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**Risk prediction model for progression of
coronary artery calcification in chronic
kidney disease patients**

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Directed by Professor Tae-Hyun Yoo

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of
Master of Medical Science

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December 2022

This certifies that the Master's Thesis of
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December 2022

ACKNOWLEDGEMENTS

First of all, I would like to express my sincerely gratitude to my thesis supervisor, professor Tae-Hyun yoo, who provided a lot of support and guidance from the beginning to the end of this study. Thanks to his warm advice and encouragement, I was able to complete my thesis. He also helped me a lot in setting the direction for my future life. Without his support, I would not have completed my degrees.

I also would like to appreciate professor Sungha Park and Young-Nam Youn for their generous advice. Although there was a problem with the presentation time coordination, thanks to the consideration through the time coordination, I was able to get the opportunity to make a presentation. I'd like to thank to professor Shin-Wook Kang for being my mentor.

Finally, I'm deeply thankful to my family for their constant support and unwavering love.

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ABSTRACT

Risk prediction model for progression of coronary artery calcification in chronic kidney disease patients

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Background: Cardiovascular disease (CVD) is the most common cause of mortality in chronic kidney disease (CKD) patients. Coronary artery calcification (CAC) in CKD patients is highly prevalent and is significantly associated with future CVD events. Therefore, the aim of this study was to produce the CAC progression prediction model in CKD patients using multiple risk factors.

Methods: A total of 1,027 patients were enrolled from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) which is a Korean multicenter prospective cohort. CAC score was calculated based on the Hokanson criterion which is the square-root transformed difference between baseline and follow up CAC scores [$\sqrt{\text{CAC score (follow-up)}} - \sqrt{\text{CAC score (baseline)}}$]. Follow-up CAC score was measured at 4 years and CAC progression was defined as the difference greater than 2.5 to minimize the effect of interscan variability. Multivariate logistic regression analysis was used to construct the risk-scoring model. By bootstrapping, the final model was internally validated using 1,000 bootstrap samples.

Results: Among 1,027 patients, 379(36.9%) patients showed CAC progression. Age, gender, BMI, history of CVD, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, baseline CAC score, estimated GFR, phosphate, FGF-23/klotho, and Urine albumin-creatinine ratio (UACR) were significantly associated with CAC progression in univariable logistic regression. In multivariable logistic regression, age, gender, the history of HTN,

DM, and dyslipidemia, baseline CAC score, calcium, and phosphate were significantly associated with CAC progression. Therefore, age, gender, baseline CAC score, calcium, phosphate, and history of HTN, DM, and dyslipidemia were selected as prediction markers for CAC progression model. Area under the receiver-operating characteristic curve for prediction of CAC progression at 4 years in this model was 0.869 (95% CI 0.847-0.892). Internal validation cohort of 1,000 bootstrap samples showed good discrimination and calibration (validation c-statistics 2.5 percentile 0.845, median 0.869, 97.5 percentile 0.890).

Conclusions: The model derived from the integrative risk factors provided more delicate prediction of CAC progression in non-dialysis CKD patients.

Key words: Chronic Kidney Disease, Coronary artery calcification, Risk prediction model

Risk prediction model for progression of coronary artery calcification in chronic kidney disease patients

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I. Introduction

Chronic kidney disease (CKD) is highly prevalent with an increasing average age of the global population. Non-dialysis CKD patients as well as dialysis patients have a higher mortality rate than the general population.^{1,2} CKD patients have a 10-200% higher risk of cardiovascular disease (CVD) than that in general population and CVD is the most common cause of mortality in CKD patients.³ A previous cohort study demonstrated that death from ischemic heart disease (IHD) was the most common cause of cardiovascular death in CKD patients.⁴

Most of the CKD patients have multiple comorbidities such as hypertension (HTN), diabetes mellitus (DM), and metabolic syndrome which are traditional risk factors for CVD.^{3,5} In addition, the reduced renal function in CKD patients is an independent risk factor for CVD.⁶ However, since traditional risk factors are insufficient to explain the incidence of CVD in CKD patients, the importance of non-traditional risk factors such as chronic kidney disease-mineral bone disease (CKD-MBD), chronic inflammation or vascular calcification is emerging.⁷⁻¹¹

Coronary artery calcification (CAC) is the pathological deposition of calcium-phosphate in the tissue inside coronary artery.^{8,11} It occurs during the normal aging process, but progression of CAC is accelerated in CKD population.^{8,12} The mechanisms of CAC are known as intimal calcification, medial calcification, heart valve calcification and refractory

calcium formation in coronary artery.⁸ Abnormal CKD-MBD markers, unique to patients with CKD, such as hyperphosphatemia is closely associated with CAC.^{7,13} Previous studies also reported that chronic inflammation is frequently observed and leads to increasing risk of CAC in CKD patients.¹⁴ In CKD, the risk factors related with CAC are closely related to each other. The presence of CAC is predictable to future cardiac events in CKD patients.¹⁵⁻¹⁸ Since CAC is important in CKD, early detection and modification of risk factors related to progression can be strategies to improve the prognosis of CKD patients. Therefore, the aim of this study was to provide the CAC prediction model comprehensively using traditional and non-traditional multiple risk factors.

II. MATERIALS AND METHODS

Study subjects

The subjects were selected from KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD).¹⁹ KNOW-CKD is a Korean multicenter prospective cohort study designed at 9 clinical centers in 2,238 pre-dialysis CKD stage 1-5 patients from February 2011 to January 2016. The participating subjects visited the center according to the follow-up schedule.

We excluded patients who were dropped out (withdrew consent, transferred to another hospital, by the physician's decisions) or expired. Patients whose multidetector computed tomography (CT) for CAC score were not performed were excluded. Furthermore, patients without demographic information or laboratory data were also excluded. A total of 1,027 patients were selected for the study. (Figure 1)

The study protocol was approved by the Institutional Review Board of each participating center, including Seoul National University Hospital (IRB number: 1104-089-359), Yonsei University Severance Hospital (IRB number: 4-2011-0163), Kangbuk Samsung Medical Center (IRB number: 2011-01-076), Seoul St. Mary's Hospital (IRB number: KC11OIMI0441), Gil Hospital (IRB number: GIRBA2553), Nowon Eulji Medical Center (IRB number: 201105-01), Chonnam National University Hospital (IRB number: CNUH-2011-092), and Busan Paik Hospital (IRB number: 11-091) and all patients were provided with written informed consent to participate in the study.

Data Collection

After screening for demographic information and medical history, patients were enrolled in this cohort study. The subjects were evaluated at the baseline for socio-demographic

information, and the anthropometric measurements were evaluated. The laboratory tests, cardiac evaluation and radiologic imaging were performed according to the specific protocol.

In this study, dyslipidemia was defined as patients taking statins or patients with an initial LDL-C of 160 or higher. The history of CVD was defined as patients with a history of coronary artery disease, peripheral heart disease, cerebrovascular disease, or arrhythmia.

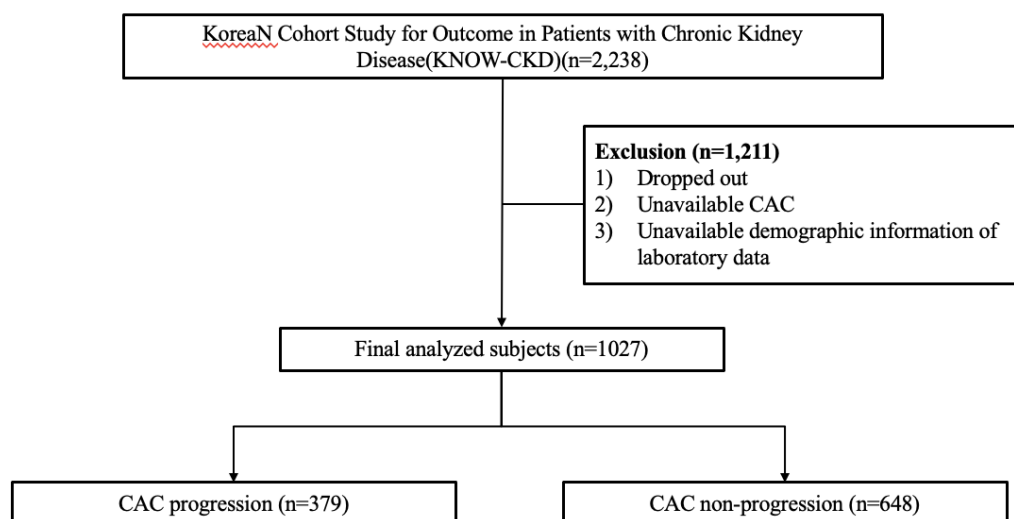


Figure 1. Flow chart of subject enrollment and analyses.

Measurement of Coronary Artery Calcification

The baseline CAC scores were measured by multidetector CT. A repeated CAC measurement was performed 4 years after baseline to assess progression of the CAC. Coronary artery calcification score was calculated by Agatston score.²⁰ CAC severity was classified by the baseline CAC score. (0 = none, 0-100 = mild, 100-300 = moderate, >300 severe)²¹ Continuous changes in CAC scores were assessed according to the square-root transformed method, which account for inter-scan variability. The progression of CAC score was calculated on the Hokanson criterion which is the square-root transformed difference between baseline and follow up CAC scores. $[\sqrt{\text{CAC score (follow-up)}} - \sqrt{\text{CAC}}$

score (baseline)]. CAC progression was defined as the difference greater than 2.5 to minimize the effect of interscan variability.²²

Statistical Analysis

Baseline characteristics of the study participants were expressed as mean \pm standard deviation for continuous variables and number (percentage) for categorical variables by baseline CAC severity and progression of CAC. Statistical differences between continuous variables were examined using Student's t-test and categorical variables were examined using a chi-square test for statistical significance.

Univariable and multivariable logistic regression were used to select the significant risk factors for CAC progression. For better understanding of the multivariable model, continuous variables were converted into binary variables using Youden index.; Age of 55, estimated Glomerular Filtration Rate (GFR) of 30, calcium of 8.5, phosphate of 4.3, Urine albumin-creatinine ratio (UACR) of 300, FGF-23/klotho of 0.052. For the selected variables, cut-off points were selected using Youden index based on a ROC curve, which is an outcome-oriented method. The risk factors to be included in the prediction model were selected as variables with p-value less than 0.2 of multivariable logistic regression.²³ The weighed value of each risk factors was determined based on the β -coefficient calculated in the multivariable logistic regression analysis. The prediction score of CAC was defined as the sum of the weighed point of each risk factors. The internal validation of this model was analyzed by the bootstrap method. 1000 samples were randomly selected, and AUC curve was obtained for each sample. SPSS for Windows, version 26 (SPSS Inc., Chicago, IL) and R statistical package (ver. 3.5.2, <https://www.r-project.org>) were used for statistical analyses. A p-value < 0.05 was considered to indicate statistical significance.

III. RESULTS

Baseline Characteristics

Among the 2,238 patients enrolled in the KNOW-CKD cohort, a total of 1,027 patients were analyzed for the CAC progression prediction model. The mean age was 52.6 ± 11.9 years. Six hundred and four (58.8%) patients were male and mean Body Mass Index (BMI) was $24.6 \pm 3.3 \text{ kg/m}^2$. Nine hundred seventy-nine (95.3%) patients had HTN, 273 (26.6%), 537 (52.3%) and 110 (10.7%) patients were treated with DM, dyslipidemia and CVD. The mean values of serum calcium, phosphate, blood urea nitrogen (BUN), creatinine, estimated GFR, FGF-23, Klotho, C-reactive protein (CRP), and UACR were $9.25 \pm 0.43 \text{ mg/dL}$, $3.54 \pm 0.56 \text{ mg/dL}$, $22.9 \pm 10.7 \text{ mg/dL}$, $1.40 \pm 0.64 \text{ mg/dL}$, $62.8 \pm 29.0 \text{ ml/min/1.73m}^2$, $20.5 \pm 29.8 \text{ RU/mL}$, $573.1 \pm 269.1 \text{ pg/mL}$, 1.90 ± 5.31 , and $521.9 \pm 809.3 \text{ mg/day}$, respectively.

Table 1 shows baseline characteristics of patients stratified according to baseline CAC severity. As the severity of CAC increased, the mean age and the proportion of male were increased significantly. Also, the proportion of patients with DM, HTN, dyslipidemia and CVD history was higher with increasing CAC severity. Regarding laboratory data, BUN, and UACR were significantly higher, while creatinine, and estimated GFR were significantly lower (Table 1).

Characteristics patients with or without CAC progression

CAC was progressed in 379 (36.9%) of the patients in this study. Patients with CAC progression were much older, more likely to be male, and had higher BMI. Baseline CAC score was significantly higher in the CAC progression group compared to that in the non-progression group (Table 2). In addition, the proportion of history of HTN, DM, dyslipidemia, and CVD was higher in patients with CAC progression. Serum phosphate, BUN, creatinine, and UACR at baseline were significantly higher and estimated GFR and Klotho were significantly lower in patients with advanced CAC. However, there was no difference in baseline CRP level between the two groups.

TABLE 1. Baseline characteristics at the enrollment among patients stratified by baseline CAC severity

	Baseline CAC severity					P value
	Total n=1027 (100%)	None n=539 (52.5%)	Mild n=306 (29.8%)	Moderate n=81 (7.9%)	Severe n=101 (9.8%)	
Age (years)	52.6±11.9	47.2±11.3	56.9±9.8	59.4±8.9	63.1±7.0	<0.001
Gender (male, %)	604 (58.8)	258 (47.9)	205 (67.0)	63 (77.8)	78 (77.2)	<0.001
SBP (mmHg)	126.0±14.6	124.2±13.6	128.0±14.7	125.7±16.1	130.3±16.8	<0.001
DBP (mmHg)	76.9±10.4	77.0±10.3	77.6±10.4	75.2±9.6	75.9±11.8	0.227
BMI (kg/m ²)	24.6±3.3	24.1±3.4	25.1±3.3	25.4±3.2	25.3±3.2	<0.001
Comorbidities						
HTN (%)	979 (95.3)	500 (92.8)	300 (98.0)	80 (98.8)	99 (98.0)	0.001
DM (%)	273 (26.6)	67 (12.4)	104 (34.0)	38 (46.9)	64 (63.4)	<0.001
Dyslipidemia (%)	537 (52.3)	222 (41.2)	183 (59.8)	61 (75.3)	71 (70.3)	<0.001
CVD (%)	110 (10.7)	26 (4.8)	40 (13.1)	15 (18.5)	29 (28.7)	<0.001
Laboratory						
Calcium (mg/dL)	9.25±0.43	9.26±0.43	9.23±0.42	9.23±0.41	9.21±0.48	0.508
Phosphate (mg/dL)	3.54±0.56	3.54±0.56	3.52±0.58	3.61±0.54	3.58±0.51	0.580

Alkaline phosphate (U/L)	84.6±61.0	82.0±59.6	91.1±69.9	86.2±55.0	78.2±38.8	0.129
FGF-23 (RU/mL)	20.5±29.8	18.0±29.6	23.7±32.5	18.8±18.3	25.3±28.3	0.016
Blood urea nitrogen (mg/dL)	22.9±10.7	21.0±9.6	24.1±11.3	25.8±10.8	26.4±12.4	<0.001
Creatinine (mg/dL)	1.40±0.64	1.32±0.68	1.45±0.61	1.53±0.52	1.58±0.57	<0.001
Estimated GFR (ml/min/1.73 m ²)	62.8±29.0	69.1±31.3	58.2±25.1	53.8±24.3	50.3±21.2	<0.001
Fasting plasma glucose (mg/dL)	107.5±31.8	99.6±19.3	114.2±38.4	117.0±40.1	121.8±43.1	<0.001
Total cholesterol (mg/dL)	175.2±35.8	179.3±34.1	172.2±37.0	170.6±36.7	165.4±36.8	<0.001
Triglyceride (mg/dL)	152.2±95.4	143.2±95.2	165.5±95.8	166.4±115.0	148.9±69.8	0.005
LDL-C (mg/dL)	97.5±29.9	100.3±28.2	95.8±32.1	95.4±27.8	89.4±32.4	0.03
HDL-C (mg/dL)	51.0±15.0	53.2±15.4	48.8±14.2	48.4±13.1	48.3±14.6	<0.001
Klotho (pg/mL)	573.1±269.1	590.6±305.5	547.4±212.0	570.6±201.9	559.8±259.2	0.149
FGF-23/Klotho	0.042±0.074	0.038±0.076	0.050±0.080	0.037±0.039	0.052±0.057	0.071
CRP (mg/L)	1.90±5.31	1.77±4.39	2.08±6.56	1.91±6.88	2.03±4.05	0.863

UACR (mg/g)	521.9±809.3	459.3±721.4	574.3±890.7	597.2±957.9	636.8±848.4	0.064
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CAC = Coronary artery calcification, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, BMI = Body mass index, HTN = Hypertension, DM = Diabetes mellitus, CVD = Cardiovascular disease, FGF = Fibroblast growth factor, GFR = glomerular filtration rate, LDL-C = Low-density lipoprotein cholesterol, HDL-C = High-density lipoprotein cholesterol, CRP = C-reactive protein, UACR = Urine albumin-creatinine ratio

TABLE 2. Baseline characteristics at the enrollment between patients stratified by CAC progression

	CAC progression status			P value
	Total n=1027 (100%)	CAC Non-progression n=648 (63.1%)	CAC Progression n=379 (36.9%)	
Age (years)	52.6±11.9	49.2±11.8	58.5±9.4	<0.001
Gender (male, %)	604 (58.8)	338 (52.2)	266 (70.2)	<0.001
SBP (mmHg)	126.0±14.6	124.9±13.9	128.0±15.6	0.002
DBP (mmHg)	76.9±10.4	77.1±10.3	76.6±10.7	0.416
BMI (kg/m ²)	24.6±3.3	24.3±3.3	25.2±3.3	<0.001
Baseline CAC score	109.8±339.1	37.4±219.8	233.5±452.9	<0.001
Comorbidities				
HTN (%)	979 (95.3)	605 (93.4)	374 (98.7)	<0.001
DM (%)	273 (26.6)	103 (15.9)	170 (44.9)	<0.001
Dyslipidemia (%)	537 (52.3)	280 (43.2)	257 (67.8)	<0.001
CVD (%)	110 (10.7)	44 (6.8)	66 (17.4)	<0.001
Laboratory				

Calcium (mg/dL)	9.25±0.43	9.26±0.42	9.23±0.44	0.264
Phosphate (mg/dL)	3.54±0.56	3.51±0.55	3.61±0.56	0.04
Alkaline phosphate (U/L)	84.6±61.0	85.9±64.3	82.6±54.8	0406
FGF-23 (RU/mL)	20.5±29.8	18.9±26.4	23.2±34.6	0.041
Blood urea nitrogen (mg/dL)	22.9±10.7	21.2±9.5	25.6±12.0	<0.001
Creatinine (mg/dL)	1.40±0.64	1.34±0.65	1.51±0.62	<0.001
Estimated GFR (ml/min/1.73 m ²)	62.8±29.0	67.0±30.4	55.6±24.9	<0.001
Fasting plasma glucose (mg/dL)	107.5±31.8	101.7±22.6	117.5±41.4	<0.001
Total cholesterol (mg/dL)	175.2±35.8	177.1±35.5	171.8±36.0	0.023
Triglyceride (mg/dL)	152.2±95.4	146.2±92.3	162.5±99.7	0.010
LDL-C (mg/dL)	97.5±29.9	99.4±29.8	94.4±30.0	0.010
HDL-C (mg/dL)	51.0±15.0	51.9±15.3	49.5±14.2	0.013
Klotho (pg/mL)	573.1±269.1	587.5±297.2	548.5±210.4	0.05
FGF-23/Klotho	0.042±0.074	0.039±0.064	0.048±0.087	0.069

CRP (mg/L)	1.90±5.31	1.74±4.14	2.15±6.85	0.233
UACR (mg/g)	521.9±809.3	459.2±701.2	629.1±958.2	0.001

CAC = Coronary artery calcification, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, BMI = Body mass index, HTN = Hypertension, DM = Diabetes mellitus, CVD = Cardiovascular disease, FGF = Fibroblast growth factor, GFR = glomerular filtration rate, LDL-C = Low-density lipoprotein cholesterol, HDL-C = High-density lipoprotein cholesterol, CRP = C-reactive protein, UACR = Urine albumin-creatinine ratio

A prediction model predicting the presence of severe CAC in CKD patients

Univariable logistic regression was performed to select significant risk factors for the severity of CAC at baseline in study subjects. Age, gender, BMI, history of CVD, DM and dyslipidemia, low estimated GFR, FGF-23/Klotho, CRP, and UACR were significantly associated with severe CAC at baseline. (Table 3)

Multivariable logistic regression was performed to confirm risk factors for the presence of severe CAC in study subjects. After adjusting age, gender, FGF-23/klotho, UACR and the history of CVD and DM, age, gender, history of CVD and DM, and UACR were significantly associated with severe CAC. The variables of the risk prediction model were selected based on p-value in multivariable logistic regression analysis. We selected age over 55 (OR 6.622; 95% CI, 3.487-12.574, $P < 0.001$), male gender (OR 2.110; 95% CI, 1.250-3.562, $P = 0.005$), the history of CVD (OR 2.559; 95% CI, 1.477-4.434, $P = 0.001$), the history of DM (OR 3.452; 95% CI, 2.163-5.509, $P < 0.001$), high FGF-23/Klotho (OR 1.524; 95% CI, 0.951-2.441, $P = 0.080$), and high UACR (OR 1.849; 95% CI, 1.165-2.935, $P = 0.009$) as a prediction markers for prevalent severe CAC in CKD patients. (Table 3)

A prediction model predicting the progression of CAC in CKD patients

According to previous study, estimated GFR, 24h urine albumin, cystatin C, phosphate, log (FGF-23), log (PTH), hemoglobin A1c (HbA1c), fibrinogen, Log (interleukin-6), and log (tumor necrosis factor- α) were significantly associated with CAC progression.²⁴ Therefore, univariable logistic regression was performed to select risk factors for CAC progression, including some of the following factors. Age, gender, BMI, history of CVD, HTN, DM, and Dyslipidemia, baseline CAC score, estimated GFR, phosphate, calcium, FGF-23/klotho, and UACR were significantly associated with CAC progression (Table 4). Multivariable logistic regression was performed to confirm risk factors for CAC progression. Age, gender, the history of dyslipidemia and DM, hypocalcemia, hyperphosphatemia, and baseline CAC score remained significantly associated with CAC progression after adjusting age, gender, the history of HTN, DM, and dyslipidemia, calcium,

phosphate, and baseline CAC score. Considering the results of multivariable logistic regression, age > 55 (OR, 1.473; 95% CI, 1.036-2.096, $P=0.031$), male gender (OR, 1.414; 95% CI, 0.983-2.035, $P=0.031$), history of DM (OR, 1.623; 95% CI, 1.115-2.362, $P=0.011$), HTN (OR, 2.574; 95% CI 0.820-8.079, $P=0.105$), and dyslipidemia (OR, 1.573; 95% CI, 1.119-2.211, $P=0.009$), low calcium (OR, 2.352; 95% CI, 1.054-5.249, $P=0.037$), high phosphate (OR, 2.482; 95% CI, 1.426-4.321, $P=0.001$), and baseline CAC (mild : OR, 10.059; 95% CI, 6.781-14.920, $P<0.001$; moderate : OR, 24.664; 95% CI, 12.822-47.442, $P<0.001$; severe : OR, 26.898; 95% CI, 14.028-51.578, $P<0.001$) with a p-value under 0.2 were selected as the risk factors of the CAC progression prediction model. (Table 4)

ROC curve analysis for Prediction model for the baseline CAC severity and CAC progression during the follow up

The prediction score was calculated as the sum of each weighed value of the risk factors determined by β -coefficient calculated in the multivariable logistic regression analysis. (Table 5-1, Table 5-2). Odds ratios of the prediction models for severe CAC at baseline and CAC progression after 4 years were 1.019 (95% CI, 1.015-1.023) (Table 6) and 1.075 (95% CI, 1.059-1.091) (Table 6) respectively. Time-dependent area under the receiver-operating characteristic curve for prediction of severe CAC and CAC progression were 0.850 (95% CI, 0.817-0.882) and 0.869 (95% CI 0.847-0.892) respectively (Figure 2, 3).

TABLE 3. Univariate logistic regression and multivariate logistic regression for CAC severity

	Univariate Regression		Multivariate Regression	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age > 55	10.014 (5.405-18.554)	< 0.001	6.622 (3.487-12.574)	< 0.001
Gender (male)	2.579 (1.591-4.180)	< 0.001	2.110 (1.250-3.562)	0.005
BMI	1.067 (1.006-1.132)	0.030		
CVD	4.202 (2.580-6.843)	< 0.001	2.559 (1.477-4.434)	0.001
HTN	2.587 (0.619-10.822)	0.193		
DM	5.934 (3.848-9.151)	< 0.001	3.452 (2.163-5.509)	<0.001
Dyslipidemia	2.336 (1.496-3.649)	< 0.001	1.372 (0.835-2.255)	0.212
eGFR < 30	1.752 (1.011-3.035)	0.046	0.963 (0.518-1.789)	0.904
Calcium < 8.5	1.607 (0.701-3.684)	0.262		
Phosphate > 4.3	1.057 (0.546-2.046)	0.870		
FGF-23/Klotho	1.940 (1.275-2.953)	0.002	1.524 (0.951-2.441)	0.080
CRP (mg/L)	1.490 (0.978-2.269)	0.063		
UACR > 300 (mg/g)	1.812 (1.197-2.743)	0.005	1.849 (1.165-2.935)	0.009

CAC = Coronary artery calcification, BMI = Body mass index, CVD = Cardiovascular disease, HTN = Hypertension, DM = Diabetes mellitus, eGFR = estimated glomerular filtration rate, FGF = Fibroblast growth factor, CRP = C-Reactive Protein, UACR = Urine Albumin-Creatinine Ratio

TABLE 4. Univariate logistic regression and multivariate logistic regression for CAC progression

	Univariate Regression		Multivariate Regression	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age > 55	3.933 (3.005-5.149)	<0.001	1.473 (1.036-2.096)	0.031
Gender (male)	2.159 (1.650-2.824)	< 0.001	1.414 (0.983-2.035)	0.031
BMI	1.078 (1.037-1.120)	< 0.001		
CVD	2.895 (1.930-4.340)	< 0.001	1.264 (0.748-2.139)	0.382
HTN	5.316 (2.087-13.542)	< 0.001	2.574 (0.820-8.079)	0.105
DM	4.304 (3.214-5.764)	< 0.001	1.623 (1.115-2.362)	0.011
Dyslipidemia	2.769 (2.123-3.611)	< 0.001	1.573 (1.119-2.211)	0.009
Baseline CAC score				
None		< 0.001		< 0.001
Mild	13.024 (9.039-18.764)	< 0.001	10.059 (6.781-14.920)	< 0.001
Moderate	38.047 (20.524-70.530)	< 0.001	24.664 (12.822-47.442)	< 0.001
Severe	46.276 (25.536-83.860)	< 0.001	26.898 (14.028-51.578)	< 0.001
eGFR < 30	1.523 (1.037-2.235)	0.032	1.174 (0.699-1.969)	0.544
Calcium < 8.5	1.919 (1.073-3.431)	0.028	2.352 (1.054-5.249)	0.037
Phosphate > 4.3	1.715 (1.147-2.564)	0.009	2.482 (1.426-4.321)	0.001
Total PTH	1.000 (0.996-1.004)	0.965		

FGF-23/Klotho	1.665 (1.265-2.192)	< 0.001	1.201 (0.835-1.728)	0.322
CRP (mg/L)	1.020 (0.995-1.045)	0.120		
UACR > 300 (mg/g)	1.347 (1.043-1.739)	0.022	1.045 (0.736-1.484)	0.807

CAC = Coronary artery calcification, BMI = Body mass index, CVD = Cardiovascular disease, HTN = Hypertension, DM = Diabetes mellitus, eGFR = estimated glomerular filtration rate, PTH = Parathyroid hormone, FGF = Fibroblast growth factor, CRP = C-Reactive Protein, UACR = Urine Albumin-Creatinine Ratio

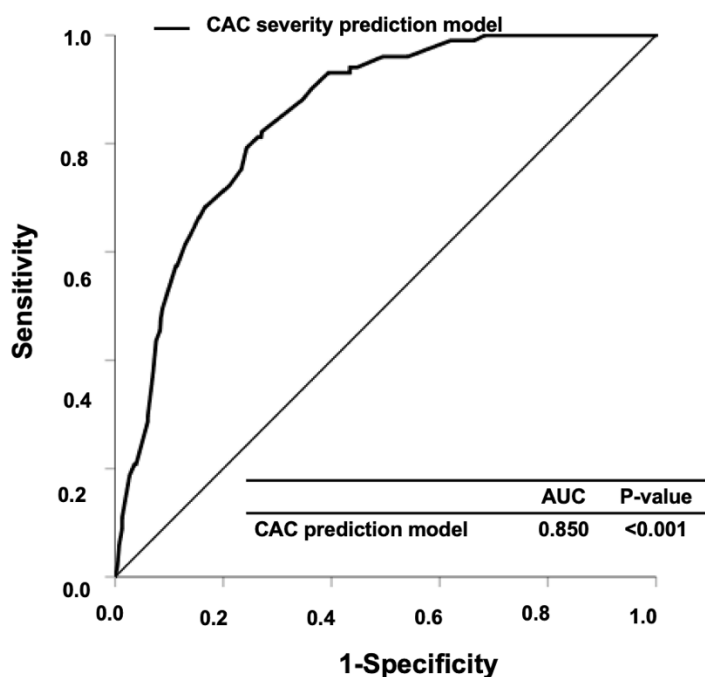


Figure 2. Time-dependent receiver-operating characteristic curve for prediction of Severe CAC

Internal Validation

The AUC was validated in the internal data set. Thousand random data were selected using bootstrapping data, and c-statistics were calculated for each data. The 2.5 percentile, median, 97.5 percentiles for bootstrap samples were 0.814, 0.852, and 0.880 for the prediction model of severe CAC at baseline, and 0.845, 0.869, and 0.890 for the prediction model of CAC progression after 4 years respectively. Since this value for internal validation included the AUC of 95% CI values of entire subjects, this suggested that prediction models in this study had good discriminant ability.

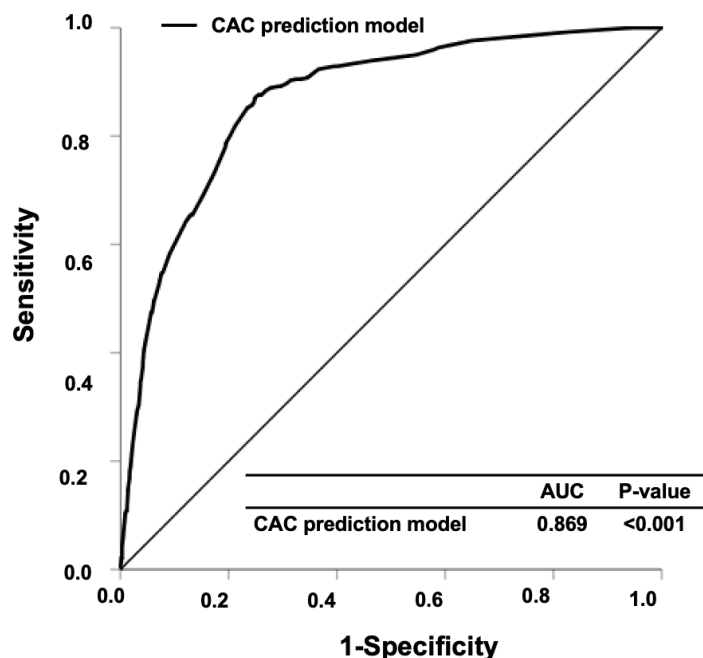


Figure 3. Time-dependent receiver-operating characteristic curve for prediction of CAC progression at 4 years

IV. DISCUSSION

The most common cause of mortality in CKD patients is CVD.¹⁴ In CKD patients, vascular calcification, including coronary arteries is much pronounced and rapidly progressing, due to two pathological processes: medial (arteriosclerosis) and intimal (atherosclerosis) deposition. Previous studies indicate that CAC is significantly associated with the risk of various kinds of CVD such as myocardial infarction, and heart failure and all-cause mortality in patients with CKD.^{15-18,25} Furthermore, progression of CAC was an independent predictive factor for future cardiac events.²⁶ Taken together, predicting progression of CAC may be helpful in future CVD development in CKD patients.

There were several previous studies which had tried to find out the factors related to CAC progression. Previous studies have shown that risk factors for CAC progression are

different depending on the study design, sample size and basic demographic characteristics in study subjects.¹⁷ A Multi-Ethnic Study of Atherosclerosis (MESA) analysis of 562 CKD patients without CVD found that diabetes was the only significant predictor of CAC progression.^{15\} However, the Chronic Renal Insufficiency Cohort (CRIC) study identified several risk factors associated with CAC progression, such as low eGFR, high 24hr-urine albumin, hyperphosphatemia, increased FGF-23 and total PTH, and hypocalcemia.²⁴ Moreover, another previous study reported that CRP, an inflammation marker, was also significantly associated with CAC progression.²⁷ In this study, we created a novel risk prediction model for CAC progression using statistically significant factors as well as previously reported traditional and non-traditional risk factors. Risk factors in this model were included kidney function, CKD-MBD associated markers, and inflammation. Age, male gender, history of DM, HTN, and dyslipidemia, hypocalcemia, hyperphosphatemia, and baseline CAC score were selected as the risk factors. Risk factors described as being associated with CAC progression in previous studies, such as total PTH were not significantly associated in this study. This model is expected to be useful for predicting the progression of CAC through baseline demographic and laboratory data. To the best of our knowledge, this model is the first risk score system for prediction of CAC progression in CKD patients.

TABLE 5-1. Allocated points to calculate the CAC severity prediction model

Variables	Points
Age > 55	100
Male	40
Cardiac history	50
DM	66
FGF-23/Klotho	22
UACR > 300	33

TABLE 5-2. Allocated points to calculate the CAC progression model

Variables	Points
Age > 55	12
Gender(male)	11
HTN	29
DM	15
Dyslipidemia	14
Calcium < 8.5	26
Phosphate > 4.2	28
Baseline CAC score	
None	0
Mild	70
Moderate	97
Severe	100

TABLE 6. Logistic regression for CAC Severity predicted score and prediction score

	Adjusted	
	OR (95% CI)	P-value
CAC severity prediction score	1.019 (1.015-1.023)	<0.001
CAC prediction score	1.075 (1.059-1.091)	<0.001

CKD-MBD were developed even in the early-stage CKD patients. Although the exact pathophysiology of CKD-MBD causing CAC in CKD patients had not yet been elucidated, it is known that the change in balance between calcification contributors (hyperphosphatemia, inflammation etc.) and calcification inhibitors (klotho etc.) accelerates CAC.²⁸ Phosphate serves as a substrate deposited on the intimal or media of blood vessel, and acts as a mediator to activate transcription of certain genes in vascular smooth muscle cell (VSMC) and pericytes.²⁹ In previous study, hyperphosphatemia had

been independently associated with inflammation and CAC in CKD^{13,30}. Furthermore, in this study, hyperphosphatemia as well as hypocalcemia, another CKD-MBD marker, were analyzed to be related CAC progression. Taken together, CKD-MBD is thought to be an important risk factor for CAC progression.

Inflammation is known to be another hallmark of CKD that can cause CAC.¹⁴ CRP, commonly used an inflammatory marker, has been reported to be associated with CAC progression in previous studies conducted on dialysis patients.²⁷ However, in our study, CRP was not associated with CAC progression, which may be due to several reasons. First, this study was performed on pre-dialysis patients. Second, most of patients in this cohort had relatively normal CRP. Based on the finding in non-dialysis and relatively stable study subjects, CRP reflecting chronic inflammation was not selected as a risk factor in this predictive model.

Since several risk factors, such as hyperphosphatemia are modifiable, it is reasonable to assume that correcting modifiable risk factors can reduce CAC. Indeed, previous studies have shown that phosphorus binders reduce the degree of progression of CAC.^{11,28} Moreover, even when limited to mild to severe CAC patients, patients who were treated by non-calcium based phosphate binders showed significantly regression of CAC.²⁸ Meanwhile, statins are medications used for patients with dyslipidemia. Paradoxically, however, previous studies have reported that statins are associated with increased progression of CAC.^{31,32} This may be the reason why the CKD-MBD markers have higher scores in our CAC progression prediction model, despite the fact that a history of dyslipidemia is a well-known traditional risk factor for CAC.

This study has several strengths. First, this study is the first attempt to build a prediction model for CAC progression in non-dialysis CKD patients. So far, a few studies have been simply conducted on the elucidation of risk factors for CAC progression in CKD patients. Second, the large samples of more than 1,000 CKD patents enrolled in the study allowed us to have statistical reliability for the predictive model. This study has several limitations. First, due to the limitations of the method to measure CAC in this cohort study, it is unable

to distinguish between intimal and medial calcifications. As the pathophysiologic mechanisms inducing two calcifications have difference, there may have a limitation in this study. To overcome the limitation, we included factors involved in each mechanism such as a history of DM and renal function in medial calcification and dyslipidemia, CKD-MBD marker and inflammation marker in intimal calcification, respectively. Second, the timing of the next CAC measurement was not determined with strong evidence. However, it has been also advantageous that a serial measurement was taken with a similar interval in all subjects. Third, external validation was not performed since there is no suitable matching cohort and some laboratory data such as FGF-23 and klotho are not routinely checked in CKD patients. Fourth, the definition of dyslipidemia is ambiguous. In this study history of dyslipidemia was defined as patient taking statin or having an LDL level of 160 or higher. The analysis may have limitation, because patients with a history of cardiac disease are taking statin drugs even though they have not been diagnosed with dyslipidemia. Fifth, this cohort was limited to Korean CKD patients. Therefore, there would be limitations in applying these results to other ethnic groups.

V. CONCLUSION

In conclusion, our model allowed us to predict CAC progression through the patient's baseline demographic and laboratory data. Further studies are needed to develop treatment or intervention to slow CAC progression in high-risk patients based on this prediction model.

Financial disclosure. None.

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ABSTRACT(IN KOREAN)

만성콩팥병 환자의 관상동맥석회화 진행의 위험예측 모델

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주 정 호

Background: 심혈관질환 (CVD)은 만성신질환 (CKD) 환자의 가장 흔한 사망 원인이다. 관상 동맥 석회화 (CAC)는 만성신질환 환자에서 매우 흔하며 미래의 심혈관질환 발생과 유의미하게 관련되어 있다고 알려져 있다. 그래서 본 연구의 목적은 여러개의 위험인자를 사용하여 만성신질환 환자의 관상 동맥 석회화 진행의 위험 예측 모델을 만드는 것이다.

Methods: 한국의 다기관 전향적 코호트인 KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) 에서 총 1,027명의 환자를 선정하였다. 관상 동맥 석회화 점수는 Hokanson 방법에 따라 후속 관상 동맥 석회화 점수의 제곱근 값과 기준 관상 동맥 석회화 점수의 제곱근 값의 차이로 계산하였다. [$\sqrt{\text{CAC score (follow-up)}} - \sqrt{\text{CAC score (baseline)}}$]. 관상 동맥 석회화의 진행은 스캔 간 변동성의 영향을 최소화하기 위해 차이가 2.5보다 큰 경우로 정의하였다. 다변량 로지스틱 회귀 분석을 사용하여 위험 점수 모델을 구축하였다. 붓스트랩 기법을 통해 최종 모델은 1,000개의 붓스트랩 샘플을 사용하여 내부검증을 시행하였다.

Results: 총 1,027명의 환자 중 379 (36.9%) 에서 관상 동맥 석회화 진행이 되었다. 위험예측 모델 구축을 위한 위험인자는 신기증 저하 및 만성신장질환에 의한 무기질 골대사 장애를 포함하여 단변량 로지스틱 분석에서 유의하며 다

변량 로지스틱 분석에서 $p\text{-value} < 0.2$ 인 인자들로 선정하였다. 단변량 로스틱 회귀 분석에서는 나이, 성별, 체질량지수, 심장 질환, 고혈압, 당뇨, 이상지질혈증 과거력, 기준 관상 동맥 석회화 점수, 신기능, 인산, FGF-23/klotho, 소변 알부민-크레아티닌 비율이 관상 동맥 석회화 진행과 유의미하게 연관되었다. 다변량 로지스틱 회귀 분석에서는 나이, 성별, 고혈압, 당뇨, 이상지질혈증 과거력, 기준 관상 동맥 석회화 점수, 칼슘, 인산이 $p\text{-value} 0.2$ 밑으로 관상 동맥 석회화 진행과 연관이 있었다. 이를 통해 나이, 성별, 기준 관상 동맥 석회화 점수, 칼슘, 인산, 고혈압, 당뇨, 이상지질혈증 과거력을 관상 동맥 석회화 진행 예측 모델의 위험인자로 선정하였다. 관상 동맥 석회화 진행 예측의 ROC curve 분석에서 곡선 아래의 면적 0.869 (95% CI 0.847-0.892) 였다. 1,000개의 붓스트랩 샘플로 구성하여 시행한 내부 검증 상 상기 모델은 우수한 식별 및 보정 능력을 갖고 있었다. (validation c-statistics 2.5 percentile 0.845, median 0.869, 97.5 percentile 0.890).

Conclusions: 통합적으로 선정된 위험 인자들로 구성된 예측 모델은 관상 동맥 석회화진행을 보다 정확하게 예측할 수 있었다.

핵심되는 말 : 만성 신질환, 관상 동맥 석회화, 위험 예측 모델