

The KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD): A Korean Chronic Kidney Disease Cohort

Kook-Hwan Oh¹, Sue K. Park^{2,3,4}, Jayoun Kim⁵, Curie Ahn⁶, Representing the KNOW-CKD Study Investigators

¹Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea; ²Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea; ³Cancer Research Institute, Seoul National University, Seoul, Korea; ⁴Integrated Major in Innovative Medical Science, Seoul National University College of Medicine, Seoul, Korea; ⁵Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Korea; ⁶Department of Internal Medicine, National Medical Center, Seoul, Korea

The KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD) was launched in 2011 with the support of the Korea Disease Control and Prevention Agency. The study was designed with the aim of exploring the various clinical features and characteristics of chronic kidney disease (CKD) in Koreans, and elucidating the risk factors for CKD progression and adverse outcomes of CKD. For the cohort study, nephrologists at 9 tertiary university-affiliated hospitals participated in patient recruitment and follow-up. Biostatisticians and epidemiologists also participated in the basic design and structuring of the study. From 2011 until 2016, the KNOW-CKD Phase I recruited 2238 adult patients with CKD from stages G1 to G5, who were not receiving renal replacement therapy. The KNOW-CKD Phase II recruitment was started in 2019, with an enrollment target of 1500 subjects, focused on diabetic nephropathy and hypertensive kidney diseases in patients with reduced kidney function who are presumed to be at a higher risk of adverse outcomes. As of 2021, the KNOW-CKD investigators have published articles in the fields of socioeconomics, quality of life, nutrition, physical activity, renal progression, cardiovascular disease and outcomes, anemia, mineral bone disease, serum and urine biomarkers, and international and inter-ethnic comparisons. The KNOW-CKD researchers will elaborate a prediction model for various outcomes of CKD such as the development of end-stage kidney disease, major adverse cardiovascular events, and death.

Key words: Chronic kidney disease, KNOW-CKD, Cohort, Outcome

INTRODUCTION

Kidney Disease Improving Global Outcomes defined chronic kidney disease (CKD) as abnormalities of kidney structure or

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Corresponding author: Kook-Hwan Oh

Department of Internal Medicine, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Korea

E-mail: khoh@snu.ac.kr

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function, persisting for >3 months, regardless of their underlying cause [1]. CKD is a growing health burden worldwide [2], as well as in Korea [3]. The global all-age mortality rate from CKD increased by 41.5% between 1990 and 2017 [2]. The prevalence of CKD in Korea is estimated to be 13% in the adult population [4]. Approximately 5% of the Korean adult population is estimated to have decreased renal function, with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m² [4]. CKD, which potentially leads to dialysis or kidney transplantation, presents a major threat for cardiovascular (CV) events and all-cause mortality. The numbers of patients with CKD and end-stage kidney disease (ESKD) are starkly increasing [5,6].

Not only is CKD a significant threat in terms of morbidity and mortality, but the overall health expenditures for CKD management are remarkably increasing.

In order to expand our medical knowledge regarding the basic features of CKD in Koreans and the clinical course and risk factors of renal progression and adverse outcomes, the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD) was launched in 2011 with support from the Korean Disease Control and Prevention Agency (KDCA) [7]. Between 2011 and 2016, KNOW-CKD recruited 2238 adult subjects with CKD at 9 tertiary care hospitals throughout Korea [8]. It is expected that KNOW-CKD will provide abundant information on various issues, such as CV comorbidities, anemia, mineral metabolic derangements, quality of life (QoL), and health-related habits in CKD patients. It is exceptional that, unlike other CKD cohort studies such as the Chronic Renal Insufficiency Cohort (CRIC) of the United States [9,10] or the Chronic Kidney Disease Japan Cohort (CKD-JAC) of Japan [11], the KNOW-CKD study also recruited subjects at early stages of CKD (stage G1 and G2), as well as advanced stages, thereby enabling research on the long-term clinical course of early CKD (Supplemental Material 1).

The study aims of KNOW-CKD are as follows: (1) to investigate the natural clinical course of CKD, such as renal function deterioration, mortality, and complications with respect to the cause, glomerular filtration rate, and albuminuria categories, (2) to evaluate the risk factors for renal progression and related complications by elucidating the mechanistic link between renal injury and adverse outcomes, (3) to establish a clinical database and obtain numerous biological resources for future CKD research, and (4) to identify the genetic and molecular influences on renal progression and related complications.

The present article provides the basic design and summary of the findings from the KNOW-CKD Study Phase I and II.

KNOW-CKD PHASE I

Organization

The KNOW-CKD was designed as a hospital-based cohort study. Nephrologists working at 9 clinical centers of major university-affiliated hospitals, epidemiologists, specialists in laboratory medicine, and biostatisticians have participated in this study. The basic study protocol was approved by the ethical committee of the 9 participating centers. The study is supervised by the CKD Advisory Committee, which comprises mem-

bers from the KDCA and the Korean Society of Nephrology (NCT01630486 at <http://www.clinicaltrials.gov>).

Study Population

Each participating center enrolled consecutive individuals over a 5-year period from May 2011 to January 2016, totaling 2238 adult patients with CKD who provided written informed consent. The participating individuals were followed until death or drop-out.

The inclusion criteria of the KNOW-CKD Phase I study were ethnic Korean patients aged between 20 years and 75 years and at CKD stages ranging from G1 to G5 (non-dialysis).

Excluded subjects were those who (1) were unable or unwilling to give written consent, (2) had a history of chronic dialysis or any organ transplantation, (3) had severe heart failure or liver cirrhosis, (4) had a past or current history of malignancy, (5) were currently pregnant, or (6) had a single kidney due to trauma or nephrectomy.

CKD stages were defined on the basis of the eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI [cr]) formula [12].

Data Collection and Management

The study protocol and information collected at each study visit are summarized in Supplemental Material 2 [8]. Demographic and anthropometric information was collected according to the pre-specified protocol, reported elsewhere [7]. Serum creatinine was measured at a central laboratory (LabGenomics, Seongnam, Korea), using an assay traceable to the international reference material. Essential laboratory tests from the serum and urine such as serum creatinine, cystatin C, urine protein/albumin, and intact parathyroid hormone were conducted at a central laboratory in order to minimize inter-assay variation. Radiographic images such as lateral abdominal X-rays and kidney computed tomography were sent to the data coordinating center and evaluated by at least 2 independent and blinded experts. Study-related clinical and laboratory data were collected on an electronic web-based case report form using the PhactaX system, developed and maintained by the Medical Research Collaborating Center of Seoul National University Hospital.

Recruitment and Follow-up

From 2011 until 2016, Phase I of the KNOW-CKD study recruited 2238 subjects with CKD from 9 university-affiliated ter-

tiary-care hospitals throughout Korea. We classified the subjects according to the underlying cause of CKD into 4 subgroups: glomerulonephritis, diabetic nephropathy, hypertensive nephropathy, and autosomal dominant polycystic kidney disease. The other causative diseases were categorized as “unclassified.” Hypertensive nephropathy and autosomal dominant polycystic kidney disease were oversampled in order to compare among the 4 major causative diseases of CKD. The basic demographic and clinical features of the KNOW-CKD Phase I subjects were reported previously elsewhere [13].

Outcomes: Definitions and Data Acquisition

Composite renal events are defined as eGFR halving or development of ESKD. CV events are defined as any first event of the following: acute myocardial infarction, unstable angina, either ischemic or hemorrhagic cerebral stroke, congestive heart failure, symptomatic arrhythmia, aggravated valvular heart disease, pericardial disease, abdominal aortic aneurysm, and severe peripheral arterial disease that require hospitalization or interventions during follow-up. Three-point major adverse cardiovascular events (3-point MACE) were defined as fatal cardiac events, acute myocardial infarction, or stroke (ischemic or hemorrhagic). Four-point MACE included 3-point MACE and unstable angina.

Data on the time and specific causes of death were also obtained from either hospital records or the Korean Statistical In-

formation Service. Other events, such as all-cause hospitalization, surgery, and fractures, were also collected during the follow-up period. All the events described above were recorded on a special report form and further adjudicated by the Central Adjudication Committee of the KNOW-CKD Study.

As of March 31, 2021, among 2238 subjects enrolled in the study, there were 157 deaths, and 177 fatal or non-fatal CV events after 6.15 years (median) of follow-up. Furthermore, 635 subjects developed ESKD (Figure 1). There were 420 drop-outs (18.7%) during follow-up as of March 2021. Basic statistics, such as the crude and adjusted incidence rates of major events, such as ESKD, CV events and death, have been reported elsewhere (Table 1 and Figure 2) [14]. The KNOW-CKD Phase I study has recently revised the study protocol in order to extend the follow-up period of the participants for up to 20 years.

Major Findings on Chronic Kidney Disease

We have conducted research in a broad range of CKD-related areas, such as (1) the influence of socioeconomics and health-related habits on the outcomes of CKD, (2) CV comorbidities, (3) anemia, (4) mineral bone disease, (5) nutrition and QoL, (5) biomarker discovery, (6) clinical courses and outcomes of Korean CKD patients, and (7) international comparisons and meta-analysis. As of December 2021, the KNOW-CKD investigators have published 87 articles in major peer-reviewed international journals and are currently conducting research on

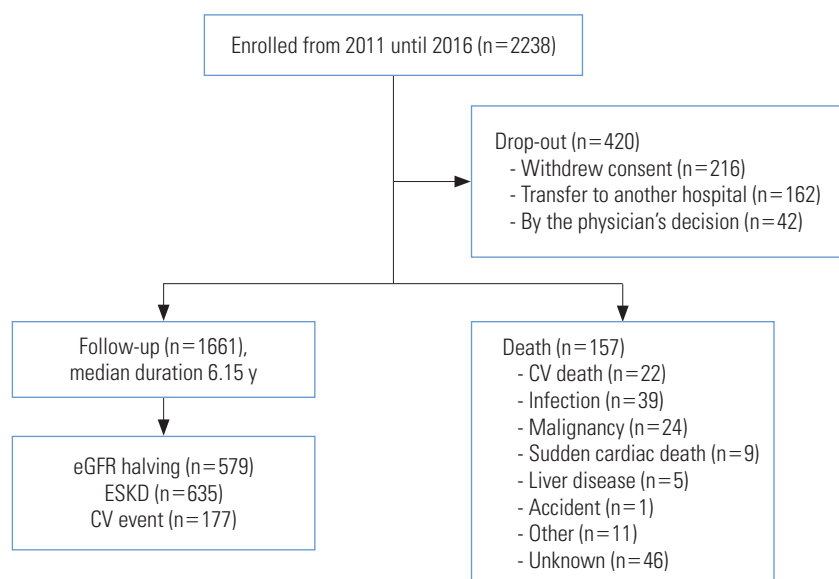


Figure 1. Flow diagram of KNOW-CKD Phase I as of March 2021. KNOW-CKD, KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; CV, cardiovascular.

Table 1. Incidence rates (per 1000 person-year) of main outcomes among KNOW-CKD participants (n=2238) as of March 2021¹

Variables	Total CKD patients			Diabetic CKD patients			Non-diabetic CKD patients			p-value ³
	Event no.	Incidence rates	Standardized incidence rates ²	Event no.	Incidence rates	Standardized incidence rates	Event no.	Incidence rates	Standardized incidence rates	
ESKD	635	54.2	47.4	307	94.0	119.3	328	39.0	36.4	<0.001
ESKD or eGFR halving	830	75.0	67.7	364	119.7	155.2	466	58.2	55.3	<0.001
eGFR halving	579	48.0	46.0	230	64.1	86.7	349	41.4	39.9	<0.001
3-point MACE	91	6.7	4.0	54	12.8	8.3	37	4.0	2.5	<0.001
4-point MACE	115	8.5	4.9	68	16.3	9.8	47	5.0	3.2	<0.001
Myocardial infarction	20	1.5	0.8	13	3.0	1.1	7	0.7	0.5	0.003
Unstable angina	29	2.1	1.0	17	4.0	1.7	12	1.3	0.8	0.003
Congestive heart failure	14	1.0	0.5	8	1.9	0.7	6	0.6	0.4	0.048
Ischemic stroke	33	2.4	1.3	20	4.7	2.9	13	1.4	0.8	0.001
Hemorrhagic stroke	14	1.0	0.6	5	1.2	0.4	9	1.0	0.6	0.733
Any death	157	11.4	7.0	89	20.5	10.7	68	7.2	5.2	<0.001
All composite outcomes	992	93.6	78.9	439	156.6	173.2	552	70.9	64.3	<0.001

KNOW-CKD, KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease; CKD, chronic kidney disease; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events; 3-point MACE, fatal cardiac events+acute myocardial infarction+stroke (ischemic, hemorrhagic); 4-point MACE, fatal cardiac events+acute myocardial infarction+stroke (ischemic, hemorrhagic)+unstable angina.

¹Median follow-up 6.15 years (range, 0.00 to 9.49).

²Standardized to the Korean population as of 2005.

³From Poisson regression model in the incidence comparisons between event rates in diabetic CKD patients and non-diabetic CKD patients.

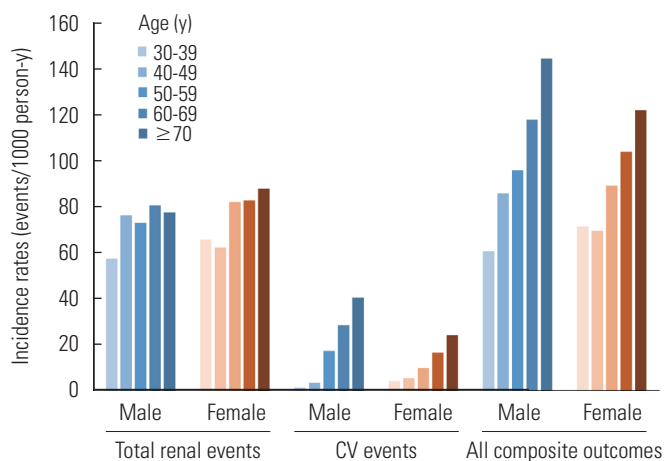


Figure 2. Age-specific incidence rates (per 1000 person-year) for renal events, cardiovascular (CV) events, and all composite outcomes in male and female, respectively. Renal events are defined as estimated glomerular filtration rate halving or development of end-stage kidney disease. CV events are defined as any first event of the following: acute myocardial infarction, unstable angina, either ischemic or hemorrhagic cerebral stroke, congestive heart failure, symptomatic arrhythmia, aggravated valvular heart disease, pericardial disease, abdominal aortic aneurysm, and severe peripheral arterial disease that requires hospitalization or interventions during the follow-up. All composite events are defined as any of the following: renal events, CV events, or death.

> 150 different research topics (Figure 1 and Supplemental Material 3). For a summary and major findings related to the KNOW-CKD Study, the readers are referred either to the recent review published elsewhere [13] or to the following website (<http://www.know-ckd.org>).

Socioeconomic status (SES), defined by education and income levels, is related to a set of socioeconomic factors, including health insurance, medical literacy, transportation, stress level, housing quality, and access to medical care [15]. Research analyzing KNOW-CKD data showed that lower SES was significantly associated with left ventricular hypertrophy, which is a major surrogate marker for future CV events [16]. An analysis of the association between SES and longitudinal outcomes is currently underway.

The subjects of KNOW-CKD were categorized into 6 groups according to a combination of body mass index (BMI; normal, overweight, obese) and waist-to-hip ratio (WHR; lower or higher than the sex-specific median WHR). Subjects with a normal BMI but higher WHR had a higher risk of coronary artery calcification than those with a normal BMI and lower WHR (odds ratio, 2.104; 95% confidence interval [CI], 1.074 to 4.121). Thus, BMI and WHR—2 surrogates of obesity—can help predict CV risk in CKD patients [17].

The KNOW-CKD researchers investigated the effect of health-

related habits [18-21] and physical activity of individuals on CKD outcomes. The study collected detailed information on exercise, alcohol drinking, and smoking through a self-reported questionnaire. Compared with non-drinkers, regular and occasional binge drinkers had 2.2-fold (95% CI, 1.38 to 3.46) and a 2.0-fold (95% CI, 1.33 to 2.98) higher risks of CKD progression, respectively. This association was particularly evident in patients who had decreased kidney function and proteinuria [20]. In a recent publication, the KNOW-CKD study investigators reported that the higher systolic and diastolic blood pressure (BP) levels are associated with a higher risk of a composite kidney outcome reflecting CKD progression. Systolic BP had a stronger association with adverse kidney outcomes than diastolic BP [22].

The incidence, prevalence, and clinical outcomes of CKD/ESKD differ depending on patients' socio-genetic backgrounds [23,24]. The KNOW-CKD investigators have been actively participating in the International Network of CKD Cohort Studies (iNET-CKD) [25], searching for determinants explaining these differences through inter-ethnic and international comparisons and meta-analyses.

A recent publication compared the prevalence of uncontrolled BP among 17 cohort studies, including 34 602 individuals with eGFR <60 mL/min/1.73 m² and treated hypertension adjusted for potential confounders [26]. The crude prevalence of BP ≥ 140/90 mmHg ranged from 28% to 61%. The adjusted prevalence ratios indicated better control in North America and high-income Asian countries, including Korea and Japan. Of particular note, KNOW-CKD exhibited the lowest prevalence of uncontrolled hypertension (27.3%) among the 17 participating CKD cohorts.

Another international meta-analysis compared the longitudinal outcomes of CKD across 8 different cohorts [27]. The KNOW-CKD cohort population, as compared to the other 7 cohorts in Europe, Japan, North America, and South America, exhibited relatively lower incidence of all-cause mortality, while exhibiting higher incidences of renal progression and ESKD, after adjustment (Supplemental Material 4).

Currently, KNOW-CKD is participating in the international collaborative research for exploring the international variability in hemoglobin and the approach to anemia treatment among individuals with CKD.

KNOW-CKD PHASE II

KNOW-CKD has recently launched the Phase II study, with a target recruitment of another 1500 subjects from the year 2019 until 2022. The Phase II KNOW-CKD study aims (1) to enhance the statistical power by enlarging the total pool of CKD subjects in the cohort, particularly those with eGFR <60 mL/min/1.73 m² and with higher risks of adverse events, (2) to further focus on diabetic nephropathy and hypertensive kidney disease, which are the 2 most common causes of CKD in Korea, (3) to strengthen the KNOW-CKD research as a resource on the health habits of CKD patients by obtaining more information on their dietary patterns, nutritional status, and cognitive function (Table 2).

In addition, with the coronavirus disease 2019 (COVID-19) pandemic, KNOW-CKD Phase II has modified its study protocol in order to investigate the impact of COVID-19 vaccination and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on the clinical course of CKD subjects. The study

Table 2. Comparison between Phase I and II KNOW-CKD studies

Variables	Phase I	Phase II
Recruitment period (year)	2011-2016	2019-2022
Study subjects (n)	2238 (actual)	1500 (target)
Age (y)	20-75	40-79
CKD stage or eGFR range	CKD stages G1-G5 (non-dialysis dependent)	15-60 mL/min/1.73m ²
Diabetes (%)	34	50 (target)
Major study objectives	Investigate the clinical course of CKD about the major events such as ESKD, CV events, and death Elucidate the major risk factors of adverse outcomes Compare the course of the 4 major etiologic diseases of CKD	Particularly focus on high-risk CKD subjects such as those with diabetic nephropathy, hypertensive nephropathy, old age, and low eGFR Collect detailed information on the nutritional status, dietary habits and cognitive functions from CKD subjects
Follow-up duration (y)	~20	~10

KNOW-CKD, KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; CV, cardiovascular.

Table 3. Basic demographic profiles of the recruited subjects of the KNOW-CKD Phase II, as of September 2021

Demographic factors		Total (n=1071)	Stage			p-value
			G3a (n=332)	G3b (n=479)	G4 (n=260)	
Age (y)	Mean ± SD	66.0 ± 8.2	65.5 ± 8.0	66.9 ± 8.1	64.9 ± 8.3	0.001 ¹
	Med [Min- Max]	67 [45-79]	66 [45-79]	68 [46-79]	65 [45-79]	
Sex	Male	749 (69.9)	257 (77.4)	328 (68.5)	164 (63.1)	0.001 ²
	Female	322 (30.1)	75 (22.6)	151 (31.5)	96 (36.9)	
Diabetes	Yes	665 (62.1)	181 (54.5)	312 (65.1)	172 (66.2)	0.003 ²
	No	406 (37.9)	151 (45.5)	167 (34.9)	88 (33.8)	

Values are presented as number (%).

KNOW-CKD, KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease; SD, standard deviation; Med, median; Min, minimum; Max, maximum.

¹Kruskal-Wallis test.

²Chi-square test.

is collecting COVID-19-related information, such as SARS-CoV-2 infections, vaccination against COVID-19, and related adverse events. This information will provide valuable insights into the long-term effects of COVID-19 on the clinical course of CKD.

As of September 2021, the KNOW-CKD Phase II has enrolled 1071 subjects, among whom 62% have diabetes. An interim analysis of the KNOW-CKD Phase II study subjects is presented in Table 3.

SUMMARY AND CONCLUSION

As the nation's largest CKD cohort, KNOW-CKD has elucidated numerous clinical features of CKD, particularly related to an East Asian population. The KNOW-CKD cohort has endeavored to answer basic questions regarding the clinical courses of the Korean population with CKD and to elucidate risk factors for adverse outcomes. Among various aspects of CKD, particular emphasis has been placed on socioeconomic factors, nutrition and QoL, health habits, CKD progression, CV comorbidities and outcomes, anemia, mineral bone disease, biomarker discovery, and international and inter-ethnic comparisons. KNOW-CKD Phase I plans to extend the follow-up period up to 20 years, and the Phase II study is currently recruiting subjects with CKD at higher risk of adverse outcomes in order to obtain more robust statistical power and to eventually offer a prediction model for the long-term consequences of CKD. The KNOW-CKD will enable us to identify the at-risk population, on whom we can focus more medical attention for risk modification. Furthermore, by pursuing biomarker discovery research using serum, urine, and DNA samples, the KNOW-CKD will provide a stepping stone for future personalized medicine.

Details on the design, patient enrollment, investigator

group, research publications, and annual report are available at the website of the KNOW-CKD study (<http://www.know-ckd.org>).

Ethics Statement

The present study protocol was reviewed and approved by the institutional review boards at each participating center: Seoul National University Hospital (1104-089-359); Seoul National University Bundang Hospital (B-1106/129-008); Yonsei University Severance Hospital (4-2011-0163); Kangbuk Samsung Medical Center (2011-01-076); Seoul St. Mary's Hospital (KC110IM10441); Gil Hospital (GIRBA2553); Eulji General Hospital (201105-01); Chonnam National University Hospital (CNUH-2011-092); Pusan Paik Hospital (11-091).

SUPPLEMENTAL MATERIALS

Supplemental materials are available at <https://doi.org/10.3961/jpmph.22.031>.

CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

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AUTHOR CONTRIBUTIONS

Conceptualization: Oh KH, Park SK, Kim J, Ahn C. Data curation: Oh KH, Kim J. Formal analysis: Oh KH, Kim J. Funding acquisition: Ahn C, Oh KH. Methodology: Park SK. Project administration: Oh KH. Visualization: Oh KH, Kim J. Writing – original draft: Oh KH. Writing – review & editing: Oh KH, Kim J, Park SK, Ahn C.

ORCID

Kook-Hwan Oh <https://orcid.org/0000-0001-9525-2179>
Sue K. Park <https://orcid.org/0000-0001-5002-9707>
Jayoun Kim <https://orcid.org/0000-0003-2234-7091>
Curie Ahn <https://orcid.org/0000-0001-7033-1102>

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