의학석사 학위논문

Development of Model to Predict End-Stage Renal Disease after Coronary Artery Bypass Grafting: The ACHE score

– ESRD-prediction model –

관상동맥우회술 후 말기신부전 발생의 예측 모형 개발

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이 연 희

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Abstract

Rationale & Objective: 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).

Study Design: Prediction model using retrospective multicenter cohort study

Setting & Participants: A cohort of 3,089 patients undergoing CABG in two tertiary referral centers recruited between January 2004 and December 2015. The recruited patients were excluded 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).

New Predictors & Established Predictors: Underlying chronic kidney disease, postoperative acute kidney injury, and the number of antihypertensive drugs.

Outcomes: The primary outcome was ESRD.

Analytical Approach: 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.

Results: During the median follow-up of 6 years (maximum 13

years), Of 3,015 patients, ESRD occurred in 60 patients (1.4%). Through stepwise selection multivariate analyses, the following three variables were finally included in the ESRD-prediction model: underlying chronic kidney disease, postoperative acute kidney injury, and the number of antihypertensive drugs. 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 0.80 (95% CI 0.53-1.00) in the external validation cohort.

Limitations: Retrospective study design, the competing risk of death, the relatively small number of ESRD events in the external validation cohort

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

Keywords: acute kidney injury; coronary artery bypass grafting; chronic kidney disease; end-stage renal disease; hypertension.

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Introduction

1-1. Study Background

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]. AKI is a common complication after CABG and is associated with adverse outcomes [14]. Although AKI, CKD, and ESRD have relationships within a continuum of disease processes, ESRD is more closely related to mortality than are the others [15]. Approximately 0.6% to 5% of patients undergoing cardiac surgery will require dialysis in the immediate postoperative period [14]. If patients undergoing CABG develop postoperative ESRD, the mortality risk increases to 25% [16]. Possible explanations for the higher mortality among patients with ESRD include accelerated atherosclerosis, anemia, cardiomyopathy, and repeated events of ischemic heart disease [17]. Therefore, it is essential to predict the risk of ESRD after CABG.

1-2. Purpose of Research

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.

Materials and Methods

2-1. Patients and study design

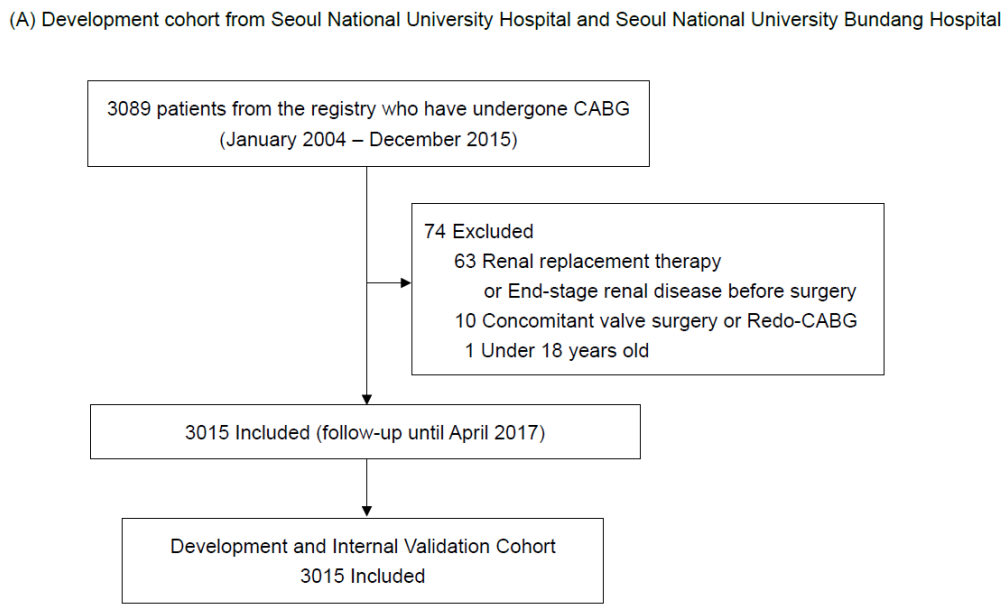
The study design was approved by the institutional review boards of all involved centers (nos. H-1702-050-831, B-1702/384-103, and 20170531/10-2017-1/071) and complied with the Declaration of Helsinki. The study was performed in two consecutive parts. In part 1, a retrospective multicenter cohort study involving 3,089 patients who comprised the development and internal validation cohort was conducted. 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. Patients were excluded 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 3,015 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, and diuretics; 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 equation [18]. AKI was defined as an increase in the serum creatinine level to ≥0.3 mg/dL or ≥1.5 times baseline within 48 hours after surgery and was classified according to the guideline proposed by Kidney Disease Improving Global Outcomes [19] 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 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 [20].

A prediction model was developed using the above cohort and its performance was validated 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 Figure 1.



(B) External validation cohort from Seoul National University Boramae Medical Center

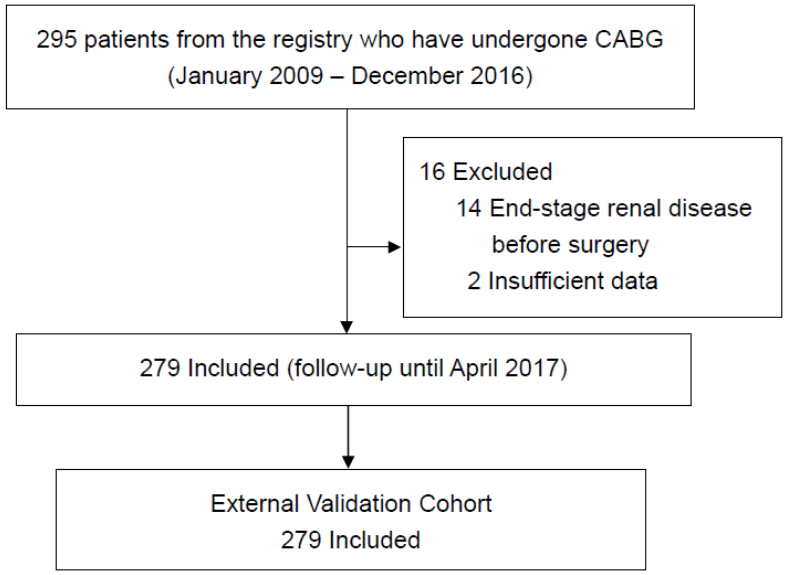


Figure 1. Flow chart for (A) development (internal) and (B) external validation cohorts.

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 [21].

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. 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 < 0.2 in the univariate model were applied to multivariate stepwise analyses. To facilitate the calculation of risks, estimates of log HRs (coefficients) were converted 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) [22,23]. 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. All tests were two-sided and performed at the .05 significance level. All 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)].

Results

3-1. Baseline characteristics

All baseline characteristics are presented in Table 1. Of 3,015 patients, 2,222 (73.7%) were male and 1,322 (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)	*P* value
Age (years)	65.5±9.84	63.1±9.92	64.5±9.67	70.5±7.72	70.6±7.83	<0.001
Male (%)	73.7	76.6	78.4	63.0	71.0	<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	0.005
Systolic blood pressure (mmHg)	126.5±20.64	126.2±19.35	127.1±22.59	125.7±21.19	128.6±22.81	<0.001
Diastolic blood pressure (mmHg)	73.3±12.42	74.3±11.79	73.3±13.72	71.2±12.18	72.0±13.30	0.002
Smoking (%)	31.8	33.6	33.9	25.9	30.0	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	<0.001
Serum creatinine (mg/dL)	1.1±0.39	0.9±0.17	0.9±0.19	1.4±0.44	1.6±0.56	<0.001
LV ejection fraction (%)	54.8±12.26	55.9±11.51	53.9±12.94	54.4±12.71	51.3±13.38	<0.001
Comorbidities (%)						
Hypertension	57.5	55.0	57.0	62.2	63.0	0.004
Diabetes mellitus	43.8	38.3	44.4	49.9	61.1	<0.001
History of Myocardial infarction	9.2	8.2	12.9	9.0	9.2	0.016

History of stroke	19.6	16.9	18.8	23.5	28.1	<0.001
Peripheral vascular disease	6.5	4.7	6.3	8.7	12.2	<0.001
Medication (%)						
ACE inhibitor or ARB	35.9	34.2	34.5	38.7	41.6	0.035
Beta-blocker	38.3	39.6	33.3	38.8	38.3	0.096
Calcium channel blocker	17.8	15.6	19.2	19.8	23.4	0.003
Diuretics	16.4	11.6	17.0	22.3	30.0	<0.001
No. of antihypertensive drugs						<0.001
0	35.5	36.6	38.4	32.2	31.7	
1-2	54.2	55.5	52.7	53.8	50.2	
≥3	10.3	7.9	8.9	14.0	18.2	
Contrast use before surgery (%)	45.7	50.1	42.2	40.0	38.9	<0.001
Cardiopulmonary bypass (%)	16.5	11.0	30.5	14.5	26.4	<0.001
Intra-aortic balloon pump (%)	9.1	5.1	15.4	10.2	18.5	<0.001
Total surgery time (min)	345.3±105.39	338.8±93.72	365.7±116.41	335.1±116.86	366.3±115.12	<0.001
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	0.009
White blood cell ($\times 10^3/\mu L$)	7.8±3.13	7.7±2.98	8.0±3.59	7.9±3.08	8.1±3.15	0.118

Albumin (g/dL)	3.8±0.64	3.9±0.61	3.8±0.61	3.7±0.69	3.5±0.66	<0.001
Cholesterol (mg/dL)	149.5±44.20	152.5±43.62	150.7±46.13	143.3±43.91	143.1±42.97	0.703

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

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

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.

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)	<0.001	2.09 (1.18-3.69)	0.011
Stage 2	5.21 (1.58-17.23)	0.007	3.58 (1.06-12.12)	0.040
Stage 3	43.29 (19.56-95.82)	<0.001	6.47 (2.75-15.21)	<0.001
Chronic kidney disease †				
None	1		1	
G3a	2.89 (1.22-6.87)	0.016	2.75 (1.16-6.54)	0.022
G3b	12.96 (5.70-29.46)	<0.001	10.46 (4.55-24.07)	<0.001
G4-5	83.56 (42.08-165.91)	<0.001	55.05 (26.68-113.60)	<0.001
Age	1.01 (0.98-1.04)	0.463		
Male	1.04 (0.59-1.85)	0.882		
Body mass index	0.99 (0.91-1.08)	0.884		
Systolic blood pressure	1.02 (1.01-1.03)	<0.001		
Diastolic blood pressure	1.03 (1.01-1.05)	0.015		

Smoking	1.05 (0.61−1.80)	0.872		
Comorbidities				
Hypertension	3.65 (1.90−7.03)	<0.001		
Diabetes mellitus	2.19 (1.30−3.70)	0.004		
History of vascular diseases	1.87 (1.12−3.10)	0.016		
No. of antihypertensive drugs				
0	1		1	
1−2	1.48 (0.77−2.87)	<0.001	1.33 (0.68−2.58)	0.407
≥3	5.63 (2.78−11.40)	<0.001	2.84 (1.37−5.86)	0.005
ACE inhibitor or ARB	3.39 (2.01−5.74)	<0.001		
Beta−blocker	1.27 (0.76−2.11)	0.356		
Calcium channel blocker	1.91 (1.09−3.35)	0.024		
Diuretics	3.47 (2.06−5.84)	<0.001		
Contrast use before surgery	1.07 (0.64−1.80)	0.798		
Use of cardiopulmonary bypass	0.43 (0.05−1.59)	0.118		
Use of intra−aortic balloon pump	1.43 (0.65−3.14)	0.375		
Total surgery time	1.00 (1.00−1.00)	0.199		
Anemia	0.32 (0.18−0.58)	<0.001		

Serum albumin level (≥3.5 g/dL vs. < 3.5 g/dL)	0.53 (0.32−0.88)	0.014
Cholesterol level	1.01 (1.00−1.01)	0.060
Left ventricular ejection fraction	1.00 (0.97−1.01)	0.195

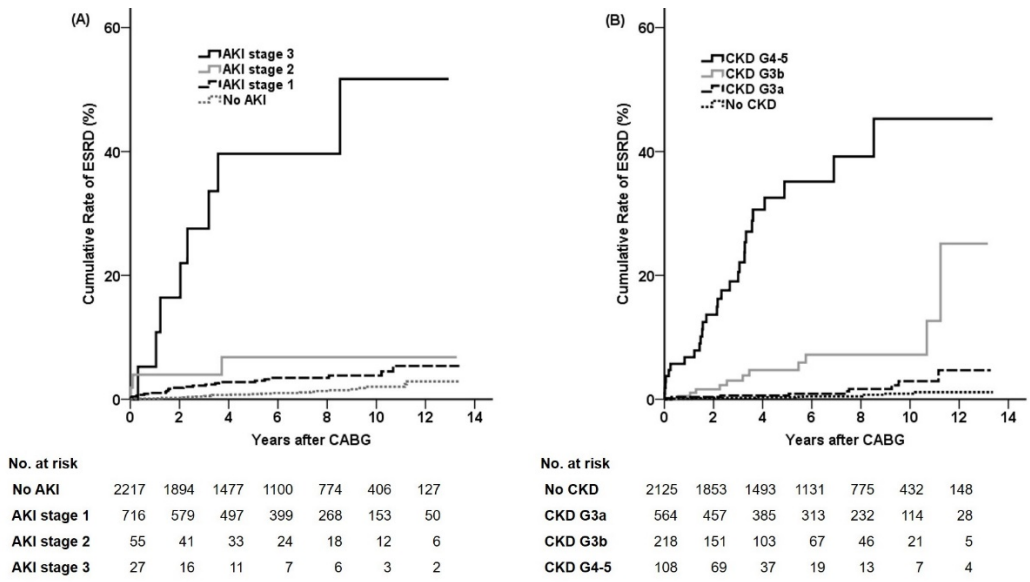
*Acute kidney injury stage 1 is defined as an increased in serum creatinine of 0.3 mg/dL or more or 1.5−1.9 times baseline; stage 2, an increased in serum creatinine of 2.0−2.9 times baseline; stage 3, an increased in serum creatinine to 4.0 mg/dL or 3.0 times baseline.

†Chronic kidney disease is defined as an eGFR below 60 mL/min/1.73 m^2; 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.

Abbreviations: HR, hazard ratio; CI, confidence interval.

Next, the ESRD risk was re-analyzed according to the three above-mentioned factors. 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 43.3, 95% CI 19.56–95.82) and grades 4 to 5 CKD (HR 83.6, 95% CI 42.08–165.91).

The risk of ESRD was higher in patients using ≥ 3 of antihypertensive drugs (HR 2.8, 95% CI 1.26–6.16) than in those using no antihypertensive drugs. The risks were similar between patients using no antihypertensive drugs and 1-2 of antihypertensive drugs (HR 1.1, 95% CI 0.51–2.21) (Figure 3).



No. at risk							
No AKI	2217	1894	1477	1100	774	406	127
AKI stage 1	716	579	497	399	268	153	50
AKI stage 2	55	41	33	24	18	12	6
AKI stage 3	27	16	11	7	6	3	2

No. at risk							
No CKD	2125	1853	1493	1131	775	432	148
CKD G3a	564	457	385	313	232	114	28
CKD G3b	218	151	103	67	46	21	5
CKD G4-5	108	69	37	19	13	7	4

Figure 2. Risk of end-stage renal disease according to the classification of (A) acute kidney injury and (B) chronic kidney disease.

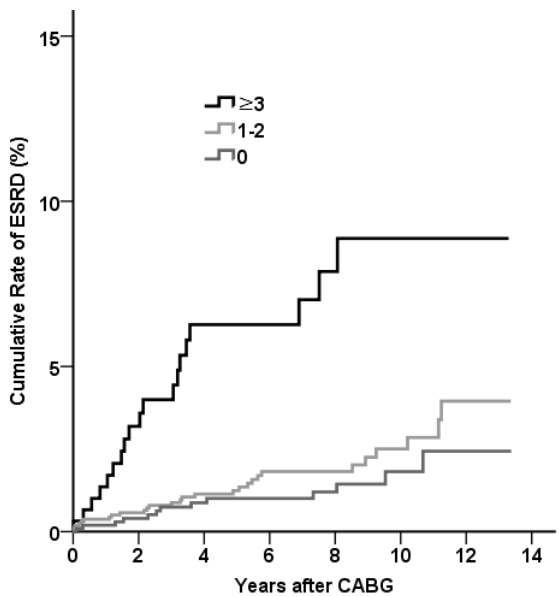


Figure 3. Risk of end-stage renal disease according to the number of antihypertensive drugs.

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 probability was equal to $P = 1 - 0.9978^{\mathrm{Exp}(X)}$ where X = 0.7365 × (1; stage 1 AKI) + 1.2764 × (1; stage 2 AKI) + 1.8667 × (1; stage 3 AKI) + 1.0112 × (1; grade 3a CKD) + 2.3475 × (1; grade 3b CKD) + 4.0083 × (1; grade 4–5 CKD) + 0.2821 × (1; 1–2 antihypertensive drugs) + 1.0426 × (1; ≥ 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 (Figure 4). The original model was assessed in the development (internal) and external validation cohorts by evaluating the discrimination ability using C-statistics (Table 3).

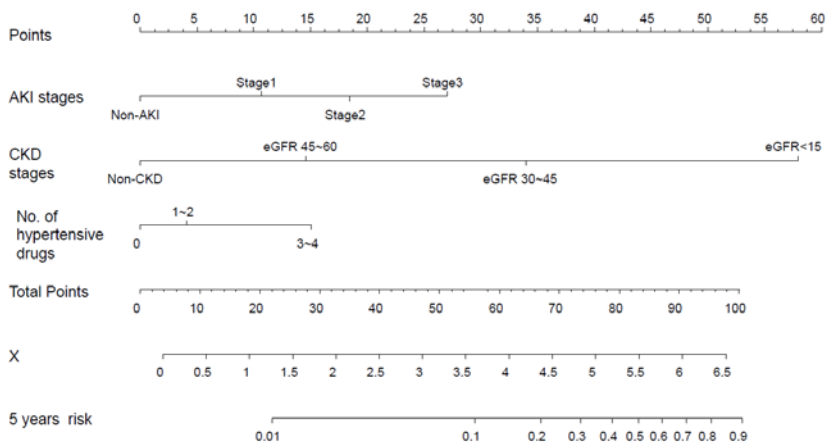


Figure 4. Nomogram.

Table 3. Regression Coefficient and integer-based simplified score.

	Regression Coefficient of original model	Integer-based simplified scoring model*
Acute kidney injury †		
None	0	0
Stage 1	0.7365	11
Stage 2	1.2764	18
Stage 3	1.8667	27
Chronic kidney disease ‡		
None	0	0
G3a	1.0112	15
G3b	2.3475	34
G4-5	4.0083	58
No. of antihypertensive drugs		
0	0	0
1-2	0.2821	4
≥3	1.0426	15
C-statistics (95% CI)		
Development (internal) cohort	0.89 (0.84-0.94)	0.89 (0.84-0.94)
External validation cohort	0.77 (0.46-1.00)	0.80 (0.53-1.00)

Abbreviations: CI, confidence interval.

*Integer-based scores were calculated as values rounded of regression coefficient scores multiplied by 14.5 (a scaling factor to a maximum score sum of 100): the ACHE score.

†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; 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.

An integer-based simplified scoring index (ACHE score) was developed to easily apply this ESRD-prediction model in clinical practice (Figure 5). 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 0.80 (95% CI 0.53–1.00) for the development and external validation cohorts, respectively. Regarding the calibration plots (Figure 6), 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 (Figure 7).

Acute kidney injury stage	Points
No AKI	0
1	11
2	18
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

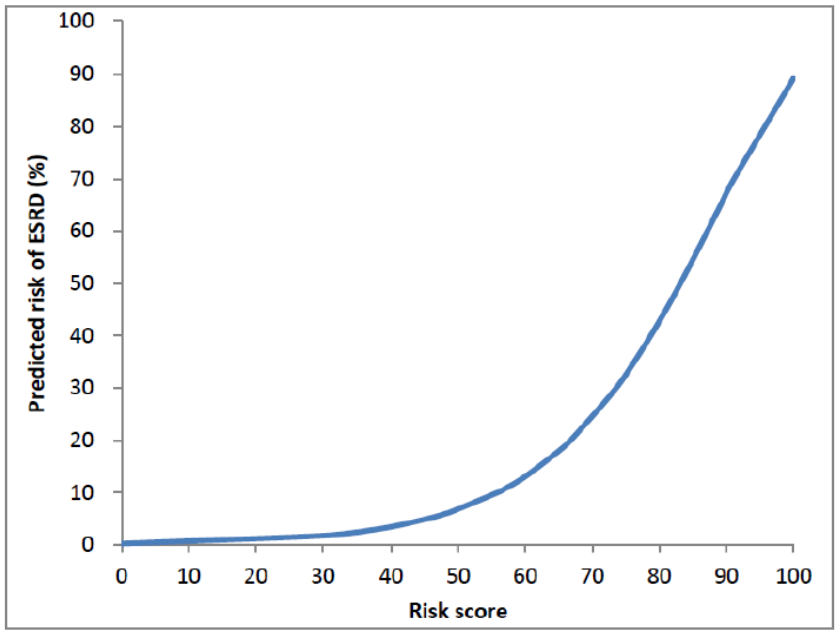


Figure 5. Simplified scoring index of the developed end-stage renal disease-prediction model (ACHE score). Points assigned to values of each variable can be summed to obtain a patient's total score, which can be used to assess the predicted risk of ESRD.

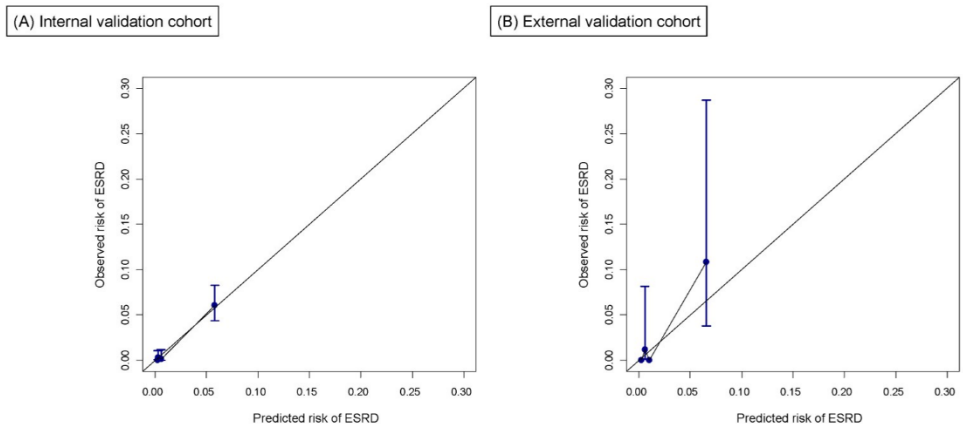


Figure 6. Calibration plots in the (A) internal and (B) external validation cohorts.

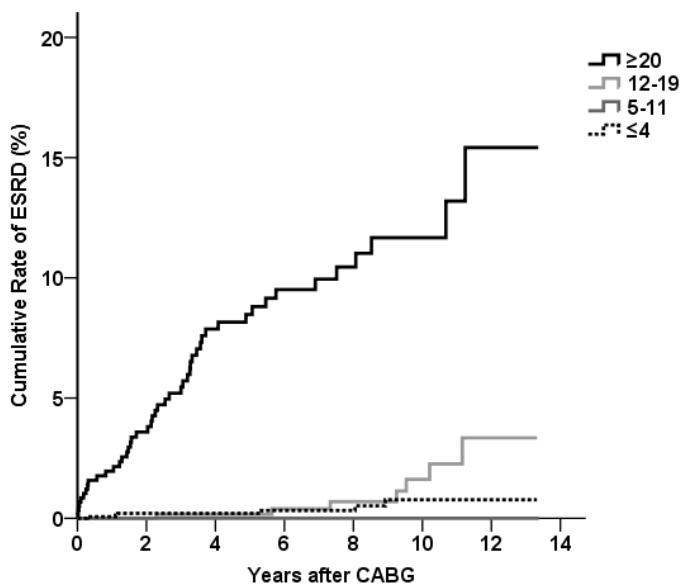


Figure 7. Risk of end-stage renal disease in the internal validation cohort, based on the quartile of scores. Scores were calculated using the simplified scoring index.

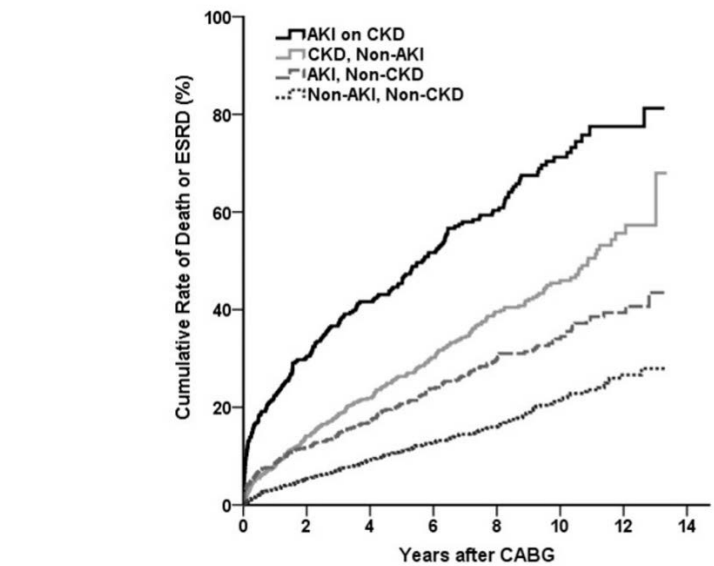
3-4. Composite risk of ESRD and all-cause mortality

During the follow-up period, 785 patients (26.0%) died. When the total events of ESRD and death were defined as the composite outcome, 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 (Table 4). The risk of the composite outcome increased depending on the presence of AKI and CKD (Figure 8). 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.

Table 4. Risk of composite outcome (end-stage renal disease and all-cause mortality) by acute kidney injury and chronic kidney disease.

	Events, n (%)	HR (95% CI)	*P* value
Non-AKI/non-CKD	246 (15.1)	1 (reference)	
AKI/non-CKD	155 (31.3)	1.53 (1.24-1.89)	< .001
Non-AKI/CKD	223 (38.0)	1.73 (1.42-2.10)	< .001
AKI/CKD	194 (64.0)	3.01 (2.44-3.71)	< .001

Abbreviations: HR, hazard ratio; CI, confidence interval; AKI, acute kidney injury; CKD, chronic kidney disease.



No. at risk							
AKI on CKD	303	206	162	119	81	35	8
CKD, Non-AKI	587	470	362	279	209	106	28
AKI, Non-CKD	495	429	378	310	210	132	49
Non-AKI, Non-CKD	1630	1425	1116	822	566	301	100

Figure 8. Risk of composite outcome according to acute kidney injury and chronic kidney disease.

Discussion

Prediction models for ESRD have been evaluated in patients with various pathologic conditions, such as CKD [24-27], light chain amyloidosis [28], and diabetes [29-32]. Nevertheless, an ESRD-prediction model after CABG has never been developed. The Cleveland Clinic score and the Society of Thoracic Surgery risk score are effective tools for predicting AKI and incidence of postoperative dialysis in patients after cardiac surgery, but there are limitations in predicting long-term ESRD over several years after surgery [9,10]. The ACHE score, developed to simplify the bedside evaluation using three independent predictors to assess ESRD risk in CABG operations, showed good accuracy and calibration, and predicted 5-year ESRD in patients after CABG.

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.

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 [33-35]. Patients with CKD may be at risk of AKI due to autoregulation failure, abnormal vasodilatation, and adverse effects of medications [34]. 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 [36]. 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 [37-39]. In this regard, 24-hour 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, I 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. This issue may be a common hindrance regarding ESRD-prediction models. 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 confidence intervals in the C-statistics, although the calibration plots showed good performance.

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 clinicians.

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국 문 초 록

관상동맥우회술 후 말기신부전 발생의 예측 모형 개발

말기신부전(ESRD) 환자의 생존율과 삶의 질은 신대체요법의 발달에 따라 과거에 비해 계속 향상되고 있으나 ESRD 환자의 이환율 및 사망률은 여전히 높은 편이다. 이에 ESRD의 조기 발견과 진행 예방은 임상적으로 중요한 문제이다.

관상동맥우회술(CABG)은 경피적 관상동맥중재술(PCI)와 함께 현재 관상동맥 질환의 치료로 널리 시행되는 수술이며, CABG를 시행 받은 환자가 수술 후 ESRD가 발생하면 사망 위험이 25%까지 증가했다는 연구 결과를 고려할 때, CABG 후 ESRD 발생을 예측하는 것이 필수적이다. 그러나 관상동맥우회술(CABG) 후 ESRD 진행에 대한 연구는 미비한 실정으로, 본 연구는 이들 환자의 ESRD 발생 위험 인자와 예측 모델을 개발하고 검증하기 위해 수행되었다.

이 연구는 2004년 1월부터 2015년 12월까지 서울대학교병원과 분당서울대학교병원에서 CABG를 시행 받은 3,089명의 환자들을 대상으로 한 후향적 다기관 코호트 연구이다. 예측 모형은 Cox 비례 위험 분석을 사용하여 개발되었으며 C-statistics를 이용하여 performance를 검증하였다. 또한 이 예측 모형은 279명의 독립된 코호트에서 외부 검증되었다.

6년 (최대 13년)의 추적 관찰 기간 동안 ESRD는 60명 (1.4%)에서

발생하였다. 단계적 선택 다변수 분석을 통해 ESRD 예측 모형에는 최종적으로 기존 만성신부전 (underlying CKD), 수술 후 급성 신손상 (postoperative AKI) 및 복용하는 고혈압 약제 종류의 개수 (the number of antihypertensive drugs)의 총 3가지 변수가 포함되었다 (ACHE score). 본 ESRD 예측 모형은 개발 코호트에서 C-statistics 0.89 (95% confidence interval [CI] 0.84-0.94), 외부 검증 코호트에서 0.80 (95% CI 0.53-1.00)로 우수한 예측력을 보였다.

본 연구를 통해 개발한 관상동맥우회술 후 ESRD 발생 예측 모형은 비교적 단순하면서도 높은 예측력을 가지고 있다는 이점이 있으며, 임상 상황에서 CABG를 시행 받은 환자들에게 적용하여 예후를 평가하고 각 환자를 추적하여 임상의가 적절한 치료 방향을 수립하는 데 도움을 줄 수 있을 것으로 생각한다.

주요어: acute kidney injury; coronary artery bypass grafting; chronic kidney disease; end-stage renal disease; hypertension.

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