data and renal biopsies were collected according to the guidelines of the respective local ethics committees (approval numbers PV3162 and PV4068). For the prospective training cohort, long-term follow-up data were acquired from clinical notes, discharge letters, and a 3 monthly questionnaire completed by health care providers. Baseline characteristics assessed were patient's age, sex, diagnosis, ANCA subtype determined by indirect immunofluorescence and enzyme-linked immunosorbent assay, serum creatinine level, eGFR calculated using the 4-variable Modification of Diet in Renal Disease equation, and immunosuppressive medication.[44] The *eGFR for dialysis-dependent patients* was defined as 0 ml/min. *Recovery of renal function* was defined as independence from dialysis after the initial need for renal replacement therapy.

Histopathologic evaluations

Details of the histopathologic evaluations are found in Supplementary Appendix S1. Biopsies were examined by 3 independent nephropathologists who were blinded to patients' data. All biopsies from the initial training cohort were reviewed by 2 pathologists, and observer agreement was also assessed. For statistical analysis, a preset level of biopsy adequacy was set at a minimum of 5 glomeruli per biopsy. A subsequent analysis of biopsies with at least 7 glomeruli was performed to verify biopsy adequacy. During the initial analysis of the 115 biopsies from the training cohort, inflammatory glomerular changes were documented in detail (Supplementary Appendix S1).

To determine a possible contribution of the predictive value for a classification, tubulointerstitial and pre- and postglomerular vascular changes were investigated (Supplementary Appendix S1).

Outcome measures

The primary end point of the study was the cumulative percentage of patients who developed ESRD over time censored by death. *ESRD* was defined as the need for long-term renal replacement therapy, for example, dialysis or renal transplantation. Renal survival time for each patient was computed from baseline evaluation at the time of biopsy to the last time of follow-up or the time point of reaching ESRD.

Statistical analyses

Data were analyzed using SPSS version 20.0 (IBM Corp., Armonk, NY), RStudio version 0.99.491, an integrated development environment for R version 3.2.2 (R Core Team, Vienna, Austria),[45] and GraphPad Prism version 5.01 software (GraphPad Software, La Jolla, CA). Data are expressed as median with IQR or as n (%). Univariate and multivariable Cox proportional hazards regression analyses were performed, as appropriate. Concordance levels using the Harrell's *c* concordance were calculated to discriminate the prediction of different glomerular damage scores for ESRD.[46] Renal survival was assessed using the Kaplan-Meier method. Regression tree analysis was performed to derive cutoff values for variables, which influence the time to ESRD in a statistically significant manner to develop a clinicopathologic scoring system. The decision tree analysis was performed using the R package *rpart* with pruning (version 4.1-8).[47] To test for influences of treatment on the scoring system, age and weight of patients needed to be taken into consideration. A multiple linear regression model was used to investigate the potential influence of the initial and cumulative cyclophosphamide dosages on score variables (eGFR, normal glomeruli, and TA/IF). Validation analysis was performed using the methodology described by Royston and Altman.[33] The IBS was used to test the inaccuracy of our regression tree for probability forecasts of a dichotomous event in

cohorts with differing patient follow-up.[34] Interobserver agreement was assessed using Cohen's κ. A 2-sided P value of <0.05 was considered statistically significant.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This work was supported by grants from the Deutsche Forschungsgemeinschaft (KFO 228 STA193/9-1 and STA193/9-2 to RAKS and SFB 1192 C1 and B6 to RAKS and TW), and SRB was a research fellow employed by Project C1 of the SFB 1192. We thank Ulrike Langbehn and her team for the excellent technical work. We acknowledge the study nurses Birgit Goldmann, Eugen Kinzler, Samaneh Liagos, and Julia Fehlert for their thorough and dedicated collection of clinical data. We also acknowledge the statistical help of Ronald Simon. We also thank the following participating physicians: J. Steinhoff, G. Wolf, M.K. Kuhlmann, J. Beige, C.S. Haas, G.v.d. Loo, K. Grass, M. Rösch, S. Böse, T. Kahlert, F. Kunigk, D. Eitze, F. Lange-Hüsken, F. Köstler, S. Pawlow-Handt, M. Weiß, S. Mees, R. Weitzell, D. Duvigneau, W. Meyer, L. Arndt, H. Altrogge, J. Wogan, H.G. Wullstein, H.D. Fernow, W. Gompf, K. Meßtorff, A. und B. Born, T. Gohlke, J. Bachmann, C. Hülst, S. Tietz, B. Perras, S. Köhler, U. Dieball, F. Köstler, P. Jahn, L. Rohland, B. Ruhberg, C. Assmus, G. Marienhagen, C. Kuhlmann-Eilers, S. Abshagen, C. Harnisch, J. Masselmann, D. Zolotov, G. Becker, E. Rensinghoff, A. Trautmann, M. Spangenberg, W. Stolle, B. Pfeiffer-Zeller, R. Abu-Daher, J. Fleck, H. Hain, A. Pustelnick, K. Bestvater, M. Schröder, B. Kaltenmaier, U. Jannert, C. Braun, E. Eger, H.J. Ludwig, K.v. Appen, A. Klemm, U. Hoffmann, G. Wirtz, C. Pätzold, T. Meiners, U. Stauf, M. Schulte-Vorwick, S. Braun, H. Bücker, R. Groddeck, D. Brückner, K.D. Tamm, K. Rickels, S. Mehnert-Aner, G. Vollgraf, and U. Neuhäuser-Piduhn.

SUPPLEMENTARY MATERIAL

Figure S1. Renal survival of patients in the training cohort with at least 7 glomeruli in their biopsy according to the individual components of the clinicopathologic score and Berden classification. Kaplan-Meier curves demonstrating renal survival of patients depending on cutoffs for the (**A**) percentage of normal glomeruli, (**B**) percentage of tubular atrophy and interstitial fibrosis (TA/IF), (**C**) glomerular filtration rate (GFR) at the time of diagnosis, and (**D**) histologic classification.

Figure S2. Correlation analyses between the initial treatment and clinicopathologic variables. The initial dosages of cyclophosphamide (CyP) of patients receiving i.v. CyP induction therapy (n = 101) were investigated for dependency on (**A**) age, (**B**) weight, (**C**) estimated glomerular filtration rate (eGFR), (**D**) tubular atrophy and interstitial fibrosis (TA/IF), and (**E**) percentage of normal glomeruli by using a multiple linear regression model. Lines represent univariate regression lines. Interactions between risk groups and other variables were used to test for differences in prescriptions between risk groups (green, low-risk group; yellow, medium-risk group; red, high-risk group). CyP prescriptions did not differ significantly.

Figure S3. Correlation analyses between the induction treatment and clinicopathologic variables. The cumulative dosages of cyclophosphamide (CyP) of patients receiving i.v. CyP therapy and with a survival of at least 3 months (n = 96) were investigated for dependency on patient's characteristics and histopathologic findings. Correlation analyses were performed for (**A**) age, (**B**) weight, (**C**) estimated glomerular filtration rate (eGFR), (**D**) tubular atrophy and interstitial fibrosis (TA/IF), and (**E**) percentage of normal glomeruli. Lines represent univariate regression lines. Interactions between risk groups and other variables were used to test for differences in prescriptions between risk groups (green, low-risk group; yellow, medium-risk group; red, high-risk group). Cumulative CyP dosages increased with weight; other variables did not significantly influence dosages.

Figure S4. Distribution of the sum score of clinicopathologic parameters. Histogram of the sum score in the training and the validation cohort. Vertical lines represent cutoff points that classify patients with end-stage renal disease into low (0 points), medium (2–7 points), and high (≥8 points) risk groups. The distribution of the sum score is comparable between training and validation cohorts.

Figure S5. Discriminatory power of the individual components of the clinicopathologic score in the validation cohort. Kaplan-Meier curves of the individual components in correlation with (**A**) normal glomeruli, (**B**) tubular atrophy and interstitial fibrosis (IF/TA), and (**C**) glomerular filtration rate (GFR) used to predict end-stage renal disease in the validation cohort. (**D**) Renal survival of the validation cohort according to the classification.

Figure S6. Regression tree analyses of the validation and the combined cohorts. Regression tree analyses were performed (**A**) for the validation cohort and (**B**) for both cohorts combined. Cutoffs were detected for the percentage of normal glomeruli (3.5%, 7.5% and 5.4%, 20.3%, 32.8% respectively), percentage of tubular atrophy and interstitial fibrosis (TA/IF; 17.5% and 27.5%), estimated glomerular filtration rate (eGFR; 24 and 15.5 ml/min per 1.73 m^2), and age (71.5 years).

Figure S7. Risk score implementation into an application for mobile devices. It is a serviceable application with a visual estimate of renal prognosis.

Figure S8. Observer agreement. Agreement between the 2 pathologists in the detection of normal glomeruli and necrosis, crescents, and sclerosis in the initial training cohort of 115 patients with a new diagnosis of antineutrophil cytoplasmic antibody–associated necrotizing glomerulonephritis.

Table S1. Histopathologic lesions in the training cohort.

Table S2. Univariate analyses of histopathologic and clinical parameters of the training cohort.

Table S3. Univariate analyses of histopathologic and clinical parameters of the training cohort with ≥7 glomeruli in the biopsy.

Table S4. Multiple linear regression of the initial treatment in the training cohort.

Table S5. Multiple linear regression of the cumulative treatment in the training cohort.

Table S6. Application of plasma exchange in the training cohort.

Table S7. Integrative Brier score (IBS).

Table S8. Organ manifestations in the training cohort.

Table S9. Observer agreement of histopathologic parameters in the training cohort.

Supplementary Appendix S1: Histopathologic evaluations

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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