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STUDY PROTOCOL

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Protocol for a prospective, longitudinal cohort study on the incidence of dementia after the onset of delirium in patients with mild cognitive impairment: MDDCohort (Mild Cognitive Impairment Delirium Dementia)

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Abstract

Background Mild cognitive impairment (MCI) is a major risk factor for delirium. Few studies with mid- to long-term follow-up periods have examined delirium, MCI, and the conversion of MCI to dementia. This prospective, longitudinal cohort study aims to assess the incidence of dementia after delirium onset in patients with MCI and to develop an artificial intelligence algorithm for predicting the conversion of MCI to dementia.

Methods A 30-day evaluation for delirium will be performed for adults aged ≥ 65 years diagnosed with MCI who score 18–23 on the Korean Mini-Mental State Exam. Individuals exhibiting delirium at least once will be classified into the delirium group and the remainder into the non-delirium group. Over 3 years, patients will undergo follow-ups for survival and conversion to dementia at 30-day intervals to analyze risk factors for delirium and clinical outcomes. Differences between the two groups will be analyzed using the chi-square and independent t-tests. Kaplan-Meier survival and Cox proportional hazard regression will be used to assess the effects on 30-day, 60-day, 12-month, 24-month, and 36-month mortality, whereas linear regression will be used to assess the length of stay at long-term care facilities and medical costs.

Discussion The results will emphasize the importance of preventing delirium in MCI patients, and preventive interventions can be strengthened.

Trial Registration NCT05113446 (ClinicalTrials.gov). *Registered 9 November 2021 - Retrospectively registered.*

Keywords Mild cognitive impairment, Delirium, Dementia, Cohort

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Introduction

Background

Delirium is defined as an acute disturbance of consciousness, memory, logical inference, concentration, and activity [1]. Common in individuals with chronic aging disease, it occurs in 14–55% of hospitalized elderly patients [2]. The onset of delirium is associated with poor outcomes in these patients [3]. Increased risk of long-term cognitive and functional impairment extends the length of stay (LOS) and readmission to long-term care facilities. This increases medical costs, caregiving burden [4], and mortality risk [5, 6].

Pre-existing cognitive impairment and dementia are major risk factors for delirium, whereas delirium is an independent risk factor for dementia [7]. The global prevalence of dementia is 5–7%, which is projected to increase more than three-fold over the next 20 years [8]. The annual medical cost of dementia is estimated at 818 billion USD worldwide, a significant socioeconomic burden [9]. Mild Cognitive Impairment (MCI) is the transitional stage between cognitive impairment and dementia [10] and affects 6.7–25.2% of older adults [11]. Importantly, the annual rate of conversion to dementia among older adults with MCI is 10–15%, which is markedly higher than that among the general older adult population (1–2%) [12]. The incidence of postoperative delirium is higher among older adults with MCI than in their healthy counterparts [13]. Coexisting preoperative frailty and MCI is the most potent risk factor for postoperative delirium [14]. Hence, if undiagnosed, MCI can lead to increased incidence of delirium and is associated with poor outcomes.

Few studies exist with mid- to long-term follow-up periods on delirium, MCI, and dementia or on the effects of delirium on the conversion of MCI to dementia. Prevention of delirium is more effective than treatment and management; additionally, prophylactic interventions for MCI or early-stage cognitive impairment are the most effective methods of preventing the conversion to dementia [4, 15, 16].

Objective

The study aims to to establish a short-term 3-year cohort in long-term care hospitals in Korea to investigate the effect of delirium on dementia conversion in MCI patients and to develop an artificial intelligence (AI) algorithm for predicting the conversion of MCI to dementia. First, we will investigate the incidence of delirium in patients with MCI and analyze the risk factors and outcomes: mortality, length of stay (LOS), and medical cost. Second, the rate of dementia conversion in patients with MCI and outcomes of the onset of delirium on dementia conversion in patients with MCI will be investigated. Third, we will develop an artificial intelligence (AI) algorithm for predicting the conversion of MCI to dementia.

Methods

Study design

This is a prospective cohort study of two parallel groups and the detailed study procedure is described in Fig. 1. Baseline assessments will be performed at study participant recruitment and serve as cross-sectional data for estimating conversion of MCI to dementia. Since this is a multicenter prospective cohort study, the STROBE (strengthening the report of observational studies in epidemiology) guidelines will be followed [17].

The plans for establishing a cohort for the first to third years are summarized below and are depicted in Fig. 2.

- Year one–establish a standardized MDD Cohort (Mild Cognitive Impairment Delirium Dementia Cohort).

Patients will be recruited according to the exclusion and inclusion criteria and initially assessed. The patients will be divided into delirium and non-delirium groups (see below for details). Conversion to dementia and survival will be checked at 30-day intervals. The first year data will be analyzed.

- Year two–continuous management of the MDDCohort.

Conversion to dementia and survival will be checked at 30-day intervals; additionally, the cohort will be managed to minimize dropouts. The 2-year data will be analyzed.

- Year three–develop a web-based application for analyzing results and managing comprehensive delirium.

Conversion to dementia and survival will be checked at 30-day intervals and the 3-year results of the cohort will be analyzed. Based on these results, an AI algorithm for predicting the conversion of MCI to dementia will be developed.

Participants and eligibility criteria

Advertisements for participant recruitment will be posted at three long-term care facilities with ≥300 beds in three Korean regions (North Jeolla, South Jeolla, South Gyeongsang) with similar inpatient environments. Since eligible participants include vulnerable individuals with diminished cognitive abilities, only individuals with written consent from their legal guardian will be enrolled. Further, upon request, the patient's consent will also be obtained. The consent form sets out the purpose of the

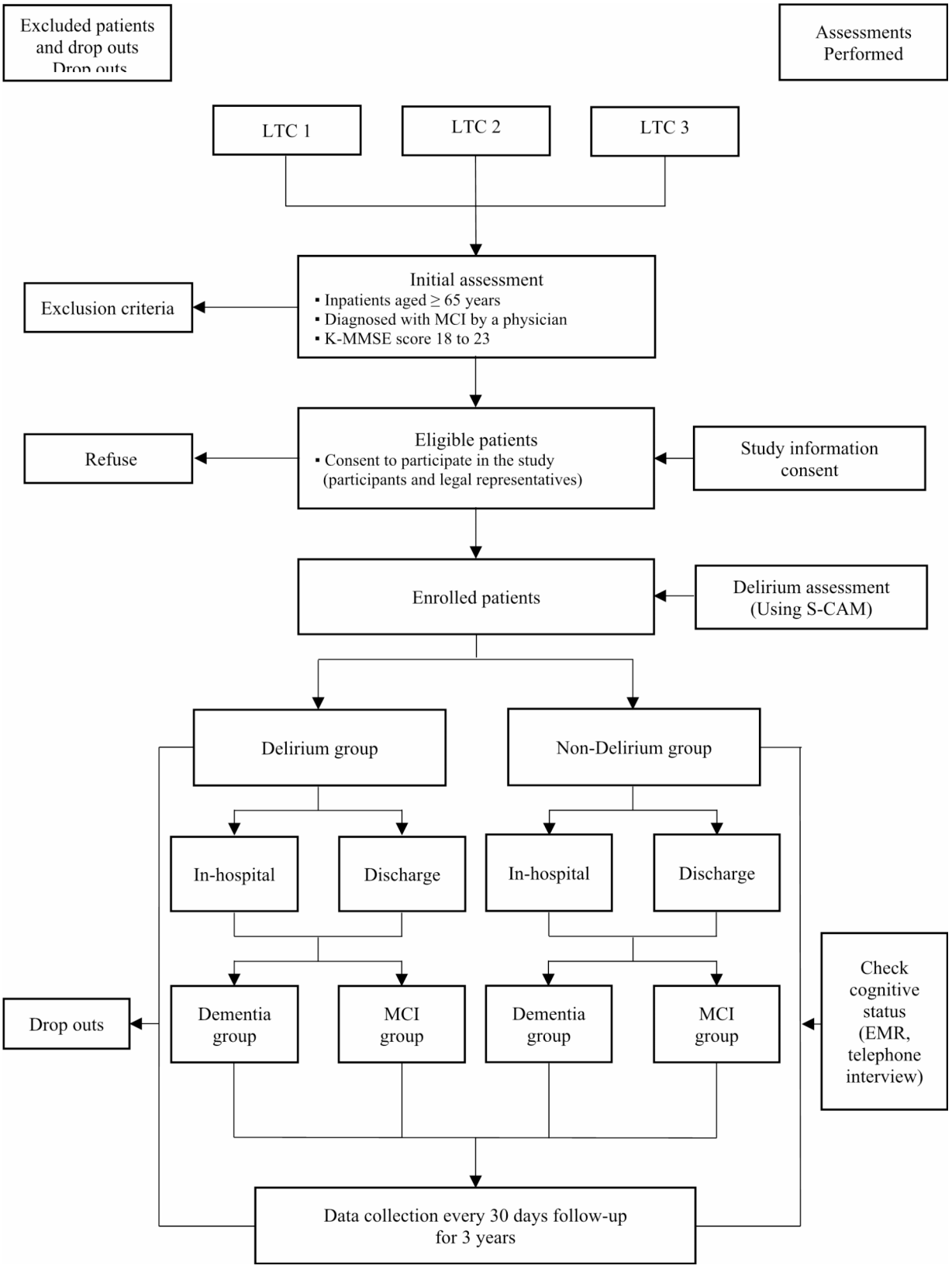

Fig. 1 Flow chart of study procedure. Abbreviations: EMR, electronic medical records; K-MMSE, Korean version of the Mini-Mental State Examination; LTC, long term care facility; MCI, mild cognitive impairment; S-CAM, Short Confusion Assessment Methods

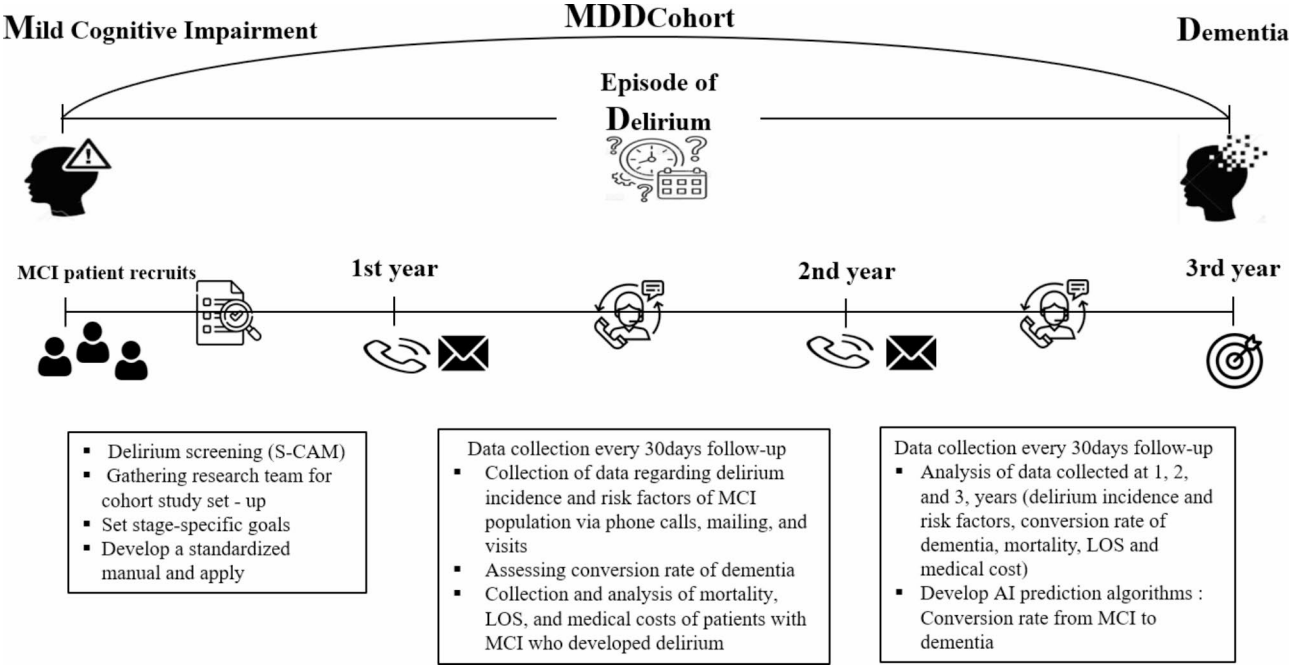

Fig. 2 MDDCohort protocol. Abbreviations: AI, artificial intelligence; LOS, length of stay; MCI, mild cognitive impairment; S-CAM, Short Confusion Assessment Methods

study, the procedures and duration of participation, the drop-outs from participating in the study, the side effects and risks, the benefits of participating in the study and the absence of a penalty for not participating, the guarantee of personal information and confidentiality, and the withdrawal of consent.

Inclusion criteria: inpatients aged ≥ 65 years who are diagnosed with MCI by a physician and with a score of 18–23 on the Korean version of the Mini-Mental State Exam (K-MMSE) [18]. Exclusion criteria: Individuals who cannot be examined using the Short Confusion Assessment Methods (S-CAM) [19] due to severe visual or hearing problems, individuals with severe mental health or neurological diagnoses, individuals who die or are transferred on the day of hospitalization, and individuals who cannot receive emergency treatment interventions during evaluation or due to hospital circumstances.

Sample size

Based on the previous study [20], to calculate the number of samples in patients with mild cognitive impairment, size effect = 0.15 (medium), α probability = 0.05, power = 0.9, and 8 predictors will be analyzed. As a result, the number of samples will be 136, and the total number of subjects considering the dropout rate will be 163.

Data collection and analysis

Data collection and follow-up are described in Table 1. The executive researcher will be responsible for monitoring study progress, reporting on missing data and taking necessary action to follow-up on missing data or discrepancies. All data will be stored securely. Original participant files and the key to the code linking personal details and coded study data will be stored securely in a locked cupboard to which only researchers have access, in a locked office, in a secure building. Original files will be stored in numerical order and maintained for a period of three years after completion of the study. Any personal data stored electronically will be kept on a secure server, in a password-protected environment to which only the researchers directly involved in administering and supervising the study have access.

Standardization

Before beginning the study, we formed a small research team to establish the cohort. The team analyzed domestic and international findings, set stage-specific goals, and developed a standardized manual to be distributed before study onset containing detailed guidelines for standardizing data collection and quality control at the study hospitals.

Initial data collection

Participants' general characteristics will be identified by researchers through electronic medical records (EMR). These include age, sex, education level, K-MMSE score, comorbidity index, route of hospitalization, smoking, drinking, body mass index, and number of drugs in use. Therapeutic factors (fall, pressure ulcer, use of and types of analgesics for pain, blood transfusion, catheterization,

Table 1 Summary of data collection and follow-up

	Study period					
	Enrollment	Follow-up				
	MCI	30 days	60 days	1 year	2 years	3 years
Screening						
Inclusion and exclusion	X					
Informed consent	X					
Patient characteristics						
General characteristics	X					
Risk factors	X					
Clinical characteristics	X					
Delirium assessment						
Short CAM	X	X				
Cognitive assessment						
Onset of dementia[a]		X	X	X	X	X
Outcomes						
Mortality		X	X	X	X	X
Hospital length of stay				X	X	X
Healthcare costs				X	X	X

[a]onset of dementia; every 30 days follow-up

Abbreviations: CAM, Confusion Assessment Methods; MCI, mild cognitive impairment

gastric tube feeding, use of sedatives) and other factors (stroke, visual/hearing impairment, dehydration, malnutrition, water-electrolyte imbalance, surgery, infection, pain, sleep deprivation, restraints, immobility) will be analyzed to identify risk factors for delirium. The geriatric depression scale [21] and activities of daily living score [22] will also be assessed.

Delirium assessment

Delirium will be assessed by trained research assistants using the Korean version of the S-CAM twice a day (8–10 AM, 4–6 PM) for 30 days. To standardize this process, nurses from each long-term care hospital with ≥10 years of experience will be selected to ensure the quality of the raters. Before study commencement, they will undergo three 2-h video training sessions regarding S-CAM administration; moreover, the expert spot checking method will be applied. The expert spot checker will be a researcher fully familiar with S-CAM administration. Each research assistant will administer the S-CAM simultaneously with the spot checker and the results will be compared outside the ward to revise errors and educate the research assistant. Research assistants with ≥95% agreement with the spot checker for 20 consecutive trials will be allowed to independently assess delirium using the S-CAM. Further, we developed a standard for processing missing or suspicious data.

Four key delirium symptoms (acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness) will be assessed. Participants who test positive at least once during this period will be classified into the delirium group and the rest into the non-delirium group for 36 months of follow up.

Survival and conversion to dementia will be based on changes in EMR and K-MMSE scores taken at 30-day intervals. Records of discharged patients will be accessed from outpatient follow-up records or by telephone interview.

Study outcomes

Primary outcomes

- Delirium prevalence in MCI and risk factors.

The incidence and risk factors for delirium will be identified based on the one-year follow-up data. The conversion rate of dementia and the time to dementia conversion will be analyzed every 12 months.

Secondary outcomes

- Mortality.

We will calculate the 30-day, 60-day, 12-month, 24-month, and 36-month mortality rates in both groups.

- Length of stay (LOS).

LOS (days) will be analyzed in 12-month units.

- Cost.

Direct medical costs incurred only for treatment during the hospital stay will be calculated in Korean Won (KRW) and analyzed in 12-month units. Table 1 describes a detailed summary of data collection and timeline.

Ethical consideration

This study has reveived approval from the Institutional Review Board (IRB) of Keimyung University(40525-202012-HR-073-02) and has been registered at ClinicalTrials.gov, which is run by the US National Institute of Health (NCT05113446). All methods employed will be in accordance with relevant guidelines and regulations. Prior to the commencement of the study, written informed consent will be obtained from all participats. In case of participants with cognitive impairment, consent will be obtained from their legal representative. To ensure confidentiality, all questionnaire and electronic data will be anonymized and assigned a unique identification number, following the appropriate guidelines.

Statistical analysis

Data analyses will be performed using the SPSS software (version 24.0, IBM, Armonk, NY). General characteristics will be analyzed using descriptive statistics. Between-group differences in the general characteristics, risk factors, and therapeutic factors will be analyzed using the chi-square test and independent t-test. The effects on 30-day, 60-day, 12-month, 24-month, and 36-month mortality will be analyzed using Kaplan-Meier survival and Cox proportional hazard regression. Moreover, the LOS and medical costs will be analyzed through linear regression.

Results

Data collection for this study is currently in progress and is expected to be completed by September 30, 2022. Afterwards, we will analyze the difference in dementia conversion rate, mortality, length of stay, and medical cost in the delirium and non-delirium groups at 12 months, 24 months, and 36 months. Based on our findings, we will develop an AI algorithm to predict dementia transition in MCI patients.

Discussion

This is a protocol for establishing and analyzing a nationwide cohort of older adults with MCI in three cities for a three-year study on the risk factors for delirium and the effects of delirium on the conversion of MCI to dementia as well as the time from delirium to conversion.

Five to eight% of the population aged≥60 years suffer from dementia [23] and 10–20% of the population aged≥65 years show increased MCI [24]. Delirium is an important risk factor for dementia [6, 25–29]; moreover, cognitive decline in older adults with frailty is a risk factor for delirium [13, 14, 30]. This suggests that delirium is associated with cognitive impairment and/or dementia. Since delirium causes not only poor outcomes for patients and their families but also socioeconomic losses [31], there is a need to elucidate the incidence of dementia with respect to cognitive impairment, time until conversion to dementia, and predictive factors.

Clinically validated tools to actively prevent delirium and closely monitor cognitive function are necessary to identify delirium patients at risk [32]. To this end, a nurse, an experienced research assistant, uses S-CAM [19] to measure delirium over a 30-day period, and based on this, we identify the participants' risk factors for delirium and analyze the associated outcomes. Our findings may increase medical staff awareness of delirium prevention interventions in long-term care facilities and reduce poor outcomes related to delirium, mortality, readmission rates, and medical costs.

We will also establish a cohort of patients with MCI as a delirium group and a non-delirium group based on the results of delirium measurements to closely monitor their cognitive changes at 30-day intervals to investigate the effect of delirium on the transition of MCI to dementia. Based on our findings, we will develop an AI algorithm to predict dementia transition in MCI patients, enabling early detection and timely intervention by medical staff for cognitive impairment. Determining the risk of delirium in patients with cognitive impairment will have a positive effect on preventing the acceleration of cognitive decline. Finally, our findings will contribute to improving the quality of medical care, promoting patient safety, and preventing dementia, ultimately reducing the socioeconomic burden associated with the onset of dementia.

Limitations

Some limitations of the study should be considered. First is the management of patients discharged during the study period. To minimize their dropout rate, research assistants will try to administer follow-ups via phone, mailing, and visitation, but a higher number of dropouts of discharged patients are expected than dropouts of inpatients. Second, it cannot be excluded that changes in the hospitalization environment, such as restrictions on family visits due to COVID-19, may affect the research results in some way.

Abbreviations

AI	Artificial intelligence
EMR	Electronic medical records
K-MMSE	Korean version of the Mini-Mental State Exam
LOS	Length of stay
MCI	Mild cognitive impairment
MDDCohort	Mild Cognitive Impairment Delirium Dementia Cohort
S-CAM	Short Confusion Assessment Methods

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-024-05480-6.

Supplementary Material 1

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Author contributions
Conceptualization or/and Methodology: KJM. Writing: original draft or/and review and editing: KJM, MAP. The author(s) read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the study will be available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board (IRB) of Keimyung University(40525-202012-HR-073-02) and registered at ClinicalTrials.gov run by the US National Institute of Health (NCT05113446).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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