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## Aims and Scope

*Annals of Geriatric Medicine and Research* (Ann Geriatr Med Res, AGMR) is a peer-reviewed journal that aims to introduce new knowledge related to geriatric medicine and to provide a forum for the analysis of gerontology, broadly defined. As a leading journal of geriatrics and gerontology in Korea, one of the fastest aging countries, AGMR offers future perspectives on policymaking for older adults, clinical and biological science in aging researches especially for Asian emerging countries. Original manuscripts relating to any aspect of geriatrics, including clinical research, aging-related basic research, and policy research related to senior health and welfare will be considered for publication. Professionals from a wide range of geriatric specialties, multidisciplinary areas, and related disciplines are encouraged to submit manuscripts for publication.

## General Information

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# Editorial board

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# New Clinical Practice Guidelines for Sarcopenia Screening and Diagnosis in Korean Older Adults: A Step Forward

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Sarcopenia, the age-related loss of muscle mass, strength, and function, has become an increasingly prevalent condition as the global population ages.[1,2] It is associated with a wide range of negative health outcomes including falls, disability, and mortality.[3] In response to this growing problem, researchers and healthcare professionals have developed various guidelines and assessment tools for the diagnosis and management of sarcopenia. In Korea, the Korean Working Group on Sarcopenia (KWGS) has established new clinical practice guidelines for sarcopenia screening and diagnosis.[4]

As Korea is one of the fastest-aging countries worldwide, preventing and treating sarcopenia in older adults to prevent further frailty and disabilities has become an overarching healthcare issue.[5] Although international guidelines for sarcopenia have been previously established, several issues support country-specific guidelines for this condition.[1,2] First, different populations may have varying characteristics that could affect the diagnosis of sarcopenia based on body composition and functional parameters. Second, healthcare systems vary among countries, which can affect sarcopenia diagnosis and management. For example, in Korea, the healthcare system is disease-oriented and specialty-centered, and the concepts of frailty and intrinsic capacity have been relatively less adopted by both the healthcare and welfare sectors.[6] Finally, the regulatory conditions may differ among countries. Specifically, sarcopenia has been considered a disease since 2021, and diagnostic procedures for this condition have become eligible for medical reimbursement.

The KWGS guidelines incorporate a diverse range of screening tools, including questionnaires and physical examinations, for easier case-finding in different research and clinical settings. The guidelines also simplify the classification flow by combining the two existing steps suggested in other guidelines into one step to reduce confusion in the selection of diagnostic tools and increase the clinical uptake of sarcopenia diagnosis.

Apart from existing sarcopenia guidelines that consider muscle mass a pivotal parameter for defining sarcopenia,[1,2] the KWGS experts determined that having low muscle strength with low physical performance also has clinical relevance, even in the absence of decreased muscle mass. Thus, the KWGS defines a state of "functional sarcopenia." This expanded conceptual definition of sarcopenia as a state with complex pathophysiology is consistent with the concept of frailty.[7]

The KWGS guidelines emphasize sarcopenia as a geriatric mobility condition with a complex pathophysiology rather than a single disease entity. Despite efforts to develop guidelines and assessment tools for sarcopenia, healthcare practitioners in Korea remain unfamiliar with diagnosing and setting up evaluation tools for sarcopenia in routine clinical practice, with inconsistencies in understanding the biological or clinical constructs of sarcopenia. Additionally, the geriatric domains of multimorbidity, polypharmacy, cognitive decline, depression, and social care needs are often overlooked in sarcopenia assessments and interventions.[8] To address these problems, the KWGS's new clinical guidelines aim to facilitate the early detection of sarcopenia by permitting diverse screening tools using a unified process. The KWGS recommendation expands the conceptual definition of sarcopenia and emphasizes the importance of designing holistic, personalized intervention plans based on comprehensive geriatric assessment (CGA), which embraces multiple domains. Hence, the KWGS recommends CGA to reveal the underlying and associated conditions of sarcopenia after making a diagnosis based on the diagnostic flow. This approach aims to ensure that healthcare professionals design holistic, personalized intervention plans based on CGA, embracing multiple domains, including not only nutrition and physical activity but also disability, medications, cognition, mood, and social support.[9] As the published guidelines in this issue mainly focus on sarcopenia screening and diagnosis, a separate guideline on intervention will soon be developed.

In conclusion, the KWGS's new clinical practice guidelines for sarcopenia diagnosis and management aim to reduce the gap between knowledge and practice and stimulate further active research on sarcopenia diagnosis and management in real-world clinical settings. These guidelines offer healthcare professionals a unified and simplified process for screening, diagnosing, and managing sarcopenia. This approach aims to reduce the pathophysiological burden of sarcopenia and improve the overall intrinsic capacity of community-dwelling older adults.[10]

In addition to providing a framework for clinical practice, the KWGS guidelines offer opportunities for future research. As healthcare professionals gain more experience using the guidelines in real-world settings, the recommendations will likely require updating and refinement. Thus, future studies can explore the effectiveness of different interventions for sarcopenia, such as different types of physical activity or nutritional interventions. Additionally, researchers could investigate the relationship between sarcopenia and other geriatric syndromes such as frailty or cognitive impairment.

Overall, the KWGS guidelines represent an important step forward in the clinical diagnosis and management of sarcopenia in older Korean adults. Moreover, by encouraging further research in this area, these guidelines can pave the way for more effective and personalized interventions. As a country's population continues to age, the importance of sarcopenia as a public health concern continues to increase. By directly addressing this issue with the new guidelines, healthcare professionals and policymakers can design effective measures to preserve the intrinsic capacity of older adults, encompassing the life course of aging, diseases, and frailty.

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### CONFLICT OF INTEREST

Hee-Won Jung co-founded Dyphi Inc., a startup based on sensor technology. The other author claims no conflicts of interest.

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# Potential Imaging Biomarkers of Cognitive Frailty

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Cognitive frailty (CF) is a state of impairment in both cognitive and motor functions. The concept of CF has been developed in several ways. However, it is difficult to identify consistent neuroimaging findings according to the application of the operational definition of different frailty models within the same concept, as well as the diversity of the concept itself of CF. This study aimed to review neuroimaging studies of CF and to determine suitable imaging biomarkers of CF. White matter abnormalities (e.g., white matter hyperintensity and microbleeds) seem likely to be considered imaging biomarkers of CF. The volume of the cerebral/cerebellar cortex and that of the subcortical nuclei are also candidates of imaging biomarkers of CF. These imaging biomarkers are expected to be more useful in discriminating the need for screening CF in visitors of clinics or health examination centers than in detecting the presence of CF in community-dwelling older adults.

**Key Words:** Cognitive frailty, Motoric cognitive risk syndrome, Physio-cognitive decline syndrome, Imaging biomarker, Magnetic resonance imaging

## INTRODUCTION

Frailty is a dynamic intermediate condition that lies between pathological aging and adverse health outcomes such as disability or death.[1,2] The concept of frailty can be divided into physical, cognitive, and psychosocial aspects.[3-5] In April 2013, the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) agreed on the definition of "cognitive frailty" (CF), which is a simultaneous state of both mild cognitive impairment (MCI) and physical frailty.[6] CF can be a precursor to degenerative neurocognitive disorders, and physical frailty can accelerate cognitive impairment as well as increase the risk of MCI and dementia.[7,8]

Initially, the concept of frailty was introduced to provide a target for primary and secondary prevention of disability in older adults. From this point of view, to detect the presence of CF, the use of cost-effective and time-saving screening tools (e.g., several frailty scales and gait speed tests) is also recommended. In addition, laboratory or imaging tests usually conducted in clinics, hospitals, or medical examination centers may help find a target for preventing adverse health outcomes, that is, for intervening the development of CF. Therefore, this study aimed to review previous studies related to imaging biomarkers of CF.

## CONCEPTS OF COGNITIVE FRAILTY DEFINED FROM VARIOUS PERSPECTIVES

CF was first introduced for the purpose of indicating cognitive vulnerability in patients with MCI who are more likely to progress towards dementia due to exposure to vascular risk factors.[9,10] According to the IANA/IAGG definition, cognitive impairment shown in CF is characterized by potentially reversible cognitive impairment, excluding the conditions in Alzheimer disease and other types of dementia—i.e., clinical dementia rating (CDR) score = 0.5.[6] After the introduction of the first operational definition of CF, even though the detailed definitions were different

from each other, the prevalence of CF in community-dwelling older adults without neurodegenerative disease was reported to be 1.0%–1.8%.[11] The prevalence of CF has been reported to increase dramatically in clinical settings, ranging from 10.7 to 39.7%.[11] Frailty is a parameter developed for the purpose of promoting the health in older adults. Based on the definitions developed thus far for CF, it is expected that its utility in the clinic will be higher than that in the community.

Ruan et al.[12] proposed two subtypes that further extended the concept of CF: potentially reversible and reversible CF. The potentially reversible CF is expressed as MCI (CDR score = 0.5) and the reversible CF is expressed as subjective cognitive decline (SCD) and/or positivity in fluid or imaging biomarkers of amyloid accumulation and neurodegeneration. Concurrently, Ruan et al.[12] extended the concept of both (potentially reversible and reversible) CF to cases with pre-physical frailty as well as physical frailty (Fig. 1). SCD is characterized by a subjective experience of impaired memory in the absence of objective cognitive deficits (CDR score = 0),[13] and is a concept known to establish an early target for dementia treatment. Many clinical trials for the treatment of Alzheimer disease fail successively, and SCD can be an important prevention target of brain diseases in older adults.

Motoric cognitive risk syndrome (MCRS) is defined as the coexistence of cognitive impairment and slow gait in older adults without dementia (Fig. 1).[14] It is known to be a predictor of both the development of Alzheimer disease and vascular dementia, the two most common causes of dementia,[14,15] and it is also used to predict cardiovascular disease and the associated risk factors.[16,17] In order to avoid confusion between the concepts of MCRS and CF, which is constantly updated, the concept of physio-cognitive decline syndrome (PCDS) was proposed by Chen and Arai[18] at the 5th Asian Conference on Frailty and Sarcopenia in 2019. PCDS is defined as physical frailty manifested as slowness and/or weakness with impairment of any cognitive domain with at least 1.5 standard deviations below the mean for the age-, sex-, and education-matched norms (Fig. 1). The following paragraphs mainly contain reviews of magnetic resonance imaging (MRI) studies in CF and similar contexts[19] such as MCRS or PCDS.

## White Matter Abnormality—An Imaging Biomarker Candidate of Cognitive Frailty

The number of studies investigating cerebral small vessel disease (CSVD) as a cause of neurodegenerative disease continues to increase.[20] White matter hyperintensity (WMH) on T2-fluid-attenuated inversion recovery (FLAIR) sequence of brain MRI is one of the characteristic imaging markers of CSVD. Although WMH is prevalent in older adults and may be associated with other neuropathologies, it is often associated with the development of sub-clinical cognitive impairment.[21] When the outcome is set to dementia, a systematic review and meta-analysis study of more than 11,000 participants[22] found that among the MRI markers of CSVD, only extensive WMH was significantly associated with incident dementia, and neither lacunes nor cerebral microbleeds were associated

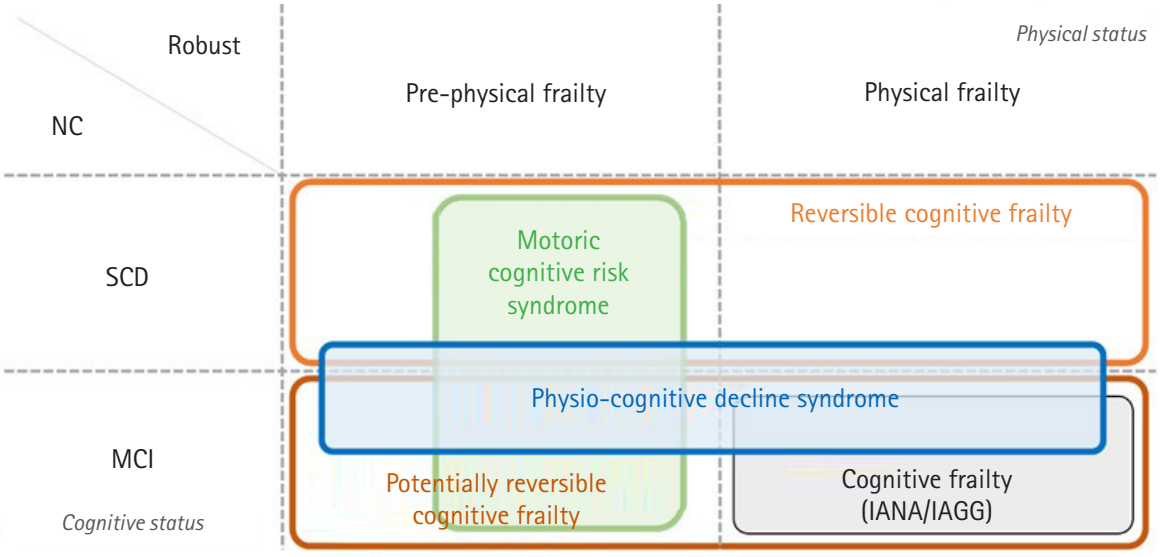


**Fig. 1.** Graphical conceptualization of different definitions of cognitive frailty. NC, normal cognition; SCD, subjective cognitive decline; MCI, mild cognitive impairment; IANA/IAGG, International Academy of Nutrition and Aging and International Association of Gerontology and Geriatrics. Adapted from Sugimoto et al.[19] with permission of the Japan Geriatrics Society.

with it.

Although CF was not defined separately, the relationship between the severity of WMH and frailty defined according to the different scales of the frailty index has already been reported.[23-25] More recently, Sugimoto et al.[26] showed that CF was associated with a significantly higher WMH volume (11.0 ± 13.2 mL with CF vs. 5.8 ± 7.7 mL without CF; $p < 0.001$) and WMH volume divided by parenchymal volume (coefficient = 0.57, standard error = 0.13; $p < 0.001$) in 333 memory clinic patients. A similar finding was reproduced in a cross-sectional study conducted in China.[27]

In the MCRS, which overlaps with CF to some extent, a conflicting result was found. A study in the clinical setting in India revealed that the WMH burden was not related with MCRS.[28] Instead, frontal lacunar infarction was found to be associated with MCRS in Indian older adults, contributing to slow gait and impaired memory.[28] In contrast, in a community-based study with a larger number of participants, the relationship between MCRS and WMH volume was found to be significant.[29] Interestingly, in the same study, the MCRS group showed lower volume in the frontal and parietal lobes as well as greater white matter abnormalities, whereas the MCI group showed volume loss across the brain regions susceptible to Alzheimer disease pathology (i.e., hippocampus, parahippocampal gyrus, entorhinal cortex, precuneus, and inferior parietal lobules).[29]

A brain MRI study in Japanese community-dwelling older adults showed more lacunar infarction and cerebral microbleeds with a severe WMH degree in the CF group.[30] In this study, the CF group had medial temporal lobe atrophy compared with that of the normal controls, but there was no difference in the degree of medial temporal lobe atrophy between the CF and MCI groups without physical frailty. An Australian memory clinic cohort study[31] revealed that there was a significant difference in WMH severity but no difference in medial temporal lobe atrophy between patients with frailty, defined as a frailty index > 0.25, and participants without frailty.

According to the results of a longitudinal study of 400 individuals with asymptomatic CSVD, mobility frailty, defined as having weaker hand-grip strength and/or slower walking speed, was significantly found to be associated with incident dementia (odds ratio = 4.8; 95% confidence interval, 1.5–14.8; $p = 0.007$) in the follow-up duration of an average of 5.7 years.[32] As such, when identifying an imaging biomarker for CF, further studies are needed to classify imaging findings regarding not only proper CF but also each component of physical frailty.

## Gray Matter (Cortical) and Subnuclei Volume—Another Imaging Biomarker Candidate of Cognitive Frailty

Osawa et al.[33] published the first longitudinal study examining the correlation between brain volume and muscle strength changes in older adults. The authors found a decreased knee extensor strength in older adults with atrophy of the frontal, temporal, and occipital gray matter. This finding may provide evidence for the potential contribution of specific regional brain atrophy affecting age-related changes in muscle strength. In addition, a multicohort (two cohorts in the United States and one in France) MRI study revealed that MCRS is associated with cortical atrophy in brain regions involving the control aspects of gait, such as motor planning and modulation (i.e., supplementary motor, insular, and prefrontal cortex), rather than that of the motor aspects of gait, such as gait initiation and maintenance (i.e., cerebellar, temporal, and parahippocampal cortex).[34]

The severity of frailty was associated with the degree of cortical and subcortical atrophy, especially in the frontal and temporal cortex and peri-insular subcortical area, in a study of most patients diagnosed with MCI or dementia.[35]

Although the study was conducted with a relatively small number of participants (52 participants), there is a unique study of the hippocampus on brain MRI divided into subregions between older adults with and without CF.[36] There was a clear decrease in the volume of hippocampal subregions, including the bilateral presubiculum, left parasubiculum, and right cornu ammonis subfield 1 (CA1). The presubiculum and parasubiculum play important roles in cognitive processing and visuospatial function, and their volume has been found to decrease in some diseases, such as diabetes mellitus, Parkinson disease, and Alzheimer disease.[37-39] CA1 is known to act as a subiculum-hippocampal interface and is functionally related to attention. Patients with Parkinson disease with cognitive impairment showed significantly lower right CA1 volume than those with cognitively normal Parkinson disease.[40]

In another study of the same participants,[41] significant volume reduction was found in the bilateral thalami, left caudate, right pallidum, and right accumbens in older adults with CF. In addition, the volume of the bilateral thalami, caudate, pallidum, and right accumbens was negatively correlated with the frailty index. Among them, the volume of regions other than that of the caudate was positively correlated with the Montreal Cognitive Assessment (MoCA) score. A previous study showed that the caudate nucleus contributed to body and extremity posture, as well as the accuracy and speed of directed movements.[42] These findings may explain why changes in the volume of the caudate nucleus are related to

the frailty index and not cognitive impairment.

In an earlier study, Chen et al.[43] proved that weakness, slowness, and low activity in physical frailty components were associated with atrophy of cerebellar gray matter, unlike exhaustion and body weight loss. Thereafter, in the I-Lan Longitudinal Aging Study (ILAS), among 1,196 participants with a mean age of 62 ± 9 years, 190 (15.9%) individuals with PCDS had reduced gray matter volume in the bilateral amygdala and thalamus, right hippocampus, temporo-occipital cortex, and left cerebellum VI and V regions compared with that of those without PCDS. In addition, individuals with PCDS had a significant association with disruption of hippocampal-amygdala-cerebellar connectivity.[44] In future studies on CF and similar entities in the same context (i.e., MCRS and PCDS), studies on other brain regions, such as the subcortical nuclei and cerebellum, should be actively conducted in addition to those targeting the cerebral cortex.

## DISCUSSION

In this review, we mainly looked at brain MRI studies of not only CF but also MCRS and PCDS, which report some concepts overlapping with CF with different names. Although further research is still needed, white matter abnormalities such as WMH and cerebral microbleeds, which are markers of CSVD, seem likely to be considered the imaging biomarkers for CF. On the other hand, the gray matter volume of the cerebrum/cerebellum related to motor planning and modulation, the volume of the hippocampal formation related to attention and cognitive processing, and the basal ganglia related to motor accuracy area are also candidates of imaging biomarkers of CF.

Del Brutto et al.'s previous study[25] can be referred to interpret the reason for the diverse results of imaging studies of CF. Interestingly, they found that the relationships of frailty with global cortical atrophy and WMH change were significantly different between those in the 60s and 70s–80s age groups in the community-dwelling older adults. As of 67 years of age, older frail adults exhibit more pronounced neuroimaging signs of extensive cortical/subcortical damage than robust adults, whereas no such relationship was observed in younger-older adult population. Thus, in the future, when identifying imaging biomarkers, there is a possibility that imaging biomarkers should be considered separately by age group.

In addition, the characteristics of neuroimaging findings may differ by country and/or race and may appear differently depending on whether the study participants are patients in clinics or residents of the community. There have been many studies related to depressive symptoms in CSVD,[45] but only a few studies on neuroimaging findings and depressive symptoms have been conducted in CF.[30] As depressed mood itself, vulnerability to stress, and other psychological factors can affect CF, longitudinal studies that comprehensively evaluate these factors and frailty should be conducted.

Immunological blood biomarkers have been explored for both frailty and CF.[46] In the future, it would be beneficial to study CF with respect to other blood biomarkers that have been studied in the research field of preclinical Alzheimer disease or SCD.[47] Thus, the corresponding blood biomarkers and imaging biomarkers on MRI can be used for the health examination of the participants.

## CONCLUSION

Establishment of screening tools to identify CF in the community population and prevent dementia or other adverse outcomes is of great significance. We believe that the imaging biomarkers listed in our review will be useful in determining the need to proceed with CF screening in patients showing specific MRI findings at a non-geriatric clinic or health examination center. In order to reduce the burden of disease in older adults and prevent dementia and other serious diseases, the discovery and establishment of several key biomarkers should continue in any population.

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### CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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### AUTHOR CONTRIBUTIONS

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# Korean Working Group on Sarcopenia Guideline: Expert Consensus on Sarcopenia Screening and Diagnosis by the Korean Society of Sarcopenia, the Korean Society for Bone and Mineral Research, and the Korean Geriatrics Society

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Despite the introduction of a diagnostic code and acceptance of a diagnostic process for sarcopenia as a new health technology in Korea, many practitioners remain unfamiliar with the evaluation of sarcopenia. Thus, the Korean Working Group on Sarcopenia (KWGS) developed clinical practice guidelines for the diagnosis of sarcopenia in older Korean adults. A two-phase Delphi interview comprising 19 questions was conducted with 40 expert panelists, 22 of whom participated in the first round between June and August 2022. The second round of the Delphi interview included the remaining 11 questions that were not agreed upon in the first round. The screening process for sarcopenia includes various questionnaires and examinations used in different research and clinical settings. The diagnostic process for sarcopenia was simplified by combining the steps of case finding and assessment. The Short Physical Performance Battery test was given particular emphasis owing to its multifaceted nature. Regardless of muscle mass, having low muscle strength with low physical performance is considered clinically relevant and newly defined as "functional sarcopenia." Comprehensive geriatric assessment is important for diagnosing sarcopenia. The KWGS's clinical guideline aims to facilitate the early detection of sarcopenia by allowing various screening tools to be used in a unified process and reducing confusion about which tools to use for diagnosis. This recommendation expands the conceptual definition of sarcopenia as a complex pathophysiological state in line with the concept of frailty and aims to stimulate further research on the diagnosis and management of sarcopenia in clinical settings.

**Key Words:** Sarcopenia, Delphi method, Practice guideline, Geriatric assessment

## INTRODUCTION

Sarcopenia is an age-related condition characterized by decreased muscle mass and impaired muscle strength or physical performance.[1)] The prevalence of sarcopenia increases with age, ranging from 5.5%–25.7% in community-dwelling older adults in Asian

countries according to the Asian Working Group for Sarcopenia (AWGS) 2014 criteria.[2,3] Korean studies have reported a 4%–45% prevalence of sarcopenia in older adults using various definitions.[4]

The clinical relevance of sarcopenia is increasing because it disproportionately affects older and vulnerable populations. The clinical outcomes include the progression of frailty, incidence of falls and fractures, further functional impairment, resultant institutionalization, and death.[5-7] Many Asian countries are experiencing rapid population aging. Considering its overarching effects on health outcomes and quality of life in older adults, sarcopenia is increasingly recognized as a clinical disease. For instance, the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) included sarcopenia as a clinical condition in 2016,[8] and the revised Korean Standard Classification of Diseases-8 (KCD-8) also included sarcopenia as a clinical condition in 2021, with diagnostic code M62.5.

Unlike many clinical conditions, including malignancies and genetic disorders, with major molecular drivers commonly targeted as mechanisms of action in new drug development, sarcopenia has a more complicated pathophysiology as a human aging phenotype or geriatric syndrome.[7,9] The direct contributors adversely affect the homeostatic maintenance of muscle mass and function, including decreased mechanical inputs, insufficient nutritional stimuli, and biological alterations, resulting in increased muscle catabolism and decreased net muscle protein synthesis due to mechanical and nutritional inputs (anabolic resistance).[10-13] Myriad geriatric clinical and functional conditions directly or indirectly affect these contributors. Sarcopenia is a multifaceted condition with extensive effects on various geriatric health domains. It retro-reflectively modulates functional states in these domains, such that sarcopenia impairs the ability of older adults to function optimally in diverse aspects of life, including activities of daily living and cognitive function (Fig. 1). Thus, given the complex nature of sarcopenia, its definition cannot be captured by a single biomarker or clinical features. Such a simplified approach is unlikely to encompass the full complexity of the condition and the underlying pathophysiological mechanisms. Therefore, a more comprehensive strategy is required to understand and manage sarcopenia in the older adult population.

Historically, the operational definitions of sarcopenia have evolved to capture its characteristics as a geriatric syndrome, reflecting longitudinal studies of muscle-related parameters and age-related outcomes. Using the same approach to defining osteoporosis, sarcopenia was initially defined using muscle mass parameters based on the population distribution.[14,15] As accumulating studies show the clinical relevance of functional parameters such as grip strength or low-extremity physical performance over muscle mass, the classification of sarcopenia has gradually better captured the components of physical frailty.[16] For instance, in 2010, the original European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia using muscle mass and function[17] and subsequently published consensus guidelines, including the Foundation for the National Institutes of Health (FNIH),[18] AWGS in 2014,[2] AWGS in 2019,[19] and EWGSOP2, which generally fol-

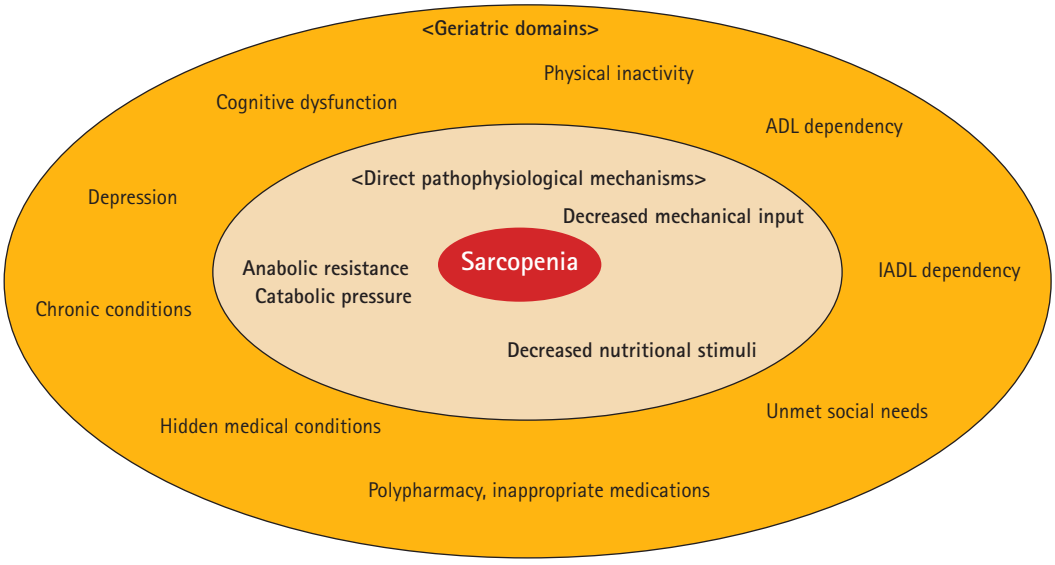


**Fig. 1.** Sarcopenia is a complex system consisting of numerous pathophysiologies in both biological and clinical aspects. ADL, activities of daily living; IADL, instrumental activities of daily living.

lowed a similar approach to operationalization. Notably, recent statements from the Sarcopenia Definitions and Outcomes Consortium (SDOC)[20] and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO) emphasized the importance of muscle function over muscle mass, both in determining sarcopenia and measuring clinical improvements, especially in intervention studies.[21]

Korea is one of the fastest-aging countries worldwide. As the baby-boomer population born from 1955 to 1963 is entering elderhood, Korea is expected to experience further growth in terms of care needs for older people with functional impairment in the coming years, making the prevention, early recognition, and intervention of sarcopenia in the Korean population an imminent issue, if not already overdue. However, despite the importance of this condition, consensus guidelines on sarcopenia in the Korean population have not yet been established. As different populations, healthcare systems, and sociocultural factors may affect the diagnosis of sarcopenia, we aimed to provide an expert consensus on the diagnosis of sarcopenia in Korean community-dwelling older adults.

## CONSENSUS PROCESS

The Korean Working Group on Sarcopenia (KWGS) guidelines were established in 2019 based on the liaison efforts of the Korean Society of Sarcopenia, the Korean Society for Bone and Mineral Research, and the Korean Geriatrics Society to provide a nation-specific consensus on sarcopenia. Following email discussions, the KWGS held six online expert brainstorming meetings to develop key questions for the Delphi interview processes to establish a Korean consensus on sarcopenia diagnosis, starting in March 2022.

The Delphi interview questionnaire was designed to bridge the gap between clinical environments and research evidence from the Korean population and existing international guidelines currently in use in the country, and included 19 questions for the first round (Fig. 2). In the interviews, we used a scale from 1 (strongly disagree) to 9 (strongly agree) to measure consensus for 15 single-choice questions. The remaining four questions were multiple-choice with no restrictions on the number of answers (Fig. 3).

For the Delphi interview, the questions were sent via email to 40 panelists who were experts in geriatric medicine, endocrinology, physical medicine, rehabilitation, oncology, orthopedic surgery, family medicine, exercise physiology, nutrition, healthcare policy, and industry. A total of 22 panelists—5 geriatricians, 4 endocrinologists, 3 rehabilitation specialists, 2 family medicine practitioners, 2 physical medicine experts, 1 exercise physiology specialist, 1 orthopedist, 1 oncologist, 1 nutrition specialist, 1 healthcare policy expert, and 1 healthcare industry expert—responded to the first round of interviews. In the first round, four of the 15 single-choice items reached agreement among the respondents (Fig. 2). We proceeded to the second round with the 11 remaining items for which we did not reach an agreement in the first round (Fig. 4). Fifteen panelists participated in the second round. To quantify the degree of agreement, we used the content validity ratio (CVR), with CVRs of 0.39 for the first round and 0.49 for the second round, considering the number of respondents.[22] Of these 11 questions, six demonstrated a high level of agreement among the experts, ultimately resulting in a consensus. For the remaining five questions, the KWGS members determined that additional rounds would not substantially affect the outcome or level of agreement among the experts. From two rounds of Delphi interviews, KWGS con-

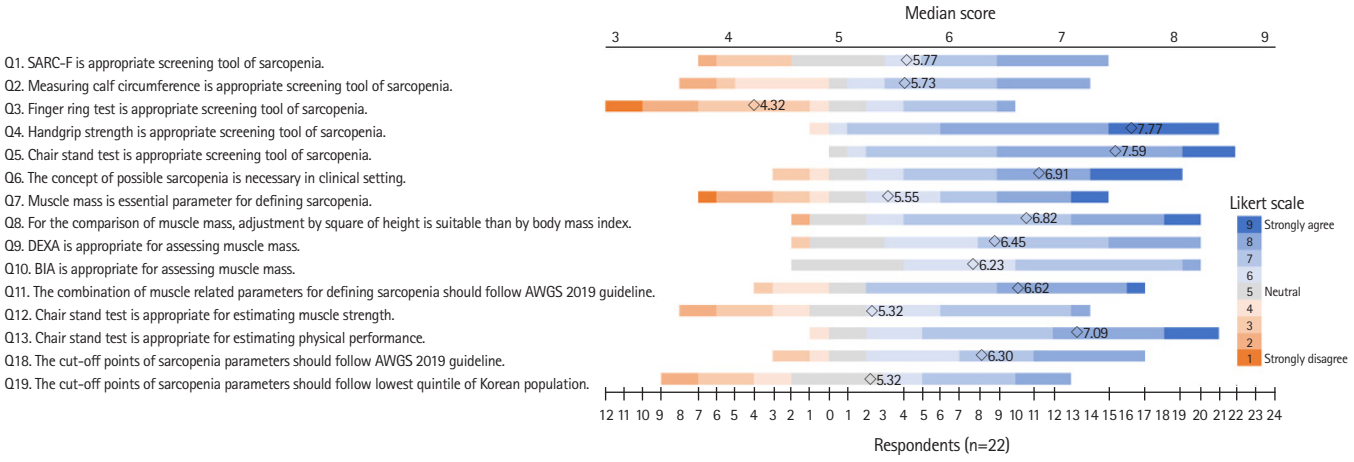


**Fig. 2.** Specific questions and the level of agreement in the first Delphi round. SARC-F, strength, assistance with walking, rising from a chair, climbing stairs, and falls; DEXA, dual-energy X-ray absorptiometry; BIA, bioimpedance analysis; AWGS, Asian Working Group for Sarcopenia.

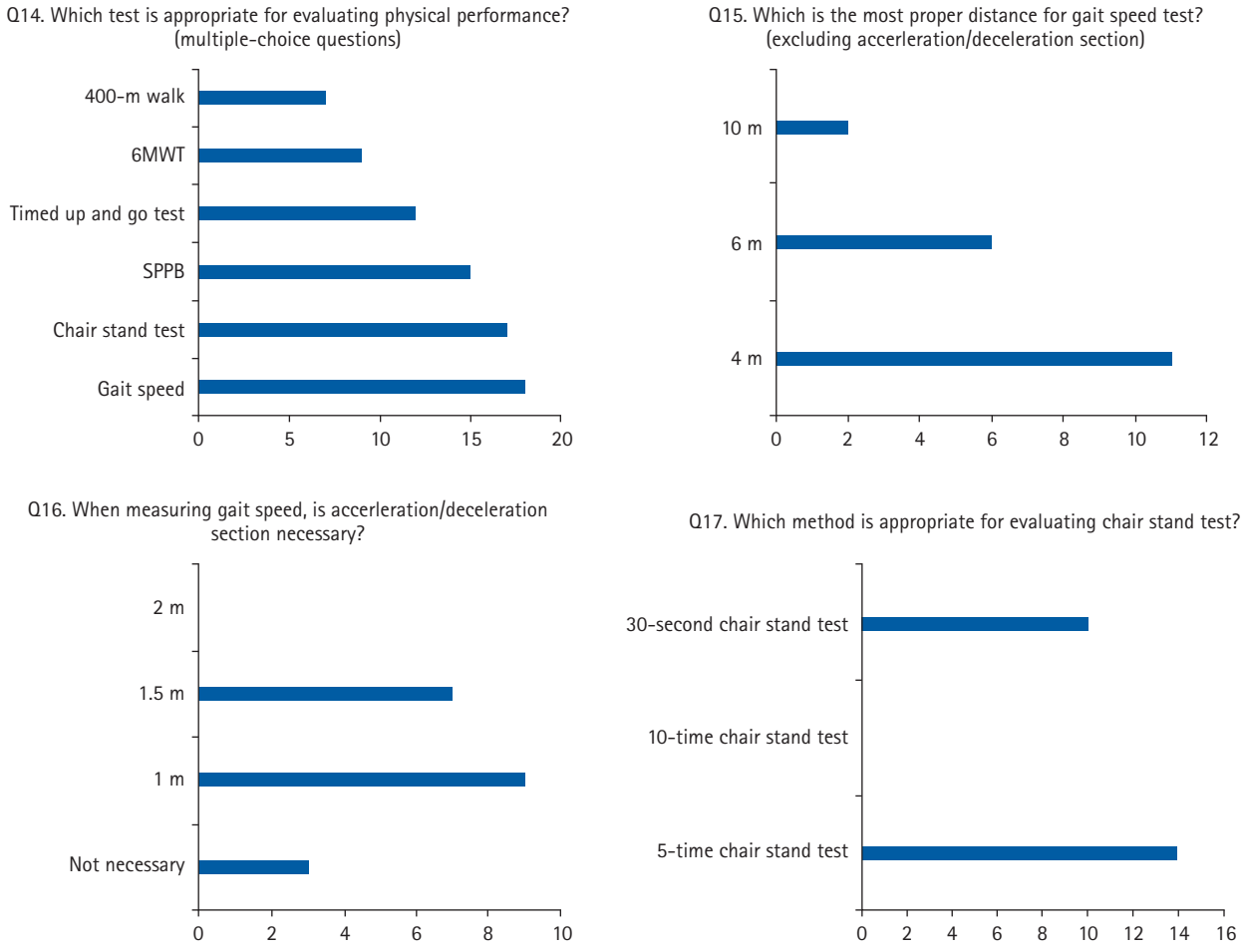


**Fig. 3.** Multiple-choice questions of the first Delphi round. 6MWT, 6-minute walk test; SPPB, short physical performance battery.

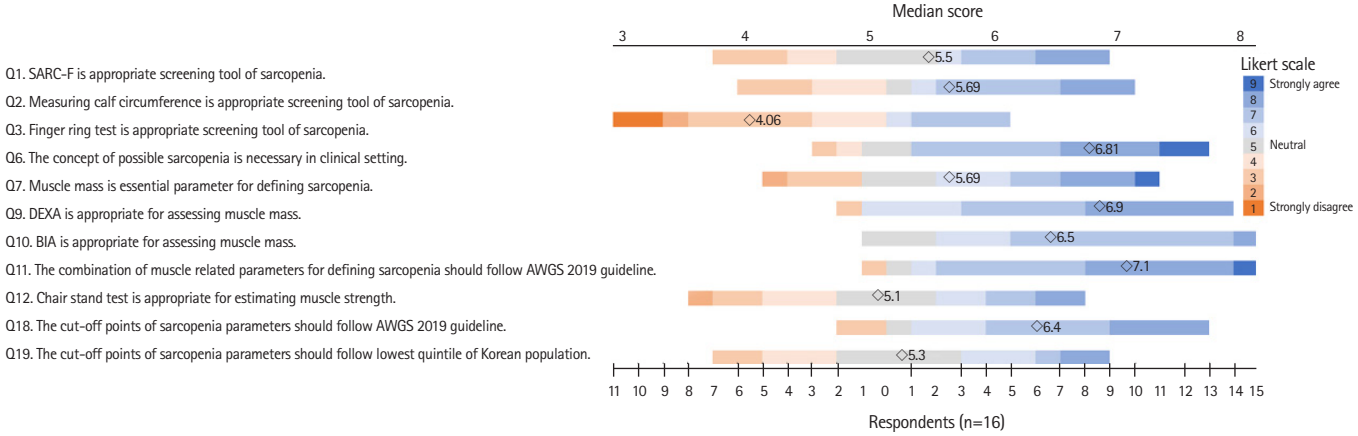


**Fig. 4.** Specific questions and the level of agreement in the second Delphi round. SARC-F, strength, assistance with walking, rising from a chair, climbing stairs, and falls; DEXA, dual-energy X-ray absorptiometry; BIA, bioimpedance analysis; AWGS, Asian Working Group for Sarcopenia.

sensus recommendations were drafted and further reviewed by board members. A draft of the recommendations was presented at the 13th Congress of the Korean Society of Sarcopenia in December 2022.

## SUMMARY OF THE ASSESSMENT FLOW FOR SARCOPENIA

The general operational classification flow for sarcopenia suggest-

ed by the KWGS is shown in Fig. 5. For case finding, the range of tools consists of questionnaires such as the SARC-F, while the examinations include calf circumference, finger ring, hand grip, chair stand, gait speed, and timed up-and-go (TUG) tests. Experts agree that various screening methods can be used for specific research or practice settings. For instance, questionnaires may be adopted with minimal additional workload, albeit with some drawbacks in sensitivity or specificity in the Korean population,[23] at least in mass-scale community-based studies or public health examinations. We maintained the concept of possible sarcopenia, similar to the EWGSOP2 and AWGS 2019.[5,19] In contrast to the AWGS 2019, we combined case finding and assessment in one step to simplify the classification flow.

To confirm the presence of sarcopenia, we recommend an evaluation that includes the following three parameters: appendicular skeletal muscle mass (ASM), muscle strength, and physical performance. We defined "sarcopenia" as decreased muscle mass with low muscle strength or poor physical performance. Severe sarcopenia was classified as a state of decreased muscle mass in the presence of both weak muscle strength and decreased physical performance. "Functional sarcopenia" was classified as a state of weak muscle strength and low physical performance without a loss of muscle mass, which deserves a similar intervention effort as sarcopenia as evidence supports the outcome relevance of this condition in older adults.

Since muscle loss is a phenotype arising from aggregated inputs of biological and functional pathophysiology, we recommend performing a comprehensive geriatric assessment (CGA) for patients with either "sarcopenia" or "functional sarcopenia" to identify interconnected geriatric conditions and establish person-specific strategies to prevent the progression of these conditions, as evidence supports the beneficial role of geriatric multicomponent in-

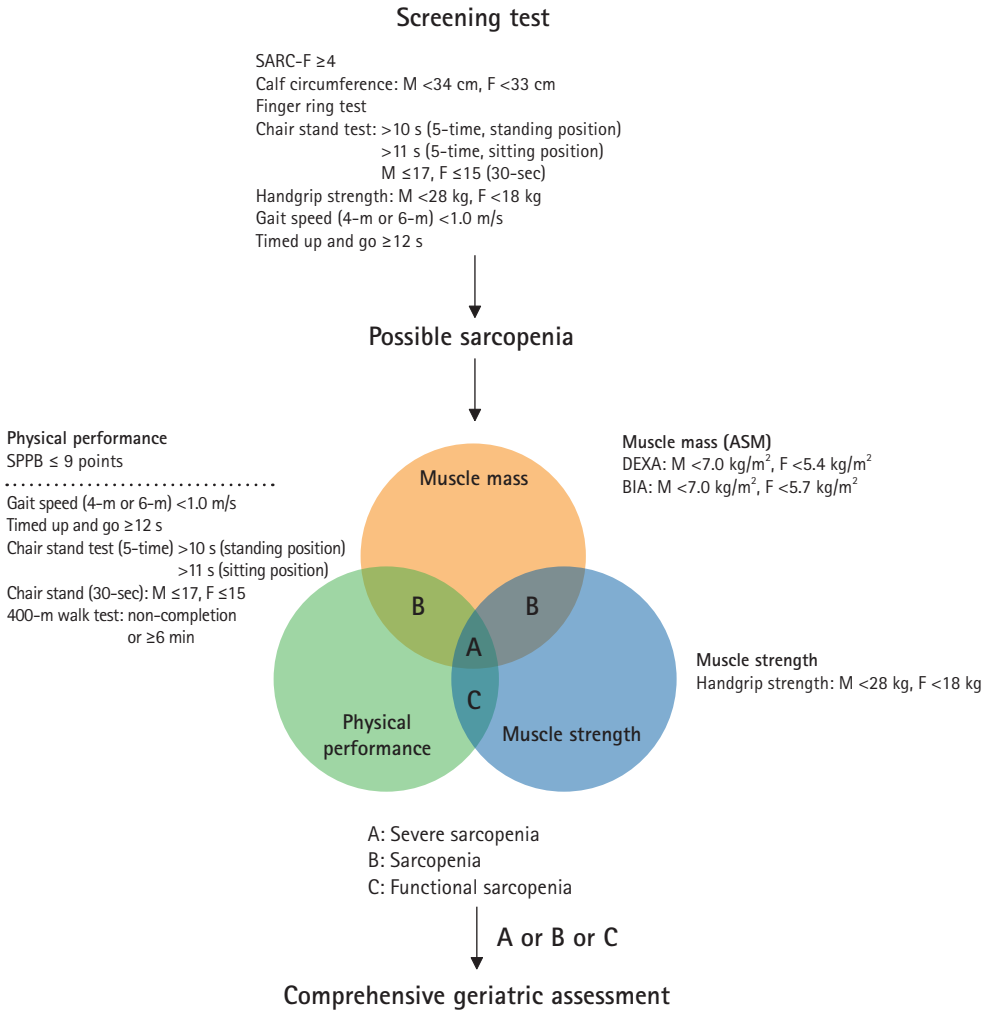


**Fig. 5.** Algorithm for sarcopenia evaluation. SARC-F, strength, assistance with walking, rising from a chair, climbing stairs, and falls; SPPB, short physical performance battery; ASM, appendicular skeletal muscle mass; BIA, bioimpedance analysis; DEXA, dual-energy X-ray absorptiometry.

terventions.[24-26] Experts in the KWGS noted that the concepts of primary and secondary sarcopenia are less obvious in patients in real-world practice, and underlying clinical conditions affecting muscle homeostasis should be identified through CGA, if possible, or appropriate evaluations for evidence-based multicomponent interventions for sarcopenia.

## SCREENING TESTS

We recommend using any validated screening tools, as various screening instruments perform well in classifying sarcopenia in the Korean population.[19,27-29] The eligible populations for sarcopenia evaluation included individuals aged ≥65 years, postmenopausal women <65 years, and younger adults with clinical presentations or a history of clinical conditions that affect muscle homeostasis (Table 1). Additionally, if there is clinical suspicion, screening can be skipped, and direct progress can be made toward diagnosis.

Consistent with existing guidelines, we recommend seven screening tools: SARC-F, calf circumference, finger-ring test, chair stand test, handgrip strength, gait speed, and TUG (Table 2). The SARC-F questionnaire consists of five components that evaluate strength, assistance in walking, rising from a chair, climbing stairs, and falling.[30] Though a SARC-F score ≥4 has shown low to moderate sensitivity and high specificity in detecting sarcopenia with the possibility of recall bias in frail older adults with cognitive decline,[31,32] it is still a good screening tool as it is simple and feasible without requiring advanced equipment; moreover, it is well-validated in many works of literature, including Korea.[23,33,34] To apply the SARC-F to a massive population, such as in the community, lowering the cutoff score from 4 to 2 could improve the sensitivity.[35,36] Calf circumference has shown moderate to high sensitivity and specificity in detecting sarcopenia, and its appropriate cutoffs are <34 cm and <33 cm in men and women, respectively.[19] As calf circumference entails muscle mass rather than muscle function, it can be used with SARC-F and SARC-C.[37-39] For an accurate and consistent assessment of calf circumference, measurement in a standing position with a non-elastic tape is recommended.[36] Further adjustments for height, weight, or body mass index (BMI) might be considered to address the underdetection of sarcopenia in obese people.[36,40] Likewise, the finger-ring test can be an alternative for calculating calf circumference by encircling the thickest part of the calf with both the thumbs and index fingers. Sarcopenia is suspected if the calf is thinner than the finger ring.[41,42] Both handgrip strength and chair stand tests are also recommended in sarcopenia screening with the same cutoff for diagnosis—handgrip strength of men <28 kg and women <18 kg; chair stand test of >10 seconds (5-time, ending with standing position) and >11 seconds (5-time, ending with sitting position), or men ≤17 and women ≤15 (30 seconds).[19,28,29] In addition, the gait speed test and TUG can be used as screening tools using the cutoff values of a gait speed of <1.0 m/s and TUG ≥12 seconds.[19,43] In clinical settings with a high prevalence of sarcopenia, adopting handgrip strength, chair stand test, gait speed, or TUG test may simplify the diagnostic steps for sarcopenia.

A recent surge in research interest in the opportunistic measurement of the psoas muscle cross-sectional area at the L3 lumbar vertebra or muscle volumetry methods using conventional or machine-learning algorithms allows the assessment of muscle mass in patients undergoing cross-sectional imaging studies for various medical or surgical purposes.[44-47] Although most studies have fo-

**Table 1.** Clinical conditions warranting evaluations for sarcopenia

| Category | Condition |
|---|---|
| Clinical presentations | Significant body weight loss |
| | General weakness and easy fatiguability |
| | Subjective sense of muscle wasting |
| Conditions leading to anabolic resistance | History of receiving treatment affecting sex-hormones |
| | Conditions requiring long-term steroid use |
| | Chronic inflammatory conditions |
| | Neoplastic conditions |
| Conditions limiting adequate nutritional intake | Mood and cognitive disorders |
| | Polypharmacy |
| | Chronic constipation |
| | Swallowing difficulty |
| Conditions affecting physical activity | Recent history of hospitalization or acute illness |
| | History of fall |
| | Mood and cognitive disorders |
| Conditions associated with prevalent sarcopenia | Other geriatric syndromes not listed above |

**Table 2.** Proposed tool for screening sarcopenia and assessing muscle mass, muscle strength, and physical performance

| | Tool | Cut-offs | Study |
|---|---|---|---|
| Screening test | SARC-F | ≥ 4 | Chen et al.[19] |
| | Calf circumference | M: < 34 cm<br>F: < 33 cm | Chen et al.[19] |
| | Chair stand (5-time or 30-second) | > 10 seconds (5-time, standing position)<br>> 11 seconds (5-time, sitting position) | Yamada et al.[29] |
| | | M: < 17 (30 seconds)<br>F: < 15 (30 seconds) | Sawada et al.[28] |
| | Handgrip strength | M: < 28 kg<br>F: < 18 kg | Chen et al.[19] |
| | Gait speed (4 m or 6 m) | < 1 m/s | Chen et al.[19] |
| | TUG | ≥ 12 seconds | Jung et al.[43] |
| Muscle mass | | | |
| Appendicular SMM, height-adjusted | DEXA | M: < 7.0 kg/m$^2$<br>F: < 5.4 kg/m$^2$ | Chen et al.[19] |
| | BIA | M: < 7.0 kg/m$^2$<br>F: < 5.7 kg/m$^2$ | Chen et al.[19] |
| Appendicular SMM, BMI-adjusted | DEXA | M: < 0.789<br>F: < 0.512 | Studenski et al.[18] |
| Muscle strength | Handgrip strength | M: < 28 kg<br>F: < 18 kg | Chen et al.[19] |
| Physical performance | SPPB | ≤ 9 points | Chen et al.[19] |
| | Gait speed (4-m or 6-m) | < 1.0 m/s | Chen et al.[19] |
| | TUG | ≥ 12 seconds | Jung et al.[43] |
| | Chair stand (5-time or 30-second) | > 10 seconds (5-time, standing position)<br>> 11 seconds (5-time, sitting position) | Yamada et al.[29] |
| | | M: < 17 (30 seconds)<br>F: < 15 (30 seconds) | Sawada et al.[28] |
| | 400-m walk test | Non-completion or ≥ 6 minutes for completion | Cruz-Jentoft et al.[5] |

SARC-F, strength, assistance with walking, rising from a chair, climbing stairs, and falls; TUG, time up and go test; SMM, skeletal muscle mass; BMI, body mass index; DEXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; SPPB, short physical performance battery.

cused on muscle mass-related parameters and clinical outcomes, patients with low muscle mass in these opportunistic imaging methods might be subjected to formal sarcopenia evaluations if muscle wasting is clinically suspected. However, the potential use of cross-sectional imaging as a screening tool should be further explored and evaluated in future studies.

## MUSCLE MASS

Muscle quantity can be estimated by ASM measured using dual-energy X-ray absorptiometry (DEXA) and bioimpedance analysis (BIA), according to the recent AWGS 2019 guidelines.[19]

DEXA uses lean mass, excluding bones, to indirectly estimate ASM and has been well validated as a standard method to assess muscle mass in many studies; however, connective tissues such as skin and blood vessels or the amount of body water could be counted as lean mass. Additionally, measurements can vary depending on the manufacturer's brand, correction technique, and post-processing method.[48-50] Using the difference in the electrical conduction rate between fat and water, BIA indirectly estimates the body fat and lean masses. BIA has several advantages; it is cost-effective, portable, easy to operate, and safe with no radiation exposure.[51] However, concerns regarding its accuracy exist according to the examinee's race, body water status, and BMI. This technology has gradually evolved from single-frequency to multi- frequency and from whole-body to segment-specific impedance, allowing the estimation of appendicular lean mass. Direct-segmental multi-frequency bioelectrical impedance analysis (DSM-BIA) has shown a good correlation with DEXA in estimating body composition and lean mass.[52-54] In addition, a segmental index of extracellular water in proportion to the total body water (ECW/TBW) for excess fluid[55-57] and a phase angle for estimating muscle quantity can be used adjunctly.[58,59]

For the ASM adjustment method, the KWGS recommends a squared value of height (m$^2$) according to the AWGS 2019. Additionally, the BMI-adjusted ASM can be used to capture sarcopenia

in obese individuals.[18] The recommended cutoff points for height-adjusted ASM follow those in the AWGS 2019: < 7.0 kg/m$^2$ (men) and < 5.4 kg/m$^2$ (women) in DEXA; < 7.0 kg/m$^2$ (men) and < 5.7 kg/m$^2$ (women) in BIA.[19] The recommended cutoff points for BMI-adjusted ASM follow the FNIH: < 0.789 (men) and < 0.512 (women) for DEXA.[18]

Although computed tomography and magnetic resonance imaging can also be used to assess muscle mass, their high costs and radiation exposure hinder their clinical use for mainly sarcopenia. Studies on opportunistically-acquired muscle mass parameters in cross-sectional imaging are insufficient in terms of compatibility between these parameters and lean mass from DEXA or BIA. The $D_3$-creatine dilution method can be considered.[60-62] Studies suggest that inconsistent associations between muscle mass and adverse health outcomes, including impaired mobility, disability, falls, and mortality, might be attributed to the indirect nature of DEXA and BIA, which measure lean mass rather than muscle mass per se (SDOC).[20] Direct measurement methods may fill this gap by acquiring muscle mass. While regulatory protocols for adopting stable isotopes such as $D_3$-creatine are still ongoing in the Ministry of Food and Drug Safety, as these compounds are considered experimental pharmaceuticals, we expect that the research use of direct muscle mass measurement will become popular in the future, especially for measuring objective intervention effects between before and after.

## MUSCLE STRENGTH

Although both handgrip strength (upper extremities) and knee joint torque (lower extremities) can be measured, we recommend handgrip strength as a surrogate index of muscle strength owing to its accessibility for community-dwelling individuals, concordant with the major guidelines of sarcopenia. Unlike EWGSOP2, which uses the chair stand test as a proxy for the strength of the lower muscles,[5] our expert group considered the chair stand test to be an indicator of muscle power (force × velocity) rather than strength (force) because it includes both velocity and strength (force). Additionally, the chair stand test represents complex physical performance, including balance, endurance, and coordination, and has shown a better association with physical performance parameters (e.g., gait speed) than with handgrip strength.[63] Hence, we included the chair stand test in the physical performance section per the AWGS guidelines.[19]

Both spring-type (Smedley) and hydraulic-type (Jamar) dynamometers can be used to assess handgrip strength; the examiner should follow the standard protocol for each type. As the hydraulic type tends to have higher test values than the spring type,[64] the test values are not interchangeable. Thus far, separate cutoff values for each test are not provided in the AWGS 2019 owing to a lack of studies comparing the two methods of measuring handgrip strength.[19] In a spring-type dynamometer, measurements should be performed in a standing position with the elbow extended.[65] If the patient cannot maintain a standing position, a sitting position with the elbow extended is recommended.[36] For the hydraulic type of dynamometer, grip strength is measured in a sitting position with the elbow flexed at 90°.[65]

The measurement can be performed in both arms or the dominant arm at least twice, with the maximum value among all these examinations defined as the grip strength. There is no time limit for the assessment and encouraging the examinee to exert maximum effort is recommended. The cutoff value for low handgrip strength is < 28 kg in men and < 18 kg in women, as per the AWGS 2019 guidelines.[19]

## PHYSICAL PERFORMANCE

Among the different instruments available to evaluate physical performance, we recommend the Short Physical Performance Battery (SPPB) as a priority because it encompasses all three phenotypes of physical performance: gait speed, balance, and chair stand test. One or two additional tests can be used complementarily to determine the state of low physical performance. If the SPPB is not executable, gait speed or TUG test can be used as an alternative. The tests are prioritized to avoid the spuriously high prevalence of a low physical performance state by interpreting any of the many executed tests as positive.[66] While deciding on an appropriate representative test based on the characteristics of individual institutions and clinical circumstances is essential, we recommend adopting up to two tests when classifying low physical performance.

The SPPB is appropriate for evaluating the functions of daily living as it comprises three basic components: usual gait speed, static balance, and five-time chair stand test. Additionally, the SPPB has been widely used as a primary prognostic factor to determine the point of sarcopenia intervention and its effectiveness in numerous clinical studies.[21,67-69] For gait speed measurement, the participants are asked to walk 3 or 4 m at their usual pace. The balance test consists of side-by-side, semi-tandem, and tandem standing with the participant holding the position for at least 10 seconds. In the chair stand test, individuals are instructed to stand up from a chair five times without using their arms. Each component's score ranges from 0 to 4, resulting in a total possible score of 12 points. The cutoff points for SPPB follow the AWGS 2019 guidelines (≤ 9 points).[19]

Gait speed is a well-validated and reliable test to assess physical

performance and has shown good correlation with sarcopenia-related outcomes, including mobility limitation, disability, falls, institutionalization, and death.[70-73] Therefore, both 4 m and 6 m test lengths are recommended, with separate 1 m or 1.5 m acceleration and deceleration lengths. Our experts from the KWGS acknowledged the necessity of the acceleration and deceleration areas because discrepancies in this section can exist in participants with severe frailty with decreased attention or a mobility disorder such as Parkinson disease (Fig. 3). The optimal acceleration and deceleration lengths for gait speed measurement remain controversial, and instrumented measurements by sensors with high spatiotemporal resolution may reduce the space required for examination, as the mean velocity section can be selected by algorithms. The AWGS 2019 cutoff for gait speed is < 1.0 m/s.[19]

The TUG comprises the elements of getting up from a chair, turning the 3 m-halfway point at the usual pace, and sitting back on the same chair. Although the TUG is not advised as an index of physical performance in AWGS 2019, experts from the KWGS determined that the TUG can reflect multiple aspects of human health by containing segments of the SPPB, such as walking at the usual pace and rising from a chair, which are also essential for daily living. Since sarcopenia per se is a multicausal and complex system in line with the concept of frailty, the TUG can be a good surrogate marker of physical performance.[5,74] Because a universal cutoff value for the TUG is lacking, we recommend a new cutoff value based on the study results of Korean community-dwelling older people.[43] Given that the lowest quintile of TUG is ≥ 11.8 seconds for men and ≥ 12.5 seconds for women, we recommend a cutoff point of ≥ 12 seconds for both sexes.[43]

The chair stand test times five consecutive rises from a chair as quickly as possible, with no assistance from either arm. In a community setting with relatively robust participants, a five-time chair stand test may have limited discrimination power. Thus, the 30-second chair stand test (counting the number of seconds spent rising from a chair) is recommended in this case.[75] The two possible ways of measuring the time for a chair to stand are starting with a sitting position and finishing in a standing position, and starting with a sitting position and finishing in a sitting position. Both practical methods can be used if measured consistently.[29,36] For the five-time chair stand test, the cutoff value is > 10 seconds (five-time, ending in the standing position), > 11 seconds (five-time, ending in the sitting position).[29] For the 30-second chair stand test, the cutoff is ≤ 17 in men and ≤ 15 in women.[28]

The 400-m walk test has the advantage of evaluating endurance and walking ability. Assessing how far individuals can walk out of their houses is critical as it is directly related to individual autonomy and quality of life. For this examination, we considered taking more than 6 minutes to be associated with decreased physical performance according to EWGSOP2.[5]

Physical performance tests are traditionally performed manually using stopwatches and floor markings. However, recent advances in sensor technology have enabled the development of automatic devices that can capture human biomechanical parameters in these tests. Devices have been developed and validated for tests such as gait speed[76] and other gait parameters,[77] TUG test, chair stand test,[78,79] and the SPPB.[80]

## CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Although the sarcopenia diagnosis code has been introduced, and the diagnostic process based on muscle mass measurement using BIA and DEXA has been accepted as a new health technology in Korea, most practitioners remain unfamiliar with making diagnoses and selecting evaluation tools for sarcopenia in routine clinical practice. This unexpected discrepancy may be attributable to inconsistencies in our understanding of the biological or clinical constructs of sarcopenia. For instance, some researchers recognize sarcopenia as a phenotype of low muscle mass relative to fat mass, a metabolic condition rather than an age-related decrease in muscle health.[81] Consequently, in our study, the selection of specific assessment tools for classifying sarcopenia was complicated by many key issues that did not reach convergence. This issue is further complicated by the tendency to approach sarcopenia as a single disease entity rather than as a problem of a complex system arising from human aging and frailty in the current Korean culture with disease-oriented, specialty-centered healthcare systems. In some instances, the intervention for sarcopenia is restricted to the domains of protein supplementation and one-size-fits-all-type exercises for logistical convenience,[82] while the geriatric domains of multimorbidity, polypharmacy, cognitive decline, depression, and social care needs are often overlooked in sarcopenia assessment and intervention.

To address these problems, in the KWGS clinical practice guidelines, we highlight the following specific points. First, we include a diverse range of screening tools consisting of questionnaires and examinations for easier case finding in different research and clinical settings. Additionally, we combined the two existing steps suggested in EWGSOP2 and AWGS 2019— case-finding and assessment—into a single step to simplify the classification flow. Second, we prioritized the various tools for measuring physical performance, making the SPPB representative owing to its multifaceted composition, including gait speed, balance, and chair stand test. As such, we intended to minimize disagreements in test results from different measuring tools to avoid the overdetection of low physi-

cal performance. Third, apart from existing sarcopenia guidelines placing muscle mass as a pivotal parameter for defining sarcopenia, experts from the KWGS determined that having low muscle strength with low physical performance also has clinical relevance, even in the absence of decreased muscle mass. Thus, we define this state as "functional sarcopenia." Finally, emphasizing sarcopenia as a geriatric mobility condition with a complex pathophysiology rather than as a single disease entity, we highlight the execution of CGA after making a final diagnosis of sarcopenia in our diagnostic flow.

The new KWGS clinical guidelines intend to facilitate the early detection of sarcopenia by permitting diverse screening tools with a unified process and reducing confusion in selecting diagnostic tools. With this recommendation, we hope to expand the conceptual definition of sarcopenia to a state of complex pathophysiology in line with the concept of frailty. Using this approach, we expect healthcare professionals to be able to design holistic, personalized intervention plans based on CGA, embracing multiple domains, not only nutrition and physical activity, but also disability, medications, cognition, mood, and social support. Reducing the pathophysiological burden of sarcopenia is an underlying element in its treatment (Fig. 6). These guidelines are expected to increase the clinical uptake of sarcopenia by reducing the gap between knowledge and practice and stimulating further active research on sarcopenia diagnosis and management in clinical settings.

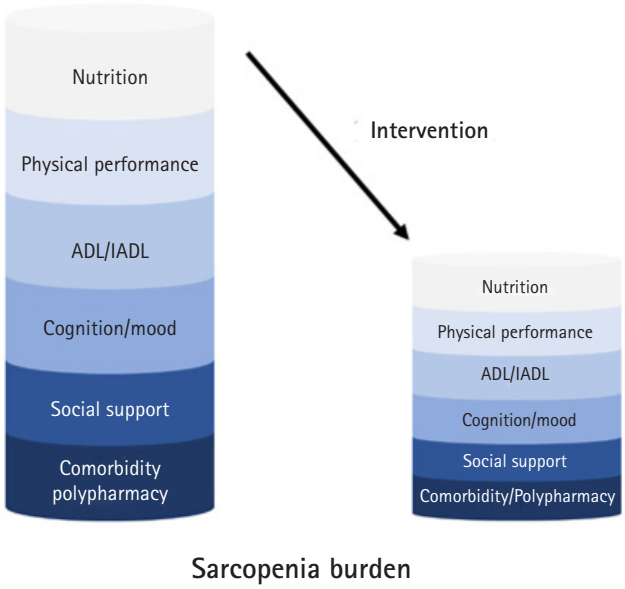


**Fig. 6.** Decreased sarcopenia burden after CGA-based intervention. ADL, activities of daily living; IADL, instrumental activities of daily living; CGA, comprehensive geriatric assessments.

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### CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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### AUTHOR CONTRIBUTIONS

Conceptualization: JYB, HWJ; Data curation: JYB, HWJ; Funding acquisition: HWJ; Investigation: JYB, HWJ, KMK, MK, CYP, KPL, SYL, IYJ, OHJ; Methodology: JYB, HWJ, KMK, MK, CYP, KPL, SYL, IYJ, OHJ; Project administration: JYB, HWJ, KMK, MK, CYP, KPL, SYL, IYJ, OHJ; Supervision: JYB, HWJ, KMK, MK, CYP, KPL, SYL, IYJ, OHJ, JYL; Writing-original draft: JYB, HWJ; Writing-review & editing: JYB, HWJ, KMK, MK, CYP, KPL, SYL, IYJ, OHJ, JYL.

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# Development of a Tool to Measure Compliance with Infection Prevention Activities Against Emerging Respiratory Infectious Diseases among Nurses Working in Acute Care and Geriatric Hospitals

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**Background:** This study developed a preliminary instrument to measure nurses' infection prevention compliance against emerging respiratory infectious diseases and to verify the reliability and validity of the developed instrument. **Method:** The participants were 199 nurses working at a university hospital with more than 800 beds and two long-term care hospitals. Data were collected in May 2022. **Results:** The final version of the developed instrument consisted of six factors and 34 items, with an explanatory power of 61.68%. The six factors were equipment and environment management and education, hand hygiene and respiratory etiquette, infection risk assessment and flow management, protection of employees in contact with infected patients, ward access management of patients with infectious diseases, and wearing and removing personal protective equipment. We verified the convergent and discriminant validities of these factors. The instrument's internal consistency was adequate (Cronbach's α=0.82), and the Cronbach's α of each factor ranged from 0.71 to 0.91. **Conclusion:** This instrument can be utilized to determine the level of nurses' compliance with infection prevention activity against emerging respiratory infectious diseases and will contribute to measuring the effectiveness of future programs promoting infection-preventive activities.

**Key Words:** Prevention & control, Communicable diseases, Emerging, Respiratory tract diseases, Nurses

## INTRODUCTION

With the global spread of the coronavirus disease-19 (COVID-19), Korea has reported 22,701,921 cumulative cases and 26,332 deaths as of August 25, 2022.[1] COVID-19 is mainly transmitted through contact with aerosolized droplets produced when infected patients cough, sneeze, or converse. Personal hygiene such as hand hygiene and social distancing are required infection prevention activities to prevent the spread of such infectious diseases.[2,3] Owing to the nature of respiratory viruses such as COVID-19, infections within hospitals result in worse outcomes than social infections because hospitals are largely occupied by older adult patients, and patients with underlying conditions or immunodeficiency rather than healthy individuals. Therefore, preventing the spread of respiratory infectious diseases is more challenging in hospitals, and infection control is crucial.[4]

Infection prevention activity refers to the extent to which isolation guidelines are followed to prevent infection transmission in hospitals per standard precautions and transmission-based precautions.[5] These activities protect patients, family members, and healthcare professionals from contracting infectious diseases, which is critical because infections not only cause the infected individual's health to deteriorate but also spread diseases to other patients with weakened immunity. Furthermore, the isolation of healthcare personnel to infections can result in gaps in healthcare.[6]

In particular, the subjects of long-term care services are older

adult patients with geriatric or other underlying diseases who are at a high risk of infection.[7] Thus, infection control by healthcare professionals is also essential in acute care hospitals and long-term care facilities.[8]

The harmful effects of healthcare-related infections can be reduced by accurately understanding the standard precautions and complying with infection prevention activities.[9-11] When suspecting or confirming an infectious disease in the event of an emerging respiratory infectious disease, such as the current COVID-19, contact precautions, droplet precautions, and air bone precautions based on the transmission route of the emerging respiratory infectious disease should be applied along with standard precautions.[9,10]

Enforcing compliance with such infection prevention activities necessitates measuring the level of practice and ensuring their accurate implementation according to the guidelines. Since the COVID-19 pandemic, nurses' infection-prevention activities have increased owing to increased awareness of these measures. These include wearing masks, hand hygiene, and visitor management in healthcare facilities.[12] Modified and supplemented versions of existing instruments or newly developed instruments targeting novel influenza,[13] Middle East respiratory syndrome,[14,15] and COVID-19[16-18] are currently being utilized. However, because researchers have developed instruments based on the guidelines for each type of emerging respiratory infectious disease, the reliability and validity of each tool vary and pose difficulties in comparing study results. In particular, infection control guidelines continuously change throughout a pandemic; for example, for COVID-19,[12] a new reliable instrument must be developed that reflects the updated guidelines to ensure compliance with infection prevention activities among healthcare professionals.

First, through literature reviews and focus group interviews (FGIs), this study developed a preliminary instrument to measure nurses' level of compliance with infection prevention activities against emerging respiratory infectious diseases. We then verified the reliability and validity of this preliminary instrument.

## MATERIALS AND METHODS

### Study Design

This methodological study developed and measured the validity and reliability of an instrument to measure nurses' compliance with infection prevention against emerging respiratory infections. The process consisted of instrument development and instrument evaluation stages.

### Instrument Development

We reviewed the infection control guidelines and instruments used in previous studies by searching the Research Information Sharing Service (RISS), Korean Studies Information Service System (KISS), and PubMed databases to identify relevant articles indexed from December, 2000 to December 2021. The search strategies were adapted to each database and included terms such as "emerging infectious diseases," "infection prevention activity compliance," and "nurses."

An FGI was conducted with five nurses working in pulmonary units, internal medicine intensive care units, emergency departments, outpatient pulmonology departments, and infection prevention and control departments to reflect the nurses' occupational characteristics. The participants of the FGI were briefed regarding the study and asked to provide informed consent. Questions related to compliance with infection prevention activities against new respiratory infectious diseases were notified in advance to provide time for the participants to prepare their answers to the questions before the interviews. On the day of the FGI, the interview lasted approximately 2 hours after providing the participants with a description of the study and obtaining their written consent, including the recording of the interview. The interview was conducted until no new statements were found. The researcher took field notes and transcribed the contents of the interview along with recording the interview. The participants were questioned about the activities, tasks, and difficulties related to responding to emerging respiratory infectious diseases as follows: "Please tell us about your activities, work, and experience in responding to new respiratory infectious diseases in your place of work," "What are the challenges of nursing and responding to new respiratory infectious diseases in medical institutions?" and "What measures are medical institutions taking to prevent and manage new respiratory infectious diseases?"

Sentences containing meaningful content related to compliance with infection prevention activities against emerging infectious diseases were derived from the literature review and the FGI. The factors were identified by grouping them into similar topics. Eight experts, comprising three infection control nurses, three professors of nursing with infection control nursing licenses, and two instrument development specialists, verified the content validity index of the questions derived from the literature review and the FGI. To investigate the opinions on the composition of the questions, such as the readability, ambiguity, and terminology, a preliminary survey was conducted on 10 nurses working in medical institutions, including four in general wards, one in an emergency unit, one in an outpatient department, and one in an infection prevention and control department.

### Instrument Evaluation

Data were collected from 222 nurses to verify the item analysis, exploratory factor analysis, convergent validity, discriminant validity, and reliability of the developed preliminary instrument.

#### *Data collection*

Because the estimated number of cases necessary for the verification of the tool was approximately 5–10 times the total number of items in the developed instrument,[19] 200 cases, which is five times the number of preliminary questions developed in the study of 40 items, were required. A total of 222 individuals were recruited, accounting for a 10% dropout rate. The sample consisted of 122 nurses from a university hospital with over 800 beds in Daejeon City and 100 nurses working at two long-term care hospitals in Seoul Metropolitan City. The inclusion criteria for the study were limited to nurses with a total work experience of 12 months or more to ensure participants with a variety of nursing experiences, except for department heads, who did not participate in patient care in person. A total of 222 questionnaires were collected, of which 199 were used for the final analysis, excluding 23 cases with missing data (10.4% dropout rate).

Before the survey, the participants were briefed regarding the purpose of the study, autonomy regarding participation and withdrawal, the time, precautions necessary for completing the questionnaire, the contents of the questionnaire, and confidentiality. Data were collected from May 5 to May 30, 2022, and the participants were asked to self-complete the questionnaire. The approximate completion time was 15 minutes, and a reward valued at 4,500 Korean won was provided to all participants upon completion of the questionnaire to conclude their participation.

#### *Ethical considerations*

This study was approved by the Institutional Review Board of Konyang University (IRB No. 2022-03-005-002). Informed consent was obtained from all participants before study initiation. Participant anonymity and confidentiality were guaranteed. Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[20]

#### *Instrument verification*

The data collected to verify the validity and reliability of the developed instrument were analyzed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA). Item analysis, exploratory factor analysis, convergent validity, and discriminant validity were used to verify the construct validity of the instrument. Cronbach's α was used to verify the instrument's reliability.

## RESULTS

### Instrument Development

#### *Instrument factors derived from the literature review and FGI*

We examined questions used in the measurement of infection control of emerging infectious diseases,[21] practices related to novel influenza,[13] and COVID-19 infection prevention and control behaviors,[22,23] as well as the standards presented by the US Center for Disease Control and Prevention[10] and factors based on the transmission route. The integration of the construct factors derived from the literature review and FGI resulted in 39 questions, including the following 12 factors: infection risk assessment and screening, hand hygiene, respiratory etiquette, personal protective equipment (PPE), patient placement, caregiver and visitor management, patient transfer and movement, equipment and environment management, medical waste disposal, colleagues' training, patient education, and visitor education.

#### *Expert investigation of the content validity and reflection of the preliminary survey results*

The validity of the content evaluated by the eight experts ranged from 0.88 to 1.0 for each item, with > 88% of the participants responding to all 39 questions with a score of three or higher. Reflecting the expert's opinions, one question regarding the epidemiological relationship of the patient's symptoms was added. After conducting a preliminary survey of 10 nurses with 40 questions, the terms used in six questions were modified.

### Application of the Instrument

#### *General participant characteristics*

The general characteristics of the participants in the application of the developed instrument are listed in Table 1. Of the 199 participants, 178 (89.4%) were female, and 108 (54.3%) were aged between 20 and 29 years. The most common level of education was a bachelor's degree (n = 143; 71.9%), and more participants lived with their families (n = 128; 64.3%) than those who did not. Slightly more nurses worked at acute care hospitals (n = 110; 55.3%) than those at long-term care hospitals (n = 9; 44.7%). The most common position was "general nurse" (n = 176; 88.4%), and most participants worked in general wards (n = 145; 72.9%). Most had 1–3 years of clinical experience (n = 48; 24.1%), followed by 47 with 5–10 years of experience (23.6%). The most common duration of experience in the current department was < 1 year (n = 63; 31.7%), followed by 1–3 years (n = 54; 27.1%). One hundred and eighty-five participants (93.0%) reported having experi-

**Table 1.** Demographic characteristics of participants (n=199)

| Variable | Value |
|---|---|
| Sex | |
| Female | 178 (89.4) |
| Male | 21 (10.6) |
| Age (y) | 34.84 ± 12.64 |
| 20–29 | 108 (54.3) |
| 30–39 | 35 (17.6) |
| 40–49 | 19 (9.5) |
| 50–59 | 26 (13.1) |
| 60–69 | 11 (5.5) |
| Level of education | |
| College | 44 (22.1) |
| University | 143 (71.9) |
| Master or higher | 12 (6.0) |
| Family members living together | |
| Yes | 128 (64.3) |
| No | 71 (35.7) |
| Type of hospital | |
| Acute care | 110 (55.3) |
| Long-term care | 89 (44.7) |
| Position | |
| Staff nurse | 176 (88.4) |
| Charge nurse | 23 (11.6) |
| Working department | |
| Emergency room | 8 (4.0) |
| Outpatient department | 5 (2.5) |
| Wards | 145 (72.9) |
| Intensive care unit | 28 (14.1) |
| Operating room | 13 (6.5) |
| Work experience in nursing (yr) | 7.92 ± 7.35 |
| < 1 | 9 (4.5) |
| ≥ 1 and < 3 | 48 (24.1) |
| ≥ 3 and < 5 | 32 (16.1) |
| ≥ 5 and < 10 | 47 (23.6) |
| ≥ 10 | 63 (31.7) |
| Duration of employment in current department (yr) | 3.50 ± 4.06 |
| < 1 | 63 (31.7) |
| ≥ 1 and < 3 | 54 (27.1) |
| ≥ 3 and < 5 | 30 (15.1) |
| ≥ 5 and < 10 | 31 (15.6) |
| ≥ 10 | 21 (10.5) |
| Experience caring for confirmed patients of emerging respiratory infectious diseases | |
| Yes | 185 (93.0) |
| No | 14 (7.0) |
| Experience caring for suspected patients of emerging respiratory infectious diseases | |
| Yes | 188 (94.5) |
| No | 11 (5.5) |
| Experience of infection control education for the past year | |
| Yes | 186 (93.5) |
| No | 13 (6.5) |
| Effect of infection control education | |
| Strongly disagree | 14 (7.0) |
| Disagree | 6 (3.0) |
| Neutral | 56 (28.1) |
| Agree | 98 (49.3) |
| Strongly agree | 25 (12.6) |

Values are presented as number (%) or mean±standard deviation.

enced caring for patients with confirmed novel respiratory infectious diseases and 188 (94.5%) reported having experienced caring for patients suspected of having contracted an emerging respiratory infectious disease. In terms of receiving infection control education in the past year, 186 participants (93.5%) responded "yes." Regarding whether infection control education "helps to practice infection-preventive behaviors when treating patients with confirmed or suspected emerging respiratory infectious diseases," most responded "yes" (n = 98, 49.3%), while 56 (28.1%) responded "neutral" (Table 1).

### *Verification of the construct validity*

Item analysis: To verify the instrument, the mean, standard deviation, skewness, and kurtosis of the 40 items were measured. The mean score for each item was 3.57 ± 0.62. The item with the lowest mean was #14 ("I always wear a mask when within 1–2 m of a patient with respiratory symptoms"), while the item with the highest mean was #7 ("I practice hand hygiene after being exposed to or highly likely to be exposed to patients' blood, body fluids, secretions, excrements, and mucous membranes, damaged skin, or actions with a high risk of exposure"). Evaluation of the normality of the response data revealed that the absolute value of skewness represented good normality. The Pearson correlation coefficients to determine the correlation of the total number of items satisfied the requirement of 0.30 or higher and ensured the suitability for conducting exploratory factor analysis (Table 2).

Exploratory factor analysis: We performed exploratory factor analysis to verify the instrument's validity. After performing the Kaiser–Meyer–Olkin test and Bartlett test of sphericity to evaluate the appropriateness of the factor analysis, we performed a principal component factor analysis using the varimax rotation method. The factor analysis identified eight factors from the 40 items, and the cumulative variance of 65.1% demonstrated the appropriate explanatory power. However, items #24, #15, #16, #3, and #6 included in Factor 4 differed in content, as they were grouped into the same factor. Therefore, four questions were excluded, aside from item #15 ("I wear an N95 or KF94 mask when performing procedures [i.e., inhalation, airway intubation, cardiopulmonary resuscitation, and bronchoscopy] in which aerosol is generated"), which experts considered essential for measuring the practice of infection-preventive activities. Among items #17, #14, #5, #25, and #33 included in Factor 6, item #25 was excluded because it differed in content from the other items included in Factor 6.

Six factors were identified by conducting a second factor analysis with 35 items, following which item #4 of Factor 1 was excluded due to its commonality of < 0.4. Ultimately, eight items for Factor 1, seven for Factor 2, six for Factor 3, five for Factor 4, four for Fac-

**Table 2.** Item analysis of scale (n=199)

| | Item | Score | Skewness | Kurtosis | Corrected item to total correlation |
|---|---|---|---|---|---|
| 1 | I determine whether an emerging respiratory infectious disease is suspected based on the patient's clinical symptoms. | 3.38 ± 0.52 | 0.175 | -1.217 | 0.485* |
| 2 | I determine a suspected emerging respiratory infectious disease based on the relation of the patient's symptoms to a contact with a previously confirmed patient. | 3.29 ± 0.57 | -0.429 | 1.282 | 0.448* |
| 3 | I report suspected or confirmed cases of emerging respiratory infectious diseases according to reporting procedures. | 3.60 ± 0.55 | -0.973 | -0.085 | 0.600* |
| 4 | I practice standard and transmission-based precautions according to the transmission route of the pathogen that causes emerging respiratory infectious diseases. | 3.58 ± 0.52 | -0.656 | -0.884 | 0.546* |
| 5 | I practice hand hygiene before coming in contact with patients. | 3.11 ± 1.07 | -0.912 | -0.497 | 0.312* |
| 6 | I practice hand hygiene before performing a clean or aseptic procedure on patients. | 3.76 ± 0.54 | -2.767 | 9.216 | 0.534* |
| 7 | I practice hand hygiene after being exposed to or highly likely to be exposed to patients' blood, body fluids, secretions, excrement, mucous membranes, damaged skin, or actions with a high risk of exposure. | 3.83 ± 0.37 | -1.811 | 1.291 | 0.655* |
| 8 | I practice hand hygiene after coming in contact with patients. | 3.73 ± 0.48 | -1.448 | 1.035 | 0.667* |
| 9 | I practice hand hygiene after coming in contact with patients' surroundings. | 3.62 ± 0.53 | -0.929 | -0.291 | 0.654* |
| 10 | I practice hand hygiene after removing gloves. | 3.68 ± 0.55 | -1.678 | 2.935 | 0.632* |
| 11 | I do not touch my eyes, nose, or mouth with unwashed hands. | 3.68 ± 0.53 | -1.614 | 2.956 | 0.600* |
| 12 | I put masks over patients' noses and mouths when they sneeze or cough. | 3.59 ± 0.57 | -1.180 | 1.333 | 0.631* |
| 13 | I wear a mask over my nose and mouth when patients sneeze or cough. | 3.73 ± 0.52 | -1.773 | 2.304 | 0.711* |
| 14 | I always wear a mask when within 1–2 m of a patient with respiratory symptoms. | 3.21 ± 1.08 | -1.020 | -0.438 | 0.398* |
| 15 | I wear an N95 or KF94 mask when performing aerosol-generating procedures (e.g., aspiration, airway intubation, cardiopulmonary resuscitation, and bronchoscopy). | 3.70 ± 0.55 | -1.885 | 3.632 | 0.645* |
| 16 | I wear an N95 or KF94 mask when collecting respiratory specimens from suspected cases or suspected or confirmed patients. | 3.78 ± 0.45 | -1.889 | 2.740 | 0.635* |
| 17 | I wear gloves when in contact with the blood or body fluids of patients with emerging respiratory infectious diseases. | 3.46 ± 0.89 | -1.612 | 1.558 | 0.464* |
| 18 | I wear a gown when there is a risk of splashing blood or fluids from patients with emerging respiratory infectious diseases. | 3.62 ± 0.61 | -1.801 | 3.820 | 0.580* |
| 19 | I wear goggles or face shields when there is a possibility of splashing blood or fluids from patients with emerging respiratory infectious diseases. | 3.63 ± 0.61 | -1.696 | 2.927 | 0.604* |
| 20 | When wearing as N95 mask, I seal the mask by pressing the contact areas around my nose and check for any leaks by wrapping the mask with both hands, then inhaling and exhaling. | 3.49 ± 0.72 | -1.203 | 0.623 | 0.602* |
| 21 | When wearing gloves, I wear them so that the gloves extend over the sleeves. | 3.75 ± 0.45 | -1.327 | 0.239 | 0.659* |
| 22 | I put on personal protective equipment in the following order after performing hand hygiene: long-sleeved gown, mask, face shield, and gloves. | 3.55 ± 0.70 | -1.792 | 3.442 | 0.346* |
| 23 | When removing personal protective equipment, I remove gloves, then the long-sleeved gown, perform hand hygiene, and remove the mask last. | 3.49 ± 0.79 | -1.725 | 2.673 | 0.394* |
| 24 | I remove personal protective equipment in a designated area after leaving the isolation room and dispose of it in a medical waste container. | 3.75 ± 0.59 | -2.960 | 9.898 | 0.372* |
| 25 | I perform aerosol-generating procedures in an area with adequate ventilation. | 2.75 ± 1.10 | -0.256 | -1.275 | 0.333* |
| 26 | I isolate patients with suspected or confirmed emerging respiratory infectious diseases 1–2 m from other patients. | 3.57 ± 0.65 | -1.669 | 3.354 | 0.598* |
| 27 | I check whether caregivers and visitors have symptoms of infection and whether they have met any previously confirmed patients. | 3.59 ± 0.56 | -1.159 | 1.358 | 0.620* |
| 28 | I request caretakers and visitors to register on the entry log. | 3.63 ± 0.60 | -1.517 | 1.958 | 0.568* |
| 29 | Visitation of confirmed or suspected patients is restricted in principle. However, in inevitable cases, visitors must enter after performing hand hygiene and wearing personal protective equipment. | 3.53 ± 0.68 | -1.629 | 3.042 | 0.554* |
| 30 | I minimize the movement of patients with emerging respiratory infectious diseases and have them wear surgical or health masks (gowns and gloves if necessary) when leaving the patient room. | 3.62 ± 0.61 | -1.801 | 3.820 | 0.575* |
| 31 | I control the transfer route of patients with emerging respiratory infectious diseases before the transfer and provide information to the receiving department. | 3.73 ± 0.48 | -1.448 | 1.035 | 0.703* |
| 32 | I put reusable items used by patients with emerging respiratory infectious diseases in a biohazard container immediately after the use to allow for disinfection and sterilization of the causative pathogens in a way they can be destroyed. | 3.59 ± 0.69 | -1.859 | 3.510 | 0.578* |

(Continued to the next page)

**Table 2.** Continued

| | Item | Score | Skewness | Kurtosis | Corrected item to total correlation |
|---|---|---|---|---|---|
| 33 | I disinfect the environmental surfaces of isolation rooms occupied by patients of suspected or confirmed patients. | 3.19 ± 0.97 | -0.799 | -0.635 | 0.470* |
| 34 | I immediately disinfect the visibly contaminated environmental surfaces with blood or body fluids in patient rooms occupied by suspected or confirmed patients. | 3.62 ± 0.61 | -1.790 | 3.946 | 0.558* |
| 35 | I place bedding, clothing, and linen used by patients in designated containers to prevent dispersion of pathogens. | 3.73 ± 0.53 | -2.286 | 6.641 | 0.608* |
| 36 | I treat patients' bedding and clothing as well as linens contaminated with discharge according to the guidelines for laundry management in medical institutions and the Enforcement Decree of the Wastes Control Act. | 3.79 ± 0.42 | -1.630 | 1.261 | 0.697* |
| 37 | I promptly place medical waste used by patients in medical waste containers at the disposal site. | 3.79 ± 0.44 | -1.936 | 2.949 | 0.599* |
| 38 | I educate and provide information to fellow healthcare workers who care for patients regarding infection control methods and procedures against emerging respiratory infectious diseases. | 3.64 ± 0.52 | -1.005 | -0.124 | 0.680* |
| 39 | I educate and inform patients who can communicate regarding infection control methods and procedures against emerging respiratory infectious diseases. | 3.61 ± 0.53 | -0.856 | -0.438 | 0.662* |
| 40 | I educate and inform visitors, including caregivers, on infection control methods and procedures against emerging respiratory infectious diseases. | 3.60 ± 0.54 | -0.906 | -0.267 | 0.712* |

Values are presented as mean±standard deviation.
*p<0.01.

tor 5, and four for Factor 6 were derived. The total variance explained by the 34 items was 61.68% (Table 3).

Convergent and discriminant validity: We used the construct reliability (CR) and average variance extracted (AVE) to verify the convergent validity of the instrument. The CR of the developed instrument was 0.71–0.91, where all factors satisfied the threshold of 0.70 or higher.[24] Of the eight factors, Factors 1, 2, and 4 satisfied the AVE value of 0.50 or higher, while Factors 3, 5, and 6 did not (Table 4).

We measured the square of the correlation coefficient between the factors to verify the discriminant validity of the instrument.[24] The results showed that the value was lower than the AVE of each factor of the developed instrument, except for Factors 1 and 3 and Factors 3 and 4 (Table 5).

Verification of the instrument's reliability: We calculated Cronbach's α to verify the instrument's reliability. Cronbach's α for the 34 items in the developed instrument was 0.82 overall, and ranged from 0.71–0.91 for each factor (Table 3).

Factor naming and instrument finalization: We selected 34 questions in the development of an instrument to measure nurses' compliance with infection prevention activities and verified the validity and reliability of the measurement. The instrument consisted of six factors: Factor 1, equipment and environmental management and education, included eight items (#36, #37, #35, #38, #39, #40, #34, and #32); Factor 2, hand hygiene and respiratory etiquette, included seven items (#8, #9, #10, #7, #13, #12, and #11); Factor 3, infection risk assessment and flow management, included six items (#2, #27, #26, #28, #1, and #31); Factor 4, protection of employees in contact with infected patients, included five items (#19, #18, #20, #21, and #15); Factor 5, ward access management of patients with infectious diseases, included four items (#17, #14, #5, and #33); and Factor 6, wearing and removing PPE, included four items (#22, #23, #30, and #29). The score ranged from 35 to 140, with higher scores indicating more frequent infection-preventive behaviors.

## DISCUSSION

The validation of the reliability and validity of the developed instrument to measure nurses' compliance with infection-prevention activities against emerging respiratory infectious diseases derived six factors consisting of a total of 34 items, as follows: equipment and environmental management and education (eight items), hand hygiene and respiratory etiquette (seven items), infection risk assessment and flow management (six items), protection of employees in contact with infected patients (five items), ward access management of patients with infectious diseases (four items), and PPE wearing and removal (four items).

Factor 1, equipment and environmental management and education, had an explanatory power of 13.96%. It comprised eight questions, including medical waste, linen, reusable products, environmental surface management, and the education of patients, caregivers, and colleagues. In contrast to measures such as hand washing, cough etiquette, use of face masks, and social distancing identified by Jung and Hong,[17] which examined COVID-19 infection-preventive practices in the general public, equipment and en-

**Table 3.** Factor loading and reliability for the each factor by exploratory factor analysis (n=199)

| Naming | Item No. | Factor 1 | Factor 2 | Factor 3 | Factor 4 | Factor 5 | Factor 6 | Cronbach's α |
|---|---|---|---|---|---|---|---|---|
| Factor 1: Equipment and environmental management and education | 36 | 0.809 | 0.118 | 0.183 | 0.222 | -0.115 | 0.156 | 0.89 |
| | 37 | 0.800 | 0.024 | 0.131 | 0.275 | -0.033 | 0.097 | |
| | 35 | 0.777 | 0.176 | 0.051 | 0.183 | -0.045 | 0.137 | |
| | 38 | 0.662 | 0.302 | 0.264 | 0.144 | -0.154 | 0.021 | |
| | 39 | 0.586 | 0.370 | 0.307 | 0.021 | -0.195 | 0.030 | |
| | 40 | 0.565 | 0.423 | 0.332 | 0.072 | -0.196 | 0.028 | |
| | 34 | 0.536 | 0.272 | 0.299 | -0.063 | -0.03 | 0.146 | |
| | 32 | 0.435 | 0.118 | 0.371 | 0.073 | -0.131 | 0.296 | |
| | 4 | 0.398 | 0.177 | 0.354 | 0.186 | 0.031 | 0.074 | |
| Factor 2: Hand hygiene and respiratory etiquette | 8 | 0.164 | 0.827 | 0.124 | 0.192 | -0.105 | 0.139 | 0.91 |
| | 9 | 0.179 | 0.812 | 0.226 | 0.087 | -0.113 | 0.094 | |
| | 10 | 0.189 | 0.764 | 0.160 | 0.132 | -0.137 | 0.103 | |
| | 7 | 0.370 | 0.650 | 0.006 | 0.325 | -0.115 | 0.000 | |
| | 13 | 0.245 | 0.629 | 0.200 | 0.256 | -0.112 | 0.293 | |
| | 12 | 0.041 | 0.586 | 0.324 | 0.206 | -0.112 | 0.348 | |
| | 11 | 0.300 | 0.555 | -0.005 | 0.410 | -0.011 | 0.189 | |
| Factor 3: Infection risk assessment and flow management | 2 | 0.071 | 0.189 | 0.731 | 0.037 | 0.046 | -0.042 | 0.82 |
| | 27 | 0.235 | 0.074 | 0.671 | 0.238 | -0.094 | 0.211 | |
| | 26 | 0.242 | -0.001 | 0.629 | 0.211 | -0.046 | 0.363 | |
| | 28 | 0.257 | 0.044 | 0.613 | 0.282 | -0.047 | 0.091 | |
| | 1 | 0.240 | 0.229 | 0.592 | 0.083 | 0.002 | -0.164 | |
| | 31 | 0.416 | 0.275 | 0.533 | 0.107 | -0.182 | 0.132 | |
| Factor 4: Protection of employees in contact with infected patients | 19 | 0.186 | 0.192 | 0.094 | 0.801 | -0.187 | 0.108 | 0.83 |
| | 18 | 0.159 | 0.253 | 0.197 | 0.704 | -0.157 | 0.006 | |
| | 20 | 0.076 | 0.198 | 0.392 | 0.650 | -0.119 | 0.110 | |
| | 21 | 0.341 | 0.286 | 0.143 | 0.572 | -0.044 | 0.253 | |
| | 15 | 0.350 | 0.282 | 0.285 | 0.419 | -0.013 | 0.153 | |
| Factor 5: Ward access management of patients with infectious diseases | 17 | -0.199 | -0.095 | -0.081 | -0.048 | 0.782 | 0.051 | 0.75 |
| | 14 | -0.125 | -0.061 | 0.023 | -0.054 | 0.748 | -0.060 | |
| | 5 | -0.006 | -0.077 | 0.086 | -0.127 | 0.741 | -0.026 | |
| | 33 | -0.013 | -0.191 | -0.260 | -0.125 | 0.638 | 0.049 | |
| Factor 6: Wearing and taking off personal protection equipment | 22 | 0.115 | 0.154 | -0.076 | 0.109 | 0.043 | 0.769 | 0.71 |
| | 23 | 0.102 | 0.151 | 0.073 | 0.123 | 0.047 | 0.683 | |
| | 30 | 0.258 | 0.121 | 0.460 | -0.009 | -0.048 | 0.612 | |
| | 29 | 0.057 | 0.266 | 0.457 | 0.103 | -0.133 | 0.465 | |
| Eigen value | | 4.89 | 4.63 | 4.12 | 3.01 | 2.49 | 2.45 | 0.82 |
| Explained variance (%) | | 13.96 | 13.22 | 11.78 | 8.60 | 7.12 | 7.00 | |
| Total variance (%) | | 13.96 | 27.18 | 38.96 | 47.56 | 54.68 | 61.68 | |
| | Kaiser-Meyer-Olkin measuring of sampling adequacy = 0.892, Bartlett test of sphericity: $\chi^2 = 4275.441$ (df = 595, $p < 0.01$). | | | | | | | |

**Table 4.** Convergent validity with CR and AVE of factors (n=199)

| | CR | AVE |
|---|---|---|
| Factor 1: Equipment and environmental management and education | 0.899 | 0.502 |
| Factor 2: Hand hygiene and respiratory etiquette | 0.910 | 0.594 |
| Factor 3: Infection risk assessment and flow management | 0.824 | 0.443 |
| Factor 4: Protection of employees in contact with infected patients | 0.843 | 0.518 |
| Factor 5: Ward access management of patients with infectious diseases | 0.754 | 0.439 |
| Factor 6: Wearing and taking off personal protection equipment | 0.710 | 0.395 |

CR, construct reliability; AVE, average variance extracted.

**Table 5.** Discriminant validity with the square of correlation coefficient between factors (n=199)

| | | $R^2$ |
|---|---|---|
| Factor 1 | Factor 2 | 0.444 |
| | Factor 3 | 0.578 |
| | Factor 4 | 0.456 |
| | Factor 5 | 0.151 |
| | Factor 6 | 0.336 |
| Factor 2 | Factor 3 | 0.329 |
| | Factor 4 | 0.489 |
| | Factor 5 | 0.137 |
| | Factor 6 | 0.318 |
| Factor 3 | Factor 4 | 0.466 |
| | Factor 5 | 0.095 |
| | Factor 6 | 0.573 |
| Factor 4 | Factor 5 | 0.150 |
| | Factor 6 | 0.278 |
| Factor 5 | Factor 6 | 0.033 |

Factor 1, Equipment and environmental management and education; Factor 2, Hand hygiene and respiratory etiquette; Factor 3, Infection risk assessment and flow management; Factor 4, Protection of employees in contact with infected patients; Factor 5, Ward access management of patients with infectious diseases; Factor 6, Wearing and taking off personal protection equipment.

vironmental management were derived as the main infection prevention activity compliance against emerging respiratory infectious diseases in this study of nurses. Specifically, in the case of emerging respiratory infectious diseases, such as COVID-19, the droplets released from a person's respiratory tract can contaminate environmental surfaces[25]; thus, the management of these surfaces is an increasingly important infection-preventive measure.

Factor 1 included three questions regarding nurses' provision of information and educating communicative patients, caregivers, and colleagues. The agents who execute standard and transmission-based precautions are not limited to hospital staff, including nurses.[10] Specifically, a standard precaution is a concept in which patients, staff, caregivers, and visitors in a healthcare facility recognize the risk of infection on their own and practice cautionary guidelines. Therefore, educating patients, caregivers, and colleagues is crucial for preventing the infection of nurses with emerging respiratory infectious diseases. In the wake of the COVID-19 pandemic, healthcare facilities have restricted visitors; however, as they allow resident caregivers to care for patients, infection prevention education for caregivers, such as hand hygiene, respiratory etiquette, and the use of face masks, is increasingly emphasized.[26] In addition, as government guidelines frequently change with the rapidly fluctuating trends of the pandemic, the education of nurses, especially those who educate and inform their peers, is a major component of infection prevention activity compliance in emerging respiratory infectious diseases.

Factor 2, hand hygiene and respiratory etiquette, had an explanatory power of 13.22% and comprised seven questions, including four questions related to hand hygiene and three questions related to respiratory etiquette. Hand hygiene and respiratory etiquette are elements of the concept of standard precautions, which were also included as the primary concepts in the instruments of prior studies.[17,25,27] Although the standard precautions include hand hygiene and respiratory etiquette, separately as an independent factor,[10] this study grouped them as a single factor of preventive action against emerging respiratory infectious diseases because of the nature of the hand-mediated transmission of respiratory droplets that cause respiratory infectious diseases.

Factor 3, infection risk assessment, and flow management, had an explanatory power of 11.78% and comprised six questions, including identifying the clinical symptoms of patients, caregivers, and visitors and history of contact with a confirmed patient; logging entries; social distancing of 1–2 m; minimizing patient transfers and providing information to receiving departments; and limiting visitation. Unlike previous studies that measured the clinical symptoms of COVID-19 in terms of knowledge,[28] the present study derived the risk of infection, clinical symptoms, and transmission route as the primary infection prevention activity in evaluating nurse compliance. Nurse assessment of infection risk and implementing appropriate isolation precautions according to the degree of infection risk are essential infection-preventive behaviors for preventing the spread of emerging respiratory infectious diseases.

Factor 4, protection of employees in contact with infected people, had an explanatory power of 11.78% and included five questions related to the selection of gowns, masks, goggles, and face shields, as well as precautions when putting on PPE. As presented in Factor 4, most prior studies[10,18,19] also include PPE as a primary component of infection prevention against novel respiratory infectious diseases. Notably, the size of respiratory droplets produced during aerosol-generating procedures is $< 5$ μm, with a very high risk of such droplets spreading with the flow of air.[22] Therefore, the use of PPE, including high-efficiency filter masks, is an imperative strategy for preventing novel respiratory infections.

Factor 5, ward access management of patients with infectious diseases, had an explanatory power of 7.12% and comprised four questions, including hand hygiene of nurses before entering a patient's room and coming in contact with patients with infectious diseases, wearing gloves, using masks, and disinfecting the environmental surfaces of isolation rooms. Factor 5 also included the elements of contact and droplet precautions of the transmission-based precautions.[8] Viruses that cause emerging respiratory infectious diseases, such as COVID-19, are mainly transmitted

through droplets. However, they are likely to aerosolize in areas with poor ventilation or insufficient environmental surface disinfection, or during procedures that produce aerosols such as suction[28]; thus, the implementation of airborne precautions is needed in such situations. The elements of airborne precautions were not constructed into a factor in this study, as the participants did not have ample experience in nursing confirmed patients with severe enough symptoms to undergo aerosol-generating procedures. Future studies should include participants who have experienced nursing patients with novel respiratory infections in a variety of situations.

Factor 6, wearing and removing PPE, had an explanatory power of 7.00%. Factor 6 comprised four questions, including the order in which PPE was put on and removed, the wearing of PPE for patient transfers, and providing hand hygiene and PPE to visitors. Many unknown aspects of emerging respiratory infectious diseases remain unknown, such as the pattern of occurrence and mutation of causative pathogens. Therefore, observing the order of wearing and removing PPE and treating patient blood, bodily fluids, secretions, and excrement as sources of infection, regardless of the diagnosis of an infectious disease[10] are important preventive measures. Hand hygiene was required after the removal of each PPE item. Specifically, it is imperative to perform hand hygiene before touching the face, eyes, nose, and mouth, which are highly vulnerable to pathogen invasion.[29]

This study developed an instrument with stable validity and reliability through a literature review, an FGI with nurses with experience in responding to emerging respiratory infectious diseases, and exploratory factor analysis. Compliance with infection prevention activity compliance against emerging respiratory infectious diseases could be accurately measured because the instrument was developed based on the experience of nurses who had treated patients with emerging respiratory infectious diseases at clinical sites, including long-term care hospitals. However, one limitation is that the instrument does not cover all infectious diseases, although it reflects preventive measures against respiratory infectious disease, as it was developed in the context of COVID-19. In addition, limitations may exist in measuring compliance with infection prevention activities against emerging infectious respiratory diseases among nurses caring for patients in other locations, such as children's hospitals, psychiatric hospitals, and outpatient clinics. The present study mainly targeted acute and long-term care hospitals where adult and older adult patients were hospitalized. However, this instrument can be validated, modified, and supplemented by repeatedly applying it to studies that target nurses working at various sites.

The developed instrument will allow the identification of nurses' level of infection prevention activity compliance with novel respiratory infectious diseases. We further recommend the development of education and training programs promoting this compliance and the utilization of the developed instrument to evaluate their effectiveness.

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### CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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### AUTHOR CONTRIBUTIONS

Conceptualization: SYJ; Data curation: MSS, SYJ; Funding acquisition: HJJ, MSS, SYJ; Investigation: HJJ; Methodology: HJJ; Project administration: HJJ, MSS, SYJ; Supervision, HJJ, MSS, SYJ; Writing-original draft, HJJ, MSS, SYJ; Writing-review & editing, HJJ.

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# Denosumab's Therapeutic Effect for Future Osteosarcopenia Therapy : A Systematic Review and Meta-Analysis

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**Background:** Osteosarcopenia, a combination of osteopenia/osteoporosis and sarcopenia, is a common condition among older adults. While numerous studies and meta-analyses have been conducted on the treatment of osteoporosis, the pharmacological treatment of osteosarcopenia still lacks evidence. Denosumab, a human monoclonal antibody, has shown encouraging results for the treatment of osteosarcopenia. Our systematic review and meta-analysis aimed to investigate the potential dual role of denosumab as an anti-resorptive agent and for other beneficial muscle-related effects in patients with osteosarcopenia, and to evaluate whether denosumab can be a treatment of choice compared to bisphosphonate. **Methods:** Relevant literature was collated from the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and Google Scholar databases. The primary outcome was denosumab's effect on lumbar spine bone mineral density (LS BMD), handgrip strength, and gait speed change. The secondary outcome was the effect of denosumab on appendicular lean mass (ALM). The outcomes were presented as mean difference (MD). A random effects model was used in the analysis to represent the population. The risk of bias was assessed using funnel plots. **Results:** Out of the 3,074 studies found, four full-text studies met the inclusion criteria, including 264 and 244 participants in the intervention and control groups, respectively. Regarding a primary outcome, our meta-analysis showed that denosumab showed no significant differences in LS BMD and gait speed changes compared to other agents—MD=0.37, 95% confidence interval (CI), -0.35 to 0.79; p=0.09 and MD=0.11; 95% CI, -0.18 to 0.40; p=0.46, respectively. Denosumab had a significant effect on handgrip strength change compared to standard agents—MD=5.16; 95% CI, 1.38 to 18.94; p=0.007, based on the random effects model. **Conclusions:** Denosumab was better than bisphosphonate and placebo in improving muscle strength (handgrip strength). Therefore, denosumab may be favored in individuals with osteosarcopenia to improve muscular performance and reduce fall risk.

**Key Words:** Denosumab, Osteosarcopenia, Osteoporosis, Sarcopenia

## INTRODUCTION

Recently, the term "osteosarcopenia" has been proposed to describe the coexistence of osteopenia/osteoporosis and sarcopenia.[1)] The negative effects of osteoporosis (bone loss) and sarcopenia (loss of muscle mass and function), such as increased risks of falls, fractures, frailty, disability, and early mortality, highlight the need to maintain musculoskeletal health in old age.[2)] Osteosarcopenia occurrence becomes more common with aging, reaching a frequency of 33.7% in individuals over 80 years of age. Mortality is also considerably higher in patients with osteosarcopenia (15.9%) than in those without (6.1%). Additionally, individuals with osteosarcopenia have a higher incidence of fractures, falls, and functional impairment compared to those without osteosarcopenia—fall:

hazard ratio (HR) = 1.60; 95% confidence interval (CI), 1.07–2.38; $p < 0.05$; fractures: HR = 1.54; 95% CI, 1.13–2.08; $p < 0.01$; functional impairment: HR = 1.83; 95% CI, 1.41–2.38; $p < 0.001$.[3]

Osteoporosis is one of the most prevalent public health problems and a significant risk factor for adverse health outcomes, including fractures.[4] Sarcopenia, an age-related decline in skeletal muscle mass, strength, and function, is defined by the degeneration of muscle quantity and quality, frequently resulting in severe unfavorable effects.[5] Increased attention has been paid to osteoporosis and sarcopenia, as the two conditions together have been called a "hazardous duet" that worsens health consequences.[4-6] The concept of a bone-muscle unit suggests communication between these tissues; hence, diseases that affect one element of the musculoskeletal unit are likely to impact the other, and vice versa.[7] However, to date, there is a dearth of evidence from randomized controlled trials (RCTs) that have studied a shared pharmacological target for osteosarcopenia even though therapeutic targets common to both bone and muscle have been postulated.[7]

The current recommendations for the treatment of osteosarcopenia include non-pharmacological and pharmacological treatments. Diet and exercise are the cornerstones of non-pharmaceutical treatments. The Framingham Osteoporosis Study reported that low protein consumption was related to bone loss in the proximal femur and spine during a 4-year period.[8] Protein consumption is beneficial for enhancing muscle mass,[9] while the effects on sarcopenia-related measures, such as strength and functional capacity, are less consistent,[9,10] and the effects of exercise are enormous.[11] As a non-pharmacological treatment for osteosarcopenia, these two treatments should be combined. Numerous Food and Drug Administration (FDA)-approved drugs are widely available,[12] however, no approved pharmacological medicines exist for the treatment of osteosarcopenia. Testosterone, denosumab, growth hormone, and anti-myostatin antibodies have all been studied as potential pharmacological treatments for osteosarcopenia, although the results have been inconsistent. Denosumab, a human monoclonal antibody, has shown encouraging results in the treatment of osteosarcopenia.[13] In bone, denosumab binds to the cytokine RANKL with high specificity and affinity to limit its effect. Consequently, osteoclast recruitment, maturation, and action are blocked, and bone resorption slows.[14] Denosumab may also affect muscle mass through the inhibition of the receptor activator of nuclear factor-B ligand (RANK/RANKL) by enhancing muscular strength and balance in older individuals at risk for falls and fractures.[15]

Several studies and meta-analyses have been conducted to assess the role of nutritional intervention and exercise in osteosarcopenia; however, the treatment of osteosarcopenia with pharmacological drugs is a novel area of exploration, and evidence on this topic is scarce. Nonetheless, the therapeutic effects of some substances on osteoporosis and sarcopenia suggest a potential dual effect on muscle and bone mass, which may be effective in treating osteosarcopenia.[7] We conducted a comprehensive review and meta-analysis to analyze the present data and provide evidence regarding the therapeutic efficacy of denosumab and assess whether denosumab can be the treatment of choice for patients with osteosarcopenia compared to bisphosphonate, which is currently the gold standard for treating osteoporosis.

## MATERIALS AND METHODS

### Eligibility Criteria

We included all research articles that analyzed the therapeutic effects of denosumab for the treatment of osteosarcopenia. We independently screened the eligible publications were screened using the following inclusion criteria: (1) patients with osteosarcopenia or osteoporosis, (2) English language, and (3) original articles. We excluded non-research articles (e.g., case reports or series, review articles, letters to the editor, study protocols, editorials, or commentaries) and studies with insufficient data. The PICO (Population, Intervention, Comparator and Outcomes) framework was used to set the eligibility requirements (Table 1).

### Search Strategy and Study Selection

This meta-analysis was performed according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow statement. We systematically searched the PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) databases using the following search terms: ("osteo-

**Table 1.** PICO criteria

| | Description |
|---|---|
| Patient | Osteosarcopenia or osteoporosis patients |
| Intervention | Denosumab |
| Comparator | Placebo/other drugs such as zoledronic/bisphosphonate/alendronate |
| Outcome | Changes in lumbar spine BMD, handgrip strength, gait speed, appendicular lean mass, and femoral neck BMD |

BMD, bone mineral density.

porosis" AND "sarcopenia") AND ("denosumab" OR "antibodies, monoclonal humanized") with the latest search performed on October 19, 2022. Articles were independently screened for relevance based on their abstracts. These articles were thoroughly read and those that fulfilled our criteria were included in the study. The final inclusion of the studies was based on the agreement of all authors. Any disagreement was settled by author consensus, in which the agreement of more than two authors was the final decision. The full texts of the remaining articles were assessed according to the inclusion and exclusion criteria. The quality of the studies was assessed using a checklist guide from the Joanna Briggs Institute (JBI) critical appraisal tool based on study design. We used a cutoff point to determine the quality of the studies. We used a cutoff point of half of the total score on each JBI critical appraisal checklist. Low-quality studies had scores below the cutoff point, while the rest were considered high-quality studies.

### Data Extraction

Data extraction was performed independently by all authors using standardized forms that included author, year of study, study design, country of study, number of subjects, location of study, subject ages, T-score in the lumbar spine (LS), study duration, subject handgrip strength, subject gait speed, study description of, and comparator drugs. The main outcome of the studies was the mean difference (MD) between change in bone mineral density (BMD) in the LS, change in handgrip strength, and change in gait speed. The changes in BMD in the LS, handgrip strength, and gait speed were defined as the differences between baseline and after denosumab treatment during the observation period. BMD was calculated using a dual X-ray absorptiometry (DXA) scan and expressed in $g/cm^2$, handgrip strength was expressed in kg, and gait speed was expressed in m/s within 4 minutes of walking.

### Definition of Osteosarcopenia

Osteoporosis was radiographically diagnosed based on BMD measurements as a DXA T-score of ≤ -2.5.[16] The diagnostic criteria for sarcopenia were based on the Asian Working Group for Sarcopenia (AWGS) criteria, which define sarcopenia as low handgrip strength ( < 26 kg for men and < 18 kg for women) and/or low gait speed ( ≤ 0.8 m/s both for men and women) and low muscle mass ( < 7.0 $kg/m^2$ for men and < 5.7 $kg/m^2$ for women).[17] Sarcopenia was confirmed by the presence of low muscle quantity or quality. The presence of low muscle strength, low muscle quantity/quality, and low physical performance was considered severe sarcopenia.[18] No further criteria exist for defining osteosarcopenia beyond the combination of the clinical and imaging criteria for low BMD and sarcopenia described above. In other words, osteosarcopenia is the presence of sarcopenia with osteopenia or osteoporosis.[19]

### Statistical Analysis

RevMan v5.4.1 (Copenhagen, Nordic Cochrane Center; The Cochrane Collaboration, 2020) was used to perform the meta-analysis by computing the MD and 95% confidence interval (CI) for the osteosarcopenia parameter (changes in BMD in LS, handgrip strength, and gait speed) from baseline to the study endpoint for the placebo or other agent treatments and denosumab treatments. The p-value was two-tailed, and statistical significance was set at $p < 0.05$. Heterogeneity was assessed using the Q-statistic and $I^2$ test. The $I^2$ statistic measures the percentage of total variation across the studies due to clinical or methodological heterogeneity rather than chance. A random-effects model was used in the analysis to better represent the population. Publication bias was assessed by visual inspection of funnel plots.

### Ethical Approval and Consent to Participate

Ethical statements and informed consent were not applicable to this review and meta-analysis. Our study was registered in PROSPERO (ID: CRD42022367533).

## RESULTS

### Baseline Characteristics and Study Selection

The initial search strategy identified 3,074 studies. Following this, 3,044 papers were excluded based on title and abstract screening, as well as other factors, leaving four relevant studies. Studies that lacked the necessary data for this meta-analysis, or those that were retracted, were excluded. After screening and qualitative analyses, we included four papers in our study. Fig. 1 presents the PRISMA 2020 flowchart.

The meta-analysis included two RCTs and two cohort studies. Between 2019 and 2022, 264 and 244 samples in the intervention and control groups, respectively, appeared in these publications. Denosumab was administered to the experimental group for 6 months to 5 years, whereas the control group received oral alendronate 70 mg once weekly, 5 mg intravenous zoledronate once yearly, or 3 mg ibandronate intravenously every 3 months. Table 2 provides an overview of the findings and the investigational characteristics.[20-23] We examined the risks of bias for cohort and RCT trials using the JBI critical appraisal tool. Each of the four articles passed the quality evaluation. The results of the risk of bias analysis are detailed in Supplementary Tables S1–S5.

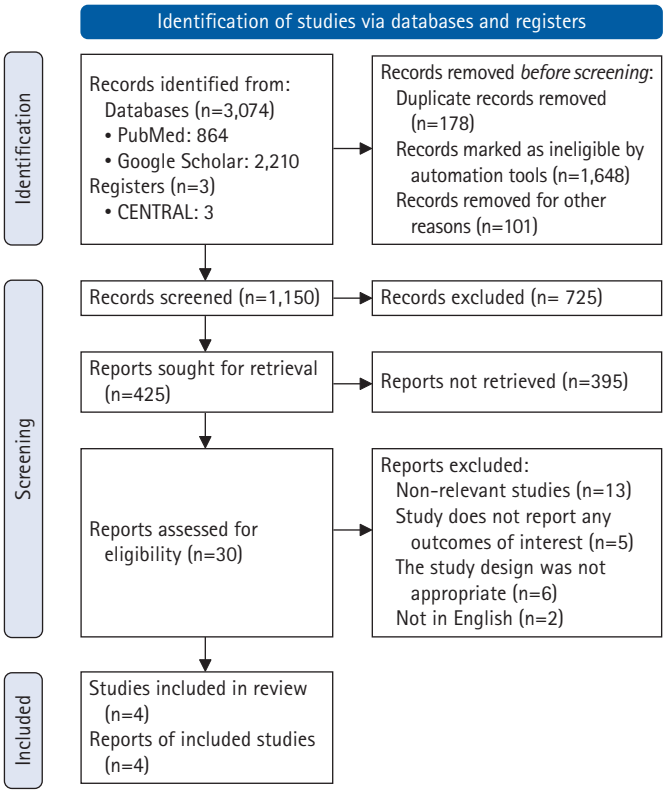


**Fig. 1.** Flowchart of search strategy.

## Denosumab Administration for Osteosarcopenia

### *Effect of denosumab on LS BMD change*

Compared to other agents, such as zoledronic acid, ibandronate, or alendronate, no significant differences were observed in LS BMD change when denosumab was administered. Based on the random-effects model ($I^2 = 94\%$; $\chi^2 = 31.19$; $p < 0.00001$), the pooled mean difference between denosumab and other agents was 0.37 g/cm$^2$ (95 CI, -0.05–0.79; $p = 0.09$) and did not differ significantly regarding LS BMD change (Fig. 2).

### *Effect of denosumab on handgrip strength change*

Our meta-analysis showed that denosumab had a significant effect on handgrip strength change compared to standard agents such as zoledronic acid, ibandronate, and alendronate. Based on the random-effects model ($I^2 = 60\%$; $\chi^2 = 5.03$; $p = 0.08$), the pooled mean difference between denosumab and other agents was 5.16 (95% CI, 1.38–18.94; $p = 0.007$) and showed a significant improvement in handgrip strength (Fig. 3).

### *Effect of denosumab on gait speed change*

The 4-m walk gait speed was used to evaluate the effect of denosumab on gait speed compared to other agents. Denosumab had no

**Table 2.** Characteristics of the studies included in the systematic review and meta-analysis

| Study | Year | Design | Country | Population | Sex and mean age | Intervention | Control | Outcome | Follow-up duration |
|---|---|---|---|---|---|---|---|---|---|
| Bonnet et al.[20] | 2019 | Single-blind RCT | Geneva, Switzerland | Post-menopausal osteoporotic women | Females only<br>Mean age: Denosumab 64.9 ± 1.5 yr, control 65.7 ± 0.9 yr | Denosumab (n = 18) | n = 20<br>BPs: alendronate (n = 8), zoledronate (n = 12) | BMD-LS, ALM, handgrip strength | 2.9 yr (range, 2.2–3.7 yr) |
| Miedany et al.[21] | 2021 | Single-blind RCT | Egypt | Patients with osteoporosis | Male and female<br>Mean ages: NA | Denosumab (n = 135) | n = 136<br>BPs: oral alendronate 70 mg once weekly, zoledronate once yearly 5 mg iv | Hip and spine BMD, calcium, vitamin D, FRAX, TUG, handgrip strength, gait speed | 5 yr |
| Rupp et al.[22] | 2022 | Retrospective cohort | Germany | Patients with osteopenia and osteoporosis | Male (n = 8) and female (n = 52) in both groups<br>Mean age: Denosumab 68.9 ± 9.2 yr, control 68.0 ± 7.6 yr | Denosumab (n = 60) | n = 60<br>BPs: alendronate 70 mg once weekly oral, ibandronate 3 mg intravenously every 3 months | 25(OH)D3 level, femoral and spinal BMD, handgrip strength, CRT force | 17.6 ± 9 mo (range, 8–59 mo) |
| Phu et al.[23] | 2019 | Cohort | Melbourne, Australia | Older adults ≥ 65 yr with history or risk of falls and/or fractures | Male and female<br>Mean age: NA | Denosumab + vitamin D (n = 51) | n = 28<br>Zoledronic acid + vitamin D | Gait speed, TUG, FSST, SPPB score, ABC | 6 mo |

RCT, randomized controlled trial; BPs, bisphosphonates; BMD, bone mineral density; ALM, appendicular lean mass; iv, intravenous; FRAX, Fracture Risk Assessment Tool; TUG, timed up and go; CRT, chair raising test; FSST, four square step test; SPPB, Short Physical Performance Battery; ABC, Activity-specific Balance Confidence Scale.

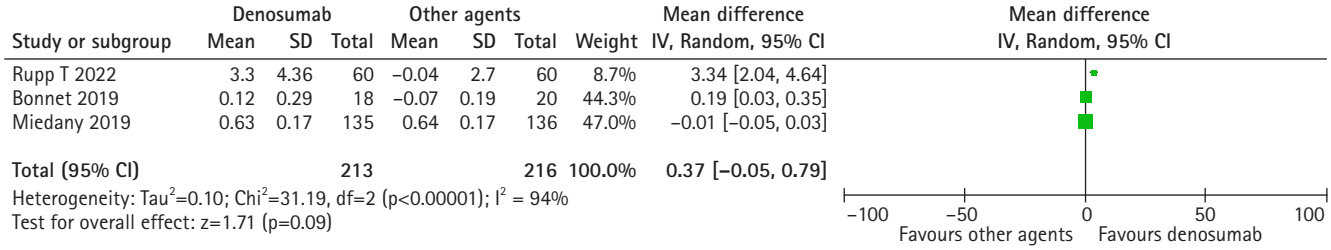


**Fig. 2.** Forest plot of denosumab's effect on lumbar spine bone mineral density change.

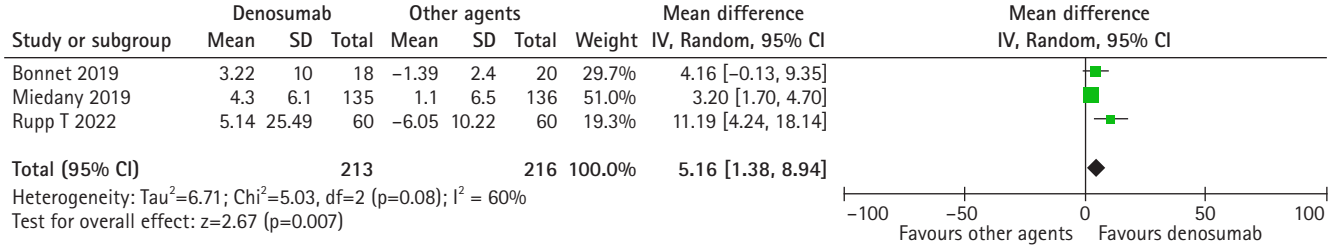


**Fig. 3.** Forest plot of denosumab's effect on handgrip strength change.

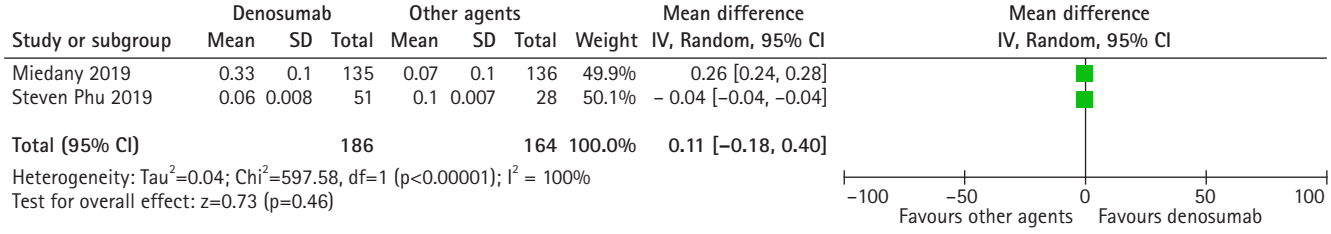


**Fig. 4.** Forest plot of denosumab's effect on gait speed change.

significant effect on gait speed change compared to standard agents such as zoledronic acid, ibandronate, and alendronate. Based on the random-effects model ($I^2 = 100\%$; $\chi^2 = 597.58$; $p < 0.00001$), the pooled mean difference between denosumab and other agents was 0.11 (95% CI, -0.18–0.40; $p = 0.46$) and showed no significant differences in gait speed change (Fig. 4).

### *Effect of denosumab on ALM*

The ALM was significantly higher in the denosumab group than that in the bisphosphonate group. After 3 years of denosumab administration, ALM increased in the bisphosphonate group (3.22 ± 10.0 kg vs. -0.07 ± 6.6 kg). Changes in ALM were strongly correlated with changes in LS BMD ($r^2 = 0.82$; $p < 0.001$) in the denosumab group but not in the other groups.[20] Women with osteoporosis receiving anti-osteoporosis agents in the treatment group, such as bisphosphonate alone in 60 patients, bisphosphonate with activated vitamin D3 in 12 patients, selective estrogen receptor modulator in four patients, and others in six patients, showed no difference in ALM change compared to placebo after 10 years. The baseline ALM before treatment in the bisphosphonate group was 14.1 ± 1.4 kg versus 14.1 ± 1.7 kg in the placebo group. After 10 years of follow-up, the ALM values were 13.9 ± 1.5 kg versus 13.9 ± 1.7 kg in the treatment group versus the control group. The change in ALM did not differ significantly between the bisphosphonate and control groups (-0.2 ± 0.9 kg vs. -0.2 ± 0.9 kg; $p = 0.543$).[24] The funnel plots of all analyses in our study did not reveal any significant asymmetry.

### *Effect of denosumab on FN BMD change*

Rupp et al.[22] showed that denosumab also has better outcomes in FN BMD compared to bisphosphonate. The mean annual percentage changes in FN BMD were higher in the denosumab and bisphosphonate groups and were significantly higher compared to the basic group—mean FN BMD in % change per year: basic (-0.78% ± 2.12%), bisphosphonate (0.68% ± 2.54%), and denosumab (1.83% ± 2.66%). We also present some results on the effect of denosumab on ALM and FN BMD changes as secondary outcomes; however, we did not perform statistical analysis due to the

limited number of studies and lack of data.

## DISCUSSION

Osteosarcopenia is a common but potentially preventable and treatable illness; if not addressed promptly, it can result in falls, fractures, loss of self-sufficiency in everyday activities, and mortality.[25] A study of 680 older adult patients with osteosarcopenia in Sydney reported an increased incidence of falls and fractures.[26] Osteosarcopenia is a potentially preventable and treatable disease. Most therapeutic therapies address low BMD and sarcopenia individually; however, the close relationship between the two disorders implies that an integrated interventional approach is more likely to be effective.[27] Several drugs are already used to prevent fractures caused by osteoporosis.

The current treatments for osteoporosis fall into two categories: anti-resorptive (bisphosphonates and denosumab) and anabolic (teriparatide and abaloparatide). Anti-sclerostin antibody is another innovative osteoporosis medication with an anabolic effect that remains under investigation.[26] Currently, anti-resorptive agents are more widely used than anabolic agents for the treatment of osteoporosis. Although pharmacological interventions for osteoporosis have been extensively explored, data and evidence for pharmacological interventions for osteosarcopenia are currently inadequate. Denosumab is a human immunoglobulin G2 monoclonal antibody with excellent affinity and specificity for RANKL.[28] RANK, its ligand RANKL, and the soluble decoy receptor osteoprotegerin (OPG) pathway are primarily responsible for bone remodeling and homeostasis. The binding of RANKL to its associated receptor RANK initiates a series of signaling events that cause osteoclast development, activity, and survival.[21] Several studies have demonstrated a strong link between osteoporosis and skeletal muscle dysfunction; however, the molecular mechanism regulating bone and skeletal muscle pathology remains unknown.[21]

The results of our meta-analysis demonstrated the lack of significant differences in the effect of denosumab on LS BMD change compared to other agents like zoledronic acid, ibandronate, or alendronate, with a pooled mean difference between denosumab and other agents of 0.37 g/cm$^2$ (95% CI, -0.05–0.79; p = 0.09). In head-to-head tests comparing denosumab and bisphosphonate, the denosumab group exhibited comparable BMD changes at all four bone locations compared to the alendronate group. Alendronate and denosumab at the LS were also associated with significant increases in BMD (p < 0.001) compared to placebo.[29] However, a meta-analysis of 11 studies that included head-to-head comparisons of 2,573 participants taking bisphosphonates and 2,873 participants taking denosumab reported results contrary to those in our meta-analysis, which suggested that denosumab significantly increased BMD at the hip, femoral neck, LS, and one-third radius but did not significantly reduce fracture risk.[30] The most likely reasons for this outcome difference compared to our study are the superior adherence, compliance, and denosumab durability compared to bisphosphonate. The mode of administration for denosumab requires subcutaneous injection by healthcare providers, which provides direct proof of patient adherence to therapy.[31] This may also be attributed to the mechanisms of action of each medicine. Denosumab, a new anti-resorptive drug, suppresses osteoclast-mediated bone resorption similarly to bisphosphonates, but via a different mechanism.[32] The actions of bisphosphonates in preventing bone loss rely mostly on bisphosphonate binding to bone minerals, while denosumab inhibits osteoclast survival and differentiation mostly by direct interaction with RANKL.[30] Oral bisphosphonates and subcutaneous injectable denosumab are currently the recommended agents for the treatment of osteoporosis; of these two drugs, oral bisphosphonates are considered the first-line therapy.[33] In terms of the reduction of osteoporosis fracture risk, neither medication differed significantly from the others. Pedersen et al.[34] performed a retrospective cohort analysis of the risk of hip fractures in individuals treated with denosumab and alendronate, reporting comparable hip fracture risk ratios for denosumab and alendronate independent of sex, age, or fracture history.

As described above, osteosarcopenia is a term used to describe older persons with both poor BMD and sarcopenia. Sarcopenia is defined as the presence of decreased muscle mass accompanied by diminished muscular function, strength, and performance.[5] We performed a meta-analysis to determine whether denosumab has a distinctly favorable influence on sarcopenia parameters. We used measurements of the changes in handgrip strength following denosumab injection to evaluate muscle strength. After denosumab treatment, we measured physical performance by quantifying the change in gait speed, while ALM was used to determine muscle mass. Because of its simplicity, uniformity, and strong connection with lower-extremity muscular strength, handgrip strength is the most preferred method to test muscle strength.[18] In addition, handgrip strength is a clinical indicator of limited movement and a predictor of clinical outcomes.[5] The results of our meta-analysis showed that denosumab significantly improved handgrip strength compared to other agents including zoledronic acid, ibandronate, and alendronate. Based on the random-effects model, the pooled mean difference between denosumab and the other agents was 5.16 kg (95% CI, 1.38–18.94; p = 0.007). In an observational prospective study, Pizzonia et al.[35] reported that denosumab increased handgrip strength. Handgrip longitudinal (T0–T1) measurements were reported in 31 female patients. A T0–T1 MD was reported in

19/22 patients treated with alendronate (0.85 ± 4.8 kg) and in 12/13 females treated with denosumab (0.97 ± 6.0 kg), respectively, indicating a positive handgrip trend over time. However, the authors did not investigate the significance of these differences in either group.

The results of our meta-analysis showed that denosumab had no significant effect on gait speed change compared to placebo or other agents, such as zoledronic acid, ibandronate, or alendronate. Based on the random-effects model, the pooled MD between denosumab and other agents was 0.11 (95% CI, -0.18–0.40; p = 0.46) and showed no significant differences in gait speed change. To date, little research has reported the effects of denosumab on gait speed. Miedany et al.[21] reported that denosumab not only enhanced BMD but also decreased the risk of falling. Compared to bisphosphonates, denosumab exhibited the most substantial favorable effect on physical performance, as indicated by the improvement in the 4-m walk test (p < 0.001 in the denosumab group vs. p = 0.05 in the alendronate and zoledronic group) to measure gait speed.[21] These contradictory findings may be a consequence of the numerous variables that impact gait speed. Gait speed diminishes with age, is controlled by various variables, and can be improved by adopting a lifestyle that strengthens the muscles of the lower extremities.[36] However, a study by Miedany et al.[21] did not specifically identify confounding variables that might influence gait speed in their study population. Denosumab-induced increases in BMD did not necessarily correlate with increased gait speed. In older adult men, agility and gait speed showed the greatest influence on BMD and structure, whereas balance was associated with BMD in older adult women.[37] One study found that older adult women with more rapid bone loss during 2 years of follow-up had a greater risk of decline in usual walking speed compared to those with higher BMD.[38]

Although our meta-analysis did not directly examine ALM changes due to restricted research data, denosumab treatment may also help improve ALM in older individuals with osteoporosis. ALM levels significantly increased in the denosumab group compared to those in the bisphosphonate group after 3 years of administration.[20] The binding of denosumab to RANKL and its associated receptor RANK results in a cascade of signaling events that induce osteoclast development, activity, and survival. OPG is a soluble decoy receptor that binds to RANKL, thereby inhibiting its interaction with RANK and reducing osteoclastogenesis and bone loss.[39,40] Recent studies have highlighted the significance of mutual communication between muscle and bone via myokine and osteokine release, indicating that the treatment of osteoporosis with anti-osteoporotic drugs may also have a positive effect on muscle condition.[24]

The RANK/RANKL/OPG pathway is important for more than just bone health and may play a role in skeletal muscle and other tissues.[41] A mouse investigation showed high RANKL expression in the bone and muscle, notably in the soleus, compared to other muscles (gastrocnemius) and soft tissues, such as the colon, liver, and white and brown adipose tissues. RANK has also been detected in muscle, but to a lesser extent than in bone[20] and skeletal muscles. As a result of NF-κB activation, RANKL/RANK signaling in skeletal muscle inhibits myogenic development, leading to skeletal muscle dysfunction and atrophy.[42] In a mouse model of Duchenne muscular dystrophy and denervation-induced muscle atrophy, the injection of recombinant OPG protein resulted in enhanced muscle strength. More recently, the effects of inhibiting RANKL and RANK on muscle mass and strength have also been reported in conditions such as osteoporosis and sarcopenia.[20] Mice containing the human RANKL genomic region (huRANKL-Tg mice) had lower muscle mass, force, fat infiltration, and glucose absorption as well as a low bone mass phenotype and increased expression of anti-myogenic and inflammatory genes.

Denosumab is a monoclonal antibody that targets RANKL.[28] Bonnet et al.[20] studied insulin signaling in C2C12-differentiated myotubes expressing both RANK and RANKL to better understand the effect of RANKL-RANK signaling on muscle cell metabolism. In these cells, RANKL enhanced Ser318 phosphorylation in insulin receptor substrate-1 (IRS1), which is known to downregulate insulin receptor activity, whereas OPG diminished it. In contrast, AKTser473, a key IRS1 activator, showed the opposite effect.[20] Consequently, the beneficial effects of OPG on insulin receptor signaling were validated in vivo in both huRANKL-Tg+ and Pparb−/− mice, as evidenced by the improved insulin tolerance test (ITT) curves.[43] Through stimulation of the IkB kinase/NF-κB pathway, TNF-α-induced inflammation in fat has been demonstrated to reduce IRS1's capacity to transduce insulin signals.[44] Protein tyrosine phosphatase receptor gamma (PTP-RG), a tyrosine phosphatase receptor, has recently been identified as a crucial link between liver inflammation and insulin resistance.[20] In the muscle, RANKL increased levels of PTP-RG, which were lowered by OPG-Fc in C2C12 myotubes and similarly diminished by denosumab in the soleus of huRANKL-Tg+ mice.[45] Thus, RANKL causes resistance to insulin signaling, which leads to poor glucose entry, while also causing limited production of inflammatory markers (such as PTP-RG and TNF-α), which may contribute to impaired glucose uptake and muscle dysfunction.[44] Changes in skeletal muscle glucose uptake have been previously described,[43] which reduce contractile characteristics and muscle function.[20]

Treatment with recombinant OPG protein or denosumab re-

stored muscle mass, function, and glucose consumption in huRANKL-Tg mice and peroxisome proliferator-activated receptor β (PPARβ)-deficient mice, which have a combination of sarcopenia and a low bone mass phenotype. Denosumab therapy for more than 3 years has also been observed to improve ALM and handgrip strength in osteoporotic women. While RANKL/RANK signaling reduces muscular strength, denosumab therapy may protect both bone and skeletal muscle functions.[46] The results of the aforementioned studies demonstrate the potential dual effect of denosumab on BMD and muscle strength in patients with osteosarcopenia.

In conclusion, denosumab was more effective than bisphosphonate and placebo for improving muscle strength (handgrip strength). Therefore, denosumab may be favored in individuals with osteosarcopenia to improve muscular performance and reduce the risk of falls. Further research is needed to investigate the potential dual role of denosumab as an anti-resorptive and for other muscle-related impacts in this highly vulnerable population of patients with osteosarcopenia.

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### CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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None.

### AUTHOR CONTRIBUTIONS

Conceptualization, IGPSA, SSR; Data curation, IGPSA, SSR, SS; Investigation, IGPSA, SSR, SS; Methodology, IGPSA, SSR; Formal analysis, IGPSA, SSR, SS; Writing-original draft, IGPSA, SSR; Writing-review & editing, IGPSA, SSR, SS.

## SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4235/agmr.22.0139.

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# Effect of Epidural Block in the Incidence of Postherpetic Neuralgia: A Population-Based Matched-Cohort Study

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**Background:** Incidence of postherpetic neuralgia (PHN) increases with age. Epidural block in patients with herpes zoster (HZ) is expected to decrease the risk of PHN. The purpose of this study was to evaluate the effectiveness of epidural block on PHN incidence in a population-based study. **Methods:** This was a retrospective matched cohort study and data were sourced from the Korean National Health Insurance Service. The study cohort comprised 427 patients diagnosed with HZ who received epidural block within 30 days after a diagnosis of HZ. The matched control cohort included 427 patients without epidural block and were randomly matched to the study cohort at a 1:1 ratio based on covariates such as sociodemographic factors. The log-rank test was used to assess differences in the incidence of PHN. Cox proportional hazards regression models were used to estimate the hazard ratio (HR) for subsequent PHN, while controlling for potential comorbidities. **Results:** Among the 854 sampled patients, 30 (7.03%) from the study cohort and 18 (4.22%) from the match-control developed PHN during follow-up. There were no significant differences in the incidence of PHN between the two cohorts (p=0.08). Cox proportional hazard regressions showed that the HR for PHN in patients with epidural block was 1.66 (95% confidence interval, 0.91–3.02; p=0.10). **Conclusion:** Our study indicates that epidural block did not effectively prevent PHN. However, further studies are needed to determine the effect of epidural block in patients with HZ for the prevention of PHN.

**Key Words:** Herpes zoster, Postherpetic neuralgia, Epidural anesthesia

## INTRODUCTION

Herpes zoster (HZ) is a viral disease characterized by a painful vesicular rash involving one or more adjacent dermatomes.[1)] HZ is caused by the reactivation of varicella-zoster virus (VZV). This virus is dormant in the cells of the dorsal root ganglia following the resolution of chickenpox.[1)] VZV reactivation occurs in patients with reduced cell-mediated immunity due to aging or immunosuppressive conditions.[2)] The affected skin area can be extremely painful, and healing of the skin and pain resolution generally take 2–3 weeks.[2,3)] In some patients, residual pain can persist beyond the pathological healing process, resulting in postherpetic neuralgia (PHN).[3)] In PHN, pain persists even after the skin lesions have healed.[4)]

The incidence of PHN in patients with HZ varies from 5% to more than 50%, depending on the PHN definition and study design. The degree of pain varies from mild to severe, and pain persists for > 1 year in approximately 30% of patients.[2)] As pain becomes chronic, PHN can negatively affect patient quality of life and cause physical, occupational, and social disabilities.[5)] Additionally, such patients are at high risk of developing mental health problems such as anxiety, depression, and sleep disturbances.[6)] Since PHN is common in older adults, its incidence is expected to increase in the upcoming aging society.[7)]

Therefore, it is important to prevent PHN and control acute viral infections and associated pain while treating patients with acute HZ. Owing to the complex pathophysiology of PHN, various strategies have been proposed for its prevention. These include antiviral agents, vaccines, corticosteroids, anticonvulsants, and antidepressants. However, recent studies have demonstrated the limited efficacy of these strategies in preventing PHN.[2)]

The application of somatic neural blocks during the acute phase of HZ has also been attempted to prevent PHN.[2)] Some studies have suggested that neural blocks in patients with HZ can prevent PHN.[8,9)] However, other studies have not demonstrated the effectiveness of neural blocks in PHN.[10,11)] The epidural block is one of the most frequently performed neural blocks in patients with HZ. The present study assessed the effect of epidural blocks on PHN in a large cohort from the Korean national population-based dataset.

## MATERIALS AND METHODS

### Study Design

We conducted a population-based retrospective cohort study of patients with HZ in Korea using data sourced from the Korean National Health Insurance Service (KNHIS) between January 1, 2002, and December 31, 2015. This study evaluated whether epidural block could cause differences in the incidence of PHN in patients with HZ. The included patients were represented by the following diagnostic names: "zoster without complications," "zoster with other complications," "zoster ocular disease," and "zoster with other nervous system involvement."

### Data Source

The data for this study were obtained from the KNHIS. The KNHIS is a national health insurance program established by the Korean government in 1963 that archives almost all healthcare data in a central database. The National Health Insurance Service is a compulsory healthcare plan for all Koreans, and qualified citizens are covered under this scheme through either employee or community-based plans. Because all Korean residents receive a unique identification number at birth, the medical records of any patient are not duplicated or omitted.

We used the Sample Research Database version 2 (NHIS-2020-2-116), which includes information on medical care utilization for approximately one million representative Koreans randomly selected from the total NHIS claim dataset (2002–2015). This database comprises various standard codes, including disease codes, codes for diagnostic and therapeutic procedures, medication codes, and duration of admission. The disease codes were based on the Korean Standard Classification of Diseases Eighth Revision (KCD-8), which is the Korean version of the International Classification of Diseases Tenth Revision (ICD-10). The codes for various procedures were based on those in the Korean Health Insurance Classification of Procedures in Medicine (KHICPM).

### Ethics Statement

The Sample Research Database consisted of de-identified secondary data for research purposes. Hence, patient consent was not required for access to the database. This study was approved with a waiver for patient written consent from the Institutional Review Board of Konyang University Hospital, Daejeon, Korea, in February 2020 (No. KYUH 2020-02-010).

This study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[12)]

### Study Population

We first identified patients diagnosed with HZ (KCD-8 codes: B02.2, B02.3, B02.8, B02.9) as the study cohort. The date on which the patients were first diagnosed with HZ was defined as the index date. To enhance the validity of the HZ diagnosis, this study included only cases in which antiviral agents were prescribed at the time of HZ diagnosis. We then excluded patients who had been diagnosed with PHN by excluding patients diagnosed with PHN (KCD-8 codes: G53.0) before the index date and those diagnosed with HZ and PHN at the same time on the index date. Subsequently, patients diagnosed with PHN within 30 days or > 180 days were excluded, based on the index date. Among these patients, we included only those treated between 2003 and 2014, including a 1-year washout period. To exclude the effects of other procedures, we excluded patients who had undergone other interventions such as sympathetic block (KHICPM codes: LA261, LA361, LA366, and LA367), paravertebral block (KHICPM codes: LA352), and subarachnoid block (KHICPM codes: LA210), > 180 days after the index date. All patients included in this study were adults (aged ≥ 20 years) (Fig. 1).

### Intervention and Control Cohort

A comparison cohort from KNHIS was selected to evaluate the effectiveness of epidural block on the occurrence of PHN after HZ. Patients who underwent epidural block (KHICPM codes: LA 223-227, LA321, LA322) within 30 days based on the index date were identified. We then randomly selected patients who did not undergo epidural block by propensity score matching (PSM) in a 1:1 ratio with the study cohort who underwent epidural block.

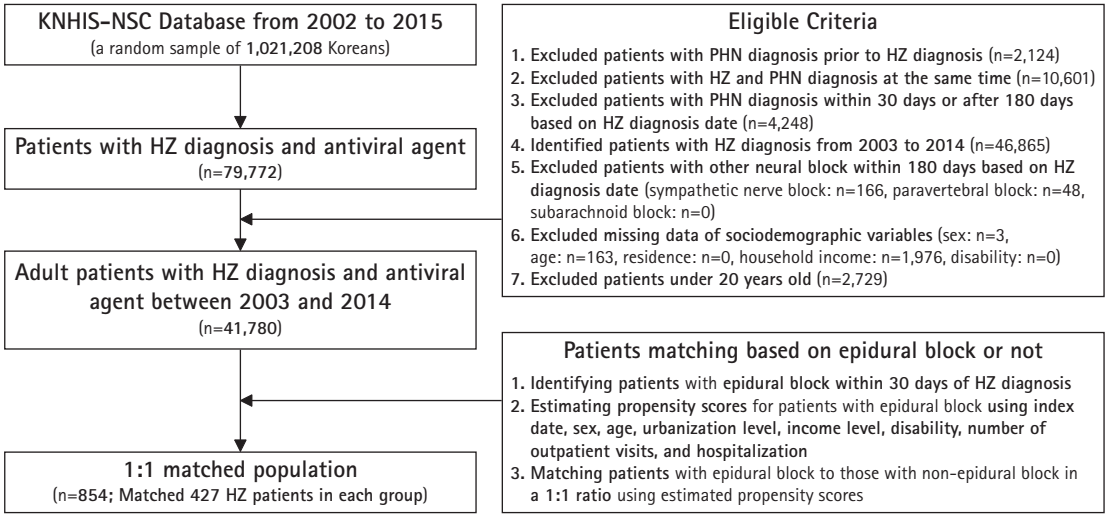


**Fig. 1.** Cohort identification. This figure shows the order using inclusion and exclusion criteria to identify study cohorts. KNHIS-NSC, Korean National Health Insurance Service-National Sample Cohort; HZ, herpes zoster; PHN, postherpetic neuralgia.

### Covariates

The PSM was based on index date, sex, age ( < 50, 50–79, and ≥ 80 years), residence urbanization level (1 "most urbanized" to 3 "least urbanized"), household income level (low, middle, high), disability, number of outpatient visits, and hospitalization during the follow-up period according to the sociodemographic characteristics. These variables were considered potential confounders for PHN development.[13] To minimize selection bias, we attempted PSM between the cohort groups for confounding variables. In addition, based on the findings of previous studies,[13,14] we considered respiratory disease (chronic obstructive pulmonary disease, asthma, other chronic lower respiratory diseases), diabetes mellitus (DM), cancer, autoimmune disease (rheumatoid arthritis, SLE, Crohn's disease, ulcerative colitis), and severe immunosuppressive status (human immunodeficiency virus, lymphoma, leukemia, multiple myeloma) as additional potential confounders for PHN.

### Outcomes

Our primary outcome measure was the difference in the incidence of PHN for 180 days from the index date between the two cohorts. By limiting the timing of PHN diagnosis from 30 to 180 days after the index date,[2,15-18] we examined the direct effect of epidural blocks performed within 30 days of the index date on PHN occurrence. Our secondary outcome measure was the risk of PHN associated with potential confounding factors.

### Statistical analysis

Despite being based on administrative data sources, we calculated sample sizes to ensure that the study analysis was feasible. Based on a pilot study, to detect a difference in the incidence of PHN between the groups, the estimated sample size with a type I error of 0.05 and a power of 90% was 246.

The study endpoint was the date of PHN diagnosis, end of follow-up (180 days from the index date), or death. Log-rank tests were used to assess differences in the incidence of PHN, while Kaplan–Meier curves were used to calculate the 180-day PHN incidence rates between the cohort groups. After adjusting for disease-related potential confounders (respiratory disease, DM, cancer, autoimmune disease, and severe immunosuppressive status), stratified Cox proportional hazards modeling (stratified by sex, age, residence urbanization level, household income level, disability, number of outpatient visits, hospitalization) was used to calculate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for subsequent PHN. The HRs associated with potential confounding factors were confirmed using a stratified Cox proportional hazards model. SAS Enterprise Guide 6.1M1 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. Statistical significance was set at $p < 0.05$.

## RESULTS

This study identified 41,780 eligible patients with HZ diagnosis and antiviral agent use, 427 of whom underwent epidural blocks. We matched these to 427 patients without epidural blocks in a 1:1 ratio (Fig. 1).

Table 1 shows the sociodemographic characteristics and medical conditions of the individuals in the study and control cohorts. Of the 427 patients in each group, most patients were aged 50–79 years—epidural group of 328 (76.8%) and comparison group of 342 (80.1%)—and approximately 65% were female—282

**Table 1.** Patient characteristics

| Variable | Comparison (n = 427) | Epidural block (n = 427) | p-value |
|---|---|---|---|
| Sex | | | 0.62 |
| Male | 153 (35.8) | 145 (34.0) | |
| Female | 274 (64.2) | 282 (66.0) | |
| Ages (yr) | | | 0.51 |
| ≤ 49 | 68 (15.9) | 79 (18.5) | |
| 50–79 | 342 (80.1) | 328 (76.8) | |
| ≥ 80 | 17 (4.0) | 20 (4.7) | |
| Residence | | | 0.42 |
| Seoul | 60 (14.1) | 72 (16.9) | |
| Other metropolitans | 133 (31.1) | 120 (28.1) | |
| Rural and small cities | 234 (54.8) | 235 (55.0) | |
| Annual household income (million KRW) | | | 0.87 |
| ≤ 30.0 (low) | 86 (20.1) | 90 (21.1) | |
| 30.1–69.9 (middle) | 158 (37.0) | 151 (35.4) | |
| ≥ 70.0 (high) | 183 (42.9) | 186 (43.6) | |
| Disability | | | 0.91 |
| No | 378 (88.5) | 380 (89.0) | |
| Yes | 49 (11.5) | 47 (11.0) | |
| Number of outpatient visit | | | 0.66 |
| 1 time | 104 (24.4) | 98 (23.0) | |
| 2–3 times | 150 (35.1) | 143 (33.5) | |
| ≥ 4 times | 173 (40.5) | 186 (43.6) | |
| Hospitalization | | | 0.52 |
| No | 418 (97.9) | 414 (97.0) | |
| Yes | 9 (2.1) | 13 (3.0) | |
| RD | | | 0.00* |
| No | 171 (40.0) | 114 (26.7) | |
| Yes | 256 (60.0) | 313 (73.3) | |
| DM | | | 0.00* |
| No | 270 (63.2) | 221 (51.8) | |
| Yes | 157 (36.8) | 206 (48.2) | |
| Cancer | | | 0.52 |
| No | 381 (89.2) | 374 (87.6) | |
| Yes | 46 (10.8) | 53 (12.4) | |
| AD | | | 0.00* |
| No | 344 (80.6) | 297 (69.6) | |
| Yes | 83 (19.4) | 130 (30.4) | |
| SIS | | | 0.04* |
| No | 21 (4.9) | 9 (2.1) | |
| Yes | 406 (95.1) | 418 (97.9) | |

Data area expressed as the mean or number (%).
KRW, Korean won; RD, respiratory disease; DM, diabetes mellitus; AD, autoimmune disease; SIS, severe immunosuppressive status.
*p<0.05.

(66.0%) and 274 (64.2%), respectively. Compared with the comparison group, patients with epidural blocks had more comorbidities including respiratory disease, DM, autoimmune disease, and severe immunosuppressive status (Table 1).

The 180-day PHN incidence rate in the patients included in the study was 5.62% (48/854; 95% CI, 4.14–7.45). Of the 427 patients in each group, 30 (7.03%) in the epidural group and 18 (4.22%) in the comparison group advanced to PHN. The Kaplan–Meier curve is shown in Fig. 2. The log-rank tests revealed no significant differences in the incidence rates of PHN between the two cohorts (p = 0.08) (Fig. 2).

Table 2 shows the HR for PHN associated with the potential confounding factors. Females, older adults, and residents living in rural areas tended to have an increased risk of developing PHN.

Additionally, respiratory and autoimmune diseases, along with a severe immunosuppressive status, increased the risk of PHN. However, the HRs associated with these factors were not significant. Meanwhile, as the number of outpatient visits increased ( ≥ 4 times), and in the case of hospitalization, the HR of PHN was significantly higher—3.55; 95% CI, 1.37–9.17; p = 0.01; and 3.08; 95% CI, 1.03–9.21; p = 0.04, respectively.

Table 3 presents the unadjusted and adjusted HRs for PHN for the cohorts. After adjusting for respiratory disease, DM, cancer, autoimmune disease, and severe immunosuppressive status, stratified Cox proportional hazard regressions showed that the HR for PHN diagnosis within the 180-day period for patients with epidural blocks was 1.66 (95% CI, 1.91–3.02; p = 0.10) that of comparison patients (Table 3).

## DISCUSSION

This population-based matched case-control study explored the effectiveness of epidural blocks for PHN prevention in the Korean population. We observed that the epidural block group did not show a decreased incidence of PHN compared to that in the control group. Epidural blocks have been used for decades to treat HZ-associated pain and prevent PHN, and their positive effects on preventing PHN have been reported in several studies.[15,19-22] A recent systematic review recommended epidural blocks to prevent PHN in patients with HZ and showed that continuous or repeated epidural blocks significantly reduced the incidence of PHN.[2] However, the conclusion of a review conducted by the International Association for the Study of Pain Neuropathic Pain Special Interest Group (NeuPSIG) disagreed with this conclusion.[23] This may be due to the lack of high-quality randomized controlled studies on the effects of epidural blocks on PHN. In addition, several studies have failed to demonstrate the effectiveness of epidural blocks in preventing PHN.[5,7,24]

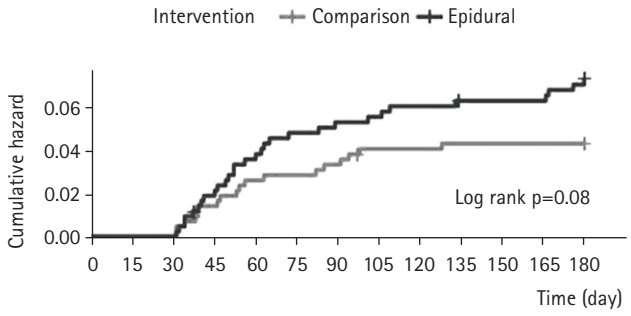


**Fig. 2.** Cumulative hazard ratio of postherpetic neuralgia (PHN) in patients with and without epidural block. There was no statistically significant different between the two cohorts.

**Table 2.** Risk of postherpetic neuralgia associated with potential confounding factors

| Confounder | Cox-regression[a] | |
|---|---|---|
| | HR (95% CI) | p-value |
| Sex (female) | 1.67 (0.91–1.98) | 0.10 |
| Ages (yr) | | |
| ≤ 49 | 1.0 | |
| 50–79 | 1.52 (0.58–3.98) | 0.40 |
| ≥ 80 | 1.70 (0.37–7.86) | 0.50 |
| Residence | | |
| Seoul | 1.0 | |
| Other metropolitans | 1.08 (0.41–2.85) | 0.88 |
| Rural and small cities | 1.39 (0.57–3.40) | 0.47 |
| Annual household income (million KRW) | | 0.87 |
| ≤ 30.0 (low) | 1.0 | |
| 30.1–69.9 (middle) | 0.5 (0.21–1.17) | 0.11 |
| ≥ 70.0 (high) | 1.07 (0.53–2.14) | 0.85 |
| Disability (yes) | 1.15 (0.49–2.73) | 0.75 |
| Number of outpatient visit | | |
| 1 time | 1.0 | |
| 2–3 times | 1.23 (0.42–3.65) | 0.71 |
| ≥ 4 times | 3.55 (1.37–9.17) | 0.01* |
| Hospitalization (yes) | 3.08 (1.03–9.21) | 0.04* |
| RD (yes) | 1.11 (0.58–2.14) | 0.74 |
| DM (yes) | 0.85 (0.46–1.58) | 0.62 |
| Cancer (yes) | 0.44 (0.13–1.46) | 0.18 |
| AD (yes) | 1.16 (0.61–2.22) | 0.65 |
| SIS (yes) | 1.12 (0.15–8.39) | 0.91 |

HR, hazard ratio; CI, confidence interval; KRW, Korean won; RD, respiratory disease; DM, diabetes mellitus; AD, autoimmune disease; SIS, severe immunosuppressive status.
[a]Multivariable stratified Cox regression analysis.
*p<0.05

**Table 3.** Incidence and risk of postherpetic neuralgia associated with epidural block

| | Cox-regression[a] | | | |
|---|---|---|---|---|
| | Unadjusted | p-value | Adjusted | p-value |
| Comparison (n = 427) | 1.00 | | | |
| Epidural block (n = 427) | 1.69 (0.94–3.03) | 0.08 | 1.66 (0.91–3.02) | 0.10 |

Values are presented as hazard ration (95% confidence interval).
[a]Stratified Cox proportional hazard regressions (stratified on sex, age, urbanization level of residence, household income level, disability, number of outpatient visits, hospitalization) with adjusting comorbidities (respiratory disease, diabetes mellitus, cancer, autoimmune disease, severe immunosuppressive status).

This discrepancy in the findings is probably due to the absence of a consensus on PHN definition. Although PHN has been defined as persistent pain after the healing of an HZ rash,[20] no clinical cutoff points for its diagnosis have been established. Generally, PHN is defined as pain persisting for > 3 months[2,15-18] after the diagnosis of HZ; however, the clinical cutoff points for PHN diagnosis vary between 1 and 6 months.[11,25,26] The absence of a single, uniform cutoff point could have affected the study results. In addition, the definition of pain in the diagnosis of PHN remains controversial. The criteria for pain intensity for diagnosis differs between studies. In each study, based on pain scales (numerical rating scale or visual analog scale), PHN was defined differently: higher than 10/100,[2,13,16-18,27] 25/100,[28] and 30/100.[2] Furthermore, PHN has a wide spectrum of symptoms including spontaneous pain, paroxysmal pain, allodynia, hyperalgesia, and abnormal sensations.[20] Therefore, the reported results may have varied depending on which of these symptoms were included in the PHN definitions.

The pathophysiology of PHN remains unclear.[21] In patients with PHN, damage to the sensory nerve, dorsal root ganglion, and dorsal horn of the spinal cord has been reported.[29] These injuries can result in pain, allodynia, and hyperalgesia. This damage may be attributed to two pathophysiological mechanisms: deafferentation and sensitization. Deafferentation is the interruption or destruction of afferent connections of nerve cells. Reactivation of VZV in the dorsal root ganglion can lead to inflammation, resulting in sequential edema, increased intrafascicular pressure, and neural destruction.[30] Sensitization is an abnormal state of responsiveness or increased gain in the nociceptive system. Peripheral nociceptors can induce ongoing discharge after acute tissue injury, which subsequently affects the neurons of the dorsal horn ganglion, leading to hyperexcitability and hypersensitivity.[7] Epidural blocks are expected to be effective in PHN by preventing deafferentation and sensitization. Epidural blocks using local anesthetics (with or without steroids) reduce inflammation and prevent profound sympathetic stimulation. These effects may prevent a decrease in intraneural blood flow and subsequent ischemic neuronal damage.[3,9] In addition, the analgesic effects of epidural blocks can prevent central sensitization by stopping the continuous accumulation of nociceptive inputs.[15]

However, the use of epidural blocks in our study did not demonstrate any significant differences in the preventive effects on PHN. These results may be attributed to the absence of standardized guidelines for epidural block in patients with HZ, such as the timing of intervention and frequency, number, duration, and types of local anesthetics with or without steroids, as previously reported.[31] It is well recognized that, for the best efficacy, HZ treatment should be started as soon as possible. Many researchers have suggested that an epidural block appears to exhibit efficacy if performed within 10–15 days of HZ diagnosis.[20] Once reactivated, VZV damage can extend centrally to the dorsal horn of the spinal cord, with central lesions generally appearing in 9–12 days.[20] Therefore, if possible, an epidural block should be performed within 2 weeks of HZ diagnosis. In clinical practice, epidural blocks are not routinely applied to HZ treatment and are considered only in patients at high risk for PHN or in the absence of a response to other HZ treatments. Hence, epidural blocks are often delayed in HZ treatment. In our study, 66.5% (n = 284) of patients underwent epidural block within 14 days of HZ diagnosis, whereas 33.5% (n = 143) of patients were administered the block after 14 days. Epidural blocks conducted later (15–30 days after HZ diagnosis) may have negatively affected PHN prevention.

The technique employed for the epidural block may have affected the results of this study. Previous reports have documented that continuous epidural catheters or repeated single-shot techniques reduce the incidence of PHN.[2] In comparison, a single-shot epidural block may be insufficient to prevent the accumulation of continuous nociceptive input. Therefore, continuous or repeated epidural blocks are necessary to effectively prevent PHN.[2] However, continuous epidural blocks requiring a catheter are limited in clinical practice because of the risk of infection and the probability of hospitalization. In this study, 98.2% (n = 397) of patients underwent epidural blocks more than twice; hence, it is unlikely that the number of epidural blocks affected our results. Meanwhile, the rate of continuous epidural block was 7.3% (n = 30). Although the proportion of continuous epidural blocks was low, both continuous and repeated single-shot epidural blocks are expected to be effective in preventing PHN. Therefore, it seems that this wouldn't have had a decisive effect on our study results.

Among the potential confounders related to PHN in this study, the age-related risk of PHN did not increase significantly. However, previous studies reported an increased risk of PHN with age.[13,14] This discrepancy may be attributed to the fact that our study included a matched cohort. The study findings cannot be generalized as the patients were matched based on epidural block. Thus, the demographic characteristics of the study population may have differed. Meanwhile, as the number of outpatient visits increased, as well as the cases of hospitalization, the risk of PHN was significantly higher in our study. Patients with severe symptoms such as pain likely visited the hospital more frequently, many of whom progressed to PHN. Similarly, considering that the epidural group showed more comorbidities such as respiratory disease, DM, autoimmune disease, and severe immunosuppressive status, due to the severe symptoms of HZ, epidural block may have been

more likely to be performed.

The limitation of this study was its retrospective nature based on the National Sample Cohort of the KNHIS. The KNHIS database does not contain important information such as the location, intensity, and quality of pain or the start time of antiviral agents after symptom onset, which are covered in the medical records. Therefore, although the use of antiviral agents is generally recommended within 72 hours of HZ onset,[32] we could not ascertain the time interval between symptom onset and the administration of antiviral agents. Moreover, the effectiveness of antiviral agents in preventing PHN has not yet been confirmed.[33] In addition, a recent systematic review and meta-analysis showed that the presence of prodromal pain, severe acute pain, and severe rash in patients with HZ increased the risk of PHN.[14] However, we could not adjust for these potential confounders in this study. Finally, a selection bias may have affected the study outcomes. As patients with severe zoster-associated pain are more likely to receive intensive treatment such as epidural blocks, the baseline pain severity may have differed between the control and epidural block groups.

In conclusion, in our study, the clinical outcome of PHN incidence in patients with HZ did not differ significantly between those with and without epidural block. This is the first population-based cohort study to investigate the preventive effects of epidural block on PHN. Additional studies are required to evaluate the effect of epidural blocks on PHN incidence. In addition, a consensus-based definition of PHN and standardized guidelines for epidural block in patients with HZ must be established.

## ACKNOWLEDGMENTS

### CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

### FUNDING

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### AUTHOR CONTRIBUTIONS

Conceptualization, CBI, JYK, JYH; Data curation, JYH, IK, MC; Funding acquisition, CBI, JYK; Investigation, CBI, JYH, IK; Methodology, CBI, JYK, JYH, IK, MC; Project administration, IK, MC; Supervision, CBI, JYK, JYH; Writing-original draft, CBI, JYK, JYH; Writing-review & editing, CBI, JYK, JYH.

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# Effects of a Dementia Special Care Unit on the Changes in Physical Function, Cognitive Function, and Problematic Behaviors among Nursing Home Residents

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**Background:** This study compared changes in physical function, cognitive function, and problematic behaviors among nursing home residents with dementia between the dementia specialized care and general units. **Methods:** To assess the effects of a dementia specialized care unit (D-SCU), this study applied the difference-in-differences method. While the D-SCU was introduced in July 2016, the service was provided in January 2017. We defined the pre-intervention period as July 2015 to December 2016 and the post-intervention period as January 2017 to September 2018. We matched long-term care (LTC) insurance beneficiaries using the propensity score matching method to minimize selection bias. After this matching, two new groups were obtained, each with 284 beneficiaries. To characterize the actual effects of the D-SCU on physical function, cognitive function, and problematic behaviors among dementia beneficiaries, we conducted a multiple regression analysis that controlled for demographics, LTC need, and LTC benefit utilization. **Results:** The physical function score significantly increased according to the time effect, and the interaction term between time and the use of D-SCU was significant. Therefore, the activities of daily living (ADL) score of the control group increased by 5.01 points more than that in the group of beneficiaries using the D-SCU ($p<0.001$). However, the interaction term had no significant effect on cognitive function or problematic behavior. **Conclusion:** These results revealed the partial effect of the D-SCU on LTC insurance. Further research is required that considers the variables of service providers.

**Key Words:** Dementia, Activities of daily living, Nursing homes, Propensity score

## INTRODUCTION

The number of people with dementia is predicted to increase globally, from 57.4 million in 2019 to 152.8 million in 2050.[1)] With rapid aging, the prevalence of dementia in South Korea is estimated to increase from 8.7% in 2010 to 15.1% in 2050, increasing the number of dementia patients from approximately 420,000 in 2008 to approximately 2.71 million in 2050.[2)]

Most people with dementia initially receive care at home but are transferred to institutions due to the informal caregiver burden related to behavioral symptoms and the need for more skilled care.[3)] In nursing homes, providing care to dementia residents requires knowledge and skills specific to the physical, cognitive, and support needs of these individuals and their families.[4)] As traditional nursing homes are similar to hospitals and cannot meet the unique care needs of residents with dementia, some countries have installed special units (for example. dementia special care unit, specialized living unit) in nursing homes since the 1980s, to provide customized services to patients with dementia.[5-7)]

Dementia-specialized care units (D-SCUs) in nursing homes

are of various types and have heterogeneous structures in each country, with no international consensus on their definition.[8-10] However, most D-SCUs apply patient admission and discharge criteria; appropriate standards of physical environment design; hire, train, place, and supervise personnel suitable for the care of residents with dementia; conduct special activity programs for patients with dementia; and allow family participation.[6]

Since the introduction of long-term care insurance (LTCI), which has been operating in the national social insurance system since July 2008, various policy measures for dementia beneficiaries have been applied in South Korea. For example, workers caring for beneficiaries with dementia receive additional training to provide patients with cognitive enhancement programs. From July 2016, the D-SCU was included in the Korean LTCI benefit and its facility, and staffing standards and details of the program were legislated into law. The reimbursed costs on a pay-per-day basis and copayment for services provided in D-SCU are higher than those of general nursing home services.

Previous studies reported that D-SCUs positively affected the social interactions of patients with dementia,[11] and improved their daily living ability,[6,7,12] cognitive function,[13] and quality of life,[5] compared to traditional nursing homes. However, a systematic review of the literature indicated that the results of these studies were inconsistent and that the studies had different numbers of patients assigned to the experimental and control groups.[9] Therefore, the present study aimed to compare changes in the functional status of Korean LTCI beneficiaries with dementia between the D-SCU and general nursing homes over 1 year and to examine the associations between LTCI service type and health outcomes.

## MATERIALS AND METHODS

### Data Sources

This study used the LTCI dataset, a national-level data source from the National Health Insurance Service (NHIS), a public insurer, between July 2015 and September 2018. More specifically, this study used data from the long-term care (LTC) needs assessment and claims databases from the LTCI dataset. All applicants for LTCI benefit eligibility were evaluated using the LTC needs assessment checklist, which consists of 52 items, including information on the presence of diseases, physical function, cognitive function, behavioral problems, nursing needs, and environmental conditions.[14] LTCI applicants are categorized into six groups (grades 1–5 and grade cognition assistance) based on the severity of the beneficiary's care needs. Grade 1 includes those with the highest level of care needs, while grade 5 includes those with the lowest care needs.[15] Grade cognition assistance is assigned to applicants with mild dementia and relatively good physical functioning. A mandatory LTC needs assessment must be conducted every 12 months, except for individuals with an initial high score[16] for LTCI beneficiaries. The LTCI claims data include the type of benefits provided to beneficiaries by the LTC institution, the date of the provision, and the frequency of provision. These data are used to determine whether dementia beneficiaries receive care in a D-SCU or a general nursing home.

### Overview of D-SCUs under LTCI in Korea

The basic directive of the D-SCU is to target dementia recipients who can perform daily life activities and live together to maintain and improve the physical and cognitive functions of older adults with dementia. Accordingly, grade 1 was excluded; among beneficiaries of grades 2–5, those with dementia listed in the doctor's note or with a medical treatment history for dementia were considered. Compared to the general nursing home unit, the D-SCU has a reinforced manpower standard; thus, with one care provider assigned per 2.5 residents in the general unit of a nursing home, the D-SCU has one provider per two residents. Additionally, in the D-SCU, caregivers and managers directly providing services to residents with dementia are required to complete separate specialized training. The D-SCU provides tailored programs that consider the functional status and characteristics of residents to maintain and improve physical and cognitive functions; reality awareness training and exercise therapy, family education and family participation programs, and cognitive stimulation activities group programs such as music and music activities are also provided. Moreover, the bedroom or common space areas of the D-SCU are wider than those of the general unit of the nursing home, making it easier to perform individual care and cognitive reinforcement programs.

### Study Sample

While D-SCUs were introduced in July 2016, the actual service was provided in January 2017. Among the 466 LTC beneficiaries who used D-SCU benefits for > 1 year between January 2017 and September 2018, 182 people who used LTC services for < 12 months between July 2015 and December 2016 were excluded. The final treatment group consisted of 284 individuals. A total of 72,299 LTC beneficiaries who used general LTC units for > 1 year between January 2017 and September 2018 were included in the control group in the first step. Among these, 9,124 LTC beneficiaries were excluded if they did not use general LTC units for > 1 year between July 2015 and December 2016. We applied propensity score matching (PSM) to minimize the effects of potential confounding factors. After PSM (1:1 nearest-neighbor matching), two new groups were obtained, each with 284 patients.

### Outcome Variables

The outcome variables in this study were changes in physical function, cognitive function, and problematic behaviors. The activities of daily living (ADL) subscale measuring physical function consisted of changing clothes, face washing, brushing teeth, bathing, eating, changing positions, sitting up, transferring to a different seat, exiting a room, using a toilet, controlling the bowel and bladder, and washing hair, with a possible score ranging from 13 to 39. Each item was assessed as totally independent, partially dependent, or totally dependent. The cognitive function subscale consists of 10 items to measure short-term memory loss; disorientation to time, place, age, and people; and inability to understand one's daily schedule/work. Each item was scored as either 1 or 0 to indicate whether the beneficiary had the symptom. The problematic behavior subscale consists of 16 items (delusions, hallucinations, sadness/crying, sleep disturbance/confusing day and night, resistance to assistance, wandering/restlessness, getting lost, verbal aggression/threatening actions, attempting to leave, destroying property, inappropriate or meaningless behaviors, hiding money/things, inappropriate dressing, poor hygiene, inability to manage fire hazards, and separation anxiety). Each ADL item and problem behavior were assessed as yes or no. In this study, we converted the total score of each scale to a perfect score of 100 points, the validity of which was demonstrated previously.[17-19]

### Ethical Approval

This study was approved by the Sangji University Institutional Review Board (IRB No. 1040782-181120-HR-19-38). Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[20]

### Statistical Analysis

We used a quasi-experimental approach that mixed PSM with difference-in-differences (DID) to measure the effect of D-SCU. The purpose of matching was to identify individuals with characteristics similar to those of the intervention participants, except for the intervention status.[19] We matched LTC beneficiaries in the D-SCU with those in general units using the PSM method (1:1 nearest-neighbor matching) to minimize selection bias. Based on a literature review of potentially explainable variables[16,21-25] related to changes in physical function, cognitive function, and problematic behavior of nursing home residents, demographic factors, LTC need factors, and utilization of LTC benefit were the factors used for PSM. The demographic factors included sex and age. The indicators of LTC need included LTC grade (2, 3, 4, and 5), subjective vision condition (having problems seeing), subjective hearing status (having problems hearing), and diseases other than dementia (yes or no). The utilization of LTC benefit factors included facility type (nursing home or small-group home) and total duration of LTC benefit use. We defined the period before the intervention as the baseline period (July 2015 to December 2016). Logistic regression models were used to calculate the propensity scores. Differences between the treatment and control groups were compared using the $\chi^2$ test for categorical variables and the t-test for continuous variables after PSM.

In this study, the primary statistical model used was the DID analysis. DID analysis is the most frequently used and informative study design to examine the effects of interventions.[25] DID assumes that the intervention and comparison groups would have shown the same trends without any intervention in pre-post assessments.[26] Because nursing home residents with dementia have a continuous decline in functional status, this study applied DID analysis to determine whether the D-SCU slowed this decline compared to the general unit. The change in scores of physical function, cognitive function, and problematic behaviors in the treatment group before the introduction of the D-SCU and after utilization of the D-SCU minus the corresponding change in the control group were assessed. Analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA). All tests were two-tailed, and a p-value $< 0.05$ was considered statistically significant.

## RESULTS

### Study Population Characteristics

The general characteristics of the participants are shown in Table 1. The proportions of LTCI grades 2–5 at baseline was 38.4% (n = 218), followed by 37.9% (n = 215), 18.5% (n = 105), and 5.3% (n = 30). The number of female participants exceeded that of male participants by 437. Subjective vision conditions were 66.2% (n = 376), compared to 33.8% (n = 192) in the group with no vision problems. Subjective hearing conditions accounted for 51.1% (n = 290) of the cases with problems, similar to the proportion of participants without problems. Moreover, 37.1% (n = 211) participants were affected by diseases other than dementia, whereas 62.9% (n = 357) were affected by dementia alone. Regarding facility types, 67.1% (n = 381) used LTC facilities, compared to 32.9% (n = 1,887) users of state and night care facilities. The average age of the participants and duration of utilization was 81.72 ± 7.72 years and 18.40 ± 3.07 months, respectively. The distributions of these general characteristics did not differ between the experimental and control groups.

**Table 1.** General characteristics of subjects after matching

| Variable | Treatment group (n = 284) | Control group (n = 284) | Total (n = 568) | p-value[a] |
|---|---|---|---|---|
| LTC grade | | | | 0.983 |
| 2 | 16 (5.6) | 14 (4.9) | 30 (5.3) | |
| 3 | 107 (37.7) | 108 (38.0) | 215 (37.9) | |
| 4 | 108 (38.0) | 110 (38.7) | 218 (38.4) | |
| 5 | 53 (18.7) | 52 (18.3) | 105 (18.5) | |
| Sex | | | | 0.370 |
| Female | 223 (78.5) | 214 (75.4) | 437 (76.9) | |
| Male | 61 (21.5) | 70 (24.6) | 131 (23.1) | |
| Subjective visual status | | | | 0.859 |
| No problem | 97 (34.2) | 95 (33.5) | 192 (33.8) | |
| Problem | 187 (65.8) | 189 (66.5) | 376 (66.2) | |
| Subjective hearing status | | | | 0.502 |
| No problem | 135 (47.5) | 143 (50.4) | 278 (48.9) | |
| Problem | 149 (52.5) | 141 (49.6) | 290 (51.1) | |
| Diseases other than dementia | | | | 0.543 |
| No | 175 (61.6) | 182 (64.1) | 357 (62.9) | |
| Yes | 109 (38.4) | 102 (35.9) | 211 (37.1) | |
| Age (yr) | 81.48 ± 7.58 | 81.97 ± 7.86 | 81.72 ± 7.72 | 0.448 |
| Duration of utilization (mo) | 18.38 ± 3.03 | 18.43 ± 3.11 | 18.40 ± 3.07 | 0.838 |

Values are presented as number (%) or mean±standard deviation.
[a]Using the $\chi^2$ test for categorical variables and the t-test for continuous variables after propensity score matching.

**Functioning and Problematic Behavior Scores Pre- and Post-intervention in the Treatment and Control Groups**

During the use of the D-SCU service, physical function scores increased in both groups, from 33.42 to 36.63 points in the experimental group and from 33.00 to 41.21 points in the control group. The cognitive function scores showed that cognitive ability increased in the experimental group by 3.13 points, from 56.16 to 59.29 points, and by 4.64 points in the control group, from 57.04 points to 61.68 points. Regarding problem behavior scores, the score in the experimental group decreased by 1.80 points from 19.73 to 17.93 points, while that in the control group decreased by 1.61 points from 19.77 to 18.16 points, showing improvement in both groups (Table 2).

Table 3 shows the results of the DID analysis for functioning and problematic behaviors. A multiple regression analysis controlling for the control variables to determine the effects of dementia-premeditated LTC facility services showed that the physical function scores increased by 8.21 points depending on the time effect ($p < 0.001$). The physical functional score of the control group increased by 5.01 points more than that of the LTC service provider because of the significant interaction term of the service type, indicating the effectiveness of the pure policy ($p < 0.001$). Similar to the results of the simple double-difference analysis, recipients using the dementia-preferred service had lower deterioration in physical function compared to recipients using the care-type service.

**Table 2.** Pre- and post-score of physical function, cognitive function, and problematic behavior in treatment and control group

| Variable | Score | |
|---|---|---|
| | Pre | Post |
| Physical functioning | | |
| Treatment group | 33.42 ± 10.88 | 36.63 ± 11.75 |
| Control group | 33.00 ± 10.69 | 41.21 ± 17.63 |
| Cognitive functioning | | |
| Treatment group | 56.16 ± 16.04 | 59.29 ± 18.88 |
| Control group | 57.04 ± 16.60 | 61.68 ± 18.47 |
| Problematic behavior | | |
| Treatment group | 19.73 ± 14.24 | 17.93 ± 13.96 |
| Control group | 19.77 ± 13.91 | 18.16 ± 13.91 |

Values are presented as mean±standard deviation.

Cognitive function scores increased by 4.64 points ($p < 0.01$) depending on the time effect ($p < 0.01$), and dementia-premeditated LTC systems did not affect cognitive performance scores due to the lack of significant interaction terms of the pure policy.

Regression analysis of problem behavior scores did not significantly affect users' behavioral change scores, nor did the statistical significance of the interaction between time and group indicate the effects of pure policies, indicating that dementia counseling services did not significantly affect the change in recipients' problem behavior scores (Table 3).

**Table 3.** Effects of D-SCU on the functioning and problematic behavior

| Variable | Physical functioning | | Cognitive functioning | | Problematic behavior | |
|---|---|---|---|---|---|---|
| | β | SE | β | SE | β | SE |
| Intercept | 30.443 | 4.054 | 67.463 | 6.557 | 36.239 | 5.536 |
| Time | 8.21* | 0.830 | 4.64* | 1.343 | -1.61 | 1.134 |
| Groups | 0.19 | 0.832 | -1.18 | 1.346 | -0.06 | 1.136 |
| Time × Groups | -5.01* | 1.175 | -1.51 | 1.900 | -0.19 | 1.604 |

D-SCU, dementia-specialized care unit; SE, standard error.
*p<0.001.

## DISCUSSION

The results of this study indicated that the D-SCU was effective in maintaining residual physical function and preventing the deterioration of physical functions. These results are consistent with those of previous studies.[5,12,27] In contrast, the D-SCU did not affect changes in cognitive function, also similar to results reported previously.[5,12] In addition, the behavioral change scores decreased in both the experimental and control groups. However, the effects of time or D-SCU service on the behavioral change score were not significant in the DID analysis. Thus, the D-SCU service did not affect changes in behavioral change scores, which is consistent with the findings of a previous study.[5] Therefore, the effects of the D-SCU were limited and did not contribute to preventing cognitive decline in nursing home residents with dementia.

There are several possible explanations for these results. First, while the D-SCU services were ineffective in preventing the deterioration of cognitive function, they were more effective than services in general LTC facilities in preventing a decline in daily activities. Dementia reduces the ability to perform daily activities, making independent life difficult and subsequently reducing the quality of life of people afflicted with dementia.[28] Impairment in performing daily activities is common in individuals with dementia and has been reported to rapidly decline with the progression of dementia.[29] Therefore, preventing a decline in the ability to perform daily activities in the early stages of dementia can contribute to improving the quality of life of individuals with dementia. In this respect, it is significant that the results of this study revealed that the D-SCU was effective in preventing the deterioration of daily life performance. Prior research has reported the effectiveness of ADL training, physical rehabilitation therapy, and exercise therapy as non-pharmacological interventions to improve daily life performance in people with dementia.[28,30] Because such content was included in the D-SCU program, the D-SCU likely prevented the decline in daily life performance.

Second, the results of the present study showed that the D-SCU did not have a significant effect in preventing cognitive decline compared to general LTC services. The change in cognitive function score in the experimental group was 2.38 points lower than that in the control group after the implementation of the D-SCU. However, the difference was only 1.51 points when considering the change between pre- and post-implementation. Two interpretations are possible for these results; first, the current D-SCU services are qualitatively insufficient to prevent cognitive decline in service recipients. Although it is currently intended to arrange facilities and personnel as stipulated by the law and implement customized programs for patients with dementia, the provision of level-specific programs or customized programs for individuals is practically difficult.[31] Accordingly, for D-SCU services to contribute to the prevention of cognitive decline, discussions are needed regarding qualitative improvements beyond the current level of service delivery. Second, although the degree of decline in cognitive function varies according to the severity of dementia, we could not perform subgroup analysis of dementia severity could not be performed due to the limited sample size. Subsequently, it was impossible to identify potential differences according to the severity.

Third, problem behavior scores showed nearly no difference or a slight decrease in both D-SCU and general LTC facility users after receiving the services. Therefore, the services provided under LTCI were associated with a reduction in problem behaviors among patients with dementia. However, the results of the DID analysis indicated no statistically significant effect of D-SCU services in reducing problem behaviors compared to general LTC services. Several studies on D-SCUs have reported improvements in both the quantity and quality of social interactions between patients with dementia or between patients with dementia and their caregivers[5,11,32] and a decrease in problem behaviors.[7,25,33] However, we observed no significant difference compared to general LTC facilities. The clinical aspects of D-SCU services in Korea do not include interventions related to drug intake. However, nursing home residents with dementia take multiple medicines and require medication management that includes prescribing, dispensing, and adherence to medication review.[34] In addition, the results of the current study indicated that the difference in these results

stems from the fact that the service provider personnel and service content of D-SCUs that showed effectiveness in prior studies differ from those in the Korean D-SCU services. A previous study reporting the effect of D-SCU on social interaction in patients with dementia proposed that, unlike traditional nursing homes, dementia-specialized units were staffed with additional personnel for recreation and activities to work three shifts from 08:00 to 21:00, and such staffing had an effect on improved social interaction.[32] The results of these prior studies are considered to have significant implications for South Korea's policy. Since the introduction of D-SCU services in July 2016, the number of providers has increased from 25 in 2016 to 175 in 2019, and the Ministry of Health and Welfare has relaxed provider-entry requirements, such as facility and staffing standards, to increase the number of facilities. However, a previous study on the relaxation of such standards argued that although service differentiation is key to improving D-SCU effectiveness, further examination is needed to determine whether this can be achieved with relaxed standards.[35] Furthermore, service fees may increase if facility staffing standards are tightened and out-of-pocket costs for beneficiaries may rise, creating unmet needs that prevent access to necessary services due to cost burdens. Therefore, policies must be formulated to differentiate between general LTC facilities and simultaneously reduce the recipients' cost burdens.

The present study has several limitations. First, although the sample size of the target analysis was sufficient, the period of data collection was < 3 years after the introduction of the D-SCU system and there was a limit to securing a large number of subjects for the analysis because the level of participation at the beginning of the implementation of the new system was low. In the future, more accurate evaluation will be possible if the follow-up period is further extended and continuous research is conducted on a larger number of subjects to suggest sophisticated directions for institutional development.

Second, the current study used secondary data extracted from the NHIS's LTCI database. Therefore, we couldn't have analyzed a wide range of variables, such as social support, nutritional status, and dementia type and severity, which can affect physical and cognitive functions as well as changes in problem behaviors.

Third, the LTC needs checklist used for outcome measures in this study was not developed for research but rather was developed to administratively select LTC beneficiaries. Therefore, we did not rigorously test its validity. In addition, under Korean circumstances, it is highly likely that the evaluators assessing the LTC needs checklist in patients with dementia residing in nursing homes differ before and after LTC. While evaluators who are NHIS staff receive sufficient training for the evaluation of the LTC checklist, differences may occur between evaluators.

Fourth, this study did not consider variables concerning providers of services to patients with dementia. In other words, although LTC facilities dedicated to dementia care arrange service personnel and the environment according to the relevant laws and regulations, staffing and environments differ among facilities; these variables cannot be controlled due to data restrictions. Therefore, further research using sophisticated research designs is necessary.

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### CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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None.

### AUTHOR CONTRIBUTIONS

Conceptualization, IS; Data curation, IS; Investigation, IS, HS; Methodology, IS, HS; Project administration, IS, HS; Supervision, HS; Writing–original draft, IS, HS; Writing–review and editing, HS.

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# Longitudinal Changes in Physical and Cognitive Functions among Participants with and without Rheumatoid Arthritis in Community-Dwelling Middle-Aged and Older Adults

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**Background:** This study evaluated the chronological changes in physical and cognitive functions in middle-aged and older adults with and without rheumatoid arthritis (RA). **Methods:** This population-based case-control longitudinal study included individuals aged 40–79 years at baseline who agreed to participate. We identified 42 participants with RA and randomly selected 84 age- and sex-matched controls. Physical function was assessed according to gait speed, grip strength, and skeletal muscle mass. Cognitive function was assessed based on the information, similarities, picture completion, and digit symbol substitution test scores of the Wechsler Adult Intelligence Scale-Revised Short Form. The general linear mixed models comprised the fixed effects of the intercept, case, age, time in years since baseline, and case×time interaction, which were used to examine longitudinal changes in physical and cognitive functions. **Results:** Regardless of RA status, grip strength decreased and the picture completion score increased in the group aged <65 years, while skeletal muscle mass index and gait speed decreased in the group aged ≥65 years. The interaction of case×follow-up years for grip strength in the group aged ≥65 years was significant (p=0.03). The decline in grip strength in the control group (slope=-0.45) was greater than that in the RA group (slope=-0.19). **Conclusion:** Chronological changes in physical and cognitive functions were comparable between participants with and without RA; however, the decline in grip strength in the control group was greater among older adults with RA.

**Key Words:** Physical examination, Cognition, Rheumatoid arthritis, Aging

## INTRODUCTION

Alterations in physical and cognitive functions with age are generally related to adverse health outcomes. Skeletal muscle mass,[1)] grip strength,[2)] and gait speed[3)] gradually decrease with age. Structural and functional changes related to disability[4,5)] increase the risk of mortality.[6-8)] Cognitive function comprises multiple domains that change with age.[9)] Some domains of cognitive function, such as memory, information processing speed, search speed, and verbal memory, are associated with survival in later adulthood.[10-12)]

Rheumatoid arthritis (RA) is a chronic inflammatory disease. Patients with RA experience pain, and insufficient disease control may result in cartilage damage.[13)] Skeletal muscle mass, gait speed, and grip strength are lower in patients with RA than in communi-

ty-dwelling adults because of this burden.[14] Additionally, the estimated number of older patients with RA is increasing[15,16] due to a surge in late-onset RA[17] and decreasing mortality.[18] The number of older patients with RA and the number of patients with RA having a high risk of disability are increasing. However, the association between RA and cognitive function is unclear. Opposing mechanisms are involved in the association between RA and cognitive function, and evidence of the association between the two is limited. A population-based case-control study reported an inverse association between a history of RA and Alzheimer disease.[19] Other studies have shown higher risks of dementia in patients with RA,[20-22] chronic inflammation with neurological involvement, accelerated atherosclerosis, and subsequent cognitive impairment.[23] Biological disease-modifying antirheumatic drugs and anti-tumor necrosis factor drugs may have beneficial effects on cognitive impairment.[24]

Most previous studies have not matched the controls for comparisons of physical and cognitive functions and have not monitored the changes in these functions using longitudinal data. Hence, in this study, we aimed to identify longitudinal changes in physical and cognitive functions in participants with RA compared with those in community-dwelling adults. We evaluated middle-aged and older adults separately because changes in physical function vary between the two age groups.[25-27]

## MATERIAL AND METHODS

### Study Participants

This study was conducted as part of the National Institute for Longevity Sciences–Longitudinal Study of Aging (NILS-LSA).[28] This population-based prospective cohort study screens for aging and age-related diseases. In this project, the normal aging process was assessed using detailed questionnaires, medical checkups, anthropometric measurements, physical fitness tests, and nutritional examinations. The participants were a random sample of community-dwelling adults who were stratified based on age and sex. They were aged 40–79 years at the time of their initial participation and lived in Obu-shi and Higashiura-cho, Aichi Prefecture, Japan. These participants were followed up every 2 years from the first (November 1997–April 2000) to the second (April 2000–May 2002), third (May 2002–May 2004), fourth (June 2004–July 2006), fifth (July 2006–July 2008), sixth (July 2008–July 2010), and seventh (July 2010–July 2012) study waves. When participants could not be followed up, new age-(decade) and sex-matched participants were randomly recruited from the second to seventh study waves, and individuals aged 40 years were newly recruited every year. The study protocol was approved by the Committee of Ethics of Human Research of the National Center for Geriatrics and Gerontology (No. 1633). Written informed consent was obtained from all participants. Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[29]

The total number of NILS-LSA participants was 3,983. We included individuals who did not report having medical conditions that could affect physical and cognitive functions, such as a history of stroke, heart disease, cancer, or dementia, using a self-administered questionnaire at baseline. Individuals were categorized into the RA and control groups. Participants with RA (RA group) were defined as those who answered that they had received RA treatment, had been treated for RA, or were not currently treated but had been treated for RA previously in the fifth to seventh study wave questionnaires because we did not distinguish between RA and other forms of arthritis, such as osteoarthritis, until the fourth study wave. The baseline for participants with RA was defined as the study wave in which they first answered that they had RA or arthritis. We excluded participants with RA who did not join the NILS-LSA more than twice. We selected the controls as follows: first, we randomly selected controls without RA whose age and sex matched those of participants with RA in the first wave in a ratio of 2:1. After excluding the participants selected as controls in the first study wave, we selected controls in the second study wave in the same manner as that in the first study wave. When those in the control group did not participate in the NILS-LSA more than twice, we selected other control participants. We repeatedly selected controls until the sixth study wave. Finally, 42 participants with RA and 84 controls were chosen.

### Measurements

#### *Physical function (baseline and follow-up survey)*

Appendicular lean mass (ALM), grip strength, and gait speed were assessed as physical functions. ALM was assessed using a dual-energy X-ray absorptiometer (QDR-4500; Hologic, Bedford, MA, USA).[30] The skeletal muscle mass index (SMI) was calculated as the ALM divided by the height squared (kg/m$^2$). Grip strength was measured using a handgrip dynamometer (T.K.K.4301a; Takei, Niigata, Japan). In this assessment, the participants were instructed to hold a hand grip dynamometer while standing with their arms at their sides and their elbows extended and to squeeze with maximum force, alternating the left and right hands twice.[31] A maximum of two readings from each hand was used as the measurement result. Gait speed was assessed using a walking analysis system (YW-3; Yagami Co., Aichi, Japan).[32] The participants walked at a comfortable speed on an 11-m straight walkway, in-

cluding acceleration and deceleration. The start and end times to walk 10 m were recorded using light sensors, and habitual gait speed was measured three times by calculating the time in meters per second. The gait speed was determined from the first trial wherein stride length, pitch, and gait speed were measured simultaneously and used as the measurement result.

***Cognitive function (baseline and follow-up survey)***

Cognitive abilities were assessed using the Japanese version of the Wechsler Adults Intelligence Scale-Revised Short Form (WAIS-R-SF).[33] The WAIS-R-SF consists of information, similarity, picture completion, and digit symbol substitution scales. Trained clinical psychologists or graduate students specializing in psychology administered the test to the participants individually. The information test evaluates general knowledge about people, places, and events (29 items; possible range, 0–29). The similarities test assesses logical abstract thinking by asking participants to state how similar two things are to each other (14 items; possible range 0–28). The picture completion test gauges visual perception and long-term visual memory by asking participants to spot the missing elements in a series of drawings (21 items, possible range 0–21). The digit symbol substitution test measures processing speed by asking participants to write as many symbols as possible that correspond to a given number in 90 seconds (possible range 0–93). In all tests, higher scores indicate better cognitive function.

***Covariates (baseline)***

At baseline, data on age, sex (male, female), education level ($\geq$ 12 years, $<$ 12 years), and history of hypertension or diabetes mellitus (none, presence) were collected using a self-administrated questionnaire. Body weight and height were measured using digital scales to the nearest 0.1 kg and 0.1 cm, respectively. The participants were requested to wear light clothing and no shoes. Body mass index (BMI) was calculated as the body weight in kilograms divided by the square of the height in meters. According to BMI, the participants were categorized into three groups: $<$ 18.5, $\geq$ 18.5 and $<$ 25, and $\geq$ 25 kg/m$^2$.[34]

**Statistical Analysis**

The participants were classified into two age groups: $<$ 65 years (40–64 years) and $\geq$ 65 years (65–79 years) at baseline because the slope of decreasing physical function differs between middle-aged and older adults.[25-27] We analyzed the data according to these groups. When certain variables were missing for a participant, the entire data for that participant in the same wave were deleted. Subsequent analysis was performed by age group. The baseline characteristics in the RA and control groups were examined using t-test or chi-square tests in each age group. General linear mixed models were used to evaluate the effects of RA presence on longitudinal changes in physical and cognitive functions. The model used in this study included fixed terms for the intercept, case (RA or control), age (at baseline), time (time in years since baseline), and case $\times$ time interaction. The case $\times$ time interaction was expected to indicate whether the change in physical and cognitive functions varied according to the presence or absence of RA. A history of hypertension or diabetes, BMI categories (for physical function),[35] and education categories (for cognitive function)[36] were considered covariates. Additionally, the models included random intercepts and slope terms that captured participant-specific deviations.

All statistical data were analyzed using SAS System (version 9.3; SAS Institute, Cary, NC, USA). Two-tailed $p < 0.05$ was considered statistically significant.

## RESULTS

Table 1 shows the baseline characteristics of the RA and control groups according to age. The physical and cognitive functions at baseline did not differ significantly between the two groups in either age group. The follow-up time in the RA group was significantly longer than that in the control group aged $\geq$ 65 years.

Table 2 presents the results of the general linear mixed-model parameter estimates for physical function in each age group. The parameter estimates of fixed effects for the follow-up years declined significantly for grip strength (both $p < 0.001$) in both age groups and for SMI ($p < 0.01$) and gait speed ($p = 0.01$) in the group aged $\geq$ 65 years. The average grip strength of the RA group aged $\geq$ 65 years was significantly lower than that of the control group ($p = 0.01$). The interaction effect of case $\times$ time was significant for grip strength in the group aged $\geq$ 65 years. Fig. 1 illustrates the grip strength changes in the group aged $\geq$ 65 years, which were estimated by substituting baseline age, follow-up years, and the effects of the case $\times$ time interaction (Fig. 1). The slope of the grip strength change in the control group was steeper (slope = −0.45) than that in the RA group (slope = −0.19). Regarding cognitive abilities, the information ($p < 0.001$) and similarity ($p = 0.01$) scores increased with follow-up years in the group aged $<$ 65 years. The average picture completion score increased with follow-up years in both age groups ($p < 0.001$ for $<$ 65 years; $p = 0.03$ for $\geq$ 65 years). However, no significant difference in cognitive function scores was observed between the RA and control groups. Furthermore, no significant effects of case $\times$ time interaction for each cognitive domain were observed in either age group (Table 3).

**Table 1.** Baseline characteristics of the RA and control groups

| | Aged < 65 years | | | Aged ≥ 65 years | | |
|---|---|---|---|---|---|---|
| | RA (n = 25) | Control (n = 50) | p-value | RA (n = 17) | Control (n = 34) | p-value |
| Age (y) | 53.2 ± 7.8 | 53.2 ± 7.7 | | 72.3 ± 4.2 | 72.3 ± 4.2 | |
| Sex, female | 20 (80.0) | 40 (80.0) | | 11 (64.7) | 22 (64.7) | |
| BMI (kg/m$^2$) | 22.9 ± 2.8 | 21.9 ± 3.1 | 0.16 | 23.3 ± 2.9 | 23.3 ± 2.9 | 1.00 |
| SMI (kg/m$^2$) | 6.8 ± 1.1 | 6.7 ± 1.0 | 0.53 | 6.8 ± 1.0 | 6.8 ± 1.0 | 0.97 |
| Grip strength (kg) | 28.4 ± 10.7 | 29.1 ± 7.1 | 0.73 | 24.2 ± 9.5 | 27.8 ± 8.0 | 0.16 |
| Gait speed (m/s) | 1.3 ± 0.2 | 1.4 ± 0.2 | 0.40 | 1.3 ± 0.2 | 1.2 ± 0.2 | 0.53 |
| Cognitive abilities score | | | | | | |
| Information | 15.5 ± 5.3 | 14.1 ± 5.9 | 0.33 | 12.2 ± 4.0 | 13.3 ± 4.7 | 0.42 |
| Similarities | 15.4 ± 4.5 | 13.5 ± 5.4 | 0.14 | 10.7 ± 4.3 | 10.6 ± 4.0 | 0.96 |
| Picture completion | 12.7 ± 3.8 | 12.3 ± 2.6 | 0.59 | 9.6 ± 3.5 | 9.9 ± 3.7 | 0.77 |
| Digit symbol substitution | 58.2 ± 15.5 | 59.6 ± 13.0 | 0.70 | 39.5 ± 10.4 | 41.6 ± 9.6 | 0.47 |
| Follow-up time (y) | 10.5 ± 2.6 | 9.1 ± 3.4 | 0.09 | 7.2 ± 3.1 | 5.2 ± 3.2 | 0.04 |
| Number of participations for the study | 5.6 ± 1.5 | 5.3 ± 1.7 | 0.49 | 4.0 ± 1.6 | 3.4 ± 1.5 | 0.22 |
| Education (y) | | | | | | |
| < 12 | 6 (24.0) | 11 (22.0) | 0.85 | 15 (88.2) | 22 (64.7) | 0.10 |
| History of hypertension or diabetes | 4 (16.0) | 10 (20.0) | 0.14 | 5 (29.4) | 18 (52.4) | 0.14 |

Values are presented as mean±standard deviation or number (%).
RA, rheumatoid arthritis; BMI, body mass index; SMI, skeletal muscle mass index.

**Table 2.** General linear mixed model of fixed effects for physical function

| | SMI | | | Grip strength | | | Gait speed | | |
|---|---|---|---|---|---|---|---|---|---|
| | β | SE | p-value | β | SE | p-value | β | SE | p-value |
| Aged < 65 years | | | | | | | | | |
| Case | -0.13 | 0.17 | 0.45 | -1.40 | 1.24 | 0.26 | -0.07 | 0.04 | 0.053 |
| Time (follow-up years) | -0.01 | 0.01 | 0.24 | -0.31 | 0.06 | < 0.001 | 0.00 | 0.00 | 0.72 |
| Case × time | -0.01 | 0.02 | 0.37 | -0.02 | 0.10 | 0.84 | 0.00 | 0.00 | 0.20 |
| Aged ≥ 65 years | | | | | | | | | |
| Case | -0.13 | 0.14 | 0.34 | -3.68 | 1.46 | 0.01 | 0.04 | 0.04 | 0.41 |
| Time (follow-up years) | -0.03 | 0.01 | < 0.01 | -0.45 | 0.07 | < 0.001 | -0.01 | 0.00 | 0.01 |
| Case × time | 0.02 | 0.01 | 0.12 | 0.26 | 0.11 | 0.03 | 0.01 | 0.01 | 0.44 |

SMI, skeletal muscle mass index; SE, standard error.
Adjusted for sex, age at baseline, history of hypertension or diabetes, body mass index, and random effect.
Case (0=control, 1=RA).

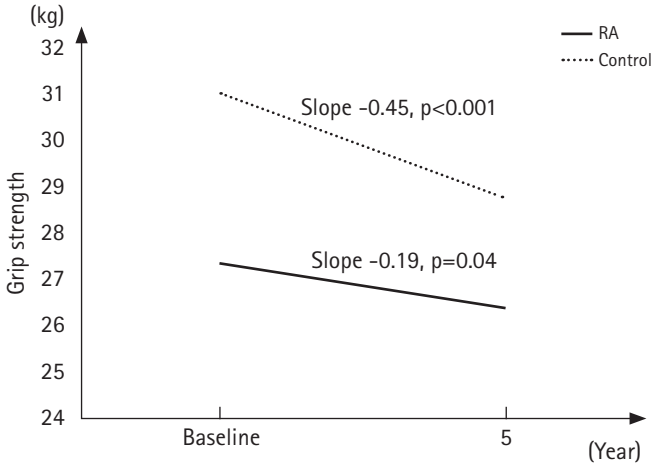


**Fig. 1.** Model-estimated 5-year changes in grip strength in the group aged ≥65 years by the rheumatoid arthritis (RA) and control groups. The solid lines are estimates for RA group, and the dashed lines are estimates for individuals without RA.

## DISCUSSION

This study examined the longitudinal changes in physical function and cognitive abilities among the RA group compared to those in non-RA controls selected from a large community-based cohort. The interaction between case and follow-up time for grip strength in the group aged ≥ 65 years was significant. The decline in grip strength in the control group was greater than that in the RA group. Our results did not reveal greater decreases or increases in physical or cognitive function in the RA group compared with those in the control group.

Furthermore, except for grip strength, we did not observe significant differences in physical and cognitive functions between the RA and control groups. In this study, grip strength decreased in both groups, with parameter estimates of grip strength for follow-up years of -0.31 and -0.45 for the groups aged < 65 years and

**Table 3.** General linear mixed model of fixed effects for cognitive abilities

| | Information | | | Similarities | | | Picture completion | | | Digit symbol substitution | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β | SE | p-value | β | SE | p-value | β | SE | p-value | β | SE | p-value |
| Aged < 65 years | | | | | | | | | | | | |
| Case | 0.71 | 1.21 | 0.56 | 0.67 | 1.09 | 0.54 | -0.02 | 0.70 | 0.98 | -1.78 | 2.38 | 0.46 |
| Time (follow-up years) | 0.16 | 0.05 | < 0.001 | 0.15 | 0.06 | 0.01 | 0.20 | 0.03 | < 0.001 | 0.14 | 0.08 | 0.09 |
| Case × time | -0.06 | 0.08 | 0.48 | -0.07 | 0.10 | 0.50 | -0.03 | 0.05 | 0.58 | -0.06 | 0.14 | 0.69 |
| Aged ≥ 65 years | | | | | | | | | | | | |
| Case | -0.71 | 1.35 | 0.60 | 0.44 | 1.18 | 0.71 | -0.13 | 1.02 | 0.90 | 0.40 | 2.61 | 0.88 |
| Time (follow-up years) | 0.01 | 0.07 | 0.85 | -0.01 | 0.10 | 0.91 | 0.19 | 0.09 | 0.03 | -0.17 | 0.13 | 0.19 |
| Case × time | -0.02 | 0.11 | 0.89 | 0.19 | 0.15 | 0.22 | -0.03 | 0.14 | 0.81 | 0.05 | 0.20 | 0.80 |

SE, standard error.
Adjusted for sex, age at baseline, history of hypertension or diabetes, body mass index, and random effect.
Case (0=control, 1=RA).

≥ 65 years, respectively. This result was unexpected; moreover, previous studies have suggested an association of chronic inflammation with disability and dementia[20,21,37] and reported that the changes in grip strength in RA populations were not affected by age but by other factors such as disease duration and disease activity.[38] A meta-analysis of the general population aged 20–100 years and RA population aged 31–65 years showed that grip strength decreased gradually with age, with a steeper decline at 50 years of age.[38] In contrast, the grip strength in the RA group was lower than that in the general population, did not show a steeper decline during middle age, and was associated with disease duration.[38] Our results were similar to those of a previous report showing that the grip strength of the RA group was lower than that of the control group and that the decline in the grip strength for the RA group was slower than that of the control group. The reduced grip strength might be due to disease duration or factors other than aging. The decline in grip strength in the RA group was slower than that in the control group, which was caused by the low grip strength of the RA group at the beginning of the follow-up. This may be because the case × time interaction for grip strength was significant in the group aged ≥ 65 years. Longitudinal studies are required to clarify the changes in grip strength in the RA and control groups.

Our results revealed a significant inverse association between SMI and aging in the group aged ≥ 65 years but not in the group aged < 65 years. Longitudinal changes in SMI did not differ significantly between the RA and control groups. A cross-sectional study of healthy community-dwelling adults aged 40–79 years reported that SMI decreased gradually from middle age.[39] A 12-year follow-up longitudinal study in community-dwelling adults aged 40–79 years showed that SMI decreased with age, except in middle-aged men.[30] The association between SMI and aging in our study is in line with the previously reported results. In our study, gait speed decreased significantly in the group aged ≥ 65 years but did not decrease in the group aged < 65 years. Gait speed began to decrease in approximately the 60s.[26] The change in SMI and gait speed with age did not differ significantly in the RA and control groups, and the decline in gait speed in the RA group also likely occurred in the control group.

Crystalized intelligence increased with follow-up years in both the RA and control groups aged < 65 years. The picture competition score, which reflects fluid intelligence, also increased with age in age groups. A cross-sectional study of participants aged 18–99 years showed that crystallized intelligence increased until the sixth decade and was maintained or decreased slightly thereafter, while fluid intelligence declined from middle age.[40] Our results on crystallized intelligence were consistent with those reported previously.[40] The difference in picture completion may be affected by participant memory. As our study participants answered the same questions repeatedly, their knowledge of the previous questions and answers might have influenced their subsequent correct answers. Chronic inflammation causes atherosclerosis and cognitive impairment.[23,41] In contrast, antirheumatic drugs may exert beneficial effects on cognitive impairment.[24] The findings regarding the association between RA and cognitive function remain debatable. We do not have a clear explanation for the lack of difference in the change in cognitive function between the RA and control groups.

This study has several limitations. First, the participants were recruited from a random sample of community-dwelling middle-aged and older adults. However, they were relatively physically or mentally healthy because they could repeatedly participate in the study at our institution. Additionally, the number of study participants was small. Therefore, our findings cannot be extrapolated to patients with RA with severe disabilities. Second, we did not define RA based on diagnostic criteria,[42] which might have led to misclassification. Third, the follow-up time in the RA group was longer than that in the control group aged ≥ 65 years. However,

these differences may not have affected the results of the analysis because the 2-year interval of each wave might have affected the difference and the number of participants did not differ significantly between the RA and control groups. Finally, patients with RA might have stiffness or deformity in their fingers, which might have caused decreased grip strength. Information on disease severity, duration, finger stiffness or deformity, and use of disease-modifying antirheumatic drugs was not collected. Although we did not collect information on the factors that affect physical function, participants with RA might have maintained their physical function because their baseline characteristics were not significantly different from those of the control group.

Chronological changes in physical and cognitive functions with aging are comparable between participants with RA and community dwellers without RA; however, the grip strength of those in the participants with RA showed a greater decline in older adults without RA.

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### CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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### AUTHOR CONTRIBUTIONS

Conceptualization, MY, MK; Data curation, CT, YN, MT, HS, RO; Methodology, MY, CT, RO, MK; Formal analysis, MY, CT, YN, MT; Funding acquisition, HS, RO, MK; Investigation, CT, YN, MT, HS, RO; Resources, RO; Data curation, RO; Writing – Original Draft, MY, CT, RW, RO, MK; Writing – Review & Editing, MY, CT, YN, MT, RW, HS, RO, MK.

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# Health-Related Unmet Needs of Community-Dwelling Older Adults: A Nationwide Representative Descriptive Study in Korea

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**Background:** South Korea has no official geriatric specialties or subspecialties. Moreover, studies on the unmet needs related to geriatric health problems in older Korean adults are scarce. Therefore, we investigated the unmet needs regarding geriatric health problems among older Korean adults. **Methods:** This cross-sectional study included 411 Korean adults aged ≥70 years. We constructed a questionnaire for a field survey that comprised 21 items to understand the geriatric challenges related to the participants' physicians and the necessity for geriatric physicians to resolve participants' health problems. We used unweighted numbers (weighted percentages) or mean±standard deviation to describe the characteristics of the study participants for categorical and continuous variables, respectively. **Results:** This study included a total of 411 men and women. The mean age was 77.6±5.9 years. Among the participants, 88.6% had one or more chronic diseases (mean number of chronic diseases, 2.0±1.3). Of the participants, 32.8% said that their physicians did not spend enough time addressing their problems and only 24.3% felt that their physicians understood geriatric problems well. Of these, 76.2% (n=313) said that geriatricians were required to fulfill their unmet healthcare needs. **Conclusions:** The participants reported the need for help from a geriatrician, although most of the participants consulted regular physicians about their health problems. The study results support that geriatricians are needed to improve health services for older adults.

**Key Words:** Unmet healthcare needs, Geriatricians, Elderly, Korean

## INTRODUCTION

Korea is one of the fastest-aging countries worldwide. Korea has become an aging society, with 7% of the population reaching ≥65 years in 2000.[1)] However, the aging speed of the Korean society is much faster than expected. It became an aged society in 2017, with 14% of the population aged ≥65 years.[2)] Although experts in Korea originally expected it to become an aged society in 2018 or 2020, Korea made this transition from an aging society in only 17 years, which is more rapid than that of any other country.

Most older Korean adults have chronic diseases. Nearly 90% of Korean older adults reported one or more chronic diseases, with approximately half of them having three or more chronic diseases.[3)] The mean number of diagnosed chronic diseases was 2.6. An increase in the number of older adults indicates an increase in the chronic disease burden in Korean society. The national medical expenses for older adults are increasing as the population increases. The expense was 32.4% of the total expense in 2010, which was al-

ready one-third of the total expense for 10% of the population and reached 43.1% in 2019.[4]

Many older adults also have specific age-related health problems; thus, they experience both geriatric problems and chronic diseases. Many developed countries have official geriatric specialties or subspecialties to address geriatric problems.[5,6] Geriatric training is offered as official residency or fellowship training in each country.

However, South Korea has no official geriatric specialties or sub-specialties. Most geriatric health problems are addressed by specialists, and each specialist usually deals with only a subset of geriatric problems in older adults. Therefore, there is a high chance of unmet needs regarding geriatric health problems among older Korean adults. To our knowledge, data on the unmet needs related to geriatric health problems in older Korean adults are scarce. Therefore, the Korean Geriatrics Society performed a field survey on the health-related unmet needs of Korean older adults using a representative sample.

## MATERIALS AND METHODS

### Study Participants

This descriptive study aimed to elucidate the perceived necessity for geriatricians among older Korean adults. The study participants were men and women aged ≥ 70 years. The nationwide proportional quota sampling method was used for representativeness, except on Jeju Island. Computer-assisted personal interviews were conducted, and a pre-constructed questionnaire was administered to participants by Gallup Korea. In total, 411 men and women responded to the survey.

### Measurement

#### *Questionnaire development*

We constructed a questionnaire for the field survey of 21 items. First, a literature review was conducted to collect the items. The review included a total of 74 items. Most of the items were collected from nationwide surveys or validated questionnaires. Additionally, we created two items that asked about the geriatric problems of the participants and the necessity for geriatric physicians to resolve the participants' health problems. Seventy-six items were included in the next step.

We selected items for inclusion in the final questionnaire through expert consensus using the Delphi technique. Thirty-nine geriatric experts participated as panelists in the process. We asked the panelists score each item regarding how much they agreed with the inclusion of the item in the final questionnaires. The iteration was stopped in the second round because most of the panelists reached an agreement on the selected items. Finally, we selected 21 items for inclusion in the final questionnaire.

#### *Items included in the questionnaire and field survey*

The final questionnaire included the following items: (1) demographic variables (age, sex, education, marital status, previous occupation, and residential region); (2) subjective health; (3) chronic diseases; (4) need for assistance in daily living; (5) having a regular physician; (6) experiences in regular physician encounters; (7) medications; (8) physician understanding of the geriatric problems; (9) necessity for geriatric physicians to resolve their health problems; and (10) physical function according to the K-FRAIL scale.[7] The language and order of items were trimmed to enhance participant understanding. Polypharmacy was defined as the taking of ≥ 4 medications. The participants were asked to answer the following question: "Do you need help from family or others to perform your daily activities?" Individuals who answered "yes" to this question were defined as having dependencies in activities of daily living (ADL).

#### *Field survey*

A field survey was conducted by a trained interviewer in Gallup, Korea, through computer-assisted personal interviews between November 17 and December 7, 2021. The questionnaire was administered to preselected respondents by an interviewer. After completing the interviews, the responses to the questionnaire were reviewed by the interviewer and the respondents were asked not to skip any items. Confidentiality was assured.

The study protocol was approved by the Institutional Review Board of the Asan Medical Center (IRB No. 2022-0262). Written informed consents were obtained from participants before interview.

Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[8]

### Statistical Analysis

All subsequent analyses were performed according to sex. Continuous variables were analyzed using the general linear model and are presented as mean ± standard deviation. Categorical variables are presented as unweighted numbers (weighted percentages) and were analyzed using chi-square tests. The statistical analyses were performed using Stata version 15.1 (StataCorp LLC, College Station, TX, USA). Statistical significance was set at $p < 0.05$.

## RESULTS

### Baseline Participant Characteristics

Table 1 presents the general characteristics of the study participants. The study included a total of 411 men and women. The mean age was 77.6 ± 5.9 years. Two hundred forty-four (59.4%) participants were women. In addition, 184 (44.8%) participants lived in the Seoul metropolitan area. Most participants (83.7%) reported < 9 years of education. Most men (82.9%) were married, whereas half the women (53.1%) were widowed.

The mean number of medications was 2.13 ± 1.17, and 74 of participants (18.0%) took ≥ 4 medications. Sixty-seven participants reported needing assistance in their daily living; half of the participants (50.1%) reported that they could not climb 10 steps and one-third (34.8%) reported that they could not walk 300 m. Most participants (86.4%) reported feeling fatigued, and 44 (10.7%) had lost 5% or more of their body weight in the previous year.

Most participants (88.6%) had one or more chronic diseases, and the mean number of chronic diseases was 1.97 ± 1.33. Hypertension was the most common chronic disease (65.9%), followed by diabetes mellitus, osteoarthritis, dyslipidemia, and musculoskeletal pain.

### Prevalence and Satisfaction of the Participants with their Regular Physicians

A total of 83.1% (n = 359) of participants reported having a regular physician. Moreover, 86.8% (n = 375) of the participants answered

**Table 1.** General characteristics of participants

| | Total (n = 411) | Men (n = 167) | Women (n = 244) |
|---|---|---|---|
| Age (y) | 77.6 ± 5.9 | 76.7 ± 5.6 | 78.1 ± 6.0 |
| Occupation | | | |
| Agriculture/fishing | 62 (14.6) | 28 (16.5) | 34 (13.3) |
| Self-employed | 75 (18.2) | 44 (25.3) | 31 (13.3) |
| Manual | 130 (31.6) | 66 (38.8) | 64 (26.6) |
| Office | 24 (6.8) | 23 (15.9) | 1 (0.4) |
| Housewife | 114 (27.3) | 0 (0) | 114 (46.5) |
| Education (y) | | | |
| < 9 | 343 (83.7) | 127 (75.7) | 216 (89.2) |
| 9–12 | 60 (14.4) | 33 (20.1) | 27 (10.4) |
| > 12 | 8 (2.0) | 7 (4.1) | 1 (0.4) |
| Marriage | | | |
| Married | 244 (59.9) | 139 (82.9) | 105 (43.6) |
| Bereaved | 153 (36.5) | 22 (12.9) | 131 (53.1) |
| Divorced/separated | 11 (2.7) | 3 (1.8) | 8 (3.3) |
| Number of medications | 2.1 ± 1.2 | 2.0 ± 1.3 | 2.2 ± 1.1 |
| Polypharmacy | 74 (18.0) | 38 (22.8) | 36 (14.8) |
| Physical function | | | |
| ADL dependency | 67 (15.8) | 27 (15.3) | 40 (16.2) |
| Climbing < 10 steps | 207 (50.1) | 61 (35.9) | 146 (60.2) |
| Walking < 300 m | 142 (34.8) | 38 (23.5) | 104 (42.7) |
| Feeling fatigued | 355 (86.4) | 147 (88.0) | 208 (85.3) |
| Weight loss, > 5%/year | 44 (10.7) | 16 (9.6) | 28 (11.5) |
| Any chronic disease | 363 (88.6) | 145 (87.6) | 218 (89.2) |
| Number of chronic diseases | 2.0 ± 1.3 | 1.6 ± 1.1 | 2.2 ± 1.4 |
| Hypertension | 271 (65.9) | 100 (60.6) | 171 (69.7) |
| Diabetes | 127 (30.9) | 45 (28.2) | 82 (32.8) |
| Dyslipidemia | 60 (13.9) | 23 (12.4) | 37 (14.9) |
| Stroke | 7 (1.7) | 4 (2.9) | 3 (0.8) |
| Angina | 36 (9.0) | 11 (7.1) | 25 (10.4) |
| Osteoarthritis | 101 (25.5) | 20 (13.5) | 81 (34.0) |
| Musculoskeletal pain | 79 (19.2) | 22 (12.9) | 57 (23.7) |
| Osteoporosis | 52 (12.9) | 9 (5.3) | 43 (18.3) |
| Depression | 14 (3.4) | 5 (2.9) | 9 (3.7) |

Values are presented as mean±standard deviation or unweighted number (weighted percentage).

that they did not have difficulty meeting their physicians when needed. A total of 82.4% (n=356) of the participants responded that they could comfortably ask questions to their physicians.

Table 2 shows that the participants' satisfaction with their physician required sufficient time for consultation based on the characteristics of the participants. Of these, 67.2% (n=275) felt that their physicians spent sufficient time seeing them during consultations. Half of the highly educated participants felt that their physicians spent enough time seeing them during their consultations. Approximately 60.7% of the participants bereaved their partners and felt that their physicians spent enough time consulting with them.

### Physicians' Understanding of Geriatric Problems

Table 3 shows the participants' responses regarding physician understanding of geriatric problems. In this study, 24.3% (n=106) of participants reported that their physician understood geriatric

**Table 2.** The characteristics of participants who satisfied with their regular physicians

| | Total | Men | Women | p-value |
|---|---|---|---|---|
| Total | 275 (67.2) | 119 (70.6) | 156 (64.7) | 0.213 |
| Age (y) | | | | |
| 70–79 | 179 (70.5) | 85 (75.8) | 94 (66.0) | 0.107 |
| 80–89 | 96 (61.2) | 34 (58.0) | 62 (62.9) | 0.565 |
| Any chronic disease (+) | 247 (68.1) | 104 (71.1) | 143 (66.0) | 0.305 |
| Polypharmacy (+) | 48 (64.9) | 29 (76.3) | 19 (52.8) | 0.680 |
| ADL dependency (+) | 51 (78.5) | 20 (80.8) | 31 (76.9) | 0.712 |
| Feeling fatigued (+) | 328 (65.0) | 95 (67.1) | 143 (637) | 0.503 |
| Education (y) | | | | |
| <9 | 234 (68.4) | 92 (71.9) | 142 (66.4) | 0.288 |
| 9–12 | 37 (65.0) | 23 (73.5) | 14 (53.8) | 0.113 |
| >12 | 4 (37.5) | 4 (42.9) | 0 (0) | |
| Marriage | | | | |
| Married | 173 (70.4) | 104 (73.9) | 69 (65.7) | 0.161 |
| Bereaved | 91 (60.7) | 11 (50.0) | 80 (62.5) | 0.268 |
| Divorced/separated | 8 (72.7) | 1 (33.3) | 7 (87.5) | 0.072 |

Values are presented as unweighted number (the percentage of participants who were satisfied with their regular physicians. To estimate the population proportion, weighted percentage was used. For example, it is estimated that 75.8% of 70-79 years old Korean men were satisfied with their regular physicians).
The p-values show statistical differences between men and women.

**Table 3.** The characteristics of participants responding that their physicians understand geriatric problems well

| | Total | Men | Women | p-value |
|---|---|---|---|---|
| Total | 106 (24.3) | 50 (27.5) | 56 (22.0) | 0.174 |
| Age (y) | | | | |
| 70–79 | 68 (25.8) | 30 (25.8) | 38 (25.7) | 0.291 |
| 80–89 | 38 (21.8) | 20 (32.0) | 18 (16.5) | 0.001 |
| Any chronic disease (+) | 96 (24.7) | 47 (28.9) | 49 (21.8) | 0.163 |
| Polypharmacy (+) | 11 (19.6) | 4 (13.8) | 7 (25.9) | 0.796 |
| ADL dependency (+) | 22 (30.8) | 8 (23.1) | 14 (35.9) | 0.193 |
| Feeling fatigued (+) | 75 (18.9) | 31 (19.4) | 44 (18.6) | 0.136 |
| Education (y) | | | | |
| <9 | 82 (21.9) | 35 (23.6) | 47 (20.9) | 0.071 |
| 9–12 | 22 (37.3) | 13 (41.2) | 9 (32.0) | 0.370 |
| >12 | 2 (25.0) | 2 (28.6) | 0 (0) | |
| Marriage | | | | |
| Married | 65 (24.7) | 41 (27.0) | 24 (21.7) | 0.212 |
| Bereaved | 37 (24.0) | 8 (36.4) | 29 (21.9) | 0.146 |
| Divorced/separated | 3 (27.3) | 0 (0) | 3 (37.5) | 0.150 |

Values are presented as unweighted number (the percentage of participants who responded that their physicians understand geriatric problems well. To estimate the population proportion, weighted percentage was used. For example, it is estimated that 25.8% of 70-79 years old Korean men responded that their physicians understand geriatric problems well).
The p-values show statistical differences between men and women.

problems well, including 16.5% (n = 18) of women aged ≥ 80 years. Only 13.8% of men taking four or more medications felt that their physician understood their geriatric problems well. Approximately 37.3% of participants educated 9–12 years reported that their physician understood their geriatric problems well.

### Necessity for Geriatric Physicians

Table 4 shows the need for geriatric physicians to resolve the participants' health problems. Of the participants, 76.2% (n = 313) answered that a geriatrician would be necessary to manage geriatric problems. In particular, 84.4% of participants who needed assistance in their daily living (84.6% of men and 84.2% of women) responded that they would need a geriatrician for geriatric problems. All participants with > 12 years of education thought that a geriatrician was needed for geriatric problems.

## DISCUSSION

Of the participants, 85% reported having one or more chronic diseases and 90% had one or two regular physicians. Most of the participants could see a physician when needed and felt comfortable asking questions about their health to their physicians. However, one-third of the participants said that their physicians did not spend sufficient time addressing their problems and only 25% felt that their physicians understood geriatric problems well. Three-quarters said that geriatricians need to fulfill their unmet healthcare needs. They claimed that help from a geriatrician was needed, although most had regular physicians to consult about their health problems.

Owing to older adults' functional decline, physical illness, and psychological needs, they have more complicated needs compared with younger adults.[9] Most older adults aged > 85 years have complex multimorbidity, frailty, disability, dementia, and palliative care needs.[10] In addition, older adults have an increased prevalence of polypharmacy and probability of the inappropriate prescription of medication. Polypharmacy leads to an increased risk of geriatric syndrome, morbidity, and mortality in older adults.[11] In addition, independence in daily life determines the quality of life of older adults.[12] Older adults need geriatricians because they can provide a full range of geriatric care.[13] Hence, facing aging society, physicians should recognize and care for geriatric syndrome.[14] However, as shown in the results of our study, most Korean primary care physicians do not understand the complicated geriatric problems in older patients. This leads to unmet healthcare needs, which is a problem with inadequate solutions.[15] These unmet healthcare needs increase disease severity, complications, and risk of mortality[16] and decrease the quality of life[17] of older adults in Korea.

Geriatricians are physicians certified in geriatric medicine who are specifically trained to care for aging and medically complex older adults. Owing to their characteristics, older patients must be systematically assessed using geriatric assessment tools.[18] Geriatrics collaborate with primary care providers, a distinct specialty of older adult care medicine,[19] or nursing home medicine.[20] The position of geriatrics, organization of older adults' care, and geriatricians' training and contents of work vary widely between countries.[13] In

**Table 4.** The characteristics of participants who need geriatric physicians

| | Total | Men | Women | p-value |
|---|---|---|---|---|
| Total | 313 (76.2) | 129 (77.1) | 184 (75.5) | 0.174 |
| Age (y) | | | | |
| 70–79 | 196 (75.8) | 90 (76.7) | 106 (75.0) | 0.753 |
| 80–89 | 117 (76.9) | 39 (78.0) | 78 (76.3) | 0.816 |
| Any chronic disease (+) | 275 (75.9) | 111 (76.5) | 164 (75.5) | 0.818 |
| Polypharmacy (+) | 54 (73.0) | 28 (73.7) | 26 (72.2) | 0.478 |
| ADL dependency (+) | 57 (84.4) | 24 (84.6) | 33 (84.2) | 0.965 |
| Feeling fatigued (+) | 285 (77.8) | 112 (79.9) | 173 (76.5) | 0.454 |
| Education (y) | | | | |
| < 9 | 263 (76.9) | 95 (75.0) | 168 (78.0) | 0.519 |
| 9–12 | 42 (69.5) | 27 (79.4) | 15 (56.0) | 0.054 |
| > 12 | 8 (100) | 7 (100) | 1 (100) | |
| Marriage | | | | |
| Married | 184 (75.4) | 108 (77.7) | 76 (72.4) | 0.395 |
| Bereaved | 120 (78.5) | 17 (77.3) | 103 (78.7) | 0.877 |
| Divorced/separated | 8 (72.7) | 3 (100) | 5 (62.5) | 0.214 |

Values are presented as unweighted number (the percentage of participants who need geriatric physicians. To estimate the population proportion, weighted percentage was used. For example, it is estimated that 76.7% of 70-79 years old Korean men need geriatric physician).

one study of 22 countries, geriatrics was considered a medical specialty in 11 European countries and a subspecialty in nine countries. However, geriatrics in Greece and Portugal is not considered a specialty or subspecialty.[13] As mentioned earlier, Korea has no official geriatric specialty or subspecialty; thus, there is an unmet need for older adults with complicated geriatric conditions.

In some countries, geriatric subspecialty training is an advanced fellowship program after the completion of the basic residency program. The advanced courses are divided into intradepartment and interdepartment subspecialty programs.[21,22] Interdepartment geriatric subspecialties are implemented in the United States and Taiwan, and the curriculum includes a fellowship course in geriatric medicine after a certain period of residency. In this type of subspecialty, candidates from various specialties such as internal medicine, family medicine, and rehabilitation medicine can apply to the same geriatrics fellowship program and receive the same certificate after program completion, regardless of their specialty in the residency program. Intradepartment geriatric subspecialties are implemented in Australia and Canada, in which the geriatric fellowship programs are run by each specialty, and candidates can apply to the subspecialty program according to their specialty of the residency program.[21,22] However, geriatrics in the UK is the largest medical specialty. Postgraduate medical training programs include basic medical education for 2 years and 3–7 years for geriatric subspecialties.[23] The period for specialization also varies from 3 to 6 years in different countries.[13]

Although the number of older adults is increasing worldwide, geriatricians are insufficient. Approximately 30% of patients aged ≥65 years are expected to require care by a geriatrician, while each geriatrician can care for 700 older adults in the United States.[24] Thus, 1,500 geriatricians per year are required over the next years to fulfill the need for certified geriatricians.[25] The number of older people aged ≥80 years per geriatrician varies from 450 in Austria to 25,000 in Turkey.[18] The results of this study suggested the need to double the number of geriatricians.[13]

Our study had several limitations. First, the sample size was small (n=411). Therefore, further studies with larger sample sizes are required. Second, our study was based on a self-reported survey and may have had recall or measurement biases. Finally, the health status of the participants and their functional capacities, such as their ability to walk, should be considered when interpreting the results. Despite these limitations, our study identified health-related unmet needs in a representative sample of Korean older adults.

In conclusion, many Korean older adults required geriatricians to fulfill their unmet healthcare needs. Unmet healthcare needs could lead to adverse events and a lack of geriatric knowledge could decrease the quality of healthcare for older adults. Therefore, geriatricians must improve health services for older adults. Korean policymakers need to determine directions by referring to health programs for older adults.

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### CONFLICT OF INTEREST

The researcher(s) claim(s) no conflicts of interest.

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### AUTHOR CONTRIBUTIONS

Conceptualization: YH, KYS, JEL; Data curation: YH, KYS; Investigation: YH, KYS, JEL, KK, BC, CWW; Methodology: YH, KYS, JEL, KK, BC, CWW; Project administration: YH, KYS, JEL, KK, BC, CWW; Supervision: KYS, KK, BC, CWW; Writing–original draft: YH; Writing–review & editing: KYS, JEL, KK, BC, CWW.

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# Effectiveness of an Exercise Program for Older Adults Using an Augmented Reality Exercise Platform: A Pilot Study

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**Background:** With the rapid progression of population aging worldwide, the health management of older adults is emerging as an important topic. To help prevent declines in physical and cognitive function due to aging, older adults must maintain consistent physical activity. The development of digital technology has recently allowed the optimization of exercise programs for older adults using augmented reality (AR) game technology. **Methods:** Fifteen older adult females were enrolled in an AR-based exercise program. The program was conducted for 30 minutes, three times weekly, for a total of 6 weeks. To verify the effectiveness of the program and assess physical function before and after exercise, the following tests were performed: timed up-and-go test, five times sit-to-stand test, 1-minute sit-to-stand test, lung capacity test, respiratory muscle strength test, and bioelectrical impedance analysis. The Trail Making Test was used to evaluate cognitive function. For statistical analysis, a paired t-test was used to verify the effects on physical and cognitive function before and after exercise. **Results:** The study results confirmed improved overall physical and cognitive function. The timed up-and-go test, maximal inspiratory pressure, and Trail Making Test part B scores showed significant increases. **Conclusion:** This study verified the effectiveness of AR exercise in community-dwelling older adult women. In the future, exercise programs with game elements that increase the interest and motivation of participants to engage in exercise routines should be developed and applied.

**Key Words:** Augmented reality, Aged, Exercise, Health services, Lower extremity

## INTRODUCTION

The global population is aging rapidly, with 73 million people aged 65 years or older in 2019. This figure is expected to double to 1.5 billion by 2050.[1)] As the older adult population increases, there is increasing interest in aging. Aging reduces physical function and activity and affects muscle strength.[2)] If muscle strength decreases, motor skills such as walking and balancing become difficult, thereby increasing the risk of falls.[3,4)] In Korea, 80.9% of older adults who visited the emergency room because of a fall reported moderate or higher degrees of physical injury that required medical intervention.[5)] Therefore, falls are a dangerous concern for older adults.

To prevent a decline in physical and cognitive function due to aging, older adults must maintain regular physical activity. Various exercise programs are used to increase physical activity in older adults. Studies have shown that older adults who participate in exercise programs have improved walking ability, lower-extremity muscle strength, grip strength, and cognitive function.[6,7)] Therefore, maintaining a high level of physical function by increasing physical activity can reduce the risk of falls in this population.[8)]

Various attempts have been made to improve physical function in older adults through strength, aerobic, and Pilates exercise programs geared towards this population.[9,10)] With progressive technological advances, exercise programs for older adults have been

developed in the form of games. Among these programs, exercise routines developed using virtual reality (VR) technology can create interest and increase exercise participation in older adults.[11] However, VR adaptation in older adults is severely limited by the inconvenience of wearing VR equipment on the face.

An alternative technology in game development is augmented reality (AR), which has an advantage over VR because of its ease of use in older adult populations.[12] However, most existing AR-based exercise programs prompt users to exercise by capturing movements using cameras, which are then viewed on a display monitor.[12] This limits the range of movement during exercise and reduces the amount of physical activity expended. Recently developed AR technology allows the exercise to be performed in a wider space because the beam is projected from the AR equipment onto the floor. This facilitates a broader range of motion and more intense physical activity through various exercises. Therefore, this study applied a recently developed exercise program using AR technology to older adult women and verified its effects on their physical and cognitive functions.

## MATERIALS AND METHODS

### Participants

This study included 15 community-dwelling older adult women aged 65 years or older (Table 1). The selection criteria included participants who could walk unassisted and had no problems accomplishing tasks of daily living. Participants with nervous system and musculoskeletal diseases who were unable to walk were excluded from the study. The ideal number of study participants was computed using an effect size of 0.7, an alpha error of 0.05, and a power of 0.80, according to previous studies. G*Power 3.1.9.4 was used for sample size calculation.[13] The study purpose and content were explained to all participants who voluntarily consented to participate. All participants consented to the use of their exercise photographs. This study was approved by the Institutional Review Board of the Pusan National University Hospital Ethics Review Committee (IRB No. 2209-007-118) and registered with the Clinical Research Information Service on the World Health Organization International Clinical Trials Registry Platform (Clinical Research Information Service No. KCT0008115). Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[14]

**Table 1.** General characteristics of the study participants

| Characteristic | Value |
|---|---|
| Age (y) | 70.47 ± 3.54 |
| Height (cm) | 156.27 ± 3.69 |
| Weight (kg) | 58.36 ± 6.64 |

Values are presented as mean±standard.

### Procedure

This study enrolled 15 older women in an exercise program using an AR exercise platform (DIDIM; Twohands Interactive, Busan, Korea) (Fig. 1). The exercise sessions ran for 30 minutes, three times weekly, for a total of 6 weeks. The exercise was facilitated using an AR game projected on the floor. The participants played the game by touching the floor controls with their feet. Before and after each exercise session, physical function was evaluated to confirm the effects of AR-based exercise.

### AR Exercise

The dedicated space for the AR game measured 4.5 m × 2.5 m. The AR equipment employs LiDAR sensors to detect and operate foot movements. The exercise program was configured for physical and cognitive function training and consisted of six routines. Tap steps, balloon pathfinding, catching bugs, speed cards, shape-stepping bridges, and random squares were performed sequentially (Fig. 2). Specifically, the tap steps involved moving both feet sequentially and rapidly in the direction of each foot, in a straight standing position (Fig. 2A). Balloon pathfinding required the participants to remember the order in which the balloons sparkled to step on and pop them (Fig. 2B). Catching bugs involved catching bugs projected onto the game floor by stepping on them (Fig. 2C). Speed cards required participants to use their feet to position the card displayed on the screen appropriately, either in the left or right direction (Fig. 2D). The shape-stepping bridge routine required the participants to memorize the shapes presented, culminating in crossing the bridge by stepping on the correct shapes

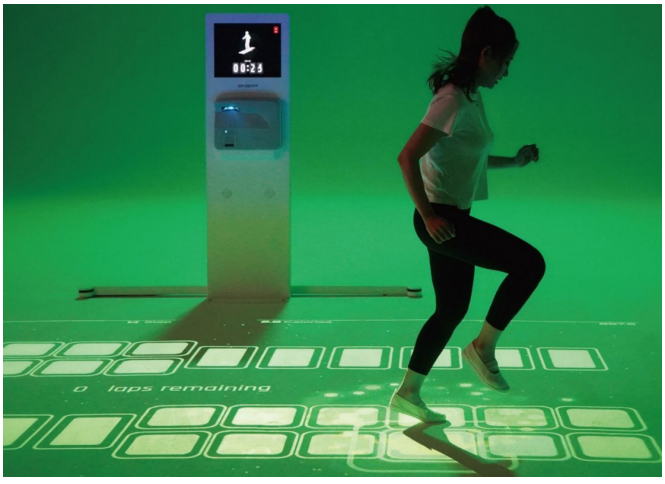


**Fig. 1.** The augmented reality (AR) exercise platform.

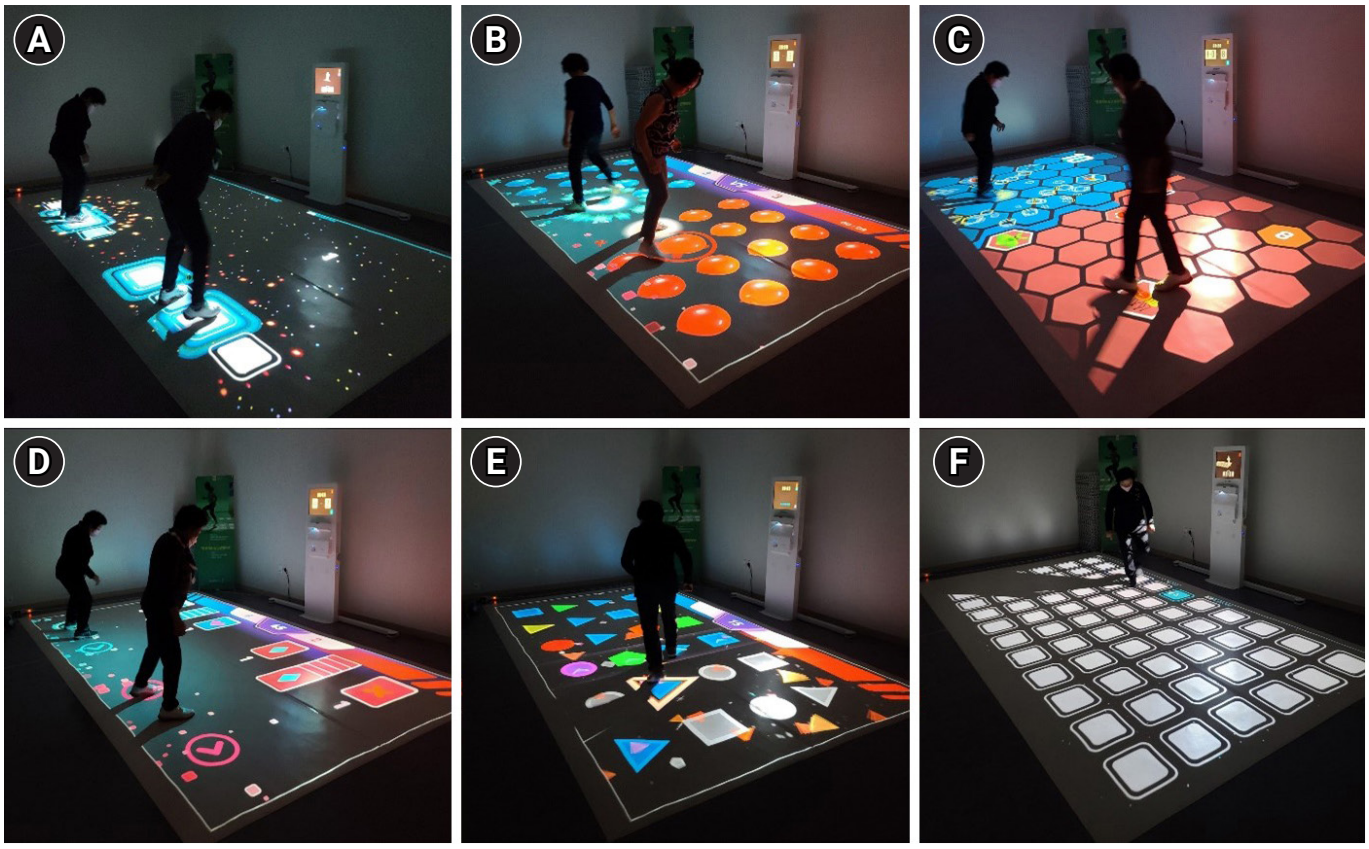


**Fig. 2.** The augmented reality (AR) exercise configuration involves the following games: (A) tap step, (B) balloon pathfinding, (C) catching bugs, (D) speed cards, (E) shape-stepping bridge movement, and (F) random square.

(Fig. 2E). Finally, random square was an exercise in which the participants were instructed to find randomly marked tiles with their feet (Fig. 2F). Each exercise was conducted for 5 minutes. When one exercise was completed, the next exercise was performed after a 1-minute break. As two people could exercise simultaneously, the participants were competitively motivated to improve their respective scores.

### Evaluation

To observe the effect of improving physical function in the study participants, lower extremity and respiratory functions were evaluated. In addition, bioelectrical impedance analysis was performed. The timed up-and-go test (TUG), five times sit-to-stand test (5TSTS), and 1-minute sit-to-stand test (1MSTS) were used to measure lower extremity function. TUG is an evaluation method that can identify the risk of falling in older adults by evaluating their balance ability.[15] This method measures the time required to stand up from a chair, move 3 m, and return to sit on the chair. The 5TSTS evaluates lower-extremity muscle strength.[16] The participants were asked to stand up and sit as fast as possible, five times. Both tests were performed twice and the minimum value was used. The 1MSTS can also evaluate lower-extremity muscle strength and function.[17] The evaluation is a measure of how many times the subject can stand up and sit on a chair in 1 minute.

Respiratory function was evaluated to assess lung capacity and respiratory muscle strength. Respiratory function was evaluated by a physiotherapist with 8 years of experience, trained according to guidelines from the American Thoracic Society/European Respiratory Society Task Force.[18,19] The lung capacity of the participants was measured for forced vital capacity (FVC) and forced expiratory volume in 1 second ($FEV_1$) using spirometry equipment (Pony FX; COSMED Srl, Rome, Italy). The respiratory muscle strength of the study participants was measured for maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) using respiratory strength measurement equipment (Pony FX). All evaluations were repeated three times after a 1-minute break after each. The highest values were used in this study.

In addition, bioelectrical impedance analysis (BIA) (InBody S10; InBody Co. Ltd., Seoul, Korea) was used to confirm the participants' body composition.[20] The Trail Making Test (TMT) was also used to evaluate cognitive function. The TMT is divided into Parts A and B, wherein visual perceptual ability, complex visual

scanning, and agility are comprehensively required.[21] Part A required connecting the displayed numbers by drawing a line through them in sequential order. Part B required the participants to alternately connect numbers and letters by drawing lines sequentially. Compared with Part A, Part B requires the additional ability to alternate between the use of cognitive functions and backward inhibition and maintain two types of parallel thinking.[22] The participants were encouraged to draw the lines at high speeds, and the time at which the inspection was completed was recorded.

### Statistical Analysis

The data collected in this study were analyzed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). The study data satisfied normality and the effects before and after exercise were compared using the paired t-test. The significance level $\alpha$ was set at 0.05.

## RESULTS

The results of applying the AR exercise program in older women are shown in Table 2. The TUG decreased from 7.05 ± 0.88 to 6.24 ± 0.58 ($p < 0.05$), the 5TSTS decreased from 8.11 ± 2.03 to 7.21 ± 1.05, and the 1MSTS increased from 39.60 ± 9.24 to 42.13 ± 8.37. In addition, the respiratory muscle strength MIP increased from 64.87 ± 18.97 to 68.87 ± 16.60 ($p < 0.05$) and the MEP increased from 79.00 ± 18.00 to 84.53 ± 16.54. The weight increased from 58.36 ± 6.64 to 59.38 ± 6.20 kg ($p < 0.05$), and body mass index (BMI) changed from 23.99 ± 2.75 to 24.43 ± 2.60 kg/m$^2$ ($p < 0.05$). In the case of BIA, the percent body fat (PBF) changed from 31.84% ± 5.77% to 32.29% ± 5.86%, skeletal muscle mass (SMM) changed from 21.21 ± 2.49 to 21.57 ± 2.52 kg ($p < 0.05$), skeletal muscle mass index (SMI) changed from 7.08 ± 0.69 to 7.09 ± 0.71 kg/m$^2$, and fat-free mass (FFM) changed from 39.59 ± 4.06 to 40.06 ± 4.09 kg ($p < 0.05$). Finally, regarding cognitive function, TMT_A decreased from 30.52 ± 6.52 to 27.34 ± 12.85 seconds, and TMT_B decreased from 76.25 ± 53.71 to 66.76 ± 60.55 seconds ($p < 0.05$).

**Table 2.** Exercise program application results

| | Pre | Post | p-value |
|---|---|---|---|
| TUG (s) | 7.05 ± 0.88 | 6.24 ± 0.58 | 0.001* |
| 5TSTS (s) | 8.11 ± 2.03 | 7.21 ± 1.05 | 0.072 |
| 1MSTS | 39.60 ± 9.24 | 42.13 ± 8.37 | 0.270 |
| FVC (L) | 2.25 ± 0.34 | 2.28 ± 0.30 | 0.446 |
| FEV1 (L) | 1.79 ± 0.27 | 1.83 ± 0.25 | 0.200 |
| FEV1/FVC (%) | 79.40 ± 4.70 | 79.73 ± 4.50 | 0.511 |
| FVC% | 102.27 ± 14.14 | 103.40 ± 12.92 | 0.476 |
| FEV1% | 99.40 ± 14.98 | 101.33 ± 15.72 | 0.217 |
| MIP ($cmH_2O$) | 64.87 ± 18.97 | 68.87 ± 16.60 | 0.016* |
| MEP ($cmH_2O$) | 79.00 ± 18.00 | 84.53 ± 16.54 | 0.186 |
| Weight (kg) | 58.36 ± 6.64 | 59.38 ± 6.20 | 0.003* |
| BMI (kg/m$^2$) | 23.99 ± 2.75 | 24.43 ± 2.60 | 0.003* |
| PBF (%) | 31.84 ± 5.77 | 32.29 ± 5.86 | 0.432 |
| SMM (kg) | 21.21 ± 2.49 | 21.57 ± 2.52 | 0.040* |
| SMI (kg/m$^2$) | 7.08 ± 0.69 | 7.09 ± 0.71 | 0.856 |
| FFM (kg) | 39.59 ± 4.06 | 40.06 ± 4.09 | 0.122 |
| TMT_A (s) | 30.52 ± 6.52 | 27.34 ± 12.85 | 0.233 |
| TMT_B (s) | 76.25 ± 53.71 | 66.76 ± 60.55 | 0.031* |

Values are presented as mean±standard.
TUG, timed up and go test; 5TSTS, five sit-to-stand test; 1MSTS, one-minute sit-to-stand test; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; MIP, maximum inspiratory pressure; MEP, maximal expiratory pressure; BMI, body mass index; PBF, percent body fat; SMM, skeletal muscle mass; SMI, skeletal muscle mass index; FFM, fat-free mass; TMT, trail making test.
*$p<0.05$, significant difference between pre- and post-exercise.

## DISCUSSION

The results of this study confirmed the effects of improving physical function by applying a 6-week AR-based indoor exercise program to older adult women. The participants in this study showed significantly increased TUG and MIP scores. In addition, significant changes in SMM and BMI were observed in BIA results. However, no significant changes in the numerical values of BIA were observed. Additionally, cognitive function also improved significantly.

The community-dwelling older adult women who participated in this study had healthy physical function. Previous studies on TUG, 5TSTS, and 1MSTS have confirmed that physical health status can be predicted using physical function tests before applying an exercise program.[16,23-26] The physical function of community-based older adult women was improved after 6 weeks of an AR-based physical exercise intervention. These results suggest that AR exercise programs should be considered to improve and maintain the physical health of healthy older adults.

In this study, only TUG improved significantly among the administered lower extremity function tests such as TUG, 5TSTS, and 1MSTS. The current exercise program was composed mainly of lower-extremity agility exercises and not muscle exercises. Therefore, the TUG test score, which contains the gait ability test component, increased significantly. However, no significant changes were observed in the 5TSTS and 1MSTS, both of which focused on lower extremity muscle strength. One explanation for the lack of significant changes in lower extremity muscle strength may be the low intensity and short intervention period of the exercise program. A previous study that applied exercise programs for 20 weeks in community-dwelling older adults reported no significant

change in the sit-to-stand evaluation in the first 10 weeks but observed a significant change by the 20th week.[27] In addition, a previous study that conducted high-intensity exercise in older adult women for 12 weeks showed significant improvement in the sit-to-stand evaluation after exercise.[28] The results of these previous studies suggest that significant changes in 5TSTS and 1MSTS may occur with longer intervention periods and higher-intensity exercises using AR content.

In this study, the respiratory function did not change significantly based on the lung capacity; however, MIP indicated a significant increase in respiratory muscle strength. While the MEP also increased, the results were not significant. Although the AR exercise program required increased levels of activity, we believe that it did not significantly impact lung capacity because the exercise was not of high enough intensity to increase lung capacity. Previous studies on aerobic exercises in young adult women suggested that lung capacity does not increase with short-term interventions.[29] However, previous studies have shown that lung capacity increases with high-intensity interval training.[30] Future studies are needed to test the hypothesis that providing sufficient high-intensity training, even for a short time, will affect lung capacity. However, a significant increase in respiratory muscle strength, indicated by MIP, in a state of unchanged lung capacity suggests that the inspiratory pressure of the thorax has increased without a change in the volume of the chest thorax.[31] This would have affected the respiratory muscle strength due to structural changes in the diaphragm caused by an increase in diaphragmatic activity, corresponding to an increased number of breaths during exercise.

Increased muscle mass is a positive factor in older adults.[32] The participants in this study had significantly increased weights and BMI after the exercise program. In the BIA results, only the SMM increased significantly. The PBF, SMI, and FFM did not differ significantly, while both muscle mass and fat mass increased. Sarcopenia is a risk factor for older adults and should be prevented by increasing or maintaining muscle mass through exercise programs.

This study assessed cognitive function using TMT. While TMT Part A showed an improvement, the change was not statistically significant. However, Part B exhibited a significant improvement. The marked improvement in cognitive function in older adult participants who engaged in this study's exercise program was similar to those reported previously.[7] Older adults who exercise regularly have better cognitive function due to continual blood, oxygen, and nutrient supply to brain cells due to physical activity.[33] Moreover, a study that conducted a mid-intensity exercise program for older adults with good cognition twice weekly for 16 weeks reported significant improvements in attentive concentration, immediate memory, and delayed memory among the cognitive functions of the frontal lobe.[34]

Over time, exercise programs for older adults have continually been developed and applied. Existing exercise programs have proven to be effective and exert positive effects on the quality of life and physical and cognitive functions of older adults.[9,35,36] However, the continuous repetition of simple exercises results in eventual disinterest. Therefore, it is crucial to add game elements to the exercise so that participants can continually experience the novelty of different exercises. Various digitalized equipment has been developed and applied in the field of exercise and will continue to be used in the future. In this increasingly digital environment, an exercise program that uses organized and easy-to-use digital equipment can allow consistent participation among older adults. The participants in this study remained interested in exercising using the AR exercise program with many game elements. In addition, the participants commented that they wanted to continue participating in the AR exercise program even after the end of the study. In the future, AR exercise programs should be implemented to improve the health of older adults.

This study has several limitations. First, the number of participants was small, as this was a pilot study. Future studies should recruit more community-dwelling older adults. Moreover, the exercise effect should be verified not only in older adult women but also in older adult men. Furthermore, an exercise program should be designed and conducted to improve muscle strength by adding muscle strength exercises content. Moreover, the exercise intervention period should be extended to obtain new results. Finally, because there was no control group, we could not compare the effects of other exercises. Future studies should verify the effectiveness of the AR-based exercise program by using a control group.

The results of this study confirmed changes in the physical and cognitive functions of older adult women who participated in a 6-week AR-based exercise program. The exercise program was confirmed to be effective even with the short intervention period of 6 weeks. In the future, more community-based exercise programs for older adults should be conducted, based on the AR exercise equipment used in this study. It is important to keep community-dwelling older adults interested in participating in exercise programs to manage their health.

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### CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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None.

**AUTHOR CONTRIBUTIONS**

Conceptualization, TSP, MJS; Data curation, TSP; Methodology, TSP; Project administration, MJS; Supervision, MJS; Writing–original draft, TSP.

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# A Case of Reversible Dementia? Dementia vs Delirium in Lyme Disease

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Lyme disease is an uncommon cause of reversible dementia. A 75-year-old male patient, with a personal history of mild memory deficit, was admitted to Alzheimer's Disease Care Unit due to hallucinations, confusion and aggressive behavior that are unresponsive to antipsychotic therapy. A computed tomography (CT) scan of the brain was negative, while blood exams showed a rise in inflammatory parameters. A complete screening of infective diseases showed a positive serology for *Borrelia burgdorferi*, confirmed at Western blot. Even though the patient refused cerebrospinal fluid (CSF) exam, the brilliant clinical improvement after the appropriate antimicrobial therapy is strongly suggestive for a diagnosis of neuroborreliosis. This case report underlines the importance of a diagnostic approach to dementia, as to find out and treat the reversible causes.

**Key Words:** Neuroborreliosis, Dementia, Lyme disease, Delirium, Cognitive impairment

## INTRODUCTION

The causes of cognitive impairment are multiple and not always clearly identifiable. As a consequence, the diagnostic process is often challenging. Cognitive impairment is usually seen as a condition destined to worsen and end in dementia, but a significant proportion of cases can be reversible. In this context, an accurate and timely identification of the underlying disease is critical. The present report has described a case of cognitive impairment (and possible delirium) due to neuroborreliosis.

## CASE REPORT

A 75-year-old man was admitted to our Alzheimer's Disease Care Unit of the Institute Golgi (Abbiategrasso, Italy) after having been discharged from a local hospital 2 weeks before with the diagnosis of "cognitive impairment, deficit of memory, and poor capacity of criticism compatible with degenerative disease."

The patient was a multilingual interpreter with a high school degree who loved walking in the countryside with its dog. His medical history included smoking habits, hyperlipidemia, an undocumented history of chest pain, and previous hospitalization for self-injurious behavior in affective psychosis.

At the recent hospital admission, his wife also reported that the patient had experienced knee pain for approximately a month, which had been treated with local infiltration without significant benefit. The pain worsened and tended to migrate to other joints. The woman said the patient had also been presenting with a mild memory deficit and ideomotor slowdown for the past couple of years. No mental confusion, aggression, or irritability was reported at home. The patient had preserved autonomy in the activities of daily living (ADLs) and most instrumental activities of daily living (IADLs).

During the previous hospital stay, brain computed tomography (CT) was performed. The examination showed slight enlargement of the ventricular system, an increased amount of peripheral cerebrospinal fluid (CSF), chronic vascular leukoencephalopathy, and signs of chronic inflammation in the left sphenoid sinus and some ethmoid cells. Blood test results were within normal ranges, except for increased indices of inflammation. The patient gradually be-

came confused and disoriented over time. He started presenting with hallucinations and aggressive behavior, requiring antipsychotic therapy and physical restraints to reduce the risk of self-injury.

Electroencephalography (EEG) was also performed, and and pathological anomalies could be excluded by the results of EEG. A neurologist was consulted for this purpose. He had described the presence of a confusional state of indeterminate genesis, recommending magnetic resonance imaging (MRI). However, this examination did not provide any relevant information. Viral and autoimmune causes on blood samples were also investigated, and the results were all negative. The urine culture test results were negative. Because of the persistence of elevated levels of inflammatory markers, empiric therapy with ceftriaxone was administered for approximately a week, without substantial benefits.

Before the hospital discharge, a second evaluation by the neurologist was conducted, classifying the case as "compatible with degenerative disease" with the subsequent referring of the patient to our center.

Upon admission, the patient was confused and disoriented. He experienced delusional ideas and persistent hallucinations. Wandering, aggressive behavior, and urinary incontinence were reported. Insomnia was another critical and hard-to-manage symptom. Migrant arthritis and acrodermatitis were also documented.

The Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR) scale, Barthel Index, and Tinetti scale scores were 22/30, 3/5, 35/100, and 7/28, respectively. The Comprehensive Geriatric Assessment showed frailty, functional dependence, and the worst outcomes in geriatric patients.

The Neuropsychiatric Inventory (NPI) underlined the presence of delusional ideas, hallucinations, irritability, depression, apathy, insomnia, and aberrant motor behavior objectives, with a final score of 80/144. The neuropsychological tests confirmed space, time, and self-disorientation. Memory loss and executive and attentional deficits were identified, along with the aforementioned symptoms. Aspects of aphasia (i.e., anomias and circumlocutions) were also described. A subsequent EEG was negative for epileptic anomalies. Clopixol, olanzapine, promazine, rivastigmine, and bromazepam were ineffective in controlling the symptoms.

Therefore, the diagnosis of dementia had been inconsistent. The negative findings of the instrumental tests and the fact that the patient, before hospitalization, was completely autonomous in the ADLs and IADLs, had no behavioral disorder, and only presented with a minimal memory disorder pushed toward the formulation of an alternative hypothesis.

Because arthritis was present, we excluded all infective causes not previously tested, including *Borrelia burgdorferi*. The patient tested positive for Lyme antibodies. Western blotting confirmed this result; however, the patient and his family refused CSF sampling.

Antibiotic treatment was initiated with intravenous ceftriaxone (2 g twice daily for 21 days). A cycle of low-dose prednisone was also administered to alleviate arthritis symptoms, and positive results were obtained. At the end of the antibiotic therapy, as the levels of inflammatory biomarkers remained elevated and neutrophilia was still present, oral doxycycline (200 mg/day for 7 days) was administered. Quetiapine was also administered for a short period to acutely control the hallucinations, after which it was discontinued.

Soon after 6–7 days of antibiotic therapy, delusional symptoms and hallucinations were attenuated, and insomnia improved. Urinary incontinence was completely resolved.

Clinical and neuropsychological evaluations at discharge revealed improved orientation (in space, time, and self), regression of delusional thoughts, and non-disturbing complaints of hopelessness. The behavioral profile also improved, with a reduction in agitation, aggression, and depression. The language was more fluent and communicative.

The memory loss and executive deficits persisted. However, the attentional deficit was attenuated compared with that before antibiotic therapy. The MMSE, CDR scale, NPI, Barthel Index, and Tinetti scale scores were 29/30, 2/5, 14/144, 62/100, and 25/28, respectively.

The informed consent for the publication of the case report was obtained.

## DISCUSSION

A detailed analysis, focused on premorbid assessment, is the first step in understanding early symptoms and their subsequent progression. The acute onset of cognitive symptoms and rapid deterioration of the behavioral profile in an autonomous person without a diagnosis of dementia or behavioral disorders should lead to the hypothesis that an inflammatory or infectious disease affects the central nervous system (e.g., meningitis, neurosyphilis, and Lyme disease).[1] This case report underlines the importance for geriatricians that old age and progressing cognitive decline do not always conclude for dementia.

First, we excluded bacterial and viral meningitis because the patient had no fever or typical symptoms (e.g., neck stiffness or focal neurologic deficits). In addition, the blood culture results were negative. We then explored the possibility of limbic encephalitis; however, the lack of a specific pattern in the examinations (i.e., MRI and immunological blood test screening) reduced the likelihood of the hypothesis.[2] We also hypothesized Creutzfeldt–Jakob

disease. However, the lack of ataxia and myoclonus and absence of signs on MRI and EEG reduced this possibility.[3] We could have conducted a CSF analysis to exclude this hypothesis; however, this was not possible.[4] Finally, a common infectious pathogenesis of the osteoarticular signs/symptoms and neurological manifestations was considered. As syphilis had already been excluded, the blood samples were analyzed for human immunodeficiency virus (negative result) and Lyme disease (positive result).

The patient confirmed a tick bite approximately 6 months before the beginning of the arthritis and could not exclude the possibility of other similar events, as he used to walk in the countryside. Migrant erythema, the first clinical sign of Lyme disease, was not observed. In contrast, the beginning of joint involvement, another typical sign of Lyme disease, was clearly evident. No clear cardiac condition or gait disturbance was reported in the patient's medical history, which sometimes occurs in Lyme disease.[2,5,6]

As for neurological symptoms, they particularly altered the cognitive and behavioral profile without signs of early neurological disorders, such as Bannwarth syndrome. The rapid onset of neurological conditions, hallucinations, delusional ideas, wandering, and aggressive behavior seemed to be associated with the manifestations of encephalitis in late neuroborreliosis.[7]

The major limitation of our case was the unavailability of CSF testing,[7,8] which could have further supported our diagnosis.[9] Accordingly, we reformulated the diagnosis of "delirium in Lyme disease." Finally, it is noteworthy that the lack of information about other comorbid conditions that can cause cognitive decline, except for a mild memory deficit and ideomotor slowdown over the past couple of years, does not exclude the possibility of pre-existing early mild cognitive impairment.

Therefore, a follow-up visit was organized for the patient at a local dementia and cognitive disorder outpatient clinic.

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### CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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### AUTHOR CONTRIBUTIONS

Conceptualization, CS, CP; Data curation, CC, TEP, MC; Investigation, CC, CS, CP, TEP; Methodology, CC, CS, CP, TEP; Project administration, CC, CS, CP, TEP; Supervision, CC, TEP, MC; Writing-original draft, CS, CP; Writing-review & editing, CS, CP.

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# Atypical Presentation of Acetylcholinesterase Inhibitor-Induced Diarrhea in Older Adults with Cognitive Decline: An Aspect not to be Underestimated

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The rivastigmine patch is the only existing transdermal delivery system used for the treatment of Alzheimer disease. Among the most common adverse events derived from its use are gastrointestinal events, particularly diarrhea. We report a clinical case of an 81-year-old patient admitted to our hospital under long-standing treatment with rivastigmine transdermal patch who presented with atypical watery diarrhea. Anamnesis showed that the patient presented with a likely infectious gastroenteric event, the diarrheal symptoms of which persisted upon resolution of the event and resolved only upon temporary discontinuation of acetylcholinesterase inhibitors. Failure to rapidly identify the causes of profuse diarrhea in older adults can have lethal consequences. When these symptoms occur, quickly recognizing the causes and providing proper management can be lifesaving.

**Key Words:** Rivastigmine, Cholinesterase inhibitors, Diarrhea, Infections, Gastroenteritis, Dementia

## INTRODUCTION

The rivastigmine patch is the only existing transdermal delivery system used for the treatment of Alzheimer disease (AD). This drug has been reported to be effective for patients with difficulty using oral preparations owing to the risk of aspiration pneumonia.[1)] However, such treatment is not without side effects. Indeed, a greater number of adverse events, such as cardiovascular events, have been reported in patients treated with acetylcholinesterase inhibitors (AchE-I) compared to a placebo.[2)] Although many types of adverse events have been reported, nausea, vomiting, and diarrhea were significantly more frequent in those receiving AchE-I compared to those receiving placebo.[3)]

Rivastigmine causes adverse events that are generally expected to occur with AchE-Is. They are usually mild to moderate, short-lived, and respond to dose reduction. Unpublished data from 3,989 patients indicated that rivastigmine and placebo were associated with a similar incidence of serious adverse events and changes in laboratory parameters, electrocardiogram (ECG), and cardiorespiratory vital signs. The most common events affected the gastrointestinal, central, and peripheral nervous, and cardiovascular systems. However, compared to placebo, rivastigmine more frequently caused adverse events that resulted in treatment discontinuation. These events were more frequent in the gastrointestinal tract (particularly diarrhea) despite other body system and more common in women than men.[4)]

The impact of diarrhea can be more pronounced in older adults than in younger patients for several reasons, including structural and functional changes in the intestines related to age, concomitant diseases, polypharmacy, alterations of the senses of hunger and thirst, decreased nutritional intake and hydration, frequent hospital admissions, higher antibiotic administration, and subtler clinical presentation.[5)]

We report a peculiar clinical case of a patient undergoing

long-standing treatment with a transdermal rivastigmine patch who was admitted to our hospital because of diarrhea.

## CASE REPORT

An 81-year-old patient was admitted to our acute care geriatrics department from the Emergency Room (ER) with diarrhea of unspecified origin and electrolyte imbalance. In his past medical history, he reported dyslipidemia, bilateral carotid atheromasia under treatment with low-intensity statins, cognitive decline in chronic cerebral vasculopathy under treatment with rivastigmine (9.5 mg patch) and escitalopram (10 mg), hypertension under treatment with amlodipine and olmesartan medoxomil, bilateral presbycusis in a hearing aid wearer, and recent left purulent otitis media treated with tympanoplasty. The patient was vaccinated against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) using three shots of the vaccine. Rivastigmine was prescribed approximately 24 months before the geriatric outpatient visit, and the schedule of dose titration was a 9.5-mg patch renewed every 6 months.

Watery diarrhea presented approximately 20 days before hospitalization in association with relapsing-remittent fever (maximum temperature 37.5°C) and was treated with rifaximin (800 mg bid), loperamide, and metoclopramide.

Blood tests performed in the ER documented acute renal failure (serum creatinine 2.2 mg/dL), severe hypokalemia (2.1 mEq/L), mild reduction of cholinesterase (2,701 IU/L), and leukocytosis (12,980 $mm^3$, 77% neutrophils). A nasopharyngeal swab tested negative for SARS-CoV-2. Plain abdominal radiography revealed hydroaeric levels in the right lumbar and iliac regions. Chest radiography revealed accentuation of the pulmonary pattern and other findings with no clinical significance. Full abdominal ultrasound showed no structural changes in the parenchymatous organs or fluid deposition in the explorable peritoneal recesses.

On admission, he presented with a fair clinical condition, alertness, and cooperation at examination despite his cognitive decline, lying in a neutral position. The vital parameters were within normal limits (temperature, 36.2°C; heart rate, 57 bpm; blood pressure, 100/60 mmHg; oxygen saturation, 99% on room air). Physical examination of the chest was unremarkable. The abdomen was soft and non-tender, although with some signs of meteorism. The diarrhea was characterized by more than four abundant ( > 100 mL) episodes per day. The stools were liquid with a yellowish color but not smelly.

At drug review, current antibiotic therapy with rifaximin, probiotics, and anti-diarrheal agents was discontinued. Fecal cultures, blood cultures, antigenic (glutamate dehydrogenase [GDH]) and molecular (nucleic acid amplification tests [NAAT]) *Clostridium difficile* tests, and parasitological examination performed during hospitalization were negative. Electrolyte solutions were administered to compensate for diarrheal losses. Because of persistent diarrhea, a second drug review was performed, and the rivastigmine patch was suspended, which resulted in diarrhea remission. Oral protein supplements were administered because of hypoalbuminemia without evidence of exacerbation of the diarrheal symptoms. Following gastroenterologic consultation and due to altered fecal calprotectin levels, the patient underwent thyroid blood tests, which revealed normal results. Ileocolonoscopy showed only internal hemorrhoids, and multi-level biopsies (ileum, right colon, transverse colon, and left colon) reported non-specific mild chronic inflammation.

The patient was discharged with activation of Home Care services to continue the rehabilitation program. The rivastigmine patch was reintroduced at discharge, first at starting dose of 4.6 mg/day and then, after 7 days, the pre-hospital dosage of 9.5 mg/day was reinstated. At the follow-up outpatient visit performed after 30 days, the patient and caregiver reported clinical stability and regression of diarrheal symptoms. The prescribed dose of a 9.5 mg/day rivastigmine patch was confirmed.

Informed consent for the processing of clinical data was obtained from the patient in the presence of the caregiver, in accordance with the best medical practice and ethics.

## DISCUSSION

The present clinical case report describes a peculiar case of adverse drug reactions that resolved successfully after discontinuation of the rivastigmine patch. Diarrhea is among the most important side effects listed in the technical data sheet of the drug (up to all tablet formulations); this effect is mainly linked to inadequate drug titration.[6] In this specific case, diarrhea occurred following a gastrointestinal event of a probable infectious nature and persisted despite the gastrointestinal infection because of increased cholinergic tone provided by the drug in use for 2 years, such that the diarrhea only resolved and reversed upon temporary discontinuation of the transcutaneous AchE-I.

Limited literature is available concerning this event. Cholinergic neurotransmission plays a key role in motility and secretory reflexes as well as in the intrinsic sensory and vascular reflexes of the intestine. Glial cells, which were not considered in the present investigation, could also be responsible for the observed influence of AchE-I on colonic motility as they detect acetylcholine through the M3 and M5 subtypes of muscarinic receptors.[7] With drug dosing administered in murine models, an approximately 50% re-

duction in AchE-I activity in colon tissue preparations and an approximately 50% increase in propulsion time (e.g., for donepezil) was achieved. Stool consistency, in turn, is highly dependent on transit time because of the duration of water reabsorption. This aspect should be considered when comparing microbiomes derived from patients with AD treated with different drugs.[5]

A multicenter clinical trial conducted in China to evaluate the efficacy and tolerability of the drug reported a 7.2% incidence of diarrhea in 222 drug-naïve patients with mild-to-moderate AD treated with rivastigmine capsules and followed for 16 weeks.[8]

Another study in African Americans studied donepezil administration for 12 weeks and observed a significant incidence of diarrhea (5.6%) among the side effects.[9]

In addition, the gastrointestinal side effects of AchE-I are more frequent during dose increase than during maintenance therapy.[10] This finding supports the hypothesis that the infectious overlap initiated diarrhea in the present case. In older adults, intestinal infections of bacterial or viral etiology are common, particularly norovirus (9.0%), followed by diarrheal *Escherichia coli* (DEC) (5.5%), rotavirus (3.9%), non-typhoidal *Salmonella* (NTS) (2.9%), and *Shigella* spp. (2.5%).[11] It is not always possible to isolate the pathogens involved, especially if testing is performed a distance from the acute event; in our case, a febrile event occurred several days before admission.[12] Other immune defense mechanisms include small intestine motility and commensal colon bacteria that protect the host. Drug-induced hypomotility can result in bacterial overgrowth, bile salt deconjugation, and diarrhea. Less commonly, diarrhea may occur because of hypermotility due to cholinergic syndrome.[13] Furthermore, age-related changes in gut microbiota with a shift towards a pro-inflammatory microbiome and higher local inflammation may make the guts of aged individuals more vulnerable to both infectious and non-infectious events.[14,15]

All the above-mentioned studies mostly refer to oral AchE-I therapies; limited literature has described the different types of administration (oral or transdermal). However, Osada et al.[1] reported a 4.2% occurrence of gastrointestinal complaints in patients using the rivastigmine patch.

In our case, the rivastigmine patch was probably responsible for the exacerbation of diarrhea. Possible confounders (e.g., other antibiotics) were ruled out, and an adequate wash-out was performed upon the patient's admission to the ward, without regression of the symptoms. It is assumed that similar physiopathogenetic mechanisms are common with both routes of drug administration (oral and transdermal), albeit less frequently with transdermal forms.

All caregivers and healthcare providers must be aware of the possible risks associated with polypharmacotherapy in older adults,[16] particularly with the use of AchE-I drugs. Therefore, it is of paramount importance to take measures to appropriately prescribe these drugs if there are well-founded suspicions.

Failure to rapidly identify the cause of profuse diarrhea in older adults can have lethal consequences. When these symptoms occur, the ability to recognize their causes and provide proper management can be lifesaving.

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### CONFLICT OF INTEREST

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# Preventing Osteoporosis, Sarcopenia and Obesity to Care about Quality of Life

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A recent review by Kumari and Khanna examined the prevalence of sarcopenic obesity using various comorbidities, diagnostic markers, and possible therapeutic approaches. The authors discussed the strong impact of sarcopenic obesity on quality of life (QoL) and physical health. In addition, there are significant interactions among bone, muscle, and adipose tissue, and the concomitant presence of osteoporosis, sarcopenia, and obesity, termed osteosarcopenic obesity, represents a terrible trio for postmenopausal women and older adults as each of these conditions is associated with adverse outcomes in terms of morbidity, mortality, and QoL in several domains. Timely diagnosis, prevention, and pro-health education are crucial for improving QoL in patients with osteoporosis, sarcopenia, and obesity. Education and prevention play a pivotal role in the long term for individuals to have longer and healthier lives. Osteoporosis, sarcopenia, and obesity share modifiable risk factors that may benefit from physical activity, a healthy and balanced diet, and lifestyle changes. "Prevention is better than cure" and planning are proven strategies for individuals and sustainable healthcare.

**Key Words:** Osteoporosis, Sarcopenia, Obesity, Quality of life, Aged, Frailty, Hip Fractures

Kumari and Khanna,[1] in a recent review, examined the prevalence of sarcopenic obesity using various comorbidities, diagnostic markers, and possible therapeutic approaches. The authors highlighted the strong impact of sarcopenic obesity on quality of life (QoL) and physical health.

Sarcopenia is defined by lower levels of three parameters: muscle strength, muscle quantity/quality, and physical performance as an indicator of severity. Advanced age and physical inactivity are among the main risk factors for osteoporosis[2] and sarcopenia.[3] The coexistence of these two conditions marks a complex clinical syndrome known as "osteosarcopenia."

The impact of osteoporosis on the QoL, economic costs, and health burdens is well documented in the literature. Osteoporosis affects 23.1% of women and 11.7% of men worldwide,[2] while Clynes et al.[4] estimated the global economic burden of osteoporotic fractures to be around $17.9 and £4 billion per annum in the United States and the United Kingdom, respectively.

Frost's mechanostat theory explains the deep interconnection between the bone and muscle quality and quantity. According to this theory, the mechanical load on the bone affects its quantity (bone mass) and architecture.[5] Subsequently, several molecular mechanisms have been identified based on hormonal crosstalk (growth hormone/insulin-like growth factor-1 and gonadal sex hormones), inflammaging (via the ubiquitin-protease pathway and increased levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha [TNF-α], interleukin-1 [IL-1], and IL-6), myokines (myostatin) and osteokines (osteocalcin), as well as the Wnt/β-catenin signaling pathway.[6] The drugs to treat osteoporosis, including bisphosphonates,[7] denosumab,[8,9] and romosozumab,[10] may also have "double effects" with beneficial effects on both bone and muscle.

Despite evidence of the protective effect of increased body fat mass on bone mineral density (BMD), the "obesity paradox" or "reverse epidemiology" remains controversial.[11] Some studies

have shown that osteoporosis is associated with lower BMD[12]; an increased expression of a pro-inflammatory phenotype, activation of the osteoclast-stimulating pathway, infiltration of adipocytes into bone tissue, and increased leptin secretion have explained this detrimental effect. However, higher levels of circulating estrogen and hyperinsulinemia have been reported to be protective against osteoporosis.[13] Therefore, understanding the complex interactions between bone and adipose tissue requires further investigation.

A decrease in muscle mass may be accompanied by an increase in fat mass, resulting in a condition called "sarcopenic obesity" or "sarcobesity," in which diseases associated both with obesity (insulin resistance, depression, cardiovascular disease, and hypertension) and sarcopenia (frailty, joint disorders, decreased muscle strength, and reduced functional capacity/disability) have a negative synergistic effect on the individual.[1]

The concomitant presence of osteoporosis, sarcopenia, and obesity, termed "osteosarcopenic obesity,"[6] represents a terrible trio for postmenopausal women and people of advanced age as each of these conditions is associated with adverse outcomes in terms of morbidity, mortality, and QoL in several domains (Fig. 1). A cross-sectional retrospective study by Kolbasi and Demirdag[14] reported a prevalence of 10.7% in community-dwelling older adults. Perna et al.[15] estimated a total prevalence of 6.86% (3.1% in males and 5.4% in females) in a population of older adults. Sarcopenia increases the risk of physical limitation and disability and is associated with a higher risk of falls, cognitive decline, reduced energy, and frailty.[3] Increased risk of fractures and hospitalization, loss of independence, pain, functional limitations, fear of falling, and inactivity negatively affect QoL in patients with osteoporosis.[16] Obesity increases the risk of coagulation alterations and chronic diseases such as diabetes mellitus, cardiovascular and cerebrovascular disease, degenerative articulation disease, cancer, and sleep apnea; it negatively impacts fatigue, energy levels, sleep quality, and rest.[17] Finally, all three conditions are associated with social isolation; psychological outcomes such as anxiety, fear, depression, and reduced self-esteem; and negative impact on the environmental domains of QoL, including security, finances, leisure, and information.[16-18]

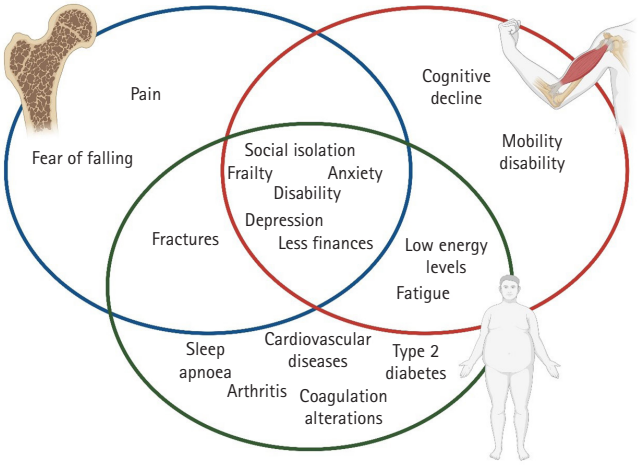


**Fig. 1.** Domains of quality of life affected by osteoporosis, sarcopenia, and obesity. Created with Biorender.com.

To improve sarcopenia awareness and treatment, the European Working Group on Sarcopenia in Older People (EWGSOP2) updated its definition and diagnostic strategies in 2018 to recommend an updated screening and assessment pathway that is easy to apply in clinical practice.[3] A recent study by Prado et al.[19] reiterates that screening is the only means to identify individuals at risk of hidden muscle loss and malnutrition. The SARC-F (strength, assistance walking, rising from a chair, climbing stairs, and falls) and the SARC-CalF (strength, assistance in walking, rising from a chair, climbing stairs-calf circumference) instruments can screen patients with sarcopenia. Surrogate instruments have been applied to identify low muscle mass in the absence of body composition techniques as not all body composition assessment methods are available in all clinical settings. Calf circumference is an anthropometric measure that correlates well with muscle mass, requires minimal training, and can be used with validated assessment tools within the Global Leadership Initiative on Malnutrition (GLIM) framework to help diagnose malnutrition.[20]

Considering the general aging of the population and the increase in chronic conditions, timely diagnosis, prevention, and pro-health education are crucial for improving health-related outcomes and QoL in osteoporosis, sarcopenia, and obesity. These three conditions share modifiable risk factors (Fig. 2) that may benefit from changes in lifestyle, physical activity, and diet (e.g., health and balanced diets such as the Mediterranean diet).[3,6,21-26] It is crucial to follow a healthy, balanced diet that limits the intake of foods high in fat or refined sugars and favors fruit and vegetable consumption to reduce obesity risk. Reducing stress, maintaining good sleep quality, and limiting sedentary time are also components of a healthy lifestyle that may play a role in preventing obesity.[21,27,28] High caloric intake due to excessive alcoholic beverage consumption fosters the deposition of excess adipose tissue and can also be a risk factor for the development of osteoporosis. Smoking is also a deleterious habit that can predispose individuals to osteoporosis. The potential measures to prevent bone loss include adequate calcium intake, increased sunlight exposure, and vitamin D intake, which have beneficial effects on sarcopenia.[22,29] Finally, dietary interventions and exercise are effective in preventing and treating

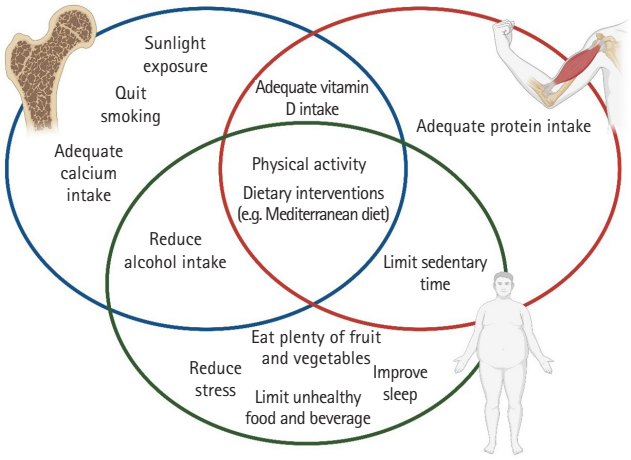


**Fig. 2.** Multi-dimensional interventions to prevent osteoporosis, sarcopenia, and obesity. Created with Biorender.com.

sarcopenia and physical disability in older people.[23]

Nutrition and exercise, parts of a healthy lifestyle, are efficient polypills for improving health outcomes and QoL. Awareness initiatives and education play a pivotal role in the long run for individuals to live longer and healthier lives. As wisdom reiterates, "prevention is better than cure," and planning represents a sure bet for individuals and allows for more sustainable healthcare.

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### CONFLICT OF INTEREST

The authors claim no conflicts of interest.

### FUNDING

None.

### AUTHOR CONTRIBUTIONS

Conceptualization, SC, CM, FL; Supervision, FL; Writing-original draft, SC, CM, FL; Writing-review & editing, SC, CM, FL.

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# The Korean Geriatrics Society News

## Courses and Conferences

Upcoming academic events in 2023 of the Korean Geriatrics Society.
We would like to invite members of the Korean Geriatric Societyand anyone who are interested.

[**The 71th Annual Meeting of the Korean Geriatrics Society**]
May 27-28 , 2023
Kim Dae Jung Convention Center
30, Sangmunuri-ro, Seo-gu, Gwangju, Republic of Korea.

## Membership Fee Information

**Membership Fee**

- Regular member (Certified by the Korean Geriatrics Society): KRW 20,000
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a. Should be a member of the Korean Geriatrics Society.
b. Should have more than 200 points recognized by the Korean Geriatrics Society.

**Benefits of Certification**
a. Discounted annual membership fee of KRW 20,000 (KRW 30,000 for general members).
b. Discount on registration fee for the Korean Geriatrics Society Meetings.

Guideline on Geriatric Medicine Certification
a. Qualifications: Those who passed the Geriatric Medicine Certification Exam
Those who had a medical license for over 5 years.
b. Certification fee: KRW 200,000
c. Procedure: Confirmation of acceptance → Confirmation of mailing address → Transfer certification fee to AGMR→ Certificate is sent by mail
Expiration policy: Valid for 5 years after acquisition
Ex. September 1, 2015 - August 31, 2020

* For doctors of earlier career with less than 5 years from acquiring license from Korean Medical Association, we encourage to take the examination for the geriatric certification. However, the geriatric certification will be valid only after 5 years since the license acquisition.

Renewal of Certification
a. Qualification: Those who earned 250 points or more within the validity period (5 years)
(The changes have been made to the article 8 of the Regulation on the Management in that one needs to earn 250 points and not 500 points for renewing the certificate.)
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→ Check mailing address
→ Send the certification renewal fee to the Korean Geriatrics Society
→ Certificate issued and sent by mail
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The Korean Geriatrics Society [Geriatric Disease ] has become an English-language journal named Annals of Geriatric Medicine and Research (Ann Geriatr Med Res, AGMR)". As a non-profit emerging global peer-reviewed journal based on Korea, we highly encourage our members to submit articles to AGMR.

## Submission Method

1. Journal website
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2. Manuscript revision according to submission guidelines
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3. Log in → Author → Article (new) Submission
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5. Submission Completed

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Annals of Geriatric Medicine and Research

# Instructions to authors

Enactment December 27, 2013
Revision March 1, 2021

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Manuscripts on geriatrics and gerontology, including clinical research, aging-related basic research, and policy research related to senior health and welfare will be considered for publication. Researchers from a wide range of geriatric specialties, multidisciplinary areas, and related disciplines of gerontology are encouraged to submit manuscripts for publication. AGMR is published quarterly on the last days of March, June, September, and December. The official website of AGMR is https://www.e-agmr.org/.

Manuscripts submitted to AGMR should be prepared according to the instructions below. For issues not addressed in these instructions, the author should refer to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/icmje-recommendations.pdf) from the International Committee of Medical Journal Editors (ICMJE).

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Copies of written informed consent should be kept for studies on human subjects. Clinical studies with human subjects should provide a certificate, an agreement, or the approval by the Institutional Review Board (IRB) of the author's affiliated institution. For research with animal subjects, studies should be approved by an Institutional Animal Care and Use Committee (IACUC). If necessary, the editor or reviewers may request copies of these documents to resolve questions regarding IRB/IACUC approval and study conduct.

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All authors of a manuscript must have agreed to its submission and are responsible for its content, including appropriate citations and acknowledgements; they must also have agreed that the corresponding author has the authority to act on their behalf on all matters pertaining to the publication of the paper. By publishing in this journal, the authors agree that the Korean Geriatrics Society

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### Reporting Guidelines for Specific Study Designs

For specific study designs, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, authors are encouraged to consult the reporting guidelines relevant to their specific research design. A good source of reporting guidelines is the EQUATOR Network (https://www.equator-network.org/) and NLM (https://www.nlm.nih.gov/services/research_report_guide.html).

### Composition of Manuscripts

The manuscript sections should be presented in the following order: Cover Letter, Title Page, Abstract and Keywords, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, and Figure Legends. Provide only one table or figure per page. Table 1 shows the recommended maximums of manuscripts according to publication type; however, these requirements are negotiable with the editor.

**Table 1.** Recommended maximums for articles submitted to AGMR

| Type of article | Abstract (word) | Text (word)[a] | Reference | Table & figure |
|---|---|---|---|---|
| Original article | Structured[b], 250 | 3,500 | 50 | 7 |
| Review | 150 | 6,000 | unlimited | 7 |
| Case report | 150 | 1,500 | 20 | 7 |
| Editorial | No | 1,200 | 15 | 7 |
| Letter to the editor | No | 1,200 | 15 | 1 |

AGMR, Annals of Geriatric Medicine and Research.

[a]Maximum number of words is exclusive of the abstract, references, tables, and figure legends.

[b]Background, methods, results, and conclusion.

### Title Page

The Title Page should include only the following information:

- Title: The title and the running title should be 25 or less and 10 or less words, respectively. Please consider the title very carefully, as these are often used in information-retrieval systems. Please use a concise and informative title (avoiding abbreviations where possible). The title should be written in sentence case (capitalize only the first word of the title and proper nouns).
- Author names and affiliations in the correct order: Where the family name may be ambiguous (e.g., a double name), please indicate this clearly. Present the authors' affiliation (where the actual work was done) below the names. Indicate all institutional affiliations, including the city and country, using lower-case superscript letters immediately after the author's name and in front of the appropriate address.
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    Sample:

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A concise and factual abstract is required. The abstract should not be more than 250 words (150 words for case reports and reviews). Abstracts should include the following headings: Background, Methods, Results, and Conclusion. Author(s) should specify the number of study participants. The abstract's conclusion should emphasize clinical relevance. Do not use vague phrases such as "We believe that …" or "We suppose that …". Non-standard or uncommon abbreviations should be avoided, but if essential, must be defined the first time they are mentioned in the abstract. After the abstract, list 3-5 keywords to be used for indexing. The keywords are from medical subject headings (MeSH; https://www.ncbi.nlm.nih.gov/mesh). Editorials and Letters to the editor do not require an abstract. An abstract is often presented separately from the article, and therefore must be able to stand alone.

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**Reference Style**

- Journal article:

1. Oh TJ, Song Y, Moon JH, Choi SH, Jang HC. Diabetic peripheral neuropathy as a risk factor for sarcopenia. Ann Geriatr Med Res 2019;23:170-5.

- Book:

2. Fillit H, Rockwood K, Woodhouse K, Young JB. Brocklehurst's textbook of geriatric medicine and gerontology. 8th ed. Philadelphia, PA: Elsevier; 2016.
3. Korea National Statistical Office. Annual report on the cause of death statistics, 2015. Daejeon: Korea National Statistical Office; 2016.

- Book chapter:

4. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh

JH, Brenner BM, editors. Hypertension pathophysiology, diagnosis, and management. 2nd ed. New York, NY: Raven Press; 1995. p. 465-78.
- Website:
5. AMA: helping doctors help patients [Internet]. Chicago, IL: American Medical Association; c2019 [cited 2019 Dec 22]. Available from: http://www.ama-assn.org.

**Tables and Figures**

Tables should be submitted separately from the main body of the paper, and figure legends should be typed on separate sheets.

- Table: Please submit tables as editable text and not as images. Avoid using vertical rules. Tables should be simple and should not duplicate information already presented in figures. Title all tables and number them using Arabic numerals in the order of their citation. Tables should be double-spaced, with each table on a separate sheet. Describe all abbreviations using footnotes. Footnotes are followed by the source notes, other general notes, abbreviation, notes on specific parts of the table (a), b), c), d)…), and notes on level of probability (*, **, *** for p-values). Each column and row should have an appropriate heading. The first letter of the first word in each column and row should be capitalized. Use Arabic numerals after "Table" in accordance with the order of citation, with a space between "Table" and the Arabic number. Mean and standard deviation (mean ± SD) and numbers of subjects are included and the significance of results is indicated through appropriate statistical analysis. The p-value should be provided to 3 decimal places and the letter "p" in "p-value" written in lower case. Table footnotes should be indicated with superscript markings. All units of measurement and concentration should be designated. Exponential terminology is discouraged. The table should be drawn in MS word and not as an image file (JPG, GIF, TIFF, etc.).
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**Other Manuscript Formats**

General guidelines are same as for original articles.

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- Case Reports
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