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Developing and validating a prognostic prediction model for patients with chronic kidney disease stages 3–5 based on disease conditions and intervention methods: a retrospective cohort study in China

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ABSTRACT

Objectives To develop and validate a nomogram model to predict chronic kidney disease (CKD) stages 3–5 prognosis.

Design A retrospective cohort study. We used univariate and multivariate Cox regression analysis to select the relevant predictors. To select the best model, we evaluated the prediction models' accuracy by concordance index (C-index), calibration curve, net reclassification index (NRI) and integrated discrimination improvement (IDI). We evaluated the clinical utility by decision curve analysis.

Setting Chronic Disease Management (CDM) Clinic in the Nephrology Department at the Guangdong Provincial Hospital of Chinese Medicine.

Participants Patients with CKD stages 3–5 in the derivation and validation cohorts were 459 and 326, respectively.

Primary outcome measure Renal replacement therapy (haemodialysis, peritoneal dialysis, renal transplantation) or death.

Results We built four models. Age, estimated glomerular filtration rate and urine protein constituted the most basic model A. Haemoglobin, serum uric acid, cardiovascular disease, primary disease, CDM adherence and predictors in model A constituted model B. Oral medications and predictors in model A constituted model C. All the predictors constituted model D. Model B performed well in both discrimination and calibration (C-index: derivation cohort: 0.881, validation cohort: 0.886). Compared with model A, model B showed significant improvement in the net reclassification and integrated discrimination (model A vs model B: NRI: 1 year: 0.339 (−0.011 to 0.672) and 2 years: 0.314 (0.079 to 0.574); IDI: 1 year: 0.066 (0.010 to 0.127), p<0.001 and 2 years: 0.063 (0.008 to 0.106), p<0.001). There was no significant improvement between NRI and IDI among models B, C and D. Therefore, we selected model B as the optimal model.

Conclusions We constructed a prediction model to predict the prognosis of patients with CKD stages 3–5 in the first and second year. Applying this model to clinical practice may guide clinical decision-making. Also, this model needs to be externally validated in the future.

Trial registration number ChiCTR1900024633 (http://www.chictr.org.cn).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study population was patients with chronic kidney disease stages 3–5 from China.
⇒ This study collected the oral medications and the chronic disease management (CDM) adherence of patients, which is not available in many studies.
⇒ Many patients were excluded due to incomplete raw data or short follow-up time.
⇒ CDM adherence in this study was divided into good and poor based only on whether patients adhered to attend monthly education.
⇒ The prediction model we established in this study has not been externally verified.

INTRODUCTION

Chronic kidney disease (CKD) was defined as kidney damage or a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for more than 3 months. Kidney damage was defined as either functional abnormalities of the kidneys (such as proteinuria or albuminuria, or abnormalities of the urinary sediment, such as dysmorphic red cells) or structural abnormalities as noted on imaging studies.[1 2]

The prevalence of CKD has been increasing in recent years. The overall CKD prevalence rate in Chinese adults has reached as high as 10.8% (10.2%–11.3%), and 1.1%–3.8% for patients with CKD stages 3–5.[3] If it progresses to end-stage renal disease (ESRD), renal replacement therapy (RRT) is required.[4] CKD stages 3–5 is an important threshold for

prevention and treatment before RRT. Due to the influence of the basic disease conditions, risk factors such as blood pressure, blood glucose and interventions, there is wide variation in patients' progression. A method that could predict patients' disease progression rates as early as possible and predict interventions' influence on the occurrence of endpoint events could guide clinical decision-making. However, the current limitation is that clinical doctors often judge disease progression based on patients' pathological results and GFR[5] as estimated by serum creatinine (Scr). But neither of these methods are sufficient for predicting disease progression. Furthermore, because pathological examination is invasive, many patients do not undergo this examination. Therefore, how can we obtain more accurate information on the likelihood of renal failure progression? Guidelines suggest[6] that prediction models can predict renal disease progression. Therefore, we have constructed a model to predict prognosis for patients with CKD stages 3–5.

According to a systematic review by Ramspek *et al*[7] on prognostic prediction models for CKD, as of 31 December 2017, a total of 16 papers have been published on prognostic prediction models for patients with CKD stages 3–5. Only five of these models were externally validated, including the Kaiser Permanente Northwest model[8] developed by Schroeder *et al*, the Chronic Renal Impairment in Birmingham risk score equations[9] developed by Landray *et al*, the Kidney Failure Risk Equation[5] developed by Tangri *et al*, the Veterans Affairs risk score[10] developed by Drawz *et al*, and the Marks formula[11] developed by Marks *et al*. However, there are two prominent deficiencies in the above 16 prediction models. First, the studied populations were all from the USA, Canada, Taiwan (China), Italy or the UK, there were no development or validation of prediction models for the prognosis of patients with CKD stages 3–5 in Mainland China. Second, most prediction models only collected data such as demographics, comorbidities and laboratory indicators, while ignoring intervention methods (refer to treatment methods including drugs, dietary/nutritional guidance, exercise guidance, disease education, etc). Therefore, the predictors in the current predictive models do not include intervention methods.

Therefore, in this study, we developed a prognostic prediction model based on patients with CKD stages 3–5 in Mainland China, including patients' basic disease conditions and intervention methods, so as to guide clinical decision-making and to delay disease progression.

METHODS

Patient screening

This is a retrospective cohort study. It included patients with CKD stages 3–5 who had first visited the Chronic Disease Management (CDM) Clinic at the Nephrology Department of the Guangdong Provincial Hospital of Chinese Medicine. Patients who had first visited between March 2010 and December 2016 were included in the derivation cohort, while patients who had first visited between January 2017 and May 2019 were included in the validation cohort. The CKD diagnosis was based on the consensus from the Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines.[1 12] We calculated estimated GFR (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI).[13] The criteria for CKD clinical staging[12] was: stage 1, GFR ≥90 mL/min/1.73 m^2; stage 2, GFR 60–89.9 mL/min/1.73 m^2; stage 3, GFR 30–59.9 mL/min/1.73 m^2; stage 4, GFR 15–29.9 mL/min/1.73 m^2; stage 5, GFR <15 mL/min/1.73 m^2 (or dialysis). Inclusion criteria: (1) patients aged 18 years and older; (2) patients on their first visits; (3) follow-up time exceeded 3 months; (4) patients who had been diagnosed as CKD stages 3–5; (5) patients who had signed an informed consent form on self-management and agreed to the use of their clinical data. Exclusion criteria: (1) started dialysis on the first visit; (2) history of kidney transplantation prior to the first visit; (3) patients with incomplete medical records.

Endpoint events

RRT (haemodialysis, peritoneal dialysis and renal transplantation) or death.

Sample size

The sample size of Cox regression analysis was based on the principle of 'events per variable' (EPV), and it is generally recommended that EPV be at least 10.[14]

Data collection

The CDM Clinic at the Nephrology Department of the Guangdong Provincial Hospital of Chinese Medicine has a standardised procedure of follow-up, education and evaluation for patients with CKD. After obtaining the informed consent, according to their willingness, first-visit patients were enrolled in CDM. Then they provided basic information, and doctors helped them formulate a CDM plan. After that, we followed up with the patients every month for treatment plan adjustment and conducted monthly health education for each patient during the first 2 years. We collected laboratory indicators every 3 months. For each patient, we defined the index date as the date at which patients had begun CDM.

The research data collected in this study included:

1. Basic information: each patient filled out a basic information questionnaire on the first visit, including sex, age, body mass index (BMI), permanent residence, payment term, education, working status, primary disease and any concomitant diseases (hypertension, diabetes, hyperuricaemia, hyperlipidaemia, urolithiasis, cardiovascular disease (CVD)). The primary disease and personal disease history were self-reported, and then the researchers would check according to the patient's examination results and oral medications.
2. Laboratory test results: we obtained the results of any blood tests completed in our hospital within 3 months after the index date through the hospital information

system (HIS). This included Scr, haemoglobin (Hb), urea, serum uric acid (UA), carbon dioxide combining power (CO_2CP), urine protein (PRO) and urine latent blood (BLD). We performed CKD staging according to eGFR calculated by the CKD-EPI formula.

3. Oral medications: we obtained data on Chinese medicine and Western medicine within 3 months after the index date via the HIS. This included diuretics, ACE inhibitor (ACEI), angiotensin receptor blockers (ARBs), calcium channel entry blockers (CCBs), alpha-blockers, beta-blockers, hypoglycaemic agents, lipid-lowering drugs, urate-lowering drugs, sodium bicarbonate, erythropoietin (EPO), polysaccharide-iron complex, folic acid, compound alpha-ketoacid tablets, calcium supplements, Chinese medicine decoction, Chinese-patent medicines for dispelling turbidity, Chinese-patent medicines for tonifying effects, other Chinese-patent medicines and immunosuppressants. Calcium supplements included calcium carbonate tablets and rocaltrol. Chinese-patent medicines for dispelling turbidity included Niaoduqing, Shenshuaining and Haikun Shenxi. Chinese-patent medicines for tonifying effects included Jinshuibao and Bailing Capsules. Other Chinese-patent medicines included Huangkui Capsules, Shenyan Kangfu Tablets, Fufang Shenyan Tablets, Shenyanshu and Yishen Huashi Granules.
4. Outcome assessment: the first day of the outcome occurrence was set as the endpoint before 30 December 2019. If no endpoint events occurred, the time of last visit was recorded.
5. Adherence to CDM: for patients who had begun CDM, doctors and nurses from the CDM Clinic would develop a management programme and set personal goals according to the patient's disease conditions. The educational contents in the management programme included diet, exercise, lifestyle and medication adherence. For the first 2 years, one-on-one, face-to-face, monthly nurse-delivered education was undertaken for the patients. The educator nurses also needed to record whether the patients had participated on time every month. For patients with follow-up time less than 2 years, if patients regularly attended the monthly education, we considered that their CDM adherence was good; otherwise, we considered their adherence was poor. For patients with follow-up time more than 2 years, in the first 2 years of follow-up, if patients regularly attended the monthly education, we considered that their CDM adherence was good; otherwise, the adherence was poor.

Patient and public involvement

No patient involved.

Statistical analysis

There are some missing data in several of this study's variables. BMI had 2.7% missing values. Education had 8.9% missing values. Working status had 10.1% missing values. There were 7.9% missing data in Hb, 2.9% missing data in urea, 2.4% missing data in UA, 5.9% missing data in CO_2CP, 1.0% missing data in BLD and 1.4% in PRO. We used multivariate multiple imputations to impute missing values to maximise the statistical power and diminish bias. We reclassified age, BMI, permanent residence, payment term, education, working status, adherence to CDM, primary disease, Hb, urea, UA, CO_2CP, BLD and PRO into categorical variables: two levels for the age factor (≤60 or >60 years), four levels for the BMI factor (<18.5, 18.5–23.9, 24–27.9 and ≥28 kg/m^2), two levels for the permanent residence factor (within Guangzhou city limits or outside Guangzhou city limits), three levels for the payment term factor (out-of-pocket, health insurance, free medical service), five levels for the education factor (primary school or below, junior high school, high school or technical secondary school, junior college, bachelor's degree and above), two levels for the working status factor (working or not working), two levels for the CDM adherence factor (good or poor), five levels for the primary disease factor (primary glomerular disease, secondary nephropathy, diabetic nephropathy (DN), other and unknown reason), two levels for the Hb factor (normal: male: Hb ≥120 g/L and female: Hb ≥110 g/L; low: lower than normal), two levels for the urea factor (≤7.5 and >7.5 mmol/L), two levels for the UA factor (normal: female: UA ≤360 g/L and male: UA ≤420 g/L; high: higher than normal), two levels for the CO_2CP factor (≤22 and >22 mmol/L), and four levels for the BLD and PRO factors (0/±, 1+, 2+, 3~4+). We set Hb, urea, UA and CO_2CP as categorical variables according to the normal reference values for laboratory indicators at Guangdong Provincial Hospital of Chinese Medicine.

For the baseline analysis, continuous variables conforming to a normal distribution are presented as mean±SD, and were analysed using a t-test. Continuous variables not conforming to the normal distribution are presented as medians (P_{25}, P_{75}), and we compared them with a Mann-Whitney U test. Categorical variables are presented as frequencies (percentages), and were compared using a χ^2 test or Fisher's exact test. We performed univariate Cox regression analysis on the derivation cohort. Then we conducted a collinearity diagnostic test on the variables with $p<0.05$ in the univariate Cox regression. Collinearity diagnostics were performed with the variance inflation factor (VIF) test. A VIF more than 5 was considered significant collinearity. We removed variables with significant collinearity one by one until no variables with VIF more than 5. Then we performed multivariate Cox regression analysis to select potential risk factors for the occurrence of endpoint events in the derivation cohort. According to the variable types screened by multivariate Cox regression analysis and combined the actual clinical situation, we built several models.

We generated a calibration curve and Harrell's concordance index (Harrell's C-index) with bootstrap methods to assess the models' discrimination and calibration power, respectively.[15 16] C-index was used to estimate the power to distinguish high-risk participants from low-risk

participants. The C-index ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination). A higher C-index indicated more discriminatory power. The calibration curve was used to compare the consistency between the actual outcomes and predicted outcomes. The diagonal line indicates perfect calibration. Hence, deviation from it indicates a lack of calibration.

We also used the models' net reclassification improvement (NRI)[17] and integrated discrimination improvement (IDI)[18] to evaluate their discriminatory power. The NRI and IDI are statistical measures quantifying the improvement of a new model compared with an old model. If NRI or IDI >0, it represents a positive improvement, indicating that the new model's predictive ability has improved compared with the old model. If NRI or IDI <0, it represents a negative improvement and the new model's predictive ability decreases. If NRI or IDI=0, it is considered that the new model's predictive ability has not improved.

We selected the best model according to the optimal combination of the above indicators. Then, we formulated a nomogram based on the independent risk factors of the best model. The basic principle of the nomogram[19] is to assign a score to different values of each risk factor according to the beta coefficients of each risk factor calculated by the Cox regression model, and then add them together to obtain the total score. Finally, the predicted values of the endpoint events are calculated through the transformation function between the total score and the probability of the endpoint events. Therefore, the nomogram transforms the complex regression equation into a visual graph, making the results of the predictive model more readable.

We assessed the clinical utility of the nomogram by decision curve analysis (DCA).[20] DCA shows the relationship between 'net benefit' and 'threshold probability' and estimates the clinical utility of the nomogram by calculating the net benefits for a range of threshold probabilities. The threshold probabilities refer to the relative harms of false positives and false negatives. The net benefit is obtained by subtracting the proportion of patients who are false positive from the proportion who are true positive, and then weighing the relative harms of false-positive and false-negative results.[21] We performed the statistical analyses in this study with SPSS V.24.0 (IBM Corp), R V.3.6.2 and Stata V.15.1, with a significance level of p<0.05.

RESULTS

Study population

From 2010 to 2019, there were 1517 patients with CKD stages 3–5 who had first visited the CDM Clinic at the Nephrology Department of the Guangdong Provincial Hospital of Chinese Medicine and signed informed consent to join the CDM. Two hundred fifty patients with a follow-up time less than 3 months were excluded, and 482 patients with more than 15% missing data were excluded. A total of 785 patients with CKD stages 3–5 were included. During a median follow-up period of 26.17 months, 169 patients initiated dialysis (21.5%), 4 patients had undergone renal transplantation and 1 patient died before dialysis initiation. Four hundred fifty-nine patients who had first visited between March 2010 and December 2016 were included in the derivation cohort, and 326 patients who had first visited between January 2017 and May 2019 were included in the validation cohort. There were 149 endpoint events (32.5%) in the derivation cohort and 25 endpoint events (7.7%) in the validation cohort. The study flow chart is illustrated in online supplemental figure 1. The cumulative incidence rate of endpoint events among patients with CKD stages 3–5 in the whole, derivation and validation cohort is shown in online supplemental figures 2–4.

Patients' baseline characteristics

The baseline characteristics of the derivation cohort and validation cohort are shown in table 1. There were no significant differences in age, sex, BMI, payment term, primary disease, Hb, Scr, urea, CO_2CP, hypertension, diabetes, urolithiasis, CVD, diuretics, ACEI/ARB, CCB, alpha-blockers, beta-blockers, hypoglycaemic agents, polysaccharide-iron complex, compound alpha-ketoacid tablets, calcium supplements, Chinese herbal decoction, Chinese-patent medicines for dispelling turbidity, other Chinese-patent medicines, or immunosuppressants between the derivation cohort and the validation cohort. Moreover, permanent residence, education, working status, CDM adherence, CKD stage, UA, BLD, PRO, hyperuricaemia, hyperlipidaemia, lipid-lowering drugs, urate-lowering drugs, sodium bicarbonate, EPO, folic acid and Chinese-patent medicines for tonifying effects showed statistically significant differences between the two cohorts. In addition, the patients in the validation cohort had higher eGFR than those in the derivation cohort.

Univariate Cox regression analysis of risk factors for endpoints

We incorporated the variables in table 1 into univariate Cox regression analysis. Table 2 shows the results of univariate Cox regression analysis of 459 patients in the derivation cohort. In the univariate Cox regression analysis, age, CDM adherence, primary disease (DN vs primary glomerular disease), Hb, Scr, eGFR, CKD stage, urea, UA, CO_2CP, BLD (1+ vs 0/±), PRO, hypertension, CVD, diuretics, ACEI/ARB, CCB, alpha-blockers, beta-blockers, sodium bicarbonate, EPO, polysaccharide-iron complex, folic acid, compound alpha-ketoacid tablets, calcium supplements, Chinese herbal decoction and Chinese-patent medicines for dispelling turbidity were correlated with endpoint events occurring in patients with CKD stages 3–5 (p<0.05).

Collinearity diagnostic test

We conducted collinearity analysis to eliminate any collinearity effectonline supplemental table 1. According to the

Table 1 Baseline characteristics for patients in the derivation cohort and the validation cohort

Characteristics	Derivation cohort (n=459)	Validation cohort (n=326)	X^2/Z	P value
Age (≤60 years)	267 (58.2%)	195 (59.8%)	0.213	0.644
Sex (male)	232 (50.5%)	186 (57.1%)	3.246	0.072
BMI (kg/m^2)			1.358	0.715
18.5–23.9	255 (55.6%)	170 (52.1%)		
<18.5	46 (10.0%)	31 (9.5%)		
24.0–27.9	119 (25.9%)	96 (29.4%)		
≥28	39 (8.5%)	29 (8.9%)		
Permanent residence			12.613	<0.001
Within Guangzhou city limits	370 (80.6%)	227 (69.6%)		
Outside Guangzhou city limits	89 (19.4%)	99 (30.4%)		
Payment term			5.370	0.068
Out-of-pocket	145 (31.6%)	129 (39.6%)		
Health insurance	282 (61.4%)	176 (54.0%)		
Free medical service	32 (7.0%)	21 (6.4%)		
Education			11.731	0.019
Primary school or below	88 (19.2%)	50 (15.3%)		
Junior high school	129 (28.1%)	84 (25.8%)		
High school or technical secondary school	149 (32.5%)	92 (28.2%)		
Junior college	48 (10.5%)	55 (16.9%)		
Bachelor's degree and above	45 (9.8%)	45 (13.8%)		
Working status (working)	106 (23.1%)	116 (35.6%)	14.659	<0.001
CDM adherence (poor)	422 (91.9%)	252 (77.3%)	33.644	<0.001
Primary disease			6.963	0.138
Primary glomerular disease	177 (38.6%)	130 (39.9%)		
Secondary nephropathy	60 (13.1%)	36 (11.0%)		
Diabetic nephropathy	52 (11.3%)	33 (10.1%)		
Other	35 (7.6%)	13 (4.0%)		
Unknown reason	135 (29.4%)	114 (35.0%)		
Hb (g/L) (normal)	257 (56.0%)	203 (62.3%)	3.097	0.078
Scr (μmol/L)	173.0 (129.0, 283.0)	158.0 (127.0, 253.5)	−1.280*	0.201
eGFR (mL/min/1.73 m^2)	32.2 (18.3, 46.5)	36.8 (21.0, 48.9)	−2.280*	0.023
CKD stage			6.431	0.040
CKD stage 3	247 (53.8%)	192 (58.9%)		
CKD stage 4	123 (26.8%)	93 (28.5%)		
CKD stage 5	89 (19.4%)	41 (12.6%)		
Urea (≤7.5 mmol/L)	95 (20.7%)	82 (25.2%)	2.167	0.141
UA (umol/L) (normal)	100 (21.8%)	100 (30.7%)	7.932	0.005
CO_2CP (≤22 mmol/L)	324 (70.6%)	235 (72.1%)	0.209	0.648
BLD			9.873	0.020
0/±	238 (51.9%)	150 (46.0%)		
1+	67 (14.6%)	75 (23.0%)		
2+	107 (23.3%)	65 (19.9%)		
3~4+	47 (10.2%)	36 (11.0%)		
PRO			11.140	0.011

Continued

Table 1 Continued

Characteristics	Derivation cohort (n=459)	Validation cohort (n=326)	X^2/Z	P value
0/±	162 (35.3%)	137 (42.0%)		
1+	86 (18.7%)	52 (16.0%)		
2+	78 (17.0%)	71 (21.8%)		
3~4+	133 (29.0%)	66 (20.2%)		
Hypertension	326 (71.0%)	235 (72.1%)	0.105	0.745
Diabetes	97 (21.1%)	67 (20.6%)	0.039	0.844
Hyperuricaemia	221 (48.1%)	195 (59.8%)	10.417	0.001
Hyperlipidaemia	152 (33.1%)	146 (44.8%)	11.023	0.001
Urolithiasis	62 (13.5%)	39 (12.0%)	0.406	0.524
Cardiovascular disease	71 (15.5%)	36 (11.0%)	3.171	0.075
Diuretics	70 (15.3%)	54 (16.6%)	0.247	0.619
ACEI/ARB	164 (35.7%)	124 (38.0%)	0.437	0.509
CCB	218 (47.5%)	144 (44.2%)	0.847	0.357
Alpha-blockers	53 (11.5%)	38 (11.7%)	0.002	0.962
Beta-blockers	108 (23.5%)	88 (27.0%)	1.221	0.269
Hypoglycaemic agents	97 (21.1%)	67 (20.6%)	0.039	0.844
Lipid-lowering drugs	103 (22.4%)	109 (33.4%)	11.691	0.001
Urate-lowering drugs	119 (25.9%)	138 (42.3%)	23.297	<0.001
Sodium bicarbonate	248 (54.0%)	218 (66.9%)	13.029	<0.001
EPO	93 (20.3%)	47 (14.4%)	4.443	0.035
Polysaccharide-iron complex	74 (16.1%)	58 (17.8%)	0.380	0.538
Folic acid	36 (7.8%)	40 (12.3%)	4.272	0.039
Compound alpha-ketoacid tablets	180 (39.2%)	109 (33.4%)	2.738	0.098
Calcium supplements	94 (20.5%)	64 (19.6%)	0.085	0.770
Chinese herbal decoction	427 (93.0%)	301 (92.3%)	0.138	0.711
Chinese-patent medicines for dispelling turbidity	259 (56.4%)	185 (56.7%)	0.008	0.929
Chinese-patent medicines for tonifying effects	129 (28.1%)	49 (15%)	18.582	<0.001
Other Chinese-patent medicines	65 (14.2%)	43 (13.2%)	0.151	0.697
Immunosuppressant	48 (10.5%)	41 (12.6%)	0.852	0.356

Values are given as n (%) or median (P_{25}, P_{75}).
Working status was classified as working or not working, CDM adherence was classified as either good or poor, Hb was classified as normal or below normal, UA was classified as normal or above normal.
*Mann-Whitney U test; other values were analysed with χ^2 test.
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BLD, urine latent blood; BMI, body mass index; CCB, calcium channel entry blocker; CDM, chronic disease management; CKD, chronic kidney disease; CO_2CP, carbon dioxide combining power; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; Hb, haemoglobin; PRO, urine protein; Scr, serum creatinine; UA, serum uric acid.

results, we took out Scr and CKD stage before multivariate Cox regression analysis (online supplemental table 1).

Multivariate Cox regression analysis of risk factors for endpoints

The multivariate Cox regression analysis results (table 2) showed that age (HR: 0.597, 95% CI: 0.390 to 0.914, p=0.018), CDM adherence (HR: 0.277, 95% CI: 0.114 to 0.671, p=0.004), primary disease (DN vs primary glomerular disease, HR: 2.017, 95% CI: 1.119 to 3.633, p=0.020), Hb (HR: 2.011, 95% CI: 1.308 to 3.090, p=0.001), eGFR (HR: 0.910, 95% CI: 0.889 to 0.931, p<0.001), UA (HR: 1.797, 95% CI: 1.080 to 2.990, p=0.024), PRO (2+ vs 0/±: HR: 2.466, 95% CI: 1.277 to 4.761, p=0.007; 3~4+ vs 0/±: HR: 3.402, 95% CI: 1.838 to 6.295, p<0.001), CVD (HR: 1.875, 95% CI: 1.137 to 3.091, p=0.014), alpha-blockers (HR: 1.695, 95% CI: 1.086 to 2.646, p=0.020), beta-blockers (HR: 1.651, 95% CI: 1.090 to 2.501, p=0.018), calcium supplements (HR: 1.538, 95% CI: 1.012 to 2.339, p=0.044), Chinese herbal decoction (HR: 0.487, 95% CI: 0.269 to 0.883, p=0.018) and Chinese-patent medicines

Table 2 Univariate and multivariate Cox regression analysis based on the derivation cohort

	Univariate analysis		Multivariate analysis	
Variables	**P value**	**Crude HR (95% CI)**	**P value**	**Adjusted HR (95% CI)**
Age (≤60 years)				
>60	0.002	0.583 (0.412 to 0.824)	0.018	0.597 (0.390 to 0.914)
Sex (male)				
Female	0.956	1.009 (0.731 to 1.394)	/	/
BMI (kg/m^2)				
18.5–23.9				
<18.5	0.744	1.091 (0.646 to 1.845)	/	/
24.0–27.9	0.854	0.964 (0.653 to 1.423)	/	/
≥28	0.977	1.009 (0.562 to 1.811)	/	/
Permanent residence				
Within Guangzhou city limits				
Outside Guangzhou city limits	0.166	1.323 (0.891 to 1.966)	/	/
Payment term				
Out-of-pocket				
Health insurance	0.591	0.909 (0.641 to 1.289)	/	/
Free medical service	0.051	0.428 (0.183 to 1.002)	/	/
Education				
Primary school or below				
Junior high school	0.758	1.078 (0.668 to 1.741)	/	/
High school or technical secondary school	0.812	1.058 (0.665 to 1.683)	/	/
Junior college	0.343	0.719 (0.364 to 1.421)	/	/
Bachelor's degree and above	0.475	0.785 (0.405 to 1.523)	/	/
Working status (working)				
Not working	0.202	0.788 (0.547 to 1.136)	/	/
CDM adherence (poor)				
Good	0.015	0.389 (0.182 to 0.831)	0.004	0.277 (0.114 to 0.671)
Primary disease				
Primary glomerular disease				
Secondary nephropathy	0.524	1.174 (0.717 to1.920)	0.319	0.746 (0.419 to 1.328)
Diabetic nephropathy	0.020	1.733 (1.091 to 2.751)	0.020	2.017 (1.119 to 3.633)
Other	0.464	1.253 (0.685 to 2.290)	0.895	0.954 (0.473 to 1.924)
Unknown reason	0.137	0.712 (0.455 to 1.113)	0.104	0.649 (0.385 to 1.093)
Hb (g/L) (normal)				
Low	<0.001	3.124 (2.236 to 4.366)	0.001	2.011 (1.308 to 3.090)
Scr (μmol/L)	<0.001	1.008 (1.007 to 1.008)		
eGFR (mL/min/1.73 m^2)	<0.001	0.901 (0.886 to 0.916)	<0.001	0.910 (0.889 to 0.931)
CKD stage				
CKD stage 3				
CKD stage 4	<0.001	4.679 (2.971 to 7.370)	/	/
CKD stage 5	<0.001	23.522 (14.857 to 37.241)	/	/
Urea (≤7.5 mmol/L)				
>7.5	<0.001	8.778 (3.875 to 19.884)	0.878	0.930 (0.369 to 2.348)
UA (μmol/L) (normal)				

Continued

Table 2 Continued

Variables	Univariate analysis		Multivariate analysis	
	P value	Crude HR (95% CI)	P value	Adjusted HR (95% CI)
High	0.020	1.665 (1.082 to 2.561)	0.024	1.797 (1.080 to 2.990)
CO_2CP (≤22 mmol/L)				
>22	<0.001	2.635 (1.891 to 3.670)	0.228	0.769 (0.501 to 1.179)
BLD				
0/±				
1+	0.017	1.712 (1.101 to 2.662)	0.227	1.376 (0.820 to 2.309)
2+	0.241	1.272 (0.851 to 1.902)	0.921	1.024 (0.640 to 1.638)
3~4+	0.418	1.246 (0.731 to 2.123)	0.515	0.817 (0.444 to 1.503)
PRO				
0/±				
1+	0.018	2.120 (1.135 to 3.960)	0.249	1.515 (0.748 to 3.069)
2+	<0.001	5.181 (2.938 to 9.139)	0.007	2.466 (1.277 to 4.761)
3~4+	<0.001	7.393 (4.402 to 12.417)	<0.001	3.402 (1.838 to 6.295)
Hypertension	<0.001	3.013 (1.937 to 4.686)	0.287	1.403 (0.752 to 2.617)
Diabetes	0.586	1.112 (0.758 to 1.631)	/	/
Hyperuricaemia	0.338	1.171 (0.848 to 1.616)	/	/
Hyperlipidaemia	0.701	0.935 (0.662 to 1.319)	/	/
Urolithiasis	0.235	1.310 (0.839 to 2.046)	/	/
Cardiovascular disease	0.025	1.604 (1.062 to 2.423)	0.014	1.875 (1.137 to 3.091)
Diuretics	<0.001	2.208 (1.497 to 3.256)	0.389	1.236 (0.763 to 2.005)
ACEI/ARB	0.009	0.617 (0.430 to 0.884)	0.148	0.725 (0.469 to 1.121)
CCB	<0.001	3.037 (2.156 to 4.279)	0.992	1.003 (0.605 to 1.661)
Alpha-blockers	<0.001	3.344 (2.260 to 4.948)	0.020	1.695 (1.086 to 2.646)
Beta-blockers	<0.001	2.132 (1.513 to 3.006)	0.018	1.651 (1.090 to 2.501)
Hypoglycaemic agents	0.586	1.112 (0.758 to 1.631)	/	/
Lipid-lowering drugs	0.531	1.128 (0.774 to 1.642)	/	/
Urate-lowering drugs	0.403	1.165 (0.815 to 1.665)	/	/
Sodium bicarbonate	<0.001	2.024 (1.444 to 2.837)	0.184	1.320 (0.877 to 1.987)
EPO	<0.001	4.768 (3.400 to 6.686)	0.303	1.284 (0.798 to 2.064)
Polysaccharide-iron complex	<0.001	3.414 (2.389 to 4.878)	0.397	1.265 (0.734 to 2.182)
Folic acid	<0.001	3.510 (2.256 to 5.460)	0.574	1.178 (0.665 to 2.090)
Compound alpha-ketoacid tablets	<0.001	2.013 (1.454 to 2.786)	0.786	1.054 (0.722 to 1.537)
Calcium supplement	<0.001	2.324 (1.647 to 3.278)	0.044	1.538 (1.012 to 2.339)
Chinese herbal decoction	0.047	0.582 (0.341 to 0.993)	0.018	0.487 (0.269 to 0.883)
Chinese-patent medicines for dispelling turbidity	0.001	1.826 (1.295 to 2.576)	0.045	0.654 (0.432 to 0.990)
Chinese-patent medicines for tonifying effects	0.417	0.862 (0.601 to 1.235)	/	/
Other Chinese-patent medicines	0.281	0.762 (0.466 to 1.248)	/	/
Immunosuppressant	0.449	0.803 (0.454 to 1.419)	/	/

Variables with p<0.05 in univariate Cox regression were tested for collinearity; Scr and CKD stage were taken out in the multivariate Cox regression analysis due to high collinearity. Crude HR: represented relative HR; adjusted HR: represented adjusted HR, adjusted for age, CDM adherence, primary disease, Hb, eGFR, urea, UA, CO_2CP, BLD, PRO, hypertension, cardiovascular disease, diuretics, ACEI/ARB, CCB, alpha-blockers, beta-blockers, sodium bicarbonate, EPO, polysaccharide-iron complex, folic acid, compound alpha-ketoacid tablets, calcium supplement, Chinese herbal decoction and Chinese-patent medicines for dispelling turbidity in the multivariate Cox regression analysis.
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BLD, urine latent blood; BMI, body mass index; CCB, calcium channel entry blocker; CDM, chronic disease management; CKD, chronic kidney disease; CO_2CP, carbon dioxide combining power; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; Hb, haemoglobin; PRO, urine protein; Scr, serum creatinine; UA, serum uric acid.

Table 3 C-indexes for the models in the derivation and validation cohorts

C-index (95% CI)	Model A	Model B	Model C	Model D
Derivation cohort	0.865 (0.840 to 0.890)	0.881 (0.857 to 0.905)	0.873 (0.849 to 0.898)	0.888 (0.866 to 0.910)
Validation cohort	0.878 (0.824 to 0.930)	0.886 (0.832 to 0.938)	0.879 (0.825 to 0.933)	0.888 (0.836 to 0.940)

Model A: including age, estimated glomerular filtration rate, and urine protein; Model B: including hemoglobin, serum uric acid, cardiovascular disease, primary disease, chronic disease management adherence and variables in Model A; Model C: including alpha-blockers, beta-blockers, calcium supplements, Chinese herbal decoction, Chinese patent medicines for dispelling turbidity and variables in Model A; Model D: including all the predictors.

for dispelling turbidity (HR: 0.654, 95% CI: 0.432 to 0.990, p=0.045) were significant independent factors of endpoint events in patients with CKD stages 3–5.

Prediction model performance in the cohort

We constructed prediction models using the variables selected by multivariate Cox regression analysis in table 2. We considered that age, eGFR and PRO were the most relevant information for reflecting patients' condition when first visiting the doctor, and therefore these variables constituted the most basic model (model A). Hb, UA, CVD, primary disease, CDM adherence and variables in model A constituted model B. Alpha-blockers, beta-blockers, calcium supplements, Chinese herbal decoction, Chinese-patent medicines for dispelling turbidity and variables in model A constituted model C. Finally, all the predictors combined constituted model D. The C-indexes of the four models in the derivation and validation cohorts are shown in table 3. The C-index of the four models in both derivation and validation cohorts exceeded 0.8, which indicated sufficient discriminatory power. The calibration curves of four models in the derivation and validation cohorts are shown in figure 1 and online supplemental figures 5–7. The calibration plots show that the four models' calibration curves for 1-year and 2-year endpoint events approached the standard diagonal lines. This indicated sufficient concordance between the estimated risk of endpoint events and the actual presence of endpoint events. Thus, the four models had sufficient discriminatory power and calibration.

NRI and IDI among the four models

The four models' NRI and IDI are shown in table 4. Compared with model A, model B's IDI showed a 6.6% and 6.3% improvement in the first and second year, respectively (p<0.001); model C showed a 4.2% improvement in the second year (p<0.001). Model B's NRI showed a 31.4% improvement in the second year. While compared with model B, the IDI and NRI in models C and D had no significant improvements. Compared with model C, model D's IDI showed a 5.5% improvement in the second year (p=0.020), while model D's NRI showed a 27.5% improvement in the second year.

The optimal model's nomogram

Based on the above analysis, model B performed well in both discrimination and calibration. Therefore, we regarded model B, which contained age, eGFR, PRO, Hb, UA, CVD, primary disease and CDM adherence as the optimal model. The nomogram for predicting the probability of no occurrence of endpoint events with patients with CKD stages 3–5 in the first and second year is shown in figure 2. We created this nomogram based on model B's independent prognostic factors. Each prognostic factor category corresponds to a point by drawing a straight line upward to the points axis. Then each point is added to get the total points; the total points located on the total points axis represent the probability of no occurrence of endpoint events in the first and second year by drawing straight down to the first and second year probability axis. For example, a 45-year-old (6 points) patient whose eGFR is 20 mL/min/1.73 m^2 (72.5 points), PRO is 3+ (22.5 points), Hb is normal (0 points), UA is above normal (7 points), primary disease is DN (17.5 points), and who had CVD (13 points) and poor CDM adherence (17.5 points) would have a total score of 156. The corresponding likelihood of no endpoint events in the first and second year would be 72% and 30%, respectively. This calculated value could be used in decision-making for treatment plans and patient counselling.

Decision curve analysis

Decision curve for the nomogram is presented in figure 3. DCAs demonstrated the net benefit associated with using model B to predict endpoint events in patients with CKD stages 3–5. The results showed that when the threshold used for the predicted risk of 1-year endpoint events was between 20% and 40%, or 2-year endpoint events between 30% and 60%, the model performed better than predicting the occurrence of endpoint events in all or no patients.

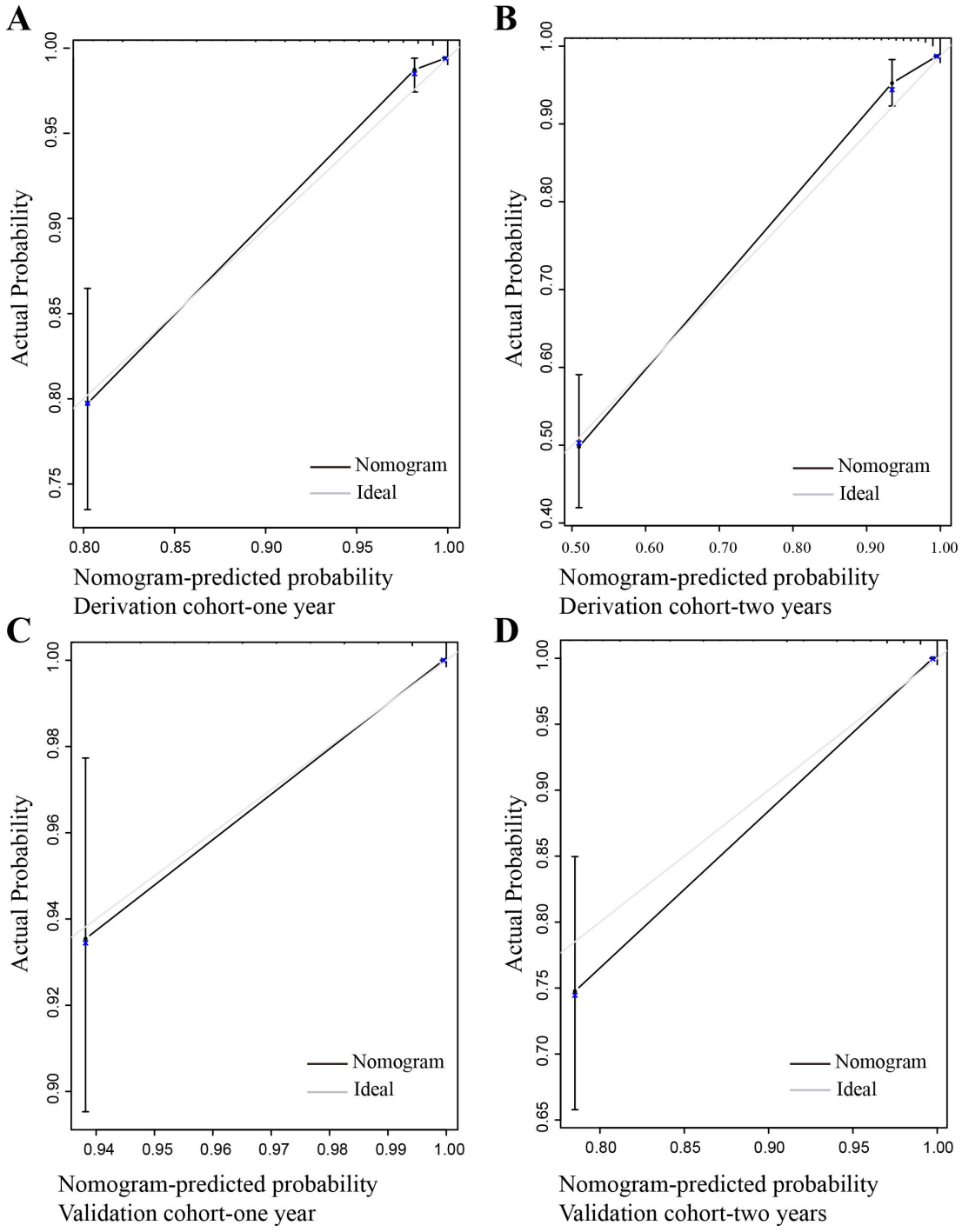

Figure 1 Calibration curves for model B. (A) Derivation cohort, 1 year; (B) derivation cohort, 2 years; (C) validation cohort, 1 year; (D) validation cohort, 2 years. The grey line represents the ideal line for a perfect match between predicted and observed likelihood of endpoint events. The dark line indicates the proposed nomogram's performance.

Sensitivity analysis

Considering that the selection of the predictors of the models in this study was only based on statistical analysis, rather than literature, some important factors may be missed and it may also bring difficulties in externalising the models. According to a previously published systematic review,[7] the researchers summarised all the predictors of the published predictive models and noted that the final predictors in almost all studies included age, sex, eGFR and proteinuria. Thus, we constructed model E including age, sex, eGFR and proteinuria. The C-indexes of the model E in the derivation and validation cohorts were 0.865 (95% CI: 0.840 to 0.921) and 0.872 (95% CI: 0.816 to 0.928), which indicated sufficient discriminatory power. The calibration curves of model E showed that model E had sufficient calibration power (online supplemental figure 8). The nomogram of model E is shown in online supplemental figure 9. We also conducted NRI

Table 4 Models' net reclassification improvement (NRI) and integrated discrimination improvement (IDI)

	Year	NRI (95% CI)	IDI (95% CI)	P value
Model A vs model B	1	0.339 (–0.011 to 0.672)	0.066 (0.010 to 0.127)	<0.001
	2	0.314 (0.079 to 0.574)	0.063 (0.008 to 0.106)	<0.001
Model A vs model C	1	0.194 (–0.056 to 0.533)	0.051 (–0.001 to 0.116)	0.059
	2	0.205 (–0.036 to 0.408)	0.042 (0.007 to 0.090)	<0.001
Model B vs model C	1	0.028 (–0.360 to 0.398)	–0.016 (–0.092 to 0.048)	0.653
	2	–0.056 (–0.364 to 0.176)	–0.021 (–0.070 to 0.034)	0.495
Model B vs model D	1	0.112 (–0.140 to 0.433)	0.028 (–0.022 to 0.089)	0.277
	2	0.152 (–0.089 to 0.364)	0.034 (–0.003 to 0.079)	0.079
Model C vs model D	1	0.296 (–0.014 to 0.621)	0.044 (–0.002 to 0.099)	0.059
	2	0.275 (0.010 to 0.525)	0.055 (0.007 to 0.095)	0.020

Model A: including age, estimated glomerular filtration rate, and urine protein; Model B: including hemoglobin, serum uric acid, cardiovascular disease, primary disease, chronic disease management adherence and variables in Model A; Model C: including Alpha-blockers, beta-blockers, calcium supplements, Chinese herbal decoction, Chinese patent medicines for dispelling turbidity and variables in Model A; Model D: including all the predictors.

and IDI of model B versus model E. Results showed that compared with model B, model E had no significant improvement in NRI and IDI (online supplemental table 2). Therefore, model B is still the optimal model in this study.

DISCUSSION

In this study, we collected and collated the basic information, intervention methods and the time of endpoint events for patients with CKD stages 3–5 who had first visited the CDM Clinic at the Nephrology Department at the Guangdong Provincial Hospital of Chinese Medicine, from 2010 to 2019. We have established a prediction model that predicts the likelihood of no endpoint events for patients with CKD stages 3–5. Model B showed good calibration and discrimination, and its net reclassification and integrated discrimination were an improvement over other models.

CDM adherence, age, eGFR, PRO, Hb, UA, CVD and primary disease were independent risk factors of the endpoint events for patients with CKD stages 3–5, and were also important predictors in model B. The results of this study showed that patients with good adherence had a 72.3% lower risk of endpoint events than patients with poor CDM adherence. Patients >60 years of age had a 40.3% lower risk of endpoint events than patients ≤60 years of age; the risk of endpoint events decreased by 9% for each unit increase in eGFR. Compared with those with normal Hb levels, patients with low Hb levels had a 1.011-fold increased risk of endpoint events. Compared with patients with PRO 0/±, patients with PRO 2+ had a 1.466-fold increased risk of endpoint events, and patients with PRO 3~4+ had a 2.402-fold increased risk of endpoint events. Compared with patients with normal UA levels, patients with higher UA levels had a 0.797-fold increased risk of endpoint events. Compared with patients without CVD, patients with CVD had a 0.875-fold increased risk of endpoint events. Compared with patients with primary glomerular disease, patients with primary disease being DN had a 1.017-fold increased risk of endpoint events.

At present, CDM for CKD aims to improve patients' understanding of the disease and treatment adherence through regular health education and follow-up, so as to promote reasonable diet, proper exercise and rational use of drugs.[22] This may help foster self-management skills for their chronic diseases and delay disease progression. Studies[23] from outside of Mainland China have shown that self-management may improve self-care activities, glycated Hb and systolic blood pressure in patients with comorbid CKD and diabetes. Results from our previous meta-analysis[24] have also shown that self-management in patients with CKD is beneficial for PRO reduction, blood pressure control, exercise capacity and C reactive protein level. Meanwhile, patients with CKD with poor management have an elevated risk of disease progression, death and atherosclerosis.[25] Therefore, CDM may play an important role in CKD prognosis, which also supports the findings of this study that there was an association between CDM and CKD prognosis. However, this study was a retrospective study, the causality of CDM and CKD prognosis could not be determined. Therefore, it remains to be further confirmed in more future prospective studies. In terms of age, a cohort study[26] among 209 622 US veterans with CKD stages 3–5 showed that the risk of ESRD decreased with ageing when eGFR levels were equivalent. Meanwhile, a retrospective cohort study[27] of 1549 patients with CKD found that the risk of dialysis decreased with each 10-year increase in age (HR: 0.95, 95% CI: 0.91 to 0.99). This is similar to the findings of a 2013 cohort study[28] conducted by Lin *et al* in

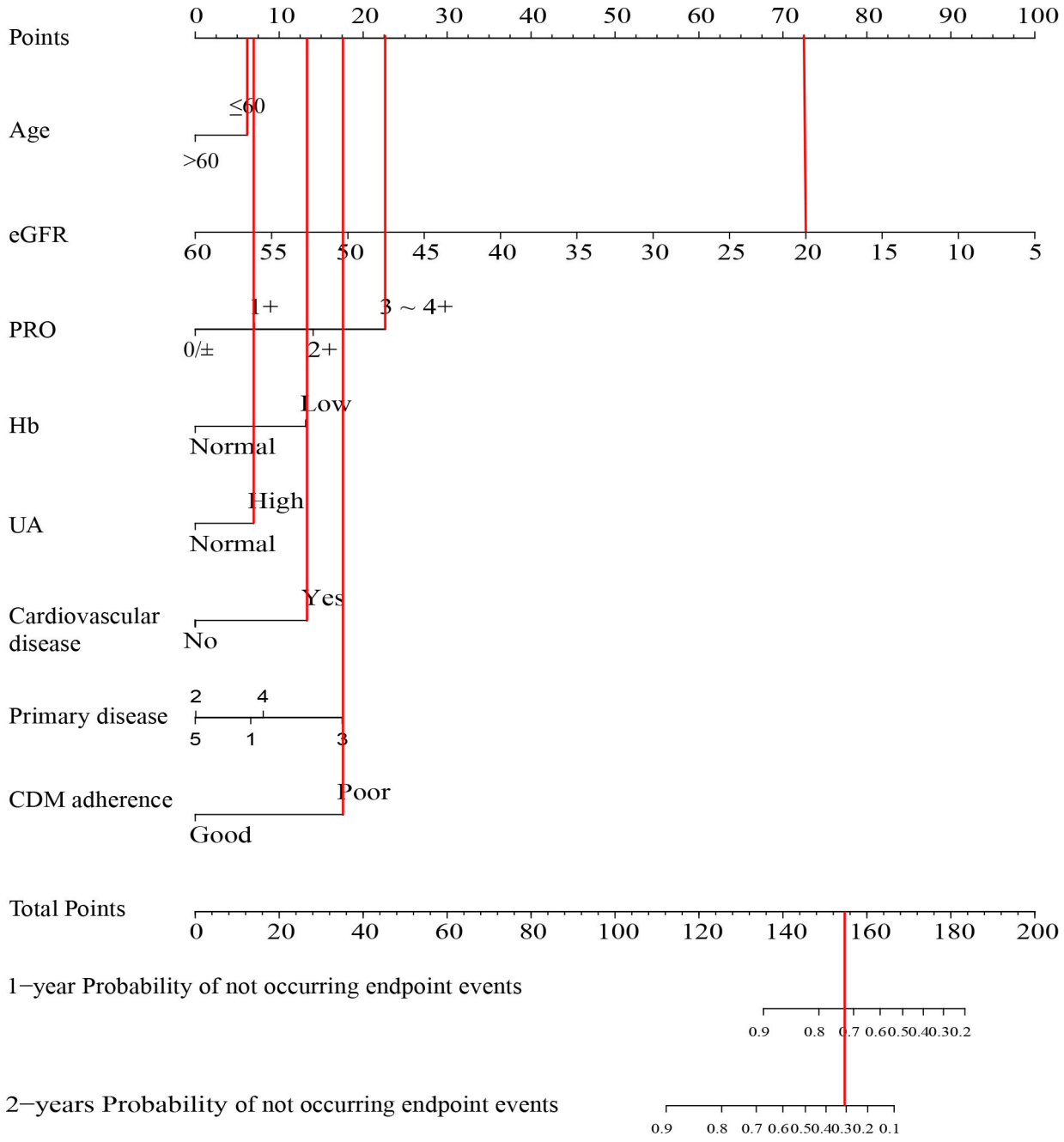

Figure 2 Nomogram for model B. Primary disease: 1 indicates primary glomerular disease, 2 indicates secondary nephropathy, 3 indicates diabetic nephropathy, 4 indicates other nephropathy, 5 indicates unknown reason. Instructions: locate age on the corresponding axis. Draw a line straight down to the axis to calculate how many points toward the probability of not occurring endpoint events in the patients at different ages. Repeat the courses for eGFR, PRO, Hb, UA, cardiovascular disease, primary disease and CDM adherence. Add all points obtained from the previous steps, and locate the final summation on the total score axis. The probability of not occurring endpoint events corresponds to the summation score on the risk scale. CDM, chronic disease management; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; PRO, urine protein; UA, serum uric acid.

Taiwan (HR: 0.99; 95% CI: 0.98 to 0.99). The findings of the above studies all indicate that with increases in age, risk of endpoint events of patients with CKD declines. In terms of eGFR, GFR is an important indicator for judging CKD severity, and serves as the basis for CKD staging at present. Previous studies[29 30] have shown that lower eGFR is an independent risk factor for all-cause, cardiovascular death and progression to ESRD in patients with CKD. The results of the present study also showed that the lower the eGFR, the higher the risk of endpoint events in patients with CKD. Therefore, eGFR could be a strong predictor of CKD prognosis. In terms of Hb, previous studies[31 32] have suggested that patients with CKD stages 3–5 with low Hb levels have an increased risk of death, ESRD and CVD. Furthermore, study results[33] have shown that patients with CKD with anaemia have about 1.3 times higher risk

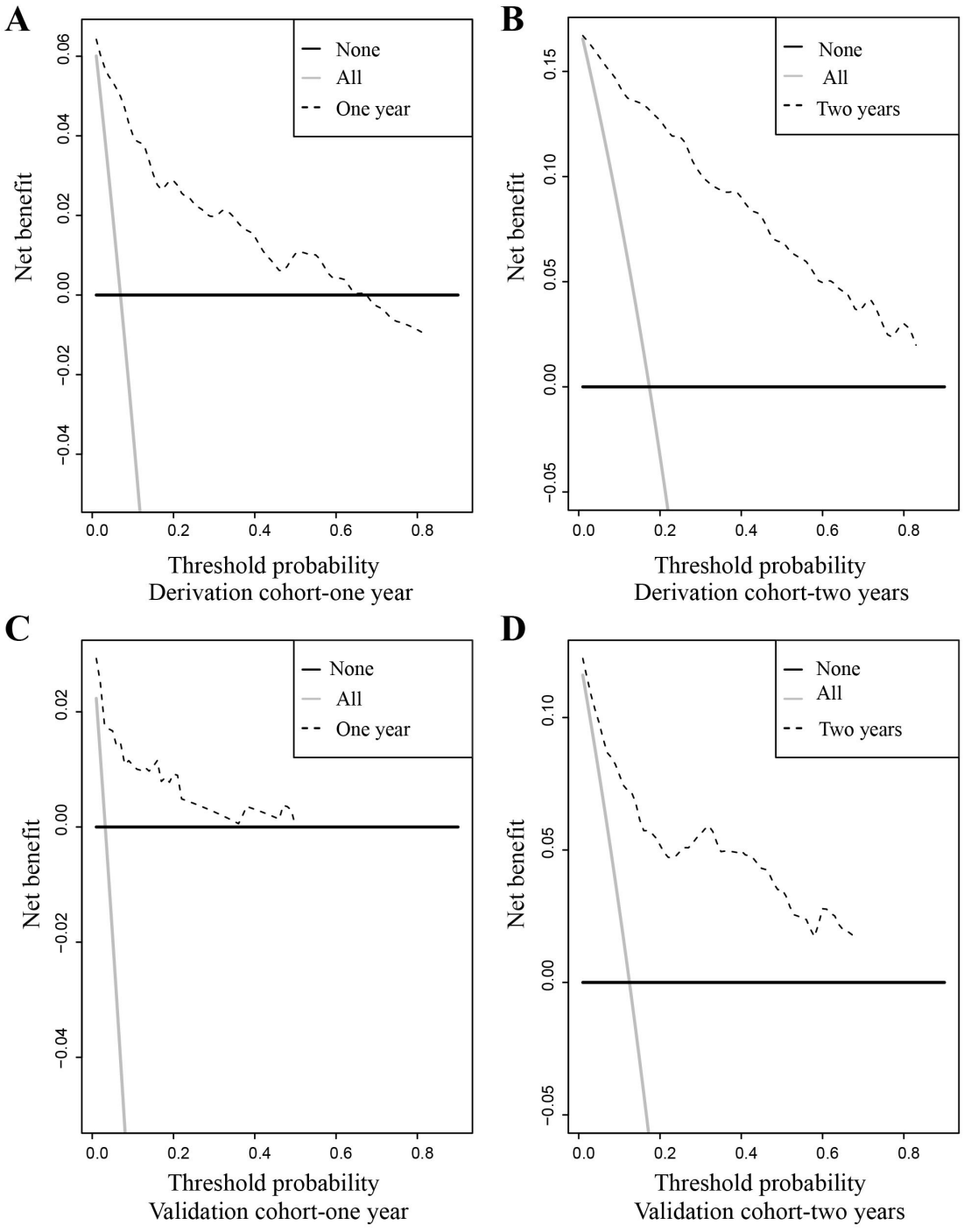

Figure 3 Decision curve for model B. (A) Derivation cohort, 1 year; (B) derivation cohort, 2 years; (C) validation cohort, 1 year; (D) validation cohort, 2 years. The horizontal line represents the net benefit of offering no intervention, assuming that none of the patients with CKD stages 3–5 would occur endpoint events; the slash line shows the net benefit of offering interventions to all patients, assuming that all patients with CKD stages 3–5 would occur endpoint events; the dashed line represents the net benefit of offering interventions based on the predictive nomogram. CKD, chronic kidney disease.

of developing RRT or death than those without anaemia. Therefore, Hb levels are a factor in the prognosis of patients with CKD stages 3–5. In terms of PRO, Marks *et al* followed up with 2289 patients with CKD stage 3 and 1044 patients with CKD stage 4, and found a strong correlation between increased proteinuria and both CKD progression and the occurrence of RRT.[34] Meanwhile, a retrospective cohort study[35] of 5586 patients with CKD by Methven *et al* showed that proteinuria was correlated with an increased risk of death in patients with CKD. Therefore, patients with CKD with higher proteinuria levels are more likely to progress to ESRD, and eventually undergo dialysis or die. This is consistent with the results of our study. In terms of UA, the results from a meta-analysis[36] showed that elevated UA levels were correlated with the risk of death in patients with CKD. Numerous studies[37–39]

have shown a correlation between elevated UA levels and increased risk of CKD progression. Therefore, elevated UA may be a predictor of poor prognosis in patients with CKD stages 3–5. In terms of CVD, a previous study[40] has shown that patients with ESRD have an increased risk of death due to CVD. Results from a cohort study[41] of 15 324 participants followed up for 14 years showed that a history of CVD was correlated with an increased risk of ESRD (RRT, catheter placement or kidney failure, and death). In many prediction models,[42 43] CVD history also serves as a predictor of CKD prognosis. In terms of DN, a previous study[28] has suggested that patients with DN have a faster eGFR decline rate and faster disease progression. At present, DN is the leading cause of ESRD in high-income countries, and even globally.[44 45] In Australia and New Zealand,[46] the number of patients undergoing RRT has increased 321% each year, and this increase is largely due to an increase in patients with DN. The results of a cohort study of 3682 patients[47] with renal insufficiency showed that if the patients had poor glycaemic control, the amount of time spent in CKD stage 3a would be 1.8 years shorter, and time in CKD stage 3b would be 1.4 years shorter. Therefore DN patients are more likely to reach ESRD than patients with other nephropathy.

Clinical prediction models have been applied to various diseases and medical environments, providing important clinical value for disease prevention and prediction of disease prognosis. For example, the Framingham Stroke Risk Score[48] and Framingham Cardiovascular Risk Score[49] are the most widely used stroke and cardiovascular risk assessment tool, and are used to predict the risk of stroke and CVD 10 years into the future. For breast cancer, the Nottingham Prognostic Index[50] has been used to predict the risk of recurrence and death in patients with breast cancer. In addition, the Acute Physiological and Chronic Health Assessment[51] score and the Simplified Acute Physiological Score[52] have been developed to predict mortality among hospitalised critically ill patients.

The prediction model in this study also has important clinical significance. Its predictors include CDM adherence, suggesting that the CDM intervention may help improve the prognosis of patients with CKD if patients have good adherence. However, the proportion of patients with good CDM adherence was low in this study. If we use this prediction model to show patients that good CDM adherence may improve disease progression, it may improve their treatment adherence, and then improve clinical efficacy, and thus reduce the risk of endpoint events. Of note, though, this study was a retrospective study, the CDM in this study is a relatively general definition, so there is no further evidence to confirm which CDM interventions (such as diet or medication) are more likely to bring better outcome benefits, and these also need to be refined in the design of future prospective studies, so as to get better answers and to better guide patients. Therefore, under the current circumstances, nephrology physicians still need to pay comprehensive attention to the patients' illness cognition, treatment adherence, diet, exercise and other conditions during follow-up, and try to correct and control risk factors that may lead to disease progression through CDM measures. Furthermore, the application of this prediction model could help doctors predict disease progression, so as to clarify treatment options and treatment goals. Additionally, this could also help with controlling the risk factors that aggravate disease progression in the prediction model, including promptly correcting anaemia, controlling UA and proteinuria, and preventing cardiovascular events, therefore delaying disease progression. Meantime, for patients with high risk of endpoint events, dialysis and transplantation-related instructions should be given in advance. Moreover, arteriovenous fistulas and peritoneal dialysis catheterisation should be planned and performed in advance to prepare for dialysis initiation. This could also improve patients' acceptance of their disease conditions; for patients with slow disease progression, we should look for corresponding risk and benefit factors, and corresponding therapeutic interventions should be given according to the risk factors.

This study does have several shortcomings. First, it was a single-centre retrospective cohort study, and many patients were excluded due to incomplete raw data or short follow-up time. This resulted in a small sample size and limited statistical power. Second, only some of the potential CKD progression risk factors were collected in this study. Some potential risk factors were excluded due to excessive missing data. In the future, we plan to collect more possible risk factors to improve the model. Third, due to patients' short follow-up times in the validation cohort, this study only predicted the likelihood of no endpoint events in patients with CKD stages 3–5 in the first and second year. In the future, we plan to follow up with patients in this cohort to verify the model's prognosis prediction for patients with CKD stages 3–5 in third and fifth year. Fourth, CDM adherence in this study was divided into good and poor based only on regular attendance at monthly health education. This is subjective, and medication adherence and diet management were not evaluated. In the future, we plan to formulate specific and objective evaluation criteria to assess CDM adherence based on patient feedback including metrics such as diet, exercise and other lifestyle indicators, disease cognition and medication adherence. Fifth, we established this prediction model based on patients' baseline variables, but patients' disease conditions and clinical characteristics were in flux. In the future, better methods are needed to develop a dynamic prediction model with time as a covariate. Sixth, the nomogram we established in this study was only based on this study's data; it has not been externally verified. Seventh, in this study, the time of blood draw and basic information collection may not be on the same day, which may bring some bias.

CONCLUSION

In this study, we developed a prediction model for the prognosis of CKD stages 3–5. The results showed that the risk of endpoint events in patients with CKD stages 3–5 was not only determined by the disease conditions themselves, but also the control of risk factors and CDM adherence. Applying the model to clinical practice may guide clinical decision-making, and improve interventions and patient prognosis.

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Contributors All the authors were involved in the study. MZ, L-ZF, FT, XL and YW designed the study. MZ, NL, X-LZ, YX and H-FC participated in the data collection. MZ, NL and YW analysed and interpreted the data. MZ and YW wrote the manuscript. YW is the guarantor of the manuscript. All authors read and approved the final manuscript for publication.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval All included patients provided written informed consent, and the study protocol was approved by the Ethics Committee at Guangdong Provincial Hospital of Chinese Medicine (ethical number: ZF2019-153-01).

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Data availability statement Data are available upon reasonable request. Original data are available on request by emailing the corresponding author, who will delete the personal identification information of patients.

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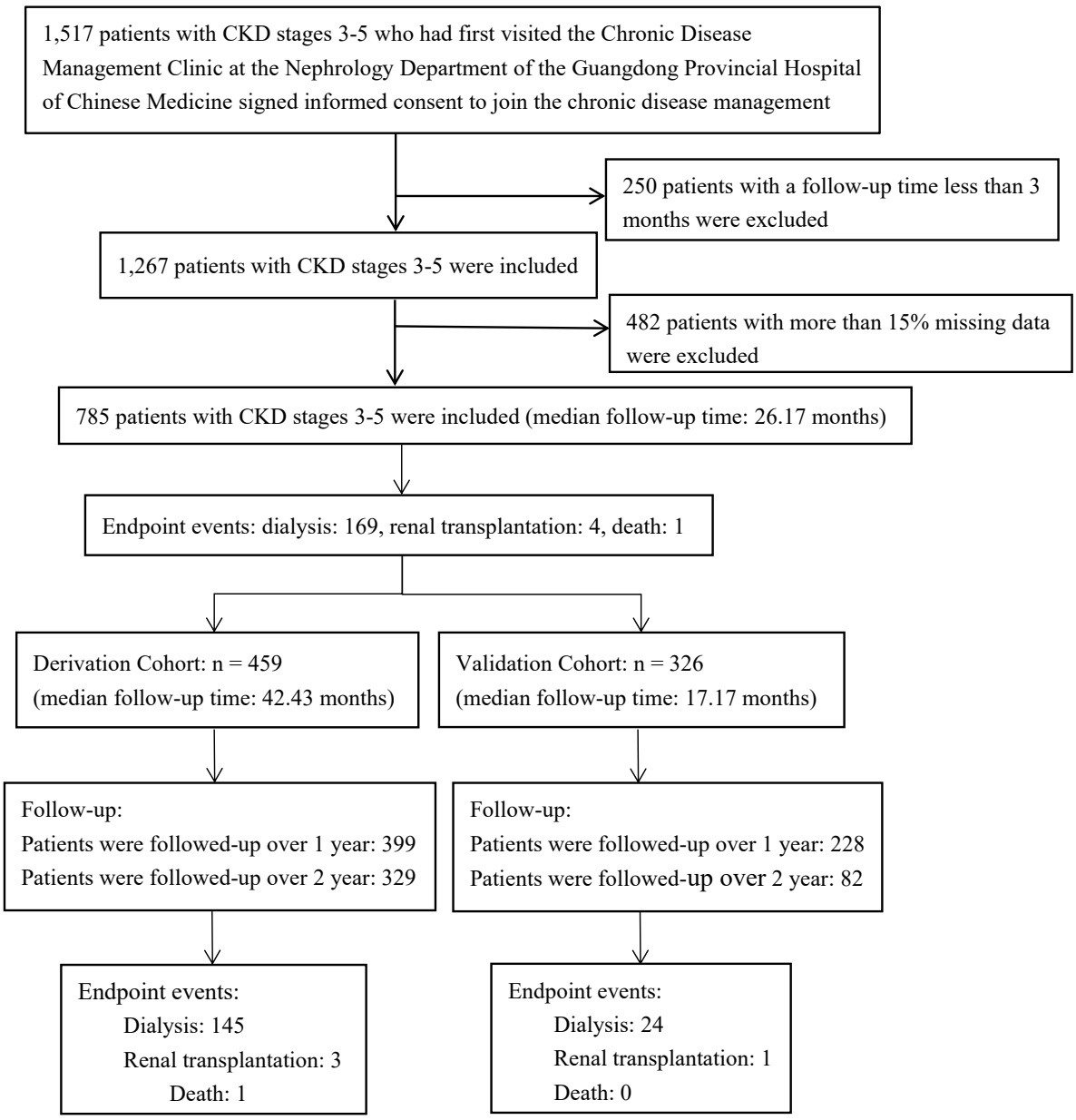

Figure S1 | The flowchart of this study.

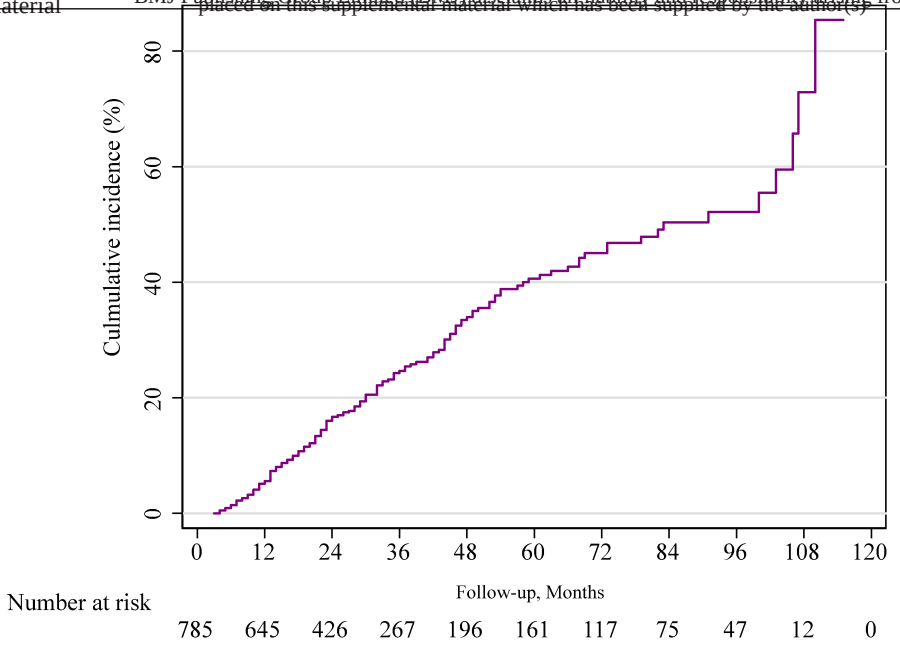

Figure S2 The cumulative incidence rate of endpoint events among patients with CKD stages 3-5 in the whole Cohort.

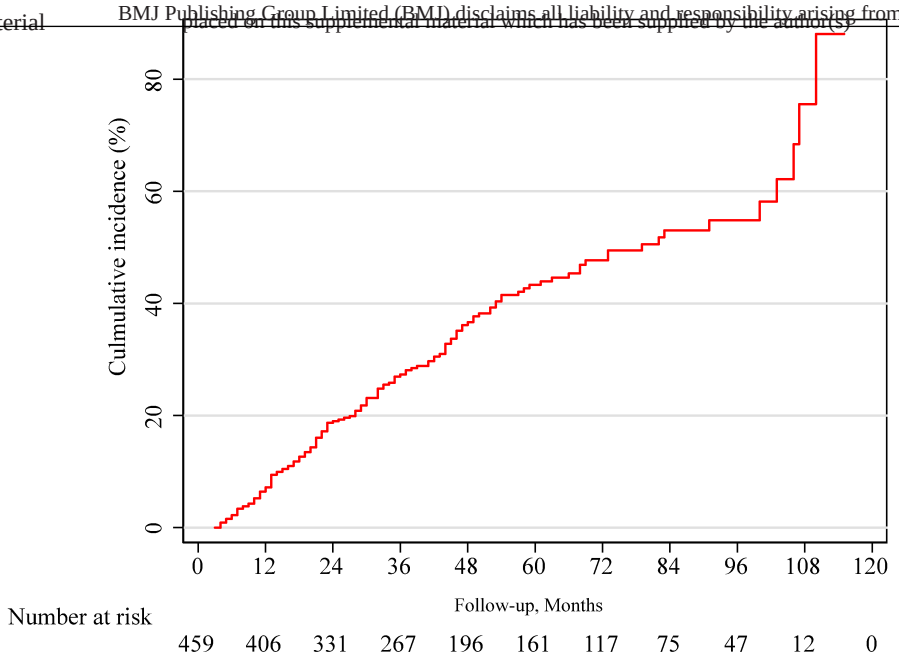

Figure S3 The cumulative incidence rate of endpoint events among patients with CKD stages 3-5 in the Derivation Cohort

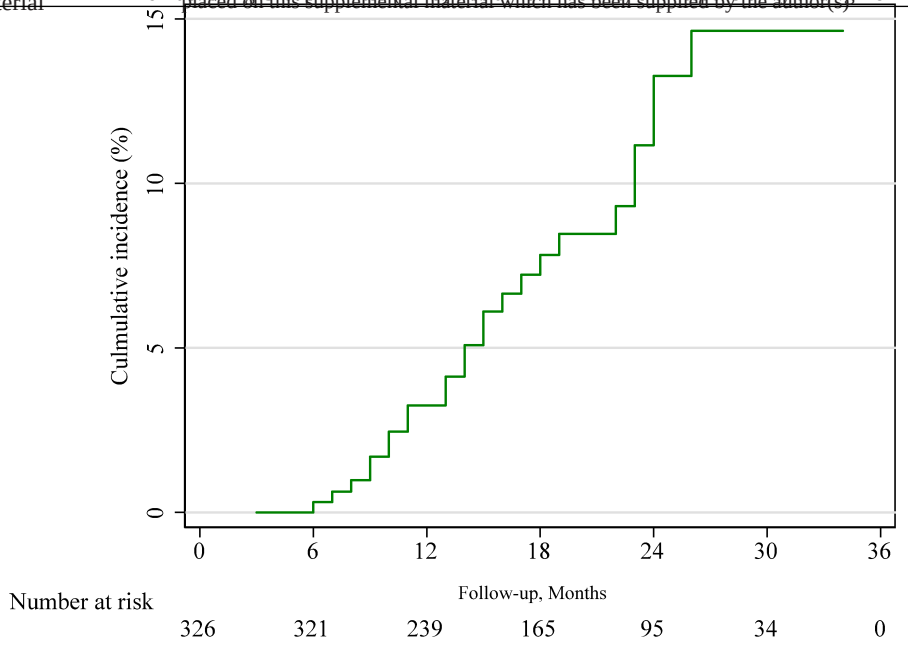

Figure S4 The cumulative incidence rate of endpoint events among patients with CKD stages 3-5 in the Validation Cohort

Table S1 Collinear analysis of potential risk factors.

Variables	Tolerance	VIF
CDM adherence	0.926	1.08
Age	0.78	1.282
Hb	0.716	1.397
Scr	0.182	5.489
eGFR	0.151	6.618
Urea	0.697	1.435
CKD Stage	0.141	7.093
UA	0.927	1.079
CO_2CP	0.815	1.227
BLD	0.85	1.177
PRO	0.706	1.417
Primary disease	0.81	1.234
Hypertension	0.573	1.745
Cardiovascular disease	0.867	1.154
Diuretics	0.847	1.181
ACEI/ARB	0.784	1.275
CCB	0.564	1.773
Alpha-blockers	0.813	1.23
Beta-blockers	0.763	1.311
Sodium bicarbonate	0.819	1.221

EPO	0.563	1.777
Polysaccharide-Iron Complex	0.565	1.768
Folic acid	0.705	1.418
Compound α-ketoacid Tablets	0.851	1.175
Calcium supplement	0.886	1.128
Chinese herbal decoction	0.98	1.021
Chinese patent medicines for dispelling turbidity	0.781	1.281

Abbreviations: CDM: chronic disease management; Hb: hemoglobin; Scr: serum creatinine; eGFR: estimated glomerular filtration rate; UA: serum uric acid; CO2CP: carbon dioxide combining power; BLD: urine latent blood; PRO: urine protein; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers; CCB: calcium channel entry blockers; EPO: erythropoietin

Table S2 Models' net reclassification improvement and integrated discrimination improvement

	Year	**NRI (95% CI)**	**IDI (95% CI)**	***P* Value**
Model B vs. Model E	1	-0.359 (-0.683, 0.037)	-0.071 (-0.128, -0.021)	<0.001
	2	-0.332 (-0.568, -0.035)	-0.067 (-0.110, -0.014)	<0.001

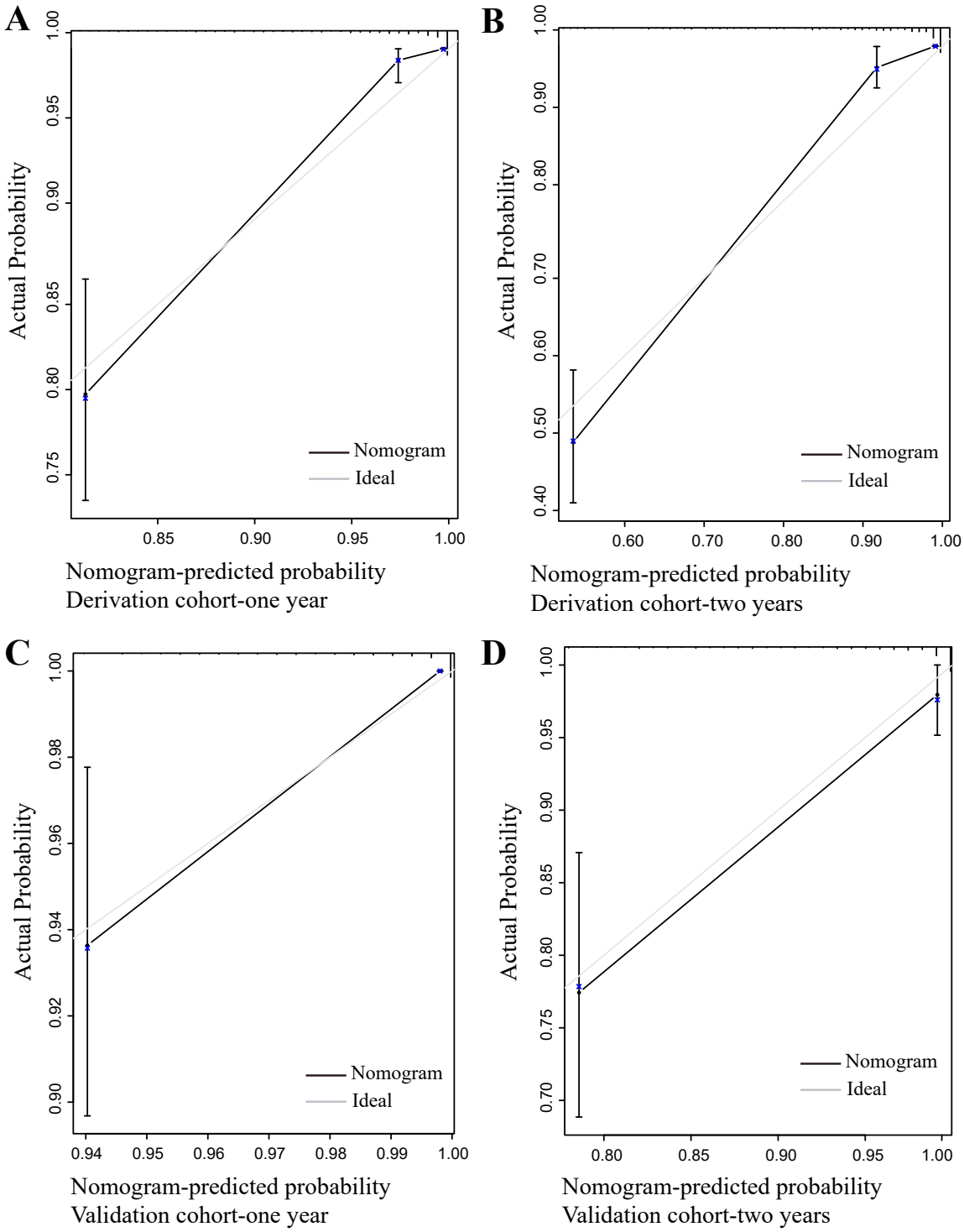

Figure S5 Calibration curves for Model A

(A) Derivation cohort, 1 year, (B) Derivation cohort, 2 years, (C) Validation cohort, 1 year, (D) Validation cohort, 2 years

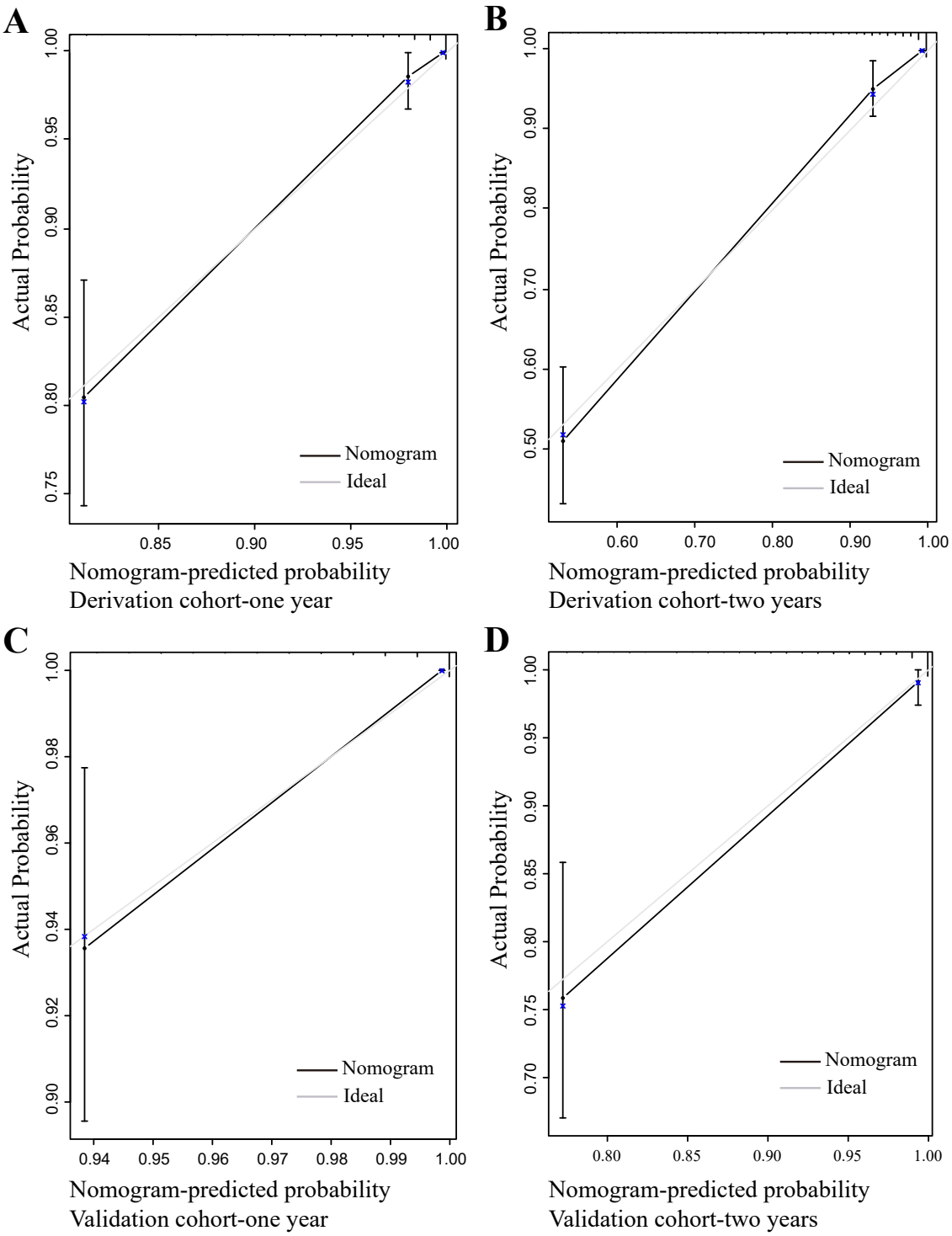

Figure S6 Calibration curves for Model C

(A) Derivation cohort, 1 year, (B) Derivation cohort, 2 years, (C) Validation cohort, 1 year, (D) Validation cohort, 2 years

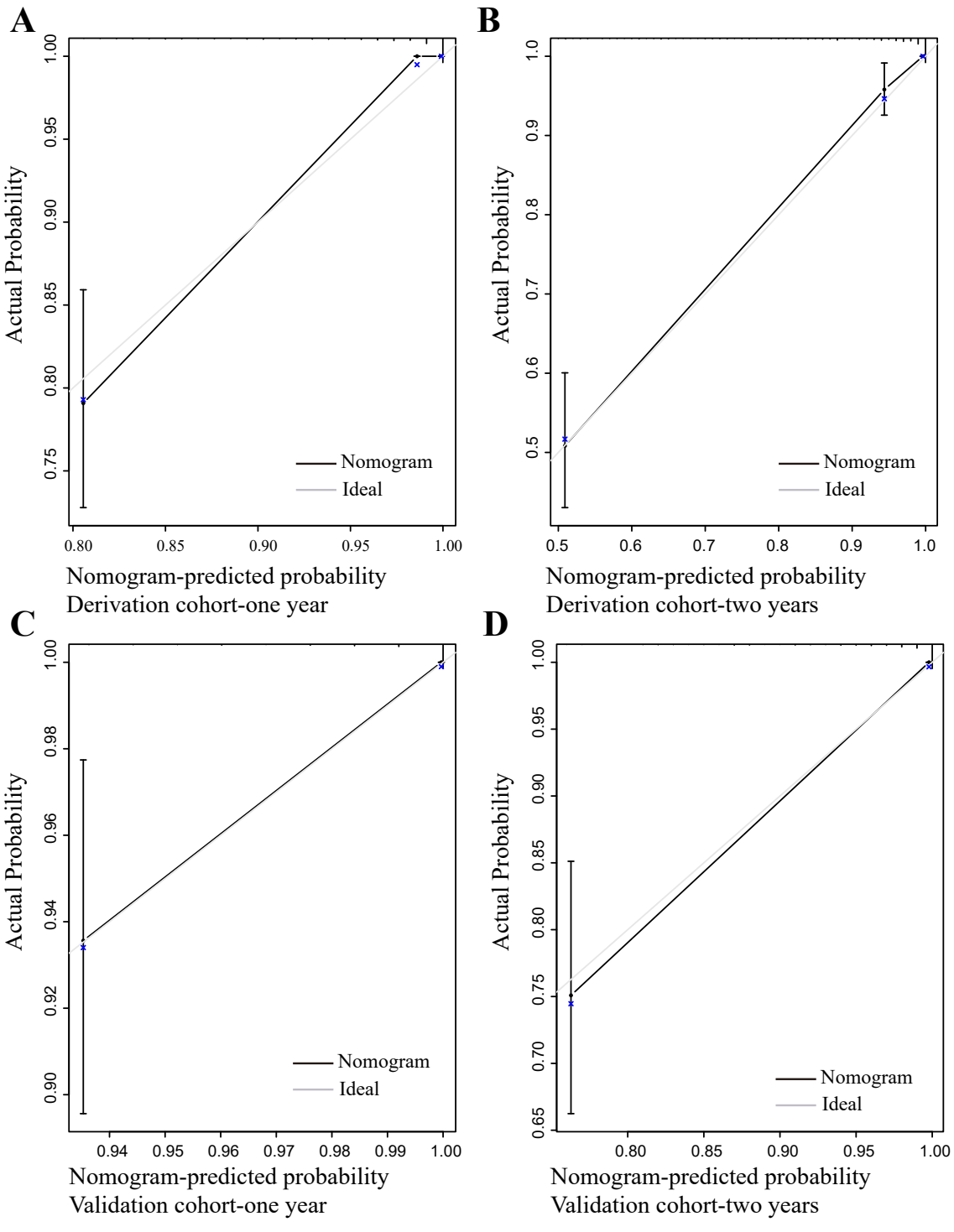

Figure S7 Calibration curves for Model D

(A) Derivation cohort, 1 year, (B) Derivation cohort, 2 years, (C) Validation cohort, 1 year, (D) Validation cohort, 2 years

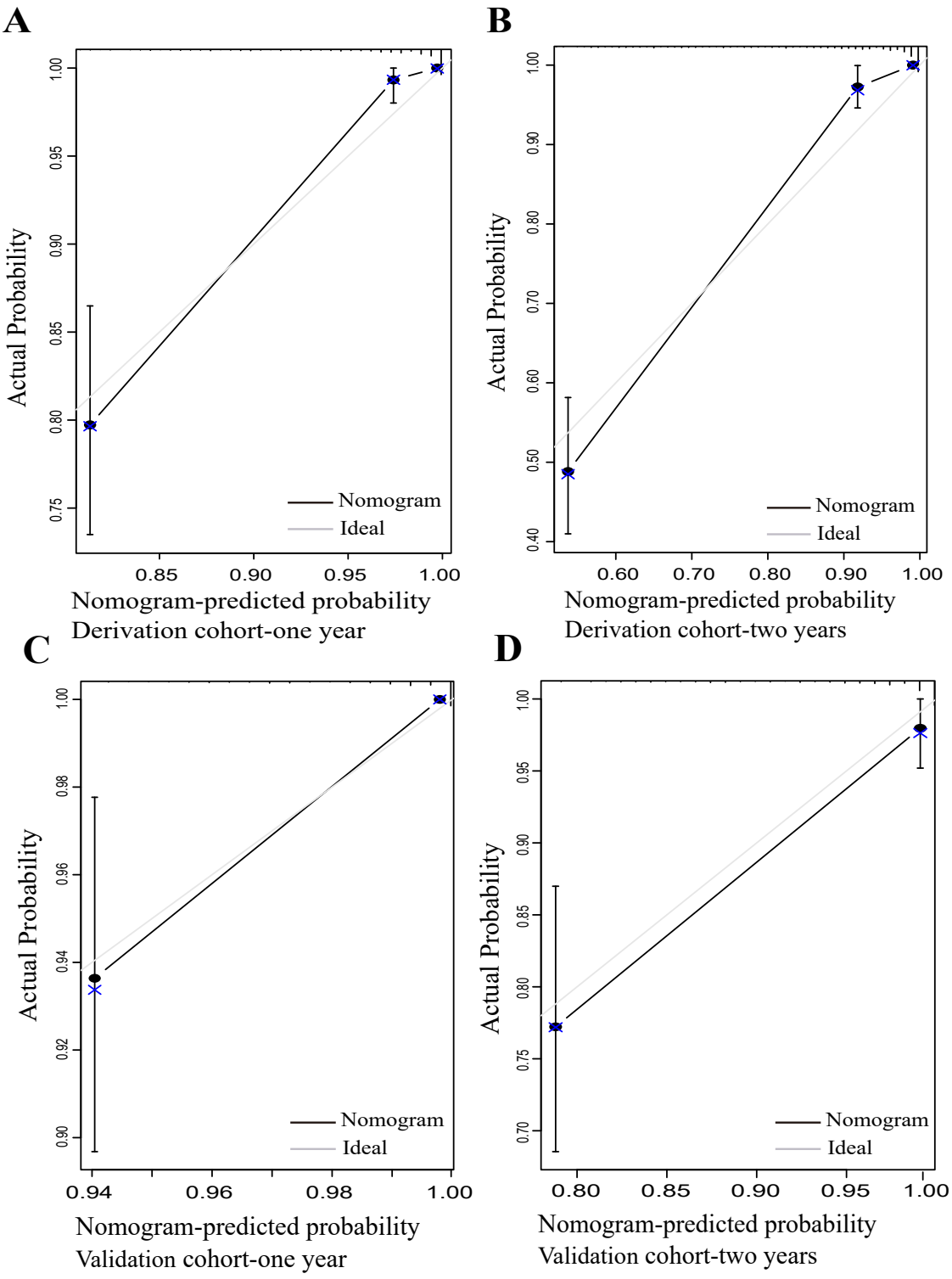

Figure S8 Calibration curves for Model E

(A) Derivation cohort, 1 year, (B) Derivation cohort, 2 years, (C) Validation cohort, 1 year, (D) Validation cohort, 2 years

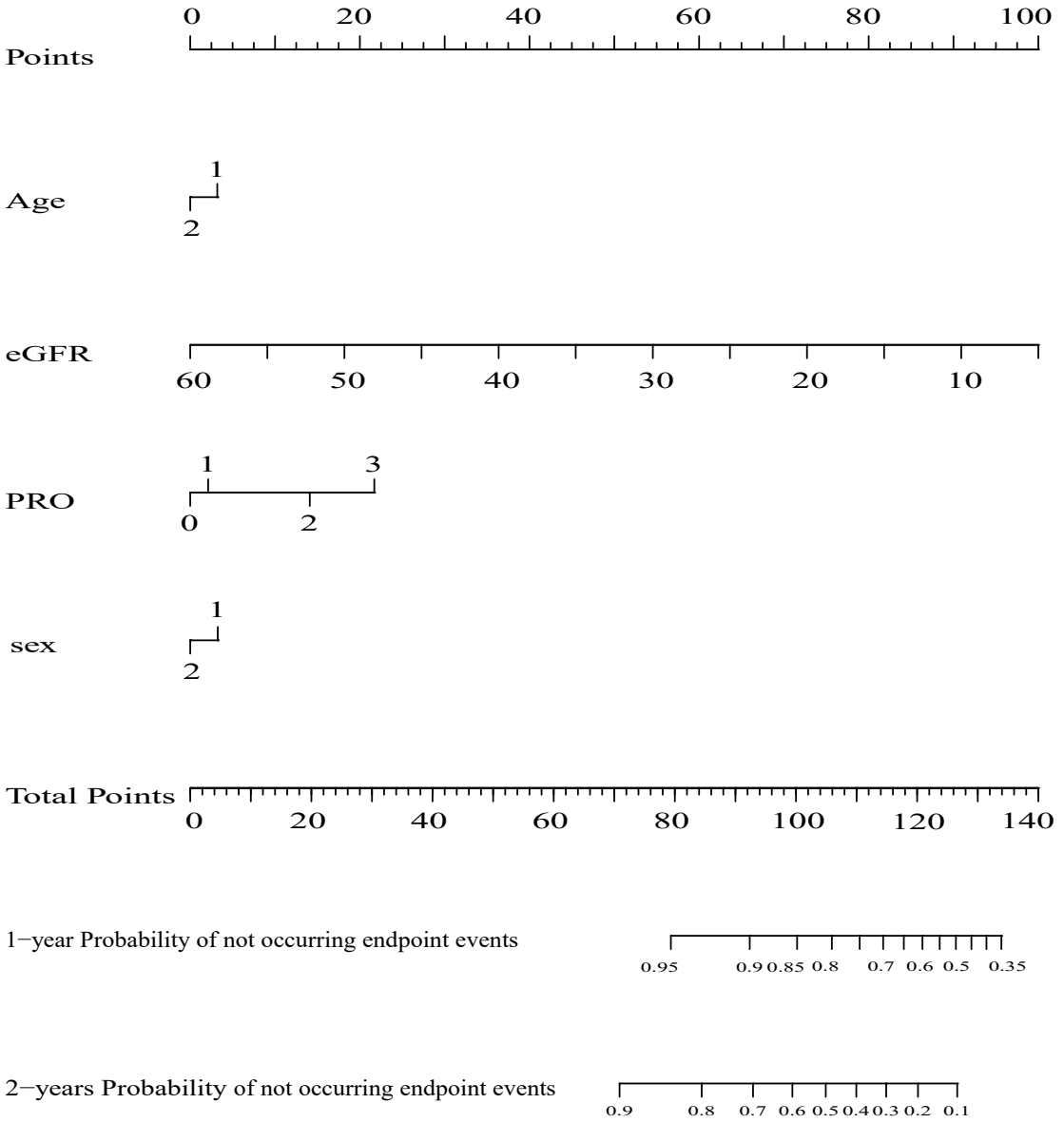

Figure S9 Nomogram for Model E

eGFR: estimated glomerular; PRO: urine protein.
Instructions: locate age on the corresponding axis. Draw a line straight down to the axis to calculate how many points toward the probability of not occurring endpoint events in the patients at different ages. Repeat the courses for eGFR, PRO, sex. Add all points obtained from the previous steps, and locate the final summation on the total score axis. The probability of not occurring endpoint events corresponds to the summation score on the risk scale.