RHEUMATOLOGY AND IMMUNOLOGY RESEARCH

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Development and internal validation of a model to predict long-term survival of ANCA associated vasculitis

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Abstract

Objectives: Risk stratification and prognosis prediction are critical for appropriate management of anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV). Herein, we aim to develop and internally validate a prediction model specifically for long-term survival of patients with AAV.
Methods: We thoroughly reviewed the medical charts of patients with AAV admitted to Peking Union Medical College Hospital from January 1999 to July 2019. The Least Absolute Shrinkage and Selection Operator method and the COX proportional hazard regression was used to develop the prediction model. The Harrell's concordance index (C-index), calibration curves and Brier scores were calculated to evaluate the model performance. The model was internally validated by bootstrap resampling methods.
Results: A total of 653 patients were included in the study, including 303 patients with microscopic polyangiitis, 245 patients with granulomatosis with polyangiitis and 105 patients with eosinophilic granulomatosis with polyangiitis, respectively. During a median follow-up of 33 months (interquartile range 15-60 months), 120 deaths occurred. Age at admission, chest and cardiovascular involvement, serum creatinine grade, hemoglobin levels at baseline and AAV subtypes were selected as predictive parameters in the final model. The optimism-corrected C-index and integrated Brier score of our prediction model were 0.728 and 0.109. The calibration plots showed fine agreement between observed and predicted probability of all-cause death. The decision curve analysis (DCA) showed that in a wide range of threshold probabilities, our prediction model had higher net benefits compared with the revised five factor score (rFFSand) and the birmingham vasculitis activity score (BVAS) system.
Conclusion: Our model performs well in predicting outcomes of AAV patients. Patients with moderate-to-high probability of death should be followed closely and personalized monitoring plan should be scheduled.

Keywords

anti-neutrophil cytoplasmic antibody associated vasculitis • long-term • mortality • prediction model • internal validation

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a group of systemic vasculitis including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).AAV is lethal if untreated. The one-year mortality rate in untreated patients with GPA could be as high as 50%-80%,[1] After glucocorticoids and cyclophosphamides were used in the treatment regimen since 1960s, the survival of AAV patients has been dramatically improved.[2] But AAV is still a group of disease with high mortality.

It is noteworthy that in patients with AAV, the three leading causes of death are cardiovascular complications, infections and malignancies.[3, 4]Therefore, the current treatment regimen recommended risk stratification-based management

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strategy to balance the benefits and side effects of glucocorticoids and immunosuppressants.[5, 6]The French Vasculitis Study Group raised the Five Factor Score (FFS) system in 1996 and revised it (rFFS) in 2009 to evaluate disease severity and predict poor outcomes in patients withsystemic necrotizing vasculitis.[7, 8] The rFFS system is the most widely used evaluation tool to predict outcomes of patients with the 3 categories of AAV and polyarteritis nodosa (PAN). In the generating cohort of rFFS, about one-third of patients were classified with PAN.[7] The rFFS was not specifically designed for AAV. Moreover, the rFFS is a binary system for each item, so patients with the same rFFS scores might have different outcomes and need different treatment regimens. In a recently published systemic literature review, the Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group summarized the currently available tools in disease activity, organ damage, and health-related quality of life assessment in AAV. However, a model for prognosis prediction is still in need.[9]

In this study, we developed a new model to predict long-term survival of patients with AAV (PRESAAV) and internally validate the performance of the model by the bootstrap resampling method. And, we compared the current prediction model with the rFFS and the birmingham vasculitis activity score (BVAS) system (version 3).

Methods

Patients

This was a retrospective cohort study. The medical charts of patients who were admitted to Peking Union Medical College Hospital (PUMCH) with the diagnosis of “AAV”, “GPA”, “MPA”, “EGPA”, “Wegener’s granulomatosis” or “Churg-Strauss syndrome” from January 01, 1999 to July 18, 2019 were reviewed. All patients were classified into each subtypes according to the American college of rheumatology (ACR) classification criteria or the Chapel Hill Consensus Conference (CHCC) definitions.[10-12] The first hospital admission was regarded as the baseline. Patients were excluded if they were younger than 14 years old at the first admission, or had concomitant malignant tumor or connective tissue diseases, such as systemic lupus erythematosus, rheumatoid arthritis, *etc*. Patients were excluded if they were followed up for less than three months as well. Because the study was based on medical charts review, informed consent was waived.

Data Collection

The demographic information, clinical involvement patterns, comorbidities, laboratory and pulmonary computed tomography (CT)scan results were carefully and thoroughly collected in all patients at the first admission and during follow-ups. The laboratory items included for data analysis were white blood cell count (WBC, 10^9/L), hemoglobin level (Hb, g/L), platelet count (PLT, 10^9/L), urine red blood cell count (RBC/HF)and protein levels, serum creatinine level (Scr, μmol/L), erythrocyte sedimentation rate (ESR, mm/h), and hypersensitive C-reactive protein (hsCRP, mg/L). ANCA subtypes (particular proteinase 3 [PR3]-ANCA or myeloperoxidase [MPO]-ANCA) was tested by the enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence assay with commercial kits under manufactories’ instructions. There were four ANCA subtypes in the present study, *i.e.*, MPO-positive, PR3-positive, Double-Positive, and Double-Negative. Renal involvement referred to proteinuria, hematuresis or Scr ≥ 125umo/L with other causes excluded.[13] Periphery neuropathy was diagnosed based on typical clinical manifestations or on electromyography.

The disease activity at admission was measured by the BVAS (version 3).[13] The rFFS was calculated according to standard protocol.[7]

Follow-ups

Patients were followed up at the outpatient clinic or during repetitive inpatient admissions in PUMCH. Telephone calls were made to ensure survival status. Survival periods were defined from the first admission to the date of death or the censoring date (December 01, 2019). For patients who didn’t answer the telephone calls, the survival periods were defined as the time between the first admission and the last inpatient or outpatient visits. And for patients admitted only once and didn’t answer the phone call, the survival periods were deemed less than one month. Outcome of interest was defined as all-cause death.

Statistical Analysis

Development of the Prediction Model for Survival and its Internal Validation

The present model was developed and reported based on the Transparent Reporting of a multivariate prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement.[14]

Sample Size and Candidate Predictors

Due to the retrospective nature of the study, we didn’t calculate the sample size. Furthermore, there is no generally accepted approaches for sample calculation in risk model development and validation. As a rule of thumb, at least ten outcome events per variable (PEV) are required for the full model.[14,15] Clinical parameters were selected as potential candidate predictors for model development based on clinical judgment and previous published studies, including age at disease onset (years), disease duration (months), BVAS, AAV subtypes, organ or system involvement related to AAV (*i.e.*, constitutional symptoms, skin andmucous, eyes andear,

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nose and throat (ENT), chest, cardiovascular, abdominal, nervous system) and laboratory test results (*i.e.*, Scr grade [Grade 0: Scr < 125 μmol/L, Grade 1: 125 ≤ Scr < 250 μmol/L, Grade 2: 250 ≤ Scr < 500 μmol/L, Grade 3: Scr ≥ 500 μmol/L]),[13] WBC, Hb, PLT, hsCRP, ESR and ANCA subtype).

Missing Data

Missing data was considered as missing at random (MAR), and the pattern of missingness was explored. The values of missing data were imputed via the Multivariate Imputation by Chained Equations (MICE) method with the mice package in the R statistical software.[16] Together with the outcome, all the candidate predictors were selected for missing data imputation. The iteration was ten. A total of five imputed data sets were generated. The kernel density estimates for the marginal distributions of the observed and imputed data was calculated to check whether the imputations by the MICE method were reasonable or not. The results of imputed data sets were combined with the Rubin's rule.[17]

Development of the Prediction Model

We operated the least absolute shrinkage and selection operator (LASSO) approach to select the most predictive variables from the candidate variables. The optimal predictors were found via cross-validation. The optimal penalty factor (lambda) was chosen at a one standard error larger value of the lowest cross-validated lambda (*i.e.*, lambda.1se). The optimal penalty factor (*i.e.*, lambda.1se) was determined within each imputed data set. The mean penalty factor of the five imputed data sets was regarded as the optimal penalty factor in the stacked data set to identify the predictors in the final model.[18] Subsequently, the final model was developed with the COX proportional hazard regression model. The survival status was analyzed with the log-rank test among different subgroups. The proportional hazard assumption was tested by the Schoenfeld residuals method.[19] The cumulative predicted survival probability for one patient with AAV at time t (months) was calculated by the following formula:

$$P_{\text{at time t (months)}} = S_0(t)^{\exp(\beta 1x1+\beta 2x2+\ldots+\beta nxn)} \text{ (Formular 1)}$$

In the formula, $S_0(t)$ referred to the baseline survival function at time t, x_n referred to the selected predictors in the final model, and β_n referred to the predictor specific coefficients. The sum of the products of the predictors and their coefficients was defined as the prognostic index (PI). $S_0(t)$ was calculated via the baseline hazard function($H_0(t)$). Specifically, $S_0(t)=\exp[-H_0(t)]$.[20, 21]

Model Presentation

The coefficients of predictors in the prediction model were estimated in the stacked data set and in each imputed data set, respectively. The coefficients and their 95% confidence intervals (CIs) in the five imputed data sets were then pooled with the Rubin's rule.[17] The estimated predictor coefficients were quite similar in these two methods.[18] Therefore, to improve the feasibility of the current prediction model in daily clinical practice, we simulated and expressed the prediction model as a nomogram with the data estimated in the stacked data set.

Internal Validation and Risk Stratification

The Harrell's concordance index (C-index) was calculated to assess the discrimination ability of the model.[14] The calibration curve was used to report the agreement between predictions of the model and observed outcomes.[14,22] The Brier score is defined as the average of the square of the difference between the prediction probabilities and the observation outcomes. It is used to evaluate the overall performance of the prediction model.[14] Bootstrapping was used to obtain optimism-corrected estimate of prediction model performance.[14] The tertiles of PI in the stacked data set were used for risk group determination in each imputed data set.[14] Kaplan-Meier curves were plotted and compared among different PI risk groups, rFFS, and BVAS subgroups based on combined results after multiple imputations. BVAS were divided into three different according to its tertiles in the present study. And the cut-off points were 18 and 23, respectively. Moreover, we used the (net reclassification index) NRIs and the DCA to compare the performance among our model, the rFFS and the BVAS system in clinical practice. A model is deemed to perform better in clinical practice if it has a higher net benefit across the wide range of threshold probabilities at which an individual is designated for all-cause death.[23, 24]

Numerical data was expressed as median (interquartile range, IQR), categorical data was expressed as percentages or numbers. Numerical data were compared with the independent sample *t*-test or the *Mann-Whitney U* test; while categorical data were compared with the *Chi-square* test or the *Fisher's* exact test, where appropriate. All probabilities were two-sided, and *P* values < 0.05 were considered to be statistically significant. Data analysis were conducted with the IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, N.Y., USA) and the R software (version 4.0.3, www.r-project.org).

Results

Patients

During the study period, a total of 2137 admissions and 949 AAV patients were identified. Based on the exclusion criteria, 51 patients were excluded (Figure 1). 245 patients were further excluded due to short follow-up time. As a result, 653 patients with AAV were included in the model

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development, including 303 patients with MPA, 245 patients with GPA and 105 patients with EGPA, respectively (Figure 1, Supplementary Table 1). The median follow-up time was 33 months (IQR 15-60 months). And a total of 120 patients died during this period.

Predictor Variables

A total of 20 parameters were selected as candidate predictors initially. The baseline characteristics of the candidate predictors in the prediction model were described in Table 1. Six variables with non-zero coefficient variables in the LASSO regression were selected as predictors in the final model. The six predictors included demographic characteristics (age at admission), system/organ involvement patterns (chest and cardiovascular involvement), AAV subtypes and laboratory information (serum creatinine grade and hemoglobin level). The coding and definitions of the six predictors were listed in Supplementary Table 2. The LASSO coefficients of the six predictors in the stacked data sets were shown in Supplementary Table 3.

Missing Values

The missing values were detected and their missing patterns were explored (Supplementary Figure1, Table 1). The Kernel density plots of the observed and the five imputed data sets were listed in Supplementary Figure2.

Model Development

The whole set of follow-up data was used for prediction model development. The results of the proportional hazard assumption of the six predictors in the imputed data sets were listed in Supplementary Table 4. The β coefficients and hazard ratios of the predictors were estimated in the imputed data sets via the Rubin's rule and in the stacked data set, respectively (Supplementary Table 5). The cumulative five-year survival probability for one single patient with AAV was predicted via the following formula:

$$P_{at\ time\ t\ (months)} = 0.9894782^{exp(PI)}$$

Where the PI = 0.182 × Age Admission/5 + 0.986 × Chest + 0.507 × Cardi-ovascular + Scr Grade (-0.232 [if Grade 0], or -0.170 [if Grade 1], or 0.037 [if Grade 2], or 0.365 [if Grade 3]) + AAV Subtype (0 [if EGPA], or 0.972 [if GPA], or 1.155 [if MPA])-0.058 × Hb/10. Our prediction model was further graphically simulated and expressed asa Nomogram (Figure 2).

Model Performance and Internal Validation

The apparent C-index and integrated Brier score of the prediction model were 0.753, and 0.112, respectively. To minimize the over-fitting bias, 200 bootstrapping samples with replacement were generated to calculate the optimism. The optimism corrected C-index, and integrated Brier score were 0.728 and 0.109 (Table 2). The one-, three-, and five-year optimism corrected C-index were 0.700, 0.716 and 0.748 (Table 2). The observed five-year cumulative incidence and predicted five-year probability of all-cause deathwere compared via the calibration plots in each imputed data set (Supplementary Figure 3).

Table 1: Baseline characteristics of 20 candidate predictors in the prediction model

	Median (IQR)/*n* OR *n* (%)	**Missing values (%)**
Male	326 (49.9)	0 (0)
Age at admission (years)	56 (41, 66)/653	0 (0)
Disease duration (months)	8 (2, 29)/653	0 (0)
Clinical manifestation		0 (0)
Constitutional symptoms	548 (83.9)	0 (0)
Skin	83 (12.7)	0 (0)
Mucous Membrane/Eyes	174 (26.6)	0 (0)
ENT	347 (53.1)	0 (0)
Chest	431 (66.0)	0 (0)
Cardiovascular	111 (17.0)	0 (0)
Abdominal	15 (2.3)	0 (0)
Nervous System	172 (26.3)	0 (0)
BVAS score	20 (16, 26)/653	0 (0)
WBC (× 10^9/L)	10.31 (8.01, 13.59)/650	3 (0.459)
Hb (g/L)	107 (89, 124)/649	4 (0.613)
PLT (×10^9/L)	296 (218,388)/650	3 (0.459)
Scr < 125 μmol/L (Grade 0)	400 (62.1)	
125 ≤ Scr < 250 μmol/L (Grade 1)	106 (16.5)	9 (1.378)
250 ≤ Scr < 500 μmol/L (Grade 2)	80 (12.4)	
Scr ≥ 500 μmol/L (Grade 3)	58 (9.0)	
hsCRP (mg/L)	44.74 (10.64,105.07)/630	23 (3.522)
ESR (mm/h)	76 (41, 99)/623	30 (4.594)
GPA	245 (37.5)	
MPA	303 (46.4)	0 (0)
EGPA	105 (16.1)	
MPO-ANCA	342 (52.4)	
PR3-ANCA	174 (26.6)	0 (0)
Double-Positive	13 (2.0)	
Double-Negative	124 (19.0)	

IQR, interquartile range; ENT, ear, nose and throat; BVAS, birmingham vasculitis activity score; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; Scr, serum creatinine; hsCRP, hypersensitive C-reactive protein; ESR, erythrocyte sedimentation rate; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; ANCA, anti-neutrophil cytoplasmic antibody.

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Table 2: Model performance

	Current model performance (95%CI)	Average optimism calculated from 200 bootstrap validation	Optimism-corrected performance	rFFS performance (95%CI)	BVAS performance (95%CI)
Overall C-index	0.753 (0.709-0.797)	0.025	0.728	0.684 (0.639-0.729)	0.578 (0.525-0.631)
C-index 1-year	0.709 (0.636-0.781)	0.009	0.700	0.671 (0.601-0.741)	0.549 (0.480-0.618)
C-index 3-year	0.725 (0.661-0.789)	0.009	0.716	0.726 (0.674-0.779)	0.522 (0.458-0.580)
C-index 5-year	0.756 (0.693-0.819)	0.008	0.748	0.735 (0.675-0.795)	0.550 (0.482-0.618)
Integrated Brier score	0.112	0.003	0.109	0.145	0.198

C-index: concordance index; rFFS: revised five factor score; BVAS, birmingham vasculitis activity score; CI, confidence interval.

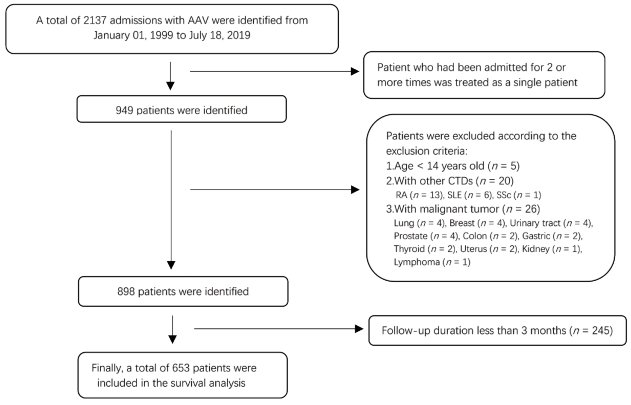

Figure 1: The diagram of patient selection strategy in the present study. AAV, anti-neutrophil cytoplasmic antibody associate vasculitis; CTD, connective tissue disease; RA, rheumatoid arthritis; SLE, systemic lupus arthritis; SSc, systemic sclerosis.

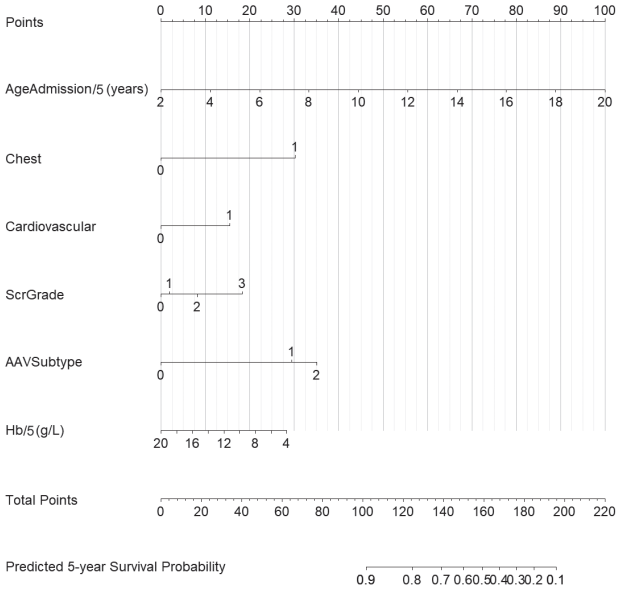

Figure 2: The Nomogram of our proposed prognostic model simulated with the stacked data set. Scr, serum creatinine; AAV, anti-neutrophil cytoplasmic antibody associate vasculitis; Hb, hemoglobin; EGPA, eosinophilic granulomatosis with polyangiitis (AAV Subtype score 0); GPA, granulomatosis with polyangiitis (AAV Subtype score 1); MPA, microscopic polyangiitis (AAV Subtype score 2).

Risk Groups and Comparison with the rFFS and the BVAS System

Based on the tertiles of PI in the stacked data set, the AAV patients were divided into 3 risk groups. The three risk groups were defined as low risk (PI < 2.294), moderate risk (2.294 ≤ PI < 3.479) and high risk (PI ≥ 3.479), respectively. The five-year survival probability in low risk, moderate risk and high risk were > 90.04%, 90.04%-70.96% and ≤ 70.96% according to the Formular 1, respectively. The Kaplan-Meier curves were plotted based on combined results after multiple imputation in different PI, rFFS, and BVAS subgroups. The Kaplan-Meier curves stratified by the rFFS and the BVAS indicated that the rFFS and the BVAS system didn't predict survival accurately. However, in the Kaplan-Meier curves stratified by risk groups of our prediction model, *i.e.*, tertiles of PI, there were significant differences in the three groups (Figure3). Compared with the rFFS and the BVAS system, our prediction model had higher C-Index (Table 2) and positive NRIs (Supplementary Table 6). Moreover, in the DCA analysis, compared with the rFFS and the BVAS system, our prediction model provided a larger net benefit across a wide range of threshold probabilities (Figure 4).

Discussion

The long-term survival of patients with AAV has been improving in the past several decades.[2,25] Precisely predicting the outcome is critical for clinicians to adjust the treatment and understand the progress of the disease. In the present retrospective cohort study, we developed and internally validated a new prognostic model to predict the probability of long-term survival in patients with AAV. Different from the published rFFS system, our prediction model was designed specifically for AAV and incorporated not only clinical organ involvement

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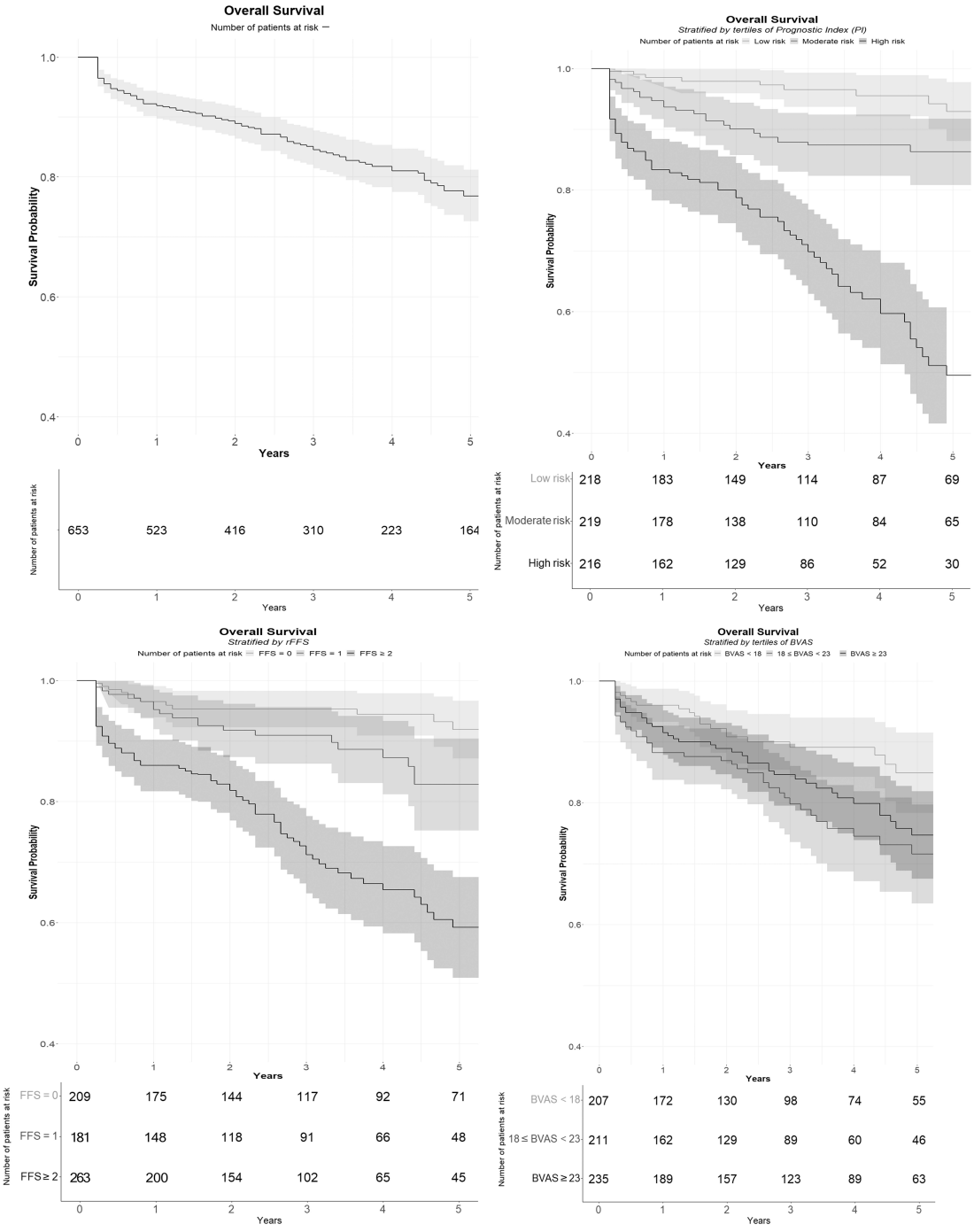

Figure 3: The Kaplan-Meier curves of observed survival in AAV patients classified by tertiles of PI based on combined results after multiple imputation, rFFS subgroup, and tertiles of BVAS. The shadows around the curves refer to the 95% confidence interval. AAV, anti-neutrophil cytoplasmic antibody associate vasculitis; PI, prognostic index; rFFS, revised five-factor score; BVAS, birmingham vasculitis activity score.

patterns but also demographic and laboratory test results. The C-index, the integrated Brier score and the calibration plots demonstrated that our prediction model performed well. We adopted the LASSO method to select the potential predictors in the final prediction model. Compared with the traditional univariate selection method used in the rFFS development,

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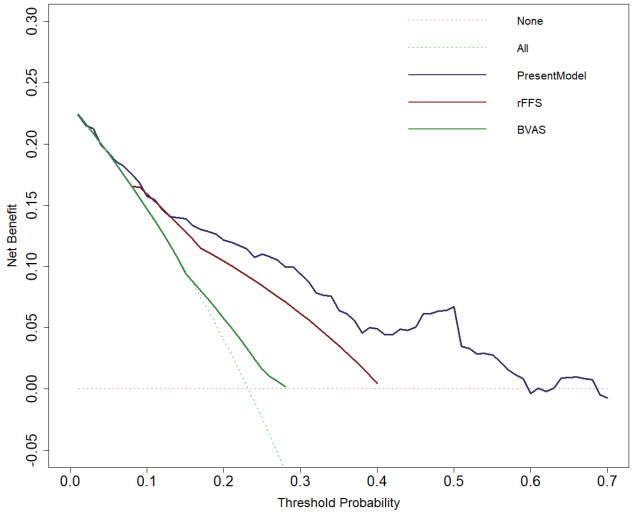

Figure 4: Decision curve analysis of our prediction model, the revised FFS system and BVAS based on combined results after multiple imputation. rFFS, revised five-factor score; BVAS, birmingham vasculitis activity score.

which is based on the set marginal significance level that might be misleading, the LASSO method is the preferred and sophisticated method for variable selection.[26,27] The multivariate analysis in the previous studies showed that age over 60 years old at diagnosis, renal involvement, ANCA positivity, high BVAS and low hemoglobin level were independent predictors of mortality. The initial FFS was developed in patients with polyarteritis nodosa, MPA and CSS.[8] And in the revised FFS developing cohort, patients with GPA were first included.[7] Except for ENT involvement, which is the protective factor especially in GPA and CSS, other four factors, *i.e.*, elder age, cardiac, renal and gastrointestinal involvement, were related to poor prognosis.[7] Partially because most of the patients in our cohort were classified as MPA, in whom the ENT involvement was less common and always minor, as a result, ENT signs were not included in our model.

In addition to the parameters in the rFFS,[7] we identified other three parameters, *i.e.*, AAV subtypes, lung involvement and hemoglobulin levels, most of which had been reported to be related to poor outcomes in patients with AAV.[28-31] Compared with patients with GPA and EGPA, those with MPA had the worst survival rate.[28,31,32] The survival of patients with AAV varied among different cohorts. It seemed that the mortality was higher in cohorts including more patients with MPA, regardless of the discrepancies in demographic and geographic factors in different studies.[32] In European and American countries, and in some Asian countries, such as Turkey and Saudi Arab, most of the AAV patients were classified as GPA, followed by MPA and EGPA.[2,28,29,31,33-36] However, in eastern Asian countries, including China, South Korea and Japan, MPA was the most common AAV subtype.[30,37-39] Similar to previously published studies, in our cohort, 46.4% of the patients with AAV were classified as MPA.

Pamuk and colleagues reported that patients with diffused alveolar hemorrhage (DAH) had lower survival probability than those without DAH.[31] However, partially due to the small number of patients with severe DAH, DAH was not regarded as a dependent risk factor for poor outcome in the rFFS developing cohort.[7] Meanwhile, Mun *et al*. noticed that not only DAH but also interstitial lung disease was related to worse survival.[30]In a systemic review, Sebastiani *et al*. found that the mortality was increased to two to four times in AAV patients with interstitial lung disease, especially in those with MPA.[40] Pulmonary involvement is uncommon in PAN.[41] Therefore, it was not surprising that pulmonary involvement was not related to poor outcomes in the rFFS generating cohort, in which about one-third of the patients were with PAN.[7] Anemia is common in patients with AAV and corelates with higher mortality.[28] Further analysis showed that low hemoglobin level was an independent risk factor for mortality.[29] To some extent, anemia associated with the severe systemic inflammation, which reflected the severity of the disease itself. Based on the coefficient in the prediction model, with the diagnosis of MPA, followed by lung involvement, was most strongly associated with mortality in the Chinese AAV population.

Discrimination refers to the ability of a prediction model to differentiate between patients who would or would not have outcome events.[14] The C-index is the most commonly used indicator of discrimination. As a rule of thumb, C-index over 0.7 indicates modest or acceptable discriminative ability.[42] The C-index of rFFS for survival prediction was 0.74 in Spanish patients with AAV implying modest discriminative ability.[43] In our patients, the C-index of rFFS for 5-year survival prediction was 0.735, which is comparable to the Spanish patients. Meanwhile, in our prediction model, the optimism corrected C-index for 5-year survival prediction was 0.748, which indicates that the discrimination of our model is comparable to rFFS. And in the Spanish cohort, the C-Index for BVAS was 0.60, similar to our findings. These results showed that high disease activity initially was not significantly correlated with poor prognosis, especially after being treated properly. Calibration is another parameter to evaluate the performance of a prediction model, which reflects the agreement between the observed and the model predicted outcomes.[14] In the present study, calibration curves were around the 45-degree line, which implied a good agreement between observed outcomes and predictive ability of the present model. However, calibration is only reported in a few of reported prediction models.[14] Prediction model with smaller Brier score might be the preferred model.[44] Compared with the rFFS and the BVAS, our prediction model had lower Brier score. The NRIs and DCA analysis are relative novel indictors for prediction model interpretation.[45] The NRIs results showed that compared with the rFFS and the BVAS system, the current

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prediction model had higher predictive power for overall survival. In a quite wide range of threshold probabilities, our prediction model had higher net befits implying probable better clinical values.

Different from the rFFS, which only classified patients as low-, medium- and high- risk of death at the fifth year,[7] our prediction model could obtain individual prediction of the probability of five-year survival via the Formula or the Nomogram. For example, there were two male patients, one was 66 years old with a Scr level of 166 μmol/L, the other was 80 years old with a Scr level of 550 μmol/L. As expected, the latter patient had lower survival probability assessed via the present model. However, they had identical rFFS scores.

The limitations of this study include the following aspects. Firstly, due to the retrospective nature of the study, some data were missing and confounding bias might occur, although we took several widely accepted statistical measures, including multiple imputation, Rubin's rule, *et al*., in the prediction model development and interpretation to minimize their impact on the results. Secondly, in this study, patients were from a single center and only in-patients were included, so patient selection bias may occur. Because PUMCH is a nation-wide referral center in China, most of the admitted patients were critically ill or had complex diseases. Thus, the prognosis in our patients was poorer compared with that in the population-or out-patient clinic-based studies. Thirdly, we only included patients who were followed up for at least three months for model development. Patients excluded had higher serum creatinine and rFFS levels, indicating more severe disease. Therefore, the survival probability was overestimated in our model. Fourthly, we only used the bootstrap resampling methods to internally validate our prediction model. In the future, more studies are needed to externally validate our results.

Conclusions

We developed and internally validated a model specifically for AAV to predict long term survival of patients with this disease. In addition to the factors included in the widely used rFFS system, our prediction model showed that lung involvement, hemoglobin levels and AAV subtypes are also predictive factors for the survival of AAV patients. And the long-term survival prediction model developed in this study performs well.

Supplementary Materials

The supplementary material for this article can be found at the Rheumatology and Immunology Research online.

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Author Contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by Chen Z, Tian X, Qu J, Chen J, Yang Y and Li J. Data analysis and interpretation were performed by Chen Z, Qu J, Yang Y. The first draft of the manuscript was written by Chen Z and Tian X. And all authors commented on previous versions of the manuscript. All authors have critically revised the manuscript critically for important intellectual content and approved the final version for publication. Li J had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Informed Consent

None declared.

Ethical Statement

None declared.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Meanwhile, Xinping Tian is the Executive Editor-in-Chief of of the journal, The article was subject to the journal's standard procedures, with peer review handled independently of the editor and the affiliated research groups.

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Data Sharing

All data required to validate the conclusions in the study are present in the article and the supplemental files. Further data are available from the corresponding authors at lijing6515@pumch.cn on reasonable requests.

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