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Protocol of a Thyroid Cancer Longitudinal Study (T-CALOS): a prospective, clinical and epidemiological study in Korea

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ABSTRACT

Introduction: Thyroid cancer incidence in Korea is the highest in the world and has recently increased steeply. However, factors contributing to this sudden increase have not been fully elucidated, and few studies have explored the postoperative prognosis. The Thyroid Cancer Longitudinal Study (T-CALOS) was initiated with three aims: (1) to identify factors predicting quality of life, recurrence, and incidence of other diseases after thyroid cancer treatments; (2) to investigate environmental exposure to radiation, toxicants and molecular factors in relation to tumour aggressiveness; and (3) to evaluate gene–environment interactions that increase thyroid cancer in comparison with healthy participants from a pool of nationwide population-based healthy examinees.

Methods and analysis: T-CALOS enrols patients with incident thyroid cancer from three general hospitals, Seoul National University Hospital, Seoul National University Bundang Hospital and National Medical Center, Korea. The study is an ongoing project expecting to investigate 5000 patients with thyroid cancer up until 2017. Healthy examinees with a normal thyroid confirmed by sonography have been enrolled at the Healthy Examination Center at Seoul National University Hospital. We are also performing individual matching using two nationwide databases that are open to the public. Follow-up information is obtained at patients' clinical visits and by linkage to the national database. For statistical analysis, we will use conditional logistic regression models and a Cox proportional hazard regression model. A number of stratifications and sensitivity analyses will be performed to confirm the results.

Ethics and dissemination: Based on a large sample size, a prospective study design, comprehensive data collection and biobank, T-CALOS has been independently peer-reviewed and approved by the three hospitals and two funding sources (National Research Foundation of Korea and Korean Foundation for Cancer Research). The results of T-CALOS will be published according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.

Strengths and limitations of this study

- Multidisciplinary collaboration launched by thyroid cancer experts in surgery, internal medicine, epidemiology and family medicine.
- Methodologically strong with a longitudinal design, standardised protocols and planned statistical analyses.
- Limitation due to the restricted geographic coverage of the participating hospitals.

INTRODUCTION

Thyroid cancer has dramatically increased all over the world in recent years.[1] Age-standardised incidence rates of thyroid cancer in Korea are about 13-fold higher than in the rest of the world, fourfold higher than in the USA and 10-fold higher than in the European Union (EU-28).[2] Research has also highlighted that thyroid cancer has become the most common cancer as well as the most rapidly increasing cancer in Korea.[3] A recent study suggested that thyroid cancer has become more significant as a public health burden in Korea during 2000–2020 in terms of years lived with disability.[4]

Advancements in medical imaging techniques and increased screening rates have been suggested as important factors in the rapid increase in thyroid cancer incidence.[3 5] However, true increases in thyroid cancer incidence are suggested by the increased number of young patients with thyroid cancer, who do not usually receive cancer screening.[1 6] Although potential contributing factors have been suggested in recent studies,[7–10] further research is needed to fully understand and control thyroid cancer.

Patients with thyroid cancer who undergo a surgical procedure usually need long-term

management including postoperative radioiodine (RAI) therapy and thyroid hormone suppression therapy.[11 12] Different treatment methods and exposure doses in RAI therapy can affect patients' quality of life, thyroid function, recurrence and long-term prognosis,[13–15] but few large-scale studies have been performed. Moreover, the involvement of environmental factors and molecular signalling pathways in cancer susceptibility, tumour aggressiveness and prognosis of thyroid cancer have not been clarified in long-term follow-up research.[10 16–18]

For these reasons, the Thyroid Cancer Longitudinal Study (T-CALOS) was initiated with three specific objectives for extending our knowledge on thyroid cancer in Koreans. The primary goal of T-CALOS is to identify factors predicting health conditions after surgical procedures or treatments for thyroid cancer. The second goal is to investigate the effects of radiation exposure, toxicants and molecules on thyroid tumour aggressiveness, including tumour size, invasion and metastasis. The third goal is to evaluate environmental factors, lifestyles and genetic susceptibility to thyroid cancer in comparison with healthy subjects from a group of population-based healthy examinees.

METHODS AND ANALYSIS

Study design and setting

In 2009, T-CALOS was designed with specific research questions and data collection methods for baseline and follow-up information based on a prospective observational study. From 6 April 2010 (protocol V.1.0), epidemiologists and thyroid surgeons initiated the study at the Seoul National University College of Medicine and Seoul National University Hospital (SNUH). In 2012, endocrinologists in family medicine and health examination clinics at SNUH started participating in the study. We expanded further by enrolling subjects from two additional medical centres, Seoul National University Bundang Hospital (SNUBH) and National Medical Center (NMC). This ongoing study was designed to enrol 5000 patients with thyroid cancer until 31 December 2014.

Calculation of sample size

For the first study aim, we focused on health-related quality of life in patients after their treatment. We obtained meta-analysis results on 637 patients with recombinant human thyrotropin stimulation: no significant difference was observed in successful ablation rates, thyroglobulin levels and health-related quality of life.[19] We will also evaluate prognostic factors for 10-year recurrence-free survival rate and 10-year crude and cause-specific survival. A recent paper reported that extrathyroidal extension, nodal metastasis and tumour size increased recurrence of thyroid cancer (HR=1.2, 95% CI 1.1 to 1.3) among 1350 patients with thyroid cancer in Denmark.[20] Considering the frequency of tumour size <1 cm (30.4%) and assuming a 10% occurrence in the unexposed group, the sample size required is 4285 subjects. For the second aim, we planned to identify environmental exposures related to thyroid tumour aggressiveness, such as radioactive iodine (^{131}I). A high dose of ^{131}I has been associated with multifocality (950–17 472 mGy vs <200 mGy: OR=4.86, 95% CI 1.30 to 18.1).[21] However, the subjects in this cohort were enrolled in contaminated areas after the Chernobyl nuclear accident, which implies that further studies are needed in the general population.[21] Thirdly, to quantify gene–environment interactions, we will compute ORs and 95% CIs using conditional logistic regression models. Because few studies have reported gene–environment interaction for thyroid cancer development, we assumed that 0.3% of healthy participants and 1.7% of patients with thyroid cancer are likely to have a first-degree familial history of thyroid cancer as well as medical or therapeutic irradiation of the neck.[22] Evaluation of the interaction of the two factors will require 4449 subjects (405 cases and 4044 healthy controls). To answer all three study aims, we have estimated that we need to recruit at least 5000 patients with thyroid cancer, with 80% power, α=0.05, two-sided 95% confidence level and 10% loss to follow-up or missing information. All sample size calculations were performed using Epi Info V.7 (Centers for Disease Control and Prevention (CDC); http://www.cdc.gov/epiinfo).

The restricted geographic coverage can be considered to be a limitation. However, based on the 2009 Korea Statistics, 91% of the population is living in urban areas (Korea Ministry of Land, Infrastructure, and Transport, Statistical yearbook for city planning, 2006–2012, available at http://www.city.go.kr/). Nearly half of the health examination study participants are living in Seoul and Kyeonggi-do. Our patients with thyroid cancer are also derived from four hospitals, but nearly 70% of the participants are living in Seoul and its satellite area, Kyeonggi-do, and the other 30% are living in other areas throughout Korea.

We comprehensively reviewed 174 epidemiological studies related to thyroid cancer: most of them (134 studies) used a case–control design, and only four case–control studies had a large sample size (1200–1500 cases).[23–26] Among 40 cohort studies, the baseline population ranged from 20 000 to 800 000 people, but thyroid cancer case ascertainment was not sufficient (43–517 cases), except in three studies using 1.2 million women fishery workers,[27] 4.5 million male veterans[28] and 27 556 survivors having fertility-preserving initiatives from Cancer Registry studies and the Medical Birth Registry of Norway.[29] Even a cohort study using 6.5 million priests found only 26 patients with thyroid cancer.[30] Therefore, T-CALOS, planning to recruit 5000 patients with incident thyroid cancer and matched healthy patients from general population study pools, will contribute to a better understanding of thyroid cancer development in relation to clinical, environmental and molecular genetic factors.

Study subjects

The source of participants was patients with thyroid cancer who had undergone surgical procedures at the department of surgery in the participating hospitals or had visited the department of internal medicine for treatment of thyroid cancer. The eligibility criteria were as follows:

1. thyroid cancer diagnosis with clinicopathological information;
2. ≥20 years old;
3. voluntarily agreed to participate and signed an informed consent form;
4. donated blood and/or urine samples;
5. no communication difficulties and able to complete a 30 min interview.

This study individually matches healthy participants with each patient using three sources of data. The first database is the Korean National Health and Nutrition Examination Survey (KNHANES), a nationwide database with large sample size based on proportional random sampling for age, gender and geographic distribution.[31–33] Although it was originally a cross-sectional design to examine the national prevalence of major exposure factors and common diseases, the Korea Center for Disease Control and Prevention (KCDC) has passively followed-up those participants who agreed to data linkage (about 91% of 42 347 enrolled subjects from 2007 to 2012). KNHANES uses a comparable questionnaire for lifestyles factors and various laboratory testing results including levels of thyrotropin and vitamin D (table 1), and the data are available to the public (http://knhanes.cdc.go.kr). The second set of healthy participants is from the Health Examinee Study (HEXA), part of the Korean Genome and Epidemiology Study (KoGES, N=170 094, from 2004 to 2009). The original aim of HEXA was to investigate epidemiological and genomic risk factors for major diseases in Koreans, and it has a comparable questionnaire and biorepository system to our study.[34] For the third set of healthy participants, we are recruiting subjects confirmed with thyroid ultrasonography among the Health Examinees from the Health Examination Center at the Department of Family Medicine of SNUH (SNUH-HEXA). SNUH-HEXA can provide valuable information on radiation exposure and environmental carcinogens and toxicants, which is also collected for patients with thyroid cancer using the same protocols for a structured questionnaire and biorepository system.

Data collection

We are collecting information using structured questionnaires, anthropometric measurements, and laboratory clinical tests (figure 1). The questionnaires include demographic characteristics, history of diseases, lifestyle factors, medical history, family history and the Food Frequency Questionnaire validated by KCDC in 2007.[35] We are also collecting laboratory clinical test results on preoperative assessment, tumour markers, and pathology reports for patients with thyroid cancer (figure 1). All data are promptly entered electronically, and we check missing information and range checks for data values once a month. We do not store personal information for data anonymity and it is kept with limited accessibility.

Biospecimens are collected on recruitment and at regular clinical visits of the participants. Each blood sample (16 mL) is drawn after at least 8 h of overnight fasting and delivered to a commercial laboratory. They are processed into serum, plasma and DNA within 24 h; the processed aliquots are stored at −70°C. Urine samples (10 mL) are also collected into a sterilised urine cup. Collected biospecimens are going to be used for later analysis of biomarkers, metabolites and nutrients.

Outcome measures: follow-up

Active follow-up is performed during the patients' outpatient clinic visits at 6, 12 and 24 months with their endocrinologist and surgeon. Patients are followed-up for their progress, laboratory tests and exposure status related to infections and/or drugs, questions about menopause, hormone therapy and chemotherapy, and interviews for lifestyle factors and family history of cancer. An annual medical chart review is scheduled for patients' vital status, disease progression including recurrence, metastasis and new diagnosis of the other diseases, and RAI therapy and its dose.

Record linkages are planned using nationwide databases including the National Cancer Registry, the Death Certificate Database, and the medical claims database of the National Health Insurance Review Agency. The diagnostic criteria and cause of death will be recorded using International Classification of Diseases (ICD)-10 and ICD-O-3 codes. We previously confirmed in a pilot study for the passive follow-up method in Korea that the efficiency of the three passive follow-up methods combined was 99.1%.[35] The objective of the passive follow-up is to detect incidence of other types of cancer, thyroid cancer deaths, and incidence of other diseases including cardiovascular.

STATISTICAL ANALYSIS

For descriptive analysis, χ^2 and t tests will be used to compare general characteristics of study participants. We will analyse the impacts of quantitative variables according to their clinical criteria if applicable, or we will use their median and quartile values for grouping if there is no established cut-off value. Non-parametric statistical methods will be applied when required. To estimate associations of predicting factors and outcomes related to thyroid cancer, we will use conditional logistic regression models for the dataset of patients with thyroid cancer and their matched healthy participants. After data linkage to national databases and identification of incidences of other diseases, we also will estimate HRs and 95% CIs using the Cox proportional hazard models. Adjustment for potential confounders and interaction

Table 1 Topics and items included in questionnaires and clinical report form (CRF), Thyroid Cancer Longitudinal Study for Prevention and Incidence (T-CALOS)

Category	Subjects	Items
CRF	Thyroid cancer patient group only	1. Laboratory clinical test and urine test 2. Biomarker testing such as BRAF mutation 3. Sonography, ECG and X-rays 4. Preoperative laboratory test 5. Report on surgery and pathology
Core variables	All subjects	1. Demographic information: age, education, marital status and social/living status 2. Disease history: hypertension, diabetes, dyslipidaemia, cerebrovascular attacks, ischaemic heart disease, lung tuberculosis, benign thyroid disease (hyperthyroidism, hypothyroidism), gastric ulcer/gastritis, duodenal ulcer, colon polyp, acute liver disease, chronic liver disease, fatty liver, chronic obstructive pulmonary disease, chronic bronchitis, asthma, other allergy, gout, osteoarthritis, osteoporosis, cataract, glaucoma, depression, periodontal disease, prostate hypertrophy, fracture, site-specific cancer 3. Medication history: aspirin, non-steroidal anti-inflammatory drugs, acetaminophen, others, vitamin supplements including vitamin E, calcium, Fe, glucosamine, ginseng and other medications 4. Occupational history 5. Family information: family history of disease and general information about family members 6. Anthropometric information: current and past weight and height 7. Lifestyle factors: active and passive cigarette smoking history, alcohol consumption history, sleep and physical activity 8. Female reproductive factors: menarche, menopause, pregnancy, pregnancy outcome, children, delivery, breast feeding, abortion, oral contraceptives, postmenopausal hormone replacement therapy, surgical procedures of hysterectomy and oophorectomy 9. Dietary habits and Food Frequency Questionnaires 10. Health examination: blood pressure, total cholesterol, triglyceride, fasting blood sugar, serum creatinine, blood urea nitrogen, albumin, glutamate–oxaloacetate transaminase, glutamate–pyruvate transaminase, haemoglobin, haematocrit, white blood cell count, platelet
Additional variables for each group	Thyroid cancer patients and healthy participants in SNU-HEXA	1. Additional medical history: the route of thyroid cancer diagnosis (symptoms, cancer screening or other), thyroiditis, thyroid adenoma, chronic hepatitis (B, C, A), systemic lupus erythematosus, chronic kidney disease, benign breast disease, uterine myoma and polycystic ovary, information on *Helicobacter pylori* infection, and average number of colds 2. Thyroid-related drug history: thyroid medication, steroid, retinol, osteoporosis-treatment drugs 3. Additional family history: thyroid adenoma, colon polyp, familial polyposis, chronic liver disease 4. Environmental toxicant information: information on exposure to a newly constructed house, flooring material in a house, smelling of a new house, use of new furniture, internal flowerpots, ventilation by season, internal heating and air conditioning 5. Environmental pollutant exposure such as incineration plant, cattle shed, etc, the number of lane and location of nearest lane from house, car driving history, use of pesticide and waterproof clothes 6. Exposure to radiation and electromagnetic fields: medical and occupational radiation exposure, use of microwave oven and electric devices 7. Exposure to chemical compounds: use of cosmetics, perfumes, nail polish, air freshener, deodorant, detergent, hair spray, hair colouring, occupational exposure to pesticides, dry cleaning, detergent use, painting, disinfectant and other hazardous chemicals including butadiene, acrylamide, benzene, ethylenoxide, bisphenolA, TCE, PCB, dioxin 8. Other: coated cookware, materials of drinking water containers, use of instant, canned, plastic packaged, bottled, or vinyl-wrapped foods 9. Socioeconomic stress: Score (visual analogue scale) of depression, stress, health status 10. Additional testing related to thyroid hormones
	Healthy participants pooled from KNHANES	1. Exposure to occupational hazardous chemicals 2. Measurement: vitamin D, parathyroid hormone, ALP, free thyroxine, thyrotropin, anti-thyroid peroxidase antibody, calcitonin, total and ionised calcium, phosphorus, 1,25-dihydroxyvitamin D3, 25-hydroxyvitamin D3, hepatitis B surface antigen/antibody, anti-hepatitis C virus and HIV
	Healthy participants pooled from KoGES-HEXA	1. Additional disease histories 2. Semiquantitative diet questionnaire and dietary habits

KNHANES, Korean National Health and Nutrition Examination Survey; KoGES, Korean Genome and Epidemiology Study; SNU-HEXA, Seoul National University-Health Examinee Study.

Table 2 Participation, response and follow-up rate in the Thyroid Cancer Longitudinal Study for Prevention and Incidence (T-CALOS), 2012–2014

	Eligible population, n	Participants with consent and blood and/or urine, n (%)	Response to questionnaire among those with blood and consent, n (%)	Response to questionnaire among those with urine and consent, n (%)
Phase I				
2010 April–December (Department of Surgery, SNUH)	1035	802 (77%)	602 (75%)	570 (71%)
Phase II–III				
January 2013– April 2014 (Department of Surgery, SNUH)	2133	1920 (90%)	1730 (90%)	1665 (87%)
February 2013– April 2014 (Department of Internal Medicine, SNUH)	425	242 (57%)	132 (55%)	124 (51%)
February 2013– April 2014 (Department of Internal Medicine, SNUH) Prevalent cases*	198	119 (60%)	88 (74%)	86 (72%)
Phase III				
2014 January–May (Department of Surgery, SNUBH)	204	174 (85%)	149 (86%)	128 (71%)
2014 February–May (Department of Surgery, NMC)	135	78 (58%)	70 (90%)	71 (91%)
Overall	4130	3093 (75%)	2771 (90%)	2558 (83%)

*Patients who had been diagnosed with thyroid cancer and had surgery before their admission to Department of Internal Medicine.
NMC, National Medical Center; SNUBH, Seoul National University Bundang Hospital; SNUH, Seoul National University Hospital.

terms related to demographics, lifestyle (drinking, smoking and regular exercise) and health conditions (menopause, medical history and medication intake) will be considered in the multivariate models. We plan to perform subgroup analyses of histological groups, tumour characteristics and mutation testing results. In addition, we will present frequencies of missing data in the results of the total sample, and the results will be confirmed with sensitivity analyses with and without missing data. All statistical analyses will be performed using SAS V.9.3.

Descriptive summaries

Overall participation rate and response rate are estimated to be 75% and 90%, respectively (table 2). In phase I of T-CALOS conducted in the department of surgery, we enrolled 802 patients (77% participation rate), and 602 patients responded to a questionnaire

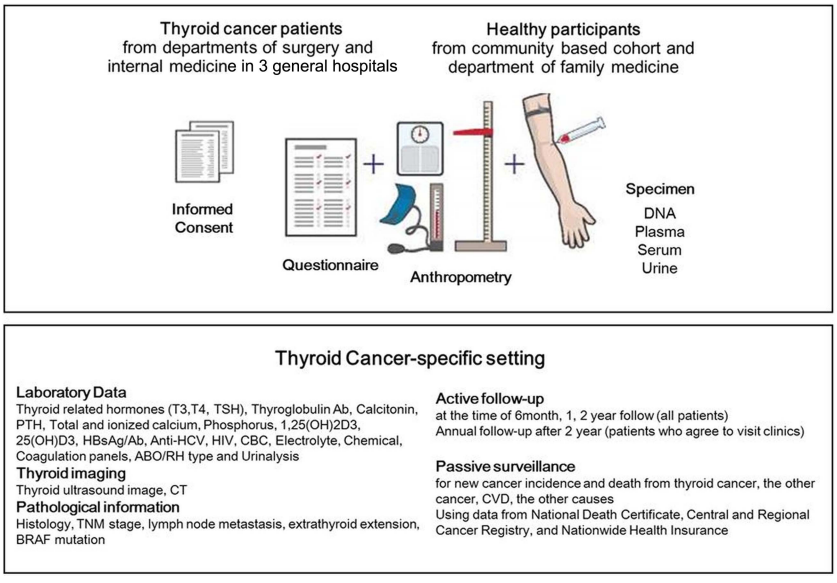

Figure 1 Study design and setting for data collection: Thyroid Cancer Longitudinal Study for Prevention and Incidence (T-CALOS).

Table 3 Baseline characteristics of patients with thyroid cancer and healthy participants, Korea Incident Thyroid Cancer Study (T-CALOS), 2010–2014

Characteristic	Thyroid cancerpatients	Matched healthy participants		
		HEXA*	KNHANES†	SNUH-HEXA‡
Age ≥50 years	46.8	46.3	44.4	70.4
Female	80.5	79.2	80.4	48.0
Educated (≥12 years)	86.4	84.8	86.4	100.0
Married	87.1	95.8	88.2	95.9
Body mass index ≥25 kg/m^2	27.2	27.9	24.6	19.6
Ever smoked	16.5	17.3	20.3	35.7
Ever consumed alcohol	46.2	43.7	85.6	66.7
Postmenopausal§	36.2	36.4	25.1	18.8
History of thyroid disease	7.5	5.1	6.1	4.1
Papillary carcinoma	95.2			
Positive BRAF mutation¶	66.5			
Tumour size >1 cm	66.8			
Lymph node metastasis	39.7			
Multifocality	37.3			
Tumour stage I	58.1			
5-year recurrence	5.9			
5-year survival	99.8			

Values are percentages.
*Thyroid cancer patients (n=2013) were individually matched with healthy participants by age, gender, education and birth year from the HEXA cohort (ratio of patients/healthy participants=1:12).
†Thyroid cancer patients (n=2009 were individually matched with healthy participants by age, gender and education, and the healthy participants were from KNHANES IV-V (ratio of patients/healthy participants=1:1).
‡Thyroid cancer patients (n=294) were individually matched with healthy participants by age, gender and education, and the healthy participants were from SNUH-HEXA (ratio of patients/healthy participants=3:1).
§Only female participants were included.
¶15.7% of thyroid cancer patients did not have information on BRAF mutation.
HEXA, Health Examinee Study; KNHANES, Korean National Health and Nutrition Examination Survey; SNUH-HEXA, Seoul National University Hospital-Health Examinee Study.

interview (75% response rate). In phase II, the participation rate and response rate were improved (to as high as 90%; table 2). After expanding recruitment to the department of internal medicine, we had 623 eligible patients (425 incident and 198 prevalent cancer); 361 patients participated (57% with incident cancer; 60% with prevalence cancer), and 220 patients responded to the interview (response rate, 55% and 74%, respectively) (table 2). In January 2014, two hospitals (SNUBH and NMC) newly joined for phase III. As of April 2014, the participation rate and response rate were estimated to be 85% and 86% for SNUBH and 58% and 90% for NMC, respectively (table 2).

Table 3 presents the summary of characteristics of patients with thyroid cancer and healthy participants from the three sources, HEXA, KNHANES and SNUH-HEXA. Among the patients, 80.5% were female and 46.8% were ≥50 years old (table 3). Patients with thyroid cancer were more likely to be diagnosed with thyroid disease than healthy participants ($p<0.05$) (table 3). Based on the thyroid sonography results for SNUH-HEXA, we identified 66 participants with supernormal thyroid and 139 with thyroid disease, including benign tumour (47.3%), cyst (35.1%) and thyroiditis (14.6%) (data not shown). Papillary carcinoma (95.2%) was the most common diagnosis among the subtypes, and 66.5% of patients were identified as being a BRAF mutation carrier (table 3). Although most patients were female, male patients had more aggressive tumours in terms of tumour size (male and female 37.0% and 32.3%, respectively, for tumour size >1 cm) and lymph node metastasis (male and female 55.2% and 36.0%, respectively).

ETHICS AND DISSEMINATION

Investigators have obtained informed consent from all subjects, and the institutional review board (IRB) of each hospital have peer-reviewed and approved the related documents and the entire study protocols for collection and use of participant data and biological specimens (IRB numbers 0809-097-258, 1001-067-307 and 1202-088-398 for SNUH, B-1304/200-401 for SNUBH, H-1308/033-005 for NMC). The data monitoring committee (DMC) members of T-CALOS are required to attend bimonthly meetings. IRB annually monitors our data collection status, and we promptly report to IRB if there is any protocol modification, including but not limited to changes in eligibility criteria, outcomes and statistical analyses. The DMC and IRB are independent of the funding sources and anyone with competing interests. The accessibility of the data will be decided after discussion of the topic and quality of the proposal, including the title, hypothesis, timeline, methods, budget

and ethical considerations, with the steering committees. We may not open our data and resources for quality control until the targeted sample size is reached. To discuss partnership and submit a research proposal, contact Dr Sue K Park (suepark@snu.ac.kr). Articles detailing the study results will be submitted for international peer-reviewed journal publication, as described in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.[36]

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Contributors KEL, YJP, BC, DJP, SKP and Y-KY contributed to the concept and design of the study. SKP and YH were involved in drafting the manuscript. JYC, S-jK, HC, H-CC and ARA critically revised for important content and ensured accuracy of the results. DJP and SKP gave final approval of the version to be published. All authors read and approved the final submitted version of the manuscript.

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Patient consent Obtained.

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