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Data Profile

Establishment of a registry of clinical data and bioresources for rare nervous system diseases

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ABSTRACT

Rare diseases are predominantly genetic or inherited, and patients with these conditions frequently exhibit neurological symptoms. Diagnosing and treating many rare diseases is a complex challenge, and their low prevalence complicates the performance of research, which in turn hinders the advancement of therapeutic options. One strategy to address this issue is the creation of national or international registries for rare diseases, which can help researchers monitor and investigate their natural progression. In the Republic of Korea, we established a registry across 5 centers that focuses on 3 rare diseases, all of which are characterized by gait disturbances resulting from motor system dysfunction. The registry will collect clinical information and human bioresources from patients with amyotrophic lateral sclerosis, spinocerebellar ataxia, and hereditary spastic paraplegia. These resources will be stored at ICreaT and the National Biobank of Korea. Once the registry is complete, the data will be made publicly available for further research. Through this registry, our research team is dedicated to identifying genetic variants that are specific to Korean patients, uncovering biomarkers that show a strong correlation with clinical symptoms, and leveraging this information for early diagnosis and the development of treatments.

Keywords: Data collection; Health resources; Nervous system; Rare diseases

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Introduction

According to the World Health Organization, a rare disease is defined as a condition affecting fewer than 6.5 individuals per 10,000. Often, these diseases have hereditary or congenital

origins. Patients with rare diseases frequently exhibit complex symptoms, many of which are neurological in nature [1]. Despite the identification of numerous rare diseases, the small patient populations for each condition and the diverse range of symptoms pose challenges for early diagnosis. Furthermore, conducting clinical trials with large participant numbers is problematic. Consequently, most rare diseases lack curative treatments, and available therapies tend to be either low in efficacy or expensive. These issues lead to severe disability or death for those affected by rare diseases and contribute to an increased socioeconomic burden [2].

In this study, we sought to establish a registry for motor neuron disease, hereditary spastic paraplegia (HSP), and spinocerebellar ataxia (SCA). These rare motor nervous system disorders are characterized by gait disturbance as a primary symptom. Although these diseases are respectively typified by muscle weakness, spastic paraplegia, and ataxia, they can present with a spectrum of overlapping motor neuron symptoms with similar initial clinical presentations. Furthermore, the absence of precise diagnostic biomarkers and identified genetic variants complicates the accuracy of diagnosis.

Amyotrophic lateral sclerosis (ALS) is a rare and incurable neurodegenerative disease that affects motor nerves in the cerebrum, brainstem, and spinal cord. The clinical manifestations of ALS are highly heterogeneous. Depending on the primary site of pathogenesis, patients may be classified as having progressive muscular atrophy, primary lateral sclerosis, or bulbar ALS [3]. However, because the diagnosis of ALS is based on clinical diagnostic criteria, it is difficult to distinguish the early stages of this disease from other conditions with similar clinical manifestations, such as progressive paraplegia and spinocerebellar atrophy [4]. Moreover, a definitive diagnosis of ALS is often elusive until symptoms have fully progressed [5–7]. According to Brown et al. [8], the pooled prevalence rate of ALS (per 100,000 people) is 6.22 in Europe, 5.20 in North America, and 3.01 in Asia, excluding Japan. Approximately 5.1% of ALS cases are considered familial ALS, with the remainder classified as sporadic ALS [8,9]. Research on familial ALS has identified major pathogenic mutations in genes associated with the disease, such as *SOD1* and *C9ORF72*. While these pathogenic mutations are rare, they have also been found in patients with sporadic ALS. Furthermore, recent findings confirm that ALS clinically and genetically overlaps with several multisystem neurodegenerative diseases [3]. Consequently, research into hereditary ALS is intensifying in an effort to enhance our understanding of the disease and to discover suitable treatments. In the Republic of Korea, the prevalence of ALS is approximately 3 per 100,000 people, markedly lower than in Western countries [10]. The genotypes identified in the Republic of Korea are predominantly *SOD1* genetic variants, in contrast to the *C9ORF72* variants that are more common in Western populations, underscoring a key regional difference in the genetic landscape of the disease [11]. Therefore, collecting clinical and genetic information on Korean patients with ALS is necessary to develop treatments appropriate for this population. To achieve this, a network of ALS researchers must be established and sustained with ongoing support, focusing on the development of diagnostics and therapies.

HSP encompasses a group of inherited neurological disorders that affect the corticospinal tract, leading to stiffness and muscle weakness in the lower limbs. Epidemiological data on HSP are scarce due to its ambiguous clinical diagnosis and classification. However, the prevalence of HSP with a confirmed genetic mutation is approximately 1.8 per 100,000 individuals [12]. HSP prevalence exhibits considerable regional variation, with figures as low as 0.2 per 100,000 in Japan, potentially indicating a lower incidence in Eastern than in Western populations [13]. HSP can be classified based on clinical phenotype, inheritance pattern, or pathogenesis [14]. From a clinical perspective, HSPs are divided into pure and complex forms. Pure HSP typically presents with progressive spastic weakness of the lower limbs, hypertonic urinary bladder disturbance, and a mild reduction in vibratory sensation. In contrast, complex HSP may include additional clinical features such as cerebellar

HIGHLIGHTS

- We established the first registry in the Republic of Korea specifically for rare neurological diseases impacting the motor nervous system: amyotrophic lateral sclerosis, hereditary spastic paraplegia, and spinocerebellar atrophy. This registry involved 5 tertiary hospitals.
- The registry will gather clinical information and bioresources from patients with rare diseases over a 3-year period, with data and materials stored within a web-based clinical research management system and the National Biobank of Korea.
- Our research team aims to identify genetic variants explicitly found in Korean patients, uncover biomarkers strongly correlated with clinical symptoms, and leverage these findings for early diagnosis and treatment development.

dysfunction, cognitive impairment, peripheral neuropathy, and dyskinesia, alongside the characteristic lower limb spastic paralysis. It is therefore important to differentiate HSP from conditions such as motor neuron disease, dementia, and genetic metabolic disorders. Regarding inheritance patterns, HSPs are classified as autosomal dominant, autosomal recessive, sex chromosome-linked, or mitochondrial. The genetic landscape of HSP is diverse, and associations between phenotype and genotype are often unclear. In many instances, genetic variants remain unidentified even when the clinical presentation is consistent with HSP. Consequently, gathering clinical and biological data from patients in the Republic of Korea is vital for advancing our understanding of this condition.

SCA encompasses a clinically and genetically diverse group of autosomal dominant inherited degenerative disorders affecting the cerebellum and its associated structures. SCA represents one of the rarest incurable diseases. The disease primarily affects the cerebellum and progresses to cause a range of cerebellar-related dysfunctions, such as gait disturbances, hand tremors, dysarthria, dysphagia, and balance issues [15]. Due to its rarity, data on national prevalence rates are scarce and variable [16]. In the Republic of Korea, a study estimated the prevalence of SCA to be 4.99 per 100,000 person-years, based on data from the Korean National Health Insurance system [17]. Another study investigating the distribution of SCA genes in this country identified *SCA2*, *SCA3*, and *SCA6* as the most prevalent [18]. However, despite the publication of several Korean studies, including multicenter research utilizing National Health Insurance data, few registries or databases detail the clinical presentation of patients with SCA. Consequently, a critical need exists to establish a registry for Korean patients with SCA. Research into actual clinical presentations can yield valuable evidence for future treatment and care, while supporting the development of initiatives to improve the welfare and legal systems necessary to improve the lives of patients.

Each of the diseases mentioned is rare and characterized by motor symptoms, with numerous genetic variants identified. Consequently, diagnosing based on a single genetic test is challenging, as different genes can lead to a range of clinical manifestations, and phenotypes may overlap across multiple genes (Figure 1). Moreover, genotype distributions vary between national and international reports. With the continuous discovery of new genetic variants, it is essential to gather and share diverse patient information for long-term research. This will enable a more comprehensive understanding along with integration into clinical practice [19].

Overall, epidemiological data on rare motor neuron diseases are limited due to their low prevalence, the complexities of clinical diagnosis, their unclear pathogenesis, and their genetic heterogeneity. Identifying biomarkers and developing targeted therapeutics are further complicated by these factors. Therefore, the need exists to create a comprehensive registry and to gather robust evidence on risk factors and early diagnosis through research efforts. To address this need, the present study was designed to establish a registry for rare neurological diseases in the Republic of Korea and to construct a biobank of high-quality human bioresources. This registry is termed the Korean Research Network for Motor Neuron Disease and Spinocerebellar Ataxia (K-MoSCA). The study also entails the development of an expert network that will lay the groundwork for a range of future studies in this field.

Collection

Five tertiary hospitals in the Republic of Korea will participate in the data collection process: Konkuk University Medical Center, Samsung Medical Center, Chungnam National University Hospital, Soonchunhyang University Cheonan Hospital, and Inje University Haeundae Paik Hospital (Figure 2). Each research center has individually obtained approval from its respective institutional review board. Our goal is to gather data from patients who have been diagnosed with the specified rare diseases within the Department of Neurology at each hospital and who have voluntarily consented to participate in the study. We are aiming for a total of 60 study participants annually over a period of 3 years, amounting to 180 participants in total, with each hospital contributing 12 participants per year. Data collection will take place at

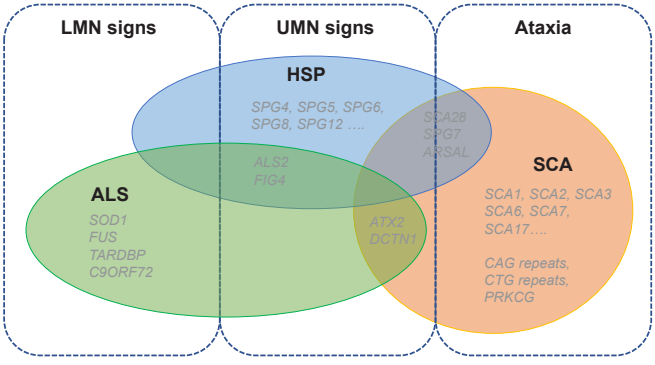

Figure 1. Clinical manifestations and genetic abnormalities observed in a representative group of rare motor neuron diseases.
LMN, lower motor neuron; UMN, upper motor neuron; ALS, amyotrophic lateral sclerosis; HSP, hereditary spastic paraplegia; SCA, spinocerebellar ataxia.

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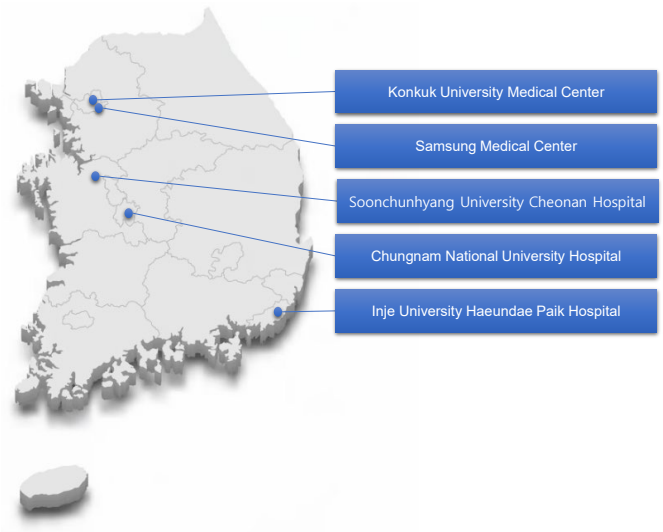

Figure 2. Participating hospitals in the rare motor neuron disease network.

each institution over a 3-year period commencing on the date of approval by the ethics committee of each institution. Additionally, information will be collected from patients who are willing to participate in the study during their baseline visit and at 6-month follow-up appointments.

Patients who agree to participate in the study will provide written informed consent and will receive a copy of the consent form. Potential participants will be clearly informed that their decision to participate or decline will not affect their clinical care. They will also be told that they have the right to withdraw their consent at any time before data collection is finalized. Patients will be given the contact details of the research team, allowing them to withdraw without the need to discuss their decision with others. Research staff will be made aware that patients may refuse to participate and withdraw their consent at any point before the completion of data collection.

Participants must be at least 19 years old and have a diagnosis of ALS, HSP, or SCA. For those with ALS, eligibility will be determined based on whether they meet any of the following diagnostic requirements: the Revised El Escorial criteria, the Awaji Criteria, or the Gold Coast Criteria [5–7]. Patients with HSP or SCA will be considered eligible if they possess relevant genetic variants and exhibit a clinical presentation that aligns with their diagnosis [12,15]. Enrollment of participants with these conditions will occur after they have completed adequate differential diagnostic testing, as determined by the investigating researcher. Conversely, individuals with other systemic diseases, vulnerable populations such as minors or those with cognitive impairments, participants from whom clinical information and biological samples cannot be obtained, and any individuals deemed unsuitable for the study by the investigator will be excluded (Table 1).

After consenting to participate in the study, during the initial visit, patients will be asked to provide a range of information. These data include demographics, personal medical history, family history, comorbidities, clinical information, treatment details, disability assessments, and patient-based quality of life measures obtained through questionnaires (Table 2). Disability assessments will employ disease-specific scales: the Korean version of the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (K-ALSFRS-R) for ALS, the Spastic Paraplegia Rating Scale (SPRS) for HSP, and the Scale for the Assessment and Rating of Ataxia (SARA) for SCA [20–22]. Quality of life will be evaluated using the Fatigue Severity Scale, the Beck Depression Inventory-II, the Pittsburgh Sleep Quality Index, the World Health Organization Quality of Life-BREF, and the Korean version of the Zarit Burden Interview as a measure of caregiver burden [23–26].

Patient clinical information will be de-identified, and all centers will utilize a standardized case record form. These case notes will document standard demographic data, categorized by disease, and a registry will be established via a web-based clinical research management system (iCreaT; https://icreat.nih.go.kr/) [27]. To ensure the efficient operation of this system, each institutional researcher will receive training on its use and be assigned identification.

Prospectively, blood samples and (when possible) cerebrospinal fluid will be collected. Each blood sample will consist of approximately 25 mL, distributed as follows: 3 ethylenediaminetetraacetic acid (EDTA) tubes (12 mL total), 1 serum separator tube (8 mL), and 1 Paxgene tube (5 mL). An additional 10 mL of blood will be collected and stored if patients consent to provide peripheral blood mononuclear cells and RNA. The blood in the EDTA tubes will be separated into DNA (10 μg per vial in 3 vials), plasma (300 μL per vial in 10 vials), and buffy coat (1.8 mL in a single vial). The blood in the serum separator tube will be processed to obtain serum (300 μL per vial in 5 vials). From the Paxgene RNA tube, 3 to 4 mL of RNA-stabilized blood will be extracted. Furthermore, if a lumbar puncture is performed for medical treatment or diagnosis and the patient consents, approximately 5 to 10 mL of cerebrospinal fluid will be collected. No cerebrospinal fluid will be collected solely for research purposes, and this material will only be stored if an excess is available over the amount required for medical procedures. Blood and cerebrospinal fluid samples will be collected, processed, and stored by the Global Clinical Central Lab and then sent to the National Biobank of Korea annually [28]. At each 6-month

Table 1. Inclusion and exclusion criteria for study participants

	Contents
Inclusion criteria	1. Adults aged 19 years or older with the ability to provide informed consent 2. Diagnosed with one of the following diseases: 1) Amyotrophic lateral sclerosis: diagnosed using the Revised El Escorial criteria, Awaji Criteria, or Gold Cost Criteria 2) Hereditary spastic paraplegia 3) Spinocerebellar ataxia 4) Others[a]: primary lateral sclerosis, progressive muscular atrophy, ALS-FTD complex, progressive bulbar palsy, benign focal muscular atrophy, and other motor neuron disease
Exclusion criteria	1. Patients with systemic diseases 2. Vulnerable research participants: minors, cognitively impaired patients 3. Participants for whom clinical information and human derivatives cannot be collected 4. Other patients who, in the judgment of the investigator, are inappropriate for the study

ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia.
[a]Atypical motor neuron diseases, for which diagnosis is not explained by other diseases.

Table 2. Case record items

Category	Specific item
Demographics	Age at registration, sex, place of birth, smoking history, drinking history
Personal medical history	Comorbidities: tumors, cardiovascular disease, Parkinson's disease, autoimmune disease, neurodegenerative disease, genetic neuropathy
Family history	Three or more generations of family tree
Clinical information	Date of onset, diagnosis, diagnosis subclassification, degree of neurological involvement at onset and at present, clinical course
Test results	Imaging tests: brain MRI, spine MRI Neurophysiology tests: NCS, EMG, EP Genetic tests: simple gene tests, gene panel tests, NGS, WES, WGS Cerebrospinal fluid tests Cognitive function tests (K-MMSE-2, MoCA-K), Pulmonary function tests (test date, test availability, FCV, FEV1)
Treatment and support	Medical treatment: riluzole, edaravone, others Invasive treatment: gastrostomy, tracheostomy Support: use of mechanical ventilator, non-invasive ventilator, and/or wheelchair
Disability level	ALS: K-ALSFRS-R HSP: SPRS SCA: SARA
Patient-based quality of life index	FFS, BDI-II, PSQI, WHOQOL-BREF, Zarit Burden Interview
Follow-up items	Disability level on each clinical scale (K-ALSFRS-R, SPRS, and SARA), application of invasive treatment, date of death

MRI, magnetic resonance imaging; NCS, nerve conduction study; EMG, electromyography; EP, evoked potential; NGS, next-generation sequencing; WES, whole-exome sequencing; WGS, whole-genome sequencing; K-MMSE-2; Korean version of the Mini-Mental State Examination-2; MoCA-K, Korean version of the Montreal Cognitive Assessment; FCV, forced vital capacity; FEV1, forced expiratory volume in 1 second; ALS, amyotrophic lateral sclerosis; K-ALSFRS-R, Korean version of the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; HSP, hereditary spastic paraplegia; SPRS, Spastic Paraplegia Rating Scale; SCA, spinocerebellar atrophy; SARA, Scale for the Assessment and Rating of Ataxia; FFS, Fatigue Severity Scale; BDI-II, Beck Depression Inventory-II; PSQI, Pittsburgh Sleep Quality Index; WHOQOL-BREF, World Health Organization Quality of Life-BREF.

follow-up, clinical scales will be reassessed for each disease. Additional information will be gathered regarding wheelchair use, gastrostomy, tracheostomy, and, if applicable, the date of death.

Data Resource Use

Descriptive statistics will be applied to the data collected from participants to estimate national demographic trends for each disease. Using the clinical information gathered, predictive determinants and risk factors associated with disease-specific clinical assessment scales—the K-ALSFRS-R for ALS, SPRS for HSP, and SARA for SCA—can be identified. Furthermore, these data will enable the discovery of factors that could be leveraged for the prevention of each disease. Genetic analysis of the collected human derivatives will be conducted to identify variants specific to the Korean population, based on the genetic profiles associated with

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each disease. An additional objective is to uncover potential biomarkers by analyzing associations between changes in clinical scales and genomic or transcriptomic data. We anticipate the discovery of specific biomarkers in these samples, particularly from participants who have provided cerebrospinal fluid. Our approach includes integrating clinical information, clinical scale assessments, genetic testing results, and detailed examinations such as imaging and electromyography to perform extensive association analyses.

Strengths and Weaknesses

The aim of this study was to develop the first registry focused on rare neurological diseases affecting the motor nervous system in the Republic of Korea. We have created a web-based platform that facilitates multi-institutional collaboration within this country, allowing for the collection of patient information on rare conditions. Previously, these data were managed independently by each institution for individual diseases. By focusing exclusively on rare motor nerve diseases and engaging experts from various institutions, we anticipate that specialized data can be more easily gathered and shared. Moreover, a broad range of data will be obtained through initial evaluation questionnaires that cover depression, sleep, quality of life, and caregiver burden. This approach is expected to aid in the identification of potential biomarkers and the discovery of genetic variants that are prevalent in the Korean population. Additional data acquired from patient follow-ups will further enhance our understanding of the epidemiology of rare movement disorders in the Republic of Korea. The insights gained from this data will help to facilitate early diagnosis, determine the appropriate timing of medical intervention, establish patient-centered management strategies, and inspire the development of novel treatments. In Europe, national registries for rare diseases, including neurological conditions, have been established. These registries facilitate information sharing, the development of diagnostic and management guidelines, and the provision of training programs based on these guidelines [29]. It is our hope that these European models will inform the creation of national registries in Asia and provide a valuable resource to support personalized medicine for patient populations that differ from those in Western countries.

Our registry has the potential to be utilized for expanded studies of the targeted diseases. Data will be collected from patients and their progress monitored under current standards of care, aiding in the identification of progressive genetic variants and analyses of treatment effectiveness in Korean patients. Additionally, it will provide information on cost-effective testing and the tracking of highly relevant biomarkers and genes for patients who are unable to participate. Biomarker monitoring, the application of new therapeutic agents, and appropriate gene therapy are expected to be prioritized to help surviving patients, and the existing genetic information can assist in the analysis of subgroups for each disease.

Ultimately, the registry will serve as a basis for medical policy decisions concerning motor neuron diseases and related disorders. It is designed to gather data on the diagnostic process and medical treatments for each rare disease. Additionally, extending our research to include the estimation of healthcare costs associated with diagnosis, treatment, and medical intervention could form a foundation for future health insurance budget allocations and coverage policies. Additionally, the registry will compile data on factors such as fatigue, sleep patterns, depression, quality of life, and caregiver burden. This information will be instrumental in understanding the real-world needs of patients and their caregivers, allowing for the prioritization of services and the reform of relevant policies.

The study does have certain limitations. Like other registries, it offers no direct benefits to participating patients. Those enrolled in the registry and contributing specimens will not gain direct financial or therapeutic incentives. They should not anticipate any specific benefits until new treatments are formulated from the analysis of their provided data, or until they are assessed for suitable interventions. These points are clearly communicated in the informed consent documentation.

Participant selection bias within the registry is also a possibility. The number of participating centers is limited, and not all patients diagnosed at each center can be enrolled. Moreover, as outlined in the exclusion criteria, patients experiencing cognitive decline who do not have a guardian are not suitable for inclusion in the registry, as it is unlikely that sufficient information can be obtained from them. Additionally, the limited participant capacity and brief enrollment window mean that patients diagnosed outside of this period, as well as those diagnosed after the target number of patients has been reached, will be excluded from the registry, potentially contributing to bias. Geographically, 2 of the 5 centers are situated in Seoul; this complicates the process of evenly recruiting patients from each region, especially when factoring in travel distance. Patients who are more educated, younger, have better mobility, or have caregivers who can readily travel to the centers and are attuned to their medical needs are relatively likely to be represented in the registry.

Limitations in the maintenance and persistence of the registry should also be expected. Enrolled patients will undergo follow-up every 6 months to evaluate their clinical symptoms, clinical measures, and the utilization of invasive treatments. However, we anticipate challenges in data management and updates following the conclusion of the 3-year study period. The diagnosis and classification of individual rare diseases may evolve, and the registry may only partially capture these changes for patients whose initial diagnosis is subject to revision due to new findings over the course of the study. Additionally, compatibility with registries from other healthcare organizations and forthcoming advancements should be considered.

Access

While the registry is under construction, clinicians and researchers involved in studies can access clinical data through iCReaT; this information will not be made public. After the data assembly is finalized, the collected data will be de-identified to the greatest extent possible in preparation for public release and will be stored under the Korea Disease Control and Prevention Agency. The stored data and human biological resources will be accessible as public resources via the National Biobank of Korea and its website [30]. Contributors will retain priority access to up to 30% of the deposited resources for a period of 3 years. Once this priority period has lapsed, the human bioresources will become fully public. Regarding these biological deposits, data may be requested through an export application even before the deposit process is complete. In such instances, the donor's right to priority distribution is considered to have been exercised. Other researchers may also request access. If their applications are approved, they will be provided with clinical information and specimens for research purposes, and any results obtained must be submitted.

Notes

Ethics Approval

Ethical approval for this study was obtained from the institutional review board of each participating research center: Konkuk University Medical Center (IRB No: KUMC 2023-04-060), Samsung Medical Center (IRB No: SMC 2023-04-045-001), Chungnam National University Hospital (IRB No: CNUH 2023-06-066), Soonchunhyang University Cheonan Hospital (IRB No: SCHCA 2023-04-042-003), and Inje University Haeundae Paik Hospital (IRB No: HPIRB 2023-05-004-003). Participants and their guardians were informed about the study, and written consent was obtained.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

The datasets are not currently publicly accessible; however, they can be obtained from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: JO, JP, JMS, BJK, ES; Data curation: MYJ; Methodology: JMS, EO, KJS; Project administration: all authors; Resources: all authors; Supervision: BJK; Writing–original draft: DK; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Additional Contributions

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