The survival nomograms for anti-neutrophil cytoplasmic antibody-associated glomerulonephritis patients with a follow-up of more than one year

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Abstract

Objective

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis with kidney injury, manifested as ANCA-associated glomerulonephritis (AAGN), often portends a poor prognosis of renal function and life survival in long term.

Methods

A cohort of 339 AAGN patients were enrolled retrospectively. These patients survived and were followed up for at least 12 months after diagnosis in our centre. Multivariate Cox regression analysis and nomogram models were performed to determine the risk factors associated with renal survival and patient survival.

Results

The median follow-up time of all 339 patients was 65.2 (IQR 45.1, 91.3) months and the median age was 61(IQR 53, 69) years. In order to analyse the impact of the factors on renal survival, we divided the patients into 2 groups: non-dialysis group (204 patients without dialysis at the final visit) and dialysis group (135 patients with maintaining dialysis). The patients in dialysis group had lower haemoglobin level, lower eGFR level, lower platelets count, more daily urine protein, and higher Birmingham Vasculitis Activity Score (BVAS) at admission than those in non-dialysis group. Multivariate Cox regression revealed that low haemoglobin (HR=0.977, 95%CI 0.965-0.990, p<0.001), low eGFR (HR=0.957, 95%CI 0.941-0.973, p<0.001) and high proteinuria (HR=1.139, 95%CI 1.055-1.230, p=0.001) at admission were independent risk factors for developing maintaining dialysis. A nomogram was established based on the results of multivariate Cox analysis and the internal bootstrap resampling approach showed the C-index of the nomogram was 0.83. Then we divided all patients into death group (n=99) and survival group (n=240). The patients in death group had older age, more hypertension, more chronic lung disease, lower platelets count, lower serum albumin, higher BVAS and lower eGFR at admission than those in survival group. Multivariate Cox regression revealed that the status of maintaining dialysis (HR 3.51, 95% CI 1.91-6.47, p<0.001) and old age (HR 1.07, 95% CI 1.04-1.09, p<0.001) were independent risk factors for all-cause mortality. Again, a nomogram was established and the C-index was 0.74.

Conclusion

We analysed the independent risk factors for maintaining dialysis and all-cause mortality in AAGN patients with a follow-up of more than 12 months. The two proposed nomograms were of predictive value.

Key words

anti-neutrophil cytoplasmic antibody, vasculitis, kidney, survival, nomogram

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Introduction

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a group of diseases characterised by inflammatory and necrotising changes of the small-vessel wall. Chapel Hill Consensus Conference (CHCC) classified AAV as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (1). MPA with positive myeloperoxidase (MPO)-ANCA is predominant in East Asian countries (2). Renal injury, manifested as ANCA-associated glomerulonephritis (AAGN), is common in AAV, and presents in almost 70% of GPA patients and almost 100% of those with MPA (3, 4).

The AAGN patients often portends a poor prognosis of renal function and life survival. In a previous study (5), we retrospectively investigated 350 AAGN patients in our centre to identify the outcomes of mortality and end-stage renal disease (ESRD) within 6 months since diagnosis. We found that AAGN patients had high rates of mortality (11.4%) and ESRD (27.1%) in the first 6 months since admission. The factors of high Birmingham Vasculitis Activity Score (BVAS), high daily urine protein and low eGFR were independent risk factors for ESRD, while the factors of age ≥65 years, high leukocyte counts, high BVAS, infection and low serum albumin were independent risk factors for all-cause mortality in the first 6 months (5).

With the development in the management of AAGN patients, many patients had relatively long survival. It was reported that the 5-year renal survival rate of AAGN was 60–75% (6, 7). Hilhorst *et al*. conducted a 30-year follow-up study which showed that the 1-, 5- and 10-year survival of AAGN was 77%, 66% and 49% respectively (8). It was reported that the factors including high serum creatinine (Cr) at diagnosis, GPA compared with MPA, high proteinuria, hypertension and interstitial lung disease (ILD) were correlated with poor renal outcomes, and old age and low renal function at diagnosis were closely correlated with mortality (6-7, 9). Most studies classified these risk factors (including parametric and categorical variables) into hierarchical variables and then combined with Kaplan-Meier curve to show the differences in prognosis based on different levels of the above risk factors. In this study, we retrospectively enrolled our AAGN patients who survived and were followed up for more than 12 months after diagnosis, aiming to identify risk factors and predict long-term outcome of AAGN patients by multivariate Cox regression analysis and nomogram models.

Patients and methods

Study patients

The AAGN patients were diagnosed at the First Affiliated Hospital of Zhejiang University School of Medicine between January 2004 and June 2018. They were followed up until December 2020, lost to follow-up or death. The patients who survived and were followed up for at least 12 months were investigated in this study. Patients included met the following criteria (10): 1. Diagnosis of AAV According to the definition from CHCC (1); 2. Renal involvement: proteinuria≥300 mg/day and haematuria (>5 erythrocytes/high-power field or >25/ul), with or without an elevated creatinine level attributed to the disease; 3. ANCA positivity. ANCA-negative patients were eligible for enrolment in the study if there was histologic confirmation of renal vasculitis.

Each patient's clinical and laboratory data at the time of diagnosis were collected from hospital records, including demographic characteristics, clinical presentations, laboratory parameters, immunosuppressive therapies and renal pathology (for those patients who received renal biopsy). Immunosuppressive therapies including prednisone only and combined immunosuppressants. The treatment protocol was decided by the competent physician. Generally, patients were treated by corticosteroids (0.6–0.8mg/kg/d) with intravenous cyclophosphamide (CTX) 15 mg/kg every 2–4 weeks and the maximum cumulative dose was 6-8g; or corticosteroids with mycophenolate mofetil (MMF) 1.0–1.5g/d (11-13). Patients with pulmonary haemorrhage, biopsy confirmed cellular crescents or

fibrinoid necrosis of small vessels received 500 mg pulse methylprednisolone for 3 days before CTX or MMF therapy. Interstitial lung disease (ILD) was defined by the following criteria: 1. The exclusion of another possible causes (such as infection, drugs and dust) of the development of ILD; 2. radiological evidence of ILD (reticular abnormality or honeycombing with or without traction bronchiectasis on CT scan) (14).

The outcomes included maintaining dialysis and all-cause mortality. Maintaining dialysis was defined as the requirement for renal replacement therapy for more than 3 months with no signs of renal recovery (7). The mortality was defined as death due to all causes. Relapse was defined as an increase in BVAS of 1 point or more during follow up (15).

In order to analyse the impact of the factors on the renal survival, we divided the patients into 2 groups. The patients who were independent of dialysis at the final visit were in non-dialysis group, and the patients who reached maintaining dialysis were in dialysis group. In order to analyse the impact of the factors on all-cause mortality, we divided the patients into death group and survival group.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation. The normality of distribution was tested by Kolmogorov-Smirnov test. Student t test was used for parametric comparisons. Not normally distributed data are presented as median with interquartile ranges (IQR), and the Mann-Whitney U-test was used for comparisons. Categorical variables were described as number and percentage and was compared by using χ^2 (Fisher's exact test). Patient and renal survival were studied by the Kaplan-Meier method, with differences between groups investigated using the log-rank test. Cox regression model with backward selection (exit threshold: $p<0.05$) was used to identify variables associated with all-cause mortality or the status of maintaining dialysis. In Cox regression model, we defined the categorical variable as yes or no, and the continuous variable as every increase of 1. Through the rms package in R version 4.0.3 (R Foundation for Statistical Computing; http://www.r-project.org/), a nomogram based on the results of multivariate analysis was built. The maximum score of each variable was set as 100. The concordance of the nomogram was measured based on the Harrell concordance index (C-index). A p-value of less than 0.05 was considered significant.

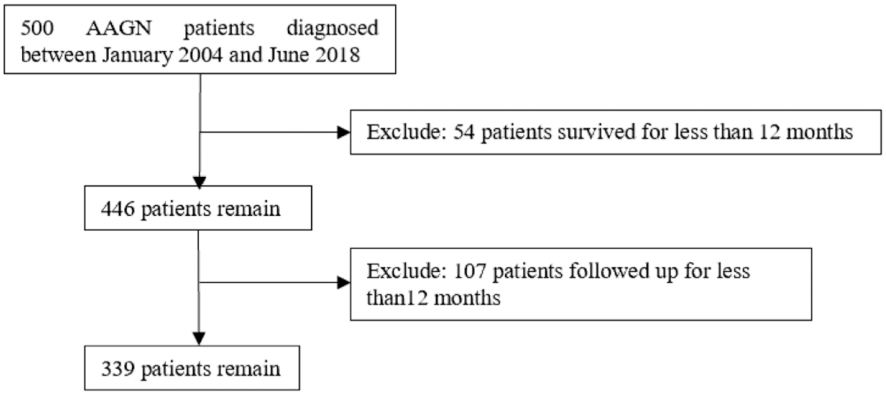

Fig. 1. Flow chart of patient screening.

Table I. Characteristics of AAGN patients with different renal outcomes.

Characteristic	Non-dialysis	Dialysis	*p* value
Case, n	204	135	
Age (years)	59.8 ± 14.0	59.5 ± 12.6	0.851
Life survival time (months)	68.9 ± 33.6	72.9 ± 41.5	0.347
Gender (Male/Female), n	82/122	62/73	0.314
Hypertension, n (%)	82 (40.2)	75 (55.6)	0.007
Diabetes, n (%)	14 (6.9)	12 (8.9)	0.535
Leukocyte counts (10^9/l)	7.9 ± 3.5	8.0 ± 3.6	0.75
Haemoglobin (g/l)	95.1 ± 20.8	76.8 ± 15.2	<0.001
Platelets counts (10^9/l)	244.4 ± 101.7	199.5 ± 77.8	<0.001
Daily urine protein (g)	1.7 ± 1.8	3.0 ± 2.2	<0.001
Urine red cell counts (n/μl)	153.0 (46.3, 571.7)	301.5 (112.4, 765.4)	0.471
Albumin (g/l)	33.1 ± 6.2	32.5 ± 4.8	0.351
Globulin (g/l)	31.3 ± 6.1	30.1 ± 5.8	0.067
Creatinine (μmol/l)	220.2 ± 197.2	558.6 ± 302.6	<0.001
EPI-GFR (ml/min/1.73m^2)	46.1 ± 35.6	12.9 ± 14.2	<0.001
ESR (mm/h)	66.3 ± 37.8	74.5 ± 38.3	0.069
CRP (mg/l)	17.2 (3.7, 71.1)	16.0 (4.4, 50.1)	0.196
MPO (RU/mL)	42.0 (19.7, 100.0)	60.0 (26.5, 100.0)	0.089
PR3 (RU/mL)	1.5 (1.1, 2.7)	1.4 (1.0, 2.0)	0.566
BVAS	14.1 ± 4.6	16.2 ± 3.8	<0.001
Renal biopsy, n (%)	106 (60.0)	54 (40.0)	
normal glomerular (%)	46.5 ± 25.6	25.1 ± 25.2	<0.001
Glomerular sclerosis (%)	22.7 ± 18.7	37.8 ± 26.7	<0.001
Cellular crescent (%)	6.4 (0, 13.8)	8.1 (0, 27.0)	0.04
Capillary necrosis, n (%)	40 (37.7)	16 (29.6)	0.381
Treatment			
Prednisone only/ combined immunosuppressants, n	67/124	47/70	0.396
Intravenous cyclophosphamide/ mycophenolate mofetil, n	61/63	38/32	0.551
Methylprednisolone impulses, n	71	52	0.083
Outcome			
Relapse, n (%)	36 (17.6)	25 (18.5)	0.886
Death, n (%)	35 (17.1)	64 (47.4)	<0.001

e-GFR: estimated glomerular filtration rate calculated by EPI formula; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANCA: antineutrophil cytoplasmic antibody; MPO, anti-myeloperoxidase; PR3: anti proteinase3; BVAS: Birmingham Vasculitis Activity Score.
Combined immunosuppressants: patients treated by prednisone combined with intravenous cyclophosphamide or mycophenolate mofetil.

Results

General data

We screened 500 AAGN patients and a total of 339 patients were finally included in this retrospective study. The flow chart was shown in Figure 1. The median follow-up time was 65.2 (45.1, 91.3) months and their median age was 61 (53, 69) years. According to the definition from CHCC (1), 306 out of 339 (90.3%) of these patients were classified as MPA and 33/339 (9.7%) as GPA. The comparison of clinical data between MPA and GPA groups is shown in the Supplementary table S1. The patients in MPA group had lower haemoglobin [83.0 (73.0, 98.0) g/l *vs*. 101.0 (81.0, 116.0) g/L, p=0.021], more daily urine protein [1.8 (0.8, 3.1) g *vs*. 1.0 (0.3, 1.7) g, p<0.001] and lower eGFR level [16.9 (8.0, 40.5) ml/min/1.73m^2 *vs*. 40.6 (11.8, 90.4) ml/min/1.73m^2, p=0.007].

Characteristics of AAGN patients with different renal outcomes

There were 204 patients in non-dialysis group and 135 patients in dialysis group. Characteristics at admission were shown in Table I. The patients in dialysis group had lower haemoglobin (76.8±15.2 g/l *vs*. 95.1±20.8 g/l, p<0.001), lower eGFR levels (12.9±14.2 ml/min/1.73m^2 *vs*. 46.1±35.6 ml/min/1.73m^2, p<0.001), lower platelets count (199.5±77.8×10^9/l *vs*. 244.4±101.7×10^9/l, p<0.001), more daily urine protein (3.0±2.2g *vs*. 1.7±1.8g, p<0.001), and higher BVAS (16.2±3.8 *vs*. 14.1±4.6, p<0.001) at admission than those in non-dialysis group. Thirty-five (17.2%) patients in non-dialysis group and 64 (47.4%) patients in dialysis group died during follow-up and the mortality was significantly different (p<0.001).

Risk factors for maintaining dialysis of AAGN patients

Multivariate Cox regression revealed that low haemoglobin (HR=0.977, 95%CI 0.965-0.990, p<0.001), low eGFR (HR=0.957, 95%CI 0.941-0.973, p<0.001) and high proteinuria (HR=1.139, 95%CI 1.055-1.230, p=0.001) at admission were the independent risk factors for developing maintaining dialysis, shown in Table II. Based on the multivariate model, the nomogram was constructed to calculate 1-, 3-, 5-year renal survival probability. At the top of the nomogram, we identified each risk factor based on the points scale and then summed the points of each factor. Finally, the 1-, 3-, 5-year renal survival probability was obtained based on the bottom point scale of the nomogram (Fig. 2). The calibration plots on bootstrap resampling validation are shown in Figure 3. The Concordance Index (C-index) for prediction of renal survival was 0.83.

Table II. Univariate and multivariate Cox regression analysis for maintaining dialysis.

Characteristic	Univariate			Multivariate		
	Hazard Ratio(95%CI)		p	Hazard Ratio(95%CI)		p
Age (years)	1.004	(0.992-1.017)	0.519			
Gender (Male *vs*. Female)	1.249	(0.890-1.754)	0.199			
Hypertension	1.648	(1.172-2.316)	0.004	1.256	(0.863-1.828)	0.233
Diabetes	1.199	(0.663-2.171)	0.548			
Leukocyte count	1.005	(0.958-1.054)	0.852			
Haemoglobin	0.960	(0.949-0.970)	<0.001	0.977	(0.965-0.990)	<0.001
Platelet count	0.996	(0.994-0.998)	<0.001	1.000	(0.997-1.002)	0.882
Daily urine protein	1.182	(1.115-1.253)	<0.001	1.139	(1.055-1.230)	0.001
Urine red cell counts	1.000	(1.000-1.000)	0.396			
Albumin	0.987	(0.958-1.016)	0.371			
Globulin	0.973	(0.945-1.001)	0.06			
Creatinine	1.002	(1.002-1.003)	<0.001			
eGFR	0.943	(0.928-0.958)	<0.001	0.957	(0.941-0.973)	<0.001
ESR	1.004	(0.999-1.009)	0.081			
CRP	0.998	(0.994-1.002)	0.324			
BVAS	1.091	(1.048-1.135)	<0.001	1.002	(0.952-1.054)	0.937
Combined immunosup pressants *vs*. prednisone only	0.840	(0.580-1.217)	0.357			
Methylprednisolone impulses	1.346	(0.878-2.063)	0.173			
Relapse	0.967	(0.626-1.494)	0.880			

eGFR: estimated glomerular filtration rate calculated by EPI formula; BVAS: Birmingham Vasculitis Activity Score.
Combined immunosuppressants: patients treated by prednisone combined with other immunosuppressants such as intravenous cyclophosphamide and mycophenolate mofetil.

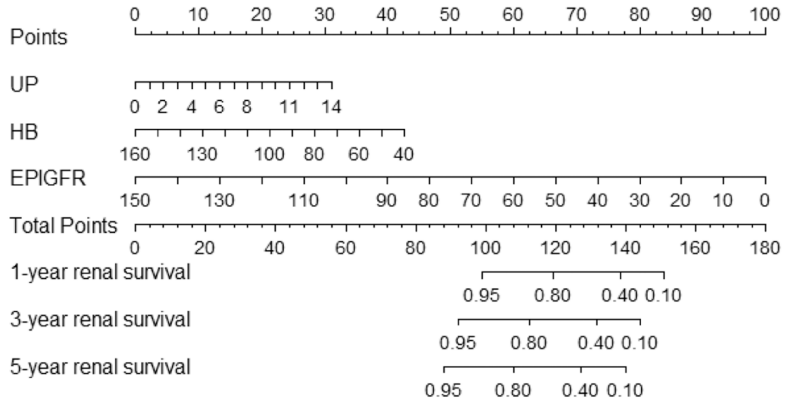

Fig. 2. Prognostic nomogram for predicting renal survival probability in AAGN patients. Prognostic factor's value is located on each variable axis, and a line is drawn upward to determine the number of point nomogram for predicting renal survival probability. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the survival axes to determine the probability of 1-, 3-, 5-year renal survival.

Characteristics of AAGN patients with different patients' survival outcomes

The overall mortality for all patients was 29.2% (99/339). According to the data available to us, the causes of death include infection, cardiovascular and cerebrovascular accidents, tumours, gastrointestinal bleeding and other unknown causes. The characteristics of

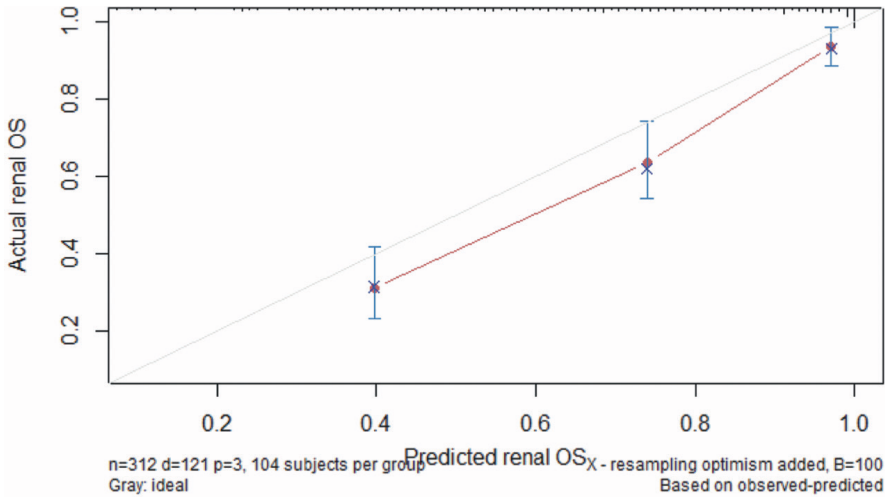

Fig. 3. Calibration curves of the nomogram predicting renal OS in patients with AAGN. Nomogram-predicted probability of OS is plotted on the x-axis; actual OS is plotted on the y-axis.
OS: overall survival.

Table III. Characteristics of AAGN patients with different survival outcomes.

Characteristic	Survival	Death	*p*
Case, n	240	99	
Age (years)	56.9 ± 13.4	66.6 ± 10.6	<0.001
Life survival time (months)	79.3 ± 36.1	49.2 ± 29.8	<0.001
Gender (Male/Female), n	96/144	48/51	0.184
Hypertension, n (%)	98 (40.8)	59 (59.6)	0.002
Diabetes, n (%)	16 (6.7)	10 (10.1)	0.272
Interstitial lung disease, n (%)	38 (35.6)	30 (47.5)	0.009
Leukocyte counts (10^9/l)	8.0 ± 3.6	7.9 ± 3.4	0.965
Haemoglobin (g/l)	89.2 ± 21.3	84.5 ± 19.3	0.056
Platelets counts (10^9/l)	235.8 ± 100.0	204.4 ± 79.3	0.002
Daily urine protein (g)	2.1 ± 2.1	2.4 ± 1.9	0.279
Urine red cell counts (n/μl)	203.6 (69.3, 575.1)	219.4 (49.4, 797.1)	0.217
Albumin (g/l)	33.3 ± 5.8	31.6 ± 5.3	0.011
Globulin (g/l)	30.7 ± 6.1	31.0 ± 5.9	0.678
Creatinine (μmol/l)	319.1 ± 272.8	442.9 ± 329.4	0.001
eGFR (ml/min/1.73m^2)	36.2 ± 34.4	24.8 ± 28.7	0.002
ESR (mm/h)	67.3 ± 37.9	74.5 ± 38.4	0.133
CRP (mg/l)	13.3 (3.3, 51.3)	29.9 (7.7, 90.1)	0.003
MPO (RU/mL)	43.1 (21.9, 100.0)	58.7 (24.0, 100.0)	0.833
PR3 (RU/mL)	1.4 (1.0, 2.2)	1.6 (1.1, 2.4)	0.348
BVAS	14.7 ± 4.3	15.6 ± 4.6	0.079
Treatment			
Prednisone only/ combined immunosuppressants, n	74/149	40/45	0.024
Intravenous cyclophosphamide/ mycophenolate mofetil, n	72/77	27/18	0.179
Methylprednisolone impulses, n (%)	90 (52.9)	33 (48.5)	0.568
Outcome			
Relapse (%)	40 (16.7)	21 (21.2)	0.352
Maintaining dialysis, n (%)	71 (29.6)	64 (64.6)	<0.001

eGFR: estimated glomerular filtration rate calculated by EPI formula; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANCA: antineutrophil cytoplasmic antibody; MPO: anti-myeloperoxidase; PR3: anti proteinase3; BVAS: Birmingham Vasculitis Activity Score.
Combined immunosuppressants: patients treated by prednisone combined with intravenous cyclophosphamide or mycophenolate mofetil.

the patients in death group (n=99) and survival group (n=240) were shown in Table III. The patients in death group had older age (66.6±10.6years *vs.* 56.9±13.4 years, $p<0.001$), more hypertension (59.6% *vs.* 40.8%, $p=0.002$), more ILD (47.5% *vs.* 35.6%, $p=0.009$), lower platelets count (204.4±79.3×10^9/l *vs.* 235.8±100.0×10^9/l, $p=0.002$), lower serum albumin (31.6±5.3g/l *vs.* 33.3±5.8g/l, $p=0.011$) and lower eGFR (24.8±28.7 ml/min/1.73m^2 *vs.* 36.2±34.4ml/min/1.73m^2, $p=0.002$) than those in survival group at admission. More patients in death group developed maintaining dialysis than survival group (64.6% *vs.* 29.6%, $p<0.001$) during follow up.

Risk factors for all-cause mortality in AAGN patients

Kaplan-Meier survival curve analysis revealed that age≥65 years (Log Rank=34.77, $p<0.001$) and the status of maintaining dialysis (Log Rank=22.23, $p<0.001$) were associated with poor survival (Fig. 4). The 5-year failure free survival rate of non-dialysis group and dialysis group were 86.3% and 71.5%, respectively. Multivariate Cox regression revealed that the status of maintaining dialysis (HR 3.51, 95% CI 1.91–6.47, $p<0.001$) and old age (HR 1.07, 95% CI 1.04–1.09, $p<0.001$) were independent risk factors for all-cause mortality (Table IV). The nomogram was constructed to calculate 3-, 5-year overall survival probability (Fig. 5). The calibration plots on bootstrap resampling validation are shown in Figure 6. The C-index for prediction of renal survival was 0.74.

Discussion

In this study, we retrospectively investigated the clinical characteristics and prognostic factors of 339 AAGN patients with a median follow up of 65.2 months. Their overall mortality was 29.2%. A European study (16) showed that the cumulative survival of AAV patients at 1, 2 and 5 years was 88%, 85% and 78%, which was higher than our cohort. This may be explained by the predominance of MPA in Asian AAV patients (2). Totally 90.3% of our patients were classified as MPA and the renal injury of MPA patients is more serious than that of GPA patients. The reason may be that the MPA patients had few ear, nose, or throat manifestations, which may lead to a delayed diagnosis and chronic and severe injury in kidneys (17). This also explained why the rate of biopsies is low, espe-

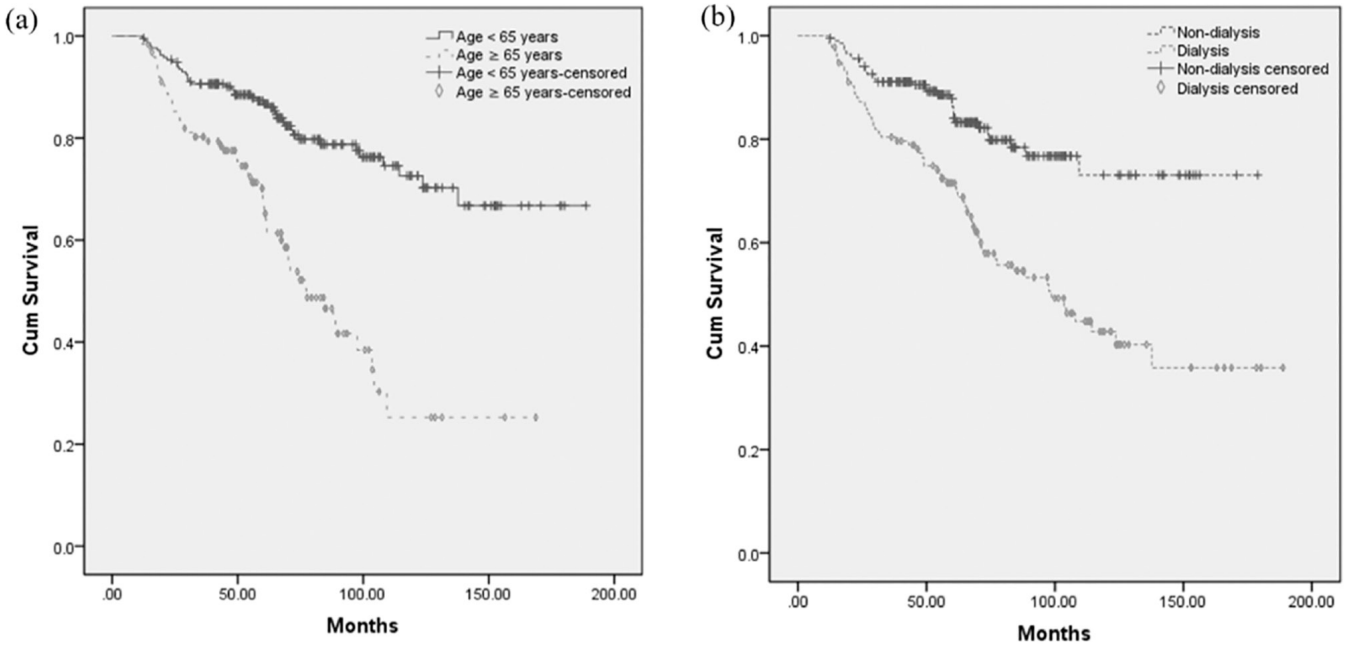

Fig. 4. Risk factors for survival of AAGN patients by the Kaplan-Meier survival curve analysis: **(a)** age; **(b)** maintaining dialysis.

Table IV. Univariate and multivariate Cox regression analysis for all-cause mortality.

Characteristic	Univariate		Multivariate	
	Hazard ratio (95%CI)	*p*	Hazard ratio (95%CI)	*p*
Age, years	1.066 (1.047-1.086)	<0.001	1.066 (1.040-1.094)	<0.001
Renal survival time, months	0.974 (0.968-0.981)	<0.001		
Gender (Male *vs*. Female)	1.325 (0.893-1.968)	0.162		
Hypertension	1.738 (1.163-2.598)	0.007	0.873 (0.536-1.422)	0.586
Diabetes	1.625 (0.844-3.127)	0.146		
Interstitial lung disease	1.663 (1.072-2.578)	0.023	1.429 (0.893-2.286	0.137
Leukocyte counts	0.986 (0.933-1.042)	0.627		
Haemoglobin	0.994 (0.984-1.003)	0.205		
Platelets counts	0.997 (0.995-0.999)	0.014	0.998 (0.995-1.001)	0.133
Daily urine protein	1.043 (0.955-1.140)	0.348		
Urine red cell counts	1.000 (1.000-1.000)	0.094		
Albumin	0.962 (0.929-0.996)	0.029	0.987 (0.937-1.040)	0.622
Globulin	1.007 (0.973-1.041)	0.703		
Creatinine	1.001 (1.000-1.001)	0.005		
EPI-GFR	0.990 (0.982-0.997)	0.005	1.003 (0.992-1.013)	0.603
ESR	1.003 (0.998-1.009)	0.257		
CRP	1.005 (1.002-1.009)	0.001	1.003 (0.998-1.008)	0.279
MPO	1.000 (0.998-1.001)	0.721		
PR3	1.004 (0.999-1.009)	0.131		
BVAS	1.058 (1.011-1.107)	0.014	1.023 (0.967-1.082)	0.432
Combined immunosuppressants *vs*. prednisone only	0.667 (0.435-1.021)	0.063		
Methylprednisolone impulses	0.828 (0.513-1.338)	0.441		
Relapse	1.157 (0.714-1.874)	0.553		
Maintaining dialysis	2.607 (1.724-3.943)	<0.001	3.514 (1.910-6.465)	<0.001

eGFR: estimated glomerular filtration rate calculated by EPI formula; BVAS: Birmingham Vasculitis Activity Score.
Combined immunosuppressants: patients treated by prednisone combined with intravenous cyclophosphamide or mycophenolate mofetil.

cially in dialysis group. A Chinese study reported that 135 out of 398 AAV patients (33.9%) died during a median follow-up duration of 25.5 months (range 1-196 months) (18). However, the above studies did not exclude deaths in the early stage of disease, which may be due to strong disease activity. Since we analysed the risk factors for outcomes in the first 6 months in our previous study (5), in the present cohort we excluded the patients who lost follow-up or died within 1 year to analyse the outcomes due to chronic disease progression in a median follow up of 65.2 months.

The present study showed that the risk factors for ESRD included lower haemoglobin, more proteinuria and poor renal function at admission. It was commonly reported that renal function at admission was associated with both short-term and long-term renal prognosis (6-7, 19). Proteinuria as a risk factor was less or not reported in studies with short follow-up time (7, 19-20). Córdova-Sánchez *et al*. (6) reported a cohort of AAV patients with a median follow-up of 40.5 months and found proteinuria was of predictive value for renal outcome. So, we may consider proteinuria as a risk factor for long-term renal prognosis, which was similar with other kidney diseases such as IgA nephropathy (21).

Old age was commonly reported as a risk factor for mortality in AAV patients (17, 22-23). Many reported studies divided people into two groups according to age (mainly 65 years old) to analysis prognosis. Then Kaplan-Meier survival curve would be plotted by two age levels and revealed that elderly patients had a worse outcome (6-7, 24). The Kaplan-Meier survival

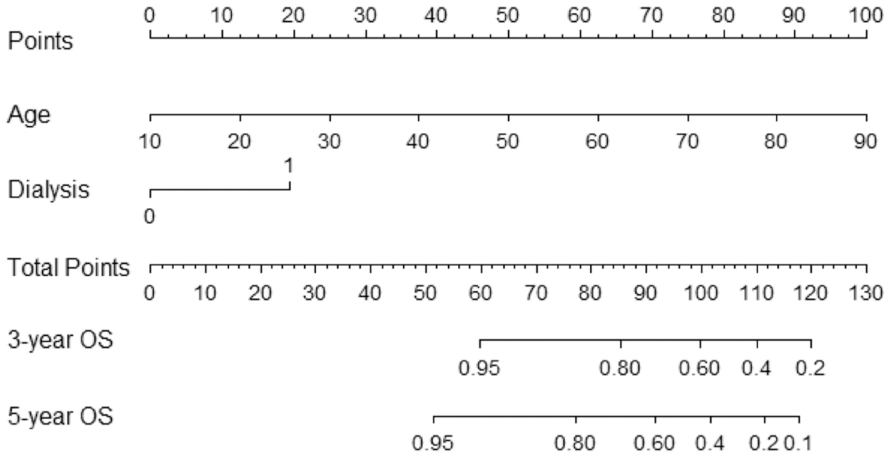

Fig. 5. Prognostic nomogram for predicting the overall survival probability of patients with AAGN. OS: overall survival proportion.

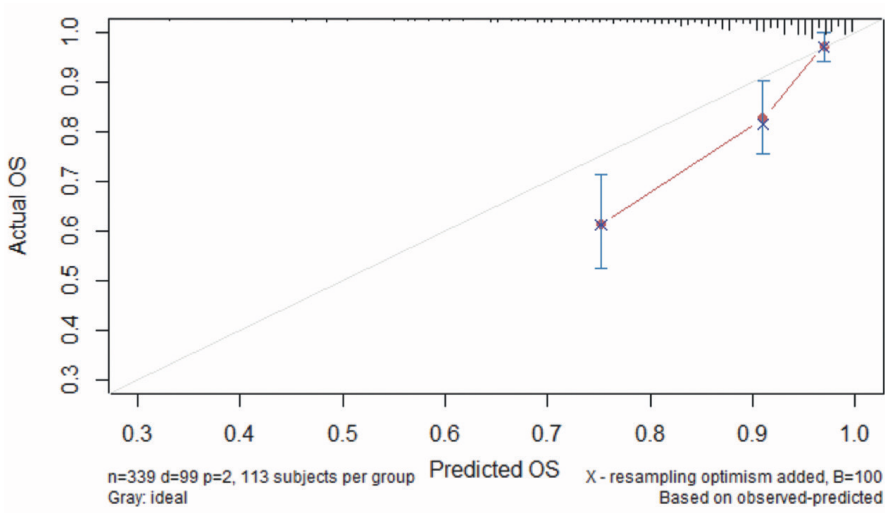

Fig. 6. Calibration curves of the nomogram predicting OS in patients with AAGN. OS, overall survival. Nomogram-predicted probability of OS is plotted on the x-axis; actual OS is plotted on the y-axis.

curve in present study showed the same results. A study in Japan found that renal function was not associated with overall survival in MPA patients with renal involvement (25). But there were more studies on the contrary (6-7, 24). The present study supported that renal function level was of predictive value for survival. However, the serum creatinine cut-off level at diagnosis for a poor outcome was quite different in studies (7, 25-26). BVAS was reported to be a predictive factor of mortality in AAGN patients (27-28), while other studies showed the opposite results (24-25). The BVAS was used to evaluate the symptoms of nine systems (29). We showed that when performing univariate analysis, BVAS was a risk factor for both ESRD and all-cause mortality. But the predictive value was absent when adjusted for other factors. To accurately predict clinical outcomes, we developed nomogram models in AAGN patients. The prognostic nomogram performed moderate accuracy in predicting survival, supported by the C-index 0.83 for renal survival and 0.74 for life survival. We showed that eGFR level at the time of diagnosis was the strongest risk factor for ESRD and advanced age was the strongest risk factor for all-cause mortality.

This study had obvious limitations. Due to the single-centre and retrospective characteristics, the established models may be limited by the potential differences among regions and treatments, so it is necessary to add perspective validation in other AAGN cohorts. Moreover, only a part of patients received renal biopsy, and we did not analyse the renal pathological results. In addition, in the survival analysis of patients, we did not obtain the exact death cause, so we did not analyse the cardiovascular death, tumour and so on.

In conclusion, we analysed the independent risk factors and plotted nomograms for maintaining dialysis and all-cause mortality in AAGN patients with a long-term follow-up. The two nomograms were of predictive value and may help in the clinical management for AAV patients with kidney injury.

Statement of ethics

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (No. [2020]571). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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