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CLINICAL PREDICTION MODELS FOR PROGRESSION OF CHRONIC KIDNEY DISEASE TO END STAGE KIDNEY FAILURE UNDER PREDIALYSIS NEPHROLOGY CARE: RESULTS FROM THE CHRONIC KIDNEY DISEASE JAPAN COHORT STUDY

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INTRODUCTION AND AIMS

- Reliable tools identifying which patients with chronic kidney disease (CKD) will develop end stage kidney failure (ESKF) at greater risk are needed for clinical decision making.
- The objective of this investigation was to develop and validate precise and simple clinical prediction models for progression of CKD to ESKF under predialysis nephrology care setting.

METHODS

- We retrospectively analyzed readily available demographic, clinical, and laboratory data from the Chronic Kidney Disease Japan Cohort (CKD-JAC) Study conducted at 17 medical institutions in Japan.
- Main outcome measure was time from baseline at study enrollment through onset of ESKF defined as need for dialysis or preemptive kidney transplantation.
- A total of 2,034 patients aged 20 to 75 years with CKD G3a to G5 (eGFR 10 to 59 ml/min) were randomly assigned to either the development or the validation cohort evenly.
- In the derivation cohort, Cox proportional hazard regression was employed to develop clinical prediction models and Akaike Information Criterion (AIC) was calculated for goodness of fit.
- In the validation cohort, these clinical prediction models were evaluated using C statistics for discrimination, Nam and D'Agostino statistics for calibration.

RESULTS

Table 1. Baseline Characteristics of Development and Validation Cohorts

Characteristics	Overall (n = 2,034)	Development Cohort (n = 1,017)	Validation Cohort (n = 1,017)	P Value
Age, mean (SD), years	60.9 (11.3)	60.6 (11.6)	61.1 (11.1)	0.26
Male, n (%)	1,300 (63.9)	642 (63.1)	658 (64.7)	0.49
SBP, mean (SD), mmHg	132 (19)	132 (18)	131 (19)	0.17
Diabetes mellitus, n (%)	785 (38.6)	394 (38.7)	391 (38.5)	0.93
eGFR, mean (SD), mL/min/1.73m^2	28.2 (12.3)	28.8 (12.5)	27.5 (12.1)	0.013
UACR, mean (SD), mg/g	1.01 (1.34)	0.97 (1.34)	1.04 (1.33)	0.22
log UACR, mean (SD), mg/g	-0.43 (0.74)	-0.45 (0.74)	-0.41 (0.75)	0.26
Serum creatinine, mean (SD), mg/dL	2.22 (1.1)	2.17 (1.08)	2.26 (1.12)	0.047
Serum albumin, mean (SD), g/dL	4.0(0.4)	4.0 (0.4)	4.0 (0.4)	0.46
Hemoglobin, mean (SD), g/dL	12.1 (1.8)	12.2 (1.9)	12.0 (1.8)	0.043
Serum calcium, mean (SD), mg/dL	9.00 (0.53)	9.01 (0.52)	8.98 (0.54)	0.19
iPTH, mean (SD), pg/mL	108 (90)	104 (81)	113 (98)	0.02
log iPTH, mean (SD), pg/mL	1.93 (0.29)	1.92 (0.29)	1.95 (0.3)	0.02
FGF23, mean (SD), pg/mL	159 (900)	171 (1229)	146 (337)	0.52
log FGF23, mean (SD), pg/mL	1.85 (0.39)	1.84 (0.39)	1.86 (0.40)	0.25
Outcomes				
ESKF onset, n (%)	422 (20.7)	206 (20.3)	216 (21.2)	0.57

Abbreviation: SD, standard deviation; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; UACR, urine-albumin to creatinine ratio; iPTH, intact parathyroid hormone; FGF23, fibroblast growth factor 23; ESKF, endstage kidney failure.

Tabele 3. Discrimination and Calibration for Models in the Validation Cohort

Variables	Model 1	Model 2	Model 3	Model 4
C statistics	0.837	0.875	0.875	0.875
Nam and D'Agostino statistics	16.0	4.20	3.27	4.38

Model 1: Age, gender, and eGFR adjusted.

Model 2: Model 1 plus log UACR, diabtes mellitus, SBP, serum aibumin, hemoglobin, and log iPTH adjusted

Model 3: Model 2 plus log FGF23 adjusted

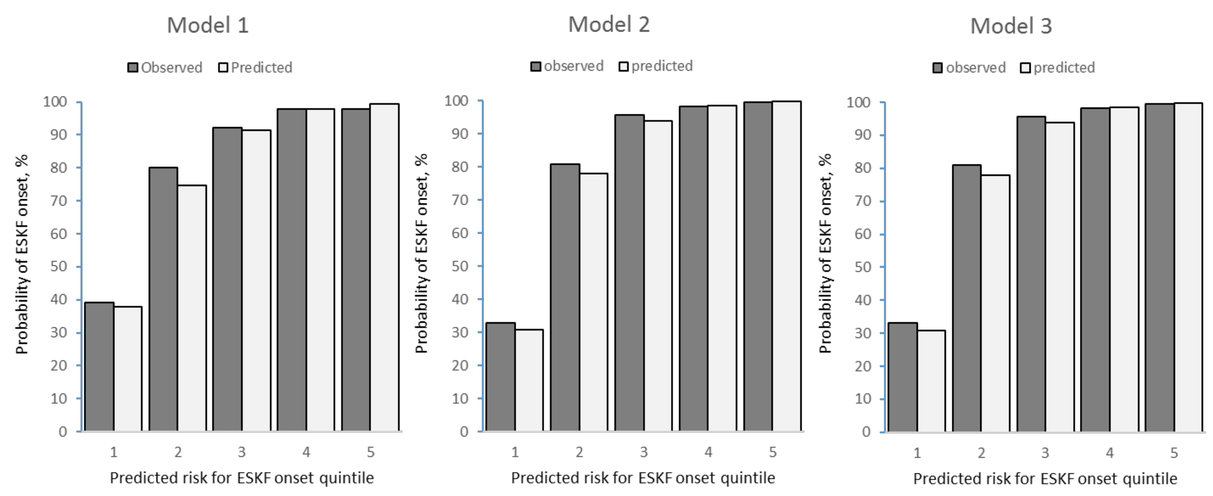
Model 4 (constructed by stepwise forward selection method using p value less equal ≤ 0.1 from possible covariates including age, gender, eGFR, log UACR, diabetes mellitus, hypertension, CVD, BMI, SBP, serum creatinine, serum albumin, hemoglobin, serum natrium, serum phosphorus, log iPTH, and logFGF23): Age, gender, eGFR, log UACR, SBP, serum creatinine, serum albumin, hemoglobin, serum calcium, and log FGF 23 adjusted.
Abbreviation: eGFR, estimated glomerular filtration rate; UACR, urine-albumin to creatinine ratio; SBP, systolic blood pressure; iPTH, intact parathyroid hormone; FGF23, fibroblast growth factor 23; CVD, cerebrovascular disease; BMI, body mass index.

Table 2. Hazard Ratios and Goodness of Fit for Models in the Development Cohort

Variables	Model 1	Model 2	Model 3	Model 4
Age, HR (95% CI), per 10 years	0.82 (0.72-0.93)	0.78 (0.68-0.89)	0.78 (0.69-0.89)	0.83 (0.73-0.95)
Gender, HR (95% CI), male vs. female	2.52 (1.84-3.44)	2.42 (1.76-3.33)	2.38 (1.73-3.28)	1.53 (1.02-2.28)
SBP, HR (95% CI), per 10 mmHg		1.12 (1.04-1.21)	1.13 (1.05-1.21)	1.14 (1.06-1.23)
Diabetes mellitus, HR (95% CI), yes vs. no		1.40 (1.05-1.86)	1.41 (1.06-1.87)	
eGFR, HR (95% CI), per 1 mL/min/1.73m^2	0.92 (0.91-0.93)	0.93 (0.92-0.95)	0.94 (0.92-0.95)	0.97 (0.95-0.99)
log UACR, HR (95% CI), per 1 mg/g		2.77 (1.95-3.93)	2.83 (1.98-4.03)	2.78 (1.94-3.99)
Serum creatinine, HR (95% CI), per 1 mg/dL				1.65 (1.22-2.22)
Serum albumin, HR (95% CI), per 1g/dL		0.64 (0.46-0.91)	0.64 (0.45-0.89)	0.70 (0.48-1.01)
Hemoglobin, HR (95% CI), per 1g/dL		0.79 (0.71-0.88)	0.81 (0.73-0.90)	0.81 (0.73-0.90)
Serum calcium, HR (95% CI), per 1 mg/dL				0.71 (0.53-0.96)
log iPTH, HR (95% CI), per 1pg/mL		1.66 (1.90-3.06)	1.74 (0.96-3.18)	
log FGF23, HR (95% CI), per 1pg/mL			1.53 (1.11-2.13)	1.51 (1.07-2.12)
AIC	2350.1	2215.6	2211.6	2203.9

Abbreviation: HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; UACR, urine-albumin to creatinine ratio; iPTH, intact parathyroid hormone; FGF23, fibroblast growth factor 23; ESKF, endstage kidney failure; AIC, Akaike Information Criterion (lower values for AIC represent better models).

Figure. Observed vs. Predicted Probability of ESKF at 3 Years in the Validation Cohort



Predicted risk categories for ESKF onset for quintiles 1 through 5 correspond with 0% to 37.2%, 37.2% to 74.8%, 74.8% to 91.3%, 91.3% to 97.7%, and 97.7% to 99.5%, respectively, for model 1; 0% to 30.7%, 30.7% to 77.9%, 77.9% to 93.8%, 93.8% to 98.5%, and 98.5% to 99.8%, respectively, for model 2; 0% to 30.5%, 30.5% to 78.3%, 78.3% to 93.9%, 93.9% to 98.5%, and 98.5% to 99.8%, respectively, for model 3.
Abbreviation: ESKF, end stage kidney failure.

- The development and validation cohort were comprised of 1,017 patients including 206 with ESKF onset (20.3%) and 1,017 patients including 216 with ESKF onset (21.2%), respectively (Table 1).
- In the derivation cohort, AIC was worse for model 1 that included age, gender, and eGFR only than model 4 that included age, gender, eGFR, log urinary albumin-creatinine ratio (UACR), systolic blood pressure (SBP), serum creatinine, serum albumin, hemoglobin, serum calcium, and log fibroblast growth factor 23 (FGF23) (2,350.1 vs. 2,203.9) (Table 2).
- In the validation cohort, model 3 that included age, gender, eGFR, log UACR, diabetes mellitus, SBP, serum albumin, hemoglobin, log iPTH, and log FGF23 improved C statistics and Nam and D'Agostino statistics compared with the model 1 (0.875 vs. 0.837, 3.27 vs. 16.0, respectively) (Table 3).
- The figure showed observed vs. predicted probability of ESKF onset at 3 years for model 1, 2, and 3 in the validation cohort. The mean absolute difference between the observed and predictive probabilities over quintiles of the risk for ESKF onset was lower for model 3 compared with model 1 and 2 (1.42% vs. 1.87% and 1.57%, respectively).

CONCLUSIONS

Clinical prediction models employing readily available data in clinical setting could precisely predict progression to ESKF in patients with CKD G3a to G5, which may facilitate more appropriate clinical decision making. Addition of log FGF23 to the models would further improve their capacities for goodness of fit, discrimination and calibration.

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