Validation of the ANCA Renal Risk Score and Modification of the Score in a majority-owned MPO positive Chinese cohort

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Abstract

Objective: We aimed to validate and modify the renal risk score for antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (AAGN) in a Chinese cohort with a majority of myeloperoxidase (MPO)-positive patients.

Methods: A total of 285 AAGN patients with biopsy-proven in our center were retrospectively included. Patients were randomly assigned to the development set (n=201) and the validation set (n=84). We calculated the renal risk score and analyzed the clinicopathological characteristics and follow-up data. The nomogram was constructed based on the independent prognostic factors identified by the multivariable Cox regression and then compared with the renal risk score.

Results: Over a median follow-up period of 41.3 (20.0-63.8) months, 84 (29.5%) patients reached end-stage kidney disease (ESKD). In the development set, hypertension (HR=2.163, 95%CI 1.083-4.322, P=0.029), high serum creatinine (HR=1.002, 95%CI 1.001-1.003, P<0.001), high daily urine protein (HR=1.343, 95%CI 1.148-1.571, P<0.001), high glomerular sclerosis (HR=13.983, 95%CI 3.496-55.923, P<0.001), and interstitial fibrosis>50% (HR=4.179, 95%CI 1.900-9.192, P<0.001) were independent risk factors for ESKD, and these indicators were included in the nomogram. The C-indices of the nomogram model in the development set, validation set, and all-data set were 0.838 (0.785-0.891), 0.794 (0.774-0.814), and 0.822 (0.775-0.869), respectively, which were higher than those of the renal risk score model, 0.801 (0.748-0.854), 0.746 (0.654-0.838) and 0.783 (0.736-0.830), respectively. And the net reclassification improvement and the integrated discrimination improvement further illustrated the higher predictive ability of the nomogram.

Conclusion: We present a nomogram as a practical tool to predict renal outcomes in Chinese patients with an MPO-ANCA glomerulonephritis.

Keywords: Anti-neutrophil cytoplasmic antibody, Vasculitis, End stage kidney disease, Prognosis

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic vasculitis, including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[1] A recent study that included 1230 patients from 31 countries showed that 82.2%, 58.6%, and 26.4% of patients with MPA, GPA, and EGPA had renal involvement, respectively.[2] Renal involvement of AAV typically presents with rapidly progressive glomerulonephritis, which is also named ANCA-associated glomerulonephritis (AAGN).[3] AAGN and its severity are associated with poor prognosis.[3-5] It was reported that the death risk of MPA patients increased to a hazard ratio of 3.7 upon the presence of renal insufficiency at diagnosis, while for GPA patients, the risk increased to 5.1 upon the presence of renal dysfunction and 8.2 upon dialysis dependence.[5]

Many studies have identified some clinical factors that could predict the renal outcome of AAV patients. For 350 AAGN patients in our center, 95 patients reached ESKD within the first 6 months after diagnosis, and the high Birmingham Vasculitis Activity Score (BVAS), high daily urine protein, and low estimated glomerular filtration rate (eGFR) were independent risk factors for ESKD in short term.[6] In addition, we included 339 AAGN patients who were followed up for at least 12 months after diagnosis, 135 patients entered maintenance dialysis, and the low hemoglobin, low eGFR, and high proteinuria were independent risk factors for developing maintenance dialysis in long term. Then we developed a nomogram with a C-index of 0.83.[7] However, we did not include renal pathological data and did not divide patients into a development set and a validation set in the above studies. Renal pathology is known to be of great value in predicting renal prognosis. Several studies showed that a high percentage of normal glomeruli predicted a good prognosis, whereas a high percentage of sclerotic glomeruli predicted a poor prognosis.[8,9] Recently, Brix *et al.* proposed a model (hereafter Brix model) for predicting renal outcomes in AAGN patients, including renal function, percentage of normal glomeruli, and percentage of interstitial fibrosis and tubular atrophy.[10] However, the patients included in their model had a ratio of myeloperoxidase (MPO)-ANCA positivity to proteinase 3 (PR3)-ANCA positivity of approximately 1:1, which was different from the Chinese population with the dominant positivity of MPO-ANCA. The main purpose of this study was to validate the Brix model and modify it in combination with other clinicopathological data to construct a nomogram to predict the risk of ESKD in Chinese AAGN patients.

Materials and Methods

Patient Selection

We retrospectively screened the AAV patients who were admitted to the First Affiliated Hospital of Zhejiang University School of Medicine between February 2004 and December 2020. The inclusion criteria were as follows: (1) newly diagnosed and previously untreated AAV, following the criteria of the Chapel Hill Consensus Conference;[1] (2) renal involvement was confirmed by renal biopsy. The exclusion criteria were as follows: (1) secondary vasculitis, including lupus nephritis, propylthiouracil-induced AAV, or other connective tissue diseases; (2) complicated with any other primary or secondary glomerular diseases, such as immunoglobulin A nephropathy, anti-glomerular basement membrane disease, or diabetic nephropathy, etc. The enrollment flowchart was shown in Figure 1. This study has been approved by the Ethics Committee of our hospital (No.2020617) and performed following the Declaration of Helsinki. All the patients provided informed consent.

Clinical and Laboratory Parameters

Clinical and laboratory data included age, gender, smoking history, routine blood analysis, serum albumin, serum creatinine, eGFR, daily urine protein, urinary red blood cell, erythrocyte sedimentation

rate (ESR), C-reactive protein (CRP), parathyroid hormone (PTH), serum ANCAs. Disease activity was scored using the BVAS.[11] Hypertension was defined as repeated systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg more than three times on different days or taking antihypertensive medication. Diabetes mellitus was defined as fasting glucose ≥7.0 mmol/l, 2-hour post-load glucose ≥11.1 mmol/l, self-reported diabetes or currently using diabetes medication. Heart disease was defined as having a history of at least one of the following diseases: congestive heart failure, coronary heart disease, and cardiac arrhythmia. Malignancy was defined by ICD-10 codes C00-C97. Infection was defined as any culture-positive infection from blood, urine, or cerebrospinal fluid specimens, or having an indication of infection in imageology. Anemia was defined as hemoglobin <130 g/l for males and hemoglobin <120 g/l for females. Since the listed predictors were relatively objective measurement indicators, and the outcome indicators were determined after the measurement of the predictors, it could ensure that the measurement results of the predictors were blinded to the outcome indicators.

Renal Histopathology

Renal tissues were examined by light microscopy, immunofluorescence, and electron microscopy using standard procedures. The percentage of glomerulosclerosis and crescents were assessed quantitatively. Tubular atrophy and interstitial fibrosis were semi-quantitatively sorted into the following two categories:≤50% and >50%. All of the renal biopsies were examined and evaluated by two experienced pathologists independently, who confirmed the diagnosis of AAGN.

Renal Risk Score Model

We calculated the renal risk score for each patient according to the Brix model,[10] which included the proportion of normal glomeruli (N0=0 point: >25%; N1=4 points: 10%-25%; N2=6 points: <10%), the degree of tubular atrophy/interstitial fibrosis (TA/IF)(T0=0 point: ≤25%, T1=2 points: >25%), the eGFR at diagnosis (G0=0 point: >15ml/min/1.73m^2; G1=3 points: ≤15ml/min/1.73m^2). Patients were classified into low-risk (0 point), medium-risk (2-7 points), and high-risk groups (8-11 points) according to the sum of their scores.

Follow-Up and Outcome Definition

The patients were followed up via out- and inpatient electronic medical record systems and telephone interviews. The last follow-up was on June 30th, 2021. Remission was defined as the absence of new-onset and persistent active manifestations of vasculitis, decreased or stable serum creatinine levels, and inactive urine sediment, as indicated by a BVAS score of zero. Recovery of kidney function was defined as independence from dialysis after the initial need for renal replacement therapy (RRT). ESKD was defined as the requirement for long-term RRT, such as dialysis and renal transplantation. Although there was no blinding of outcome assessment, the outcome measurement was unlikely to be influenced by the lack of blinding.

Statistical Analysis

Statistical analysis was carried out using R software (version 4.0.2; http://www.R-project.org) and SPSS 26.0 software (SPSS Inc., Chicago, IL, USA). Continuous data with normal distribution were represented as the mean ± standard deviation (SD) and analyzed using the t-test, while data with non-normal distribution were expressed as the median (interquartile range) and tested with the nonparametric Mann–Whitney U-test. Categorical variables were expressed as numbers (proportion), and compared by chi-square or Fisher's exact test. Survival analysis was conducted by the Kaplan-Meier Analysis (Log Rank test).

For nomogram construction and validation, the cohort was randomly divided into the development set and validation set in a ratio of 7:3 by R software. To achieve the reproducibility of results, the initial seed was set to 131. The final nomogram model was built based on the results of the multivariate Cox regression analysis. In the nomogram, vertical lines should be drawn from the correct status or value of each prognostic factor to the "points" axis to obtain the corresponding risk score. It could also be based on the predictor value and the corresponding β coefficient value to calculate the risk score of each factor. The nomogram coefficient for each variable was calculated according to the formula: Nomogram (i) = (max (Wi) – min (Wi)) × βi. Max (W) and min (W) represented the maximum and minimum values of each variable. We selected creatinine as the scoring scale, with a total score of 100. Then, we calculated the score corresponding to each variable according to the β coefficient: Score = 100 / Nomogram (creatinine) × predictor value × β coefficient. Each variable score was added together to give a total risk score. And then, drew a vertical line from the "total points" axis to the bottom axes, and converted the total score into probabilities for 6-month, 1-year, 3-year, and 5-year renal survivals. The Harrell's concordance index (C-index) and calibration curve were used to validate the predictive ability of the model. To perform the validation of the predictive model, the bootstrap technique with 500 resampling method was used and the 95% confidence interval (CI) was calculated. The "nomogramFormula" package in R software was used to calculate the total risk score of each patient according to the generated nomogram. The cut-off values of the risk score were determined by X-tile software (version 3.6.1). Using the "compareC" package to compare the C-index values across different models. The net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were applied to compare the predictive ability of the nomogram model and the Brix model. No variable had more than 10% of missing values in our study, thus, missing values were treated with deletion. P<0.05 was considered to be statistically different.

Results

Clinicopathological Characteristics and Prognosis

A total of 571 AAV patients were screened and 285 patients were enrolled. Their average age was 59.3 ± 12.5 years. Of these patients, 231 (81.1%) had MPO-ANCA, 17 (6.0%) had PR3-ANCA, and 11 (3.9%) had both MPO-ANCA and PR3-ANCA. The comparison of clinicopathological characteristics and outcomes between ANCA-positive and ANCA-negative patients were summarized in Supplementary Table 1 and Supplementary Table 2, respectively. And the Kaplan-Meier analysis showed that there were no significant differences in renal survival (Log Rank=3.222, P=0.073) or patient survival (Log Rank=0.281, P=0.596) between ANCA-positive and ANCA-negative patients (Supplementary Figure 1A-B). The induction therapies included prednisone only (1mg/kg per day, n=47) or prednisone (0.6-0.8mg/kg per day) combined with intravenous cyclophosphamide (CYC, 0.75-1.0g/m² in monthly pulses, n=158) or prednisone (0.6-0.8mg/kg per day) combined with mycophenolate mofetil (MMF, 1.0-1.5g per day, n=74). The induction treatment data of 6 (2.1%) patients were not available. Fourteen patients received at least one infusion of rituximab in addition to prednisone or prednisone combined immunosuppressants. One hundred and seventy-three patients received methylprednisolone pulses (500mg/d, for 3 days) and seven patients received plasma exchange. Maintenance therapy included low-dose prednisone (5mg per day) only or plus azathioprine/MMF. The 285 cases were randomly assigned to the development set (n=201) and the validation set (n=84). Except for treatment and the rate of coronary heart disease, there were no statistically significant differences in baseline clinicopathological characteristics and comorbidities between the development set and the validation set (P>0.05), indicating that the distribution of variables in the two sets was similar (Table 1).

During a median follow-up of 41.3 (20.0-63.8) months, 50 (17.5%) patients died and 84 (29.5%) patients reached ESKD. Fifteen patients recovered enough renal function after short-term dialysis to come off dialysis and were assigned to the non-ESKD group. The outcomes of the development and validation sets were shown in Supplementary Table 3. For the development set, there were 57 (28.4%) incident ESKD cases and the overall cumulative renal survival rates at 6-month, 1-, 3-, and 5- years were 86.0%, 83.1%, 77.8%, 68.4%, respectively; while there were 30 (14.9%) cases died, and the patient's survival rates at 6-month, 1-, 3-, and 5- years were 95.8%, 94.6%, 87.3%, 82.6%, respectively. For the validation set, there were 27 (32.1%) incident ESKD cases, and the cumulative renal survival rates at 6-month, 1-, 3-, and 5- years were 83.0%, 79.5%, 74.9%, 62.2%, respectively; while there were 20 (23.8%) cases died, and the patient's survival rates were 93.3%, 91.7%, 85.0%, 75.3%, respectively. Following the Kaplan-Meier analysis, there were no significant differences in renal survival (P=0.680) or patient survival (P=0.186) between two sets.

Renal Risk Score Validation

According to the Brix model, we calculated the renal risk score for every patient, with a median score of 2 (0-7) points in the developmental set and 2 (0-6) points in the validation set. We divided 285 patients into the low-risk group (n=77), medium-risk group (n=148), and high-risk group (n=60). During the follow-up time, 10.4% and 24.3% of patients in low- and medium-risk groups entered ESKD, respectively. In the high-risk group, 40 (66.7%) patients reached ESKD. Among the other 20 high-risk patients not reaching ESKD, 4 patients recovered renal function after short-term dialysis and were weaned off dialysis. The C-indices of the Brix model in the development and validation sets were 0.801 (0.748-0.854) and 0.746 (0.654-0.838), respectively. For the all-data set (n=285), the C-index was 0.783 (0.736-0.830).

Development and Validation of the Nomogram

Then we proposed a nomogram model by combining other clinicopathological data. Clinicopathological variables were evaluated by univariate and multivariate Cox regression analysis to identify variables that have predictive values for ESKD in the development set (Table 2). Variables with P<0.05 in univariate analysis were included in multivariate analysis. Finally, five essential variables including hypertension (HR=2.163, 95%CI 1.083-4.322, P=0.029), high serum creatinine (HR=1.002, 95%CI 1.001-1.003, P<0.001), high daily urine protein (HR=1.343, 95%CI 1.148-1.571, P<0.001), high glomerular sclerosis (HR=13.983, 95%CI 3.496-55.923, P<0.001), and interstitial fibrosis>50% (HR=4.179, 95%CI 1.900-9.192, P<0.001) were independent risk factors for ESKD.

Based on multivariable Cox regression analysis, the nomogram was established with independent prognostic factors (Figure 2A). The beta coefficients for the nomogram model were shown in Table 3. We calculated the nomogram coefficient of creatinine as per the formula defined in the methods. Nomogram (creatinine) = 1300 × 0.0026=3.38. The total risk score for each patient was calculated based on the predictor values and the corresponding beta values using the following formula: Nomogram total risk score=100/3.38 × [0.7027 × 1(if Hypertension=yes) + 0.0026 × Creatinine + 0.2277 × Daily urine protein + 1.7315 × Glomerular sclerosis + 0.9309 × 1(if Interstitial fibrosis>50%)]. The C-indices of the nomogram in the development and validation sets were 0.838 (0.785-0.891) and 0.794 (0.774-0.814), respectively, indicating that our model exhibited good sensitivity and specificity. The calibration curves showed that the predicted calibration curves were close to the standard curves in the validation sets (Figure 2B-E), which indicated that the nomogram had relatively high precision in predicting renal survival.

Comparison between nomogram and Brix model

We re-calculated the total risk score of each patient according to this developed nomogram, which ranged from 7.37-184.85 in the development set and 6.92-212.01 in the validation set. In the development set, the best cut-off points of the total score of the nomogram were determined as 85 and 122 by X-tile software, and then patients were stratified into the low-risk group (< 85 points), medium-risk group (85-122 points) and high-risk group (> 122 points). According to the above nomogram risk stratification, 285 patients were divided into low-risk (n=182), medium-risk (n=67), and high-risk (n=36) groups.

In both the Brix model and our nomogram model, there were statistical differences in renal survival among patients in different risk groups (P<0.001, by Log-rank test), as shown in Figure 3A-B. For the all-data set (n=285), the C-index of the nomogram model was 0.822 (0.775-0.869), which was higher than the Brix model of 0.783 (0.736-0.830), with a statistically significant difference (P<0.05). In the nomogram renal risk stratification, 36 patients were in the high-risk group, 30 of whom reached ESKD (83.3%). Among the other 6 high-risk patients not reaching ESKD, 3 patients recovered their renal function after dialysis and came off dialysis. The above indicated that the nomogram model had better clinical prediction ability than the Brix model, especially for high-risk patients.

Furthermore, the NRI values of the nomogram risk classification compared with the Brix model at 6-month, 1-, 3-, and 5- years were 19.9%, 22.9%, 22.3%, and 24.4%, respectively. Meanwhile, the IDI values of 6-month, 1-, 3- and 5-years renal survival for the nomogram risk classification compared with the Brix model were 7.7%, 9.0%, 10.3%, and 11.7%, respectively. All of the values above were greater than zero, indicating that the diagnostic accuracy of the nomogram risk classification was higher than that of the Brix model.

Discussion

In this study, we have validated the Brix model and combined with other clinicopathological data to propose a nomogram to predict renal outcomes in AAGN patients. The nomogram demonstrated that the risk of ESKD was significantly increased in AAGN patients with hypertension, high levels of serum creatinine and daily urine protein, increased proportion of glomerulosclerosis, and interstitial fibrosis > 50%.

Several studies have suggested associations between histopathologic parameters in renal biopsies and renal outcomes, such as the proportion of normal glomeruli, glomerulosclerosis, tubular atrophy, and interstitial fibrosis (TA/IF).[8,12,13] In 2010, Berden *et al.* proposed new histopathologic classification criteria of AAGN, which classified glomerular lesions into focal, crescentic, mixed, and sclerotic, with progressively worse renal prognosis.[14] Studies have validated this histopathological classification, drawing relatively consistent conclusions that the focal class had the best renal prognosis and the sclerotic class the worst, whereas the results of the crescentic and mixed classes were controversial, which could be attributed to the different baseline renal function or proportion of glomerular sclerosis in groups.[15-18] In our study, we found a high glomerulosclerosis rate was an independent risk factor for ESKD, and the risk of ESKD increased with a higher proportion of glomerulosclerosis. We also observed that the fibrous crescent was a risk factor for ESKD in univariate Cox regression, but it was not significant after multivariate adjustment. Crescents, especially cellular crescents, were suggestive of active lesions, whereas fibrous crescents suggested chronic lesions. The proportions of cellular and fibrous crescents were low in our study, which may weaken their impacts on ESKD. In addition to glomerular lesions, renal interstitial fibrosis was associated with renal prognosis in our research, which was consistent with previous studies.[12,13] Renal interstitial fibrosis, a hallmark of chronic kidney disease (CKD), was the common pathway of progressive kidney diseases and correlated with a poor renal prognosis.[19,20] Unlike

other studies, for tubular atrophy, although univariate Cox regression reached statistical significance, multivariate Cox regression revealed that it may not be an independent prognostic factor.

Previous studies have shown that baseline high serum creatinine was an independent risk factor for ESKD in AAV patients.[17,21,22] Patients with eGFR<50 ml/min had a 50% risk of death or renal failure at 5 years.[3] In this study, we found that hypertension and high proteinuria were also strong predictors for ESKD. Hypertension may cause progressive renal injury, including arteriosclerosis, glomerulosclerosis, tubular atrophy and loss, and cortical fibrosis.[23-25] In turn, renal damage may increase blood pressure possibly by reducing GFR with sodium retention or by renal ischemia, oxidative stress, and inflammation[26]. Proteinuria, as a result of a damaged glomerular filtration barrier, was an early hallmark of glomerular disease. Consistent with the previous literatures,[27,28] the degree of proteinuria at diagnosis was associated with the long-term renal outcome in AAGN patients in our study.

Recently, Brix *et al.* proposed a renal risk score by combining kidney function at baseline, percentage of normal glomeruli, and percentage of interstitial fibrosis and tubular atrophy.[10] A study validating the model found that of 14 patients with the highest score, 43% recovered renal function after the initial episode, and 14% remained dialysis-free.[29] In another validation study, only one of the five patients with the highest risk score developed renal failure.[30] It was suggested that the score should be used in combination with other prediction parameters to improve the prediction ability.

In this study, we fully integrated the independent risk factors of renal prognosis, constructed a clinicopathological prediction model, weighted and quantified the impact of different risk factors on renal prognosis, and more intuitively displayed the prediction results in the form of the nomogram realizing the visualization of data. We compared the predictive performance of the constructed nomogram model with that of the Brix model, and the results showed that the nomogram model had better accuracy in predicting renal prognosis. Our prediction model could potentially help nephrologists to identify patients before the onset of CKD progression, thus enabling them to individualize the treatment of patients in different risk groups.

There were several limitations. First, this was a retrospective study with a large time span, patients' treatment regimens were somewhat biased from those recommended up to now, and the use of rituximab was low, which may affect the prognostic analysis to some extent. Second, the follow-up time of some patients who entered the study late may be not long enough, especially for the patients enrolled in recent years, possibly leading to the introduction of bias into prognosis analysis. Third, the sample size was relatively small and most patients were MPO-ANCA glomerulonephritis, which limited the generalization of the results. Forth, despite we showed that the nomogram model performed better than the Brix model, we still needed to acknowledge that the predictors in our model had their limitations. Similar parameters were changed in our model compared to the Brix model. We included creatinine instead of eGFR, IF instead of TA/IF, and glomerulosclerosis not normal glomeruli in our model as our cohort had few cellular crescents. And the low proportions of glomerulosclerosis and cellular crescents may also have affected the results of our study. Fifth, the patients in the development set and validation set were all from a single center, which might affect the accuracy of the prediction model to some extent, and still need validation in other centers or multicenter cohorts to further determine the accuracy and applicability of the prediction model.

In conclusion, the nomogram proposed in this study improved the accuracy of renal survival prediction for AAGN patients and could be used as a practical and convenient tool in clinical practice.

Disclosures

The authors declare they have no conflicts of interest.

Data availability statement

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Online Supplement

Supplementary material accompanies the online version of this article.

Author Contributions

Anqi Ni: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Liangliang Chen:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Resources. **Lan Lan:** Conceptualization, Methodology, Resources. **Yaoming Wang:** Investigation, Data curation. **Pingping Ren:** Investigation. **Yilin Zhu:** Investigation. **Ying Xu:** Investigation. **Xiaoqi Shen:** Investigation. **Qin Zhou:** Investigation. **Xiaohan Huang:** Investigation. **Huiping Wang:** Investigation. **Jianghua Chen:** Conceptualization, Supervision, Project administration. **Fei Han:** Conceptualization, Methodology, Validation, Formal analysis, Writing - review & editing, Supervision, Visualization, Project administration, Resources.

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Figure legends

Figure 1. Flowchart of patient enrollment.

Figure 2. Construction and validation of the nomogram. (A) The nomogram for renal outcome prediction; (B) Calibration curves for 6-month renal survival in validation set; (C) Calibration curves for 1-year renal survival in validation set; (D) Calibration curves for 3-year renal survival in validation set; (E) Calibration curves for 5-year renal survival in validation set.

Figure 3. Kaplan-Meier curves for renal survival in different models. (A) Kaplan-Meier curves of the Nomogram model; (B) Kaplan-Meier curves of the Brix renal risk score model.

Table 1. Clinicopathological characteristics and comorbidities in Development set and Validation set

Characteristics	Development set	Validation set	P
Case, n(%)	201(70.5)	84(29.5)	
Age, years, mean (SD)	59.0±12.7	59.9±12.0	0.566
Male, n(%)	96(47.8)	35(41.7)	0.347
Smoking history, n(%)	64(31.8)	22(26.2)	0.343
Leukocyte counts(10^9/l), mean (SD)	8.2±3.6	8.0±3.4	0.584
Hemoglobin(g/l), mean (SD)	90.8±19.5	89±22.4	0.496
Platelets counts(10^9/l), median (IQR)	233.5(176.5-301.5)	217.0(160.5-306.3)	0.374
Albumin(g/l), mean (SD)	32.8±5.8	32.7±6.0	0.848
Alanine aminotransferase(U/l), median (IQR)	12.0(8.0-19.0)	12.0(8.0-20.0)	0.621
Creatinine(μmol/l), median (IQR)	258.0(151.0-427.0)	246.5(142.8-406.3)	0.705
eGFR, ml/min/1.73m^2, median (IQR)	19.9(11.2-35.2)	19.2(10.7-40.3)	0.942
ESR, mm/h, mean (SD)	65.6±36.8	72.2±36.7	0.178
CRP, mg/l, median (IQR)	13.4(3.3-52.1)	13.9(3.5-56.7)	0.917
BVAS, mean (SD)	16.5±3.9	16.6±3.6	0.756
PTH(pg/ml), median (IQR)	84.0(44.1-138.0)	80.0(42.7-156.8)	0.727
Hematuria(red cell counts), n/μl, median (IQR)	330.9(107.0-754.8)	310.9(95.4-685.1)	0.440
Daily urine protein(g), mean (SD)	2.3±1.8	2.4±2.0	0.604
ANCA specificities			0.792
MPO-ANCA(+) only, n(%)	163(81.1)	68(81.0)	
PR3-ANCA(+) only, n(%)	11(5.5)	6(7.1)	
MPO-ANCA(+) / PR3-ANCA(+), n(%)	7(3.5)	4(4.8)	
ANCA negative, n(%)	20(10.0)	6(7.1)	
Renal pathology			
Normal glomeruli(%), median (IQR)	38.5(21.4-60.9)	43.9(22.2-62.3)	0.559
Glomerular sclerosis(%), median (IQR)	21.4(9.8-40.5)	17.0(9.2-35.3)	0.487
Cellular crescent(%), median (IQR)	5.0(0.0-13.8)	5.5(0.0-14.1)	0.744
Fibrous crescent(%), median (IQR)	0.0(0.0-3.9)	0.0(0.0-3.1)	0.410
Tubular atrophy >50%, n(%)	56(27.9)	20(23.8)	0.481
Interstitial fibrosis >50%, n(%)	74(36.8)	24(28.6)	0.182

Renal risk score, median (IQR)	2(0-7)	2(0-6)	0.630
Treatment			
Prednisone/Prednisone+CYC/Prednisone+ MMF, n	35/102/60	12/56/14	0.030
Rituximab, n(%)	11(5.5)	3(3.6)	0.707
Methylprednisolone pulses, n(%)	120(60.0)	53(63.9)	0.545
Comorbidities			
Hypertension, n(%)	113(56.2)	41(48.8)	0.252
Diabetes mellitus, n(%)	29(14.4)	14(16.7)	0.630
Heart diseases, n(%)	22(10.9)	15(17.9)	0.113
Coronary heart disease, n(%)	2(1.0)	6(7.1)	0.013
Heart failure, n(%)	8(4.0)	6(7.1)	0.366
Cardiac arrhythmia, n(%)	15(7.5)	9(10.7)	0.367
Malignancy, n(%)	3(1.5)	3(3.6)	0.508
Infection, n(%)	61(30.3)	32(38.1)	0.203
Anemia, n(%)	189(94.0)	77(91.7)	0.466

Abbreviations: eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BVAS, Birmingham Vasculitis Activity Score; PTH, parathyroid hormone; ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase3; CYC, cyclophosphamide; MMF, mycophenolate mofetil.

Table 2. Univariate and multivariate Cox regression analysis for renal survival in Development set

Characteristic	Univariate		Multivariate	
	Hazard Ratio(95%CI)	P	Hazard Ratio(95%CI)	P
Age	0.995(0.974-1.017)	0.652		
Gender (Male vs Female)	0.810(0.478-1.371)	0.432		
Smoking history	0.679(0.371-1.242)	0.209		
Leukocyte counts	1.018(0.945-1.095)	0.642		
Hemoglobin	0.973(0.957-0.989)	<0.001	1.007(0.988-1.027)	0.489
Platelets counts	0.999(0.995-1.002)	0.356		
Albumin	0.959(0.914-1.005)	0.079		
Creatinine	1.003(1.002-1.003)	<0.001	1.002(1.001-1.003)	<0.001
eGFR	0.909(0.879-0.940)	<0.001		
ESR	1.007(0.999-1.014)	0.067		
CRP	0.999(0.993-1.005)	0.799		
BVAS	1.059(0.987-1.136)	0.110		
PTH	1.005(1.003-1.008)	<0.001	1.003(0.999-1.007)	0.143
Hematuria (red cell counts)	1.000(1.000-1.000)	0.508		
Daily urine protein	1.185(1.080-1.300)	<0.001	1.343(1.148-1.571)	<0.001
ANCA specificities				
ANCA negative	Reference			
MPO-ANCA (+) only	2.869(0.698-11.800)	0.144	1.549(0.305-7.864)	0.598
PR3-ANCA (+) only	1.071(0.097-11.840)	0.956	7.304(0.547-97.470)	0.133
MPO-ANCA (+)/ PR3-ANCA (+)	6.497(1.082-39.020)	0.041	2.417(0.332-17.601)	0.384
Renal pathology				
Glomerular sclerosis	22.860(7.201-72.570)	<0.001	13.983(3.496-55.923)	<0.001
Cellular crescent	2.486(0.596-10.370)	0.212		
Fibrous crescent	38.93(1.624-932.90)	0.024	0.798(0.013-48.083)	0.914
Tubular atrophy>50%	2.652(1.557-4.516)	<0.001	0.537(0.239-1.207)	0.133
Interstitial fibrosis>50%	3.435(1.982-5.951)	<0.001	4.179(1.900-9.192)	<0.001
Treatment				
Prednisone only	Reference			
Prednisone+CYC	1.097(0.546-2.207)	0.795		
Prednisone+MMF	0.667(0.300-1.486)	0.322		
Rituximab				
NO	Reference			
YES	1.331(0.412-4.304)	0.633		
Methylprednisolone pulses				
NO	Reference			
YES	1.446(0.832-2.514)	0.191		
Comorbidities				
Hypertension	1.788(1.029-3.107)	0.039	2.163(1.083-4.322)	0.029
Diabetes mellitus	1.236(0.554-2.755)	0.605		
Heart diseases	0.701(0.217-2.270)	0.554		

Infection	1.492(0.855-2.604)	0.160

Abbreviations: eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BVAS, Birmingham Vasculitis Activity Score; PTH, parathyroid hormone; ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase3; CYC, cyclophosphamide; MMF: mycophenolate mofetil.

Table 3. Coefficients, Hazard Ratios, and 95% Confidence Intervals of the 5 predictors in the final model

	Coefficients	HR(95%CI)	P
Hypertension			
No	Reference		
Yes	0.7027	2.019(1.108-3.679)	0.022
Creatinine	0.0026	1.003(1.002-1.003)	<0.001
Daily urine protein	0.2277	1.256(1.103-1.429)	<0.001
Glomerular sclerosis	1.7315	5.649(1.900-16.794)	0.002
Interstitial fibrosis			
≤50%	Reference		
>50%	0.9309	2.537(1.388-4.635)	0.002

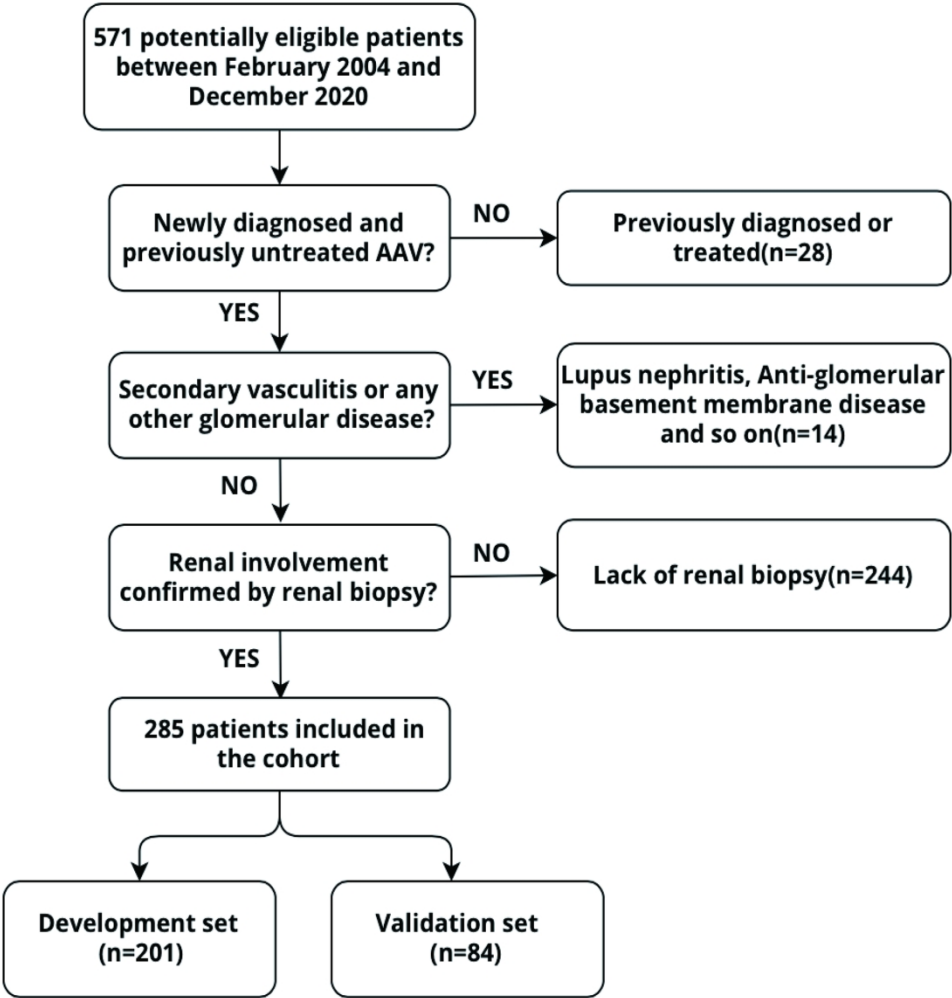Abbreviations: HR, hazard ratio; CI, confidence interval.

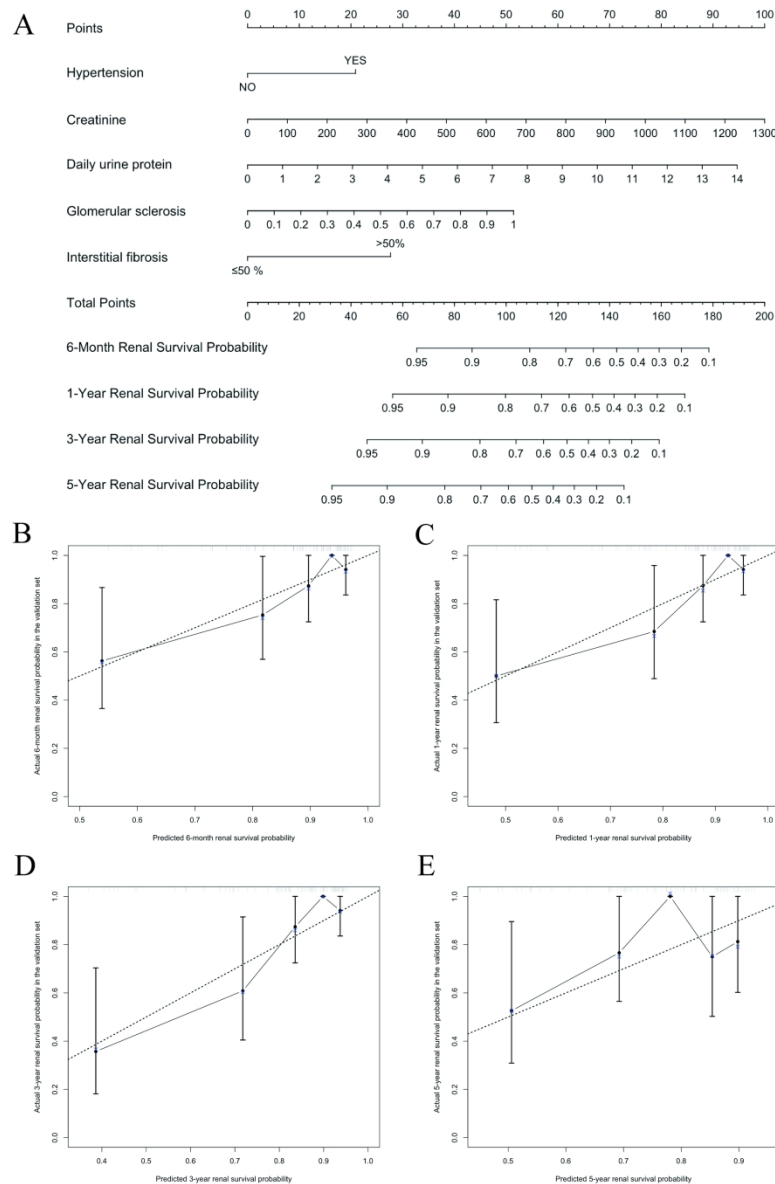Figure 1. Flowchart of patient enrollment.

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Figure 2. Construction and validation of the nomogram. (A) The nomogram for renal outcome prediction; (B) Calibration curves for 6-month renal survival in validation set; (C) Calibration curves for 1-year renal survival in validation set; (D) Calibration curves for 3-year renal survival in validation set; (E) Calibration curves for 5-year renal survival in validation set.
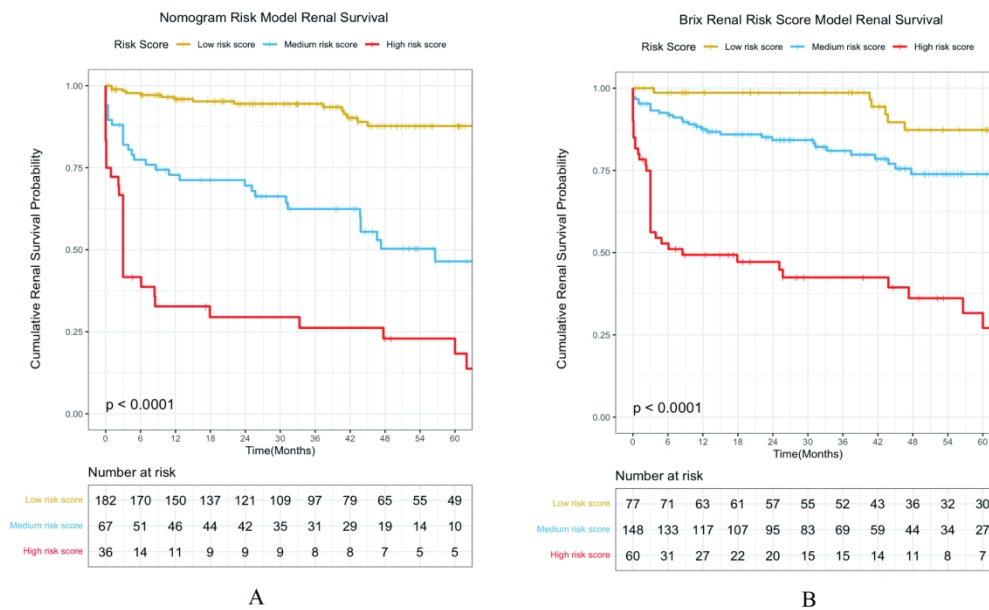
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Figure 3. Kaplan-Meier curves for renal survival in different models. (A) Kaplan-Meier curves of the Nomogram model; (B) Kaplan-Meier curves of the Brix renal risk score model.

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