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A time-averaged serum bicarbonate-based nomogram to predict the probability of residual kidney function preservation for patients undergoing peritoneal dialysis

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Abstract. – OBJECTIVE: Residual kidney function (RKF) is an important prognostic indicator in peritoneal dialysis (PD) patients. So far, there are no prediction tools available for RKF, and the association between serum bicarbonate and RKF has received little attention in patients with PD. We aimed to develop a nomogram for the preservation of RKF based on the time-averaged serum bicarbonate (TA-Bic) levels.

PATIENTS AND METHODS: A prediction model was established by conducting a retrospective cohort study of 151 PD patients who had been treated at the First Affiliated Hospital of Anhui Medical University. The nomogram was developed using a multivariate Cox regression model. The discrimination, calibration, and clinical utility of the model were evaluated by the C-index, receiver operating curve (ROC) curve, calibration curve, and decision curve analysis.

RESULTS: In the elderly PD onset, higher baseline values of residual glomerular filtration rate, total Kt/V and higher TA-Bic levels were identified as protective predictors of RKF loss. The nomogram was conducted on the basis of the minimum value of the Akaike Information Criterion and Bayesian Information Criterion with a reasonable C-index of 0.766, showing great discrimination, proper calibration, and high potential for clinical practice. Through the total score of the nomogram, the patients were classified into the high-risk group and low-risk group, and a higher cumulative incidence of complete RRF loss was found in the high-risk group compared with the patients in the low-risk group.

CONCLUSIONS: The novel predictive nomogram model can predict the probability of RKF preservation in long-term PD patients with high accuracy. Future studies are needed to externally validate the current nomogram before clinical application.

Key Words:
Peritoneal dialysis, Serum bicarbonate, Residual kidney function, Risk factors, Nomogram.

Introduction

Decline of residual kidney function (RKF) is well known[1] to be an independent risk factor for poor outcomes in patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD). In dialysis patients, the preservation of RKF is associated with better fluid and calcium-phosphorus balance, improvement of anemia, and elimination of uremic toxins[1]. Maiorca et al[2] reported that an increased glomerular filtration rate of 1 ml/min was associated with the risk of death decreased by 40% in dialysis patients. Therefore, the International Society for Peritoneal Dialysis (ISPD) guideline[3] recommends that peritoneal dialysis (PD) management focus on protecting and monitoring RKF.

Several factors, including sex, age, peritonitis rate, hemoglobin, inflammatory, nutritional status, acid-base imbalance, blood pressure, transport type and renal function at PD initiation, and end-stage renal disease (ESRD) etiology were all reported[4,5] to be related to the loss of RKF, with acidosis, in particular, accelerating renal function progression even in the compensatory phase. Metabolic acidosis (MA), mainly characterized by low serum bicarbonate concentration, is often encountered in patients with an estimated glomerular filtration rate (eGFR) < 25 ml/min/1.73 m^2 and probably contributes to a number of deleterious clinical effects, including protein-energy wasting, aggravation of bone disease, inflamma-

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tion, endocrine dysfunction, and decreased nutritional status, etc[6]. These undesirable consequences may be the reason for the association between low serum bicarbonate and higher mortality in patients with hemodialysis (HD). It is generally accepted that acid-base status should be easily improved in continuous ambulatory peritoneal dialysis (CAPD) patients with 40 mmol/L lactate dialysate. However, one study found that MA existed in nearly half of the PD patients[7]. Notwithstanding, the harmfulness of acidosis in dialysis patients is often ignored. An observational cohort study of CKD patients conducted by Dobre et al[8] demonstrated that an increase in serum bicarbonate concentration of 1 mmol/L was associated with a 3% reduction in the risk of renal function or > 50% reduction in eGFR. However, to our knowledge, only a few studies were conducted on the relationship between serum bicarbonate levels and RKF in PD patients, and by far, there is a lack of recommended evaluation to predict the RKF loss or preservation in patients with peritoneal dialysis.

At present, nomograms are graphical mathematical models that have been extensively used to evaluate the probability of outcomes (predictive models) or occurrence (diagnostic models) of a particular disease. This study divided patients with PD into two groups based on whether or not loss of RKF occurred. Clinical demographic, laboratory, and dialysis-related data were compared to obtain the risk factors associated with RKF loss. Our study aimed to develop an effective and easy-to-use prediction model on the basis of serum bicarbonate levels and other clinical parameters for evaluating the probability of RKF preservation in long-term PD patients, which would assist clinicians in providing appropriate management and suggestions to improve the long-term prognosis of PD patients.

Patients and Methods

Study Population

The patients who had catheter insertion and used continuous ambulatory peritoneal dialysis as the first choice for renal replacement therapy in our peritoneal dialysis center from January 1, 2018, to January 1, 2021, were enrolled in this study. Eligible subjects must meet the following criteria: (1) Age > 18 and < 80 years at PD onset; (2) patients had been on PD for more than 3 months. The exclusion criteria were (1) patients who lacked baseline data before 3 months of dialysis; (2) follow-up interval > 3 months/time; (3) prior history of a kidney transplant or HD before the onset of PD; (4) baseline residual urine volume < 100 ml/24 h at the initiation of dialysis; (5) congestive heart failure, malignant tumor, blood disease, and severe infection; (6) the onset of PD for other reasons, such as acute kidney injury or acute renal failure. All patients were treated with standard lactate peritoneal dialysate produced by Huaren Company (Qing-Dao, China), containing 1.5% glucose and 2.5% glucose. This study was performed in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (Ethics approval number: PJ2022-04-36). All participants involved in this study provided written informed consent.

Data Collection

Baseline demographic and clinical data were collected at the onset of PD, including gender, age, body mass index (BMI), original disease, health history (e.g., cardiovascular disease, diabetes, and peritonitis), blood pressure, and medications, which were collected from electronic medical records in our hospital. The medication history consisted of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (ACEI or ARBs), alpha-blockers, beta-blockers, and calcium channel blockers.

Baseline laboratory and dialysis-related data at the beginning of PD included serum bicarbonate concentrations, white blood cell count, C-reactive protein (CRP), residual glomerular filtration rate (rGFR), hemoglobin, serum albumin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, serum uric acid, calcium, phosphorus, intact parathyroid hormone (iPTH), dialysate/plasma creatinine ratio (D/P Cr) at 4 h, 24-h urine volume, 24-h ultrafiltration volume, total CCr, total Kt/V, and peritoneal function. All baseline data were extracted within 3 months of PD onset. Time-averaged serum bicarbonate (TA-Bic) was calculated as an average of the mean of bicarbonate measurements every 3 months. All biochemical data were examined on automated chemical analyzers (Beckman AU5800, USA) using standard laboratory methods.

Data on RKF were also obtained within 3 months of the onset of PD and followed up at 3-month intervals thereafter. RKF expressed as

rGFR was estimated from the average creatinine and urea clearance and adjusted for body surface area[9].

Outcomes

The primary outcome of this retrospective observational cohort study was the full loss of RKF. The complete RKF loss of this study was defined as continuous secondary urine volume < 100 ml/24 h[4]. All patients were followed up until RKF loss, HD, kidney transplant, or end of the study period (January 1, 2022).

Statistical Analysis

Patients were divided into the RKF loss group and the RKF preservation group. The normally distributed quantitative data were expressed as the mean and standard deviations (SDs) and median *M* (1/4, 3/4) for skewed distribution. Count data were expressed as frequencies and percentages, and the Chi-square test or Fisher's exact probability method was applied to compare the differences between groups. Normally distributed variables were compared using the *t*-test among different groups, and the Mann-Whitney *U* test was used for comparison in asymmetrically distributed variables.

To determine risk factors for loss of RKF, Cox proportional hazard analysis was performed to assess the relationship between TA-Bic and loss of RKF initially without adjustment. We also performed the multivariate Cox regression analysis to adjust for the covariates, which showed a significant correlation ($p < 0.05$) with the outcome of interest, and 3 different models were adjusted for demographic variables (age, gender, and BMI; model 1), potential risk factors associated with RKF loss in CKD patients (age, gender, BMI, cardiovascular disease, peritonitis, hemoglobin, and albumin; model 2), and confounding factors associated with RKF loss (total CCr, total Kt/V together with age, gender, and BMI; model 3) to increase the reliability of results. The minimum values of the Akaike Information Criterion and Bayesian Information Criterion[10] were selected to build the final model, and a nomogram was constructed on this basis, on which the score of each predictor was calculated. To assess the covariance of the final multivariate model, the variance inflation factor (VIF) was also calculated for each variable. In addition, we used Somers' D correlation to evaluate the calibration of the model. The AUC of time-dependent receiver operating characteristic (ROC) analysis and concordance index (C-index) were also used for model accuracy assessment. Segmentation was subsequently conducted using the median value determined by the total score of the nomogram, and patients were categorized into 'low' or 'high' risk groups. The cumulative survival rates of the two groups were compared using the Kaplan-Meier method. Additionally, the calibration curves and decision curve analysis (DCA) were performed to examine the correctness and clinical net benefit of the prediction model. Finally, a bootstrap with 1,000 resampling and a sensitivity analysis were also carried out for internal validation to further verify the robustness of the prediction model. All data analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA), and R software version 4.1.3 (The R Foundation for Statistical Computing, Vienna, Austria). A value of $p < 0.05$ was considered to be statistically significant.

Results

Baseline Patient Characteristics

There were 181 incident PD patients catheterized at our PD center from January 1, 2018, to January 1, 2021, of whom 2 patients were younger than 18 years, 4 patients underwent dialysis for less than 3 months, 7 patients lacked baseline data, 4 patients were lost to follow-up, 8 patients underwent HD or kidney transplant before the initiation of PD, and 5 patients were anuric at PD onset. The remaining 151 patients were enrolled in this study. The mean age of 151 patients was 48.31 ± 13.26 years with a median follow-up of 17 months, of whom 51.7% were females, 23.8% had a history of cardiovascular disease, 25.2% had a history of peritonitis, and 17.9% were diabetic. The primary cause of patients entering ESKD was chronic glomerulonephritis (43.7%), followed by IgA nephropathy (11.2%) and diabetic nephropathy (10.5%). In addition, the median TA-Bic level was 24.40 mmol/L (range 22.80 to 25.90). Table I shows the demographic and clinical characteristics of the 151 patients.

As described in Table I, serum TA-Bic levels were significantly lower in patients without RKF than in patients with RKF. In contrast, age at PD onset, the baseline eGFR, and total CCr were also comparable between the two groups ($p < 0.05$), while differences in gender, BMI, comorbidities, medications, blood pressure, laboratory characteristics (white blood cell count, CRP, he-

Table I. Baseline characteristics of the study populations.

Variables	Total (n=151)	Without RKF (n=82)	With RKF (n=69)	*p*-value
Age (years)	48.31 ± 13.26	46.28 ± 13.39	50.72 ± 12.78	0.040
Female [n (%)]	78 (51.7)	44 (53.7)	34 (49.3)	0.591
Follow-up time (month)	17.27 ± 9.24	14.85± 9.10	20.14 ± 8.61	<0.001
BMI (kg/m^2)	22.17 ± 3.15	22.41 ± 3.49	21.89 ± 2.69	0.318
Diabetes [n (%)]	27 (17.9)	16 (19.5)	11 (15.9)	0.395
Left ventricular hypertrophy [n (%)]	56 (37.1)	34 (41.5)	22 (31.9)	0.225
Cardiovascular disease [n (%)]	36 (23.8)	16 (19.5)	20 (29.0)	0.174
Incidence of peritonitis [n (%)]	38 (25.2)	21 (25.6)	17 (24.6)	0.891
Systolic blood pressure (mmHg)	140.25 ± 16.00	141.84 ± 14.97	138.36 ± 17.07	0.184
Diastolic blood pressure (mmHg)	90.00 ± 11.72	91.55 ± 12.12	88.16 ± 11.04	0.077
ACEI/ARBs [n (%)]	29 (19.2)	13 (15.9)	16 (23.2)	0.254
Alpha blockers [n (%)]	16 (10.6)	9 (11.0)	7 (10.1)	0.869
Beta blockers [n (%)]	63 (41.7)	35 (42.7)	28 (40.6)	0.794
Calcium channel blockers [n (%)]	130 (86.1)	73 (89.0)	57 (82.6)	0.256
TA-Bic (mmol/L)	24.40 (22.80, 25.90)	23.35 (22.40, 25.10)	25.00 (23.60, 26.10)	<0.001
rGFR ml/min/1.73 m^2	3.75 (2.67, 5.31)	3.23 (1.80, 4.61)	4.20 (3.23, 5.78)	<0.001
White blood cell count (10^9/L)	5.97 (4.82, 7.23)	5.64 (4.72, 7.23)	6.24 (5.12, 7.18)	0.173
CRP (mg/L)	1.40 (0.77, 3.87)	1.60 (0.80, 5.10)	1.22 (0.70, 2.50)	0.113
Serum ferritin (ug/L)	177 (98, 320)	179 (111, 343)	174 (85, 285)	0.370
Hemoglobin (g/L)	106.67 ± 18.87	104.73 ± 19.05	108.97 ± 18.52	0.170
Albumin (g/L)	36.07 ± 5.12	35.62 ± 5.01	36.60 ± 5.23	0.243
Total cholesterol (mmol/L)	4.42 (3.88, 5.25)	4.52 (3.95, 5.37)	4.42 (3.81, 5.13)	0.501
Triglyceride (mmol/L)	1.30 (0.94, 1.95)	1.26 (0.92, 1.95)	1.34 (0.95, 1.94)	0.512
LDL-C (mmol/L)	2.73 (2.19, 3.37)	2.66 (2.25, 3.47)	2.73 (2.12, 3.28)	0.712
HDL-C (mmol/L)	1.15 (0.98, 1.44)	1.19 (1.00, 1.41)	1.07 (0.96, 1.46)	0.297
Uric acid (μmol/L)	441 (380, 490)	445 (385, 490)	430 (361, 489)	0.454
Calcium (mmol/L)	2.21 ± 0.15	2.19 ± 0.16	2.23 ± 0.15	0.107
Phosphorus (mmol/L)	1.63 (1.33, 1.94)	1.66 (1.35, 1.96)	1.59 (1.32, 1.92)	0.405
iPTH (pg/ml)	235 (128, 350)	233 (97, 338)	244 (129, 353)	0.647
D/P Cr at 4 h	0.61 ± 0.13	0.61 ± 0.13	0.60 ± 0.13	0.637
24-h residual urine volume (L)	0.80 (0.60, 1.10)	0.80 (0.50, 1.10)	0.90 (0.70, 1.10)	0.114
24-h ultrafiltration volume (L)	0.45 (0.05, 0.65)	0.40 (0.03, 0.72)	0.45 (0.10, 0.60)	0.737
Total Ccr (L/week)	71.42 (57.54, 85.46)	66.86 (52.93, 82.33)	76.41 (63.13, 94.40)	0.002
Total Kt/V	1.90 ± 0.60	1.84 ± 0.64	1.98 ± 0.54	0.179
Peritoneal function				0.254
High/High average transport [n (%)]	51 (33.8)	31 (37.8)	20 (29.0)	
Low/Low average transport [n (%)]	100 (66.2)	51 (62.2)	49 (71.0)	

Values are presented as means ± SD or interquartile range or percentages. BMI: body mass index; ACEI: angiotensin-converting enzyme inhibitor; ARBs: angiotensin-receptor blockers; TA-Bic: time-averaged serum bicarbonate; rGFR: residual glomerular filtration rate; CRP: c-reactive protein; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; iPTH: intact parathyroid hormone; D/P Cr: dialysate/plasma creatinine ratio; CCr: creatinine clearance rate; Kt/V: urea clearance index.

moglobin, serum albumin, serum ferritin, total cholesterol, HDL-C, LDL-C, triglycerides, uric acid, calcium, phosphorus, and iPTH), and dialysis characteristics (D/P Cr at 4 h, 24-h urine volume, 24-h ultrafiltration volume, total Kt/V, and peritoneal function) were not statistically different (all $p > 0.05$).

Univariate and Multivariate COX Regression Analysis

By the end of the follow-up, 82 patients had no RKF. The HRs for complete loss of RKF after initiation of dialysis are presented in Table II. The incidence of RKF loss in univariate analysis was associated with the age at PD onset (HR 0.980; 95% CI 0.964 to 0.996), TA-Bic levels (HR 0.777; 95% CI 0.690 to 0.874), baseline rGFR (HR 0.765; 95% CI 0.670 to 0.873), total CCr (HR 0.984; 95% CI 0.973 to 0.995), and total Kt/V (HR 0.581; 95% CI 0.381 to 0.885). The results of the multivariable analysis were significant and consistent, indicating that the loss of RKF in patients with continuous ambulatory peritoneal dialysis (CAPD) was only correlated with four parame-

Table II. Results of univariate and multivariate Cox regression analysis.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (years)	0.980 (0.964-0.996)	0.013	0.981 (0.963-0.999)	0.042
TA-Bic (mmol/L)	0.777 (0.690-0.874)	<0.001	0.760 (0.676-0.855)	<0.001
rGFR ml/min/1.73 m^2	0.765 (0.670-0.873)	<0.001	0.715 (0.598-0.854)	<0.001
Total Ccr (L/week)	0.984 (0.973-0.995)	0.004	—	—
Total Kt/V	0.581 (0.381-0.885)	0.011	0.627 (0.405-0.971)	0.036

HR: hazard ratio; CI: credible interval; TA-Bic: time-averaged serum bicarbonate; rGFR: residual glomerular filtration rate; CCr: creatinine clearance rate; Kt/V: urea clearance index.

ters: the age at PD onset, TA-Bic levels, baseline rGFR, and total Kt/V, in which the risk of RKF loss decreased by 24% for every 1 unit increase of TA-Bic (mmol/L).

Construction of the Nomogram

Along with the clinical parameters, we established a series of consecutive multivariate COX regression models (Table III). A nomogram predicting RKF preservation after initiation of PD for ESKD patients was constructed on the basis of the minimum value of the Akaike Information Criterion and Bayesian Information Criterion, and the predictors were scored according to their regression coefficients (Figure 1). As shown in the nomogram plot, patients with PD who had lower age and lower values of TA-Bic, rGFR, and total Kt/V were more inclined to develop the loss of RKF throughout the treatment period. The C-index for the prediction model, including only the TA-Bic levels, was 0.658, which was further improved by adding the age at PD onset, baseline levels of rGFR, and total Kt/V. Ultimately, the C-index of the final model was 0.766, demonstrating good discrimination. The variance expansion coefficients for each variable were less than 2, indicating that there was no collinearity in the final model. The Somers' D correlation was -0.532 ($p < 0.05$), showing a well-calibrated model between the predicted and observed probability of RKF preservation in PD patients.

Model Evaluation

The nomogram showed reliable performance in the prediction of RKF preservation, with a time-dependent AUC of 0.858 (95% CI 0.793 to

Table III. Multivariate COX regression model for predicting renal function loss in patients with peritoneal dialysis.

Variable HR (95% CI)	Final model	Model 1	Model 2	Model 3
Age (years)	0.981 (0.963, 0.999)	0.975 (0.958, 0.992)	0.975 (0.958, 0.993)	0.977 (0.959, 0.995)
Gender		1.023 (0.657, 1.591)	0.959 (0.596, 1.543)	1.041 (0.461, 2.347)
BMI		1.075 (1.001, 1.155)	1.063 (0.985, 1.147)	0.764 (0.678, 0.860)
Cardiovascular disease			0.881 (0.490, 1.585)	
Incidence of peritonitis			0.986 (0.571, 1.703)	
TA-Bic	0.760 (0.676, 0.855)			
rGFR	0.715 (0.598, 0.854)			
Hemoglobin			0.993 (0.979, 1.007)	
Albumin			0.984 (0.935, 1.036)	
Total Ccr				0.989 (0.973, 1.004)
Total Kt/V	0.627 (0.405, 0.971)			0.646 (0.326, 1.283)
C-index	0.766	0.623	0.642	0.731
C-index (Se)	0.027	0.036	0.036	0.031
AIC value	659.916	696.873	702.080	670.347
BIC value	671.985	705.925	723.201	685.434

BMI: body mass index; TA-Bic: time-averaged serum bicarbonate; rGFR: residual glomerular filtration rate; CCr: creatinine clearance rate; Kt/V: urea clearance index; Se: standard error; AIC: Akaike Information Criterion; BIC: Bayesian information criterion.

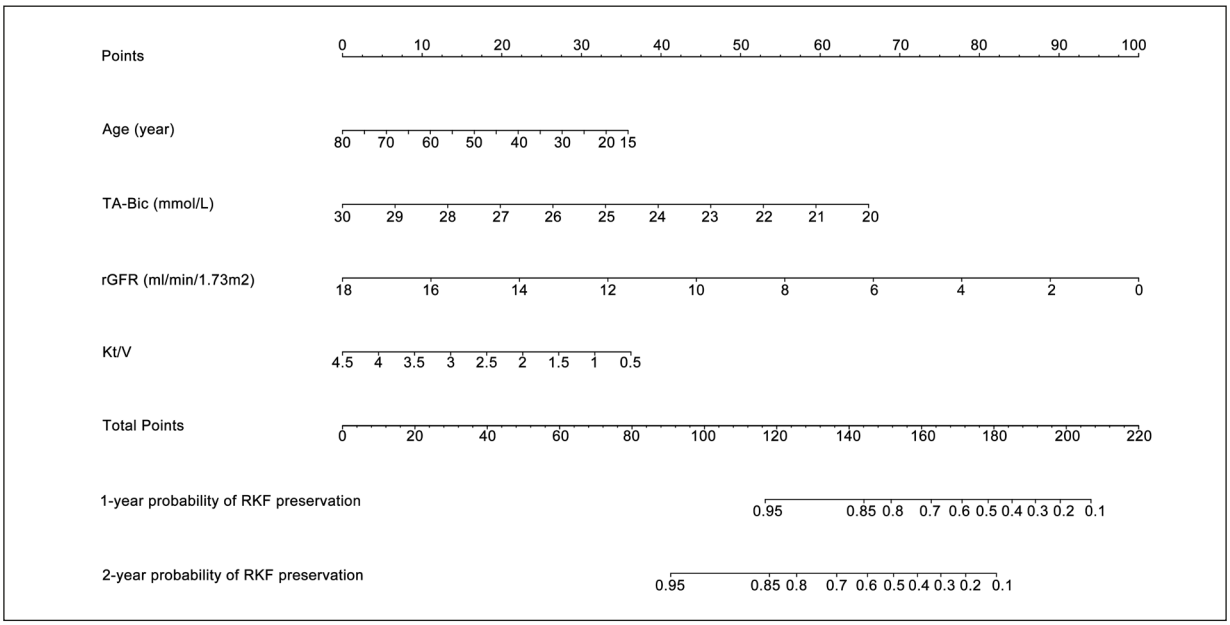

Figure 1. A nomogram for predicting the probability of residual kidney function (RKF) preservation in PD patients.

0.924) and 0.804 (95% CI 0.712 to 0.897) at 1 and 2 years, respectively (Figure 2). The score for each predictor is shown in Table IV. The median value determined by the total score of the nomogram is 156.46. When the score was greater than 156.46, it was classified as a high-risk group. The Kaplan-Meier curves suggested that the risk of RKF loss after the initiation of PD was significantly higher in the high-risk group compared with those in the low-risk group, and the difference was statistically significant among the two groups (Figure 3). The nomogram calibration plot revealed virtually ideal predictions (Figure 4). As shown in Figure 5, the DCA indicated that the nomogram had superior overall net benefits over a wide and practical range of threshold probabilities, suggesting high potential for clinical application.

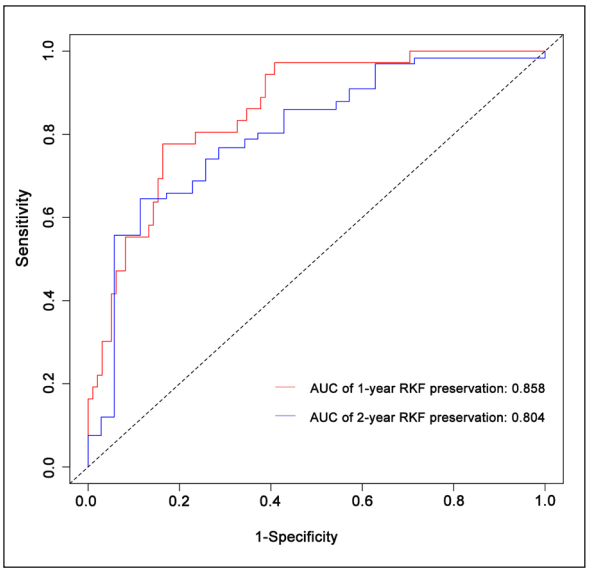

Figure 2. ROC curve for time-dependent residual kidney function (RKF) preservation in PD patients.

Table IV. Nomogram score for each indicator

Variable	Levels	Point
Age (years)	15	36
	20	33
	25	30
TA-Bic (mmol/L)	20	66
	21	59
	22	53
rGFR ml/min/1.73 m^2	0	100
	2	89
	4	78
Total Kt/V	0.5	36
	1.0	32
	1.5	27
	2.0	23

TA-Bic: time-averaged serum bicarbonate; rGFR: residual glomerular filtration rate; Kt/V: urea clearance index.

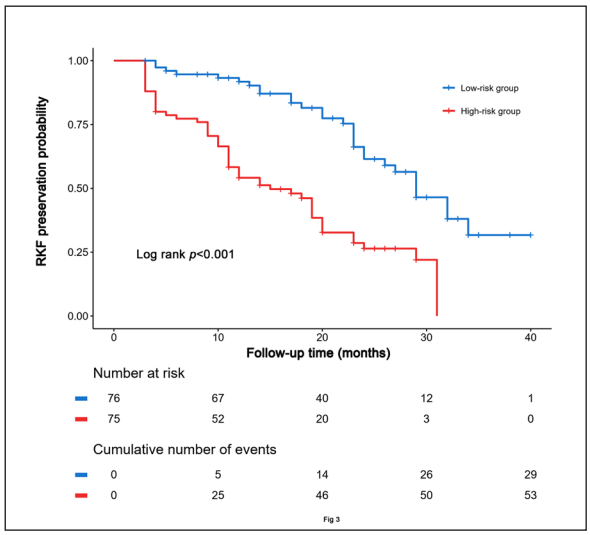

Figure 3. Kaplan-Meier survival curves on the basis of the nomogram.

Sensitivity Analysis and Internal Bootstrap Validation

To test the robustness of the predictive model further, sensitivity analysis and internal bootstrap validation were carried out in this study. There was no significant difference in the pooled effect after excluding patients with early-onset RKF loss (6 months after PD onset), suggesting that the results of sensitivity analysis were stable. Furthermore, the regression results of the bootstrap resampling showed similar conclusions, exhibiting good robustness and sensitivity (Table V).

Discussion

RKF refers to the filtration, reabsorption, and endocrine function of residual nephrons in renal tissues of ESKD patients and plays a key role in controlling total solute clearance, maintaining fluid balance, improving nutritional and anemia status, and decreasing mortality of PD[11]. GFR, the best measure of renal function, is associated with age, gender, and body size[12]. Mean values decrease by 0.75-1 ml/min/1.73 m^2 per year after the age of 40, with steeper declines in patients with PD[13]. Compared with HD, PD requires more RKF preservation. Therefore, it is crucial to identify the risk factors that accelerate the decline of RKF in PD patients.

Although a majority of PD patients lose residual kidney function within two years of dialysis initiation, no prediction model for RKF loss or retention in PD patients has been reported by far. In the present study, we sought to identify specific factors that influence the loss of RKF in patients with PD. Considering that the mechanism leading to the rapid decline of RKF is multifactorial, 36 variables, including demographic, comorbidities, medications, laboratory, and dialysis-related data, were plotted. The multivariate Cox regression analysis identified four potential determinants from the derivation cohort. These determinants included advanced age at PD initiation, higher baseline values of rGFR and Kt/V, and higher TA-Bic levels. These parameters have been found to be protective against the loss of RKF. The final

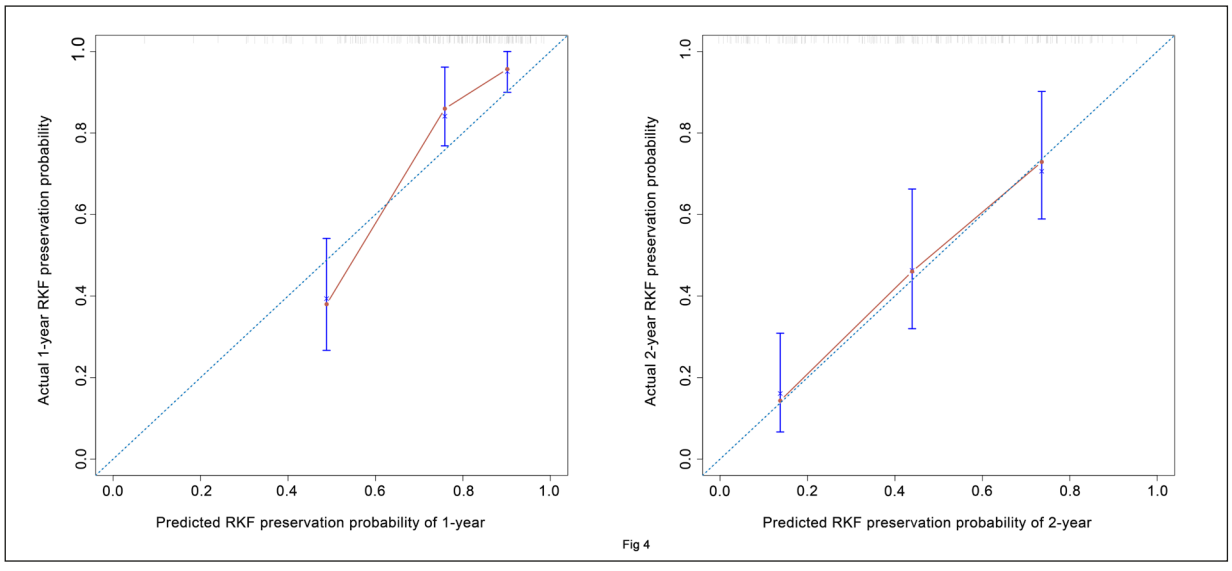

Figure 4. Time-dependent residual kidney function (RKF) preservation for plots depicts the calibration of the nomogram in terms of the agreement between predicted and observed.

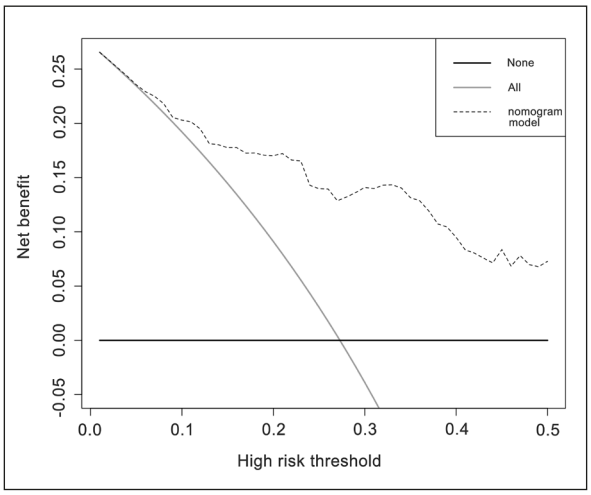

Figure 5. Decision curve analysis of the nomogram.

nomogram was well identified and calibrated in predicting the probability of RKF preservation at 1- and 2-year in patients with PD, showing good performance and high value for clinical application.

The effect of age on residual kidney function in PD patients has received less attention. A cohort study[14] including 174 HD patients reported that the rate of decline of RKF was slower in the elderly, which was unaffected by gender and ethnicity, but was age dependent. Consistent with this finding[14], increasing age seems to have a "protective" effect on the loss of RKF. The reasons for this effect are currently unknown. First of all, the differential tendency in RKF among younger and older individuals could be confounded by differences in severity or etiology of underlying disease. In other words, chronic kidney disease may be more severe in younger individuals. Secondly, the rate of decline of residual kidney function may depend less on nephron supply than on the need for GFR. In relation to a relative reduction of dietary protein intake, body cell mass, and other factors, older individuals may "require" less GFR and exhibit less hyperfiltration. The loss of RKF, in turn, may be attenuated with this mechanism.

Mounting evidence[15,16] has reported that a low serum bicarbonate level is strongly related to poor prognosis in multiple diseases, including septic shock, coronary heart disease, and leukemia. Furthermore, prospective studies[17,18] in CKD patients suggested that a clear relationship between low serum bicarbonate levels and poor prognosis may be associated with a more rapid loss in RKF related to metabolic acidosis. This finding was further supported by a systematic review and meta-analysis[19], including 14 studies using either oral alkali supplementation or dietary interventions, showing that correction of MA might offer an RKF-preserving effect in pre-dialysis patients. In addition to these adverse effects, serum bicarbonate levels are independently related to the increased risk of cardiovascular and all-cause death in patients undergoing renal replacement therapy. For example, a cross-sectional study of 384 patients with regular HD conducted by Silva et al[20] found that serum bicarbonate was more valuable in predicting mortality risk than conventional indicators. As for PD, Chang et al[21] observed 441 CAPD patients and evaluated the influencing risks of poor prognosis, believing that serum bicarbonate level had a 17% decreased risk of mortality in PD patients, and the rapid decline of RKF might be an intermediate link. Although the underlying mechanism by which low serum bicarbonate increases the mortality of dialysis patients is not clear yet, chronic inflammation and loss of RKF may be involved.

Several mechanisms are the underlying explanation for the decline of RKF in dialysis patients with lower bicarbonate levels. First of all, chronic acidosis stimulates the metabolism of glutamine in proximal renal tubular epithelial cells, thereby increasing the excretion of

Table V. Sensitivity analysis and bootstrap internal validation to test the robustness of the prediction model.

Variable HR (95% CI)	Nomogram model (n=151)	Late-onset RKF loss (n=139)	Bootstrap
Age (years)	0.981 (0.963, 0.999)	0.978 (0.958, 0.999)	0.978 (0.960, 0.996)
TA-Bic (mmol/L)	0.760 (0.676, 0.855)	0.774 (0.684, 0.876)	0.765 (0.667, 0.878)
rGFR ml/min/1.73 m^2	0.715 (0.598, 0.854)	0.703 (0.578, 0.856)	0.799 (0.660, 0.967)
Total Kt/V	0.627 (0.405, 0.971)	0.718 (0.447, 1.154)	0.691 (0.458, 1.043)
C-index	0.766	0.755	0.752

HR: hazard ratio; CI: credible interval; RKF: residual kidney function; TA-Bic: time-averaged serum bicarbonate; rGFR: residual glomerular filtration rate; Kt/V: urea clearance index.

ammonia[22]. Kidney injury is attributed to the increased ammoniagenesis and overproduction of several inflammatory mediators (e.g., aldosterone, endothelin, and angiotensin II) induced by acid load[22-24]. Secondly, dialysis patients with chronic acidosis had lower insulin secretion during sustained hyperglycemia and greater insulin resistance during sustained hyperinsulinemia compared with controls without metabolic acidosis or CKD[25]. These effects are thought[25] to result from decreased insulin-receptor substrate-1 (IRS-1) production and suppressed phosphoinositol-3 kinase (PI-3 kinase) activity. Recently, it has been suggested[26] that insulin resistance has a crucial effect on the activation of the renin-angiotensin-aldosterone system (RAAS), which is one of the primary causes of the development of hypertension, atherosclerosis, and heart failure. In this study, we found the proportion of patients with diabetes between the two groups is incomparable, and an expansion of the sample size is needed for further verification. Thirdly, decreased protein synthesis, increased protein catabolism, inflammation, increased insulin resistance, and reduced serum leptin levels are five underlying mechanisms by which metabolic acidosis may lead to nutritional abnormalities[27], and malnutrition is shown to be closely associated with the decline of RKF[11]. Serum albumin, as a reliable indicator of nutrition, is the most commonly used clinically. In this study, 60 subjects had a serum albumin level lower than 35g/L (40%), which is basically consistent with a previous report[28]. Nutritional status, therefore, is generally poor among PD patients. A prospective, interventional study[29] in Italy showed that the correction of MA improves nutrition and, consequently, morbidity and mortality in dialysis patients. Finally, increased synthesis of a key proinflammatory cytokine tumor – tumor necrosis factor-α (TNF-α) – by peritoneal macrophages exposed to the low environmental PH suggested a possible link between MA and inflammation[30]. This response was caused by the activation of nuclear factor-κB, which also contributed to further TNF-α production[30]. Emerging evidence[31,32] showed that chronic inflammation is an important contributor to the decline of RKF in patients under dialysis. However, we did not find a significant association between serum bicarbonate and inflammation in this study, which would require an expanded sample size for further exploration.

We also found that a higher baseline rGFR is independently associated with a lower risk of developing anuria, which could readily be explained by the phenomenon of time bias. On the one hand, it has been shown[33] that patients with higher baseline rGFR levels are related to a faster decline in rGFR after PD initiation. On the other hand, when anuria was used as the endpoint event, Johnson et al[34] found that higher baseline rGFR was independently associated with a lower risk of anuria. Kt/V is an international index for evaluating dialysis adequacy[35]. This study revealed that the total Kt/V in the RKF loss group was lower than that in the RKF preservation group, which indicates that dialysis adequacy affects the RKF of PD patients. Inadequate peritoneal dialysis would induce increased anemia, retention of toxins in the body, and volume overload, thereby accelerating the loss of RKF[35,36].

In this study, we constructed and validated a simple nomogram model based on variables available at the time of the first dialysis adequacy assessment to predict the preservation of RKF in PD patients. Current studies[1,2] have found that the longer the RKF is preserved, the better the prognosis for PD patients. This study, however, did not observe differences in the model to predict early-onset RKF loss and late-onset RKF loss because of the small sample size of early-onset RKF loss. Meanwhile, the internal bootstrap resampling validation also shows the model's robustness and sensitivity. Here, we cite an example to show how to use the nomogram model, assuming a 25-year-old PD patient with a TA-Bic of 22 mmol/L, a rGFR of 4 ml/min/1.73 m^2, and a total Kt/V of 2. According to Figure 1, the scores corresponding to different parameters on the "points" axis are obtained. The total score can be calculated by summing up the points for all parameters [30 (Age) + 53 (TA-Bic) + 78 (rGFR)+23 (total Kt/V)=184]. This score indicates that this patient has an approximately 42% and 7.4% probability of RKF preservation at 1 and 2 years, respectively. Therefore, the care strategies for PD patients include timely dialysis, maintenance of acid-base balance, and good dialysis adequacy to delay the loss of RKF.

Strengths and Limitations

The strength of this study is that a predictive model for RKF in PD patients was established for the first time. Additionally, the study had relatively single outcome events with no competing

risk events. Nevertheless, several limitations to this present study should be considered. First, optimal serum bicarbonate levels in PD patients have not been established in this study based on the limited sample size. Second, this is a single-center retrospective study using a small sample size and no external verification was performed, limiting our exploration and comparison to the overall PD population. To verify the precision of our approaches, we require additional prospective randomized clinical trials. Third, the indicators included in this study were limited, as nutritional status (subjective global assessment, dietary protein intake, and anthropometry), history of infection, and use of nephrotoxic agents were not included. Importantly, data from arterial gas analyses such as PCO_2 and arterial pH were not available in our study. Despite these limitations, our results made an important contribution to clinicians in determining the prognosis of PD patients by constructing a predictive model with high accuracy.

Conclusions

In conclusion, this study developed a novel nomogram based on age, TA-Bic, rGFR, and total Kt/V to accurately estimate the probability of RKF preservation in ESKD patients within two years of PD therapy. However, the current nomogram model requires further validation with external data before clinical application.

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Conflict of Interest
The authors have no conflicts of interest to declare.

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Informed Consent
All participants involved in this study provided written informed consent.

Ethics Approval
This study was performed in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (Ethics approval number: PJ2022-04-36).

Data Availability
The data for this study are available at reasonable request from the corresponding author.

Authors' Contributions
(I) Conception and design: D.-S. Li and Y.-G. Wu; (II) Provision of study materials or patients: J. Zhang and X.-M. Qi; (III) Collection and assembly of data: D.-S. Li, Z. He, and J. Zhang; (IV) Data analysis and interpretation: D.-S. Li; (V) Manuscript writing: D.-S. Li; (VI) Final approval of manuscript: All authors.

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