


Predictive Value of Kidney Failure Risk Equation and Neutrophil Gelatinase-Associated Lipocalin for Chronic Kidney Disease Progression in Chinese Population – A Retrospective Study

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Objective: To analyze the independent associations of the Kidney Failure Risk Equation (KFRE) and neutrophil gelatinase-associated lipocalin (NGAL) with end-stage renal disease (ESRD) among patients with chronic kidney disease (CKD) stages 3–5 in China and evaluate their predictive values for ESRD.

Patients and Methods: A total of 716 patients with CKD stages 3–5 at the time of the initial renal medicine referral were retrospectively enrolled, and the study outcome was the observed incidence of ESRD at 2 years after the initial referral. Baseline characteristics were collected, and relevant laboratory indexes, including neutrophil gelatinase-associated lipocalin (NGAL), were detected. The binary *logistic* regression model was used to analyze the independent associations, and the receiver operating characteristic (ROC) curve was used to assess the predictive values.

Results: The 2-year incidence of ESRD was 20.5% (147/716). The 4-variable KFRE, 8-variable KFRE and NGAL were independently associated with ESRD after adjusting for potential confounding factors. The AUCs of the 4-variable KFRE, 8-variable KFRE and NGAL for predicting ESRD among patients with CKD stages 3–5 were 0.711 [standard error (*SE*): 0.026, 95% confidence interval (*CI*): 0.662–0.761], 0.725 (*SE*: 0.025, 95% *CI*: 0.677–0.774) and 0.736 (*SE*: 0.024, 95% *CI*: 0.686–0.785), respectively. The AUC of the 4-variable KFRE plus NGAL was significantly higher than those of the 4-variable KFRE and NGAL alone (0.900 vs 0.711, $Z = 6.297$, $P < 0.001$; 0.900 vs 0.736, $Z = 5.795$, $P < 0.001$), and the AUC of the 8-variable KFRE plus NGAL was also significantly higher than those of the 8-variable KFRE and NGAL alone (0.911 vs 0.725, $Z = 6.491$, $P < 0.001$; 0.911 vs 0.736, $Z = 6.298$, $P < 0.001$).

Conclusion: The KFRE was able to independently predict progression of CKD stage 3–5 to ESRD in Chinese population. The addition of NGAL to the KFRE was able to elevate the predictive value when applied in predicting 2-year ESRD.

Keywords: chronic kidney disease, end-stage renal disease, kidney failure risk equation, neutrophil gelatinase-associated lipocalin

Introduction

Chronic kidney disease (CKD) has become a major public health problem worldwide with rapidly increasing prevalence and mortality.^{1,2} Worsening kidney function is independently associated with progression to end-stage renal disease (ESRD) and increased risk of cardiovascular events in CKD patients.^{3–5} In China, the number of patients undergoing hemodialysis treatment has demonstrated a rapid growth trend, rising to 379.1 per million people in 2017 from 174.1 per million people in 2011.⁶ Therefore, accurate prediction for ESRD is critical for prognosis of CKD patients, which enables targeted treatment in high-risk patients including appropriate prioritisation of treatment pathways and supporting better risk communication with patients.^{7–9}

The Kidney Failure Risk Equation (KFRE), developed in 2011, is an extensively validated model to predict the risk of progression to ESRD among patients with CKD stages 3–5.^{9,10} It utilizes laboratory data that can be obtained routinely in CKD patients to predict the risk of progression to ESRD among patients with CKD stages 3–5.^{8,10} The KFRE can be easily integrated into a clinic electronic medical record or laboratory information system prompts. The KFRE includes 4-variable and 8-variable equation. The 4-variable KFRE relies on sex, age, eGFR and urine albumin-to-creatinine ratio (ACR), whilst the 8-variable KFRE incorporates the additional laboratory data including serum albumin, phosphate, calcium and bicarbonate. To date, validation of the original KFRE equation has been carried out in many countries, demonstrating good-to-excellent performance in identifying patients at high-risk of ESRD.^{11–16} However, it has not been validated in China. Moreover, the area under the receiver operator characteristic curve (AUC) for prediction of ESRD is less than 0.800 in some study cohorts,¹⁷ and recalibration of the KFRE equation can increase the AUC significantly.¹⁸

Neutrophil gelatinase-associated lipocalin (NGAL), also named lipocalin, siderocalin or lipocalin-2 (LCN2), is one of the first molecules inducing development of the kidney. NGAL is associated with the formation of tubules and complete nephrons through transforming embryonic mesenchymal cells into epithelial cells.^{19,20} The main sources of NGAL include leucocytes, collecting ducts and loop of Henle in the body.^{21,22} NGAL is produced in response to tubulointerstitial damage, which frequently happens during the progression of kidney disease.²³ It has been shown that urinary and plasma NGAL can reflect the severity of renal disease and can be applied in predicting progression of CKD even with adjustment for estimated glomerular filtration rate (eGFR).²⁴

In this study, independent associations of the KFRE equation and NGAL with ESRD in CKD patients were first analyzed by binary *logistic* regression model, and their values of predicting ESRD individually or jointly were then evaluated by ROC curves. Therefore, we aimed to validate the KFRE in China and elevate the predictive value for ESRD in CKD patients through adding NGAL to the KFRE equation.

Patients and Methods

Patients

This retrospective cohort study was performed at Jiangjin Central Hospital between January 2020 and June 2022. Patients with CKD stages 3–5 at the time of the initial renal medicine referral were enrolled. The enrollment criteria included (1) patients with the age of ≥ 18 years and meeting the criteria of CKD stages 3–5; (2) patients having all measurements available for the 4-variable and 8-variable KFRE; and (3) patients were regularly followed up for at least 2 years in this department from as frequently as every half a month to a minimum of semiannually, which depended on the discretion of the nephrologist. The follow-up period was defined as the interval between the date of the initial referral and the date of last data collection or progressing to ESRD. The exclusion criteria were (1) patients had no records of baseline albuminuria or eGFR levels; and (2) kidney transplantation or renal replacement therapy had already been initiated at the initial referral. This study received the approval of the Ethical Committee of Jiangjin Central Hospital (JJ2019018036) and was conducted according to the guidelines of the *Declaration of Helsinki*. Informed consents were obtained from the study participants prior to the study commencement.

Definitions

CKD is defined as renal structure or function abnormality >3 months. In this study, individuals with one of the following indexes at least for 3 months were diagnosed as CKD: (1) eGFR < 60 mL/min/1.73 m²; (2) urine albumin excretion rate (ACR) ≥ 30 mg/24 h or albumin-creatinine ratio ≥ 30 mg/g; (3) urine sediment abnormality; (4) renal tubule-associated lesions; (5) renal histological abnormality; and (6) renal imaging abnormality.²⁵ Kidney Disease Improving Global Outcomes guidelines were used to perform CKD staging,²⁶ with stage 3 defined as an eGFR of 30–59 mL/min/1.73 m², stage 4 defined as an eGFR of 16–29 mL/min/1.73 m² and stage 5 defined as ≤ 15 mL/min/1.73 m².

Study Outcome

The study outcome was the observed incidence of ESRD at 2 years after the initial referral. The definition of ESRD was reception of a pre-emptive renal transplantation or initiation of peritoneal dialysis or haemodialysis.

Detection of NGAL

Blood samples were collected within 6 h after the initial referral, centrifuged at $1820 \times g$ and 4°C for 5 min, and the plasma was stored -80°C until detection. NGAL was detected by commercially available ELISA kit (Shanghai Kexing Biotechnology Company, China). Both the intra- and inter-assay variances were less than 15%.

Statistical Analysis

All data were statistically analyzed with SPSS version 20.0 (SPSS Inc., USA), and a P value of <0.05 was considered significant. For quantitative data, Kolmogorov–Smirnov test was first used to assess their normality, and then Student's t test was used to conduct intergroup comparisons of the normally distributed ones between ESRD group and non-ESRD group, while Mann–Whitney U -test was used to conduct intergroup comparisons of the non-normally distributed ones. For qualitative data, chi-square test was used to conduct intergroup comparisons between ESRD group and non-ESRD group. The binary *logistic* regression model was used to conduct multivariate analysis for the variables with $P < 0.10$ in univariate analysis, which could identify independent associations between the KFRE scores, NGAL levels and ESRD progression. The receiver operating characteristic (ROC) curve was used to assess the values of the KFRE scores, NGAL levels and their combination for the prediction of ESRD progression. Z test was used to conduct the comparison of the area under curve (AUC).

Results

General Information

A total of 716 patients meeting the inclusion criteria were included in this analysis, and the 2-year incidence of ESRD was 20.5% (147/716). The baseline characteristics of the whole cohort were shown in Table 1. The whole cohort included 429 (59.9%) males and 287 (40.1%) females with an average age of 67.3 ± 13.5 years. Among the cohort, the Han nationality accounted for 92.0% (659/716), while other nationalities accounted for 8.0% (57/716). The cohort had a median eGFR level of $32.1 \text{ mL/min/1.73 m}^2$ (interquartile range [IQR] 28.2–36.0).

Independent Associations of the 4-Variable and 8-Variable KFRE with ESRD

In order to analyze the independent association of the 4-variable KFRE with ESRD, univariate analysis was first performed between ESRD group and non-ESRD group. The variables incorporated into the 4-variable KFRE, including sex, age, eGFR and urine ACR, were not compared again in univariate analysis. The results (Table 2) demonstrated that 4-variable KFRE, BMI, smoking, diabetes mellitus, hypertension, atrial fibrillation, serum albumin, phosphate, bicarbonate, potassium and NGAL were significantly different between ESRD group and non-ESRD group, and the rest variables were not significantly different. But coronary artery disease had a P value of <0.10 . Multivariate analysis (Table 3) demonstrated that the 4-variable KFRE [odds ratio (OR): 1.139, 95% confidence interval (CI): 1.058–1.278], NGAL (OR: 1.209, 95% CI: 1.051–1.427), hypertension (OR: 1.485, 95% CI: 1.187–3.072), diabetes mellitus (OR: 1.514, 95% CI: 1.196–3.073), serum albumin (OR: 1.197, 95% CI: 1.078–1.428), phosphate (OR: 1.159, 95% CI: 1.070–1.412) and bicarbonate (OR: 0.673, 95% CI: 0.502–0.845) were independently associated with ESRD after adjusting for BMI, smoking, atrial fibrillation, coronary artery disease and serum potassium.

For the analysis of independent association of 8-variable KFRE with ESRD, the variables incorporated into the KFRE, including sex, age, eGFR, urine ACR, serum albumin, phosphate, calcium and bicarbonate, were not compared again in univariate analysis. As shown in Table 2, 8-variable KFRE, BMI, smoking, diabetes mellitus, hypertension, atrial fibrillation, serum potassium and NGAL were significantly different between ESRD group and non-ESRD group, and coronary artery disease had a P value of <0.10 . Multivariate analysis (Table 4) demonstrated that the 8-variable

Table 1 Baseline Characteristics of the Whole Cohort (N = 716)

Characteristics	No.(%)/mean±SD/M(IQR)
Age(years)	67.3±13.5
Male	429(59.9%)
BMI(Kg/m ²)	25.9±3.12
Smoking	95(13.3%)
Han nationality	659(92.0%)
Diabetes mellitus	432(60.3%)
Hypertension	608(84.9%)
Atrial fibrillation	42(5.9%)
Coronary artery disease	168(23.5%)
Hyperlipidemia	274(38.3%)
eGFR(mL/min/1.73 m ²)	32.1(28.2–36.0)
Urine ACR(mg/g)	242(64–865)
Serum albumin(g/dL)	3.47±0.93
Serum calcium(mg/dL)	9.28±2.17
Serum phosphate(mg/dL)	3.72±0.98
Serum bicarbonate(mEq/L)	22.93±4.25
Serum potassium(mEq/L)	4.82±1.37
NGAL(ng/mL)	5.16±1.82
4-variable KFRE(%)	34.57±10.65
8-variable KFRE(%)	30.79±9.74

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ACR, albumin excretion rate; KFRE, Kidney Failure Risk Equation; NGAL, Neutrophil gelatinase-associated lipocalin, IQR, interquartile range; M, median; SD, standard deviation.

Table 2 Univariate Analysis Results Between ESRD Group and Non-ESRD Group

Variables	ESRD group (n1=147)	Non-ESRD group (n2=569)	χ^2 /Z/t	P
BMI(Kg/m ² , mean±SD)	26.3±2.89	25.8±3.18	2.197	0.031
Smoking(n, %)	29(19.7%)	66(11.6%)	6.707	0.010
Han nationality(n, %)	137(93.2%)	522(91.7%)	0.339	0.561
Diabetes mellitus(n, %)	102(69.4%)	330(58.0%)	6.334	0.012
Hypertension(n, %)	133(90.5%)	475(83.5%)	4.464	0.035
Atrial fibrillation(n, %)	14(9.5%)	28(4.9%)	4.482	0.034
Coronary artery disease(n, %)	43(29.3%)	125(22.0%)	3.451	0.063
Hyperlipidemia(n, %)	63(42.9%)	211(37.1%)	1.649	0.199
Serum albumin(g/dL, mean±SD)	3.26±0.85	3.52±0.95	3.225	0.001
Serum calcium(mg/dL, mean±SD)	9.04±2.35	9.34±2.12	-1.407	0.166
Serum phosphate(mg/dL, mean±SD)	3.95±1.06	3.66±0.96	3.013	0.003
Serum bicarbonate(mEq/L, mean±SD)	21.84±3.92	23.21±4.34	-3.693	<0.001
Serum potassium(mEq/L, mean±SD)	4.53±1.56	4.89±1.32	-2.570	0.011
NGAL(ng/mL, mean±SD)	6.03±2.04	4.94±1.76	5.933	<0.001
4-variable KFRE(%, mean±SD)	37.18±9.92	33.90±10.84	3.505	<0.001
8-variable KFRE(%, mean±SD)	34.26±9.12	29.89±9.90	5.087	<0.001

Abbreviations: BMI, body mass index; KFRE, Kidney Failure Risk Equation; ESRD, end-stage renal disease; NGAL, Neutrophil gelatinase-associated lipocalin; SD, standard deviation.

KFRE (*OR*: 1.143, 95% *CI*: 1.060–1.287), NGAL (*OR*: 1.211, 95% *CI*: 1.055–1.434), hypertension (*OR*: 1.490, 95% *CI*: 1.191–3.085) and diabetes mellitus (*OR*: 1.503, 95% *CI*: 1.187–3.028) were independently associated with ESRD after adjusting for BMI, smoking, atrial fibrillation, coronary artery disease and serum potassium.

Table 3 Multivariate Analysis Results for Determining Independent Association of 4-Variable KFRE with ESRD

Variables	β	SE	Wald χ^2	OR	95% CI	P
NGAL	0.948	0.265	5.713	1.209	1.051–1.427	<0.001
Serum bicarbonate	−0.712	0.204	4.896	0.673	0.502–0.845	<0.001
4-variable KFRE	0.532	0.190	3.247	1.139	1.058–1.278	0.006
Serum albumin	0.453	0.171	3.008	1.197	1.078–1.428	0.010
Serum phosphate	0.349	0.106	2.747	1.159	1.070–1.412	0.021
Diabetes mellitus	0.317	0.088	2.195	1.514	1.196–3.073	0.039
Hypertension	0.286	0.062	2.083	1.485	1.187–3.072	0.042
Smoking	0.467	0.149	1.638	1.356	1.184–2.805	0.138
Serum potassium	−0.445	0.138	1.543	0.729	0.594–1.226	0.160
BMI	0.308	0.130	1.356	1.108	0.720–1.223	0.254
Atrial fibrillation	0.296	0.127	1.328	1.257	0.713–1.514	0.273
Coronary artery disease	0.251	0.094	1.194	1.235	0.682–1.497	0.389

Abbreviations: KFRE, Kidney Failure Risk Equation; ESRD, end-stage renal disease; NGAL, Neutrophil gelatinase-associated lipocalin; BMI, body mass index; β , regression coefficient; SE, Standard error; OR, odds ratio; CI, Confidence interval.

Table 4 Multivariate Analysis Results for Determining Independent Association of 8-Variable KFRE with ESRD

Variables	β	SE	Wald χ^2	OR	95% CI	P
NGAL	0.983	0.257	5.894	1.211	1.055–1.434	<0.001
8-variable KFRE	0.547	0.192	3.405	1.143	1.060–1.287	0.004
Diabetes mellitus	0.338	0.091	2.346	1.503	1.187–3.028	0.035
Hypertension	0.302	0.074	2.199	1.490	1.191–3.085	0.040
Smoking	0.449	0.145	1.542	1.348	1.177–2.795	0.163
Serum potassium	−0.439	0.135	1.498	0.732	0.598–1.231	0.197
BMI	0.316	0.129	1.373	1.110	0.719–1.226	0.282
Atrial fibrillation	0.305	0.131	1.367	1.255	0.708–1.512	0.288
Coronary artery disease	0.274	0.089	1.206	1.241	0.693–1.503	0.381

Abbreviations: KFRE, Kidney Failure Risk Equation; ESRD, end-stage renal disease; NGAL, Neutrophil gelatinase-associated lipocalin; BMI, body mass index; β , regression coefficient; SE, Standard error; OR, odds ratio; CI, Confidence interval.

Individual Predictive Values

ROC curves were used to evaluate the values of the 4-variable KFRE, 8-variable KFRE and NGAL in individually predicting ESRD. As shown in Figure 1, the AUCs of the 4-variable KFRE, 8-variable KFRE and NGAL were 0.711 [standard error (SE): 0.026, 95% confidence interval (CI): 0.662–0.761], 0.725 (SE: 0.025, 95% CI: 0.677–0.774) and 0.736 (SE: 0.024, 95% CI: 0.686–0.785), respectively. Their predictive values were all moderate. Z test demonstrated that the AUC had no significant difference between the 4-variable KERE and 8-variable KFRE (0.711 vs 0.725, $Z = -0.388$, $P = 0.697$).

Joint Predictive Values

In order to further elevate the predictive value for ESRD, the KFRE and NGAL were combined to predict ESRD. ROC curves (Figure 1) showed that the AUCs of the 4-variable KFRE plus NGAL and the 8-variable KFRE plus NGAL were 0.900 (SE: 0.015, 95% CI: 0.870–0.930) and 0.911 (SE: 0.014, 95% CI: 0.881–0.942), respectively. The AUC had no significant difference between the 4-variable KERE plus NGAL and 8-variable KFRE plus NGAL ($Z = -0.536$, $P =$

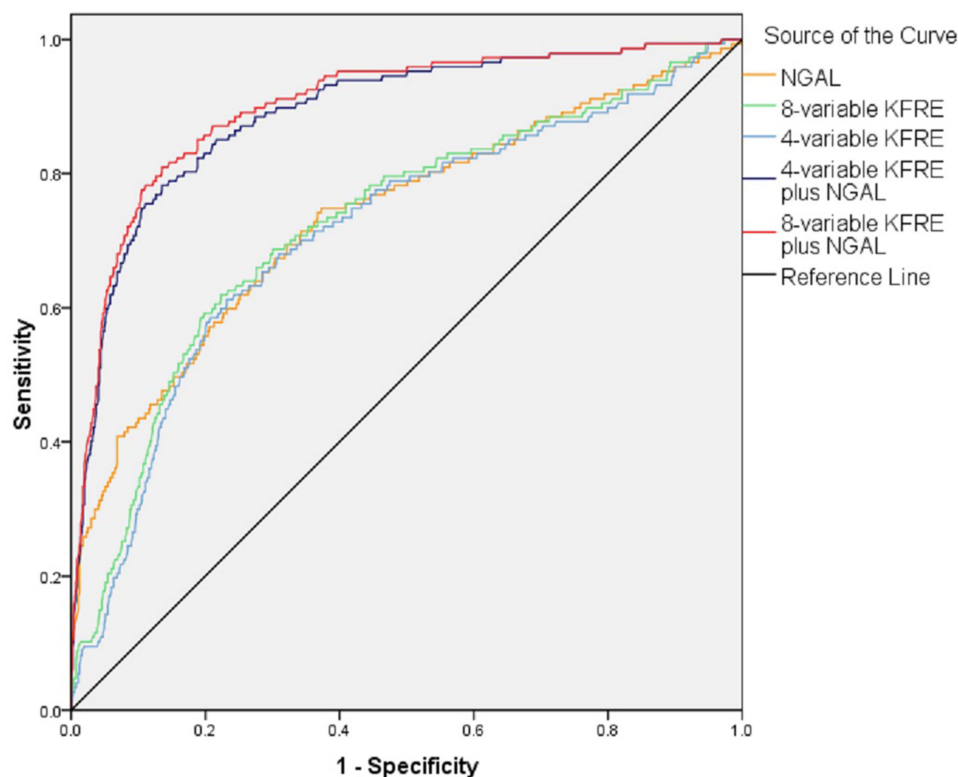


Figure 1 ROC curves of 4-variable KFRE, 8-variable KFRE, NGAL, 4-variable KFRE plus NGAL and 8-variable KFRE plus NGAL in predicting ESRD.
Abbreviations: ROC: receiver operating characteristic, KFRE: Kidney Failure Risk Equation, NGAL: Neutrophil gelatinase-associated lipocalin, ESRD: end-stage renal disease.

0.594). However, the AUC of the 4-variable KFRE plus NGAL was significantly higher than those of the 4-variable KFRE and NGAL alone (0.900 vs 0.711, $Z = 6.297$, $P < 0.001$; 0.900 vs 0.736, $Z = 5.795$, $P < 0.001$), and the AUC of the 8-variable KERE plus NGAL was also significantly higher than those of the 8-variable KERE and NGAL alone (0.911 vs 0.725, $Z = 6.491$, $P < 0.001$; 0.911 vs 0.736, $Z = 6.298$, $P < 0.001$). The clinical utility indexes of the 4-variable KERE plus NGAL and 8-variable KFRE plus NGAL were demonstrated in [Table 5](#).

Discussion

To date, the KFRE has been validated in many countries. Kwek et al validated the KFRE in a multi-ethnic Singapore chronic kidney disease cohort with stages 3–5.²⁷ The C-index of the 4-variable and 8-variable KFRE was 0.874 and 0.872, respectively, demonstrating excellent discrimination and predictive performance. Whitlock et al validated the KFRE among stage 3–5 CKD patients from the Diagnostic Services of Manitoba database in Canada.¹⁵ The AUC of the 4-variable KFRE for prognostic discrimination was 0.90 and significantly higher than that of eGFR alone (0.78). The KFRE threshold of 3% over 5 years yielded a specificity of 62% and a sensitivity of 97%, while 5% yielded a specificity

Table 5 Clinical Utility Indexes of the 4-Variable KERE Plus NGAL and 8-Variable KFRE Plus NGAL in Predicting 2-Year ESRD Among Patients with CKD Stages 3–5

	Sensitivity	Specificity	Accuracy	FPR	FNR	PPV	NPV
4-variable KERE plus NGAL	93.9%	88.9%	89.9%	31.3%	1.7%	68.7%	98.3%
8-variable KFRE plus NGAL	95.9%	88.6%	90.1%	31.6%	1.2%	68.4%	98.8%

Abbreviations: KFRE, Kidney Failure Risk Equation; ESRD, end-stage renal disease; NGAL, Neutrophil gelatinase-associated lipocalin; CKD, chronic kidney disease; FPR, false positive rate; FNR, false negative rate; PPV, positive predictive value; NPV, negative predictive value.

of 80% and a sensitivity of 86%. Ibrahim et al validated the KFRE in patients in the Salford Kidney Study, which enrolled patients with non-dialysis CKD.¹⁷ The AUCs of the 4-variable KFRE for the prediction of ESRD at 5-years and 2-years were 0.773 and 0.796, respectively, demonstrating good discrimination. Moreover, there was good-to-excellent discrimination across disease aetiologies with the AUCs of ranging 0.713–0.850, including glomerulonephritis, hypertensive nephropathy, autosomal dominant polycystic kidney disease, diabetic nephropathy and other diseases. Wang et al validated the KFRE in CKD patients visiting primary care clinics in Singapore, recalibrated the KFRE for further elevation of predictive value, and determined optimally feasible KFRE thresholds for dialysis planning and nephrologist referral.¹⁸ The recalibrated KFRE demonstrated better predictive performance and discrimination than existing KFRE equations, the AUCs of the recalibrated KFRE were 0.96 at 2 years and 0.94 at 5 years, and the optimally feasible KFRE thresholds were >45% for 2-year dialysis planning and >10–16% for 5-year nephrologist referral.

Additionally, Ali et al validated the performance of the 4-variable and 8-variable KFRE in predicting the 5-year death-censored risk of graft failure among patients in the United Kingdom.²⁸ The AUCs of the 4-variable and 8-variable KFRE were 0.743 and 0.751, respectively, demonstrating good discrimination. Salman et al evaluated the association of 2-year KFRE score categories with CKD care metrics, which demonstrated low-risk patients with a 2-year KFRE score of <3% had reduced odds of influenza vaccination, while high-risk patients with a 2-year KFRE score of $\geq 40\%$ had elevated odds of completing advance directives.²⁹ Hundemer et al assessed the influence of age on the predictive performance of the KFRE for kidney failure in patients with advanced CKD, which demonstrated that the KFRE overestimated the risk of kidney failure in elderly ones.³⁰

In this study, the AUCs of the 4-variable and 8-variable KFRE in predicting 2-year ESRD among patients with CKD stages 3–5 were 0.711 and 0.725, respectively, showing moderate predictive performance. The predictive ability of the 8-variable KFRE was not significantly improved compared with that of the 4-variable KFRE. In order to further elevate the predictive value for ESRD in CKD patients, NGAL was added to the KFRE. NGAL level may be helpful in identifying high-risk patients with faster decline in kidney function. NGAL can activate the mitogenic function of epidermal growth factor receptor signaling, which leads to CKD progression and renal damage through stimulating hypoxia-inducible factor.³¹ The NGAL level in urine has been demonstrated to be an advisable predictive indicator for renal injury preceding detectable changes of eGFR.^{23,32} A study showed that the plasma NGAL level was inversely associated with eGFR in children with CKD stages 2–4.³² In addition, the NGAL levels in both plasma and urine have been demonstrated to have a good predictive performance for CKD progression. De Silva et al demonstrated that the increase of NGAL levels was correlated with detectable damage happening in distal convoluted tubule and loop of Henle.²²

Our study showed that NGAL was independently associated with 2-year ESRD among patients with CKD stages 3–5, and had a moderate predictive performance with an AUC of 0.736. Excellent predictive performances were achieved after adding NGAL to the 4-variable and 8-variable KFRE with the AUCs of 0.900 and 0.911, respectively. Therefore, the KFRE could be applied in predicting 2-year ESRD among patients with CKD stages 3–5, and the addition of NGAL to the KFRE could elevate the predictive value for 2-year ESRD.

This study had two main limitations. The first was a small sample size of ESRD group, and the other was its retrospective characteristic.

Conclusion

The KFRE was independently associated ESRD among patients with CKD stages 3–5 in China and was able to be applied in predicting 2-year ESRD, and the addition of NGAL to the KFRE was able to elevate the predictive value for 2-year ESRD. The combination of the KFRE and NGAL provided a new tool for predicting 2-year ESRD and had clinical application potential.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All the authors do not have any conflict of interest.

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