The predictive value of Berden's classification *versus* renal risk score for renal survival of Chinese patients with myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated glomerulonephritis

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Abstract

Objective

This study aims to compare the prognostic values of two histopathological classification, Berden's classification versus renal risk score (RRS) by Brix et al. for predicting renal survival in Chinese patients with myeloperoxidase-anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (MPO-AAGN).

Methods

The medical records of 225 patients with MPO-AAGN diagnosed in our centre between February 2004 and December 2020 were retrospectively analysed. The predictive model of Berden's classification or RRS was established by Cox regression, respectively. The above two models were compared on aspects of discrimination, calibration, and decision curve analysis for predicting the 0.5-, 1-, 3-, and 5-year renal survival.

Results

After a median follow up of 38.99 months, 32.44% of patients developed end-stage renal disease (ESRD). In the Kaplan-Meier analysis, there were significant differences in renal survival among groups according to Berden's classification or RRS (both log-rank p<0.001). According to time-dependent receiver operating characteristic (ROC) curve analysis, the model based on RRS showed better discrimination ability than the model based on Berden's classification for predicting 0.5-, 1-, and 3-year renal survival. For calibration analysis, the model based on RRS showed worse calibration than the model based on Berden's classification for predicting 1- and 3-year renal survival. According to the decision curve analysis, the clinical decisions based on RRS could achieve more clinical benefits than those based on Berden's classification in predicting 0.5-, 1-, and 3-year renal survival.

Conclusion

The model based on RRS has better predictive value for renal survival than Berden's classification in aspect of discrimination and clinical decision from 0.5- to 3-year renal survival.

Key words

anti-neutrophil cytoplasmic antibody, glomerulonephritis, histology classification, predictive model, renal survival

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Introduction

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a collection of autoimmune systemic diseases characterised by necrotising inflammation of small- to medium-size vessels (1, 2). There are two major antigens targeted by ANCAs, including leukocyte proteinase 3 (PR3) and myeloperoxidase (MPO). Therefore, some investigators have recommended that AAV could be classified into MPO-AAV and PR3-AAV (3, 4). ANCA-associated glomerulonephritis (AAGN) would occur in more than 80% patients with AAV during the disease course. Despite significant advances in therapies, 20–35% patients with AAGN will develop into end-stage renal disease (ESRD) in 5 years after diagnosis (5, 6). Detecting the risk factors to predict renal survival remains an urgent demand in AAGN.

There is a close correlation between the changes in renal histology and renal prognosis. Thus, histology data can contribute to the prognosis prediction (7-10). In 2010, Berden *et al*. proposed a histology classification method (Berden's classification) for AAGN, which divided patients into the focal, crescentic, mixed, and sclerotic classes (11). This simple classification can help to predict the renal prognosis. The worst prognosis can be found in patients of sclerotic group, while the best prognosis can be found in patients of focal group. In 2018, Brix *et al*. designed the renal risk score (RRS) base on histology data and baseline renal function to predict renal outcomes in patients with AAGN (12). The RRS can separate patients into three groups for low-, medium- and high-risk for ESRD. Some studies compared the prognostic values of Berden's classification versus RRS for renal outcomes and revealed that RRS had better predictive ability than Berden's classification. However, these studies were limited to comparing discrimination ability and predicting overall survival (13-15). A more comprehensive comparison between Berden's classification and RRS are needed. Besides, both Berden's classifications and RRS were developed based on the data from western AAGN patients. The subtype of AAGN in China and other Asian countries are different from that in western countries. (16). Therefore, it is necessary to compare the role of Berden's classification and RRS in predicting renal survival in Chinese. To the best of our knowledge, this study is the first scientific effort to compare Berden's classification and RRS in terms of different time courses of renal survival in Chinese MPO-AAGN patients based on three aspects including discrimination, calibration, and clinical decision.

Materials and methods

Study patients

A total of 225 patients with MPO-AAGN diagnosed at the First Affiliated Hospital of Zhejiang University School of Medicine between February 2004 and December 2020 were included retrospectively. The inclusion criteria included a) patients with AAV who were newly diagnosed or previously untreated as per the criteria of the Chapel Hill Consensus Conference (17) and 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Microscopic Polyangiitis (18); b) patients who were identified as positive ANCA, presenting positive MPO-ANCA but negative PR3-ANCA; c) patients who had renal involvement and a renal biopsy specimen containing>5 glomeruli under light microscopy. The exclusion criteria included a) patients who had secondary vasculitis, including lupus nephritis, propylthiouracil-induced AAV, or other connective tissue diseases; b) patients who were complicated with any other primary or secondary glomerular diseases, such as immunoglobulin A nephropathy, anti-glomerular basement membrane disease, or diabetic nephropathy. The enrolment flowchart is shown in Figure 1. The occurrence of ESRD was recorded after the patient was diagnosed with AAGN. ESRD was defined as the requirement for long-term renal replacement therapy (19).

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (No.

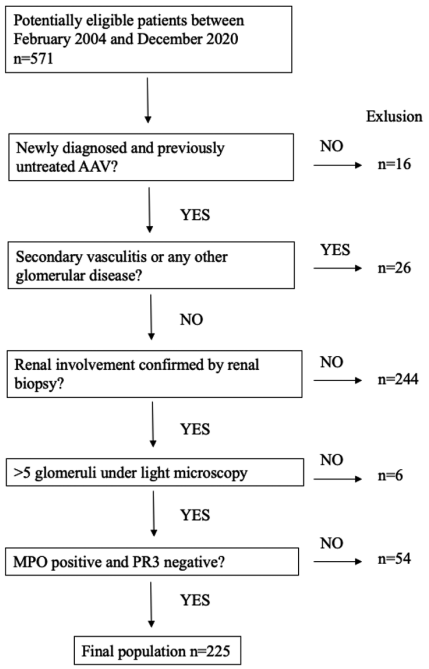

Fig. 1. The flow chart of patient's inclusion.

2020571). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the World Medical Association Declaration of Helsinki.

Data collection

The clinical and laboratory data of these patients at admission and during follow up were collected from the electronic medical records, including age, gender, hypertension history, routine blood analysis, serum albumin, serum creatinine, estimated glomerular filtration rate (eGFR), 24-h urine protein excretion, red blood cell count in the urine sediment.

Renal histology

The renal biopsy specimens were examined with light microscopy, immunofluorescence, and electron microscopy according to standard procedures. According to Berden's classification, these patients were classified into focal group (≥50% normal glomeruli), crescentic group (≥50% glomeruli with cellular crescents), mixed group (<50% normal, <50% crescentic, and <50% global sclerotic glomeruli), or sclerotic group (≥50% sclerotic glomerulus) (11). Based on the RRS, each patient was evaluated depending on the percentage of normal glomeruli (0 point: >25% of normal glomeruli; 4 points: 10% to 25% of normal glomeruli; 6 points: <10% of normal glomeruli), the eGFR on diagnosis (0 point: >15 ml/min/1.73 m^2; 3 points: ≤15 mL/min/1.73 m^2), and the degree of TA/IF (0 point: ≤25%, 2 points: >25%). According to the total risk score, patients was separated into low-risk group (0 point), medium-risk group (2–7 points), or high-risk group (8–11 points) for ERSD. Normal glomeruli were defined as there was no vasculitic lesion or glomerulosclerosis in glomeruli (12).

Treatment

The treatment protocol was decided by competent physicians. These patients were treated by prednisone (1 mg/kg per day) or prednisone (0.6–0.8 mg/kg per day) combined with intravenous cyclophosphamide (CYC, 0.75-1.0 g/m^2 in monthly pulses) or mycophenolate mofetil (MMF, 1.0–15g per day). Patients with pulmonary haemorrhage, biopsy-confirmed cellular crescents or fibrinoid necrosis of small vessels received 500mg pulse methylprednisolone for 3 days before CYC or MMF therapy. Eleven patients received at least one infusion of rituximab. After reaching complete remission or stable partial remission, the patients received maintenance therapy, which included low-dose prednisone (5 mg per day) only or plus CYC/MMF.

Statistical analysis

Statistical analysis was performed with the assistance of the R software (v. 4.0.2; http://www.R-project.org) and SPSS 26.0 software (SPSS Inc., Chicago, IL, USA). The continuous data following normal distribution were expressed as the mean ± standard deviation (SD) and analysed with the one-way ANOVA, while the data following non-normal distribution were expressed as the median (interquartile range) and tested with the Kruskal-Wallis test. Categorical variables were expressed as the number and proportion, and compared

Table I. Baseline information of the groups according to the Berden's classification.

Variable	Focal group n=74	Crescentic group n=60	Mixed group n=44	Sclerotic group n=47	*p*-value
Age, years	59.65±13.34	60.57±13.02	58.61±8.66	56.65±13.40	0.421
Male/female, n	39/35	29/31	18/26	20/27	0.575
Hypertension, n	42	31	21	29	0.547
Diabetes, n	13	11	4	4	0.311
Haemoglobin, g/l	92.64±22.23	88.52±18.94	84.70±19.78	81.59±12.96	0.015
Serum albumin, g/l	33.78±5.99	32.58±6.41	31.07±4.64	33.07±4.80	0.091
SCr, mg/dl	1.95(1.18, 3.09)	2.94(1.94, 4.79)	4.83(3.15,6.82)	3.89(2.77,6.57)	<0.001
Urine protein, g/24h	1.44±1.16	2.53±1.67	2.91±2.05	2.82±2.02	<0.001
Haematuria, /ul	347.9(53.0, 688.8)	305.0(109.3, 1198.1)	350.0(222.7,731.7)	316.2(137.1, 586.0)	0.757
Treatment					
Pred/Pred+IS, n	18/55	3/57	0/43	11/35	<0.001
CTX/MMF, n	36/19	41/16	31/12	23/12	0.821
MP pulses, n	40	46	36	29	0.004
Rituximab, n	1	5	4	1	0.091
ESRD, n	8	18	19	28	<0.001

CTX: cyclophosphamide; ESRD: end stage renal disease; IS: immunosuppressants; MMF: mycophenolate mofetil; MP: methylprednisolone; Pred: prednisone; SCr: serum creatinine.

Table II. The univariate Cox regression for ESRD.

	Univariate	
Parameter	HR (95%CI)	*p*
Age	0.989 (0.971-1.008)	0.246
Gender	0.922 (0.578-1.469)	0.733
Hypertension	1.214 (0.763-1.932)	0.413
Diabetes	0.753 (0.301, 1.887)	0.546

HR: hazard ratio; 95% CI: 95% confidence interval.

by the chi-square or Fisher's exact test. Survival analysis was conducted by the Kaplan-Meier analysis (Log-rank test). Univariate and multivariate analyses of survival were performed by Cox regression (Table II) . The results were expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Model of Berden's classification or RRS was adjusted with baseline clinical parameters (age, gender, and hypertension history) respectively. The time-dependent receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) were used to evaluate the discrimination for predictive models. The calibration was evaluated by plotting a calibration curve to reflect the consistency between the predictive value and the actual one. Decision curve analysis was conducted to determine the clinical utility of the predictive model by quantifying the net benefits at different threshold probabilities. $p<0.05$ was considered to be statistically different.

Results

The clinical and pathologic characteristics of the groups classified by Berden's classification or RRS in 225 MPO-AAGN patients are listed in Table I and Table III, respectively. Based on Berden's classification (Table I), there were 74, 60, 44, and 47 patients in the focal, crescentic, mixed, and sclerotic groups, respectively. Based on the RRS (Table III), there were 49, 143, and 33 patients in the low-, medium-, and high-risk groups, respectively. Among the groups based on Berden's classification or groups based on RRS, the factors of haemoglobin, serum creatinine, urine protein, methylpredniso-

Table III. Baseline information of the groups according to renal risk score RRS by Brix *et al*.

Variable	Low-risk group n=49	Medium-risk group n=143	High-risk group n=33	*p*-value
Age, years	57.89±13.27	60.23±11.79	55.75±13.80	0.136
Male/female, n	24/25	70/73	25/8	0.017
Hypertension, n	23	79	21	0.336
Diabetes, n	7	22	3	0.728
Haemoglobin, g/l	99.77±22.53	85.32±16.29	80.09±20.86	<0.001
Serum albumin, g/l	34.83±5.74	32.24±5.85	32.01±4.18	0.016
SCr, mg/dl	1.54(1.02, 2.26)	3.20(2.12, 4.83)	5.08(4.35,8.11)	<0.001
Urine protein, g/24h	1.51±1.48	2.26±1.59	3.70±2.22	<0.001
Haematuria, /ul	319.9(119.7, 688.8)	310.7(82.3, 705.3)	387.0(310.9,1033.3)	0.072
Treatment				
Pred/Pred+IS, n	10/38	20/122	2/30	0.217
CTX/MMF, n	27/11	84/38	20/10	0.821
MP pulses, n	28	95	28	0.028
Rituximab, n	3	6	2	0.730
ESRD, n	6	46	21	<0.001

CTX: cyclophosphamide; ESRD: end stage renal disease; IS: immunosuppressants; MMF: mycophenolate mofetil; MP: methylprednisolone; Pred: prednisone; SCr: serum creatinine.

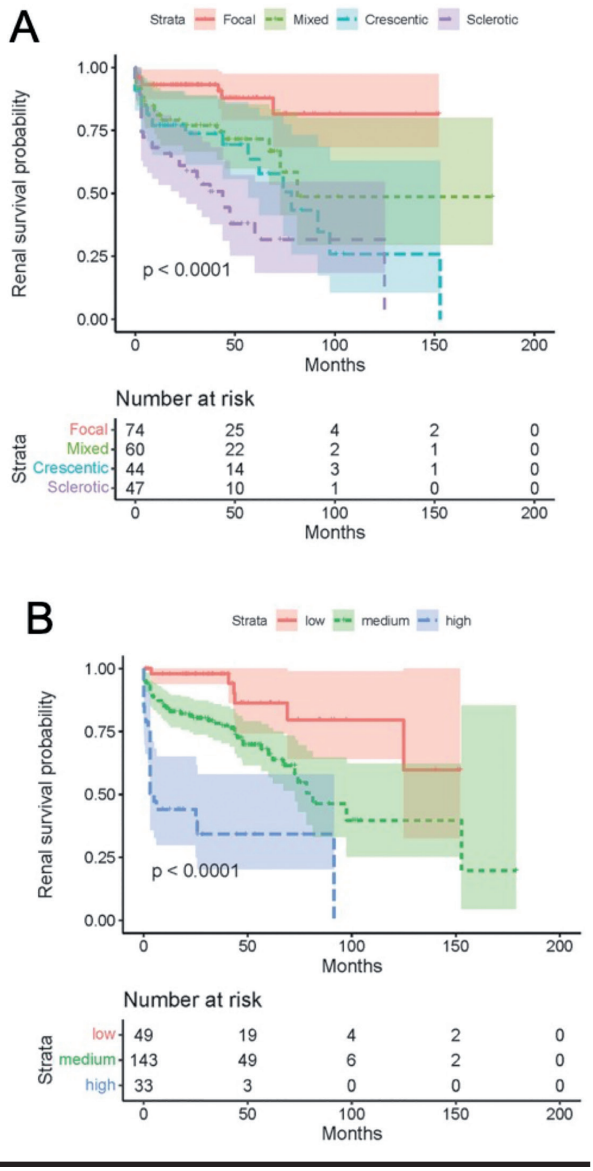

Fig. 2. Renal survival according to Berden's classification and renal risk score (RRS) by Brix *et al*. Kaplan-Meier curves show the renal survival of patients with MPO-antineutrophil cytoplasmic antibody–associated glomerulonephritis according to the groups of (**A**) the Berden's classification and (**B**) the RRS.

Table IV. Univariate and multivariable Cox regression for ESRD in the models based on Berden's classification or renal risk score (RRS) by Brix *et al*.

	Univariate		Model 1		Model 2	
Parameter	HR (95%CI)	*p*	HR (95%CI)	*p*	HR (95%CI)	*p*
Age			0.985 (0.964-1.007)	0.181	0.979 (0.959-0.999)	0.045
Gender			1.153 (0.701-1.896)	0.575	1.341 (0.801-2.243)	0.264
Hypertension			1.253 (0.765-2.050)	0.370	1.201 (0.735-1.961)	0.465
Berden						
Focal	Ref		Ref			
Crescentic	2.938 (1.275-6.769)	0.011	3.148 (1.355-7.314)	0.008		
Mixed	4.122 (1.798-9.448)	<0.001	4.381 (1.899-10.107)	<0.001		
Sclerotic	7.249 (3.293-15.957)	<0.001	7.166 (3.246-15.817)	<0.001		
RRS						
Low risk	Ref				Ref	
Medium risk	3.220 (1.364,7.603)	0.008			3.464 (1.456-8.236)	0.005
High risk	12.162 (4.819-30.691)	<0.001			14.028 (5.408-36.383)	<0.001

RRS: renal risk score; HR: hazard ratio; Ref: reference; 95% CI: 95% confidence interval.
Model 1 for Berden's classification: adjusted for age, gender and hypertension history. Model 2 for renal risk score (RRS) by Brix *et al*: adjusted for age, gender and hypertension history.

lone pulse treatment and ESRD occurrence were significantly different.

The median follow-up time of these patients was 38.99 months. During follow up, 73 (32.4%) MPO-AAGN patients progressed to ESRD. The Kaplan-Meier curves of renal survival in groups based on Berden's classification or groups based on RRS are shown in Figure 2. For Berden's classification (Fig. 2A), the renal prognosis among the four groups (focal, crescentic, mixed, and sclerotic) was significantly different ($p<0.001$). *Post-hoc* tests with Bonferroni correction showed that the focal group had the best renal survival compared to other groups (*vs*. crescentic group, $p=0.008$; *vs*. mixed group, $p=0.001$; *vs*. sclerotic group, $p<0.001$) and sclerotic group had the worst renal survival (*vs*. focal group, $p<0.001$; *vs*. crescentic group, $p=0.004$; *vs*. mixed group, $p=0.048$). There was no significant difference on renal survival between crescentic group and mixed group ($p=0.359$). For RRS (Fig. 2B), renal survival showed difference among the low-, medium-, and high-risk groups by the Kaplan-Meier survival curves (log-rank test $p<0.001$). *Post-hoc* tests with Bonferroni correction also showed significant differences among these three groups.

The Cox regression analysis for ESRD is shown in Table IV. The univariate Cox regression analysis revealed that both Berden's classification and RRS were significant predictors for renal survival. Then we used multivariate Cox regression to establish model 1 (included parameters of Berden's classification and adjusted with clinical parameters) and model 2 (included parameters of RRS and adjusted with clinical parameters). The clinical pa-

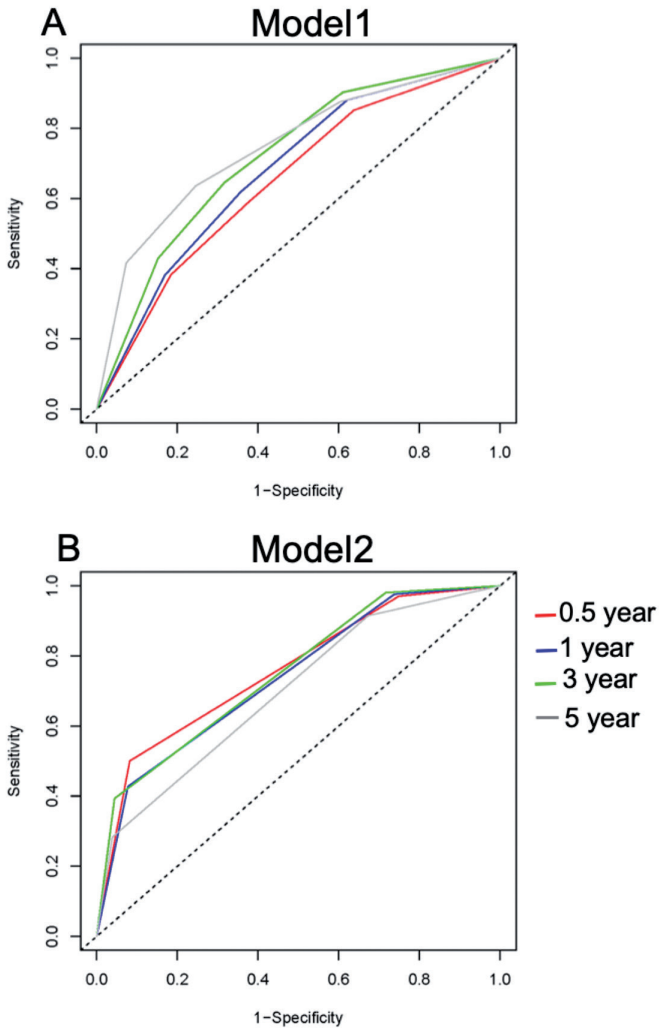

Fig. 3. Time dependent receiver operating characteristic curve for predicting 0.5-, 1-, 3- and 5-year renal survival of patients with MPO-antineutrophil cytoplasmic antibody–associated glomerulonephritis. (A) Model 1 for Berden's classification. (B) Model 2 for renal risk score (RRS) by Brix *et al*. Both models were adjusted for age, gender and hypertension history.

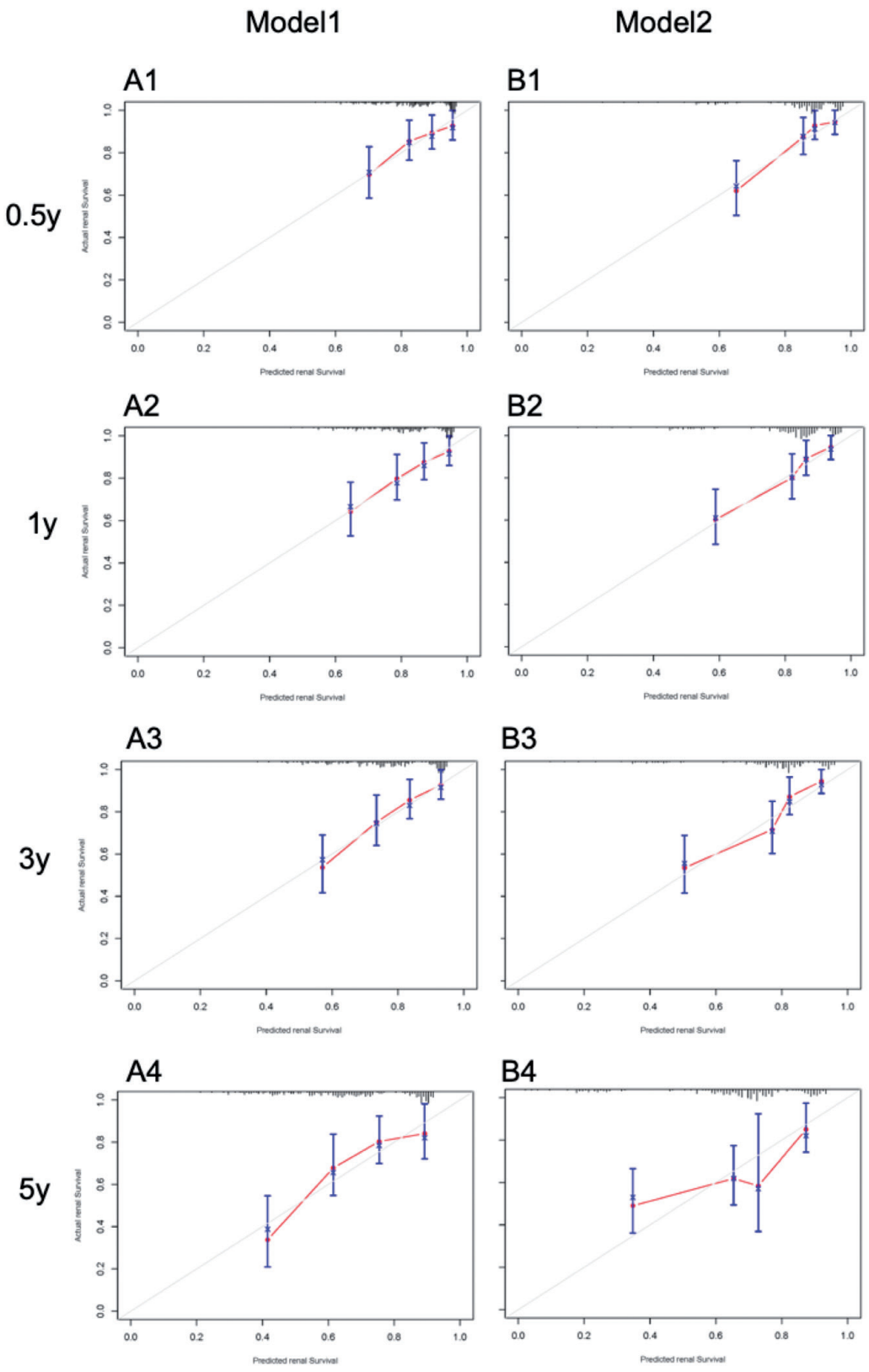

Fig. 4. Calibration curve for predicting 0.5-, 1-, 3- and 5-year renal survival of patients with MPO-antineutrophil cytoplasmic antibody–associated glomerulonephritis. (**A**) Model 1 for Berden's classification. (**B**) Model 2 for renal risk score (RRS) by Brix *et al*. Both models were adjusted for age, gender and hypertension history.

rameters for adjustment included age, gender and hypertension history, which were in reference to previous studies (15). The multivariate Cox regression analysis revealed that Berden's classification and RRS were both independent predictors for ESRD.

Discrimination refers to the ability of a predictive model to separate data into different groups. To evaluate the discrimination ability, time-dependent ROC analysis was performed and shown in Figure 3. The AUC of the model 1 and model 2 for 0.5-, 1-, 3-, and 5-year renal survival were 0.652 *versus*

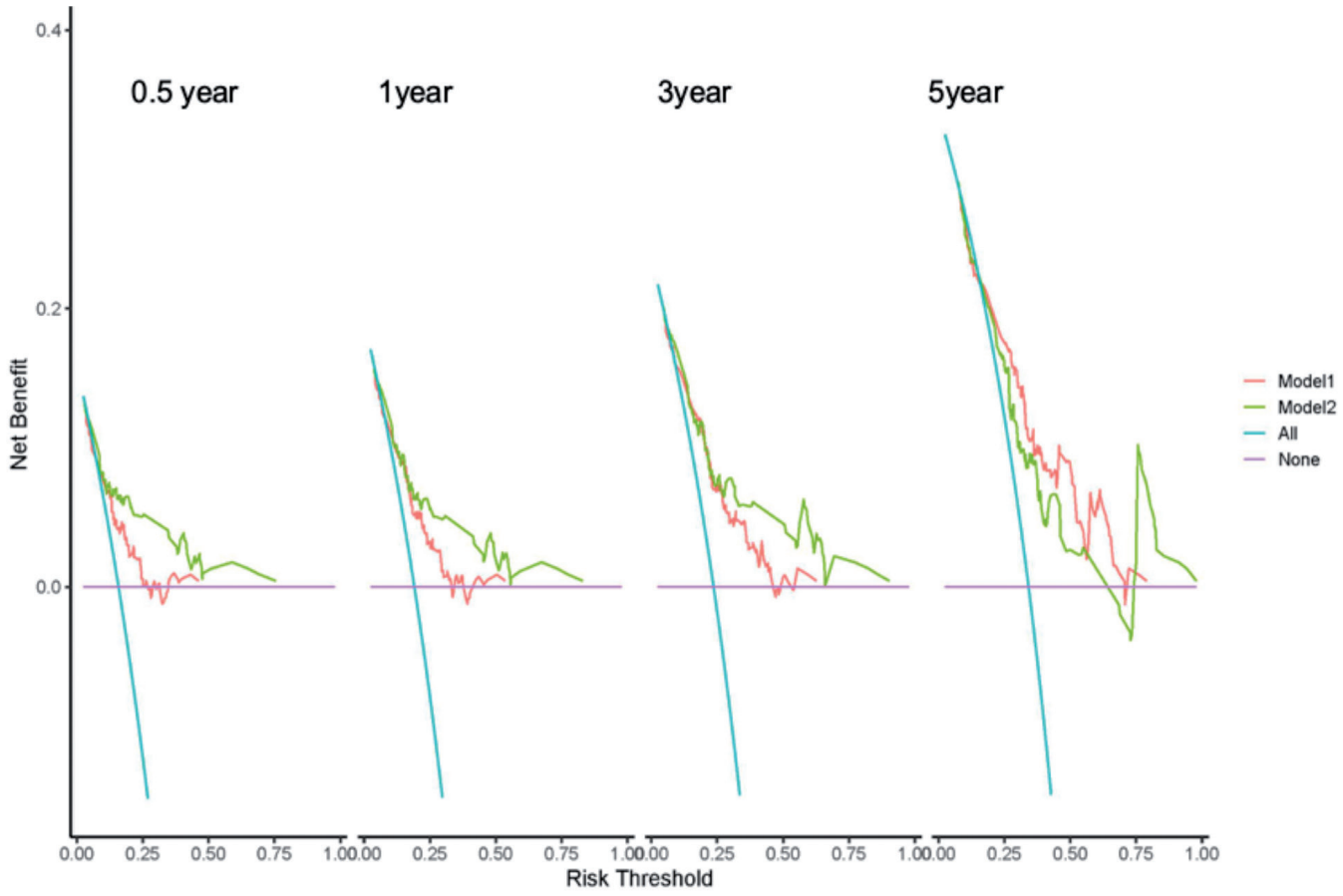

Fig. 5. The decision curve analysis for predicting 0.5-, 1-, 3- and 5-year renal survival of patients with MPO-antineutrophil cytoplasmic antibody–associated glomerulonephritis. Model 1: for Berden's classification. Model 2: for renal risk score (RRS) by Brix *et al*. Both models were adjusted for age, gender and hypertension history.

0.758, 0.680 *versus* 0.738, 0.719 *versus* 0.751, and 0.748 *versus* 0.698, respectively. The model 1 showed AUCs increased from 0.5- to 5-year, while the model 2 showed AUCs decreased from 0.5- to 5-year.

Calibration refers to the degree that a risk model reflects the consistency between the predictive value and the actual one. To evaluate the calibration ability, calibration curves are shown in Figure 4. The model 1 based on Berden's classification showed better calibration in 1- and 3-year renal survival prediction. Both the model 1 based on Berden's classification and the model 2 based on RRS did not show ideal calibration fit for predicting the 5-year renal outcome in these MPO-AAGN patients.

The decision curve analysis can be employed to evaluate whether patients could obtain better clinical benefits according to the risk model (20). The decision curve analysis is shown in Figure 5. In terms of predicting 0.5-, 1- and 3-year renal survival, clinical decisions based on the model 2 could achieve higher net benefit than those based on the model 1. In reverse, for predicting of 5-year renal outcomes, the model 1 showed more net benefit than the model 2.

Discussion

The histopathologic analysis of renal biopsy is expected to provide a status of the activity and chronicity in renal disease, which may help predict the renal prognosis (5, 21). This study aims to evaluate the predictive value for renal survival of Chinese MPO-AAGN patients based on two different histopathologic classification methods, namely Berden's classification and RRS by Brix *et al*.

Berden *et al*. developed a simple histopathologic classification which focused on the glomerular findings. Since the publication of Berden's classification, its predictive value for renal survival has been verified in many studies. Among the four groups of Berden's classification, the patients in the sclerotic group had the worst prognosis and those in the focal group had the best prognosis (13). Different from the focal and sclerotic groups, there was a controversy about renal outcomes of the crescentic and mixed groups. In some studies, the crescentic group had worse renal outcome than the mixed group (22, 23). But in some other studies, the renal outcome of the crescentic group was better than that of the mixed group (11, 24). Besides, some studies showed no differences in renal outcomes between the crescentic group and the mixed group (25-27). In a Chinese clinical study including 215 patients with MPO-AAGN, the focal group had the lowest risk of ESRD and the sclerotic group had the highest risk of ESRD, but the renal outcome of the mixed group was similar to that of the crescentic group (8). The present study

showed the similar results with the above Chinese study.

Brix *et al*. developed a relatively complex classification based on a risk score in a German AAGN cohort. This score included three parameters, namely normal glomeruli ratio, tubular atrophy/interstitial fibrosis, and baseline renal function. They determined the appropriate cut-off value for these three parameters through regression tree analysis, assigned score for the parameters and performed grouping according to the total sore. Finally, the patients can be classified into 3 groups for the risk of ESRD, including the low-, medium-, and high-risk groups (12). Recently, a Chinese research group by Luo *et al*. validated RRS in a group of Chinese patients and found there was no significant difference between the low- and medium-risk groups in Kaplan-Meier analysis by *post-hoc* tests with Bonferroni correction (28). Interestingly, the present study showed that low-, medium- and high-risk groups had significant differences in *post-hoc* tests with Bonferroni correction, which was consistent with Brix's results. The possible reason for this controversy may be the difference in time period of follow up. The average follow-up time of our study (38.99 months) was similar with that of Brix's study (34 months), but the average follow-up time was shorter in Luo's study (14.3 months) (28).

Till now, some reports have evaluated the prognostic value of Berden's classification and RRS, and found that RRS showed better discrimination than Berden's classification for predicting overall renal survival (13, 29). However, these studies only evaluated predictive value in terms of discrimination ability and compared predictive ability for overall renal survival. The present study was the first scientific effort to compare Berden's classification and RRS in terms of different time courses of renal survival in terms of the discrimination, calibration, and clinical use. Similar with previous study, we found that the discrimination ability of RRS was better than Berden's classification. The time-dependent ROC analysis revealed us more time-dependent information: RRS showed a decreasing trend and Berden's classification showed an increasing trend in discrimination of renal survival from 0.5- to 5-year. For discrimination ability, RRS was better than Berden's classification in most time courses (0.5-, 1- and 3-year renal survival), but Berden's classification was better than RRS for 5-year renal survival. In terms of calibration, the RRS showed worse calibration for the 1- and 3- year renal survival than Berden's classification, and similar calibration for 0.5- and 5- year renal survival compared with Berden's classification. For decision curve analysis, RRS brought more benefit net for most time courses (0.5-,1- and 3-year renal survival) compared with Berden's classification, and Berden's classification was better than RRS for 5-year renal survival in the clinical benefit.

A study has reported that treatment choice showed difference between different renal outcomes in AAGN (30). In our study, we found that some treatments were different among groups of Berden's classification or RRS, such as the numbers of patients receiving methylprednisolone pulses. For the groups based on RRS, high-risk group had higher proportion of methylprednisolone pulse than medium-risk group and low-risk group. For the groups based on Berden's classification, the crescentic and mixed groups had higher proportion of methylprednisolone pulse than sclerotic and focal groups. Clinically, the therapeutic intensity of AAGN mainly depends on the clinical manifestations and histological results. Thus, it is reasonable that there was difference for the methylprednisolone pulse in different groups with different severity in renal injury. We should admit that the different choice of therapy was a limitation of this study. The other limitations of this study were that all patients included came from a single centre and were all Chinese nationality. Therefore, the results of this study may need to be validated in other centres and populations.

Conclusion

In conclusion, both Berden's classification and RRS were able to predict the renal prognosis of MPO-AAGN patients. The RRS can better predict the renal survival in short term (less than 3 years) and Berden's classification showed better predictive ability for 5-year renal survival. The RRS presented better discrimination and clinical decision, but Berden's classification showed its advantage in calibration.

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