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Development of model to predict end-stage renal disease after coronary artery bypass grafting

The ACHE score

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Abstract

Because end-stage renal disease (ESRD) increases the risks of morbidity and mortality, early detection and prevention of ESRD is a critical issue in clinical practice. However, no ESRD-prediction models have been developed or validated in patients undergoing coronary artery bypass grafting (CABG).

This is a retrospective multicenter cohort study, recruited between January 2004 and December 2015. A cohort of 3089 patients undergoing CABG in two tertiary referral centers was analyzed to derive a risk-prediction model. The model was developed using Cox proportional hazard analyses, and its performance was assessed using C-statistics. The model was externally validated in an independent cohort of 279 patients.

During the median follow-up of 6 years (maximum 13 years), ESRD occurred in 60 patients (2.0%). Through stepwise selection multivariate analyses, the following three variables were finally included in the *E*SRD-prediction model: postoperative *A*cute kidney injury, underlying *C*hronic kidney disease, and the number of anti*H*ypertensive drugs (ACHE score). This model showed good performance in predicting ESRD with the following C-statistics: 0.89 (95% confidence interval [CI] 0.84–0.94) in the development cohort and 0.82 (95% CI 0.60–1.00) in the external validation cohort.

The present ESRD-prediction model may be applicable to patients undergoing CABG, with the advantage of simplicity and preciseness.

Abbreviations: AKI = acute kidney injury, CABG = coronary artery bypass grafting, CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, HR = hazard ratio.

Keywords: acute kidney injury, chronic kidney disease, coronary artery bypass grafting, endstage renal disease, hypertension

1. Introduction

End-stage renal disease (ESRD) increases the risks of morbidity and mortality.[1] ESRD is a contributor to high medical costs, poor quality of life, and several comorbidities including ischemic heart disease, stroke, infection, and frailty.[2–5] More than two million patients are being treated for ESRD worldwide, and the prevalence is expected to rise sharply in the next decade despite the fact that patients with ESRD are receiving increasingly more attention because of worsening outcomes.[1,6] When kidney function falls, kidney transplantation confers survival advantages over dialysis[7]; however, accessibility to transplantation is limited because of donor scarcity. Although dialysis successfully replaces kidney function, patients frequently encounter various complications and high mortality even under dialysis.[1,6] Therefore, early detection and prevention of ESRD are urgent issues.[1,8] However, there are no validated models with which to predict ESRD, although models such as the Cleveland Clinic score and the Society of Thoracic Surgery risk score had been proposed to predict acute kidney injury (AKI) after cardiac surgery.[9,10]

Coronary artery bypass grafting (CABG) is one of the most commonly performed major surgeries for the treatment of severe multivessel coronary artery disease.[11] Nevertheless, the overall outcomes of CABG are not perfect with regard to postsurgical morbidity and mortality.[12] This issue may be particularly problematic for patients with kidney dysfunction including AKI, chronic kidney disease (CKD), and ESRD.[12,13] Although AKI, CKD, and ESRD have relationships within a continuum of disease processes, ESRD is more closely related to mortality than are the others.[14] If patients undergoing CABG develop postoperative ESRD, the mortality risk increases to 25%.[15]

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Possible explanations for the higher mortality among patients with ESRD include accelerated atherosclerosis, anemia, cardiomyopathy, and repeated events of ischemic heart disease.[16] Therefore, it is essential to predict the risk of ESRD after CABG. To the best of our knowledge, no ESRD-prediction models have been developed or evaluated in patients undergoing CABG. This study was performed to derive the most effective and clinically applicable model and validate it in an independent cohort.

2. Materials and methods

2.1. Patients and study design

The study design was approved by the institutional review boards of all involved centers (nos. H-1702–050–831, B-1702/384–103, and 20170531/10–2017–1/071) and complied with the Declaration of Helsinki. The study was performed in two consecutive parts. In part 1, we conducted a retrospective multicenter cohort study involving 3089 patients who comprised the development and internal validation cohort. Patients who had undergone CABG in two tertiary referral centers (Seoul National University Hospital and Seoul National University Bundang Hospital) were recruited from January 2004 to December 2015. We excluded patients if they had undergone renal replacement therapy before surgery or had ESRD (n = 63), had undergone concomitant valve surgery or redo-CABG (n = 10), or were ≤18 years of age (n = 1). Finally, the cohort comprised of 3015 patients.

Baseline clinical preoperative, intraoperative, and postoperative data were recorded, including age; sex; body mass index; systolic and diastolic blood pressures; current smoking status; hypertension; diabetes mellitus; history of myocardial infarction, stroke, or peripheral vascular disease; medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, and others; contrast use within 1 week before surgery; perioperative use of an intra-aortic balloon pump or cardiopulmonary bypass; and total surgery time. The number of antihypertensive drugs used was categorized into 0, 1–2, and ≥3. The left ventricular ejection fraction was determined by Simpson's modified biplane method from the apical two- and four-chamber views on echocardiography. Laboratory data, such as the serum creatinine, albumin, cholesterol, hemoglobin, and white blood cell count, were obtained. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Eq.[17] AKI was defined as an increase in the serum creatinine level to ≥0.3 mg/dL or ≥1.5 times baseline within 48 h after surgery and was classified according to the guideline proposed by Kidney Disease Improving Global Outcomes[18] as follows: stage 1, an increase in the serum creatinine level to ≥0.3 mg/dL or 1.5–1.9 times baseline; stage 2, an increase in the serum creatinine level of 2.0–2.9 times baseline; and stage 3, an increase in the serum creatinine level to 4.0 mg/dL or 3.0 times baseline. The postoperative serum creatinine level recorded was the highest level measured within a 48-hour timeframe. CKD was defined as an eGFR of <60 mL/min/1.73 m^2 for 3 months and classified as G3a (45–60 mL/min/1.73 m^2), G3b (30–45 mL/min/1.73 m^2), or G4–5 (<30 mL/min/1.73 m^2) according to the guideline.[19]

We developed a prediction model using the above cohort and validated its performance in both the internal cohort and separate dataset (part 2), wherein a total of 279 patients undergoing CABG were recruited from an independent tertiary referral center (Boramae Medical Center). Patient selection flow charts for the development (internal) and external cohorts are shown in Fig. S1, Supplemental Content, http://links.lww.com/MD/D4).

2.2. Outcome variables

The primary outcome was ESRD. The onset of ESRD was defined as the initiation of renal replacement therapy or kidney transplantation due to failed kidney function after CABG. Patients were followed until April 2017 or death. The information on ESRD was obtained from the Korean Renal Registry, which is a database of all patients who have undergone renal replacement therapy in Korea.[20]

The secondary outcome was all-cause mortality. The data on death were obtained from the National Database of Statistics Korea.

2.3. Statistical analysis

The data are described as mean with standard deviation for continuous variables and as proportion for categorical variables. We compared the baseline characteristics using chi-square test, one-way ANOVA, and Fisher's exact test, as appropriate. Kaplan–Meier curves were drawn to compare the risks between groups. A Cox proportional hazard ratio (HR) model was used to estimate the HR of ESRD risk. Restricted cubic splines were used to check the assumption of proportional linearity between variables and their log hazards. Variables with a P value of $<.2$ in the univariate model were applied to multivariate stepwise analyses. To facilitate the calculation of risks, we converted estimates of log HRs (coefficients) to integer scores, which were calculated as (rounding of the coefficients × 100)/(sum of the largest coefficient in each predictor) to obtain a total score of 100. The performance of the model was assessed with respect to calibration and discrimination using development (internal) and external validation cohorts. Discrimination ability was evaluated with Harrell's C-statistics from the jackknife method in the somersd package of STATA (StataCorp, College Station, TX, USA).[21,22] Calibration was assessed by plotting the predicted 5-year risk of ESRD against the observed risk with 95% confidence intervals (CIs) for the quartiles of the predicted value.

As a sensitivity analysis, we have applied a formal competing-risks (Fine-Gray) proportional HR regression model, which estimated the cumulative incidence of an ESRD or death before ESRD by considering the sub-distribution hazard. All tests were two-sided and performed at the .05 significance level. The analyses were conducted with the statistical software packages (SPSS [version 22; IBM Corp., Armonk, NY, USA], SAS [version 9.3; SAS Institute, Cary, NC, USA], and STATA [version 12]).

3. Results

3.1. Baseline characteristics

All baseline characteristics are presented in Table 1. Of 3015 patients, 2222 (73.7%) were male and 1322 (43.8%) had diabetes mellitus. The mean baseline eGFR was 70.1 ± 20.17 mL/min/1.73 m^2. Postoperative AKI occurred in 798 patients (26.5%), including stage 1 in 23.8% and stages 2 and 3 in 2.7%. Preoperative CKD was identified in 890 patients (29.5%). Among them, 303 patients developed postoperative AKI. The median follow-up duration was 6.1 years (interquartile range, 2.9–9.2 years; maximum, 13.3 years).

Table 1

Baseline characteristics of patients according to the presence of acute kidney injury and chronic kidney disease.

	Total (n = 3015)	Non-AKI/non-CKD (n = 1630)	AKI/non-CKD (n = 495)	Non-AKI/CKD (n = 587)	AKI/CKD (n = 303)	Global *P*[*]
Age (years)	65.5 ± 9.84	63.1 ± 9.92	64.5 ± 9.67	70.5 ± 7.72	70.6 ± 7.83	< .001
Male (%)	73.7	76.6	78.4	63.0	71.0	< .001
Body mass index (kg/m^2)	24.3 ± 3.10	24.3 ± 2.40	24.7 ± 3.50	24.2 ± 3.21	24.3 ± 3.00	.005
Systolic blood pressure (mm Hg)	126.5 ± 20.64	126.2 ± 19.35	127.1 ± 22.59	125.7 ± 21.19	128.6 ± 22.81	< .001
Diastolic blood pressure (mm Hg)	73.3 ± 12.42	74.3 ± 11.79	73.3 ± 13.72	71.2 ± 12.18	72.0 ± 13.30	.002
Smoking (%)	31.8	33.6	33.9	25.9	30.0	.004
Baseline renal function						
eGFR (mL/min/1.73 m^2)	70.1 ± 20.17	80.3 ± 13.21	79.3 ± 14.04	47.3 ± 10.61	43.6 ± 12.66	< .001
Serum creatinine (mg/dL)	1.1 ± 0.39	0.9 ± 0.17	0.9 ± 0.19	1.4 ± 0.44	1.6 ± 0.56	< .001
LV ejection fraction (%)	54.8 ± 12.26	55.9 ± 11.51	53.9 ± 12.94	54.4 ± 12.71	51.3 ± 13.38	< .001
Comorbidities (%)						
Hypertension	57.5	55.0	57.0	62.2	63.0	.004
Diabetes mellitus	43.8	38.3	44.4	49.9	61.1	< .001
History of Myocardial infarction	9.2	8.2	12.9	9.0	9.2	.016
History of stroke	19.6	16.9	18.8	23.5	28.1	< .001
Peripheral vascular disease	6.5	4.7	6.3	8.7	12.2	< .001
Medication (%)						
ACE inhibitor or ARB	35.9	34.2	34.5	38.7	41.6	.035
Beta-blocker	38.3	39.6	33.3	38.8	38.3	.096
Calcium channel blocker	17.8	15.6	19.2	19.8	23.4	.003
Diuretics	16.4	11.6	17.0	22.3	30.0	< .001
Others	0.9	0.2	0.8	1.5	3.3	< .001
No. of antihypertensive drugs						< .001
0	35.4	36.5	38.0	32.0	31.4	
1–2	53.8	55.4	52.9	53.0	48.5	
≥3	10.8	8.1	9.1	15.0	20.1	
Contrast use before surgery (%)	45.7	50.1	42.2	40.0	38.9	< .001
Cardiopulmonary bypass (%)	16.5	11.0	30.5	14.5	26.4	< .001
Intra-aortic balloon pump (%)	9.1	5.1	15.4	10.2	18.5	< .001
Total surgery time (min)	345.3 ± 105.39	338.8 ± 93.72	365.7 ± 116.41	335.1 ± 116.86	366.3 ± 115.12	< .001
Laboratory findings						
Hemoglobin (g/dL)	12.5 ± 2.10	13.0 ± 1.96	12.6 ± 2.15	11.8 ± 2.12	11.4 ± 1.85	.009
White blood cell (×10^3/μL)	7.8 ± 3.13	7.7 ± 2.98	8.0 ± 3.59	7.9 ± 3.08	8.1 ± 3.15	.118
Albumin (g/dL)	3.8 ± 0.64	3.9 ± 0.61	3.8 ± 0.61	3.7 ± 0.69	3.5 ± 0.66	< .001
Cholesterol (mg/dL)	149.5 ± 44.20	152.5 ± 43.62	150.7 ± 46.13	143.3 ± 43.91	143.1 ± 42.97	.703

Data are presented as the proportion or means ± standard deviations.

ACE = angiotensin-converting enzyme, AKI = acute kidney injury, ARB = angiotensin II receptor blocker, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, LV = left ventricular.

[*] Values indicate the comparison between four groups.

3.2. Risk factors for ESRD

ESRD occurred in 60 patients (2.0%) and 5 patients (1.8%) in the development cohort and the external validation cohort, respectively. Estimation of the ESRD risk of each variable showed that the following were significantly associated with the risk: diabetes mellitus, a history of cardiovascular disease (sum of myocardial infarction, stroke, and peripheral vascular disease), postoperative AKI, underlying CKD, the number of antihypertensive drugs, the use of cardiopulmonary bypass, total surgery time, hemoglobin level, albumin level, and left ventricular ejection fraction (Table 2). After stepwise selection, the following three variables were significant: postoperative AKI, underlying CKD, and the number of antihypertensive drugs.

Next, we re-analyzed the ESRD risk according to the three above-mentioned factors. The proportions of ESRD were as follows: non-AKI/non-CKD group, 0.4%; AKI/non-CKD group, 1.2%; non-AKI/CKD group, 3.4%; and AKI/CKD group, 9.2% (Table 3). The incidence rates of ESRD were 0.6 per 1000 person-years in the non-AKI/non-CKD group, 1.7 in the AKI/non-CKD group, 5.8 in the non-AKI/CKD group, and 19.4 in the AKI/CKD group. Figure 1 shows the cumulative risk curves of ESRD. As shown in Table 3, both AKI (hazard ratio [HR] 3.2, 95% CI 1.01–9.80) and CKD (HR 13.8, 95% CI 5.36–35.44) were associated with the risk of ESRD. Particularly, the extent to which AKI increased the risk of ESRD was greater in the CKD group (HR 3.4, 95% CI 1.91–6.04) than in the non-CKD group (HR 2.9, 95% CI 0.95–9.16).

Figure 2 shows the risk curves of ESRD according to the stages of AKI or CKD. The ESRD risk increased with advancing stages, especially in stage 3 AKI (HR 6.59, 95% CI 2.80–15.52) and grades 4 to 5 CKD (HR 54.2, 95% CI 26.21–112.22).

The risk of ESRD was higher in patients using ≥3 of antihypertensive drugs (HR 2.7, 95% CI 1.34–5.62) than in those using no antihypertensive drugs. The risks were similar between patients using no antihypertensive drugs and 1–2 of antihypertensive drugs (HR 1.3, 95% CI 0.66–2.54) (Fig. 3).

3.3. Development of prediction model

Collectively, three variables (AKI, CKD, and the number of antihypertensive drugs) were included in the 5-year ESRD-prediction model. The Cox model provided the estimated probability of failure for the 5-year prediction of ESRD. This

Table 2

Cox proportional hazards regression results for the risk of end-stage renal disease.

	Unadjusted		Adjusted	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Acute kidney injury*				
None	1		1	
Stage 1	2.73 (1.56–4.78)	< .001	2.04 (1.16–3.61)	.013
Stage 2	5.21 (1.58–17.23)	.007	3.63 (1.08–12.25)	.038
Stage 3	43.29 (19.56–95.82)	< .001	6.59 (2.80–15.52)	< .001
Chronic kidney disease†				
None	1		1	
G3a	2.89 (1.22–6.87)	.016	2.75 (1.16–6.54)	.022
G3b	12.96 (5.70–29.46)	< .001	10.44 (4.54–24.05)	< .001
G4–5	83.56 (42.08–165.91)	< .001	54.23 (26.21–112.22)	< .001
Age	1.01 (0.98–1.04)	.463		
Male	1.04 (0.59–1.85)	.882		
Body mass index	0.99 (0.91–1.08)	.884		
Systolic blood pressure	1.02 (1.01–1.03)	< .001		
Diastolic blood pressure	1.03 (1.01–1.05)	.015		
Smoking	1.05 (0.61–1.80)	.872		
Comorbidities				
Hypertension	3.65 (1.90–7.03)	< .001		
Diabetes mellitus	2.19 (1.30–3.70)	.004		
History of vascular diseases	1.87 (1.12–3.10)	.016		
No. of antihypertensive drugs				
0	1		1	
1–2	1.43 (0.74–2.77)	.290	1.30 (0.66–2.54)	.448
≥3	5.63 (2.80–11.32)	< .001	2.74 (1.34–5.62)	.005
ACE inhibitor or ARB	3.39 (2.01–5.74)	< .001		
Beta-blocker	1.27 (0.76–2.11)	.356		
Calcium channel blocker	1.91 (1.09–3.35)	.024		
Diuretics	3.47 (2.06–5.84)	< .001		
Contrast use before surgery	1.07 (0.64–1.80)	.798		
Use of cardiopulmonary bypass	0.43 (0.05–1.59)	.118		
Use of intra-aortic balloon pump	1.43 (0.65–3.14)	.375		
Total surgery time	1.00 (1.00–1.00)	.199		
Anemia	0.32 (0.18–0.58)	< .001		
Serum albumin level (≥3.5 g/dL vs <3.5 g/dL)	0.53 (0.32–0.88)	.014		
Cholesterol level	1.01 (1.00–1.01)	.06		
Left ventricular ejection fraction	1.00 (0.97–1.01)	.195		

The number of antihypertensive drugs used was categorized into 0, 1–2, and ≥3. The antihypertensive drugs include medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, and others.

ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker, CI = confidence interval, HR = hazard ratio.

* Acute kidney injury stage 1 is defined as an increased in serum creatinine of 0.3 mg/dL or more or 1.5–1.9 times baseline; stage 2, an increased in serum creatinine of 2.0–2.9 times baseline; stage 3, an increased in serum creatinine to 4.0 mg/dL or 3.0 times baseline.

† Chronic kidney disease is defined as an eGFR below 60 mL/min/1.73 m^2 for 3 months; G3a, eGFR 45 to <60 mL/min/1.73 m^2; G3b, eGFR 30 to <45 mL/min/1.73 m^2; G4–5, eGFR <30 mL/min/1.73 m^2.

Table 3

Risk of end-stage renal disease according to the presence of acute kidney injury and chronic kidney disease.

			Univariate		Multivariate*	
	Patients, n (%)	Events, n (%)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Non-AKI/non-CKD	1630 (54.1)	6 (0.4)	1 (reference)		1 (reference)	
AKI/non-CKD	495 (16.4)	6 (1.2)	2.99 (0.96–9.28)	.058	3.15 (1.01–9.80)	.047
Non-AKI/CKD	587 (19.5)	20 (3.4)	9.80 (3.94–24.41)	< .001	13.78 (5.36–35.44)	< .001
AKI/CKD	303 (10.0)	28 (9.2)	33.17 (13.72–80.18)	< .001	36.82 (14.61–92.80)	< .001

AKI = acute kidney injury, CI = confidence interval, CKD = chronic kidney disease, HR = hazard ratio.

The AKI/non-CKD group, the non-AKI/CKD group, and the AKI/CKD group were each compared with the non-AKI/non-CKD group (a reference group) using a single Cox proportional hazard ratio (HR) model.

* Adjusted for age, gender, body mass index, systolic blood pressure, diastolic blood pressure, current smoking status, hypertension, diabetes mellitus, history of myocardial infarction, stroke and peripheral vascular disease, medications such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, and others, contrast use within 1 week before surgery, perioperative use of intra-aortic balloon pump or cardiopulmonary bypass, surgery time, left ventricular ejection fraction, and laboratory findings, such as albumin and cholesterol, hemoglobin level and white blood cells.

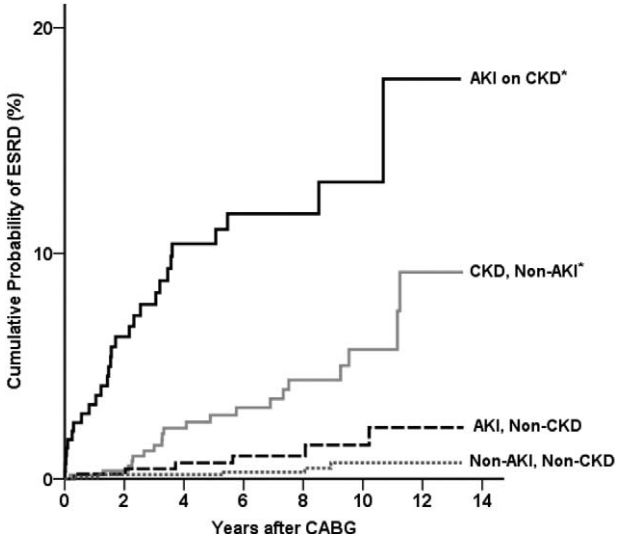


Figure 1. Kaplan–Meier curves for the cumulative probability of end-stage renal disease according to the presence of acute kidney injury and chronic kidney disease. *$P < .001$ compared with the non-AKI/non-CKD group by the log-rank test.

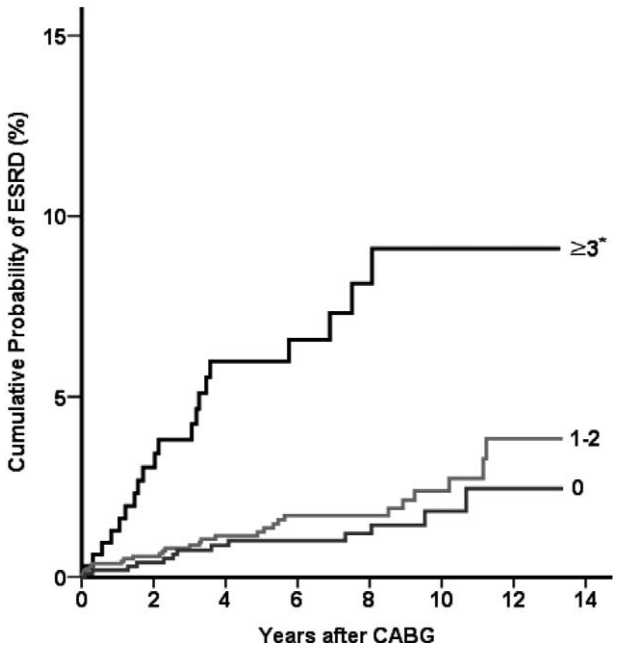


Figure 3. Kaplan–Meier curves for the cumulative probability of end-stage renal disease according to the number of antihypertensive drugs. *$P < 0.001$ compared with the group without the use of antihypertensive drugs by the log-rank test.

probability was equal to $P = 1 - .9978^{\mathrm{Exp}(X)}$ where $X = 0.7149 \times (1;$ stage 1 AKI$) + 1.2892 \times (1;$ stage 2 AKI$) + 1.8858 \times (1;$ stage 3 AKI$) + 1.0115 \times (1;$ grade 3a CKD$) + 2.3460 \times (1;$ grade 3b CKD$) + 3.9932 \times (1;$ grade 4–5 CKD$) + 0.2602 \times (1;$ 1–2 antihypertensive drugs$) + 1.0095 \times (1; \geq 3$ antihypertensive drugs). Based on this model, a nomogram was developed using three variables to allow the clinician to easily estimate the 5-year risk of ESRD (see Fig. S2, Supplemental Content, nomogram, http://links.lww.com/MD/D4). The original model was assessed in the development (internal) and external validation cohorts by evaluating the discrimination ability using C-statistics (see Table S1, Supplemental Content, http://links.lww.com/MD/D4, which shows regression coefficient and integer-based simplified score).

We developed an integer-based simplified scoring index (ACHE score; postoperative *A*cute kidney injury, underlying *C*hronic kidney disease, and the number of anti*H*ypertensive drugs in the *E*SRD-prediction model) to easily apply this ESRD-

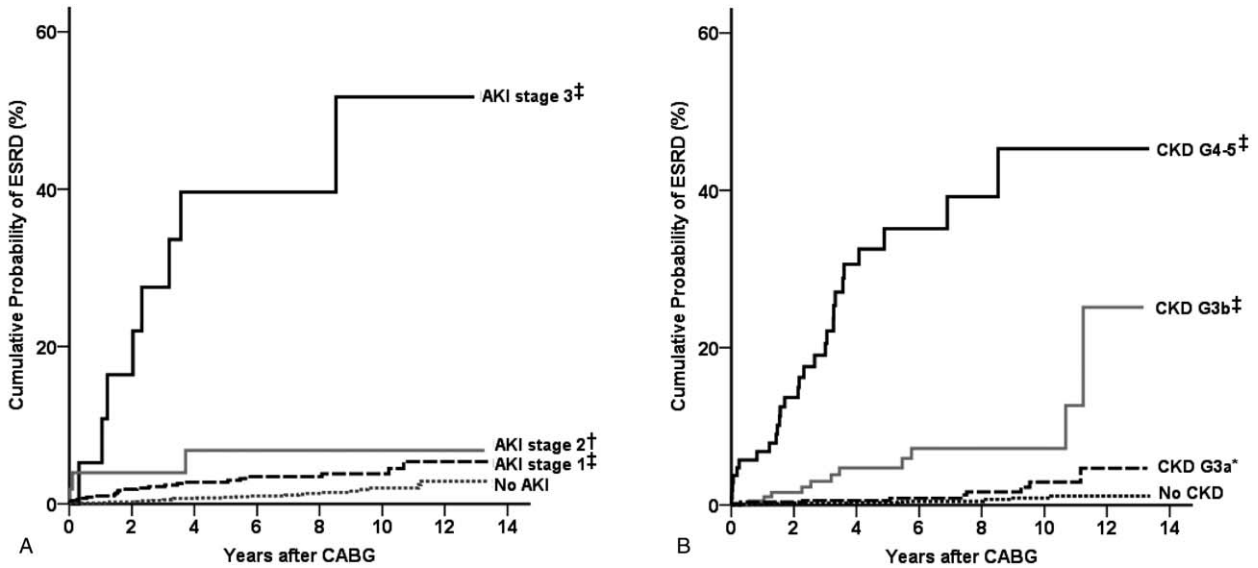
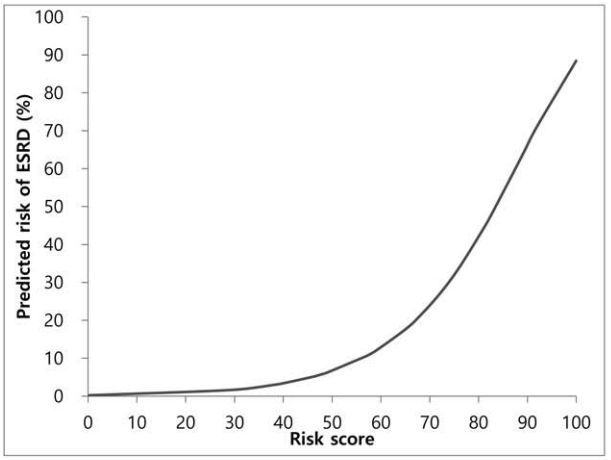


Figure 2. Kaplan–Meier curves for the cumulative probability of end-stage renal disease according to the classification of (A) acute kidney injury and (B) chronic kidney disease. *$P < .05$; †$P < .01$; ‡$P < .001$ compared with the non-AKI or non-CKD group by the log-rank test.

Acute kidney injury stage	Points
No AKI	0
1	10
2	19
3	27
Chronic kidney disease stage	
No CKD	0
G3a	15
G3b	34
G4-5	58
No. of hypertensive drugs	
0	0
1-2	4
≥3	15



Points assigned to values of each variable can be summed to obtain a patient's total score, which can be used to assess the predicted risk of ESRD.

Figure 4. Simplified scoring index of the developed end-stage renal disease-prediction model (ACHE score).

prediction model in clinical practice (Fig. 4). Points assigned to the values of each variable can be summed to obtain a patient's total score, which can be used to assess the predicted risk of ESRD. The C-statistics of simplified scoring model were 0.89 (95% CI 0.84–0.94) and 0.82 (95% CI 0.60–1.00) for the development and external validation cohorts, respectively. Regarding the calibration plots (Fig. 5), the predicted probability appeared to be almost consistent with the actual probability of ESRD, indicating good calibration. When patients were categorized by the quartile of scores, the risk curves of ESRD were well separated (see Fig. S3, Supplemental Content, http://links.lww.com/MD/D4, which represents the risk of ESRD in the internal validation cohort, based on the quartile of scores).

3.4. Composite risk of ESRD and all-cause mortality

During the follow-up period, 785 patients (26.0%) died. When we defined the composite outcome as the total events of ESRD and death, this outcome occurred in 818 patients (27.1%), including 246 (15.1%) in the non-AKI/non-CKD group, 155 (31.3%) in the AKI/non-CKD group, 233 (38.0%) in the non-AKI/CKD group, and 194 (64.0%) in the AKI/CKD group (see

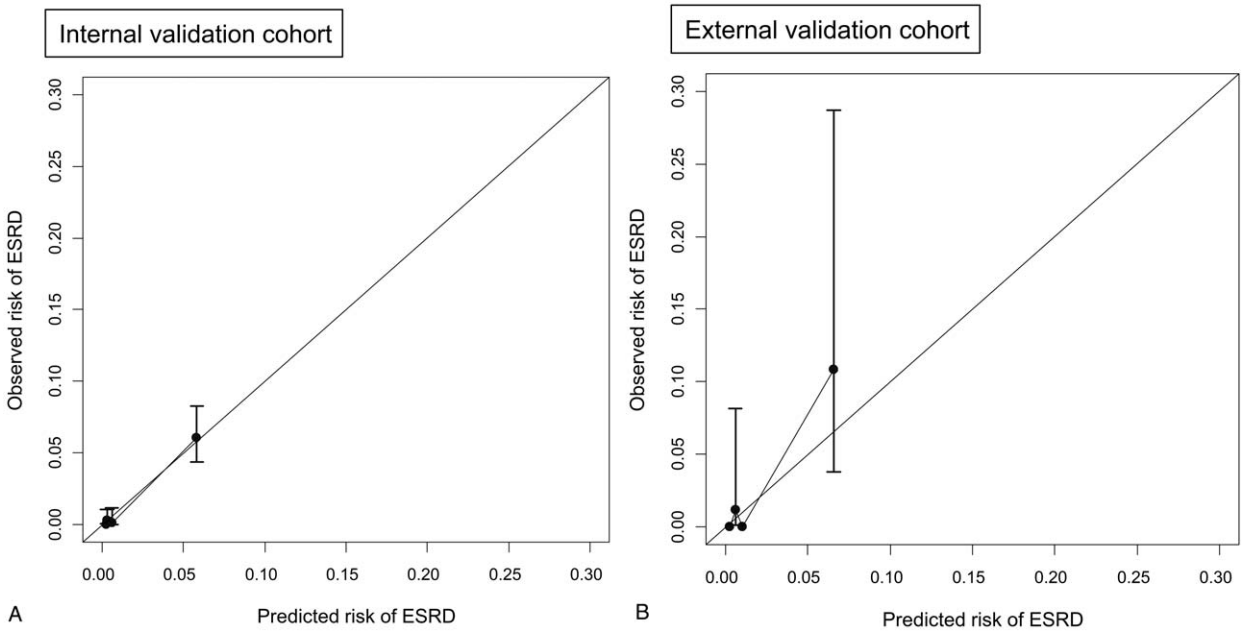


Figure 5. Calibration plots in the (A) internal and (B) external validation cohorts.

Table S2, Supplemental Content, http://links.lww.com/MD/D4, which shows the risk of composite outcome by AKI and CKD). The risk of the composite outcome increased depending on the presence of AKI and CKD (see Fig. S4, Supplemental Content, http://links.lww.com/MD/D4, which represents the risk of composite outcome according to AKI and CKD), similar to the results of Fig. 1. The HR was 1.53 (95% CI 1.24–1.89) in the AKI/non-CKD group, 1.73 (95% CI 1.42–2.10) in the non-AKI/CKD group, and 3.01 (95% CI 2.44–3.71) in the AKI/CKD group, compared with the non-AKI/non-CKD group. The composite risk of ESRD and death was not associated with the number of antihypertensive drugs. Although the death events were considered as a competing risk, all of AKI, CKD, and the number of antihypertensive drugs predicted the risk of ESRD with a similar pattern to previous analyses (see Table S3, Supplemental Content, http://links.lww.com/MD/D4, which shows the risk of ESRD from sub-distribution hazard models with death as a competing risk).

4. Discussion

Prediction models for ESRD have been evaluated in patients with various pathologic conditions, such as CKD,[23–26] light chain amyloidosis,[27] and diabetes.[28–31] Nevertheless, an ESRD-prediction model after CABG has never been developed. The Cleveland Clinic score and the Society of Thoracic Surgery risk score have a limitation in predicting a risk of ESRD over several years.[9,10] Despite the difficulty in deriving such a model because of the relatively high mortality during the perioperative period, we successfully created an ESRD-prediction model with a long-term follow-up. This finding could be of significance in the perioperative management of patients undergoing other type of cardiac surgery. In outpatient setting, clinicians can focus on appropriate care of kidney disease progression in patients undergoing CABG who has AKI, CKD, or high number of anti-hypertensive drugs.

Regarding the best predictor, kidney dysfunction itself (i.e., AKI and CKD) predominantly determined the risk of ESRD, although other factors such as comorbidities and intraoperative problems could be also considered in each case. Furthermore, the number of antihypertensive drugs, representing the severity of hypertension, was chosen in the final model. The estimation of ESRD risk could be simplified by these kidney function and antihypertensive drug data with good performance for the internal and external validations. Furthermore, the predictability of these factors was confirmed despite taking the competing risk for death into account.

AKI and CKD are risk factors for each other. AKI has long been regarded as completely reversible, but recent studies have shown that AKI may cause permanent kidney injury (inducing renal fibrosis) and increase the risk of long-term subsequent progression of kidney dysfunction because of incomplete recovery.[32–34] Patients with CKD may be at risk of AKI due to autoregulation failure, abnormal vasodilatation, and adverse effects of medications.[33] Throughout this series of processes, the loss of renal reserve gradually progresses, and kidney function eventually fails until ESRD develops. This pathophysiologic issue may underlie the primary selection of AKI and CKD during development of the present prediction model.

Hypertension is a well-known risk factor for the progression from CKD to ESRD.[35] Various parameters may reflect the severity of hypertension. Among them, the number of antihypertensive drugs was selected as the best predictive factor in the present model. The advantage of this variable over other hypertension-representative factors, including measured blood pressure, is that it is not temporary. For example, the blood pressure might be unstable during the perioperative period or due to the white coat effect.[36–38] In this regard, 24-h blood pressure monitoring may be the most effective way to reflect the patient's hypertensive condition. However, because this perfect measurement technique is not always feasible, particularly in emergency or surgical settings, the number of antihypertensive drugs may be clinically useful to elucidate the patient's hypertensive condition.

The strengths of our study are that the model was developed from relatively large multicenter cohorts of adults undergoing CABG and that the primary outcome (ESRD) was well documented. The total period was 13 years, and this enabled us to develop the ESRD-prediction model. The predictor variables in the model were readily available patient demographics and laboratory test parameters. The model was finally validated in an independent cohort. Nevertheless, we acknowledge the limitations inherent to a retrospective study design. Some patients died before ESRD events, although these were appropriately censored. This was reflected by the fact that the number of deaths was 10 times higher than the number of ESRD events. As a sensitivity analysis, we further applied a formal competing-risks (Fine-Gray) model. The difference in the risk of ESRD among various baseline diseases is another issue. The present cohort included only patients undergoing CABG; thus, application of the model to other disease subsets such as patients undergoing non-cardiac surgery or nonsurgical treatment may be limited. Another issue is that external validation was conducted in a single-center cohort of 279 patients, among whom a relatively small number developed ESRD. This resulted in wide CIs in the C-statistics, although the calibration plots showed good performance. Finally, the information on the cause of AKI was not available, which could strengthen the understanding of the relationships.

5. Conclusions

Because the outcomes of CABG are inseparable from ESRD, the present study was performed to develop an ESRD-prediction model following CABG, with the clear advantage of simplicity and preciseness of prediction. Such risk estimation can lead to prognostic assessment and follow-up of each patient, helping to guide appropriate treatment by the nephrologists as well as other clinicians to identify the risky patients. Forthcoming studies will validate the present model in other types of cardiac surgery in addition to CABG.

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Author contributions

YL designed the study, collected the data, analyzed and interpreted the results, and drafted the manuscript. JP and MJJ analyzed and interpreted the results. HRM, DKK, and KHO collected the data. CSL and YSK conceived the study and assisted

in the analyses. KYN conceived the study, analyzed the results, and interpreted the data. SSH conceived the study, analyzed the results, interpreted the data, and reviewed the manuscript. All of the authors read and approved the final manuscript.

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