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Development and Validation of a Machine Learning-Based Prognostic Model for IgA Nephropathy with Chronic Kidney Disease Stage 3 or 4

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Keywords
IgA nephropathy · Prognostic model · Random survival forests · Machine learning

Abstract

Introduction: Immunoglobulin A nephropathy (IgAN) patients with lower estimated glomerular filtration rate (eGFR) and higher proteinuria are at a higher risk for end-stage kidney disease (ESKD) and their prognosis is still unclear. We aim to develop and validate prognostic models in IgAN patients with chronic kidney disease (CKD) stage 3 or 4 and proteinuria ≥1.0 g/d. ***Methods:*** Patients who came from Xijing Hospital, spanning December 2008 to January 2020 were divided into training and test cohorts randomly, with a ratio of 7:3, achieving ESKD and death as study endpoints. Created prediction models for IgAN patients based on 66 clinical and pathological characteristics using the random survival forests (RSF), survival support vector machine (SSVM), eXtreme Gradient Boosting (XGboost), and Cox regression models. The concordance index (C-index), integrated Brier scores (IBS), net reclassification index (NRI), and integrated discrimination improvement (IDI) were used to evaluate discrimination, calibration, and risk classification, respectively. ***Results:*** A total of 263 patients were enrolled. The median follow-up time was 57.3 months, with 124 (47.1%) patients experiencing combined events. Age, blood urea nitrogen, serum uric acid, serum potassium, glomeruli sclerosis ratio, hemoglobin, and tubular atrophy/interstitial fibrosis were identified as risk factors. The RSF model predicted the prognosis with a C-index of 0.871 (0.842, 0.900) in training cohort and 0.810 (0.732, 0.888) in test cohort, which was higher than the models built by SSVM model (0.794 [0.753, 0.835] and 0.805 [0.731, 0.879], respectively), XGboost model (0.840 [0.797, 0.883] and 0.799 [0.723, 0.875], respectively) and Cox regression (0.776 [0.727, 0.825] and 0.793 [0.713, 0.873], respectively). NRI and IDI showed that the RSF model exhibited superior performance than the Cox model. ***Conclusion:*** Our model introduced seven risk factors that may be useful in predicting the progression of IgAN patients with CKD stage 3 or 4 and proteinuria ≥1.0 g/d. The RSF model is applicable for identifying the progression of IgAN and has outperformed than SSVM, XGboost, and Cox models.

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Introduction

Immunoglobulin A nephropathy (IgAN) is the most prevalent primary glomerulonephritis globally, of which 15–50% cases have clinical manifestations ranging from asymptomatic to end-stage kidney disease (ESKD) [1]. Patients with reduced estimated glomerular filtration rate (eGFR), especially chronic kidney disease (CKD) stage 3 or 4 (eGFR 15–60 mL/min/1.73 m^2), have a significantly elevated risk of, such as cardiovascular events, ESKD, and mortality [2, 3]. Considering that a significant number of patients have an eGFR ranging from 20 to 50 mL/min/1.73 m^2 upon admission, and there is ongoing controversy regarding their treatment options, these patients are rarely included in studies, thereby increasing the difficulty of assessing their prognosis [4, 5]. Recent studies have shown that patients starting treatment when the proteinuria is ≥1.0 g/d have a significantly increased risk of composite kidney endpoint events [6]. Treatments like rituximab or immunosuppressants had no significant effects on reducing proteinuria or protecting kidney function in IgAN patients with proteinuria ≥1.0 g/d [7, 8]. In addition, proteinuria ≥1.0 g/d is always recommended by nephrologists as the referral threshold for proteinuria and reducing urinary protein excretion to below 1.0 g/d as a therapeutic target [9], suggesting that whether proteinuria is greater than 1.0 g/d is an important detection indicator. However, it is still unclear what factors can affect their prognosis and there is no unified treatment method for this type of high-risk patients.

Over the past few decades, extensive research has been conducted on clinical and histopathological risk factors associated with the progression of IgAN to ESKD. Several important risk factors have been identified, including proteinuria ≥1.0 g/d, histology grading, baseline kidney function, patient demographics (age, sex, etc.), presence of comorbidities, etc., which have been well-validated in clinical practice [10–13]. Several prognostic models based on the above risk factors have been established. For example, a prognostic score was devised to predict the incidence of ESKD over a 7-year period based on eight variables identified in a Japanese cohort [14]. Chen et al. [15] applied three models to construct a prognostic prediction and risk stratification system. However, these prognostic models have some limitations, such as the use of different pathologic scoring criteria [15, 16], the inclusion of fewer variables [12], and difficulty in evaluating the contribution of individual factors [17]. Therefore, precise prognostication of the timing and likelihood of clinical events in individuals with lower eGFR and higher proteinuria is essential for guiding interventions aimed at ameliorating and forestalling disease progression.

Machine learning (ML) methods are increasingly utilized in medical research, surpassing traditional statistics in predictive accuracy, modeling complexity, and data noise tolerance for precise survival predictions [18, 19]. Currently, multiple ML models have been applied to the prognostic analysis of IgAN, but these results have not yet been validated in patients with high-risk progression of IgAN [15, 20, 21]. The random survival forests (RSF) algorithm improves predictive performance by building decision trees [22], while the survival support vector machine (SSVM) specializes in processing survival and time-series data [23], and eXtreme Gradient Boosting (XGboost) enhances model performance through gradient boosting [24]. Cox regression provides an intuitive interpretation of the hazard ratio and is widely used in survival analysis [25]. With the development of ML, comparing the characteristics of both methods is crucial for providing accurate model selection in practical applications and deepening our understanding of data and model characteristics. Therefore, this study aimed to construct and validate ML models to predict the incidence of ESKD or death in IgAN patients with CKD stage 3 or 4 and proteinuria ≥1.0 g/d and to compare its predictive accuracy with a benchmark model established through Cox regression analysis, with the goal of enabling early intervention and guiding treatment.

Methods

Study Population

We retrospectively reviewed the pathological and clinical data of 2,831 IgAN patients diagnosed by kidney biopsy at Xijing Hospital (Air Force Military Medical University) from December 2008 to January 2020. The patients were recruited consecutively if they had: (1) patients over 18 years old with complete follow-up records; (2) eGFR 15–60 mL/min/1.73 m^2; and (3) proteinuria ≥1.0 g/d. Patients were excluded if they had: (1) secondary IgAN including purpura nephritis, lupus nephritis, hepatitis B-associated glomerulonephritis, and Sjogren's syndrome and so on; (2) comorbid conditions (such as diabetes mellitus and severe cardiovascular disease); (3) less than 6 months of follow-up period unless they met the endpoints; (4) <8 glomeruli in biopsy specimens or no biopsy data; (5) no outcome data available. The last follow-up in this study was in May 2023. The Ethics Committee of Xijing Hospital approved this study (ethical number: KY20213027-1) and the Ethics Committee waived the informed consent from patients because this was a retrospective study. The Transparent Reporting of a Multivariable Prediction

Model for Individual Prognosis or Diagnosis reporting guidelines (TRIPOD) was adhered to by this study [26] (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000540682).

Data Collection

The demographic characteristics, clinical manifestations, pathological characteristics, and treatment strategies of the enrolled population at kidney biopsy were collected by reviewing medical records. Treatment methods used in this study were divided into the following 5 types: supportive therapy, corticosteroids alone, immunosuppressant alone, corticosteroids plus cyclophosphamide, corticosteroids plus other immunosuppressants. Immunosuppressants mainly included mycophenolate mofetil, tacrolimus, and cyclosporin. Then, excluding those with missing data exceeding 10% (online suppl. Fig. S1; Table S2) and highly correlated variables (correlation coefficient >0.75). Finally, combining clinical experience identified variables. The missing data were addressed using the "missforest" package, which employs an iterative imputation method based on a random forest [27].

Definition of Variables

The classification and definition of CKD were based on the clinical practice guideline provided by KDIGO 2021 Clinical Practice Guideline [1]. The formula developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) was used to calculate eGFR [28]. ESKD was defined as eGFR <15 mL/min/1.73 m^2, starting hemodialysis or peritoneal dialysis, or receiving a kidney transplant [1]. The grading of kidney histology was determined according to the revised Oxford MEST-C classification of IgAN [29]. Additionally, scoring was conducted for renal small artery sclerosis, renal middle artery sclerosis, and renal arteriolar hyalinosis. The post-discharge follow-up duration should be a minimum of 6 months. The follow-up assessment encompassed information on survival outcomes, the occurrence of ESKD or dialysis, overall physical condition, and levels of creatinine. We rigorously ensured the confidentiality of participants' data throughout and after the data collection process. The definition of clinical outcome in this study was a combined event, which is the occurrence of ESKD or death whichever comes first.

Statistical Analysis

Continuous variables that followed a normal distribution were analyzed using the *t* test, while those that did not follow a normal distribution were analyzed using the Mann-Whitney U-test. Categorical data were analyzed using the χ^2 test. *p* value of less than 0.05 is considered statistically significant. All data analyses were performed using R software 4.3.3 (R Project for Statistical Computing) and SPSS software 25.0 (IBM, Armonk, NY, USA).

Model Development

In order to select the main variables, we conducted a feature selection procedure combined with the least absolute shrinkage and selection operator (LASSO) regression and RSF algorithm [30]. After conducting the ten-fold cross-validation by the "CV.glmnet" function, we selected the variables screened by lambda.1se as the prognostic variables for Lasso. The same 66 variables were incorporated into the RSF model and finally filtered out 10 important prognostic variables as RSF prognostic variables based on variable importance (VIMP). The overlapping parts of the two methods were incorporated into the final model. Bootstrapping resampling with 1,000 replications was conducted, and the resulting 95% confidence interval (CI) of VIMP was calculated to rank the final variables.

We used four algorithms for right-censored time-to-event data: RSF [31], SSVM [32], XGboost [33], and Cox regression [25]. RSF algorithm, which employs log-rank tests to distinguish survival statuses and constructs numerous decision trees, results in enhanced prognostic performance and greater flexibility, with individual probabilities derived from the average prediction results across all trees [17]. SSVM combines survival analysis with support vector machine (SVM), specializing in processing survival and time-series data with strong generalization performance, especially in small sample datasets [18]. XGboost, an upgraded version of the Gradient Boosting algorithm, trains weak classifiers using the negative gradient information of the loss function, effectively preventing overfitting and improving model performance [19]. The dataset was randomly divided into training cohort and test cohort according to 7:3, and the best parameters of each model were selected by using the method of grid search to train the model and verify the model on the test set. Specific R packages used were "survival," "glmnet," "pec," "randomForestSRC," "survivalsvm," "e1071," and "xgboost."

Model Validation

The performance of the model was evaluated based on discrimination and calibration metrics. Discrimination was quantified using the area under receiver

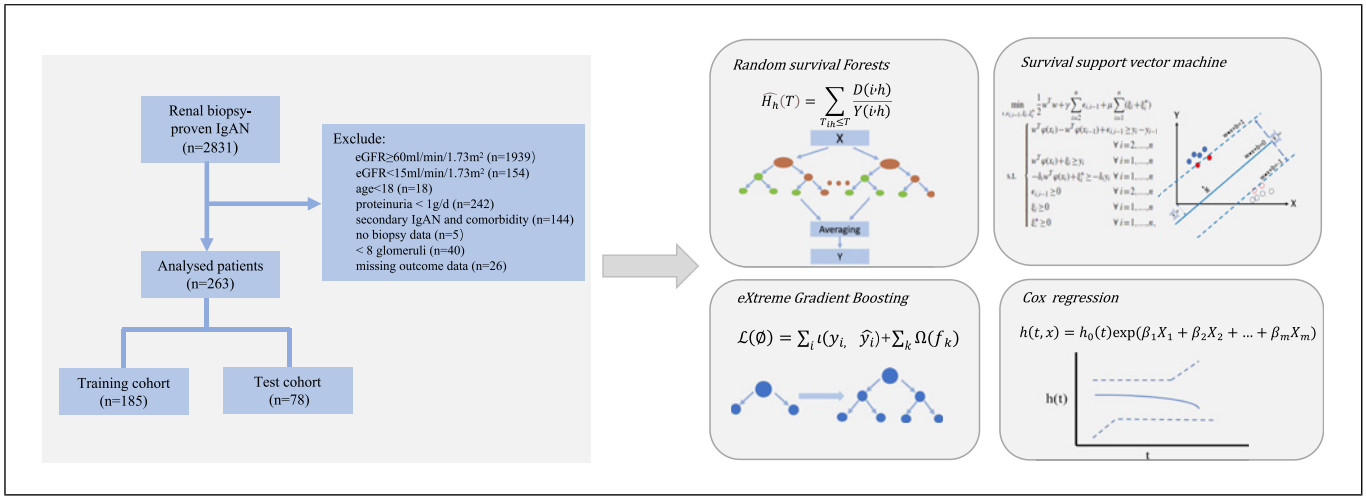

Fig. 1. Inclusion flowchart of patient selection. IgAN, immunoglobulin A nephropathy; eGFR, estimated glomerular filtration rate.

operating characteristic curve (AUC), concordance index (C-index), and time-dependent area under curve (tAUC) [34]. The higher C-index or AUC indicates the excellent discriminatory power of the model.

Calibration plots were constructed to evaluate the predicted and observed probabilities of a model and a closer alignment between the two indicates a better calibration [35]. Additionally, the integrated Brier score (IBS) was calculated, with a lower score indicating greater predictive accuracy [36]. The comparative performance of the two models was assessed through decision curve analysis (DCA), which involves the evaluation of the net benefit of model predictions across a range of decision thresholds. Models with superior performance exhibit a greater net benefit across all probability thresholds [37]. The integrated discrimination improvement (IDI) [38] and net reclassification improvement (NRI) [39] were calculated to evaluate the improvement of model prediction ability. Specific R packages used were "ggDCA," "glmnet," "nricens," "survIDINRI," and "riskRegression."

Results

Baseline Characteristic

A total of 2,831 biopsy-proven IgAN patients were initially introduced and 263 patients were included eventually (Fig. 1). The median age was 36 (29, 47) years. 183 (69.6%) patients were diagnosed with hypertension. The MAP was 102.7 (93.2, 113.5) mm Hg. The proteinuria was 1,912 (1,376, 2,971.5) mg/d and the eGFR was 41.6 (30.4, 49.9) mL/min/1.73 m^2. 124 (47.1%) patients attained the endpoint (111 patients of ESKD and 13 deaths) during a median follow-up of 57.3 (32.7, 82.9) months. 263 patients were randomly split into 185 training samples and 78 test samples. The clinical and pathological variables and follow-up were well-balanced between the training and test cohorts, indicating a robust study design (Table 1).

Model Development

Following the application of the RSF algorithm for data imputation and the elimination of collinear data, a total of 66 covariates were chosen from among 77 variables for subsequent analysis (online suppl. Table S3). Through ten-fold cross-validation of the minimum criterion for the preferred parameter (lambda.1se), the trajectory of each prognostic index coefficient (online suppl. Fig. S2) and the logarithmic transformation of lambda in the Lasso algorithm were observed (Fig. 2a). Eleven variables corresponding to lambda.1se = 0.109 were selected as Lasso regression variables (Fig. 2b). Then, the same 66 variables were included in the RSF model, and 10 important prognostic variables were filtered out as RSF prognostic variables based on variable importance scores (Fig. 2c). The two algorithms identified seven overlapping prognostic variables (age, hemoglobin [Hb], serum uric acid, blood urea nitrogen [BUN], serum potassium, glomeruli sclerosis ratio, tubular atrophy/interstitial fibrosis [T]), which were incorporated into the final model as the ultimate variables (Fig. 2d). Using the VIMP method based on the RSF model, the results showed that BUN is the factor that contributes the most to the model

Table 1. Baseline characteristics of the study subjects

Characteristic	All patients (n = 263)	Training cohort (n = 185)	Test cohort (n = 78)	p value
Demographic characteristics at biopsy				
Age, years	36 (29.0, 47.0)	40 (29.0, 48.0)	34 (29.0, 43.0)	0.06
Male	180 (68.4)	123 (66.5)	57 (73.1)	0.3
BMI, kg/m^2	24 (21.5, 26.6)	24 (21.6, 26.8)	24 (21.5, 26.3)	0.3
RAAS blockade before biopsy	91 (34.6)	60 (32.4)	31 (39.7)	0.3
Glucocorticoid before biopsy	36 (13.7)	25 (13.5)	11 (14.1)	0.9
Hypertension	183 (69.6)	130 (70.3)	53 (67.9)	0.7
Clinical characteristics				
MAP, mm Hg	102.7 (93.2, 113.5)	103.0 (93.3, 116.0)	101.7 (90.5, 108.3)	0.2
Proteinuria, mg/d	1,912 (1,376.0, 2,971.5)	1,848 (1,330.0, 3,000.0)	2,040 (1,494.0, 2,907.0)	0.7
eGFR, mL/min/1.73 m^2	41.6 (30.4, 49.9)	41.6 (30.7, 49.5)	40.5 (30.3, 52.3)	0.9
BUN, mmol/L	8.3 (6.8, 11.5)	8.7 (6.9, 11.3)	7.8 (6.7, 12.0)	0.8
Serum uric acid, μmol/L	388 (337.0, 467.5)	383 (335.0, 466.0)	404 (352.8, 475.8)	0.5
Serum potassium, mmol/L	4.3±0.5	4.3±0.5	4.3±0.4	0.3
Glomeruli sclerosis ratio	0.36 (0.2, 0.6)	0.38 (0.2, 0.6)	0.31 (0.1, 0.5)	0.9
Hb, g/L	128.1±23.1	127.7±22.8	128.9±23.9	0.5
Treatment[a]				0.06
Only supportive treatment	12 (4.6)	8 (4.3)	4 (5.1)	
Corticosteroids	18 (6.8)	14 (7.6)	4 (5.1)	
Immunosuppressants	32 (12.2)	24 (12.9)	8 (10.3)	
Corticosteroids plus cyclophosphamide	128 (48.7)	87 (47)	41 (52.6)	
Corticosteroids plus other immunosuppressants	73 (27.8)	52 (28.1)	21 (26.9)	
CKD stage				0.9
Stage 3	199 (75.7)	140 (75.7)	59 (75.6)	
Stage 4	64 (24.3)	45 (24.3)	19 (24.4)	0.06
Oxford Classification[b]				
M1	166 (63.1)	118 (63.8)	48 (61.5)	0.7
E1	55 (20.9)	40 (21.6)	15 (19.2)	0.7
S1	233 (88.6)	166 (89.7)	67 (85.9)	0.4
T1-2	204 (77.5)	141 (76.2)	63 (80.7)	0.06
C1-2	121 (46)	86 (46.5)	35 (44.9)	0.5
Follow-up, months	57.3 (32.7, 82.9)	57.7 (35.3, 83.0)	55.9 (31.7, 79.6)	0.9
Combined event	124 (47.1)	88 (47.6)	36 (46.2)	0.8
ESKD	111 (42.2)	80 (43.2)	31 (39.7)	
Death	13 (0.05)	8 (0.04)	5 (0.06)	

Values for continuous variables are expressed as mean ± standard deviation or median (interquartile range); values for categorical data are given as numbers (percent). BMI, body mass index; RAAS, renin-angiotensin system; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; ESKD, end-stage kidney disease. [a]All patients received supportive treatment if they can tolerate it. [b]The Oxford classification: mesangial hypercellularity (M0, mesangial score ≤0.5; M1, mesangial score >0.5), endocapillary hypercellularity (E0, absent; E1, present), segmental glomerulosclerosis (S0, absent; S1, present), tubular atrophy/interstitial fibrosis (T0, ≤25%; T1, 26 %–50%; T2, >50%) and cellular or fibrocellular crescents (C0: absent; C1: 1–24%; and C2: ≥25% of the glomeruli).

(Fig. 3). The parameters for the RSF model were set to mtry = 1, nodesize = 7, and ntree = 400, respectively. For the SSVM model, the configuration was set with type = "regression," diff.meth = "makediff3," gamma.mu = 5. Additionally, the XGboost parameters include eta = 0.01, max_depth = 1, subsample = 1, colsample_bytree = 1, and gamma = 0.5.

Model Performances

Discrimination

Compared with the Cox regression model with a score of 0.776 (95% CI: 0.727, 0.825), the RSF, SSVM, and XGboost model has a better C-index of 0.871 (95% CI: 0.842, 0.900), 0.794 (95% CI: 0.753, 0.835), and 0.840 (95% CI: 0.797, 0.883), respectively, in the

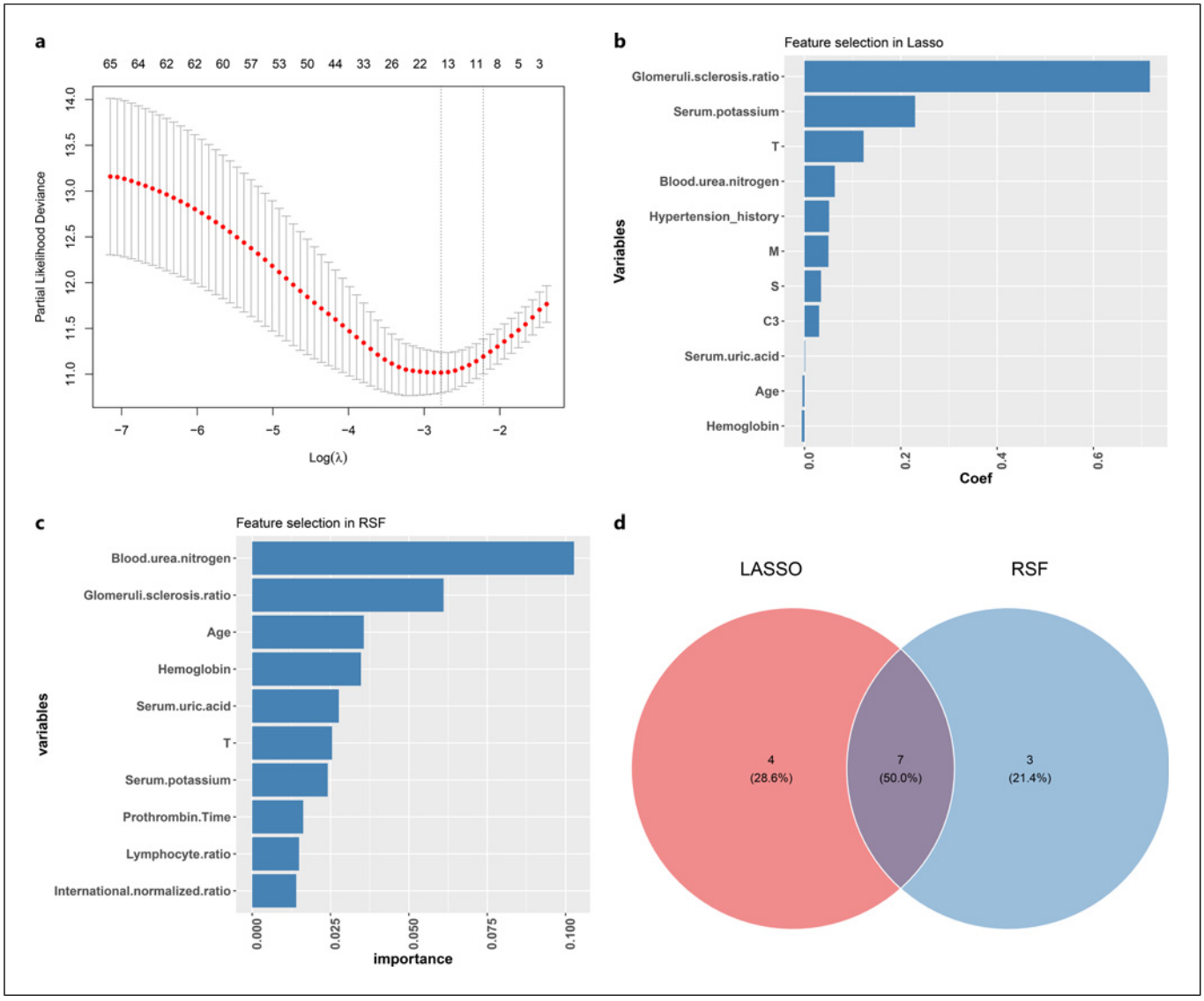

Fig. 2. The process of variable selection using Lasso regression and RSF algorithms. **a** Determination of the optimal parameter value in Lasso regression using the 10-fold cross-validation method. **b** Selection of 11 variables through lambda.1se and their ranking of importance. **c** Evaluation of the importance of 10 variables using RSF model. **d** Venn diagram showing overlapping variables. RSF, random survival forest; T, tubular atrophy/interstitial fibrosis; M, mesangial hypercellularity; S, segmental glomerulosclerosis.

training set. In the test set, the C-index was 0.810 (95% CI: 0.732, 0.888) for the RSF model, 0.805 (95% CI: 0.731, 0.879) for the SSVM model, 0.799 (95% CI: 0.723, 0.875) for the XGboost model and 0.793 (95% CI: 0.713, 0.873) for the Cox model (Table 2). The tAUC results of all patients demonstrated that the RSF model achieved the highest values, followed by XGboost, SSVM, and Cox models (online suppl. Fig. S3).

Figure 4 displays the performance of the RSF, SSVM, XGboost, and Cox models in the training and test cohort. In the training set, the RSF model exhibited superior discrimination, with an AUC of 0.912 (95% CI: 0.856, 0.967) at 1 year. The AUC values for 3 and 5 years were 0.943 (95% CI: 0.909, 0.976) and 0.935 (95% CI: 0.899, 0.972), respectively. The AUC values of the SSVM model for 1, 3, and 5 years were 0.858 (95% CI: 0.788, 0.928), 0.867 (95% CI: 0.811, 0.924), and 0.849 (95% CI: 0.788,

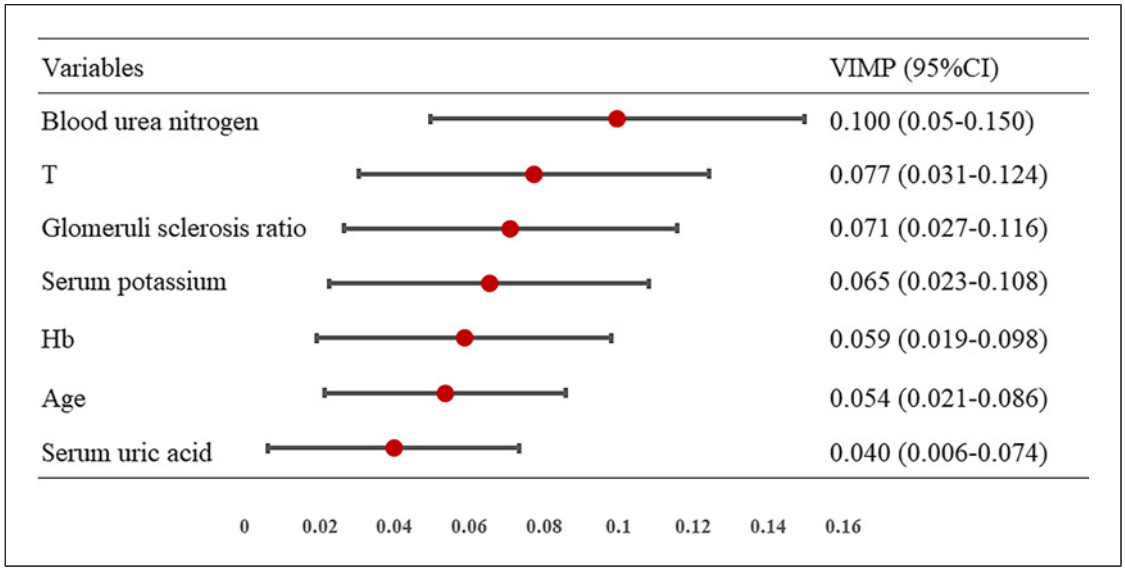

Fig. 3. Variable importance of ultimate variables used in RSF model. VIMP, Variable Importance; T, tubular atrophy/interstitial fibrosis; Hb, hemoglobin.

Table 2. Predictive performance of four survival models in IgAN patients with CKD stage 3 or 4 during the follow-up period

Models	C-index (95% CI)	Integrated brier score (95% CI)
Training cohort		
RSF	0.871 (0.842, 0.900)	0.103 (0.091, 0.126)
SSVM	0.794 (0.753, 0.835)	0.144 (0.126, 0.167)
XGboost	0.840 (0.797, 0.883)	0.144 (0.130, 0.165)
Cox	0.776 (0.727, 0.825)	0.135 (0.119, 0.166)
Test cohort		
RSF	0.810 (0.732, 0.888)	0.140 (0.104, 0.195)
SSVM	0.805 (0.731, 0.879)	0.140 (0.109, 0.182)
XGboost	0.799 (0.723, 0.875)	0.164 (0.132, 0.214)
Cox	0.793 (0.713, 0.873)	0.143 (0.112, 0.197)

IgAN, IgA nephropathy; CKD, chronic kidney disease; 95% CI, 95% confidence interval; RSF, random survival forests; SSVM, survival support vector machine; XGboost, eXtreme Gradient Boosting; Cox, Cox regression; C-index, concordance index.

0.911). The AUC values of the XGboost model for 1, 3, and 5 years were 0.862 (95% CI: 0.765, 0.959), 0.905 (95% CI: 0.848, 0.962), and 0.904 (95% CI: 0.852, 0.956). The Cox model had an AUC of 0.790 (95% CI: 0.684, 0.897), 0.837 (95% CI: 0.768, 0.907), and 0.844 (95% CI: 0.783, 0.906) at 1, 3, and 5 years, respectively. In the test cohort, the ROC analysis showed an AUC of 0.879 (95% CI: 0.729, 1.00), 0.850 (95% CI: 0.745, 0.955), and 0.848 (95% CI: 0.755, 0.941) for 1-, 3-, and 5-year survival predictions, respectively, in the RSF model. The AUC values of the SSVM model for 1, 3, and 5 years were 0.898 (95% CI: 0.768, 1.00), 0.874 (95% CI: 0.783, 0.966), and 0.821 (95% CI: 0.721, 0.921). The AUC values of the XGboost model for 1, 3, and 5 years were 0.876 (95% CI: 0.735, 1.00), 0.861 (95% CI: 0.761, 0.961), and 0.841 (95% CI: 0.745, 0.936). The AUC values of COX model for 1, 3, and 5 years were 0.88 (95% CI: 0.753, 1.00), 0.841 (95% CI: 0.733, 0.950), and 0.831 (95% CI: 0.729, 0.934).

Calibration

We used the IBS to assess the calibration ability. In the training cohort, the RSF model showed the lowest IBS at 0.103 (95% CI: 0.091, 0.126), followed by Cox model with 0.135 (95% CI: 0.119, 0.166), then the SSVM and

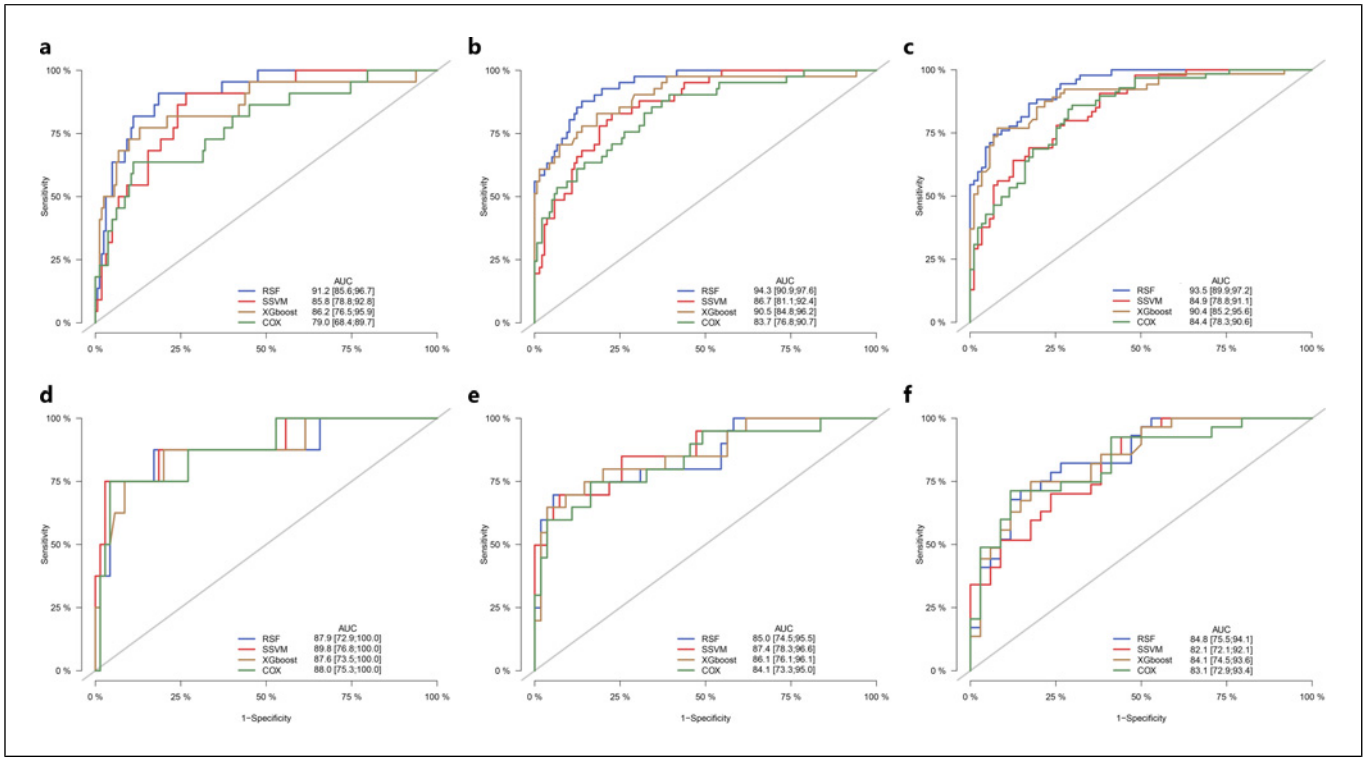

Fig. 4. The receiver operating characteristic curve of all prediction models in the training and test cohorts at 1 year, 3 years, and 5 years. **a** The ROC at 1 year in the training cohort. **b** The ROC at 3 years in the training cohort. **c** The ROC at 5 years in the training cohort. **d** The ROC at 1 year in the test cohort. **e** The ROC at 3 years in the test cohort. **f** The ROC at 5 years in the test cohort. ROC, receiver operating characteristic curve; RSF, random survival forests; SSVM, survival support vector machine; XGboost, eXtreme Gradient Boosting; Cox, Cox regression model.

XGboost model attained an IBS of 0.144 (95% CI: 0.126, 0.167) and 0.144 (95% CI: 0.130, 0.165), respectively. The IBS in the RSF model was 0.140 (95% CI: 0.104, 0.195), 0.140 (95% CI: 0.109, 0.182) in the SSVM model, 0.164 (95% CI: 0.132, 0.214) in the XGboost model and 0.143 (95% CI: 0.112, 0.197) in the Cox model in the test cohort (Table 2). Smoothed calibration plots showed that the observed and predicted risks are generally consistent throughout the entire spectrum of predicted risks, although there are some slight overpredictions in the training cohort and test cohort (Fig. 5).

Decision Curve Analysis

We investigated the clinical usefulness of all models utilizing DCA. Among the RSF, SSVM, XGboost, and Cox models, the DCA curve demonstrated that the RSF model achieved superior performance across the entire range of threshold probabilities at 1-, 3-, and 5-year predictions in the training cohort. In the test cohort, all models have similar net benefit at 1, 3, and 5 years (Fig. 6).

Net Reclassification Index and IDI

Compared with the Cox model, the categorical NRI of the RSF model for the 1-, 3-, and 5-year occurrence of combined events was 0.537 (95% CI: 0.151, 0.764), 0.503 (95% CI: 0.128, 0.668), and 0.33 (95% CI: 0.046, 0.541). The SSVM was 0.026 (95% CI: −0.215, 0.241), −0.053 (95% CI: −0.258, 0.123), and −0.136 (95% CI: −0.325, 0.067), and the XGboost model was 0.063 (95% CI: −0.031, 0.153), −0.018 (95% CI: −0.091, 0.055), and −0.085 (95% CI: −0.152, −0.011). The RSF model had an IDI of 0.113 (95% CI: 0.041, 0.178), 0.134 (95% CI: 0.066, 0.190), and 0.106 (95% CI: 0.038, 0.162). The SSVM model had an IDI of −0.002 (95% CI: −0.047, 0.042), −0.014 (95% CI: −0.06, 0.027), and −0.031 (95% CI: −0.078, 0.014) and the XGboost had an IDI of 0.045 (95% CI: −0.217, 0.284), −0.121 (95% CI: −0.293, 0.085), and −0.202 (95% CI: −0.389, −0.022) at 1, 3, and 5 years, respectively. These results indicated that the RSF model exhibited superior predictive capability than the Cox model in the 1-, 3-, and 5-year prediction (Table 3).

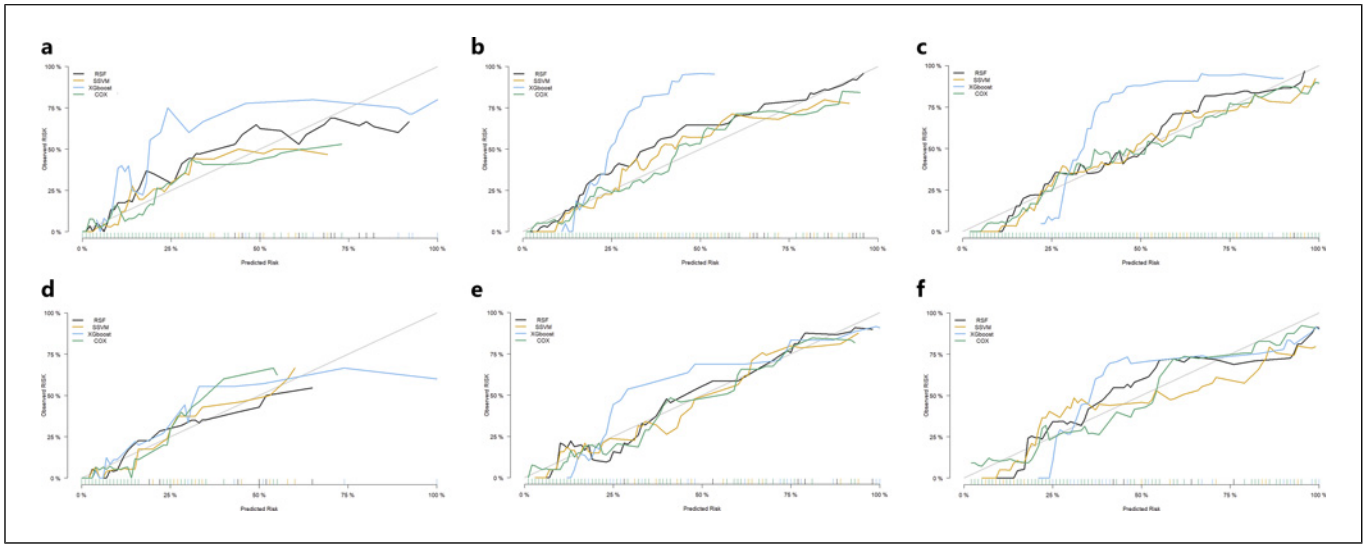

Fig. 5. The calibration curves of all prediction models in the training and test cohorts at 1 year, 3 years, and 5 years. **a** Calibration carves at 1 year in the training cohort. **b** Calibration carves at 3 years in the training cohort. **c** Calibration carves at 5 years in the training cohort. **d** Calibration carves at 1 year in the test cohort. **e** Calibration carves at 3 years in the test cohort. **f** Calibration carves at 5 years in the test cohort. RSF, random survival forests; SSVM, survival support vector machine; XGboost, eXtreme Gradient Boosting; Cox, Cox regression model.

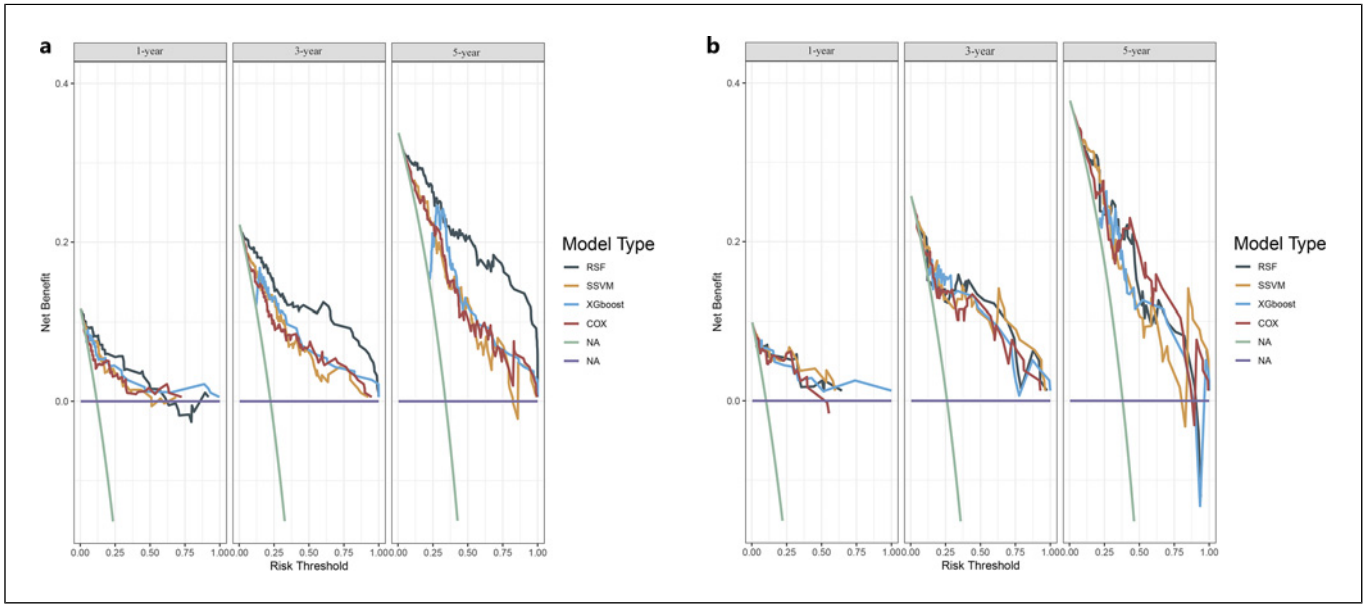

Fig. 6. The decision curve analysis of all prediction models in the training and test cohorts at 1 year, 3 years, and 5 years. **a** DCA plot in the training cohort. **b** DCA plot in the test cohort. DCA, decision curve analysis; RSF, random survival forests; SSVM, survival support vector machine; XGboost, eXtreme Gradient Boosting; Cox, Cox regression model.

Table 3. Comparison of NRI and IDI of RSF, SSVM, and XGboost models versus the Cox model in IgAN patients with CKD stage 3 or 4 during the follow-up period

	NRI (95% CI)	*p* value[a]	IDI (95% CI)	*p* value
RSF, years				
1	0.537 (0.151, 0.764)	<0.05	0.113 (0.041, 0.178)	<0.05
3	0.503 (0.128, 0.668)	<0.05	0.134 (0.066, 0.190)	<0.05
5	0.33 (0.046, 0.541)	<0.05	0.106 (0.038, 0.162)	<0.05
SSVM, years				
1	0.026 (−0.215, 0.241)	0.789	−0.002 (−0.047, 0.042)	1.037
3	−0.053 (−0.258, 0.123)	0.513	−0.014 (−0.06, 0.027)	0.561
5	−0.136 (−0.325, 0.067)	0.172	−0.031 (−0.078, 0.014)	0.2
XGboost, years				
1	0.063 (−0.031, 0.153)	0.156	0.045 (−0.217, 0.284)	0.857
3	−0.018 (−0.091, 0.055)	0.591	−0.121 (−0.293, 0.085)	0.252
5	−0.085 (−0.152, −0.011)	<0.05	−0.202 (−0.389, −0.022)	<0.05

NRI, net reclassification improvement; IDI, integrated discrimination improvement; RSF, random survival forest; SSVM, survival support vector machine; XGboost, eXtreme Gradient Boosting; Cox, Cox regression model; IgAN, IgA nephropathy; CKD, chronic kidney disease. [a]*p* value of less than 0.05 is considered statistically significant.

Discussion

Approximately 30–40% of IgAN patients are at risk of developing ESKD, especially those with low eGFR [2]. Therefore, early identification of risk factors and personalized treatments are crucial for delaying IgAN progression and improving patient outcomes [40]. In this study, we developed and evaluated the ML models in predicting the risk of the occurrence of ESKD or death in biopsy-proven IgAN patients with CKD stage 3 or 4 and proteinuria ≥1.0 g/d. Out of 66 clinical indicators, we identified seven major factors (age, BUN, serum uric acid, serum potassium, glomeruli sclerosis ratio, Hb, and T). The RSF model exhibited exceptional predictive ability, particularly in predicting 3-year survival outcomes. Furthermore, compared to the SSVM, XGboost, and Cox models, the RSF model demonstrated superior performance in both discrimination and calibration, which increased the availability of personalized predictions and enhanced the information accessible to patients and clinicians.

In terms of predictive accuracy, the RSF model emerged with the highest C-index and tAUC values. Additionally, the RSF model showed higher NRI and IDI values compared to the Cox model, suggesting superior discrimination ability. These results revealed that compared with the SSVM, XGboost, and Cox model, the RSF model demonstrated strong robustness in discriminating the development of IgAN patients with CKD stage 3 or 4, and provided better-calibrated probability estimates as time functions. The RSF algorithm, a variant of random forest, mitigates overfitting through two random sampling processes, unrestricted by assumptions such as proportional hazards and log-linear relationships [31, 41]. In contrast, the Cox model only identifies linear relationships [42]. The superior performance of RSF may be attributed to the potential nonlinear associations between variables and outcomes. Previous studies have built several prognostic models to predict the outcome of IgAN patients. The International IgA Nephropathy Prediction Tool has enrolled more than 4,000 patients and is currently the largest and most widely used prognostic tool. However, this tool cannot rank the importance of variables [13]. Bartosik et al. [43] and Goto et al. [10] both used different cohorts and clinical outcomes to obtain the scoring system but had limitations in fewer characteristics and inconsistent data accuracy. Pesce et al. [12] developed an artificial neural network algorithm for predicting IgAN outcomes but used a simplistic pathological scoring system that differs from the MEST-C scoring system used by Barbour et al. [44], which may affect the accuracy of the predictive results. A recent study [15] performed an XGboost system and simplified scoring scale (SMM) model to predict the development of ESKD, whereas these models are sensitive to outliers and noisy data, requiring data cleaning and feature selection, which may reduce the reliability of data. In addition, we chose to include patients with CKD stage 3 or 4 due to their increased risk of developing ESKD, and the importance of precise prediction in this population. Zhang et al. [45] conducted a Cox model of CKD stages 3–4 and the C-index was 0.760. The difference may be due to the feature selection procedure and different population.

Major independent risk factors identified for IgAN include decreased eGFR, baseline proteinuria >1.0 g/d, hypertension, more severe pathological scores, male, hyperuricemia, hyperlipidemia, and so on previously [13, 15, 17, 46]. In our study, we found that BUN is a stronger independent factor in the occurrence of ESKD, a finding that was confirmed by Liu et al. [47] and Han et al. [48]. BUN is commonly used as a short-term indicator of kidney function too. Elevated BUN levels are associated with conditions such as hypovolemia and acute kidney hypoperfusion, indicating that baseline kidney function plays a crucial role in determining the likelihood of developing ESKD [49]. Patients with more severe histopathology tend to have significantly higher BUN levels, highlighting the predictive value of BUN in assessing kidney function [48]. Consistent with previous studies, glomeruli sclerosis ratio also has a significant impact on kidney prognosis, which can predict long-term outcomes [50, 51]. Additionally, tubular atrophy/interstitial fibrosis as a pathological scoring criterion is of great significance as it serves as a crucial indicator of the likelihood of progressive kidney damage, signifying the unfavorable long-term prognosis in IgAN patients [15, 52, 53]. Our results were consistent with previous studies in verifying that younger age [10], higher uric acid [54], and decreased Hb level [11, 55] are risk factors for aggressive IgAN. Regarding the common CKD stage 3 or 4 models, Zhang et al. [56] found that factors such as age, eGFR, hemoglobin, serum uric acid, cardiovascular disease, and the primary disease are closely related to the prognosis of patients with CKD stages 3–5, which aligns with our research. Kidney failure risk equation (KFRE) is a common prognostic model for CKD and typically includes age, sex, eGFR, and albumin creatinine ratio. Bravo-Zuniga et al. [57] conducted an external validation of the KFRE model using 10,317 patients with CKD stages 3–4 and discovered that while the models demonstrated good discrimination, they exhibited poor calibration.

Serum potassium is the first independent risk factor identified for the development of IgAN with CKD stage 3 or 4. K^+, an electrolyte that is crucial for the maintenance of bodily functions, is highly susceptible to metabolic abnormalities, particularly in the presence of kidney dysfunction [58]. The incidence of hyperkalemia was found to be significantly higher in CKD patients. In addition, the likelihood of developing hyperkalemia defined as a serum potassium concentration of 5.5 mEq/L or higher, exhibits a positive correlation with declining kidney function in individuals with CKD stage 3 and beyond [59]. Thus, it is recommended to restrict the dietary potassium intake to 2,000 mg/d or less in stage 3b and 1,500 mg/d or less in stage 4 patients whereas individuals in stage 1 or 2 are advised to consume potassium at levels similar to those of healthy individuals (2,700–3,000 mg/d) [60, 61]. These studies emphasized the importance of monitoring and managing potassium levels in IgAN patients especially CKD stage 3 or 4.

We have specifically focused on patients diagnosed with IgAN and exhibited an eGFR ranging from 15 to 60 mL/min/1.73 m^2. Given the gradual decline in eGFR that characterizes the progression of the disease [13] and the relatively lower eGFR levels (only 15–60 mL/min/1.73 m^2) of the patients included in our study. In addition, we think it is of great significance to explore the additional factors, apart from the limited range of eGFR that may impact the prognosis of IgAN patients with CKD stages 3–4. Nonetheless, we also recognize the crucial role of eGFR in kidney disease. To investigate its potential influence, we incorporated eGFR into our model and the results showed that the C-index of models which added eGFR is similar to the original model (online suppl. Table S4), indicating the robustness of our model. Therefore, we think that refrained from incorporating eGFR levels in our model is reasonable. The urinary protein was not included in the final model as the patients selected in our study were those with urinary protein excretion levels of more than 1.0 g/d probably.

Our model has some advantages over previous studies that rely on clinical and pathological factors to provide prognostic measures, in terms of both background data and target outcomes. First, we introduced the RSF model, as the novel method for personalized risk evaluation, in the prognostic research in IgAN patients with CKD stage 3 or 4 for the first time. Second, we found serum potassium is an important independent risk factor, influencing the prognosis of IgAN patients, which has been previously overlooked. Then, our results demonstrated that the prognostic scoring model performs well; RSF models using a variety of predictors have reported a C-index of 0.81, even when based on randomly selected derived samples, the accuracy of the score in predicting the combined event risk in the remaining validation sample is equivalent to that from the entire dataset. Therefore, our estimates for all participants were deemed valid and when developing intensive treatment plans for patients, clinicians can refer to these predictors to provide better treatment plans.

There are also some limitations in terms of this study. At first, the relatively modest sample sizes and the lack of external validation is the main limitation. We will prospectively enroll a larger cohort of eligible patients and conduct a longitudinal study to further validate our model. In addition, as the patients included in the study were excluded from China and only a single-center study, further verification is required to determine the generalizability of

the results of this prediction model to other ethnic groups. Eventually, we only collect the basic data of treatment strategy and are unable to evaluate the effect of therapy during the follow-up period, although treatment is not a prognostic factor in our model, additional investigations targeting treatment may be warranted.

Conclusion

This study is the first to introduce the RSF model for prognosticating the risk of ESKD or death in IgAN patients with CKD 3 or 4 which demonstrated that seven variables (age, BUN, serum uric acid, serum potassium, glomeruli sclerosis ratio, Hb, and T) may accurately predict the disease progression. In comparison with the Cox model, the RSF model has shown superior survival prediction and remarkable prognostic stratification. These findings may enhance clinical decision-making in medical practice, while well-designed studies are warranted for further verification.

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Statement of Ethics

The studies involving human participants were reviewed and approved by the Ethics Committee of Xijing Hospital (ethical number: KY20213027-1). The need for informed consent was waived by the Ethics Committee of Xijing Hospital.

Conflict of Interest Statement

The authors report there are no competing interests to declare.

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Author Contributions

Conceptualization: Zixian Yu, Xiaoxuan Ning, Jin Zhao, and Shiren Sun; methodology: Zixian Yu and Xiaoxuan Ning; software: Zixian Yu, Yunlong Qin, and Yan Xing; validation: Yunlong Qin, Yan Xing, and Jinguo Yuan. supervision: Jinguo Yuan, Yumeng Zhang, and Qing Jia. visualization: Yumeng Zhang and Qing Jia; writing – original draft: Zixian Yu, Jin Zhao, Xiaoxuan Ning, and Shiren Sun; writing – review and editing: Zixian Yu, Xiaoxuan Ning, Jin Zhao, and Shiren Sun. Each of the authors contributed an important role in drafting the manuscript, accepting accountability, and ensuring the accuracy or completeness of the overall work is properly investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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