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Frailty, commonly defined as a state of increased vulnerability to potential stressors with decreased physiological reserve owing to aging, has long been considered a geriatric syndrome.\(^1\)\(^-\)\(^3\) Research interest in frailty has increased following observations of vast inter-individual heterogeneities in accumulating deficits or functional impairments among functional or biological parameters with the progression of chronological aging.\(^2\) In the last three decades, researchers have attempted to capture frailty in various ways, from operational definitions to counting percentages of deficits arising owing to human aging.\(^4\)\(^-\)\(^6\) Although their methods of determining or quantifying frailty differ, studies have shown correlations between frailty spectrums defined by phenotype definition or deficit accumulation.\(^7\)

The clinical relevance of frailty as an aging phenotype has been validated with respect to multiple aspects. By incorporating age-related parameters that are also interconnected to form complex systems of human physiology,\(^8\) the burden of frailty in individuals reflects a systemic disturbance in response to various stressors.\(^9\) Population-based longitudinal studies have assessed the ability of the frailty index in predicting mortality, an unequivocal outcome indicator of human aging.\(^10\),\(^11\) Similarly, studies on patients with medical or surgical conditions have reported the superiority of the frailty spectrum in predicting adverse health outcomes compared with conventional measures.\(^12\)-\(^14\) As a dynamic aging marker that responds to structured interventions, frailty is gradually becoming a cornerstone of geriatric medicine to deliver patient-centered management.\(^15\),\(^16\)

With recent advances in clinical and biological knowledge on frailty, the *Annals of Geriatric Medicine and Research* planned a special issue covering this geriatric syndrome from multifaceted aspects of biology, clinical medicine, and public health. In this issue, Ji et al.\(^17\) discussed frailty starting from molecular biology and demonstrated the validity of the frailty index as a measure of human aging compared to omics-based epigenetic clocks and biomarkers. Kwak\(^18\) discussed delirium, a geriatric giant and an important inpatient adverse outcome that occurs disproportionately in frail older people and can often be prevented by appropriate measures. Baek et al.\(^19\) reviewed the establishment and evolution of the Aging Study of Pyeongchang Rural Area (ASPRA), a cohort that was originally designed to determine the natural course of frailty in a Korean rural population and design effective interventional strategies that are feasible even in underserved regions in terms of healthcare resources.

The results of the studies support frailty as a clinically relevant measure of the human aging phenotype, with frailty a plastic and manageable geriatric syndrome. Unknowns still exist regarding the biology of frailty, which require further elucidation. While clinical interventions can improve frailty phenotypes and functional states, it remains unknown whether these improvements lead to the alleviation of the hallmarks of aging. Preclinical and early clinical studies have shown the potential to reverse or attenuate aging phenotypes with modalities related to energy metabolism or cellular senescence.\(^20\)-\(^22\) These efforts have attracted research interest in rejuvenation and reverse-aging technologies. Moreover, the results of these studies revealed that some parameters of physical frailty improve with the underlying biological aging status.\(^20\) Geriatric interventions with proven clinical efficacies should be assessed with endpoints such as aging biomarkers to provide bi-directional evidence of the relationship between aging biology and frailty to eventually support the biological roles of geriatric interventions in the human aging spectrum.

**ACKNOWLEDGMENTS**

**CONFLICT OF INTEREST**
Hee-Won Jung cofounded Dyphi Inc., a startup company on sensor technology.

**FUNDING**
This work was supported by the National Research Foundation of Korea...
REFERENCES


Frailty and Biological Age

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Received: July 26, 2021
Accepted: August 10, 2021

A reliable model of biological age is instrumental in the field of geriatrics and gerontology. This model should account for the heterogeneity and plasticity of aging and also accurately predict aging-related adverse outcomes. Epigenetic age models are based on DNA methylation levels at selected genomic sites and can be significant predictors of mortality and healthy/unhealthy aging. However, the biological function of DNA methylation at selected sites is yet to be determined. Frailty is a syndrome resulting from decreased physiological reserves and resilience. The frailty index is a probability-based extension of the concept of frailty. Defined as the proportion of health deficits, the frailty index quantifies the progression of unhealthy aging. The frailty index is currently the best predictor of mortality. It is associated with various biological factors and provides insight into the biological processes of aging. Investigation of the multi-omics factors associated with the frailty index will provide further insight.

Key Words: Aging, Healthy aging, Frailty, Gene expression, DNA Methylation

INTRODUCTION

As we age, our ability to withstand damage and stress declines, and the incidence of disability, disease, and mortality increases.¹ Time underlies all these biological processes and events. As it is universal and readily available, calendar age is a popular estimate of the rate of biological aging in daily life. Indeed, as living matter constantly and dynamically changes with time, numerous age-related changes occur throughout all organizational levels, from molecular to organismal to populational levels. With increasing age, however, age-related changes occur at varying rates.² For example, older individuals of a certain chronological age differ in their physical and cognitive functioning. Thus, biological aging is heterogeneous and often disproportionate with the amount of time passed.

In addition to heterogeneity, plasticity is another property of biological aging that chronological age cannot accommodate. Tales abound of a Fountain of Youth or a Chinese emperor who sought an elixir of life that would enable him to live forever. Experimental evidence suggests that these mythical or legendary tales may not be entirely baseless. The pace of aging may be delayable or even reversible. The evidence is mostly based on genetic or interventional studies using model organisms such as yeast, fruit flies, nematodes, mice, and even monkeys.³⁻⁵ When mutated, many genes can modify the lifespans of non-mammalian model organisms. Some of these genes include SIR2 in brewer’s yeast,⁶ daf-2 in nematodes,⁷ and methuselah in fruit flies.⁸ Gene therapy using genes involved in aging or age-related disease extended both lifespan and health span in mice.⁹ Pharmaceutical and nutritional interventions, such as the administration of the immunosuppressive drug rapamycin and calorie/dietary restriction, also significantly extended the lifespan and improved the fitness or health of model organisms.³⁻⁵

Biological age is equivalent to physiological or functional age, whereas chronological age is physical or mathematical. As aging progresses, mortality increases exponentially not because time passes at an exponential speed but because aging-related detrimental events occur exponentially. The biology of aging concerns the biological processes of aging, which occur separately from the invariant passage of time. Thus, a reliable measure of biological age will better suit our pursuit of precision gerontology or personalized geriatrics. While the hallmarks of aging have been described,¹⁰ the
mechanisms underlying biological aging remain largely unknown. One approach to the biology of aging is to model biological age and investigate its associated factors.

**MODELS OF BIOLOGICAL AGE**

Different types of cells age differently. Heterogeneity in tissue aging contributes to the heterogeneity of aging in different organs and body systems. Thus, no single biological marker of aging can faithfully represent organismal aging. Biomarkers of aging have long been sought from age-related changes; however, the relevance of all age-related changes to the biology of aging remains unknown. As some age-related changes may not be relevant to the biology of aging while others constitute the true mechanisms of aging, multiple biomarkers of aging are used to estimate or models the true biological age. Epigenetic age-based models of biological age were first proposed a decade ago, and all such models are based on DNA methylation data. Another type of biological age models that has been gaining momentum is based on frailty. These frailty-based models use health deficits or health-related changes found in aging individuals. We will first discuss models based on epigenetic age before reviewing frailty-based models of biological age.

**Epigenetic Age Models**

Genomic DNA methylation sites that we are currently focusing on are conveniently called CpG sites as the methylation of cytosine occurs predominantly in CpG dinucleotides ("p" represents the phosphodiester bond linking the nucleotides). A recent study compiled 11 epigenetic age models, one of which was based on 71 CpG sites in the leukocyte genome. These CpGs were selected using a regularized regression method, which showed that their DNA methylation levels were highly correlated with chronological age. The predicted epigenetic age was obtained using actual methylation data in the regression model. Individuals with epigenetic ages greater and less than their calendar ages are categorized as fast aging and slow aging, respectively. Similarly, DNA methylation age and related measures were calculated based on 353 CpGs whose methylation levels were highly correlated with chronological age in multiple tissues. A change in epigenetic age depends on a change in the methylation levels of selected CpGs. As shown in Fig. 1, a decrease in the overall DNA methylation level of 353 CpGs resulted in decreased epigenetic age. Since the genomic DNA methylation level tends to decrease with increasing chronological age, the epigenetic age is likely to decrease with increasing chronological age among the oldest of older individuals.

Recent epigenetic age models combine health-related data with DNA methylation data using complex multi-step mathematical or statistical approaches. “DNAm PhenoAge” is based on 513 CpGs associated with the Gompertz model-based phenotypic age. This phenotypic age incorporates laboratory blood test findings and chronological age. Other models use CpGs as proxy markers for age-related changes or biological events. For example, age-correlated CpGs have been combined with biological data to build a mitotic-like clock model to predict cancer risk. “GrimAge” uses CpGs that are selected by regressing plasma proteins and smoking on 485,000 CpG sites and chronological age.

Epigenetic-based models of age are associated with mortality. Slow epigenetic aging is associated with healthy aging-related factors such as healthy diet, physical activity, lifestyle, and low morbidity. This is potentially interesting in that healthy aging is determined largely by non-genetic factors, including various environmental factors and lifestyle, and DNA methylation is an epigenetic interface between genes and non-genetic determinants. Nevertheless, the biological function of the DNA methylation level in CpGs used in the models remains unknown.

The human genome contains an estimated 28 million CpGs. A cross-sectional compilation found that approximately 11% of 485,577 CpGs examined were significantly correlated with chronological age and approximately 30% of them also significantly changed longitudinally. If we assume random sampling of CpGs examined, the DNA methylation of approximately 3 million CpGs甲methylation-age.
CpGs in the genome is correlated with chronological age, and 0.9 million of them will change longitudinally. With that many age-associated CpGs, one can select any subset of CpGs to predict chronological age or any age-associated changes. One can even select a subset of CpGs in the genome to predict any randomly generated numeric variable (Table 1). Note that in Table 1, the variable importance scores generated using a random forest method for the randomly generated numeric variable are comparable to those for the frailty index. Similar results were obtained using the regularized regression method. The abundance of CpGs associated with chronological age may also explain why subsets of selected CpGs used in epigenetic age models overlap sparsely (Fig. 2). Thus, the biological roles of these CpGs, if any, remain unknown.

**Biological Functions of CpG Sites Associated with Age**

DNA methylation affects important biological phenomena such as gene expression, DNA imprinting, X-chromosome inactivation, and genome stability. Of these, differential gene expression is most relevant to the biology of aging. Changes in the other phenomena tend to have drastic, often pathological, effects, although their contributions to the biology of aging cannot be completely ruled out.

The transcriptional regulation of gene expression is primarily mediated by DNA sequence-based genetic factors. DNA methylation also affects gene transcription via epigenetic mechanisms. Following the erasure of DNA methylation patterns of the previous generation, genomic DNA of fertilized eggs is methylated de novo in a tissue-specific manner during implantation and differentiation—the erasure seems incomplete, which explains in part why DNA methylation is heritable. DNA methylation may serve as a safety lock to ensure the long-term repression of certain genes. For genes whose expression is responsive to environmental

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**Table 1.** Top 10 DNA methylation sites associated with the prediction of age, frailty index, or a sequence of randomly generated numbers

<table>
<thead>
<tr>
<th>CpG site</th>
<th>Importance</th>
<th>CpG site</th>
<th>Importance</th>
<th>CpG site</th>
<th>Importance</th>
</tr>
</thead>
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<td>12.9</td>
<td>cg02271560</td>
<td>12.0</td>
</tr>
<tr>
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<td>27.0</td>
<td>cg26188685</td>
<td>4.6</td>
<td>cg10332616</td>
<td>7.9</td>
</tr>
<tr>
<td>cg26811352</td>
<td>14.9</td>
<td>cg01290856</td>
<td>4.4</td>
<td>cg26565544</td>
<td>4.9</td>
</tr>
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<td>14.5</td>
<td>cg23765086</td>
<td>4.2</td>
<td>cg09981070</td>
<td>4.7</td>
</tr>
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</tr>
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<td>3.7</td>
</tr>
<tr>
<td>cg01874084</td>
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</tr>
<tr>
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<td>cg05304366</td>
<td>3.2</td>
<td>cg10697491</td>
<td>3.4</td>
</tr>
</tbody>
</table>

---

*a* The calendar ages (60–103 years) of 211 participants in the Louisiana Healthy Aging Study were regressed on DNA methylation values (beta) of 10,000 randomly selected CpG sites using a random forest regression method in R. 

*b* The same random forest as in *a*, with a frailty index, FI34, instead of calendar age.

*c* The same random forest as in *a*, with a variable of randomly generated numbers instead of calendar age.

*d* Probes used to assess DNA methylation levels of the CpG sites using the Infinium HumanMethylation450K BeadChip Kit (Illumina Inc., San Diego, CA, USA).

*e* Scaled permutation-based variable importance scores calculated using the random forest.
Disability is defined as the inability to perform activities of daily living, while frailty along with disability, comorbidity, or even old age. One practicable definition of frailty is age greater than 65 years and dependence on others to perform activities of daily living. Disability is defined as the inability to perform activities of daily living, while frailty along with other morbidities contributes to disability. Frailty may develop from diminished physiological reserve before disability, comorbidity, or other adverse outcomes. Frailty is a multidimensional phenotype that manifests through various signs, symptoms, or other health-related events. To operationalize frailty as a clinical syndrome, the Fried frailty uses five phenotypic criteria: (1) weight loss (> 10 lb in the previous year); (2) self-reported exhaustion; (3) muscle weakness (the lowest quintile of hand grip strength); (4) slow gait speed (the lowest quintile in walking time per 15 feet); and (5) low physical activity (the lowest quintile in kilocalories expended per week). Individuals meeting three or more of these criteria are considered frail. Related to the Fried frailty, Edmonton frailty uses nine criteria: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance. The maximum score of Edmonton frailty is 17.

Geriatric status classification in clinical settings requires a streamlined operationalization of frailty. Based on activities of daily living, a clinical frailty scale has been proposed to classify older people. A recent version of the Clinical Frailty Scale (CFS) has nine categories, from “very fit” to “terminally ill.” It relies on the level of dependence in daily living activities and clinical judgment. The CFS is simple, inexpensive, and easy to perform but has been criticized as potentially subjective. However, a recent study of the CFS reported a general agreement of participants in diverse medical professions and health occupations in the classification of scenario cases. The CFS was a significant predictor of survival of patients with coronavirus disease (COVID-19) and the outcome of coronary artery bypass grafting.

**FRAILTY/DEFICIT INDEX**

The criteria for frailty scales described above yield semiquantitative measures. By including more health items and using a continuous scoring method, one can build a fully quantitative model of frailty. The frailty index is defined as the proportion of health deficits among a set of surveyed health items. The deficit index uses the same calculation method as the frailty index. The health items include various symptoms, signs, disabilities, and diseases. These data are collected from medical history questionnaires, clinical assessments, laboratory measurements, and other data collection instruments. As the proportion of health deficits that an aging individual carries at the time of survey, raw frailty index scores range from 0 (no deficit in all health items surveyed) to 1 (at least one problem in every health item). Unlike frailty scales, calculation of the frailty index does not require a fixed set of specific health items. When the number of health items is sufficiently large (typically ≥ 20), different frailty indices based on different sets of health items yield comparable properties and performances. However, including health items with predictive power can significantly improve the performance of a frailty index.

**Frailty Index as a Model of Biological Age**

The end of aging is death, and the oldest of older adults (those aged > 90 years) are most prone to this and other adverse outcomes. The frailty index shows an age-dependent exponential increase with mortality (Fig. 3). Frailty index scores vary among aged peers and may decline individually while their group average increases over time, accounting for the heterogeneity and plasticity of aging. In the general population, chronological age is a strong
predictor of mortality and other time-dependent phenomena. The Klemera-Doubal models of biological age, termed therein Equa-
tion 25 (BE) and Equation 34 (BEC), outperformed chronologi-
cal age and biological age measures based on multiple linear regres-
sion or principal component analysis in predicting mortality.53,54) This finding makes sense in that both health data and chronologi-
cal age are used in the derivation of BE and BEC. In particular, 
BEC explicitly incorporates chronological age as an additional bio-
marker to improve its performance over BE. After adjusting for age 
and sex, however, the frailty index outperformed not only DNA 
methylation age but also both BE and BEC in predicting mortality 
in the oldest of older adults (Fig. 4). Thus, the frailty index is the 
best predictor of age-related mortality.

**Biological Factors Associated with Frailty or Frailty Indexes**
The frailty index quantifies the extent of unhealthy aging. In other 
words, it is an unhealthy aging index (and subtraction of it from 1 
gives a healthy aging index). Therefore, examining biological fac-
tors associated with the frailty index can provide insights into the 
biological mechanisms of unhealthy (or healthy) aging.

The resting metabolic rate (RMR) estimates the amount of en-
ergy used for the maintenance of body systems under resting con-
ditions. RMR, which comprises 60%–70% of the total daily energy 
expenditure, decreases with increasing age in the general popula-
tion.55) In the oldest of older adults, however, RMR increases as the 
frailty index increases.56) One interpretation of this is that a higher 
RMR is required for this population to maintain homeodynamics 
as their health deteriorates. Some factors also show sex specifici-
ties; for instance, the association of frailty index with body com-
position (fat and fat-free mass) is specific to female nonagenarians, 
whereas circulating creatine kinase (CK) is specific to male nona-
genarians. Detailed analyses of these sex specificities led to the 
identification of the associations of UCP2 and UCP3 with frailty 
index in women57) and XRCC6 and LASS1 in men.58) UCP2 and 
UCP3, which encode uncoupling proteins in the mitochondria, 
function as metabolite transporters important in energy metabo-
lism. In contrast, XRCC6 and LASS1, which encode the protein 
Ku70 and ceramide synthase, respectively, are involved in pro-
grammed cell death. Muscle damage caused by strenuous physical 
activity or exercise is a major factor leading to elevated blood CK 
levels.59) Thus, one interpretation of the male-specific findings is 
that an elevated CK level reflects an increased number of damaged 
muscle cells undergoing programmed death.58)

The genetic basis of longevity is not as substantial as previously 
estimated, indicating that non-genetic and environmental factors 
are much more influential in aging.60) Frailty is associated with var-
ious transcriptomic, proteomic, and metabolomic factors.61-68) 
Overall, the number and species of identified omics factors vary 
across studies and no omics factors have been convincingly repli-
cated in multiple independent studies. Nevertheless, several stud-
ies merit further investigation. CK is a major protein associated 
with the Fried frailty scale.53) Although it is unknown whether the 
association is specific to males, the proteomics finding is consistent 
with the previous association using the frailty index,60) as described 
above. In their proteomics study, Sathiyan et al.52,59) analyzed plas-
ma proteomic profiles using the same technology but different de-

![Fig. 3. Exponential increase in the frailty index and mortality. (A) Box plot of FI28 scores of 592 individuals in the Louisiana Healthy Aging 
Study.51) FI28 is a frailty index based on 28 health items. Each box represents an inter-quartile range with the line in the middle showing the medi-
an position. (B) Proportions of the deceased in the same age groups.](image-url)
dependent variables. Based on the frailty index as a dependent variable, the fatty acid-binding proteins showed the most significant association, while proteins that showed enrichment in the bioinformatic analysis were involved in lipid metabolism, cell-to-cell signaling, and interactions. For chronological age, the most significantly associated proteins were pleiotrophin, WNT1-inducible-signaling pathway protein 2, chordin-like protein 1, transgelin, and R-spondin-1, while the bioinformatically enriched proteins were related to inflammatory response, organismal injury and abnormalities, and cell and organismal survival. Thus, these two studies further demonstrated that the biological factors and pathways associated with the frailty index differed from those associated with chronological age. In other words, the biological interpretations or hypotheses to test depend on which dependent variable is used in the association analysis. Therefore, it is critical to use a reliable and accurate metric of biological age.

While single omics analysis is useful, aging is a complex phenomenon that occurs across interconnected, yet heterogeneous, biological systems. The simultaneous analysis of multiple omics data obtained from the same specimens can greatly enhance the accuracy of data analysis and interpretation. Therefore, integrative multi-omics using a reliable measure of biological age may be a more useful approach for elucidating the biology of aging.

CONCLUSION

One fruitful approach to understanding the biology of aging is to establish a reliable measure of biological age and study its associated biological factors. Epigenetic age models, which are based on DNA methylation data, are promising in that lower epigenetic ages are associated with healthy aging and DNA methylation is considered an interface between the genome and environment. However, the biological significance and function of epigenetic model ages and model CpGs are yet to be elucidated. Frailty reflects the deteriorating physiological processes of aging. The extent of frailty is fully quantifiable by calculating the proportion of various health deficits. The frailty index is the best predictor of mortality, especially among older patients. Thus, the frailty index is a simple
A mathematical and easily rationalized method of quantifying biological age. Various biological factors are associated with frailty index, providing valuable insights into various aspects of aging. Simultaneous analysis of multi-omics datasets using the frailty index may be a fruitful approach to understanding the biology of aging.

ACKNOWLEDGEMENTS

We thank the people of Louisiana for their participation in our study. Lixin Ji participated in the research and manuscript preparation as a recipient of the Acquiring Skills and Practice in Research Excellence (ASPIRE) fellowship at Tulane School of Medicine.

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

This work was supported by grants from the U.S. National Institutes of Health (No. AG022064, AG027905, and GM103629), the Louisiana Board of Regents through the Millennium Trust Health Excellence Fund (No. HEF[2001-2006]-02), and the Louisiana Board of Regents RC/EEP Fund through the Tulane–LSU CTRC at LSU Interim University Hospital.

AUTHOR CONTRIBUTIONS

Conceptualization, SK; Data curation, LJ, SMJ, SK; Writing–original draft, LJ, SK; Writing–review & editing, LJ, SMJ, SK.

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54. Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological
Delirium and frailty are both important geriatric syndromes that commonly occur among older adults. Delirium is an acute medical condition characterized by changes in mental and cognitive status and usually occurs among hospitalized older adults, with a prevalence ranging from 15% to 75%, depending on the clinical setting. Frailty is a chronic condition characterized by decreased functional status and increased vulnerability to various stressors, with a prevalence ranging from 12% to 24%. Although they are different conditions, delirium and frailty also share commonalities and have overlapping features. This study reviewed the definitions and pathophysiologicals of these two geriatric conditions, described their similarities and differences, and provided current evidence of delirium management among older adults with frailty.

Delirium and frailty are prevalent geriatric syndromes and important public health issues among older adults. The prevalence of delirium among hospitalized older adults ranges from 15% to 75%, while that of frailty ranges from 12% to 24%. The exact pathophysiology of these two conditions has not been clearly identified, although several hypotheses have been proposed. However, these conditions are considered to be multifactorial in etiology and are associated with inflammation related to aging, alterations in vascular systems, genetics, and nutritional deficiency. Furthermore, clinically, they are significantly associated with each other, for example, frailty increases the risk of delirium almost two- to three-fold among hospitalized older adults. With their multifactorial etiology and unknown pathophysiology, current evidence supports more practical multicomponent patient-centered approaches to prevent and manage delirium among hospitalized older adults. These comprehensive and organized bundled approaches can identify high-risk patients with frailty and more effectively manage their delirium.

Key Words: Frailty, Delirium, Geriatric assessment
health problem that is associated with poor clinical outcomes. Delirium is independently associated with a two- to four-fold increased risk of mortality, a pattern that has been mostly consistent across various clinical settings and illnesses.6-16) The additional adverse outcomes of delirium in older adults include prolonged hospitalization, higher chances of discharge to nursing homes, declines in cognitive function, and increased healthcare costs.2,6,13-17,19) Pathophysiology of Delirium While the pathophysiology of delirium remains unclear, its etiology is widely accepted to be multifactorial. Delirium was previously considered to be a disorder of neurotransmitters such as acetylcholine, melatonin, dopamine, norepinephrine, glutamate, 5-hydroxytryptamine, serotonin, histamine, and/or gamma-aminobutyric acid.20) However, more recent theories suggest that the pathophysiology of delirium is more complex. For example, delirium may result from a combination of neurotransmitter disorders coupled with a failure in processing sensory signals or motor effectors and a breakdown in the brain network. Furthermore, such conditions may interact with neuroinflammation, excess oxidative stress, neuroendocrine dysfunction, circadian rhythm, or melatonin dysregulation.20) This complex pathophysiology of delirium becomes more complicated in patients with acute medical illnesses. Acute illnesses such as sepsis or pneumonia can cause brain hypoperfusion and impair glucose supply, subsequently leading to insufficiency of brain bioenergetics and breakdown of the brain network.21,22) However, the alterations in body composition in older adults, including a reduction in lean mass and an increase in fat mass, could also play an important role in the development of delirium by adding more inflammatory stimuli via the endocrine secretion of pro-inflammatory adipokines.23) FRAILTY Epidemiology of Frailty Frailty is a clinical condition characterized by a progressive decline in homeostatic capacity and increased vulnerability to endogenous and exogenous stressors.5,24,25) Frailty is prevalent among older adults, and along with the growing aging population, it is an important public health issue worldwide.5) Although it varies across studies and diagnostic tools, the prevalence of frailty worldwide ranges from 8% to 24%.3,4) In America, the prevalence of frailty based on physical phenotype and deficit accumulation models was 17% and 23%, respectively.4) Furthermore, as the consequence of increased vulnerability to various stressors, frailty is associated with an increased risk for adverse health outcomes, including a decline in functional status, prolonged length of stay in the hospital, increased risk of institutionalization, and higher mortality.5,24,25) Pathophysiology of Frailty Like delirium, the pathophysiology of frailty has not been completely elucidated. Furthermore, despite its significance in public health and its association with negative health outcomes, there is no internationally agreed definition for frailty. Two models are widely used to assess frailty: the frailty phenotype25) and the deficit accumulation frailty index.20) The frailty phenotype views frailty as a condition with certain clinical characteristics based on the presence or absence of specific physical conditions such as weight loss, exhaustion, weakness, low walking speed, and decreased physical activity. The deficit accumulation frailty index assesses frailty using the scale of the total burden of age-related health deficits in older adults, including symptoms, signs, diseases, and disabilities.30) Regardless of approach, age-related changes in multiple physiological systems or organs with certain characteristics are the foundation of the development of frailty. Among physiologic changes in the aging body, alterations in the neuromuscular, neuroendocrine, and immunological systems play important roles.30) Furthermore, changes in each system interact cumulatively, leading to an overall decline in function, eventually reaching the threshold beyond which older adults’ capacity to sustain minor stress is compromised.31) SIMILARITIES AND DIFFERENCES BETWEEN DELIRIUM AND FRAILTY As both delirium and frailty result from the disintegration of balance and homeostasis across multiple body systems, they are intuitively related and share several commonalities. They occur commonly among older adults, are multifactorial in their etiology, and are associated with poor clinical outcomes, including increased risk of functional loss, institutionalization, and mortality.32) The exact pathophysiologies of these conditions have not yet been identified, although they share common biologic processes, including inflammation, alterations in vascular systems, genetics, and nutritional deficiency in their development (Fig. 1).33) As individuals age, their levels of circulating inflammatory cytokines increase, a condition that may be heightened in frailty. With higher baseline cytokine levels, the pro-inflammatory response to stressors becomes more prominent, making individuals more susceptible to stressors and explaining the development of both delirium and frailty.34,35) Additionally, alterations in the vascular system, particularly small vessel disease, have been associated with geriatric syndromes. As common geriatric syndromes, delirium and frailty are
also likely to be associated with small vessel diseases. \(^{35}\) Moreover, frailty is a subclinical marker of cardiovascular disease, and delirium occurs twice as often among individuals undergoing cardiovascular surgery compared with that among patients undergoing orthopedic or abdominal surgeries.\(^{37-39}\) Malnutrition, reduction in caloric intake, and subsequent weight loss are prevalent in older adults and may lead to sarcopenia and thus frailty.\(^{10}\) According to the phenotype frailty model, weight loss is a prominent characteristic of frailty.\(^{20}\) Furthermore, malnutrition is considered an important predisposing risk factor for delirium.\(^{21}\)

Although frailty and delirium share common features, as described above, there are also differences between the two conditions (Fig. 1). Frailty results from a long-term decline in functions across an individual’s multiple systems, and its process is considered chronic and progressive. In contrast, delirium is an acute process or reaction to a newly introduced stressor. Delirium may progress and resolve rapidly compared to frailty, although full recovery could take weeks or even months.\(^{23}\) Delirium is mainly characterized by alterations in mental and cognitive functions, while frailty is more often characterized by changes in physical function and the accumulation of physical deficits. When multiple insults affect an already susceptible individual, the brain may not compensate, leading to delirium.

**DELIRIUM IN FRAIL OLDER ADULTS**

Therefore, despite their differences, from a practical perspective, frailty and delirium show important overlapping pictures: individuals already vulnerable to various stressors, e.g., older adults with pre-existing frailty, are at a greater risk for delirium. Several studies on the association between delirium and frailty in older adults showed that frailty was associated with an increased risk of delirium compared to those who do not have frailty. In 2018, a systematic review and meta-analysis of 999 patients by Presco et al.\(^ {42}\) showed a 2.19-fold increased risk of delirium among frail patients (risk ratio [RR] = 2.19; 95% CI, 1.65–2.91). Although limited to surgical patients, a meta-analysis of the cohort study by Fu et al.\(^ {43}\) reported that frailty patients had an increased risk for delirium, with an odds ratio (OR) of 3.23 (95% CI, 2.56–4.07). More recently, in 2021, Zhang et al.\(^ {44}\) reported a meta-analysis study including 217,623 patients and showed that frailty was associated with an increased risk for delirium compared to the risk in patients without frailty (OR = 2.96; 95% CI, 2.36–3.71). They also conducted further analyses to assess the association in different patient groups. Frailty was associated with a 2.43-fold increased risk of delirium (95% CI, 1.88–3.14) in selective surgical patients, a 3.61-fold increased risk (95% CI, 1.65–7.89) in medical patients, a 3.76-fold increased risk (95% CI, 2.88–4.92) in surgical patients, and a 6.66-fold increased risk (95% CI, 1.41–31.47) in emergency or critical patients (Table 1).\(^ {45}\)

However, the studies also found significant heterogeneity in the instruments used to identify delirium and frailty. These instruments include at least 10 different frailty index or scales (including but not limited to the frailty phenotype, FRAIL Scale, Frailty Index, Clinical Frailty Scale, Edmonton Frail Scale, Erasmus frailty score, Emergency General Surgery Frailty Index, Japanese version of the Cardiovascular Health Study criteria, Groningen Frailty Indicator, mobility impairment, Clinical judgment frailty, Kihon Checklist score, and Comprehensive Geriatric Assessment) and more than five measurement tools for identifying delirium (the Confusion Assessment Method for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; the intensive care delirium screening checklist; the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; the Confusion Assessment Method for the intensive care unit, the Delirium Rating Scale Revised-98; and the interRAI-Acute Care for Comprehensive Geriatric Assessment).\(^ {45,46}\) Although more studies have examined the interplay between frailty and delirium, historically, studies on this topic have not been sufficient. In their 2017 systematic review, Presco et al.\(^ {42}\) identified only 20 studies eligible for systematic review and eight studies for the meta-analysis. Fortunately, more studies have been published since that time; in 2020, Zhang et al.\(^ {44}\) identified 30 studies for their meta-analysis. It is promising that the association between frailty and delirium is receiving more attention because the number of patients who may experience these two geriatric conditions is likely to increase along with the rapidly growing number of older adults worldwide.
ROLE OF THE INTERACTION BETWEEN FRAILTY AND DELIRIUM IN CLINICAL OUTCOMES

Although it is reassuring that more studies on these two important geriatric syndromes are being conducted, exactly how their interplay results in adverse clinical outcomes and to what extent it affects outcomes remain unknown. As both frailty and delirium are independently associated with adverse clinical outcomes, patients with frailty who develop delirium during hospitalization may experience worse clinical outcomes. However, the existing literature is scarce and is mainly limited to outcomes of mortality or surgical patients as the populations. Furthermore, given the overlapping characteristics between frailty and delirium, frailty may act as a confounder in the association between delirium and clinical outcomes. The inconsistent results from various studies support this hypothesis. Eeles et al.45) assessed the impact of frailty on mortality among older inpatients who had delirium in a single-center study and reported that frail patients had greater long-term mortality among those with delirium compared with that among those without frailty—median survival of 88 days (95% CI, 5–171) for frail patients vs. 359 days (95% CI, 118–600) for fit patients. However, Mazzola et al.46) reported that delirium alone was not associated with mortality after adjusting for frailty, supporting the role of frailty as a confounder in the association between delirium and clinical outcomes. The inconsistent results from various studies support this hypothesis. Dani et al.47) conducted a survival analysis to identify the impact of delirium on frailty in hospitalized older adults; interestingly, they reported an inverse gradient of association, with a stronger association observed in the fitter group and a higher hazard ratio for delirium in patients with a lower frailty index.

In addition to mortality as a clinical outcome, Ogawa et al.48) assessed the impact of postoperative frailty on major adverse cardiac events after cardiac surgery in a single-center study. They reported that delirium increased the risk of postoperative frailty (HR = 2.98; 95% CI, 1.46–6.20). Moreover, postoperative frailty increased the risk of a major cardiac adverse event after cardiac surgery (HR = 2.21; 95% CI, 1.01–4.82). However, after adjusting for delirium, preoperative frailty was not significantly associated with major adverse cardiac events after discharge.

CHALLENGES IN CLINICAL PRACTICE FOR OLDER ADULTS WITH THE COEXISTENCE OF DELIRIUM AND FRAILTY

Given the high prevalence and complex interactions between the two conditions, managing older adults with both frailty and delirium also becomes challenging. One of the most important challenges in clinical practice is that these two conditions are usually under-recognized, despite their strong associations with adverse clinical outcomes. Hospitalized older adults may experience different types of delirium, including hyperactive, hypoactive, mixed, and without motor symptoms.49) However, while hyperactive delirium, mixed-type delirium, or delirium without motor symptoms is easily recognized because of their distinguishing behaviors, hypoactive delirium may occur more commonly than hyperactive delirium.50-51) Moreover, several studies reported a worse prognosis among patients with hypoactive delirium compared with those among patients with hyperactive delirium.52,53) The under-recognition of delirium may increase its adverse impact on various clinical outcomes. Frailty is also easily missed in clinical practice because there is no standardized systematic screening tool, and some measures are not practical to perform in routine clinical settings.49) For example, Beckert et al.55) reported frailty in a high proportion of patients (68.8%) deemed to be surgical candidates and referred for surgeries. They speculated that physicians did not recognize a patient’s frailty at the time of referral for surgery. As frailty is a risk factor for delirium, under-recognized frailty among hospitalized older adults can result in a higher incidence of delirium and associated adverse clinical outcomes. Similarly, since delirium may increase the risk of postoperative frailty, the early recogni-

Table 1. Recent meta-analysis studies of the association between delirium and frailty

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Number of pooled participants</th>
<th>Increased risk of delirium due to frailty (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presico et al.,42) 2018</td>
<td>999</td>
<td>2.19 (1.65–2.91)</td>
<td>Meta-analysis mainly included observational studies</td>
</tr>
<tr>
<td>Fu et al.,43) 2021</td>
<td>3,250</td>
<td>3.23 (2.56–4.09)</td>
<td>Meta-analysis only included postoperative patients</td>
</tr>
<tr>
<td>Zhang et al.,42) 2021</td>
<td>217,623</td>
<td>2.96 (2.36–3.71)</td>
<td>Subgroup analyses of different types of hospitalizations</td>
</tr>
</tbody>
</table>

- Selective surgical patients (OR = 2.43; 95% CI, 1.88–3.14)
- Medical patients (OR = 3.61; 95% CI, 1.65–7.89)
- Urgent surgical patients (OR = 3.76; 95% CI, 2.88–4.92)
- Emergency or critical illness patients (OR = 6.66; 95% CI, 1.41–31.47)

CI, confidence interval; OR, odds ratio.
tion, prevention, and proper management of delirium is also important for providing optimal care for older adults in hospitals. Another challenge is that as much as they are ignored in routine clinical settings, studies assessing the prevalence of the coexistence of the two conditions or their combined impact on patient outcomes are also scarce. Most studies have focused on the association between these two conditions. Individual estimates for each study with relevant information in the most recent systematic review study by Zhang et al.44) showed a prevalence of the coexistence of the two conditions ranging from 2% to 26%. Studies with a high prevalence (> 20%) had cohorts with an older age group (mean age, 82.3 or 82.1 years) or included only critically ill patients. Studies with older age groups included patients in either acute general medicine wards45) or an acute geriatric unit.53) However, some studies also showed relatively high prevalence, approximately 15%, in a relatively younger population (mean age, 71 years) and in patients undergoing selective surgery.55) Nevertheless, accurate determination of the association between the prevalence and age or type of admission will require more investigations and systematic reviews. Moreover, very few studies have assessed the impact of the coexistence of the two conditions on patient outcomes. Eeles et al.45) reported that the combination of delirium and frailty was associated with poor survival among patients admitted to general medicine wards. A single-center study by Gandossi et al.57) revealed that the combination of frailty and postoperative delirium was associated with poor functional status upon discharge among hospitalized patients with hip fracture (RR = 1.47; 95% CI, 1.28–1.69). Kwak et al.58) estimated the economic outcomes of various combinations of three geriatric syndromes—delirium, frailty, and dementia—among patients who underwent transcatheter aortic valve replacement procedure and reported that delirium with frailty but without dementia showed the strongest association with higher hospital cost (a 45.1% increase in hospital cost; 95% CI, 26.45–66.45).

**FUTURE DIRECTIONS**

**Identifying High-Risk Patients with Frailty**

The exact pathophysiologic mechanisms of the impact of these two geriatric syndromes on adverse clinical outcomes may be difficult to decipher given their overlapping characteristics. However, previous studies have reported that both frailty and delirium are associated with adverse clinical outcomes; therefore, it is critical to identify these two conditions among hospitalized older adults. Regardless of whether frailty directly or indirectly increases inpatient mortality, since older adults with frailty are at higher risks for both mortality and delirium, identifying these conditions at an early stage during hospitalization is critical for maximizing patients’ clinical outcomes. Subsequently, the American College of Surgeons recommends frailty screening as a part of preoperative assessments, and frailty screening has been tested in various clinical settings.59,60) However, one impediment to such efforts is the lack of consensus on the gold-standard tool for evaluating frailty, as evidenced by the significant heterogeneity in evaluation tools described in previous systematic review or meta-analysis studies.62) Nevertheless, efforts are ongoing to customize frailty assessment tools to accommodate the conditions and specialties of individual clinical settings.44,62,63) Surgery is one specialty that has been actively incorporating frailty assessment in routine preoperative evaluations.43) In orthopedic surgery, Krishnan et al.63) explored the use of a frailty index that was integrated into a comprehensive geriatric assessment for hip fracture patients. More specific frailty assessment tools based on the patient population have also been validated, including the 15-item Trauma-Specific Frailty Index for trauma patients and the 15-variable Emergency General Surgery Specific Frailty Index for patients undergoing emergent surgeries.56,67) In cardiovascular surgery, frailty assessment has become an important part of preoperative assessments to determine if a patient qualifies for less-invasive surgical options such as transcatheter aortic valve replacement rather than surgical aortic valve replacement.63) Additional efforts to facilitate the use of frailty screening in the clinical setting include the incorporation of frailty assessment into the electronic health record system for the convenience of providers and further research on frailty.

**Management of Delirium in Hospitalized Older Adults**

Despite efforts to identify higher-risk patients with frailty, delirium still occurs among hospitalized older adults. The management of delirium in patients with frailty should not differ significantly from the standard management for delirium. The best strategy for preventing delirium among older adults is through multicomponent non-pharmacologic interventions. In their meta-analysis, Hshieh et al.70) showed that a multicomponent non-pharmacologic intervention reduced the incidence of delirium, decreased the length of stay, and improved cost-effectiveness. Moreover, implementing such systematic interventions would reduce the under-recognition of delirium, especially hypoactive delirium, which could be easily missed in routine clinical settings. Indeed, there are several existing models that hospitals could adopt to prevent delirium. Among these, the Hospital Elder Life Program (HELP), developed by Inouye, is one of the most widely used.71-73) The HELP model encourages hospitals to utilize interdisciplinary teams and volunteers to provide practical interventions. These interventions include reorientation of the patient, promo-
tion of physical mobilization, therapeutic activities, enhancing nutrition, sleep hygiene, and hearing or visual adaptations. The ABC-DEF bundle is another care model that can be used in an intensive care setting. It is a bundled approach to address multiple components of patient care as follows: “A” element: Assess, Prevent, and Manage Pain; “B” element: Both Spontaneous Awakening Trials and Spontaneous Breathing Trials; “C” element: Choice of Analgesia and Sedation; “D” element: Delirium—Assess, Prevent and Manage; “E” element: Early Mobility and Exercise; and “F” element: Family Engagement and Empowerment. Such bundled multicomponent approaches that allow healthcare providers to evaluate the components of frailty domains should be beneficial for patients with frailty.

However, the real challenge is that the implementation of such multicomponent interventions requires important resources, which could make the effort non-achievable and non-practical. Alternatively, since the implementation would require an important shift in institutional culture, it may also face barriers from the hospital staff. One of the solutions could be the most recent movement in delirium prevention, the Age-Friendly Health System by the Institute for Healthcare Improvement, and the John A. Hartford Foundation, in partnership with the American Hospital Association and the Catholic Health Association of the United States. The Age-Friendly Health System initiative suggests that the healthcare system focus on a set of four evidence-based elements for high-quality care, known as the “4Ms”: (1) What Matters—align care strategy with the patient’s values or goals; (2) Medication—avoid inappropriate medications; (3) Mentation—recognize delirium, depression, and/or dementia; and (4) Mobility—promote mobility. Under these four core values for a better quality of care, each healthcare institution can create specific strategies based on its available resources. For example, an institution can choose its own method of assessing mentation (delirium) or mobility (frailty) based on its existing routine practice or documentation tools. In this way, they can incorporate multicomponent interventions to prevent delirium.

As much as multicomponent non-pharmacologic interventions are critical for preventing delirium, the same philosophy regarding multicomponent non-pharmacologic approaches should be applied to the management of delirium. Delirium commonly showed multiple etiologies; thus, the management of delirium should focus on addressing all possible causes of delirium. One strategy is the use of a convenient step-wise approach using the mnemonic DELIRIUM as follows. First, the management of delirium should focus on evaluating and treating modifiable contributors to delirium, including Drug, Electrolyte disturbances, Lack of drugs, Infection, Reduced sensory input, Intracranial disorders, Urinary and fecal disorders, and Myocardial and pulmonary disorders. Second, the management of delirium should address the prevention and management of any complications such as urinary incontinence, immobility and falls, pressure ulcers, sleep disturbance, and feeding disorders. Then, we should ensure that the patient is comfortable and safe based on the application of behavioral interventions such as de-escalation techniques for agitated patients, family engagement, or pharmacologic interventions, including low-dose antipsychotics, when absolutely necessary. The final step of delirium management is to restore function by optimizing the hospital environment (minimizing clutter and noise and providing adequate lighting and or familiar objects at the bedside), cognitive reconditioning by reorientation, physical therapy, occupational therapy, family support, family participation, and, finally, appropriate discharge planning. These approaches allow the early identification of older adults with frailty to identify high-risk patients, prevent delirium, provide proper management of delirium, and prevent further deterioration of physical dysfunction or disability, while simultaneously addressing the components of frailty (Fig. 2).

Although non-pharmacological interventions should be the first-line treatment, there may be cases in which the patient requires pharmacological intervention. Low-dose antipsychotics can be considered in patients who become severely agitated and non-verbal or for whom verbal de-escalating techniques are not effective. However, there has been a debate regarding the use of antipsychotics for hyperactive delirium. Recent systematic reviews have reported different findings. Riviere et al. found evidence that quetiapine and olanzapine could be alternatives to haloperidol; however, because of the high levels of heterogeneity among studies, they could not perform a meta-analysis. In contrast, anoth-
A systematic review by Nikooei et al. concluded that there was insufficient evidence to support the routine use of haloperidol or second-generation atypical antipsychotics for the management of delirium. Furthermore, although there is no superior medication that has shown better efficacy, most antipsychotics can cause adverse effects such as prolonged QT interval or extrapyramidal symptoms. Therefore, the choice of antipsychotics is often based on their potential side effects and the patient’s specific conditions. Nevertheless, specific medication may be indicated in particular cases. For example, benzodiazepine could be first considered for patients with delirium caused by alcohol withdrawal; patients with contraindications to the use of antipsychotics, including neuroleptic malignant syndrome or Parkinson’s disease; or patients with dementia with Lewy bodies or seizure disorder.

Geriatric Co-management Model for the Optimal Management of Delirium and Frailty

As described above, the pathophysiology and management of delirium and frailty require multiple and simultaneous interventions from several different aspects. While these requirements appear holistic and ideal, they are not feasible in busy and highly specialized surgical wards. Therefore, there has been increasing awareness of geriatric co-management and management by both the primary team and geriatricians for high-risk older adults in hospitals. Most studies assessing the effects of geriatric co-management focused on the orthopedic geriatric population. Several studies reported that multidisciplinary geriatric consultation for patients with hip fracture surgery resulted in a reduced incidence of delirium and improved overall quality of care. Therefore, the idea of geriatric co-management has expanded in surgical oncology. Shahrokni et al. conducted a cohort study to assess the impact of geriatric co-management in older adults undergoing surgery for cancer, in which geriatricians provided delirium risk-reduction interventions. However, the main outcome in that study was 90-day postoperative mortality. While the intervention group (geriatric co-management) showed lower 90-day mortality, the authors did not report the impact on delirium incidence. Nevertheless, the geriatric co-management model could be a solution for optimal delirium prevention and management among older adults with physical frailty. Thus, additional studies are warranted.

CONCLUSION

Delirium and frailty are highly prevalent geriatric syndromes among older adults and are associated with adverse clinical outcomes. While the exact pathophysiology of these two conditions remains unclear, the etiology is multifactorial. Although they are distinct conditions, delirium and frailty share similarities and are significantly associated. Hospitalized older adults with frailty are more likely to develop delirium. Thus, the identification of high-risk patients with frailty is critical for the proper management of delirium. Given the multifactorial etiology of delirium and frailty, the prevention and management of delirium must incorporate a multicomponent patient-centered approach to improve the quality of care among hospitalized older adults.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researcher claims no conflicts of interest.

FUNDING

None.

REFERENCES


The Aging Study of Pyeongchang Rural Area (ASPRA): Findings and Perspectives for Human Aging, Frailty, and Disability

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Received: September 4, 2021
Revised: September 23, 2021
Accepted: September 24, 2021

INTRODUCTION

The accumulation of diseases and functional deficits with age has resulted in the development of care models for the aging population to address healthcare and welfare issues that may differ among individuals.1) Population-based longitudinal studies are corner-
stones for studying the natural course and healthcare impact of aging-related conditions, such as frailty and sarcopenia.4,5) Studying these age-related conditions requires distinct features, such as the availability of functional measures that cover multiple facets of human health, as both baseline parameters and outcome measures. However, these functional parameters have been considered less important than disease- or organ-related factors in traditional population-based studies or drug development studies targeting chronic diseases in younger adult populations.4)

Korea has developed policies to meet the care needs of the growing aging population. These policies include long-term care insurance, which started in 2009.3) As the number of older people increases, care demands to serve these populations threaten to overwhelm the Korean health system. Researchers have noted unmet needs for effective management strategies using concepts from geriatric medicine to prevent functional decline in community-dwelling older adults,6,7) as the results of early Korean studies have suggested that frailty is a common geriatric condition associated with future adverse health outcomes.6,8) However, to our knowledge, when the Aging Study of Pyeongchang Rural Area (ASPRA) was conceptualized in 2014, no longitudinal population-based studies had comprehensively recorded geriatric functional and medical parameters, including frailty and physical performance, in Korea.7)

To provide evidence on the longitudinal functional outcomes according to geriatric parameters, the cohorts have to meet following characteristics: (1) participants of the cohort should be representative of the target population;10) (2) outcome measures should include functional parameters, mortality, and state of institutionalization into facilities, including nursing homes or convalescent hospitals;11,12) and (3) for long-term outcomes, attrition rate should be as low as possible.13) As a rural area surrounded by mountains, most of the population of Pyeongchang county depends on healthcare services from the community health posts (CHP) of the public sector network for medical services, which are operated by the Ministry of Health and Welfare, including annual vaccination for influenza and health examinations. As agriculture is the main industry in this area, the annual population movement rate has been innately low in Pyeongchang county, with the annual immigration or emigration rates being < 5% of the total population. Therefore, by targeting the older population of this area registered in the CHP network, the cohort may easily meet the requirements to provide information regarding long-term outcomes.

Hence, the ASPRA was designed to capture these in-depth geriatric features in a longitudinal study. The researchers hypothesized that frailty is a dynamic phenotype of human aging, a modifiable condition addressed by multicomponent interventions designed with geriatric principles targeting person-centered problems in mobility, nutrition, medication, and social needs. In the present study, we aimed to (1) evaluate the impact of baseline geriatric features on the natural course of functional changes, (2) develop and validate appropriate screening tools for geriatric conditions, including frailty, targeting massive older populations or resource-limited public health settings, and (3) establish individual-centered health promotion schemes, which are both effective and feasible even in resource-limited rural areas, to delay the incidence of disabilities due to frailty. This review summarizes the findings of observational and intervention studies from the ASPRA to obtain future perspectives in designing community-based public health strategies targeting age-related conditions.

ASPRA DESIGN AND POPULATION

The ASPRA is a population-based, prospective, rural cohort study of older adults living in Pyeongchang county (total population 43,592; aged ≥ 65 years, 24% in 2017) in Gangwon province, Korea. The study was initially designed and established without a specific funding source and planned to leverage the opportunity to interview eligible participants for routine annual influenza vaccination by volunteering health care personnel of CHP in the study area. Afterwards, this study was mainly supported by the Pyeongchang County Hospital, Asan Institute for Life Science, and the Division of Geriatrics at Asan Medical Center. Several national grants and philanthropic personal donations also partially contributed to the funding.

The eligible participants in the ASPRA were aged 65 years and older, registered in the National Healthcare Service (NHS), ambulatory with or without an assistive device, living at home, and able to provide informed consent by themselves or via their proxies. Participants who had lived in a nursing home, hospital or received nursing home-level care at home were excluded. Potentially eligible participants were screened using the NHS member registry and received an email or a phone call to visit the CHP for annual checkups or vaccination. The study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea (No. 2015-0673) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

More than 90% of the eligible population in Pyeongchang participated in the ASPRA. Their sociodemographic characteristics were similar to those of the national sample of rural population, apart from the high proportions of individuals without a formal education (44% vs. 22.6%) and currently working (mostly in agri-
culture) (60.7% vs. 39%), observed in the first year of the study.

The cohort gradually expanded its footprint in Pyeongchang county. The study that had initiated with 382 participants from three small villages in 2014 included 1,529 individuals who had undergone at least one examination in December 2018. Among 1,529 people, 50 died and 127 were institutionalized owing to functional decline, based on the available records in December 2018. Among the remaining population, 241 were censored because of moving to another area (n = 102), decline for follow-up (n = 110), and unavailability for contact (n = 19) by December 2018.

Compared to an urban cohort in Korea (the Korean Longitudinal Study on Health and Aging [KLoSHA]), the ASPRA population showed a higher frailty status (17.4% vs. 10.3%) as measured by the CHS frailty criteria. Among the CHS criteria components, low activity had the highest discriminative ability in the ASPRA, while weight loss had the highest discriminative power in the KLoSHA. Moreover, the rural population of the ASPRA had a greater disease burden and activities of daily living (ADL)/instrumental activities of daily living (IADL) disability than those in the KLoSHA. These results suggest the need for customized approaches based on regional discrepancies when public health professionals plan to screen for frailty status or designate targeted components of frailty for intervention.

MEASUREMENTS AND DATA STRUCTURE

Comprehensive geriatric assessment was annually performed by trained nurses at regional CHP or Pyeongchang County Hospital; this included frailty assessment (Cardiovascular Health Study [CHS] frailty criteria, Korean version of the FRAIL criteria), multimorbidity, sarcopenia (muscle mass, hand grip strength, and gait speed), ADL/IADL disability, cognitive dysfunction, depression, fall, malnutrition, and polypharmacy. Additionally, information about prognosis (vital status, hospitalization, and institutionalization to either nursing home or convalescent hospitals due to functional decline), falls, malnutrition, body mass index (BMI), and disability were gathered every 3 months (Table 1). The history of hospital visits, including emergency room and outpatient clinic visits, was collected based on memory recall.

While core geriatric parameters remained the same throughout the examination, some variables were included for logistical issues and study purposes. For example, the Short Physical Performance Battery (SPPB) was introduced in 2015 as a key measure of physical performance both at baseline and as an outcome measure, and the Physical Activity Scale for the Elderly (PASE), a proprietary tool to assess physical activity, was replaced by the International Physical Activity Questionnaire (IPAQ) in 2015. Some parameters were included temporarily for research purposes, including questionnaires for erectile dysfunction, constipation, oral health, and pulmonary function.

For longitudinal analysis, the annual follow-up of core geriatric parameters made the data structure of the study an unbalanced panel data, providing opportunities for in-depth longitudinal analyses of geriatric features, including trajectory analysis and study of meaningful clinical differences.

FINDINGS AND IMPLICATIONS

Beginning with the initial article on the cohort profile in March 2016, the ASPRA published 23 articles in several journals, including the Journal of Cachexia, Sarcopenia and Muscle, Age and Ageing, the Journal of Gerontology, Series A: Medical Science, Journal of the American Geriatrics Society, and Journal of Medical Internet Research et al. to date (September 2021). Our research collaboration encompassed 32 researchers working in the Asan Medical Center, CHP in PyeongChang, PyeongChang Health Center and Country Hospital, Yonsei University College of Medicine, Eunpyeong St. Mary’s Hospital, Ilsan Paik Hospital, Seoul National University Bundang Hospital, Kyung Hee Hospital, Marcus Institute for Aging Research, Beth Israel Deaconess Medical Center, Harvard T. H. Chan School of Public Health, University of Maryland School of Medicine, Dalhousie University & Nova Scotia Health, and Dyphi Research Institute. Our collaborative researchers had diverse career statuses; they included medical residents, clinical fellows, professors, and public officials and their specialties. These methodologies, which involved family medicine, pulmonology, gastroenterology, urology, psychiatry, epidemiology, biomedical informatics, and biostatics, were not limited to geriatrics.

Frailty Assessment and Screening Tests

Historically, two main models have prevailed in defining frailty: the phenotype and cumulative deficit models. Briefly, the CHS frailty phenotype consists of five components: exhaustion, low activity, slowness, weakness, and weight loss, in which the presence of more than three components indicates a frailty state of an individual. Otherwise, the cumulative deficit model is the sum of the impaired items as a proportion of the total assessment items, which is represented as a frailty index.

To assess the frailty status using the CHS frailty phenotype, it was essential to define low physical activity. The PASE is a commonly used tool for evaluating physical activity; however, its drawbacks include the time required to perform the assessment and the inability to convert the results to a standardized quantity, the total
Table 1. Study component schedules

<table>
<thead>
<tr>
<th>Procedure</th>
<th>YR1(^{a})</th>
<th>YR2</th>
<th>YR3</th>
<th>YR4</th>
<th>YR5</th>
<th>YR6(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline interview(^{i})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Body weight and height</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Frailty assessment (CHS criteria, the FRAIL scale)</td>
<td>X</td>
<td>X(^{d})</td>
<td>X(^{d})</td>
<td>X(^{d})</td>
<td>X(^{d})</td>
<td>X(^{d})</td>
</tr>
<tr>
<td>Social frailty questionnaire</td>
<td>X(^{c})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical performance (SPPB, grip strength)</td>
<td>X(^{i})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bioimpedance analysis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Disability (ADL, IADL)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Depression (CES-D)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nutrition (MNA-SF)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Quality of life (EQ-5D-3L)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urologic symptom, male (IPSS, IIEF-5)</td>
<td>X(^{j})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urologic symptom, female (OABSS, ICIQ)</td>
<td>X(^{h})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bowel habits questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Oral health (GOHAI)</td>
<td>X(^{j})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pulmonary function (PEFR, mMRC)</td>
<td>X(^{k})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fall history</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hospitalization/institutionalization/death</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

ADL, activities of daily living; CES-D, The Center for Epidemiological Studies Depression Scale; CHS, Cardiovascular Health Study; EQ-5D-3L, the EuroQol-5 Dimensions-3 Levels; FRAIL, Fatigue, Resistance, Ambulation, Illness, and Loss of weight; GOHAI, General Oral Health Assessment Index; IADL, instrumental activities of daily living; ICIQ, International Consultation on Incontinence Questionnaire; IIEF-5, five-item version of the International Index of Erectile Function; IPSS, International Prostate Symptom Score; K-PASE, Korean version of Physical Activity Scale for the Elderly; mMRC, modified Medical Research Council Dyspnea Scale; MNA-SF, The Mini-Nutritional Assessment Short-From; OABSS, overactive bladder symptom score; PEFR, peak expiratory flow rate; Q1–3, first through third quarters; SPPB, short physical performance battery; YR, year.

\(^{a}\)When new regions were added to the cohort, new enrollments were made.

\(^{b}\)The annual follow-up in 2020 was not fully evaluated due to coronavirus disease 2019 (COVID-19).

\(^{c}\)The baseline interview includes questions on demographic characteristics (age, sex, marital status), living status, occupation, income, education level, drinking and smoking habits, underlying diseases, current use of prescription, and history of fall in the past year.

\(^{d}\)For low activity assessment, the K-PASE was replaced by the International Physical Activity Questionnaire.

\(^{e}\)The social frailty questionnaire was conducted from July 2018 to January 2020.

\(^{f}\)SPPB was not conducted in 2014.

\(^{g}\)The urologic symptom questionnaires for men (IPSS, IIEF-5) was used from February 2016 to December 2017.

\(^{h}\)The urologic symptom questionnaires for women (OABSS, ICIQ) was used in February 2016.

\(^{i}\)The termination periods differed: OABSS in December 2017 and ICIQ in February 2018.

\(^{j}\)The frailty-related section of the GOHAI was used from February 2016 to December 2017.

\(^{k}\)PEFR and mMRC were measured from October 2019.

Assessing frailty status of individuals using these two models might be less feasible in a large-scale population setting, as there is always an issue of limited resources. Hence, there is a need for a simple and rapid screening tool to identify at-risk older adults, especially those in community and hospital settings. The ASPRA applied the Korean version of the Fatigue, Resistance, Ambulation, Illness, and Loss of weight (FRAIL scale) to screen for frailty. The simple FRAIL questionnaire was not inferior to the Kihon + 3 in-

metabolic equivalent task minutes per week (MET-min/wk); these might limit the application of this method in large population-based community studies. Therefore, in the ASPRA, we compared agreements in calculating the physical activity of the CHS frailty criteria between the PASE and IPAQ short form, which is simpler and can be transformed to MET-min/wk. We found that a simpler IPAQ short form could replace PASE in assessing frailty based on the CHS frailty criteria in Korean older adults. 22)
Frailty and Geriatric Parameters

Frailty is an overall health condition of individuals with increased vulnerability to stressors, which leads to adverse health outcomes, including falls, disability, loss of independence, institutionalization, and death. Hence, frailty is a comprehensive concept that encompasses geriatric syndromes, sarcopenia, and physical performance. In the ASPRA, urologic symptoms and erectile dysfunction were common in older adults (prevalence rates of 41.4% and 52.4%, respectively) and were associated with frailty, multimorbidity, sarcopenia, polypharmacy, SPPB score, and ADL/IADL disability. Likewise, chronic constipation (prevalence 10.7%) also showed a good correlation with frailty.

In the ASPRA, the social frailty rates, as evaluated by the questionnaire, were 20.5% and 9.1% and overlapped with physical frailty. Social frailty was associated with an increased risk of ADL disability and depression. Moreover, future disability was better predicted by using both physical frailty and social frailty (C-statistic, the probability of predicting the outcome was better than chance by logistic regression models, 0.73) compared to a single frailty index (C-statistic 0.68 for physical frailty and 0.71 for social frailty), which underlined the importance of screening for social frailty. The results of these studies suggested that the frailty spectrum might be a single, global indicator reflecting the burden of age-related conditions in individuals (biological age spectrum), which may serve as a guiding criterion for delivering individualized interventions.

Frailty was a dynamic predictor of risk. The results of the longitudinal analysis showed that baseline frailty, defined by either phenotype model or deficit accumulation models, was associated with adverse health outcomes, including functional decline and a composite outcome of death or institutionalization due to disability (C-statistic 0.79; CHS phenotype 0.78 for the 26-item frailty index and 0.79 for the 34-item frailty index). Longitudinally, the frailty spectrum dynamically changed, and we identified the frailty index as a sensitive indicator to capture the smallest changes among individuals over time. In addition to its importance in predicting health outcomes, we recognized that the frailty spectrum per se may serve as an indicator of clinical outcome in intervention studies, which target aging related conditions.

Physical Performance as a Core Measure of Human Aging Phenotypes

Although the two main models of frailty (phenotype and cumulative deficit models) are well validated in various contexts, there remains an unmet need for more objective and clinically feasible markers in frailty assessment. Both models can be influenced by cultural differences in the population, as these include subjective questionnaires about respondents’ physical, functional, and mood statuses. Moreover, comorbidities and laboratory abnormalities may significantly affect the cumulative deficit model score. For instance, by overweighting some features pointing in a similar direction (e.g., blood pressure parameters and laboratory abnormalities related to hypertensive heart diseases), a frailty index may have biased characteristics tracing certain clinical features (e.g., vascular aging spectrum), rather than alterations of human global fitness associated with aging.

In the ASPRA data, gait speed was associated with age, sex, and frailty and was a good predictor of composite outcomes, including mortality and institutionalization. Subsequently, we reported that calculating functional age using three SPPB parameters (standing balance, walking speed, and chair rise test) was correlated with the frailty index and had more discriminative power in assessing frailty status compared to chronological age. From these observations, we hypothesized that the physical performance spectrum might be a core feature reflecting the global burden of human aging, serving as a measure of biological age and a potential linker between varying definitions of frailty. In a recent report, we showed that the SPPB can be a crosswalk between two main frailty models, as the SPPB showed not only a good correlation with the two frailty models but also comparability in predicting composite outcomes, thus supporting our hypothesis.

Moreover, a meaningful difference in the SPPB score was observed according to the trajectory group of disability measured by the total number of disabled domains of ADL and IADL. The mean SPPB score of the relatively stable group in disability was 10.2, while that of the rapidly deteriorated group was 3.1, which also implied the important role of SPPB in assessing future severity of disability and burden of aging phenotype.

Sarcopenia as another Phenotype of Frailty

The clinical construct and definition of sarcopenia, defined as an aging-related condition with decreased muscle mass, muscle strength, and/or physical performance, remains controversial. Increasingly regarded as a disease, most clinical guidelines on sarcopenia have supported operational classification to identify this
condition. However, we hypothesized that sarcopenia is an age-related mobility phenotype and that potential caveats exist in defining sarcopenia using decision trees. As frailty reflects a state of cumulative physiological dysfunction, we searched for this quantitative characteristic in sarcopenia. We propose a new sarcopenia index, the sarcopenic phenotype score (SPS). The SPS counts the total number of impaired domains of sarcopenic parameters (muscle mass, muscle strength, and physical function), which ranges from 0 to 3. We found that the sarcopenic spectrum defined by the original and revised European Working Group on Sarcopenia in Older People (EWGSOP1 and EWGSOP2) criteria showed inconsistent relationships with the composite outcome of mortality and institutionalization, while the SPS showed dose-response associations with composite outcome. Additionally, among various existing sarcopenic definitions, including the original and revised EWGSOP and the Asian Working Group for Sarcopenia (AWGS), only the SPS predicted future cognitive decline as assessed by the Mini-Mental State Examination (MMSE). These results suggest that sarcopenia can be better captured by methods combining incremental sarcopenic burden in a manner similar to that used in the frailty index, rather than by an operational, dichotomous manner of determining sarcopenia.

### Multicomponent Interventions

While several types of intervention studies targeting frailty in older adults have been conducted, the results have been inconsistent. Moderate improvements in physical function were observed in some multicomponent interventions, but not in single-exercise interventions. However, limited improvement was observed even after providing multicomponent interventions. This inconsistency might be due to differences in adherence rates, target populations, and intervention program composition, enabling the satisfaction of both vulnerable older adults and resource-limited public health centers.

This prospective non-randomized study enrolled 383 older adults, 187 of whom received a multicomponent intervention for 24 weeks. The intervention program consisted of group exercise, nutritional support, depression management, deprescribing, and home hazard reduction (Table 2). In particular, exercise intensity was individualized, starting from low intensity and increasing up to 60%–70% of the maximal exercise capacity based on the perceived exertion scale. After 6 months of the multicomponent intervention, physical function, as measured by SPPB, frailty, sarcopenia, depression, and nutritional status, improved and were sustained for 12 months. As the observation period extended to 30

#### Table 2. Contents of the multicomponent intervention program

<table>
<thead>
<tr>
<th>Focus</th>
<th>Intervention description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise</strong></td>
<td>Intervention: 60-minute group exercise session led by licensed exercise trainers. The intensity of the exercises were low at the beginning and increased every month; the exercises focused on the following:</td>
</tr>
<tr>
<td>- Resistance (20 minutes): squat, plank, side plank, straight-leg raises</td>
<td></td>
</tr>
<tr>
<td>- Balance (20 minutes): one-leg standing, shifting from side to side, heel-to-toe walk</td>
<td></td>
</tr>
<tr>
<td>- Aerobic/endurance (20 minutes): step up and down, quick pace, dancing</td>
<td></td>
</tr>
<tr>
<td>- The exercise trainer was given instructions not to exceed 60%–70% of the maximal exercise capacity based on the perceived exertion scale</td>
<td></td>
</tr>
<tr>
<td>Target: all participants</td>
<td></td>
</tr>
<tr>
<td>Frequency: twice weekly</td>
<td></td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td>Intervention: a 125-mL commercial liquid formula containing 200 kcal of energy, 24.5 g carbohydrates, 13 g protein, 5.63 g essential amino acids, and 7 g fat</td>
</tr>
<tr>
<td>Target: all participants</td>
<td></td>
</tr>
<tr>
<td>Frequency: twice daily</td>
<td></td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>Intervention: evaluation by a geriatrician or psychiatrist, and supportive psychotherapy or anti-depressant medication as clinically indicated</td>
</tr>
<tr>
<td>Target: participants with CES-D scores &gt; 20 points at baseline</td>
<td></td>
</tr>
<tr>
<td>Frequency: monthly</td>
<td></td>
</tr>
<tr>
<td><strong>Polypharmacy</strong></td>
<td>Intervention: medication review by a geriatrician, with dose reduction or discontinuation of potentially inappropriate medications according to the 2012 Beer's criteria</td>
</tr>
<tr>
<td>Target: participants taking ≥ 5 prescription medications at baseline</td>
<td></td>
</tr>
<tr>
<td>Frequency: monthly</td>
<td></td>
</tr>
<tr>
<td><strong>Home hazards</strong></td>
<td>Intervention: evaluation of the home environment by a visiting nurse and a social worker using the Centers for Disease Control and Prevention Home Fall Prevention Checklist, and modification of the environment to remove the identified hazards</td>
</tr>
<tr>
<td>Target: all participants with any identified home hazards at baseline</td>
<td></td>
</tr>
<tr>
<td>Frequency: 3 months</td>
<td></td>
</tr>
</tbody>
</table>

CES-D, Center for Epidemiologic Studies Depression Scale.
months, the difference between the control and intervention groups was attenuated in frailty from 18 months and disability from 24 months.\(^{46,47}\) However, the benefits of the intervention in SPPB and institutionalization-free survival were maintained for 30 months.\(^{46}\)

The positive results of the multicomponent interventions observed in the present study may be attributed to the high adherence rate resulting from regional characteristics and group approaches and targeting socioeconomically vulnerable older adults who will benefit from such treatment. In addition, addressing common geriatric syndromes of the community such as polypharmacy and depression after conducting comprehensive geriatric assessments, and providing tailored exercise programs might have contributed to our remarkable results. In conclusion, the findings of these studies may help public health providers to concretize their intervention plans in resource-limited communities by providing not only estimated effect sizes and intervention periods but also the timing for re-evaluation.

**Application of Wearable Device and Home IoT**

Population aging is now a global phenomenon and is inevitably associated with an increased number of frail older adults. Although these adults need more assistance, most prefer to age in place and live in their own homes with autonomy.\(^{49}\) Hence, while the demand for home care is ever increasing, limited resources and the current coronavirus disease 2019 (COVID-19) situation make it difficult to fulfill these needs. In these circumstances, technology-incorporated healthcare may be a solution. However, the wide adoption of technology-based devices and services is delayed, at least in part, due to the usability issues of vulnerable older populations.\(^{49}\)

To identify the possible obstacles to the application of health care technology, we first observed the effect of a wearable pedometer on physical health in 2017. After participating in a wearable device-based walking program for 6 months, the prefrail group and not the robust group showed improved physical fitness and quality of life. In addition, adherence to wearing the device was higher in the presence of coaching management.\(^{50}\) In the home Internet of Things (IoT) study, we identified a discrepancy in the demand for home IoT services according to the position of care receiver, caregiver, and health care provider. In addition, the requirements of home IoT differed according to the degree of disability among vulnerable older adults.\(^{51}\) Subsequently, we investigated the practical usability of integrated home IoT services in vulnerable older adults. During the 12-month study period, the usability was consistently higher in the prefrail group than that in the frail group. In addition, the usability patterns differed according to the type of service and frailty status. We observed a discrepancy in selecting the most satisfying service before and after experiencing home IoT services, which revealed an unawareness of home IoT, in other words, digital literacy. Collectively, these results suggest that evaluating frailty status and disability in older adults, providing appropriate human interaction, and reducing unawareness and the perception gap toward technologies might be key to facilitating the adoption of technology-based healthcare services.

**STRENGTH AND LIMITATIONS**

Taking advantage of its strength as a well-designed cohort from the initial stage of establishment, the ASPRA has shown the feasibility of conducting observational and multicomponent interventional studies in resource-limited contexts, such as community settings. In the ASPRA, the short-term follow-up period (1 year) allowed the observation of the micro-dynamics of frailty and accompanying geriatric syndrome. In addition, the relatively isolated study region with less population migration showed reduced follow-up loss, which allowed the evaluation of long-term effects. In addition, the ASPRA has bridged the academic research field and community as it focused on a simple and feasible measurement of frailty and on identifying obstacles in adapting healthcare-related technologies. Strong support from local governments and participation by healthcare personnel in CHPs allowed data acquisition on living status, including the institutionalization, and helped to minimize follow-up losses.

However, the ASPRA has some limitations. First, the measurement methods changed during the course of the study; for example, the SPPB was introduced and PASE was replaced with IPAQ in 2015 for physical activity assessment. However, gait speed, one of the SPPB parameters, had already been measured in the initial cohort, and full-scale physical performance was analyzed after adoption of the SPPB. In addition, we verified that the IPAQ could replace PASE for assessment of frailty phenotypes before replacing PASE with the IPAQ.\(^{53}\) Second, due to the lack of financial support during the initial study period, no blood samples were collected for various geriatric measurements. Third, the assessment of the “disease” domain was relatively insufficient compared to the domain of frailty and functional decline. Lastly, the annual follow-up in 2020 was not properly evaluated because of COVID-19.

**CONCLUSION**

The ASPRA has produced numerous meaningful study results over a prolonged period thanks to the active support from local governments, public health institutions, and public health doctors.
Moreover, the ASPRA has been credited with practically improving the real health status and quality of life of local residents beyond simply bearing study results. The future directions of the ASPRA include in-depth cross-sectional and longitudinal investigations of functional decline, the occurrence of geriatric syndrome, and time-series changes in frailty. These efforts will embody various study designs that are uncommon in established domestic cohorts and verify unresolved hypotheses.

ACKNOWLEDGMENTS

We sincerely appreciate the long-term, multifaceted contributions of the Pyeongchang County Hospital in establishing and maintaining the study. This support was possible thanks to future insights of the Pyeongchang County Hospital on population aging and implications of frailty.

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Ministry of Science and ICT (No. 2021R1A2C300580111).

AUTHOR CONTRIBUTION

Conceptualization, JYB, HWJ, IYJ, DHK; Data curation, JYB, HWJ, IYJ; Funding acquisition, EJL, IYJ; Investigation, JYB, EJL, GHO, YRP, HYL, JHL, HCP, CMP, CKL, HWJ, IYJ, DHK; Methodology, JYB, EJL, GHO, YRP, HYL, JHL, HCP, CMP, CKL, HWJ, IYJ, DHK; Project administration, JYB, EJL, GHO, YRP, HYL, JHL, HCP, CMP, CKL, HWJ, IYJ, DHK; Supervision, EJL, HWJ, IYJ, DHK; Writing-original draft, JYB, HWJ; Writing-review & editing, JYB, HWJ, IYJ, DHK.

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Findings and Perspectives of ASPRA


INTRODUCTION

Epidemiology and Pathophysiology of Alzheimer’s Disease

Alzheimer’s disease (AD) is the most common cause of dementia worldwide, affecting over 40 million people, primarily older adults. The pathophysiology of AD is believed to result from the loss of cholinergic neurons, resulting in atrophy of cholinergic nuclei and reduced levels of the neurotransmitter acetylcholine in the brain. Acetylcholine is involved in brain functions including attention, memory, motivation, and arousal, which are often affected in patients with the disease. The β-amyloid protein plaques found in the brains of patients with AD are also thought to negatively impact cholinergic synapses. Acetylcholine is broken down into acetate acid and choline by acetylcholinesterase enzymes in the synaptic cleft, thereby ending signal transmission and postsynaptic receptor activation.

Management of Alzheimer’s Disease

There are no well established disease-modifying treatments for AD; thus, prevention and behavioral interventions comprise the bedrocks of management. There has been a focus on improving cardiovascular (CV) and neural health using diet and exercise as preventative measures. Implementing a Mediterranean diet and performing regular aerobic exercise have been shown to help reduce the risk of AD and preserve function in those with the disease. Dietary elements that may modify AD progression and maintain brain health include polyunsaturated fatty acids, curcumin, magnesium, and vitamin supplementation. Further lifestyle modifications include consistently engaging in neural-stimulating activities, maintaining social engagement, minimizing stress, and optimizing sleep patterns.

The current pharmacologic treatment of AD consists of cholinesterase inhibitors with or without memantine, an NMDA receptor antagonist. Three acetylcholinesterase inhibitors are available for the treatment of AD: donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon). However, these treatments are hypothesized to slow disease progression and improve symptoms and do not directly modify the underlying disease process. Attention has also been paid to anti-amyloid therapy, such as monoclonal antibodies against amyloid-beta and tau-targeted therapies, but none have yet been approved for use for clinical AD except for aducanumab (Aduhelm) that recently approved by the Food and
Drug Administration (FDA) for people with mild cognitive impairment or mild dementia stage of disease.

**Acetylcholine and Acetylcholinesterase Inhibitors**

**Mechanism of Action**
Acetylcholine (ACh) is a neurotransmitter involved in the coordination of neuronal firing, modulation of rhythmic activity in the periphery, and induction of the transmission of excitatory signals from muscle cells to adjacent neurons, and vice versa. A specific class of enzymes, called acetylcholinesterases (AChEs), breaks down acetylcholine to prevent excessively high levels, thus halting coordinated synaptic firing and reciprocal neuronal signaling to various circuits, neurons, and cholinergic receptors. AChE inhibitors are drugs that competitively bind AChEs to prevent the degradation of ACh, which increases its levels in the synaptic cleft, thus enhancing the duration of cholinergic signaling and modifying the response of targeted neuronal networks. AChE inhibitors have clinical application in the treatment of myasthenia gravis and AD.11

AD is hypothesized to result from the degradation of cholinergic neurons, which play significant roles in mediating and reinforcing learning and memory pathways (the so-called “cholinergic hypothesis”).12 As such, results of experimental studies have demonstrated that increases in AChE inhibition are correlated with an overall improvement in cognitive function and in the capacity to perform activities of daily living in patients with AD.13,14

**Clinical Profile**
Although no disease-modifying treatments are available for clinical AD, AChE inhibitors have been shown to produce modest improvements in cognitive function and global function scores.15-17 Additional analysis has also shown reduction in mortality in patients prescribed AChE inhibitors.17,18 Three AChE inhibitors (donepezil, galantamine, and rivastigmine) have been approved by the Food and Drug Administration (FDA) to slow the progression of cognitive decline in patients with mild-to-severe AD.

The adverse events associated with the use of these medications are generally related to the overstimulation of the central and peripheral cholinergic systems, which are found throughout the body. The most commonly associated symptoms are nausea, vomiting, diarrhea, weight loss, bradycardia, and syncope.19,20

**Cardiovascular Effects of AChE Inhibitors**
AChE inhibitors are chiefly used to target cholinergic receptors in the central nervous system but also affect other organs, including the heart. ACh mediates multiple crucial CV processes through cholinergic receptor stimulation. In the past decade, research has consistently shown that exposure to AChE inhibitors significantly increases ACh levels in the heart, leading to increased excitatory input.

**Bradycardia and syncope**
While available data on the CV effects of AChE inhibitors are mixed, some concerning results have been reported. For example, increased ACh levels can augment parasympathetic tone in the sinoatrial (SA) node, slowing the sinus rate and various complementary CV conduction systems.21 Bradycardia, a noted adverse effect of AChE inhibitors that may cause or contribute to syncpe, has also been reported, particularly when administered in excessive doses.22,23 The results of an administrative database study showed that there was a 1.4-fold increased risk of bradycardia in patients with dementia treated with AChE inhibitor (compared to that in patients not taking these medications) and that there was a dose-dependent increase in risk for patients on donepezil.24 A recent population-based study demonstrated a two-fold increased risk of bradycardia in older patients (aged 67 years or older) who had recently started AChE inhibitor regimens.25

In a population-based analysis in Ontario, Canada, after controlling for time to hospitalization, patients receiving AChE inhibitors had increased risks of hospitalization for syncope (hazard ratio [HR] = 1.76), bradycardia (HR = 1.69), pacemaker insertion (HR = 1.49), and falls (HR = 1.18).26 Other studies also reported that the use of these medications was associated with increased risks of heart block, sinus bradycardia, and syncope.26-28 Moreover, dizziness and syncope occurred in 1%–10% of patients, in addition to bradycardia, atrial arrhythmias, myocardial infarction, angina, seizures (0.01%–1%), and sinoatrial and atrioventricular block (0.001%–1%).29

Patients prescribed these medications are older and vulnerable to age-related changes that can predispose to them orthostasis and syncope, including impaired thirst mechanisms, abnormal baroreceptor and autonomic function, and myocardial diastolic dysfunction. They may also have pre-existing CV disease, which may exacerbate any tendency toward bradycardia (e.g., sinus node dysfunction, heart block), or the drug could interact with concurrent medications (i.e., beta-blockers, calcium channel blockers, and antiarrhythmic medications). Thus, there are valid concerns regarding the risks of adverse effects caused by the use of these agents.

**Adverse effects of donepezil**
Donepezil is a commonly prescribed AChE inhibitor with numerous reports of adverse CV effects. Moreover, the package insert for
donepezil warns that:

Because of their pharmacologic action, cholinesterase inhibitors may have vagotoxic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without underlying cardiac conduction abnormalities. Syncope episodes have been reported in association with the use of Donepezil.

Donepezil overdose has been shown to result in profound sinus bradycardia, which is reversible with atropine. In a randomized, open-label, real-world comparative trial, adverse effects accounted for 73.1% of discontinuations of donepezil, galantamine, and rivastigmine. The adverse events listed as CV were "fast or slowed heart rate," and "irregular heartbeat," and the total CV adverse effects ranged from 6.5% for galantamine to 12.2% for rivastigmine. Other adverse events listed under other categories may have had, at least in part, an unrecognized CV contribution. Examples include fainting, dizziness, falls, and fatigue. The overall rates of discontinuation after the 18-week trial were 38.8% for donepezil, 53% for galantamine, and 58.7% for rivastigmine. These rates were much higher than those reported in pre-marketing clinical trials (5%-13% for mild-to-moderate AD).

Other reports have noted QT prolongation and polymorphic ventricular tachycardia (torsades de pointes [TdP]) in patients taking donepezil for AD. Furthermore, donepezil was recently added to the CredibleMeds database of medications with a known risk of causing TdP. This is their highest level of caution and is used to describe "drugs [that] prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended." Lower-level cautions in the database are characterized as "possible risk of TdP" and known to cause QT prolongation BUT currently lack evidence of TdP when taken as recommended, "conditional risk of TdP" (these drugs are associated with TdP BUT only under certain conditions such as hypokalemia, or when taken with interacting drugs) OR by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP). The last category, "Drugs to avoid in congenital long QT syndrome," includes drugs from all of the other categories and "additional drugs that do not prolong the QT interval per se, but which have a special risk because of their other actions."

The mechanism by which donepezil increases the risk of TdP may, in part, be due to bradycardia, which increases the frequency of pause-dependent onset of polymorphic VT in patients with a prolonged QT. Edrophonium, an anticholinesterase, also showed a marked ability to induce syncope during head-up tilt-testing. Notably, one study of syncope in AD patients treated with donepezil found that most patients who developed syncope had pre-existing CV conditions. Thus, care providers (e.g., primary care providers and cardiologists) should carefully and critically evaluate patients on these medications before starting these agents as well as after a patient experiences a syncope event.

Beyond bradycardia and syncope, these side effects can cause significant risks for patients on AChE inhibitors, leading to their discontinuation as therapy. Previous population-based cohort studies have demonstrated the associations between AChE inhibitors, hip fractures, and pacemaker placement. More serious complications of syncope and falls, such as fractures or head injury, can lead to hospitalization, and even death, especially in frail older adults.

**CV benefits of AChE inhibitors**

It remains difficult to draw firm conclusions regarding the cardiac effects of AChE inhibitors. While some studies and reviews have shown adverse cardiac side effects associated with the use of AChE inhibitors, others appear to show beneficial cardiac effects. The possible mechanisms for these beneficial effects include anti-inflammatory actions and favorable effects on nitric oxide pathways and redox, mitochondrial, and calcium modulation.

A recent study from Taiwan reported a dose-response-dependent decrease in CV events in patients with AD administered AChE inhibitors (i.e., the higher the cumulative dose the patients received, the fewer the CV events they experienced). The outcomes measured were a composite of CV events, including coronary heart disease, stroke, heart failure, and CV death. This was a retrospective cohort study from a health and welfare database that utilized propensity score-matching. However, the study excluded patients with pre-existing CV disease (stroke, coronary artery disease, heart failure, or sudden cardiac death), thus reducing the generalizability of the results as many older adults have these conditions. The additional limitations that the authors specifically mentioned included bias by indication as well as unmeasured confounders, an important limitation of non-randomized studies.

A meta-analysis and systematic review by Isik et al. showed that AChE inhibitor use was associated with a greater risk of bradycardia but also resulted in a lower risk of other CV events such as stroke and acute coronary syndromes in patients with dementia. As noted by the authors, the limitations of the analysis included the absence of randomized controlled trials, leaving open the possibility that patients on AChE inhibitors were receiving different, and perhaps more aggressive or effective, preventative CV care. In addition, they acknowledged an inability to evaluate the impact of other medications that the patients had also been prescribed (i.e., that data were not available) in most of the included studies. As such, it is difficult to discern whether the use of antiarrhythmics,
anti-hypertensives, anti-platelets, anticoagulants, and other medications or procedures may have played a role in the measured outcomes.40

Other studies (included in the analysis by Isik et al.) showed improved CV and all-cause mortality in patients administered donepezil.21,45 The Donepezil Cardiac TEst Registry (DOCTER) study examined the CV effects of donepezil in a 6-month prospective cohort study of 49 patients with dementia with New York Heart Association Functional Class I or II (asymptomatic or mildly symptomatic) congestive heart failure (CHF). The researchers observed no adverse CV effects during the treatment course or the 6-month follow-up period. However, they noted a reduction in brain natriuretic peptide (BNP, a marker for heart failure) levels in patients with subclinical (based on mildly elevated BNP) CHF.46 Other studies examining donepezil in older adult patients with AD showed no significant changes in electrocardiogram (ECG) parameters (heart rate, PR, QT, QTc, QRS duration) or arterial blood pressure relative to the controls.47 These results suggested that further research is needed to more fully evaluate the various CV effects of AChE inhibitors and identify factors that may enhance the risk of adverse CV events, particularly in patients with and without pre-existing CV disease or with multiple risk factors for CV disease.

MANAGEMENT OF (POTENTIAL) SIDE EFFECTS

Because the understanding of the development of bradycardia, syncope, and other adverse effects of AChE inhibitor use is incomplete, there are few guidelines regarding the management of patients on or being considered for placement on these agents.79 The suggestions for managing possible AChE inhibitor CV side effects include monthly pulse checks and symptom monitoring. If bradycardia is noted (< 50 bpm) or if syncope or seizures are reported, the investigation of all possible causes is recommended before attributing these signs to AChE inhibitors.28

While it may be tempting to simply stop the medication if a patient on one of these agents presents with syncope and/or symptomatic (or asymptomatic) bradycardia to see if the symptoms resolve or improve, this approach should not be undertaken lightly. Clinicians should consider the drug dose, as a dose reduction may lessen side effects. Clinicians must also consider other possible etiologies of the adverse effect, the impact of other concurrent medications that may contribute to the effect, and whether the patient appears to be responding cognitively to the AChE inhibitors.

Many patients are on other medications as well as AChE inhibitors; thus, there is the potential for harmful drug interactions between AChE inhibitors and, in particular, other CV agents that can reduce the heart rate. Many studies have suggested caution in prescribing AChE inhibitors to patients taking such medications,50,52 including beta-blockers, calcium channel blockers, and digoxin, which are commonly used in older adult patients who have high rates of coronary artery disease (including those with post-myocardial infarction or angina), heart failure, atrial fibrillation, or other tachyarrhythmias (supraventricular or ventricular). Antiarrhythmics such as amiodarone may also affect heart rate and predispose patients to other arrhythmias. Thus, episodes of bradycardia and syncope must be carefully evaluated to determine the underlying cause. It is important to note that virtually all the adverse CV events mentioned in this article can be multifactorial and may not necessitate cessation of AChE inhibitor use.

Although AChEIs are not considered disease-modifying agents, they provide some clinical improvements.69 At some point, the disease is expected to progress, and providers may elect to stop the medication due to concerns regarding polypharmacy and diminishing benefits. Some data suggest that patient cognitive and neuropsychiatric conditions may deteriorate if these medications are stopped abruptly, and withdrawal-like symptoms have been reported.50-52 Thus, simply stopping the agent may not be a wise option for all patients.

If a patient may benefit from an AChE inhibitor, it may be advisable to consider ways to mitigate the effects of possible adverse effects instead of completely stopping them. This can be accomplished through interdisciplinary efforts by working with the patient’s care team (e.g., geriatricians and/or primary care physicians, geriatric psychiatrists, neurologists, cardiologists). When symptomatic bradycardia or syncope is a concern, evaluations including EKGs, Holter or longer-term rhythm monitors, or other cardiac testing, such as exercise treadmill tests to evaluate chronotropic competence, may be indicated. If there is a concern for seizures, this should be evaluated as well.

If, after an appropriate workup, it is ultimately determined that a patient is experiencing a significant (even dangerous) side effect that is likely to be from the AChE inhibitor or the patient has comorbidities that place him or her at an increased risk of adverse outcomes that outweigh the possible cognitive benefits, then AChE inhibitors should be tapered off (or not started).53 Drug doses should be tapered before cessation due to reports of adverse cognitive effects following abrupt cessation.53

Given the aforementioned side effects, these subtle and overt CV complications should be strongly considered when prescribing AChE inhibitors, especially in at-risk patients. Most patients using AChE inhibitors are older adults. The ability to increase heart rate decreases with increasing age, as does the incidence of conduction system disease, including sinus node dysfunction, which may often
be subclinical. Given the possibility of adverse, and sometimes unknown, underlying interactions, particular caution should be taken when devising treatment plans for older adult patients on AChE inhibitors, taking into consideration the possibility of bradycardia and syncope, which may be induced by medication alone or in combination with other medications, comorbidities, or age-related changes.

One suggested approach for cardiac evaluation and monitoring of patients on AChE inhibitors is shown in Fig. 1. Some considerations should be given to a baseline ECG, heart rate monitoring, medication review, and rhythm monitoring if symptoms are observed. This approach should be evaluated prospectively to evaluate its possible benefits.

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**Baseline & Periodic Evaluation**

1. **Review heart rate on routine vital signs (each visit).** Monthly HR checks during titration, and then q6mo.

2. **Obtain 12-lead ECG (baseline, and q 1 year or with symptoms)**
   a. Heart rate (presumes asymptomatic)
      i. HR < 50 bpm, consider not starting AChEi immediately, search for causes
      ii. HR 50-60 bpm, carefully weigh risks and benefits of starting or continuing or dose reducing AChEi or other contributing medications, consider rhythm monitor or more frequent assessments for symptoms
      iii. HR >60, standard follow-up
   b. Heart block
   c. Sinus pauses or other rhythm disturbances
   d. Prolonged QTc

3. **Review past medical history for diagnosed cardiovascular diseases or risk factors for them (each visit)**

4. **Review medications (each visit)**
   a. Agents that may induce or exacerbate bradycardia (e.g. beta-blockers, calcium channel blockers, digoxin)
   b. Agents that may prolong the QT interval (e.g. certain antibiotics, antipsychotics, CredibleMeds.org)
      i. Offending agents should typically be stopped or dose reduced with re-measurement of the QTc

5. **Screen for symptoms of bradycardia or other arrhythmias (each visit)**
   a. Exercise intolerance
   b. Dyspnea on exertion
   c. Syncope or pre-syncope*
   d. Palpitations

6. **If symptoms are present, the evaluation may include**
   a. Long-term rhythm monitoring
      i. 24/48h Holter
      ii. 1-2 week Patch monitor
      iii. 4-week Event monitor or mobile telemetry
      iv. Implanted Loop Recorder
   b. Formal or informal exercise test for chronotropic competence

*Syncope episodes especially in the setting of a prolonged QTc should prompt urgent consultation with a cardiologist or electrophysiologist

**At any point in the evaluation, referral to Cardiology can be considered

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**Fig. 1.** Suggested approach to the cardiac evaluation and monitoring of patients being considered for or taking an acetylcholinesterase inhibitor. Unless otherwise indicated, each item should be reviewed at each visit.

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CONCLUSION

Currently, there remains a lack of a complete understanding of the interplay between AChE and patient factors that can predispose patients to adverse effects and potentially life-threatening clinical outcomes. Therefore, more studies are needed to clarify these pathways to maximize the positive effects and minimize the negative impacts of the use of these agents. The most prominent CV side effects of AChE inhibitors are bradycardia and syncope, which can result in devastating outcomes such as falls, fractures, and other trauma as well as necessitate pacemaker placement. Given the aging of the world's population and the attendant increase in the global population of patients with AD, this is an important area for further research. When a patient has experienced a possible side effect, in consultation with the provider who prescribes the AChE inhibitor, the patient or their surrogate should undergo a thorough history and evaluation, including a medication review, rhythm monitoring, consideration of neurologic symptoms, lowering the doses of other medications that might contribute to bradycardia, stopping or reducing the AChE inhibitor dose, or even pacemaker placement. Many of these factors should be considered before the initiation of these medications and periodically thereafter to optimize patient care and mitigate possible adverse events.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

None.

AUTHOR CONTRIBUTION

Conceptualization, MC; Writing, review & editing, SY, EC, MC; Supervision, MC.

REFERENCES


Prevalence of Knee Osteoarthritis and Health-Related Quality of Life in Stroke Patients over 60 Years Old: A Cross-Sectional Study Using Korean National Health and Nutrition Examination Survey V

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Background: This study investigated the prevalence of knee osteoarthritis among stroke survivors aged over 60 years and analyzed the association between knee osteoarthritis and health-related quality of life (HRQOL) in stroke survivors. Methods: We analyzed data of 287 participants who had experienced a stroke (stroke group) from the 2010–2012 Korean National Health and Nutrition Examination Survey. Among the participants, 65 stroke survivors also had knee osteoarthritis. We used the European Quality of Life-5 Dimensions (EQ-5D) questionnaire to compare the differences in HRQOL according to the presence or absence of knee osteoarthritis in the stroke group. Multiple regression analysis was performed to determine associated factors affecting HRQOL in the stroke group. Results: The prevalence of knee osteoarthritis was 21% in the stroke group. The EQ-5D index score was significantly lower in patients in the stroke group with knee osteoarthritis than in those without knee osteoarthritis (adjusted mean ±standard error [SE], 0.680±0.011 for stroke with knee osteoarthritis and 0.817±0.003 stroke without knee osteoarthritis; p<0.0001). Knee osteoarthritis, age, income level, education level, smoking, diabetes, and cardiovascular disease significantly influenced HRQOL in the stroke group. Conclusion: The study results confirmed that the prevalence of knee osteoarthritis was 21% in the stroke group and that HRQOL was significantly lower among patients in the stroke group with knee osteoarthritis. These findings suggest the importance of active management of knee osteoarthritis in stroke survivors for HRQOL.

Key Words: Nutrition surveys, Osteoarthritis, Prevalence, Quality of life, Stroke

INTRODUCTION

Stroke can cause physical and mental impairments and is often accompanied by a decline in the quality of life owing to chronic sequelae. According to an epidemiological report published by the Korean Stroke Society in 2018, one in 40 Korean adults have had a stroke and 232 strokes occur per 100,000 people each year. With the advancement of medical care, the mortality rate of patients with stroke has decreased over time, resulting in an increased number of patients living with the disease and its associated disorders. The disabilities that result from stroke include not only neurological disorders but also decreased physical function. Musculoskeletal issues are reported in 29%–32% of patients affected by stroke. The decline in muscle strength and/or motor control function, in addition to muscle spasticity, can cause limb abnormalities and an irregular gait. These symptoms may result in increased pain and may limit patient activities of daily living.
In particular, osteoarthritis caused by a degenerative joint disorder typically accompanies stroke owing to its increasing prevalence with age.1-13 Osteoarthritis is characterized by chronic joint pain and functional limitations, including gait instability; it also affects mental health, with increased risks of stress and depression.14 Osteoarthritis can also worsen the function of patients with stroke,15,16 negatively impacting their health-related quality of life (HRQOL).17 In addition, stroke survivors often have comorbidities such as hypertension, diabetes, and cardiovascular disease, which can also affect HRQOL.18 Decreased HRQOL is associated with depression, decreased motivation, and social withdrawal.19 These can also lead to the deterioration of other functions, activity, and mobility. Therefore, improving the HRQOL of patients with stroke not only improves their mental outlook but may also lead to functional improvements and increased social participation.

Korea’s progression to a super-aged society and the increase in the number of stroke survivors have resulted in increased stroke- and osteoarthritis-related research.6,20 Thus, as a representative musculoskeletal disease that can accompany stroke, osteoarthritis is expected to become increasingly important.

However, few studies have assessed the prevalence and effect of knee osteoarthritis on HRQOL in patients with stroke. Therefore, this study investigated the prevalence of knee osteoarthritis among stroke survivors and analyzed the association of knee osteoarthritis and HRQOL in stroke survivors aged over 60 years.

MATERIALS AND METHODS

Research Design and Participants

This cross-sectional study analyzed raw data from the 5th Korean National Health and Nutrition Examination Survey (KNHANES) between 2010 and 2011. The 5th KNHANES documented health behavior, prevalence of chronic disease, dietary intake, and results of radiological tests such as knee and hip X-rays to evaluate osteoarthritis.

Among 25,534 respondents in the 5th KNHANES, we selected 287 for the final analysis. The inclusion criteria for the stroke group in this study were as follows: (1) diagnosis of stroke, (2) currently having stroke, or (3) currently undergoing stroke treatment, and (4) age ≥ 60 years (Fig. 1). This study was approved by the Institutional Review Board of Jeju National University Hospital (No. 2020-05-001). As the present study used non-personally identifiable data, the requirement for participant consent was waived and the study was conducted according to the principles of the Declaration of Helsinki and the International Council for Harmonisation-Good Clinical Practice (ICH-GCP).

Explanatory Variables

The knee osteoarthritis group comprised individuals who reported having knee pain and knee joint Kellgren-Lawrence radiological grades ≥ 2. We used the European Quality of Life-5 Dimensions (EQ-5D) questionnaire to compare the differences in HRQOL according to the presence or absence of knee osteoarthritis in the stroke group. EQ-5D comprises five dimensions related to HRQOL: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression. Each domain of EQ-5D is scored using a three-point scale: 1, no problems; 2, moderate problems; and 3, severe problems. A higher score indicates greater discomfort in each dimension. The EQ-5D results were then converted into the EQ-5D index according to the EQ-5D measurement standards proposed by the Korea Centers for Disease Control and Prevention.21 An EQ-5D index of 1 (when all five items were 1) defined a perfectly healthy condition. EQ-5D indices ranged from 1 to −0.171, with smaller values indicating worse health conditions.22

The sociodemographic variables included in our analysis were age (years), age group (60–69, 70–79, and ≥ 80 years), sex (male, female), income, and education. Income was divided into quartiles (lower, lower-middle, upper-middle, and upper). The levels of education were divided into ≤ middle school or ≥ high school. We assessed smoking status, alcohol intake per week, and number of walking days as lifestyle factors. Smoking status was divided into currently smoking and non-smoking. Alcohol intake per week was divided into no drinking, ≤ 1 time/week, 2–3 times a week, and ≥ 4 times a week. The number of walking days was categorized as ≤ 2 times/week, 3–4 times/week, and ≥ 5 times/week. We obtained data on body mass index (BMI, kg/m²) and arterial blood pressure from health examination surveys. As obesity was considered a variable that could affect knee osteoarthritis, we defined

![Study flowchart](image-url)
BMI values of < 25 kg/m² as normal and ≥ 25 kg/m² as obese. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg, or use of antihypertensive agents.

We defined the presence of diabetes as participants who responded that they had been diagnosed with diabetes, were currently experiencing diabetes, or were currently undergoing diabetes treatment. We defined the presence of cardiovascular disease (myocardial infarction or angina pectoris) as participants who responded that they had been diagnosed with cardiovascular disease, were currently experiencing the disease, or were currently undergoing treatment for the disease.

**Statistical Analysis**

The sampling in the KNHANES follows a multi-stage clustered probability design, which is a complex sample design method to improve sample representativeness and estimation accuracy. Therefore, this study reflected the weight, strata, and cluster variables for accurate data analysis, and we performed all statistical analyses using the complex sample data analysis method. All missing values were reflected without omission to avoid bias in the variance (standard error [SE]) of the estimate.

Chi-squared tests were performed to compare the proportions of categorical variables, and independent t-tests were performed to compare differences in continuous variables between participants in the stroke group with and without knee osteoarthritis.

The prevalence of knee osteoarthritis in the stroke group was estimated using complex sample logistic analysis adjusted for age. Univariate logistic regression and age- and sex-adjusted multivariate logistic regression analyses were used to identify factors significantly related to knee osteoarthritis in the stroke group. To compare the differences in HRQOL according to the presence or absence of knee osteoarthritis in the stroke group, we calculated the adjusted means of each dimension of the EQ-5D after adjusting for age and sex. The mean scores of each domain of EQ-5D between intergroups were compared using t-tests.

To identify the significance of sociodemographic factors (sex, age, income, education), lifestyle factors (obesity, weekly alcohol intake, smoking status, number of weekly walking days), and comorbidities (hypertension, diabetes, cardiovascular disease) on HRQOL in the stroke group, a simple linear regression analysis was performed. Variables with p-values < 0.05 in the simple linear regression analysis were included in the multiple linear regression analysis. All data analyses were performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA), with p-values < 0.05 indicating statistical significance.

**RESULTS**

**Distributions of Characteristics according to Knee Osteoarthritis in the Stroke Group**

Among 25,534 individuals who participated in the 5th KNHANES from 2010 to 2012, the stroke group included 287 individuals. Patients in the stroke group with knee osteoarthritis were older than those in the stroke group without knee osteoarthritis (73.7 vs. 70.0 years; p < 0.0001). The prevalence of knee osteoarthritis was significantly higher in women than in men in the stroke group (31.7% vs. 11.7%). The prevalence of knee osteoarthritis trend tended to increase with age; it was 14.9% among participants in their 60s, 22.1% among those in their 70s, and 38.4% among those aged ≥ 80 years (p for trend = 0.018).

We observed no significant differences in income (p = 0.288), obesity (p = 0.350), smoking status (p = 0.103), aerobic exercise (p = 0.178), hypertension (p = 0.119), diabetes (p = 0.910), or cardiovascular disease (p = 0.095) between the intergroups (Table 1).

**Age-adjusted Prevalence of Knee Osteoarthritis and its Related Factors in the Stroke Group**

The prevalence of knee osteoarthritis in stroke patients aged ≥ 60 years was 21%. Even after adjusting for age, the prevalence of knee osteoarthritis tended to decrease with income (25.3%, 22.1%, 16.4%, and 12.3% in the low, middle-low, middle-high, and high income groups, respectively) and education (24.2% in ≤ middle school and 5.5% in ≥ high school). The unadjusted odds ratios (ORs) for the association between knee osteoarthritis and each variable were significant for sex, age, education, and alcohol consumption 2–3 times/week. After adjusting the ORs for age and sex, only education (≥ high school: adjusted OR = 0.304; 95% confidence interval [CI], 0.113–0.818) was a significantly related factor (Table 2).

**Differences in HRQOL according to Knee Osteoarthritis Status in the Stroke Group after Adjusting for Age and Sex**

The average score for each dimension was significantly higher in the knee osteoarthritis group, indicating a poor HRQOL (p < 0.001). The EQ-5D index was significantly lower in the knee osteoarthritis group (adjusted mean ± SE, 0.680 ± 0.011) than in the non-knee osteoarthritis group (0.817 ± 0.003) (p < 0.0001) (Table 3).

**Factors Affecting HRQOL in the Stroke Group**

The simple linear regression models for the EQ-5D index showed significant (p < 0.05) associations between the presence of knee osteoarthritis and sex, age, education, alcohol intake, smoking sta-
Table 1. Distribution of characteristics of knee osteoarthritis in the stroke group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Knee osteoarthritis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 222)</td>
<td>Yes (n = 65)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>136 (88.3)</td>
<td>19 (11.7)</td>
</tr>
<tr>
<td>Female</td>
<td>86 (68.3)</td>
<td>46 (31.7)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>70.0 ± 0.5</td>
<td>73.7 ± 0.8</td>
</tr>
<tr>
<td>Age group (y)</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>60–69</td>
<td>110 (85.1)</td>
<td>23 (14.9)</td>
</tr>
<tr>
<td>70–79</td>
<td>94 (77.9)</td>
<td>29 (22.1)</td>
</tr>
<tr>
<td>≥ 80</td>
<td>18 (61.6)</td>
<td>13 (38.4)</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>64 (74.3)</td>
<td>22 (25.7)</td>
</tr>
<tr>
<td>Middle-low</td>
<td>41 (73.5)</td>
<td>18 (26.5)</td>
</tr>
<tr>
<td>Middle-high</td>
<td>61 (82.7)</td>
<td>18 (17.3)</td>
</tr>
<tr>
<td>High</td>
<td>54 (86.2)</td>
<td>7 (13.8)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Middle school</td>
<td>147 (73.7)</td>
<td>59 (26.3)</td>
</tr>
<tr>
<td>≥ High school</td>
<td>73 (94.4)</td>
<td>6 (5.6)</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td>0.350</td>
</tr>
<tr>
<td>No</td>
<td>35 (84.0)</td>
<td>7 (16.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>174 (77.0)</td>
<td>58 (23.0)</td>
</tr>
<tr>
<td>Alcohol intake per week</td>
<td></td>
<td>0.041</td>
</tr>
<tr>
<td>No drinking</td>
<td>108 (73.0)</td>
<td>43 (27.0)</td>
</tr>
<tr>
<td>≤ 1</td>
<td>70 (85.0)</td>
<td>15 (15.0)</td>
</tr>
<tr>
<td>2–3</td>
<td>22 (95.7)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>20 (81.0)</td>
<td>5 (19.0)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td>0.103</td>
</tr>
<tr>
<td>No</td>
<td>180 (77.2)</td>
<td>84 (22.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>39 (89.0)</td>
<td>8 (11.0)</td>
</tr>
<tr>
<td>Walking days per week</td>
<td></td>
<td>0.178</td>
</tr>
<tr>
<td>≤ 2</td>
<td>85 (75.6)</td>
<td>29 (24.4)</td>
</tr>
<tr>
<td>3–4</td>
<td>37 (90.2)</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>97 (78.6)</td>
<td>30 (21.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>0.119</td>
</tr>
<tr>
<td>No</td>
<td>46 (87.3)</td>
<td>7 (12.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>174 (77.0)</td>
<td>58 (23.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>0.910</td>
</tr>
<tr>
<td>No</td>
<td>130 (79.8)</td>
<td>35 (20.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>63 (80.5)</td>
<td>19 (19.5)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td>0.095</td>
</tr>
<tr>
<td>No</td>
<td>197 (77.8)</td>
<td>60 (22.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>25 (89.1)</td>
<td>5 (10.9)</td>
</tr>
</tbody>
</table>

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

DISCUSSION

This cross-sectional study aimed to identify the overall prevalence of knee osteoarthritis in patients with stroke aged over 60 years and assess factors related to HRQOL in this group. This comprehensive study assessed the prevalence of osteoarthritis and HRQOL in patients with stroke aged over 60 years. Our results will help improve the HRQOL and health management of the anticipated increasing numbers of older adult stroke survivors.

First, the prevalence of osteoarthritis in patients in the stroke group aged over 60 years was 21% and was higher in women than in men. Osteoarthritis in patients with stroke may be accelerated owing to biomechanical problems such as paralysis, spasticity, sensory loss, and movement disorders.23,24) However, the comparison of the prevalence of knee osteoarthritis between the stroke and no-stroke groups of patients aged over 60 years showed no significant difference in our study (Supplementary Table S2). This is probably because this study included only patients aged over 60 years; thus, their knee osteoarthritis was likely because of aging or previous injuries. Additional research in an expanded age range of study subjects is needed. In addition, the prevalence of osteoarthritis was higher in women, those in the low-income group, and those in the low-educational level group. The high prevalence of osteoarthritis in women has been previously reported.25,26) Women are anatomically different from men, with narrower femurs, thinner patellae,
Table 2. Prevalence of knee osteoarthritis and its related factors in the stroke group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Knee osteoarthritis (%)</th>
<th>uOR (95% CI)</th>
<th>aORb) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>21.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10.3</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>30.1</td>
<td>3.491 (1.717–7.100)</td>
<td>-</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td>1.103 (1.049–1.161)</td>
<td>-</td>
</tr>
<tr>
<td>Age group (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>23.4</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>70–79</td>
<td>37.2</td>
<td>1.621 (0.764–3.437)</td>
<td>-</td>
</tr>
<tr>
<td>≥ 80</td>
<td>14.9</td>
<td>3.574 (1.401–9.112)</td>
<td>-</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>24.3</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Middle-low</td>
<td>22.4</td>
<td>1.046 (0.438–2.496)</td>
<td>0.822 (0.331–2.041)</td>
</tr>
<tr>
<td>Middle-high</td>
<td>4.8</td>
<td>0.606 (0.278–1.321)</td>
<td>0.641 (0.270–1.521)</td>
</tr>
<tr>
<td>High</td>
<td>5.9</td>
<td>0.465 (0.164–1.314)</td>
<td>0.463 (0.155–1.385)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Middle school</td>
<td>22.6</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>≥ High school</td>
<td>8.1</td>
<td>0.167 (0.066–0.424)</td>
<td>0.304 (0.113–0.818)</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20.6</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>19.7</td>
<td>1.569 (0.606–4.063)</td>
<td>0.946 (0.359–2.496)</td>
</tr>
<tr>
<td>Alcohol intake per week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No drinking</td>
<td>21.6</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>≤ 1</td>
<td>17.3</td>
<td>0.478 (0.220–1.036)</td>
<td>0.844 (0.372–1.914)</td>
</tr>
<tr>
<td>2–3</td>
<td>6.5</td>
<td>0.121 (0.015–0.966)</td>
<td>0.276 (0.035–2.172)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>22.9</td>
<td>0.634 (0.200–2.010)</td>
<td>1.192 (0.352–4.039)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20.0</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>15.7</td>
<td>0.421 (0.145–1.226)</td>
<td>0.823 (0.272–2.489)</td>
</tr>
<tr>
<td>Walking days per week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2</td>
<td>19.5</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>3–4</td>
<td>10.0</td>
<td>0.336 (0.105–1.081)</td>
<td>0.482 (0.132–1.761)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>22.4</td>
<td>0.841 (0.426–1.662)</td>
<td>1.295 (0.615–2.724)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14.6</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>20.7</td>
<td>2.052 (0.816–5.165)</td>
<td>1.391 (0.533–3.634)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>19.2</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>17.0</td>
<td>0.960 (0.477–1.933)</td>
<td>0.788 (0.354–1.757)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20.9</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>9.2</td>
<td>0.429 (0.152–1.211)</td>
<td>0.359 (0.119–1.076)</td>
</tr>
</tbody>
</table>

uOR, unadjusted odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

aAdjusted for age, b) adjusted for age and sex.

larger quadriceps angle, and differences in the tibia condyle size. Moreover, differences in knee cartilage volume may play a major role, in addition to hormones.26-29) The higher rates of osteoarthritis in the low-income and low-educated groups is consistent with findings of previous studies reporting a higher osteoarthritis burden for individuals with poor socioeconomic status.30,31) People with lower socioeconomic status are more likely to perform knee-stressing work than office work; thus, the prevalence of os-
### Table 3. Health-related quality of life according to knee osteoarthritis status in the stroke group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Knee osteoarthritisa)</th>
<th>t</th>
<th>p-valueb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D index score</td>
<td>0.817 ± 0.003</td>
<td>0.680 ± 0.011</td>
<td>−10.83 &lt; 0.0001</td>
</tr>
<tr>
<td>Mobility</td>
<td>1.581 ± 0.029</td>
<td>1.915 ± 0.027</td>
<td>7.51 &lt; 0.0001</td>
</tr>
<tr>
<td>Self-care</td>
<td>1.305 ± 0.029</td>
<td>1.518 ± 0.019</td>
<td>5.25 &lt; 0.0001</td>
</tr>
<tr>
<td>Usual activities</td>
<td>1.487 ± 0.028</td>
<td>1.632 ± 0.019</td>
<td>3.72 0.0003</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>1.517 ± 0.028</td>
<td>1.923 ± 0.027</td>
<td>9.19 &lt; 0.0001</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>1.272 ± 0.028</td>
<td>1.520 ± 0.024</td>
<td>5.87 &lt; 0.0001</td>
</tr>
</tbody>
</table>

Values are presented as adjusted mean±standard error.

EQ-5D, European Quality of Life-5 dimension.
a) Adjusted for age and sex, b) using the chi-square test.

### Table 4. Factors affecting the health-related quality of life in the stroke group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multiple linear regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td>(constant)</td>
<td>1.103</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>−0.145</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Reference</td>
</tr>
<tr>
<td>Female</td>
<td>−0.007</td>
</tr>
<tr>
<td>Age</td>
<td>−0.004</td>
</tr>
<tr>
<td>Income</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Reference</td>
</tr>
<tr>
<td>Middle-low</td>
<td>0.042</td>
</tr>
<tr>
<td>Middle-high</td>
<td>−0.017</td>
</tr>
<tr>
<td>High</td>
<td>0.080</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>≤ Middle school</td>
<td>Reference</td>
</tr>
<tr>
<td>≥ High school</td>
<td>0.064</td>
</tr>
<tr>
<td>Alcohol intake per week</td>
<td></td>
</tr>
<tr>
<td>No drinking</td>
<td>Reference</td>
</tr>
<tr>
<td>≤ 1</td>
<td>0.0001</td>
</tr>
<tr>
<td>2–3</td>
<td>−0.088</td>
</tr>
<tr>
<td>≥ 4</td>
<td>0.011</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>−0.066</td>
</tr>
<tr>
<td>Walking days per week</td>
<td></td>
</tr>
<tr>
<td>≤ 2</td>
<td>Reference</td>
</tr>
<tr>
<td>3–4</td>
<td>−0.066</td>
</tr>
<tr>
<td>≥ 5</td>
<td>0.026</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>−0.029</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>−0.023</td>
</tr>
</tbody>
</table>

B, estimate; β, standardized estimate; SE, standard error.
osteoarthritis is higher in this population. The age- and sex-adjusted ORs of knee osteoarthritis in this study showed that the lower the education level, the higher the risk of knee osteoarthritis. Therefore, it is important to educate stroke survivors who are women or with low levels of education and income on proper exercise and lifestyle habits to prevent osteoarthritis in these populations.

Second, we found that the presence of osteoarthritis negatively affected HRQOL in the stroke group. All five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the EQ-5D index showed significantly worse HRQOL in the stroke group with knee osteoarthritis. Knee osteoarthritis in stroke patients was associated with an increased length of hospitalization and was related to the degree of patient daily activities. Gait issues in patients with stroke were significantly related to knee pain at rest; moreover, knee osteoarthritis is also closely related to functional recovery after stroke onset. Our findings indicated that knee osteoarthritis contributed to functional limitation and could worsen HRQOL in the stroke group, suggesting that rapid screening tests for osteoarthritis in patients with stroke and prompt management of knee osteoarthritis in these patients can improve their quality of life.

Finally, in addition to osteoarthritis, age, middle-high income, low education level, smoking, alcohol intake 2–3 times/week, diabetes, and cardiovascular disease were negatively related to HRQOL in the stroke group. After a stroke, nerves are damaged and the muscle structure changes to fast-contractile fibers, resulting in a rapid decline in muscle mass. In addition, sarcopenia caused by aging further reduces muscle strength, limiting the activities of daily life and resulting in decreased HRQOL. In addition, social interaction decreases and psychological conditions such as depression worsen with age, which further adversely affects HRQOL. Among the factors examined in this study, the controllable factors were smoking, alcohol intake, and walking. Although there were positive and negative effects depending on the subgroup of each item, when combined with other studies to date, smoking cessation and aerobic exercise such as walking positively affect HRQOL. Regular physical activity improves functional health and energy balance; reduces the risks of cardiovascular disease, stroke, and diabetes; and is a major factor in preventing sarcopenia. Therefore, walking and smoking cessation are expected to play important roles in the management of diabetes and cardiovascular disease, which are risk factors for HRQOL among stroke patients.

This study had several limitations. First, this was a retrospective cross-sectional study that included a survey; thus, we could not identify the sequential or causal relationships between stroke and osteoarthritis. Second, although we conducted a secondary analysis of the KNHANES data, the final analysis included 287 samples, which is less than the total number of stroke patients in Korea. Third, we did not perform detailed classifications and analyses according to lesions as well as osteoarthritis and stroke severities. Future research considering the severity and characteristics of stroke and knee osteoarthritis is needed.

The study results confirmed that the prevalence of knee osteoarthritis was 21% among patients with stroke aged over 60 years and that HRQOL was significantly lower in the group of patients with stroke and knee osteoarthritis than in the group of patients with stroke and without knee osteoarthritis. Therefore, improving the quality of life of stroke survivors requires active management of knee osteoarthritis, including appropriate medical approaches such as preventive exercise, pain control, physical therapy, and rehabilitation considered to be helpful in daily life.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4235/agmr.21.0053.

ACKNOWLEDGMENTS

We express our appreciation to team of Biostatistics in Ajou Research Institute for Innovative Medicine.

This work has been shared via the preprint server (http://doi.org/10.21203/rs.3.rs-37188/v1)

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

None.

AUTHOR CONTRIBUTIONS

Conceptualization, HJL; Data curation, HJL; Investigation, KYJ, HJL; Methodology, HJL; Project administration, KYJ, HJL; Supervision, HJL; Writing–original draft, JKY, HJL; Writing–review & editing, KYJ, HJL.

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Differences in Pain Characteristics and Functional Associations between Nursing Home Residents and Community-Dwelling Older Adults: A Cross-Sectional Study

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2Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Izmir Katip Celebi University, Izmir, Turkey
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Background: Pain is one of the most critical issues in older adults, and the place of residence may play an important role in pain characteristics and related factors. However, it is an understudied subject. This study investigated differences in pain characteristics and functional associations between nursing home residents and community-dwelling older adults.

Methods: Older adult participants were recruited from nursing homes (n=73) and the community (n=73). Pain characteristics, including type, intensity, and number of pain sites, were evaluated. Other outcome measures were functional mobility, walking speed, functional independence, physical activity, anxiety, depression, and health-related quality of life.

Results: Nursing home residents experienced musculoskeletal pain more frequently and had a greater number of pain sites than community-dwelling older adults (p<0.05). Walking speed and mobility were significantly lower and anxiety and depression were significantly higher in nursing home residents (p<0.05). While higher pain intensity was significantly correlated with low scores on physical measures, low health-related quality of life, and higher depression and anxiety symptoms in both groups (p<0.05), the magnitudes of the correlations were much higher in nursing home residents. The number of pain sites was significantly correlated with low scores on physical measures, low health-related quality of life, and higher depression and anxiety symptoms mainly in nursing home residents (p<0.05).

Conclusion: Compared to community-dwelling older adults, nursing home residents experienced musculoskeletal pain more frequently and at more sites in the body. Higher pain intensity and number of pain sites were associated with worse clinical variables, mainly in nursing home residents. This study highlights the importance of regular pain assessment, especially in nursing home care settings.

INTRODUCTION

With decreased birth rates and improved life expectancy, the older population has increased accordingly. For multiple reasons, many older adults prefer staying at home to living in a nursing home. Therefore, determining the risk factors presented in nursing homes is important not only for older adults but also for their families, clinicians, researchers, and policymakers. Pain is an important outcome measure in the geriatric field because it can influence many aspects of physical, emotional, and social functions. For example, studies have shown significant associations between pain and depression, anxiety, social isolation, sleep and cognitive disorders, de-
Several individual characteristics, such as care setting, can influence the prevalence of pain; therefore, pain prevalence in older adults may vary according to the place of residence. The prevalence of significant pain problems is 25%–50% in community-dwelling older adults and 45%–80% in nursing home residents. Pain leads to higher healthcare costs in older adults; therefore, improving pain management should be an important goal for healthcare services, especially in long-term care settings such as nursing homes. However, pain management is often inadequate among older adults and is a significant problem in home healthcare.

The prevalence of neuropathic pain is generally considered to be underestimated in older adults. Moreover, the prevalence of neuropathic pain is likely to increase soon because the population is ageing and the survival rates of people with diseases associated with neuropathic pain are increasing. However, studies on the influence of neuropathic pain on older adult functioning are scarce and have inconsistent results. In addition, most such studies mainly focused on specific conditions such as diabetic peripheral neuropathy and postherpetic neuralgia. Musculoskeletal pain is a common problem in older adults and often leads to their decreased functional ability and quality of life. Since neuropathic and musculoskeletal pain have different characteristics and treatment methods, determining their prevalence and impact is essential. However, there is less precise information about the types of pain and pain-related factors among nursing homes or community-dwelling older adults, which is important for designing targeted prevention and intervention programs. Thus, the current study investigated the pain characteristics and associated factors in nursing home residents and community-dwelling older adults.

MATERIALS AND METHODS

Design and Ethical Considerations
This cross-sectional study was approved by the Ethics Review Board of Near East University (IRB No. 2019/65-716, date: 22.01.2019) and performed in accordance with the ethical standards in the Declaration of Helsinki. Before study commencement, all participants provided written informed consent.

Participants and Recruitment
The convenience sampling method was used to recruit participants from four different nursing homes located in Gazimagusa and Lefkosa, as well as community-dwelling older adults from Gazimagusa and surrounding villages in Turkish Republic of Northern Cyprus. A researcher from the study visited these nursing homes and explained the aims and scope of the study to older adults during their collective activities such as breakfast and lunch. Individuals who volunteered to participate in the study were screened according to the inclusion and exclusion criteria. The tests and questionnaires were then administered to the eligible participants. For the recruitment of community-dwelling people, brochures about the study were distributed to local residents, and posters were attached to places that were likely to grab attention. Older adults who were interested in this study were then evaluated.

The inclusion criteria were age > 65 years, ability to walk outdoors, and independence in activities of daily living. Participants who were living in their homes were classified as community-dwelling adults, while those living in a nursing home were classified as nursing home residents. Participants with uncontrolled diabetes and hypertension, severe vision and hearing loss, and a Mini-Mental State Examination score of < 22 for educated or < 18 for uneducated older adults were excluded.

A systematic review reported the frequencies of pain in older people varying between 49% and 83%. Based on pain frequencies of 49% and 83% in each of the two groups, the required study sample size was calculated to be 144 for a power of 99% and 95% confidence level using Open Source Epidemiologic Statistics for Public Health (OpenEpi) version 3.01 (http://www.openepi.com).

Measures

Pain assessments
Musculoskeletal pain results from the activation of nociceptors that innervate ligaments, small joints, muscles, and tendons, whereas neuropathic pain results from a lesion or dysfunction of the peripheral or central nervous systems. The painDETECT questionnaire can be used to distinguish between these two types of pain. The maximum and minimum possible scores of the painDETECT questionnaire were 38 and −1, respectively. Scores ≤ 12 indicate a non-neuropathic component (i.e., musculoskeletal pain), while scores ≥ 19 indicate a neuropathic component (i.e., neuropathic pain). Even though the results are uncertain between these thresholds, a neuropathic pain component may be present. Therefore, we categorized these uncertain results as neuropathic pain. This study used the Turkish version of the painDETECT questionnaire, which demonstrated good psychometric properties. The frequencies of pain in different body regions were determined using the Nordic Musculoskeletal Questionnaire, which assessed the presence of pain within the last year and week among the nine different body parts.
version of the Nordic Musculoskeletal Questionnaire is reliable and valid, with excellent internal consistency and moderate to almost perfect test-retest reliability.\textsuperscript{13} The current pain intensity was evaluated using a visual analog scale.

**Functional mobility and physical activity assessments**

The Timed Up and Go (TUG) test was used to assess mobility, static balance, and dynamic balance.\textsuperscript{13} The TUG test has good psychometric properties in community-dwelling older adults\textsuperscript{13} and frail older adults referred to a hospital.\textsuperscript{16} The participants were asked to sit in a chair, walk 3 m away, turn, walk back to the chair, and sit down. The score was recorded in seconds, with higher scores indicating decreased mobility.

The 10-m walk test is a valid and reliable measure used to assess walking speed in older people.\textsuperscript{15,17,18} The participants were asked to walk at a comfortable speed, which was reported in m/s.

Performance in activities of daily living and mobility were assessed using the modified Barthel Index.\textsuperscript{19} Higher scores on the modified Barthel Index indicate a greater degree of independence.

Physical activity level was assessed using the Turkish version of the Rapid Assessment of Physical Activity (RAPA), a self-reported measure.\textsuperscript{20,21} The RAPA has two subscales: RAPA-Aerobic and RAPA-Flexibility and Strength. However, only two participants from the community-dwelling group reported that they were performing strength exercises; therefore, we analyzed and reported only the RAPA-aerobic scores.

**Anxiety, depression, and health-related quality of life**

Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS), which has two subscales. Higher scores indicate higher levels of anxiety and depression for each subscale.\textsuperscript{22} The internal consistency of the HADS was excellent in the general population aged 65–80 years,\textsuperscript{23} and its Turkish version is valid and reliable.\textsuperscript{24}

Health-related quality of life was measured with the Short Form-36 Health Survey (SF-36), which measures eight health-related quality of life domains.\textsuperscript{25} We reported the sum scores of the physical and mental components, with higher scores indicating higher levels of quality of life. The SF-36 has stronger evidence of reliability and validity than other generic health-related quality of life instruments in older adults in different settings,\textsuperscript{16} and its Turkish version is psychometrically sound.\textsuperscript{27}

**Statistical Analysis**

Kolmogorov-Smirnov test results and histograms were used to assess the data distributions, which were mostly non-normal. Therefore, Mann-Whitney U tests were conducted to compare the differences between the study groups (community-dwelling older adults vs. nursing home residents). Categorical variables were compared using chi-squared tests. For correlation analysis, we calculated Spearman rank-order correlation coefficients, which were categorized as strong (>0.5), moderate (0.3–0.5), and weak (0.2–0.3).\textsuperscript{26} The Holm-Bonferroni sequential correction method was used to correct for type 1 errors due to multiple correlations. Statistical significance was set at \( p < 0.05 \). The IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) was used to perform the statistical analyses.

**RESULTS**

The participants in this study included 73 community-dwelling residents and 73 nursing home residents. Age, sex, and body mass index did not differ significantly between the two groups \((p > 0.05)\) (Table 1). The frequency of musculoskeletal pain and the number of pain sites in the last year and week as well as the TUG, HADS-anxiety, and HADS-depression scores were significantly higher in nursing home residents \((p < 0.05)\). The modified Barthel Index, walking speed, and RAPA were significantly lower in nursing home residents \((p < 0.001)\). We observed no significant differences in SF-36 scores between the two groups \((p > 0.05)\). Table 1 presents the results of the comparisons of the participants’ pain characteristics, physical functions, anxiety, depression, and quality of life.

The nursing home residents reported significantly higher frequency of musculoskeletal pain in the hips/thighs, knees, and ankles/feet regions in the last year and week \((p < 0.05)\) (Fig. 1). Moreover, they reported significantly higher frequency of neuropathic pain in the last year in the upper back, lower back, knees, and ankles/feet regions \((p < 0.05)\). In addition to these regions, they reported significantly higher frequency of neuropathic pain in the hips/thighs in the last week (Fig. 2). In contrast, community-dwelling older adults reported significantly higher frequency of neuropathic pain in the wrist/hand region in the last year and week \((p < 0.05)\) (Fig. 2).

Regardless of the type of pain, the nursing home residents reported significantly higher frequency of upper back, hips/thighs, knees, and ankles/feet pain in the last year and week \((p < 0.05)\). In contrast, community-dwelling older adults reported significantly more wrist/hand pain in the last year and week \((p < 0.05)\). Fig. 3 shows the distribution of pain sites during the previous year and week.

Table 2 presents the correlations between current pain intensity and the number of pain sites during the last year and week as well as other study measures. Current pain intensity was significantly...
related to all study variables in community-dwelling older adults (p < 0.05). Current pain intensity was also significantly related to all study variables, except for the physical activity class (p = 0.435) in nursing home residents. The correlations were much stronger in nursing home residents. The number of pain sites in the last year was not significantly correlated with any study outcome measures in the community-dwelling older adults (p > 0.05) but was significantly correlated with all study measures (p < 0.05) except for the RAPA (p > 0.05) in nursing home residents. The number of pain sites in the last year was significantly correlated with the TUG, SF-36-physical and mental components in community-dwelling older adults (p < 0.05) and with all study measures (p < 0.05), except for the RAPA (p > 0.05) in the nursing home residents.

**DISCUSSION**

This study investigated pain characteristics and related factors among nursing home residents and community-dwelling older adults. We observed a significantly higher frequency of musculoskeletal pain in nursing home residents; however, pain intensity did not differ significantly between nursing home residents and community-dwelling older adults. In addition, nursing home residents had a greater number of pain sites than community-dwelling older adults. While pain intensity and the number of pain sites were significantly associated with physical function, independence level, depression, anxiety, and quality of life in both nursing home residents and community-dwelling older adults, these associations were stronger among nursing home residents.

The frequency of pain in older people can vary according to the place of residence. Studies have indicated that the prevalence of pain ranges from 25% to 50% in community-dwelling older adults and from 45% to 80% in nursing home residents. However, all participants experienced pain regardless of their place of residence. Our results showed a significantly higher frequency of musculoskeletal pain in nursing home residents (67.1%) than in community-dwelling older adults (42.5%). A large, multicenter study reported a 52.5% prevalence of neuropathic pain in older people presenting to outpatient clinics in Turkey. However, a population-based study of 5,326 older adults reported prevalences of neuropathic and musculoskeletal pain of 13.7% and 30%, respectively. Various factors, such as pain definitions and recall periods, can be related to inconsistency in pain prevalence in different studies.

In our study, regardless of the type of pain, nursing home residents reported more upper back, hips/thighs, knees, and ankles/feet pain in the last year and week than community-dwelling older adults. In contrast, community-dwelling older adults reported more wrist/hand pain in the previous year and week. The upper limbs are used in many daily living activities, from performing the simplest tasks related to self-care, which involves the basic activities of daily living, to the most complex, such as instrumental activities.
of daily living mainly related to independence in the management of family life, use of domestic appliances, personal or public transport, and control of their medication and finance.\(^{31}\) In addition, upper limb function tends to decrease with age in older people.\(^{32}\) We speculate that since community-dwelling older adults perform these upper limb-related activities of daily living more often than nursing home residents, overuse disorders such as entrapment neuropathies occur more commonly in this population. This might explain the higher frequency of neuropathic pain and wrist/hand region involvement in community-dwelling older adults. However, we did not investigate the origin of pain, although the frequency of neuropathic pain was usually higher in nursing home residents than in community-dwelling older adults. Therefore, further research is required to confirm our results. A detailed assessment of pain distribution according to the body regions identified in our study may help rehabilitation professionals to design preventive rehabilitation programs targeting pain in older people. In this process, it would be reasonable to target different body regions according to the place of residence.

The number of pain sites was also a notable risk factor for physical dysfunction. For example, multiple pain sites were associated with fall risk in older adults.\(^{33}\) Moreover, the number of joint pain sites was associated with incident mobility disability in older adults\(^{4,35}\) and was a better predictor of disability measures than pain intensity and interference with activities.\(^{36}\) Musculoskeletal pain was also associated with mobility disability, walking speed, depressive symptoms, body mass index, and physical activity in community-dwelling older adults.\(^{34,35}\)

Similarly, we found that the

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**Fig. 1.** Distribution of pain sites according to the place of residence in the last year (A) and week (B) in people with musculoskeletal pain (n=66). Values are presented as percent. *Statistically significant difference.
number of pain sites was associated with low physical measure scores among nursing home residents. These residents had a significantly greater number of pain sites, which were associated with worse physical function, depression, anxiety, and health-related quality of life.

Functional limitations and depression are common complaints in older adults and, when accompanied by pain, may significantly impact daily life. A recent study showed that pain was significantly associated with physical frailty, as determined by exhaustion, slowness, weakness, low physical activity, and weight loss, in community-dwelling older adults. Another study showed that pain was associated with functional limitations, fatigue, sleeping problems, depressed mood, and quality of life. However, previous research was conducted on the general older population and little is known about the differences between nursing home residents and community-dwelling older adults. Our results indicated that higher current pain intensity was correlated with slower walking speed, mobility, functional independence, and quality of life in nursing home residents and community-dwelling older adults. Higher current pain intensity was also correlated with higher anxiety and depression in both groups, with much stronger correlations observed among nursing home residents.

Previous studies have suggested that nursing home residents believed their pain to be intractable and often did not complain to staff. Our results showing the close association of pain with poor quality of life, physical dysfunction, and high depression and anxiety in nursing home residents suggests that pain must be assessed regularly, even in the absence of a complaint by an older adult. In
### Fig. 3. Distribution of pain sites according to the place of residence in the last year (A) and week (B) in the whole sample (n=146). Values are presented as percent. *Statistically significant difference.

In this context, regular rehabilitation programs targeting pain management and prevention should be implemented in nursing home settings. In addition, pharmacological treatment options should be evaluated. Longitudinal studies are also needed to investigate the most effective pain treatment options and their effects on quality of life, physical function, depression, and anxiety in older adults, especially those living in nursing homes.

Our results suggest the importance of pain assessment to guarantee the health of older adults by demonstrating the high prevalence of pain and the factors associated with pain. In addition, the factors associated with pain differed between nursing home residents and community-dwelling older adults. Pain assessment should aim to characterize the pain type and physical, emotional, functional, and social impairments associated with pain in older adults based on the place of residence.

Our results may have clinical implications. Our finding that nursing home residents were significantly more affected by pain than community-dwelling older adults highlights the importance of including regular pain assessment and management programs in nursing home care settings, even in the absence of complaints by older adults. The musculoskeletal pain sites observed in this study might guide clinicians and researchers in planning rehabilitation programs targeting musculoskeletal pain. However, due to the cross-sectional design of our study, we cannot conclude that the associated factors will decrease when pain decreases. Studies investigating the effects of pain management programs on these associated factors are needed. While we observed no significant difference in pain intensity between the nursing home residents and

<table>
<thead>
<tr>
<th>Site</th>
<th>Community-dwelling older adults (n=73)</th>
<th>Nursing home residents (n=73)</th>
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</thead>
<tbody>
<tr>
<td>Neck</td>
<td>67.1%</td>
<td>69.9%</td>
</tr>
<tr>
<td>Shoulders</td>
<td>60.3%</td>
<td>62.6%</td>
</tr>
<tr>
<td>Elbows</td>
<td>9.6%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Wrist/hands</td>
<td>5.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Upper back</td>
<td>38.8%</td>
<td>*</td>
</tr>
<tr>
<td>Low back</td>
<td>82.6%</td>
<td>83.0%</td>
</tr>
<tr>
<td>Hip/thighs</td>
<td>53.4%</td>
<td>68.5%</td>
</tr>
<tr>
<td>Kness</td>
<td>47.2%</td>
<td>*</td>
</tr>
<tr>
<td>Ankle/feet</td>
<td>30.1%</td>
<td>*</td>
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</tbody>
</table>

### Notes
- *Statistically significant difference.
- The table and figure illustrate the distribution of pain sites according to the place of residence in the last year (A) and week (B) in the whole sample (n=146). Values are presented as percent. The musculoskeletal pain sites observed in this study might guide clinicians and researchers in planning rehabilitation programs targeting musculoskeletal pain. However, due to the cross-sectional design of our study, we cannot conclude that the associated factors will decrease when pain decreases. Studies investigating the effects of pain management programs on these associated factors are needed.
community-dwelling older adults, less pain intensity was significantly associated with physical function, independence, anxiety, depression, and quality of life in nursing home residents. Therefore, clinicians should consider the patient’s place of residence. Our study has several limitations. First, we did not investigate the origin of pain. Disease-specific pain might have different effects on the variables assessed in our study. Moreover, the types and severity of diseases that cause musculoskeletal and neuropathic pain require further investigation. Second, we accepted pain in a broad context and did not differentiate between acute and chronic pain. Third, we included only older adults without significant cognitive impairment. However, cognitively impaired older adults tend to have communication problems and cannot report pain properly; thus, their pain is under-detected. Therefore, our results cannot be generalized to such individuals. Fourth, owing to its cross-sectional design, our study can only reveal associations and cannot infer causality or provide an explanatory clarification for such associations. Finally, the sample size was small and our results are prone to significant bias due to the convenience sampling method. Therefore, longitudinal studies with large sample sizes and more robust sampling methods are needed to draw definitive conclusions.

In conclusion, the frequency of musculoskeletal pain was significantly higher in nursing home residents, whereas that for neuropathic pain was higher in community-dwelling older adults. While current pain intensity was associated with walking speed, mobility, functional independence level, anxiety, depression, and quality of life in both nursing home residents and community-dwelling older adults, these associations were much stronger in nursing home residents. A higher number of pain sites during the last year and week was significantly associated with lower walking speed, mobility, independence level, health-related quality of life, and more anxiety and depression symptoms in older adults living in nursing homes, while only the number of pain sites during the last week, mobility, and health-related quality of life in were significantly associated in community-dwelling older adults. The number of pain sites during the last year was not associated with any study variables in community-dwelling older adults. The results of this study highlight the importance of including regular pain assessment in nursing home care settings, even in the absence of complaints by older adults.

### ACKNOWLEDGMENTS

**CONFLICT OF INTEREST**

The researchers claim no conflicts of interest.

**FUNDING**

None.

**AUTHOR CONTRIBUTION**

Conceptualization, MT, TK, AG; Data curation, MT; Investigation, MT, TK, AG; Methodology, MT, TK, AG; Project administration, AG; Supervision, TK, AG; Writing—original draft, MT, TK; Writing—review & editing, MT, TK, AG.
REFERENCES


A Bibliometric Analysis of Publications on COVID-19 and Older Adults

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Background: Bibliometric analysis is important for guiding future research priorities. We evaluated the most relevant scientific research on coronavirus disease 2019 (COVID-19) and older adults, analyzed current hot topics, and identified the 50 most cited publications. Methods: Articles published between December 1, 2019 and March 17, 2021 were identified using the search terms “COVID-19” or “Novel Coronavirus” or “SARS-CoV-2” or “2019-nCoV” and “geriatrics” or “older adults” or “elderly” appearing in the title, abstract, keywords, or keywords plus. Original research articles, reviews, editorial materials, and letters were included. Information on articles year, journal, title, author, country, affiliation, keywords, document type, and counts of citations was collected. VOSviewer was used to analyze keywords. Results: A total of 784 publications were included. The most common keywords were “COVID-19” and “older adults,” which were strongly related to “social isolation,” “dementia,” “mortality,” and “loneliness.” The most active (40.8%) and most cited (1,578) country was the United States. The Journal of the American Geriatric Society had the largest number of publications (22.7%) and citations (947). The most researched (84.0%) and most cited areas were geriatrics-gerontology (2,882). The median number of citations for the most cited 50 articles was 46.8. Conclusion: The results of the bibliometric analysis provided information about the quality and research areas of published studies on COVID-19 and older adults. Social and psychological support, nutrition, vaccines, and telemedicine may be hot research topics for the future.

Key Words: Bibliometrics, COVID-19, Geriatrics, Older adults, Web of Science

INTRODUCTION

The pneumonia outbreak that started in Wuhan, China in December 2019 and became a global pandemic was named coronavirus disease 2019 (COVID-19) and was caused by the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of March 5, 2021, over 110 million cases and over 2.5 million deaths have been reported worldwide.

Many diseases cause greater morbidity and mortality in patients aged 65 years and older owing to the frailty, comorbidities, and age-related physiological changes in this population. Older adults are at serious risk for COVID-19 and also have higher mortality rates owing to the disease. Furthermore, older adults have experienced social and psychological effects, apart from the disease, during the pandemic.

Bibliometry is a statistical method that determines which topics are trending by quantitatively analyzing articles in a particular field. The results of bibliometric analyses may guide future studies by determining the quality and main research areas of existing publications in specific fields. Bibliometric analysis also enables researchers to easily obtain information about subjects of interest from among numerous and increasing number of published articles. The Web of Science (WoS) is an online database comprising almost all relevant research articles and various bibliometric analysis tools. Bibliometric analysis studies have been reported on various fields of medicine.

The pandemic has not yet been controlled, and older adults are the most affected population. Therefore, bibliometric analysis of
COVID-19 and older adults is important to identify related subjects that require further research by determining which areas have been researched thus far and which have been most cited. However, to date, there has been no bibliometric analysis of COVID-19 in older adults. Thus, to guide future research priorities, the present study evaluated the most relevant scientific research on COVID-19 and older adults, analyzed current hot topics, and identified the 50 most cited publications.

**MATERIALS AND METHODS**

The data used in this bibliometric citation analysis were obtained from the Thomson Reuters WoS Core Collection database (Philadelphia, PA, USA). As the WoS database provides bibliometric analysis, it has been used in most previous bibliometric analysis studies. Therefore, we also used this database. We scanned the global literature on geriatric COVID-19 published between December 1, 2019 and March 17, 2021 for articles containing the terms “COVID-19” or “Novel Coronavirus” or “SARS-CoV-2” or “2019-nCoV” and “geriatrics” or “older adults” or “elderly” in the title, abstract, keywords, or keywords plus (additional relevant but overlooked keywords not listed by an article’s author or publisher but identified by Thomson Reuters). The corresponding author then reviewed the titles of all articles. We also read the abstracts of articles whose titles were not clear and excluded articles not related to COVID-19 or older adults. Missing article information was obtained by linking to other search platforms such as PubMed. The examination of the titles, abstracts, keywords, or keywords plus of studies on older adults and geriatrics showed that some studies included patients aged 60 years, while others included patients aged 65 years. We included studies that performed subgroup analyses of older adults. The keywords were the most common terms in all research fields and were selected using a combination of the research results from multiple search queries in the WoS Core Collection. We recorded article information such as the year of publication, journal, title, author, country, affiliation, keywords, document type, and citation counts, all of which were exported to CSV format. We defined authorship as primary and co-authorship. We also recorded authors’ countries and affiliations for each article. If more than one author of an article had the same country or affiliation, only one author was recorded. The number of citations was determined using WoS database analyses to identify the top 50 cited articles. From these results, we also recorded the journals in which the top 50 articles were published, article type, country of the corresponding author, publication date, and number of citations. VOSviewer (version 1.6.16, https://www.vosviewer.com) is a software tool for constructing and visualizing bibliometric networks that we used to analyze keyword frequency to clarify the research trends on COVID-19 in older adults.

**Statistical Analysis**

We applied descriptive statistical methods using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). All data are reported as numbers, percentages, and bar charts in the tables and figures.

**RESULTS**

We identified a total of 2,728 articles. After excluding articles that were not relevant to “COVID-19 and older adults,” we analyzed 784 publications on COVID-19 and older adults indexed in the WoS database between December 1, 2019 and March 17, 2021, which included 350 (49.0%) original research articles, 58 (8.1%) review articles, 123 (17.3%) editorial materials, and 182 (25.5%) letters (Fig. 1). Among them, 63 (7.6%) papers were published in 2021 (through March 17), and the other 650 articles were published in 2020. No papers on COVID-19 and older adults were published in 2019. Almost all the publications (710, 99.6%) were written in English (two German and one French).

More than 1,200 institutions in 70 countries or regions have reported the results of COVID-19 research in older adults. The leading countries in the literature analyzed were the United States (291 reports, 40.8%), China (84 reports, 11.8%), Canada (62 reports, 8.7%), England (59 reports, 8.3%), and Italy (58 reports, 8.1%). The most cited countries were the United States (1,578), China (815), England (433), Canada (432), and Italy (340) (Table 1). The most active organizations were Harvard University (35,
4.9%), US Veterans Health Administration (34, 4.8%), and University of California System (26, 4.6%), while the most cited organizations were Harvard University (245), University of London (237), and University of California (202) (Table 1).

The Journal of the American Geriatric Society had the highest number of publications (178, 22.7%), followed by the Journal of Gerontological Social Work (61, 7.8%) and The American Journal of Geriatric Psychiatry (57, 7.3%). The most cited journals were The Journal of the American Geriatric Society (947), American Journal of Geriatric Psychiatry (283), and Journal of Nutrition, Health and Aging (271) (Table 2).

The most highly researched areas were geriatrics-gerontology (599, 84.0%), psychiatry (143, 20.0%), and social work (58, 8.1%). The most cited research areas were geriatrics-gerontology (2,882), psychiatry (670), and nutrition dietetics (395) (Fig. 2). The most cited author was Joseph G. Ouslander from Florida Atlantic University/Charles E. Schmidt College of Medicine, with 10 articles and 159 citations (Table 2).

Keywords that were provided by the authors and that occurred more than five times in the WoS core database were enrolled in the final analysis. Among the 1,028 keywords, 49 met this threshold. The most common keywords were “COVID-19” (total link strength 231) and “older adults” (total link strength 102), which were strongly linked to “social isolation,” “dementia,” “mortality,” and “loneliness” (Fig. 3).

In addition to the analysis of 784 publications on COVID-19 and older adults, the top 50 most cited publications are listed in Supplementary Table S1. These 50 articles had a median of 46.8 citations (range, 18–312 citations).

**DISCUSSION**

This is the first bibliometric study to summarize the most relevant evidence on COVID-19 in older adults. Evidence is quickly accumulating because this is a vulnerable population with worse outcomes. The COVID-19 pandemic has affected the entire world in a short time. While vaccination is becoming widespread, some countries still cannot obtain the vaccine. Moreover, as shown in this bibliometric analysis, few studies have focused on vaccination in older adults. It is unclear whether these findings will remain consistent by the time the pandemic ends. Thus, it is essential to support older adults and protect them from both COVID-19 and pandemic-related social and psy-

<table>
<thead>
<tr>
<th>Table 1. The most active countries and organizations associated to publications on COVID-19 and older adults</th>
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<tbody>
<tr>
<td><strong>Top 10 countries</strong></td>
</tr>
<tr>
<td>USA</td>
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<tr>
<td>China</td>
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<tr>
<td>Canada</td>
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<td>Netherlands</td>
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<tr>
<td><strong>Top 10 organizations</strong></td>
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<tr>
<td>Harvard University</td>
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<tr>
<td>US Veterans Health Administration</td>
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<tr>
<td>University of California System</td>
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<tr>
<td>University of London</td>
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<tr>
<td>Geriatric Research Education Clinical Center</td>
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<tr>
<td>Institut National de la Sante et de la Recherche Medicale</td>
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<tr>
<td>University of Toronto</td>
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<tr>
<td>Pennsylvania Commonwealth System of Higher Education</td>
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<td>State University System of Florida</td>
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<td>University of Michigan</td>
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Values are presented as number (%). COVID-19, coronavirus disease 2019.
The results of the current study showed that “COVID-19” and “older adults,” the two most prevalent keywords, were strongly linked to “social isolation,” “dementia,” “mortality,” and “loneliness.” These keywords were strongly linked likely because the disease mortality was the highest in older adults whose mental health is affected by restrictions and social isolation.

The most cited article was “Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients” published in The Journal of Infection. This article focused on factors associated with COVID-19 severity and mortality in older adults, such as the presence of malignancy, and also demonstrated higher COVID-19 mortality and severity in older adults compared to younger people. Moreover, the 784 publications included in the present study mostly investigated factors affecting mortality in older adults and suggested the need for future research based on these factors (such as the presence of malignancy, symptoms of dyspnea, high neutrophil-to-lymphocyte ratio, C reactive protein level, lymphopenia, and basic biological mechanisms of aging). The hotspots of future research on this subject may be prospective studies on reducing COVID-19 mortality in older adults.

The second most cited article, “Mental health services for older adults in China during the COVID-19 outbreak,” published in The Journal of the American Geriatric Society, one of the journals with a high impact factor, had the highest number of publications and citations on COVID-19 and older adults.

Most publications were in the fields of geriatrics-gerontology and psychiatry. Although there have been few studies on nutrition, it was the third most cited topic after geriatrics-gerontology and psychiatry. This result suggests that this topic is of interest, and further research is needed.

Among the top 50 cited publications of COVID-19 in older adults, the most cited articles were reviews. Seven articles were based on long-term care. Among these publications, Italy was the non-English-speaking and European country with the highest number of articles.

The results of the current study showed that knowledge of existing publications on older patients and COVID-19 may help researchers better understand issues that require further research.

The present study found that the United States had the highest number of publications on COVID-19 and older adults. This finding could be related to several factors such as its large population, its status as one of the countries most affected by the pandemic, its significant resources for medical research, and its well-developed and reliable data management systems. The Journal of the American Geriatrics Society, one of the journals with a high impact factor, had the highest number of publications and citations on COVID-19 and older adults.

Most publications were in the fields of geriatrics-gerontology and psychiatry. Although there have been few studies on nutrition, it was the third most cited topic after geriatrics-gerontology and psychiatry. This result suggests that this topic is of interest, and further research is needed.

Table 2. The most active journals and authors of publications on COVID-19 and older adults

<table>
<thead>
<tr>
<th>Top 10 journals</th>
<th>Number of publications</th>
<th>Count of citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal of the American Geriatrics Society</td>
<td>178 (22.7)</td>
<td>947</td>
</tr>
<tr>
<td>Journal of Gerontological Social Work</td>
<td>61 (7.8)</td>
<td>87</td>
</tr>
<tr>
<td>American Journal of Geriatric Psychiatry</td>
<td>57 (7.3)</td>
<td>283</td>
</tr>
<tr>
<td>International Psychogeriatrics</td>
<td>48 (6.1)</td>
<td>161</td>
</tr>
<tr>
<td>Aging-US</td>
<td>43 (5.5)</td>
<td>174</td>
</tr>
<tr>
<td>Journal of Nutrition Health Aging</td>
<td>43 (5.5)</td>
<td>271</td>
</tr>
<tr>
<td>Age and Ageing</td>
<td>36 (4.6)</td>
<td>210</td>
</tr>
<tr>
<td>Frontiers in Psychiatry</td>
<td>35 (4.5)</td>
<td>26</td>
</tr>
<tr>
<td>Journal of Aging Social Policy</td>
<td>33 (4.2)</td>
<td>191</td>
</tr>
<tr>
<td>Geriatrics Gerontology International</td>
<td>31 (4.0)</td>
<td>65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Top 10 authors</th>
<th>Number of publications</th>
<th>Count of citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouslander, Joseph G.</td>
<td>10 (4 first author)</td>
<td>159</td>
</tr>
<tr>
<td>Annweiler, Cedric</td>
<td>7 (1 first author)</td>
<td>30</td>
</tr>
<tr>
<td>Arai, Hidenori</td>
<td>7 (0 first author)</td>
<td>48</td>
</tr>
<tr>
<td>Cesari, Matteo</td>
<td>7 (1 first author)</td>
<td>40</td>
</tr>
<tr>
<td>Rolland, Yves</td>
<td>6 (2 first author)</td>
<td>16</td>
</tr>
<tr>
<td>Lapid, Maria I.</td>
<td>5 (2 first author)</td>
<td>13</td>
</tr>
<tr>
<td>Morley, John E.</td>
<td>5 (3 first author)</td>
<td>99</td>
</tr>
<tr>
<td>Reynolds, Charles F.</td>
<td>5 (3 first author)</td>
<td>36</td>
</tr>
<tr>
<td>Rosen, Tony</td>
<td>5 (3 first author)</td>
<td>33</td>
</tr>
<tr>
<td>Sacco, Guillaume</td>
<td>5 (2 first author)</td>
<td>15</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
Lancet Psychiatry, emphasized the effects of the pandemic on mental health in older adults with increased depression. Along with increased depression, the study also reported decreased cognitive functions and consequently daily functionality. Therefore, there is a need for psychological services for older adults. Retrospective studies reported increased suicide rates among older adults during the past SARS outbreak. This situation highlights the importance of examining the impact of COVID-19 on mental health in older adults and finding solutions to prevent the pandemic from adversely affecting their mental health. Based on this identified need, The American Journal of Geriatric Psychiatry proposed to act as a forum for research on COVID-19 and mental health in older adults. One study, which was among the 50 most cited articles, reported risk factors that may increase suicide and proposed solutions for prevention in older adults during COVID-19. Future studies may include the implementation and results of these proposed solutions to protect mental health in older adults.

Dementia was strongly linked to the most prevalent keywords. A study examining the effect of the COVID-19 pandemic on Alzheimer’s dementia (AD) reported that COVID-19 increases mortality and morbidity in patients with AD and may have affected AD diagnosis and clinical management, emphasizing that the clinical presentation of COVID-19 may be atypical in dementia patients and demonstrating that identifying symptoms in these patients may be challenging owing to cognitive dysfunction, resulting in potential delays in diagnosis and hospitalization. Thus, many studies have been conducted on dementia and COVID-19, and there is a need for additional studies that provide recommendations and practices to allow close follow-up of patients with dementia.

Loneliness has become an increasing problem for older adults in recent years. Several group interventions have been described to help alleviate loneliness in older adults. Among these, “Circle of Friends” is an evidence-based intervention that has proven to be effective and sustainable for the socialization of older adults and has been adapted to telehealth during the pandemic. Additional studies are needed to develop telehealth and online group interventions to help lonely and isolated older adults to connect. Among the 50 most cited articles, some included loneliness in older adults owing to social isolation and the importance of supporting older adults on these issues. Among these, some studies also proposed solutions, including staying connected with relatives; ex-
ercising; practicing telehealth; and using digital resources, online tools, and social media.\textsuperscript{26,27} The current data highlight the need to develop projects focusing on psychological services to support older adults during the pandemic. Furthermore, as technology advances, the importance of telemedicine has increased, which has been made obvious in the medical literature. It is essential to provide this service to older adults who cannot visit the hospital owing to the pandemic. As long as the pandemic continues, the need for research on telemedicine is likely to increase. Therefore, this may be an important future research topic.

The current study had strengths and limitations. The strengths of the study are that it provided quick access to the core of evidence around a topic and identified articles focused on older adults. One of the limitations was that it searched only one database (WoS Core Collection database); thus, it did not collect all available evidence. In addition, we did not analyze co-authorship and the relationships between publications and research groups. With changes in results over time and additional publications, future analyses could re-evaluate these findings at the end of the pandemic.

In conclusion, the results of the present bibliometric analysis revealed that most research has evaluated mortality, social isolation, dementia, and loneliness in COVID-19 and older adults. Most studies have been conducted to reveal these problems. Future hot research topics may include social and psychological support, vaccination, nutrition, and telemedicine, all of which could be the means to address the problems identified.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4235/agmr.21.0060.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researcher claims no conflicts of interest.

FUNDING

None.

Fig. 3. Bibliometric analysis of the keywords in publications on coronavirus disease 2019 (COVID-19) and older adults.
REFERENCES

Perceived Recovery Time from Common Cold as a Possible Indicator of Physical Resilience

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Background: Resilience refers to the ability to recover function after encounter with stressors. While psychological resilience refers to the ability to cope with psychological stress, physical resilience refers to functional restoration after biomedical challenges. However, there is no gold standard to assess physical resilience. Accordingly, we explored whether the perceived recovery time from common cold could be used to represent physical resilience.

Methods: We analyzed data of individuals aged 72–86 years who had participated in the Korean Frailty and Aging Cohort Study in 2019. Among the 1,455 survey participants, 594 with asthma and chronic obstructive pulmonary disease and missing data were excluded. The remaining 861 participants were divided into three groups according to the number of days required for recovery from common cold (Group 1, 1–4 days; Group 2, 5–7 days; and Group 3, ≥8 days). The relationship between recovery time and psychological resilience scale (Brief Resilience Scale [BRS]) score, physical frailty (Fried’s physical frailty phenotype and the Korean Frailty Index for Primary Care [KFI-PC]), and frailty outcome was investigated.

Results: Group 3 comprised individuals more likely to be women, sleep less, be less physically active, fall more often, and have a low EuroQol visual analogue scale score. BRS scores differed significantly among the three groups (Group 1, 13.29; Group 2, 14.32; Group 3, 15.22; p<0.001). In multivariate analysis, post-hoc analysis with the Bonferroni method revealed significant differences in BRS between Groups 1–2 and Groups 1–3. However, the KFI-PC and number of falls did not differ significantly.

Conclusions: Longer days of recovery from cold were associated with worse BRS scores. However, neither frailty nor the number of falls was related.

Key Words: Common cold, Frailty, Psychological resilience

INTRODUCTION

Frailty is defined as a significant decline in the functional reserve of multiple organ systems and the resultant extreme vulnerability of an individual to endogenous and exogenous stressors (such as infection, injury, surgery, or some medicines), leading to a higher risk of accelerated functional decline and adverse health-related outcomes.1) The adverse health-related outcomes caused by frailty include falls, delirium, immobility, or disability, and, consequently, hospitalizations, institutionalization, or mortality.2)

Over the past decade, resilience has increasingly become a focus of research in the behavioral and medical sciences. Frail older adults have a preexisting vulnerability to stressors, often resulting in poor outcomes. However, some people recover rapidly from stressors without such outcomes. These individuals are categorized as resilient. Resilience has been defined in various ways, in-
cluding the ability to rapidly recover from various stressors. The factors that promote resilience, including physical health, a sense of self, social belonging, self-belief, and altruism, overlap with those that reduce frailty. Therefore, an understanding of resilience may help in the study of frailty. Furthermore, a deeper understanding of why some individuals maintain or regain function following stressors, while others do not, may help identify protective factors and strategies to promote lasting health.

There are two types of resilience. The first is “psychological resilience,” which refers to a person’s ability to adapt well in the face of adversity, trauma, tragedy, threats, or significant sources of stress. The second is “physical resilience,” which focuses on the maintenance or recovery of functions after biomedical or pathological challenges. Physical resilience is presumed to reflect adaptive physiological responses at the level of organs, cells, and molecules of the musculoskeletal, neurological, and immunological systems that support homeostasis under changing conditions.

Psychological resilience is measured with well-organized standard assessments such as the Brief Resilience Scale (BRS). However, there is no gold standard test for measuring physical resilience.

We hypothesized that the time needed to recover from a common cold could be an indicator of physical resilience, as the immunologic response is one component of physical resilience. A previous study showed that self-reported health was related to the duration of common cold. Therefore, we investigated whether the day(s) required for recovery from common cold could represent physical resilience by comparing this number with BRS scores, physical frailty, and health variables to ensure validity.

MATERIALS AND METHODS

Participants
The Korean Frailty and Aging Cohort Study (KFACS) is a multicenter longitudinal study with a baseline survey conducted from 2016 to 2017 in Korea with follow-ups every 2 years. The inclusion criteria of the KFACS were age 70–84 years, currently living in the community, no plans to move out in the next 2 years, and no problems with communication and no prior dementia diagnosis. In 2018, 1,455 participants aged 72–86 years who were included in the study in 2017 were asked to complete a questionnaire on the time required to recover from a common cold. Patients with asthma and chronic obstructive pulmonary disease (n = 145) were excluded from the analysis because they may not be able to differentiate common cold from their disease. Participants who answered, “have never caught a cold” (n = 320) were also excluded. Finally, those who did not answer the entire questionnaire were also excluded (Fig. 1).

Measures

Perceived days to recover from common cold
We asked the following question: “If you have a common cold, how many days does it usually take for recovery?” (Based on the start date of the cold).

Brief Resilience Scale
We used the Korean version of the BRS to assess psychological resilience. The six items of the BRS are (1) I tend to bounce back quickly after hard times, (2) I have a hard time making it through stressful events (R), (3) It does not take me long to recover from a stressful event, (4) It is hard for me to bounce back when something bad happens (R), (5) I usually come through difficult times with little trouble, and (6) I tend to take a long time to get over setbacks in my life (R). “R” refers to the reverse coding applied to items 2, 4, and 6. The following instructions were used to administer the scale: “Please indicate the extent to which you agree with each of the following statements using the following scale: 1 = strongly agree, 2 = agree, 3 = neutral, 4 = disagree, and 5 = strongly disagree.” We summed these scores, with higher scores indicating worse psychological resilience.

Frailty and frailty outcome
Frailty: We defined frailty using Fried’s physical frailty phenotype and the Korean Frailty Index for Primary Care (KFI-PC). The KFI-PC comprehensively evaluates many aspects of physical, social, and emotional health.

Frailty outcomes: The frailty outcomes included the number of hospitalizations and falls over the past year, along with instrumental activities of daily living (IADL) disability. IADL disability was
defined as the need for assistance in one or more of the 10 items. The answer “I do not know” was treated as a missing value.

Ethical Approval
The study protocol was approved by the Institutional Review Board of Kyung Hee University Hospital (No. 2021-03-060) and complied with the ethical rules for human experimentation in the Declaration of Helsinki. Informed consent was obtained from all participants or their proxy.

Statistical Analysis
We used the analysis of variance and chi-square test for continuous and categorical variables, respectively. Analysis of covariance (ANCOVA) was used to control for confounding variables.

RESULTS
The participants were divided into three groups according to the numbers of perceived days required for recovery from common cold (Group 1, 1–4 days; Group 2, 5–7 days; Group 3, ≥ 8 days) (Table 1). The mean ages of the three groups did not differ significantly, and the mean age of all subjects was approximately 78 years. Participants in Group 3 (≥ 8 days for recovery) were more likely to be women (60.8%, p = 0.004), sleep less, less physically active, fall more, and have a low EuroQol visual analogue scale (EQ-VAS) score. The BRS scores differed significantly among the three groups (Group 1, 13.29; Group 2, 14.32; Group 3, 15.22; p < 0.001). The KFI-PC was higher in Group 3 than in other groups (Group 1, 0.15; Group 2, 0.16; Group 3, 0.17; p = 0.034).

Tables 2–4 show the results of ANCOVA. Model 1 was adjusted for sex, Model 2 was further adjusted for sleep time, Model 3 was additionally adjusted for IPAQ, and Model 4 was additionally adjusted for EQ-VAS scores. Table 2 shows the differences in BRS scores among the three groups. Even after adjusting for the aforementioned factors, the difference between the three groups was significant in Model 4 (Group 1, 13.55; Group 2, 14.32; Group 3, 14.84; p < 0.001). Table 3 presents the relationships with the number of falls and shows no significant results. Table 4 shows the results for KFI-PC, in which we observed no significant differences.

The Bonferroni method was used for post-hoc analysis in Tables 2–4. In Table 2, which was related to the BRS score, the differences between Groups 1 and 2 in Models 1, 2, and 3 were significant. The difference between Groups 1 and 3 was also significant after adjusting for all confounding factors. In Table 3, which represented the number of falls, we observed a significant difference between the groups only for Model 1. We observed no significant difference in KFI-PC.

Table 1. Participant characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Perceived days required to recover from common cold</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–4 (n = 335)</td>
<td>5–7 (n = 299)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>77.9 ± 4.0</td>
<td>77.9 ± 3.7</td>
</tr>
<tr>
<td>Sex, female</td>
<td>158 (47.2)</td>
<td>146 (48.8)</td>
</tr>
<tr>
<td>Income per month (&lt; 2,000,000 Korean won)</td>
<td>217 (64.8)</td>
<td>171 (57.2)</td>
</tr>
<tr>
<td>Education (y)</td>
<td>9.7 ± 4.8</td>
<td>9.8 ± 6.9</td>
</tr>
<tr>
<td>EQ-VAS score</td>
<td>77.1 ± 15.9</td>
<td>75.1 ± 16.6</td>
</tr>
<tr>
<td>Sleep at night (hr)</td>
<td>6.4 ± 1.5</td>
<td>6.3 ± 1.4</td>
</tr>
<tr>
<td>MNA, malnutrition risk (score &lt; 12)</td>
<td>52 (15.5)</td>
<td>52 (17.4)</td>
</tr>
<tr>
<td>IPAQ (cal/wk)</td>
<td>3,648.3 ± 3,959.6</td>
<td>3,670.0 ± 3,977.6</td>
</tr>
<tr>
<td>Number of chronic diseases</td>
<td>2.0 ± 1.4</td>
<td>1.9 ± 1.4</td>
</tr>
<tr>
<td>Number of medications</td>
<td>3.9 ± 2.9</td>
<td>4.1 ± 3.2</td>
</tr>
<tr>
<td>Number of hospital admissions in the last year</td>
<td>0.2 ± 0.6</td>
<td>0.2 ± 0.5</td>
</tr>
<tr>
<td>Number of falls in the last year</td>
<td>0.3 ± 0.7</td>
<td>0.5 ± 1.9</td>
</tr>
<tr>
<td>IADL disability</td>
<td>13 (3.9)</td>
<td>12 (4.0)</td>
</tr>
<tr>
<td>Brief Resilience Scale score</td>
<td>13.3 ± 4.3</td>
<td>14.3 ± 4.7</td>
</tr>
<tr>
<td>Physical frailty</td>
<td>2 (0)</td>
<td>14 (4.7)</td>
</tr>
<tr>
<td>KFI-PC score</td>
<td>0.15 ± 0.07</td>
<td>0.16 ± 0.08</td>
</tr>
</tbody>
</table>

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

EQ-VAS, EuroQol visual analogue scale; MNA, Mini Nutritional Assessment; IPAQ, International Physical Activity Questionnaire; IADL, instrumental activities of daily living; KFI-PC, Korean Frailty Index for Primary Care.
The results of this study showed the association between increased days of recovery from a common cold and lower psychological resilience (BRS score), lower quality of life (EQ-VAS score), and lower physical activity level (IPAQ score). However, we observed no association between recovery days and frailty index and frailty outcomes, such as the number of falls.

It may be not surprising that the number of perceived days required for recovery from a cold was not related to frailty, as frailty refers to a “functionally declined and stressor-vulnerable state,” while physical resilience refers to the ability to recover from stressors. Moreover, several factors influence physical resilience, including both emotional and social as well as physical factors. Previous studies have shown that an individual’s degree of frailty and resilience are not simply opposite concepts. Although there is a conceptual overlap between frailty and resilience, frail individuals tend to have a lower resilience and resilience is a continuous spectrum that can change throughout life. In contrast, frailty often evolves near the end of life and manifests in only a small proportion of older adults. The lack of association between recovery days from cold and frailty outcomes such as the number of falls.

### Table 2. Brief Resilience Scale scores according to the number of days required to recover from common cold

<table>
<thead>
<tr>
<th>Perceived days required to recover from common cold</th>
<th>1–4 (n = 335)</th>
<th>5–7 (n = 299)</th>
<th>≥ 8 (n = 227)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>13.33 ± 0.25</td>
<td>14.35 ± 0.27*</td>
<td>15.13 ± 0.31*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>13.40 ± 0.25</td>
<td>14.34 ± 0.27*</td>
<td>15.04 ± 0.31*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>13.40 ± 0.25</td>
<td>14.35 ± 0.27*</td>
<td>15.03 ± 0.31*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model 4</td>
<td>13.55 ± 0.24</td>
<td>14.32 ± 0.25</td>
<td>14.84 ± 0.29*</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard error.
Model 1, adjusted for sex; Model 2, Model 1 + sleep time at night; Model 3, Model 2 + International Physical Activity Questionnaire score; Model 4, Model 3 + EuroQol visual analogue scale score.
Each model was analyzed using an analysis of covariance model and post-hoc Bonferroni correction tests.
*p<0.05, significant difference compared with the “4 days or less” group.

### Table 3. Falls in the past year according to the number of days required to recover from common cold

<table>
<thead>
<tr>
<th>Perceived days required to recover from common cold</th>
<th>1–4 (n = 335)</th>
<th>5–7 (n = 299)</th>
<th>≥ 8 (n = 227)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>0.28 ± 0.07</td>
<td>0.53 ± 0.08*</td>
<td>0.43 ± 0.09*</td>
<td>0.049</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.29 ± 0.07</td>
<td>0.53 ± 0.08</td>
<td>0.42 ± 0.09</td>
<td>0.069</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.29 ± 0.07</td>
<td>0.53 ± 0.08</td>
<td>0.43 ± 0.09</td>
<td>0.069</td>
</tr>
<tr>
<td>Model 4</td>
<td>0.31 ± 0.07</td>
<td>0.53 ± 0.08</td>
<td>0.40 ± 0.09</td>
<td>0.108</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard error.
Model 1, adjusted for sex; Model 2, Model 1 + sleep time at night; Model 3, Model 2 + International Physical Activity Questionnaire score; Model 4, Model 3 + EuroQol visual analogue scale score.
Each model was analyzed using an analysis of covariance model and post-hoc Bonferroni correction tests.
*p<0.05, significant difference compared with the “4 days or less” group.

### Table 4. KFI-PC according the number of days required to recover from common cold

<table>
<thead>
<tr>
<th>Perceived days required to recover from common cold</th>
<th>1–4 (n = 335)</th>
<th>5–7 (n = 299)</th>
<th>≥ 8 (n = 227)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>0.155 ± 0.004</td>
<td>0.163 ± 0.004</td>
<td>0.167 ± 0.005</td>
<td>0.187</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.156 ± 0.004</td>
<td>0.163 ± 0.004</td>
<td>0.166 ± 0.005</td>
<td>0.231</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.156 ± 0.004</td>
<td>0.163 ± 0.004</td>
<td>0.165 ± 0.005</td>
<td>0.318</td>
</tr>
<tr>
<td>Model 4</td>
<td>0.159 ± 0.004</td>
<td>0.163 ± 0.004</td>
<td>0.161 ± 0.005</td>
<td>0.777</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard error.
KFI-PC, Korean Frailty Index for Primary Care; Model 1, adjusted for sex; Model 2, Model 1 + sleep time at night; Model 3, Model 2 + International Physical Activity Questionnaire score; Model 4, Model 3 + EuroQol visual analogue scale score.
Each model was analyzed using an analysis of covariance model and post-hoc Bonferroni correction tests.
Resilience is a dynamic construct that can be ascertained through dynamic stimulation tests. As an alternative approach in an observational study, comparing two measurements—one before and one directly after the stressor—with an outcome is needed. We could not present either way in this study, which can be a limitation of this study. Nonetheless, infection is known to be one of the stressors used to evaluate physical resilience, and recovery trajectories after a recent disease (e.g., influenza) is suggested to be one of the best available assessments of resilience. In a similar approach, we surveyed the recovery time from common cold, and we believe that it could be an indirect marker for physical resilience, at least with respect to immunity. Dynamic resilience measurements (trajectories, stimulus-response tests) are not yet sufficiently robust, but recovery trajectories after a recent disease (e.g., influenza, cardiac decompensation, or chronic obstructive pulmonary disease exacerbation) may be one of the best available examples of resilience assessment. However, the common cold is a milder disease than influenza, and therefore, the plausibility of recovery from common cold as a physical resilience marker needs to be studied further.

This study has some limitations. First, we retrospectively gathered information about recovery from cold; thus, participant recall errors were possible. However, individuals frequently catch the common cold, and self-awareness of days required to recover from a cold is a part of everyday culture. Adults are estimated to experience 2–5 cold events per year; thus, adults aged > 25 years will have experienced over 100 episodes of common cold during their lives, making the common cold a familiar part of life. In ideal circumstances, a clinical examination would also have been conducted; however, a more reasonable approach is the use of self-diagnosis in clinical research studies of common cold because of the familiarity of the subjects with common cold and the lack of a biological definition for common cold. Therefore, data on the subjective days required for recovery from a cold are expected to be precise. Second, this study gathered information about colds using a self-report questionnaire; therefore, the answers regarding experiences with common cold might have referred to an illness other than it. However, the self-report format is often used in research because people are generally familiar with colds. Furthermore, the Food and Drug Administration encourages the use of patient-reported surveys that come directly from the patient because they are not biased by interpretations of physicians or others. Third, the perceived time required to recover from common cold may be influenced by subjective health and mood. For instance, respondents with lower EQ-VAS scores recalled more days to recover from the cold, which could be a recall bias. However, the EQ-VAS score was adjusted in these multivariate analyses and the possibility of recall bias was low. We also analyzed its association with the BRS score while considering the EQ-VAS score for subjective health. However, the ANCOVA did not include mood or depression, which may have led to recall bias. Fourth, while the BRS has been validated for Korean college students, it has not yet been validated for Korean older adults. Fifth, although we showed an association between days required for recovery from a cold and the psychological resilience scale score, quality of life score, and physical activity level, these relationships may not be enough evidence to represent physical resilience.

Almost all older adults experience common colds; thus, this common stressor may be useful for evaluating physical resilience. Moreover, patient-reported surveys of common colds are reliable. Therefore, our finding of the association between the average number of days required for recovery from common cold and psychological resilience supports its potential as a marker of physical resilience.

In conclusion, the average number of days required for recovery from common cold was strongly associated with psychological resilience. The number of days required to recover from common cold may be an indirect marker for physical resilience, at least with respect to immunity, as it may represent the recovery capacity after a stressor such as a viral infection. Although the recovery days were not related to the frailty index or number of falls in this cross-sectional study, a longitudinal study is needed to measure health outcomes immediately before and after encounter with a stressor.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

The Ministry of Health and Welfare of the Republic of Korea financed this research (No. HI15C3153). The Korean Health Industry Development Institute (KHIDI) provided funding for this study under the Korea Health Technology R&D Project.

AUTHOR CONTRIBUTIONS

Conceptualization, CWW, SK; Data curation, YKK, SK; Funding acquisition, CWW; Investigation, CWW, SK; Methodology, CWW, SK, YKK; Writing—original draft, YKK, SK; Writing—review & editing, YKK, SK, BSK, MJJK, JSY, EJJ, HNL, CWW.

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Combined Impact of Positive Screen for Sarcopenia and Frailty on Physical Function, Cognition and Nutrition in the Community Dwelling Older Adult

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Background: While sarcopenia and frailty independently contribute to functional impairment and disability, the combined impact resulting from their interplay is unclear. We investigated if functional, physical, cognitive, and nutritional measures were more adversely affected in community-dwelling older adults who were screened positive for both frailty and sarcopenia. Methods: Using the FRAIL (≥1) and SARC-F (Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls) (≥1) scales for screening, we categorized 200 participants (age, 67.9±7.9 years) as combined (both positive, 12.5%), intermediate (either positive, 25.5%), or robust (both negative, 62%). Results: Comparisons of the three groups showed that the combined group had significantly worse functional ability (Frenchay Activities Index and Modified Barthel Index), physical performance (knee extension, gait speed, and Short Physical Performance Battery score), cognition/mood (Chinese Mini-Mental State Examination [CMMSE] score and Geriatric Depression Scale), and nutrition (Mini Nutritional Assessment [MNA] score) (p<0.05, one-way analysis of variance). Post-hoc comparisons revealed similar findings between the combined and robust groups, except for knee extension and CMMSE scores. Only MNA scores were significantly lower between the intermediate and robust groups. Conclusion: Functional ability, physical performance, and nutrition were more adversely affected in our study population of community-dwelling older adults who screened positive for both frailty and sarcopenia than in those who screened positive for either or neither, supporting the use of community screening for early detection and intervention for both frailty and sarcopenia as opposed to either alone.

Key Words: Sarcopenia, Frailty, Community-dwelling

INTRODUCTION

Frailty is a modern geriatric giant,1,2) defined as a state of increased vulnerability with a poor restoration of homeostasis after a stressor event that increases an individual’s susceptibility to increased dependency, adverse outcomes, and death.3-5) The reported prevalence of frailty in community-dwelling older adults in the Asia-Pacific region is 3.5%–27%.3) With the worldwide demographic trend of population aging, the impact of frailty is expected to rise in tandem, resulting in an increasing burden on healthcare systems and the escalation of healthcare costs.6,7) Sarcopenia is a related but a distinct condition8) that refers to the progressive loss of skeletal muscle mass and strength that occurs with aging.9) Similar to frailty, sarcopenia predisposes older individuals to adverse consequences such as falls, disability, and mortality.3,10) The reported prevalence of sarcopenia is 6%–22% in adults aged ≥ 65 years, depending on the care setting.11) The plausible biological mechanisms linking sarcopenia and frailty include

Received: June 24, 2021
Revised: September 7, 2021
Accepted: September 7, 2021
inflammatory responses, oxidative stress, and hormonal dysregulation. The complex intertwining relationship between sarcopenia and frailty has been likened to a “chicken and egg” situation. Sarcopenia is believed to be a fundamental component and possible antecedent of frailty, resulting in reduced muscle strength and gait speed, which characterize the physical manifestation of frailty. Conversely, weight loss, sedentary behavior, cognitive impairment, and social isolation, which are commonly associated with frailty, can lead to reduced muscle mass and impaired muscle function.

While sarcopenia and frailty independently contribute to functional impairment and disability, the combined impact resulting from the interplay between these two conditions is unclear. The presence of both syndromes was associated with poorer self-rated health, recurrent hospital admissions, polypharmacy, multiple medical clinic appointments, higher fall rate, and increased falls with serious consequences. However, the study did not compare the combined effects of frailty and sarcopenia relative to the presence of either condition alone. It is also unclear whether these findings can be generalized to a population of more robust community-dwelling older adults.

Thus, we investigated whether functional, physical, cognitive, and nutritional measures were more adversely affected in community-dwelling older adults who were screened positive for both frailty and sarcopenia than in those who were screened positive for either condition alone. If true, this finding would support the use of community screening for the early identification of both conditions to facilitate early intervention and reduce poor health outcomes.

MATERIALS AND METHODS

Study Setting

We studied 200 cognitively intact and functionally independent community-dwelling adults aged ≥50 years who participated in the “Longitudinal Assessment of Biomarkers for characterization of early Sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults Study.” The details of the study have been described previously. In brief, the inclusion criteria included community-dwelling older adults aged 50–99 years who were cognitively intact and independent in both basic activities of daily living (bADL) and instrumental ADL (iADL). The exclusion criteria were (1) presence of dementia or cognitive impairment—defined as a Chinese Mini-Mental State Score (CMMSE) ≤21, (2) inability to walk at least 4.5 m independently, and (3) residing in nursing or sheltered homes. Informed written consent was obtained from the participants in the presence of a trained research assistant. This study was approved by the Institutional Review Board of the National Healthcare Group (NHG DSRB No. 2012/00897).

Study Groups

We used the five-item self-report FRAIL scale to screen for the presence of frailty. The FRAIL contains five components: fatigue, resistance, ambulation, illnesses, and weight loss. The scores range from 0 to 5 and correspond to frail (3–5), pre-frail (1–2), and robust (0) health status. Sarcopenia was screened using the five-item self-report SARC-F scale, which includes items related to slow speed while walking, assistance in walking, rising from a chair, climbing stairs, and falls. The total scores range from 0 to 10, with scores of ≥4 indicating sarcopenia and adverse outcomes. Because our sample comprised fairly healthy community-dwelling older adults who were cognitively and functionally intact, we used a FRAIL scale cut-off score of ≥1 to identify pre-frail/frail participants. Similarly, we ascertained sarcopenia using a SARC-F scale cut-off score of ≥1, which showed higher sensitivity and reasonable specificity for the detection of probable sarcopenia among community-dwelling older adults. Using the aforementioned FRAIL and SARC-F scales cut-offs, we categorized the participants into three groups: (1) combined (positive for both frailty and sarcopenia), (2) intermediate (positive for either condition), and (3) robust (negative for both conditions).

Data Collection

We collected demographic data and information on vascular risk factors, including hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, ischemic heart disease, stroke, transient ischemic attack, and smoking. We evaluated functional ability using the Modified Barthel Index (MBI) for bADL, Lawton and Brody’s iADL index, and the Frenchay Activities Index as a measure of physical activity. The MBI examines performance in bADL such as personal hygiene or grooming, dressing, toileting, transferring, or ambulation. The scores range from 0 to 100, with higher scores indicating greater independence. The iADL index examines activities that allow for independent community living, such as the ability to use the telephone, shopping, food preparation, housekeeping, laundry, transportation, handling finances, and taking medications. The scores range from 0 to 8, with higher...
scores indicating greater independence. The Frenchay Activities Index is complementary to the MBI by measuring higher-order activities of daily living, such as social and lifestyle activities. Broadly, they assess three subscales: domestic chores, leisure/work, and outdoor activities. Scoring is based on the frequency with which 15 activities are performed, each of which is scored on a four-point scale (0 to 3) to yield a total score ranging from 0 (inactive) to 45 (active).

Regarding physical performance, we measured the upper and lower limb muscle strength and gait speed while walking a distance of 4.5 m; we also used the Short Physical Performance Battery (SPPB). Handgrip strength was measured using a hydraulic hand dynamometer (North Coast Medical Inc., Morgan Hill, CA, USA). Each subject had two readings of grip strength for each hand; we averaged all four readings to obtain a final value. Knee extension was measured using an electronic push/pull dynamometer (BASELINE 12-0342; Fabrication Enterprises Inc., White Plains, NY, USA). The participants sat with their legs over the edge of a chair with their hands resting on their thighs and their hips and knees flexed at 90°. The dynamometer was positioned immediately above the malleoli and perpendicular to the tibial crest with the monitor facing downward.

We assessed cognition using the CMMSE, which was locally validated. We also assessed depressive symptoms using the 15-item Geriatric Depression Scale. Nutritional status was assessed in three ways: (1) body mass index (BMI), derived from measurements of standing height and weight of the participant; (2) Mini Nutritional Assessment (MNA) scale, which was locally validated; and (3) vitamin D level, with deficiency defined as a serum concentration of < 20 ng/mL based on modified Holick’s classifications.

Statistical Analysis
Descriptive data are presented as mean ± standard deviation or median (interquartile range, IQR) for quantitative variables and as absolute and relative frequencies for categorical variables. Inferential statistics were applied to compare differences in functional, cognitive, physical performance, and nutritional states between the three groups. We used one-way analysis of variance with Bonferroni correction for post-hoc comparisons; the Kruskal-Wallis test for parametric and non-parametric continuous variables; and the chi-square test for categorical variables. SPSS Statistics for Windows, version 23.0 (IBM, Armonk, NY, USA) was used for data analysis. All statistical tests were two-tailed, with the level of statistical significance set at 5%.

RESULTS
Baseline Characteristics
Our study population comprised 200 older adults with a mean age of 67.9 ± 7.9 years, with female predominance (68.5%), and mostly Chinese ethnicity (92%). Using the FRAIL and SARC-F scales for screening, we identified 10 pre-frail/frail and 41 sarcopenic subjects. The robust, intermediate, and combined groups comprised 124 (62%), 51 (25.5%), and 25 (12.5%) subjects, respectively. Age increased and educational level decreased moving from the robust to intermediate and combined groups. We observed no significant differences in sex, ethnicity, or cardiovascular risk factors. Not surprisingly, the combined group scored the highest on the FRAIL and SARC-F scales, followed by the intermediate and robust groups (both p < 0.001) (Table 1).

Outcome Characteristics
The combined group performed significantly worse in functional measures of bADL (100 [IQR 100–100] vs. 100 [IQR 100–100] vs. 100 [IQR 95–100]; p = 0.002) and on the Frenchay Activities Index (32.77 ± 4.50 vs. 31.55 ± 6.09 vs. 29.80 ± 5.24; p = 0.025), but not on iADL, than other groups. For physical performance measures, the combined group had significantly worse SPPB scores (12 [IQR 11–12] vs. 12 [IQR 11–12] vs. 11 [IQR 8–12]; p = 0.013), knee extension (36.22 ± 7.55 vs. 33.63 ± 7.88 vs. 32.63 ± 7.84 kg; p = 0.031), and gait speed (1.49 ± 0.26 vs. 1.49 ± 0.26 vs. 1.27 ± 0.37 m/s; p = 0.01). We also observed a significant decrease in CMMSE scores from the robust to the intermediate/combined groups. Regarding nutritional measures, the MNA score was significantly lower in the intermediate and combined groups (27.40 ± 1.77 vs. 26.52 ± 1.99 vs. 25.98 ± 2.33; p = 0.001), but we observed no significant differences in vitamin D levels and BMI. Post-hoc comparisons between the combined and robust groups revealed similar findings, except for knee extension and CMMSE scores. In contrast, only MNA scores were significantly lower in the post-hoc comparisons between the intermediate and robust groups (Table 2).

DISCUSSION
Conventionally, sarcopenia, being organ-specific, has been researched in the basic science domain, whereas frailty has been predominantly applied in clinical settings. In the recent few years, their relationship has converged largely as a result of concerted efforts in recent consensus recommendations of sarcopenia to promote the translation of current knowledge into improved diagnosis and treatment in clinical practice. Sarcopenia is now formally rec-
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Robust (n = 124)</th>
<th>Intermediate (n = 51)</th>
<th>Combined (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>67.35 ± 7.77</td>
<td>68.10 ± 8.11</td>
<td>70.52 ± 7.57</td>
<td>0.18</td>
</tr>
<tr>
<td>Sex, female</td>
<td>83 (67)</td>
<td>34 (67)</td>
<td>20 (80)</td>
<td>0.42</td>
</tr>
<tr>
<td>Chinese ethnicity</td>
<td>112 (90)</td>
<td>49 (96)</td>
<td>23 (92)</td>
<td>0.48</td>
</tr>
<tr>
<td>Education (y)</td>
<td>9.81 ± 4.51</td>
<td>8.39 ± 5.53</td>
<td>6.48 ± 4.17*</td>
<td>0.004</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (18)</td>
<td>13 (26)</td>
<td>8 (32)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58 (47)</td>
<td>25 (49)</td>
<td>13 (52)</td>
<td>0.88</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>85 (69)</td>
<td>30 (59)</td>
<td>17 (68)</td>
<td>0.46</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (5)</td>
<td>2 (4)</td>
<td>1 (4)</td>
<td>0.96</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>0.44</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack</td>
<td>2 (2)</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (4)</td>
<td>2 (4)</td>
<td>1 (4)</td>
<td>0.49</td>
</tr>
<tr>
<td>Frailty/sarcopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRAIL score</td>
<td>0 (0–0)</td>
<td>0 (0–0)*</td>
<td>1 (1–1)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FRAIL ≥ 1</td>
<td>0 (0)</td>
<td>10 (20)*</td>
<td>25 (100)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SARC-F score</td>
<td>0 (0–0)</td>
<td>1 (1–1)*</td>
<td>2 (1–2)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SARC-F ≥ 1</td>
<td>0 (0)</td>
<td>41 (80)*</td>
<td>25 (100)*</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%) or median (interquartile range).
*p<0.01, compared with the robust group (post-hoc test).

Table 2. Outcome characteristics

<table>
<thead>
<tr>
<th>Functional ability</th>
<th>Robust (n = 124)</th>
<th>Intermediate (n = 51)</th>
<th>Combined (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>bADL (0–100)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>100 (95–100)*</td>
<td>0.002</td>
</tr>
<tr>
<td>iADL (0–23)</td>
<td>23 (23–23)</td>
<td>23 (23–23)</td>
<td>23 (23–23)</td>
<td>0.089</td>
</tr>
<tr>
<td>FAI (0–45)</td>
<td>32.77 ± 4.50</td>
<td>31.55 ± 6.09</td>
<td>29.80 ± 5.24**</td>
<td>0.025</td>
</tr>
<tr>
<td>Physical performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPPB (0–12)</td>
<td>12 (11–12)</td>
<td>12 (11–12)</td>
<td>11 (8–12)*</td>
<td>0.013</td>
</tr>
<tr>
<td>Gait speed (m/s)</td>
<td>1.49 ± 0.26</td>
<td>1.49 ± 0.26</td>
<td>1.27 ± 0.37*</td>
<td>0.001</td>
</tr>
<tr>
<td>Knee extension (kg)</td>
<td>36.22 ± 7.55</td>
<td>33.63 ± 7.88</td>
<td>32.63 ± 7.84</td>
<td>0.031</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>22.44 ± 6.70</td>
<td>21.02 ± 5.75</td>
<td>19.57 ± 6.70</td>
<td>0.089</td>
</tr>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMMSE (0–28)</td>
<td>26.44 ± 1.66</td>
<td>25.68 ± 1.79</td>
<td>25.84 ± 1.84</td>
<td>0.042</td>
</tr>
<tr>
<td>Mood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS (0–15)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>1 (0–5)</td>
<td>0.083</td>
</tr>
<tr>
<td>Nutritional measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNA (0–30)</td>
<td>27.40 ± 1.77</td>
<td>26.52 ± 1.99**</td>
<td>25.98 ± 2.33*</td>
<td>0.001</td>
</tr>
<tr>
<td>Vitamin D (ng/mL)</td>
<td>29.64 ± 9.52</td>
<td>29.20 ± 8.77</td>
<td>28.25 ± 11.90</td>
<td>0.809</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.94 ± 3.54</td>
<td>23.96 ± 4.11</td>
<td>24.16 ± 4.34</td>
<td>0.963</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or mean±standard deviation.
bADL, basic activities of daily living; iADL, instrumental activities of daily living; FAI, Frenchay Activities Index; SPPB, Short Physical Performance Battery; CMMSE, Chinese Mini-Mental State Examination; GDS, Geriatric Depression Scale; MNA, Mini-Nutrition Assessment; BMI, body mass index.
*p<0.01, **p<0.05, compared with the robust group (post-hoc test).

recognized as a muscle disease, with an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis code that can be used to bill for care in some countries.34) Thus, instead of attempting to determine the precise clinical relationship between frailty and sarcopenia or to focus on each condition in isolation,33) screening for the combination of both condi-
sarcopenia may be a more pragmatic approach.

The results of our study support this approach in two ways. First, they demonstrate that the community proportion of older adults with both frailty and sarcopenia is not low. While the prevalence of 12.5% observed in our study is half of that reported in an earlier study of medical outpatients, this could reflect differences in characteristics between study populations as well as the tools used to screen for or ascertain frailty. Second, our results affirmed that physical performance, ADL, cognition, and nutrition were more adversely affected in our study population of community-dwelling older adults who screened positive for both frailty and sarcopenia. Notably, the combined effect of both syndromes on adverse outcomes was greater than that of either condition alone.

It is interesting to consider the theoretical framework that underpins this observation. Consistent reports of sarcopenia as opposed to the converse situation of sarcopenia with concomitant frailty in frail older adults supports the premise that sarcopenia may precede physical frailty. Nonetheless, there lies a subset of older adults who are frail but not sarcopenic, presumably owing to other non-physical mechanisms of frailty such as cognitive impairment, mood disorders, and social isolation. The combined presence of sarcopenia and frailty may thus identify the subset of older adults (1) with a more severe degree of sarcopenia with the onset of concomitant frailty or (2) who are initially frail not owing to physical reasons but who subsequently go on to develop physical consequences of frailty with resultant sarcopenia. This line of reasoning is supported by the latest European Working Group on Sarcopenia in Older People consensus. Physical performance measures such as gait speed and SPPB, which overlap with the physical phenotype of frailty, are also used to define the severity of sarcopenia, corroborating concomitant frailty and the association with more severe sarcopenia.

Another finding was the lower CMMSE scores in the intermediate/combined group. A recent meta-analysis showed that sarcopenia was independently associated with cognitive impairment. Moreover, sarcopenia-related mechanisms such as oxidative stress, inflammation, and insulin resistance can lead concurrently to vascular aging and neuronal dysfunction that, in turn, precipitate cognitive impairment with a risk of dementia. Additionally, there is increasing appreciation for “cognitive frailty,” in which physical frailty co-exists with cognitive impairment and results in an increased risk of functional decline and dementia. Similarly, the association between the combined group and worse nutritional status as measured using MNA scores may be attributable either to nutritional factors linked to sarcopenia/frailty, notably vitamin D and insufficient protein intake, or conversely, the resultant functional impairment from sarcopenia/frailty, which may impact food access and preparation, causing nutritional deficits. Taken together, our study results add to the growing body of evidence regarding the intertwined relationship between sarcopenia and frailty by corroborating the deleterious impact of the combination of sarcopenia and frailty on functional, physical, cognitive, and nutritional domains beyond those for either condition alone. These findings support the use of a community screening strategy based on the FRAIL and SARC-F scales for the early identification of the combination of conditions (as opposed to either alone) to facilitate early intervention and reduce poor health outcomes, especially in at-risk groups such as older adults with diabetes and cognitive symptoms. A recent study on persons with diabetes mellitus reported that 42.5% of sarcopenic subjects were frail or pre-frail and that individuals with both conditions had an increased risk of adverse outcomes. Similarly, two-thirds of individuals with mild cognitive impairment were physically frail or pre-frail, which was closely associated with physical and functional impairments. Thus, the early identification in at-risk groups followed by the timely institution of evidence-based interventions to address sarcopenia and frailty such as improving protein and calorie intake, prescribing exercise programs with resistive components, addressing polypharmacy, and treating vitamin D deficiency may help avert downstream deleterious consequences such as falls, disability, and institutionalization.

This study had some limitations. For instance, we included community-dwelling older adults who were functionally independent and had high baseline scores on the functional assessment scale. As such, small differences in function may not be detected by these scales owing to the ceiling effect. This limitation probably accounted for the lack of differences in iADL scores among the three groups. As an exploratory cross-sectional study, it could determine associations but could not infer causality as temporality was not known. Analysis of the 2-year follow-up data of our cohort will demonstrate whether these findings hold true in longitudinal follow-ups. Our results, based on a cohort of functionally well community-dwelling older adults, may not be readily generalizable to other settings with more heterogeneous populations of older adults. In addition, the small sample size precluded further subgroup analysis of the independent effects of sarcopenia or frailty in the intermediate group. Hence, the emphasis of our study was on the comparison of outcomes among the combined, intermediate, and robust groups. Future studies are needed to examine the trajectory of changes in blood biomarkers that may be involved in the underlying pathogenesis before and after its development to delineate the relationship between sarcopenia and frailty in the combined group.

In conclusion, functional ability, physical performance, and nu-
trition were more adversely affected in our study population of community-dwelling older adults who screened positive for both frailty and sarcopenia than in those positive for either or neither condition. Our findings support screening for both sarcopenia and frailty among community-dwelling adults to effect interventional measures to preserve function and avoid disability.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST
The researchers claim no conflicts of interest.

FUNDING
This study was funded by a 2013 Lee Foundation Grant. We thank the following Senior Activity Centers (SACs): Wesley SAC, Care Corner SAC, Xin Yuan Community Service, Potong Pasir Wellness Centre, Tung Ling Community Services (Marine Parade and Bukit Timah), Viriya Community Services-My Centre (Moulmein, House of Joy) and the study participants who have graciously consented to participate in the study.

AUTHOR CONTRIBUTIONS
Conceptualization, WSL, YYD, LT; Data Curation, AY, CNT, SY; Formal Analysis, WSL, HXL, CNT; Funding Acquisition, WSL, YYD, Methodology, WSL, YYD; Project Administration, WSL; Supervision, WSL; Visualization, WSL, HXL; Writing-original draft, WSL, YYD, HXL; Writing-review and editing, WSL, YYD, HXL.

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Drug-Resistant Hyponatremia after Escitalopram Intake: A Series of Two Case Reports

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The consumption of new selective serotonin reuptake inhibitors (SSRIs) is raising dramatically especially in European countries. It contributes to occurrence of clinically important drug side effects. One of which can be hyponatremia. We present two case reports of 85-year-old and 84-year-old women who developed hyponatremia after escitalopram administration. We hypothesize that in both cases hyponatremia was connected with antidepressants administration. However, due to multiple comorbidities and polypharmacy it is often impossible to establish the exact mechanism of hyponatremia. Moreover, it is crucial to distinguish subtypes of drug-induced syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH), such as SSRI-induced SIADH, reset osmostat SIADH, thiazide-associated hyponatremia, thiazide-induced hyponatremia, mineralocorticoid responsive hyponatremia of older adults, in order to properly diagnose and treat geriatric patients. Administration of antidepressants or thiazides should be followed by a regular monitoring of serum sodium level.

Key Words: Hyponatremia, Serotonin uptake inhibitors, Geriatrics, Case reports

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INTRODUCTION

Mental health problems have been increasing worldwide in recent years. Thus, an inevitable increase in the consumption of antidepressants is expected soon, which is predicted to be much greater than that observed at the beginning of the current century. Simultaneously, increased rates of clinically important side effects of new and old psychiatric drugs will also occur. Drug-induced hyponatremia was previously reported after the administration of fluoxetine, sertraline, paroxetine, and fluvoxamine and has also recently been described for escitalopram, a new selective serotonin reuptake inhibitor (SSRI).

The prevalence of hyponatremia among hospitalized older adult (age > 75 years) patients ranges from 11.6% to 42.6% and up to 22.5% among patients in long-term care facilities. Hyponatremia leads to a lack of stability, frequent uncontrolled falls, bone fractures, and deterioration of cognitive functioning. Although a serum sodium level (SSL) of 135 mmol/L is considered within the normal range, increased hospital mortality is observed for levels below 138 mmol/L. Moreover, managing hyponatremia can be challenging due to a variety of potential causes (Table 1). Thus, this condition should be distinguished from other ailments such as motoric cognitive risk syndrome, which is common among older adults and may also manifest in falls. Our report highlights the possible life-threatening side effects of seemingly safe medications that are widely used in clinics.

CASE REPORT

Case Study 1
An 85-year-old woman with symptoms of cognitive impairment (CI) was admitted to the geriatric outpatient clinic in October
2015. She had multiple comorbidities, including arterial hypertension (AH), cholecystolithiasis, and osteoarthritis, and was prescribed amlodipine, omeprazole, hydroxyzine, piracetam, and vitamin D3 (the treatment characteristics and disease timeline are detailed in Table 2). Throughout the diagnostic process, head computed tomography (CT) images showed cortical and subcortical atrophy. The patient’s thyroid function, serum electrolyte, and vitamin B12 levels were all within the normal ranges. Comprehensive Geriatric Assessment (CGA) resulted in the diagnosis of mild dementia with no functional disability and low risk of falls. Due to the diagnosis of Alzheimer disease, memantine was also prescribed. In April 2017, the patient was admitted with behavioral and psychological symptoms of dementia (BPSD). Escitalopram (5 mg/day) was administered. Meanwhile, general practitioners modified the treatment for hypertension and added indapamide and ramipril. During the next 12 months, a major improvement was observed with no signs of BPSD. In April 2018, the patient experienced a lack of stability and fell. Blood tests revealed hyponatremia (serum sodium level [SSL], 129 mmol/L), with no signs of hyper- or hypovolemia. Escitalopram was withdrawn due to suspicion of the potential side effects of SSRI use. The patient was prescribed oral sodium chloride and fluid restriction was recommended. In addition, quetiapine and doxepin were added to manage the patient’s symptoms of agitation, anxiety, and somatization. Despite the sodium levels being in the normal range for short periods.

Case Study 2
An 84-year-old woman was admitted to the geriatric outpatient clinic in April 2016 with symptoms of CI, restlessness, and anxiety. Her medical history included gastroesophageal reflux disease and essential head tremor. Head CT images showed cortical-subcortical atrophy and multiple focal hypodense lesions. The patient’s pharmacological treatment before admission consisted of atorvastatin, lutein, pantoprazole, and ginkgo biloba. Her thyroid function, serum electrolytes, and vitamin B12 levels were within the normal ranges. In CGA, the patient was diagnosed with CI and vascular dementia (the treatment characteristics and disease timeline are detailed in Table 3). In April 2017, the patient was admitted with symptoms of depressive episodes and anxiety. She was prescribed alprazolam with escitalopram (5 mg/day). Three months later, the patient was admitted after a fall with an SSL of 131 mmol/L despite being euvoletic. The previously administered pharmacotherapy was sustained, sodium chloride (orally) was prescribed, and fluid restriction was recommended. In 10 months of follow-up, the patient was admitted to the neurology department with transient speech disorder after another fall. Head CT images showed no new findings; however, laboratory tests showed hyponatremia (124 mmol/L) despite the discontinuation of escitalopram. In the next 3 months, the SSL remained below the normal range. The supplementation of sodium chloride was changed to fludrocortisone acetate because of nausea. During this treatment, the SSL normalized, but her blood pressure (BP) increased to 170/100 mmHg and lercanidipine was prescribed. In January 2019, the patient’s SSL was 135 mmol/L and her BP was

---

Table 1. Etiology of hyponatremia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Table 1. Etiology of hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>Extrarenal loss (For example, diarrhea, vomiting, and burns)</td>
</tr>
<tr>
<td></td>
<td>Renal loss (For example, diuretics use, nephropathy, osmotic diuresis osmotic diuresis induced by excessive excretion of glucose or urea or urea induced)</td>
</tr>
<tr>
<td>Euvoletic</td>
<td>SIADH (For example, due to cancer, use of drugs, CNS-related disorders, pulmonary diseases, stress, hereditary factors)</td>
</tr>
<tr>
<td></td>
<td>Thiazides-induced</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td></td>
<td>Psychiatric diseases (polydipsia)</td>
</tr>
<tr>
<td></td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Hypervolemic</td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Liver cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
</tr>
</tbody>
</table>

SIADH, syndrome of inappropriate secretion of antidiuretic hormone; CNS, central nervous system.
normal. Until July 2020, her SSL was within the normal range. We obtained informed consent from the participants before their participation.

**DISCUSSION**

We present two case reports of women aged 85 and 84 years, respectively, who developed hyponatremia, most likely after escitalopram administration (escitalopram-induced syndrome of inappropriate secretion of antidiuretic hormone [SIADH]). The lack of symptoms of hypervolemia at the time of initial diagnosis excluded kidney, thyroid, cardiovascular, and adrenal cortex disorders, as well as neoplasms as other possible explanations.

A few types of SIADH have been described in the literature.

---

**Table 2. Course of treatment of Patient 1**

<table>
<thead>
<tr>
<th>Date of visit</th>
<th>Pharmacotherapy</th>
<th>Frequency of drug-induced hyponatremia (%)</th>
<th>Serum sodium level (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct 2015</td>
<td>2,000 UI vitamin D3 qd</td>
<td>0</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td>2.5 mg amlodipine qd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 mg omeprazole qd</td>
<td>0.01–0.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg hydroxyzine qd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,200 mg of piracetam bid (withdrawn during the first visit)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nov 2015</td>
<td>+5 mg memantine qd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Jan 2016</td>
<td>+5 mg memantine qd (10 mg in total)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Apr 2017</td>
<td>New treatment regimen:</td>
<td>2.5 mg ramipril qd</td>
<td>Unknown frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg amlodipine qd</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5 mg indapamide qd</td>
<td>1–5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg memantine qd</td>
<td>Unknown frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg escitalopram qd</td>
<td>Unknown frequency</td>
</tr>
<tr>
<td>Apr 2018</td>
<td>+2 g natrium chloride bid</td>
<td>0</td>
<td>129</td>
</tr>
<tr>
<td></td>
<td>–5 mg escitalopram</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Sep 2018</td>
<td>+25 mg quetiapine qd</td>
<td>0.1–1</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>+10 mg doxepin qd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Apr 2019</td>
<td>–1.5 mg indapamide</td>
<td>–</td>
<td>129</td>
</tr>
<tr>
<td>Aug 2019</td>
<td>+2.5 mg torasemide qd</td>
<td>0</td>
<td>123</td>
</tr>
<tr>
<td>Jul 2020</td>
<td>The end of follow-up</td>
<td>–</td>
<td>129</td>
</tr>
</tbody>
</table>

qd, quaque die (daily); bid, twice daily; +, drug added; –, drug withdrawn.

**Table 3. Course of treatment of Patient 2**

<table>
<thead>
<tr>
<th>Date of visit</th>
<th>Pharmacotherapy</th>
<th>Frequency of drug-induced hyponatremia (%)</th>
<th>Serum sodium level (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apr 2016</td>
<td>40 mg atorvastatin qd</td>
<td>0</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td>20 mg pantoprazole qd</td>
<td>Unknown frequency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lutein</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ginkgo biloba</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+75 mg acetylsalicylic acid qd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Aug 2017</td>
<td>+0.25 mg alprazolam ad hoc</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+5 mg escitalopram qd</td>
<td>Unknown frequency</td>
<td></td>
</tr>
<tr>
<td>Nov 2017</td>
<td>+2 g natrium chloride bid</td>
<td>0</td>
<td>131</td>
</tr>
<tr>
<td>Sep 2018</td>
<td>–escitalopram, natrium chloride</td>
<td>–</td>
<td>124</td>
</tr>
<tr>
<td>Oct 2018</td>
<td>+0.1 mg fludrocortisone acetate qd</td>
<td>0</td>
<td>132</td>
</tr>
<tr>
<td>Nov 2018</td>
<td>+10 mg lercanidipine qd</td>
<td>0</td>
<td>139</td>
</tr>
<tr>
<td>Jul 2020</td>
<td>The end of follow-up</td>
<td>–</td>
<td>135</td>
</tr>
</tbody>
</table>

qd, quaque die (daily); bid, twice daily; +, drug added; –, drug withdrawn.
First, syndromes associated with excessive ADH production are usually caused by antidepressants (SSRIs, SNRIs, serotonin and noradrenaline reuptake inhibitors, and tricyclic antidepressants [TCAs]), antipsychotics, antiepileptics, and antineoplastic drugs. Furthermore, many drugs, including carbamazepine, cyclophosphamide, and nonsteroidal anti-inflammatory drugs, can induce hyponatremia by the peripheral receptor effect rather than by stimulating the secretion of the hormone itself. Moreover, reset osmostat (RO) SIADH in older adults might also occur due to alterations in osmoreceptor cell metabolism. The condition is frequently observed in residents of long-term care facilities with simultaneous quadriplegia, psychosis, cerebral hemorrhage, dementia with Lewy bodies, alcoholism, malnutrition, malignancy, and infections. Lastly, hyponatremia after the administration of thiazide or thiazide-like diuretics can occur in up to 30% of older adult patients. Advanced age, female sex, and low body mass index have been identified as risk factors for the development of thiazide-associated hyponatremia.

Establishing an exact diagnosis for the first patient was challenging because of the use of multiple drugs that could cause SIADH (memantine, quetiapine, and doxepin). In the second patient, hyponatremia seemed to be more directly connected with the use of escitalopram owing to the lack of other diseases or drugs that could contribute to the development of SIADH. SSRI-induced SIADH is one of the most common mechanisms of hyponatremia in older adults, although only 14 cases of escitalopram-induced SIADH have been described in the literature. However, it must be emphasized that in the presented cases, even small doses of escitalopram (5 mg) caused serious side effects. In other reports, the doses of escitalopram were usually 10 mg. Recent reports suggest a lower risk of hyponatremia with the use of TCAs and noradrenergic and specific serotonergic antidepressants compared to SSRI and SNRI; thus, changing SSRI to TCA (doxepin) might have been reasonable.

In both patients, the hyponatremia did not resolve after escitalopram withdrawal or standard treatment. In the second patient, SSL normalization was achieved after treatment with fludrocortisone acetate. According to the available data, the SSL should normalize approximately 2 weeks after SSRI discontinuation and the introduction of limited fluid intake and sodium chloride supplementation (as stated by guidelines). However, despite this treatment, hyponatremia persisted in our patients for months. Abnormal homeostatic mechanisms, such as RO syndrome, may explain the observed resistance to treatment. This theory is supported by the fact that hyponatremia due to RO does not respond to fluid restriction (as non-RO SIADH hyponatremia), oral sodium supplementation, or fludrocortisone treatment. Another explanation could be adrenal insufficiency or mineralocorticoid-responsive hyponatremia of the elderly (MRHE), which requires the exclusion of SIADH and adrenal dysfunction. MRHE is considered a mildly hypovolemic hyponatremia caused by renal sodium loss.

Age-related decreased sodium reabsorption by proximal renal tubules and hyposresponsiveness of the renin-angiotensin-aldosterone system may cause constantly increased urinary sodium excretion. Decreased sodium retention leads to volume depletion, which causes elevation of plasma antidiuretic hormone levels. The recommended treatment for MRHE is, instead of water restriction, which may worsen hyponatremia, an administration of mineralocorticoids such as fludrocortisone acetate. Unfortunately, both fludrocortisone treatment and dietary sodium chloride supplementation may be limited by an increase in BP.

In conclusion, managing hyponatremia in older adults is complex. Regular monitoring of SSLs should be mandatory in this population, particularly following the initiation of antidepressants or thiazides. Unfortunately, due to the unpredictability of drug-related hyponatremia, the timing or frequency of such monitoring cannot be precisely defined and should be based on clinical experience. In addition to informing patients and their caregivers of the potential risks of hyponatremia, preventive fluid moderation or restriction and ordering SSL assessment should be considered. Treatment of hyponatremia requires a multimodal approach that considers patient comorbidities and pharmacotherapy. However, despite the best care, it can last for months. Reporting side effects, especially of the most popular drugs to the local center for drug monitoring, is crucial in terms of increasing our awareness of the benefits of our patients.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST
The researchers claim no conflicts of interest.

FUNDING
None.

AUTHOR CONTRIBUTION
Conceptualization, AP, JK, MS; Data curation, AP, JK, MS; Funding acquisition, AP, JK, MS; Investigation, AP, JK; Methodology, JK, MS; Project administration, JK, MS; Supervision, MS; Writing—original draft, JK, AP, MS; Writing—review & editing, JK, AP.

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1. Leth-Moller KB, Hansen AH, Torstensson M, Andersen SE,


INTRODUCTION

Hemiballism and hemichorea are rare hyperkinetic movement disorders that are characterized by irregular unilateral flinging or throwing movements of the limbs and involve the contralateral basal ganglia. These disorders can be caused by various medical conditions such as cerebrovascular diseases, infections, tumors, drugs, and metabolic and immunological disorders.

Hyperglycemic hemichorea frequently occurs in older patients with poorly controlled type 2 diabetes mellitus (T2DM) and occasionally in those with type 1 diabetes mellitus. In most cases, chorea improves gradually over several days after achieving stable glycemic control, although some cases can last for months or even years.

This report describes hyperglycemic hemichorea occurring in six older patients with poorly controlled T2DM, one of whom experienced recurrence.

CASE REPORT

We identified six cases of hyperglycemic hemichorea from 2017 to 2020 in our tertiary hospital (Table 1). The mean age of the patients was 77.2 years (range, 67–84 years), and five patients were women. The duration of diabetes varied (range, 1–35 years); however, initial glycated hemoglobin (HbA1c) levels at the patients’ first visit were consistently high (range, 9.3%–13%). The patients had multiple comorbidities such as hypertension (n = 4), dyslipidemia (n = 4), and chronic kidney disease (n = 4). Three patients were treated with insulin, and most patients had poor compliance with medication and irregular visits to the outpatient clinic. This is a retrospective observational study, and we could not obtain written informed consents.

Brain T1-weighted magnetic resonance imaging (MRI) showed high signal intensities in the basal ganglia on the contralateral side to the disordered movements in four of five patients (Fig. 1A, 1B). One patient underwent 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) for the differential diagnosis of bilat-
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>DM duration (y)</th>
<th>Comorbidity</th>
<th>Medication before event</th>
<th>HbA1c (%)</th>
<th>PG (mg/dL)</th>
<th>Serum osmolarity (mOsm/kg)</th>
<th>Affected side</th>
<th>Brain MRI</th>
<th>Glycemic control</th>
<th>Symptom control</th>
<th>Chorea duration (day)</th>
<th>Recurrence</th>
<th>Follow-up</th>
<th>HbA1c (%)</th>
<th>PG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>F</td>
<td>12</td>
<td>HTN, dyslipidemia, CKD, DMR</td>
<td>Basal insulin</td>
<td>13</td>
<td>300b)</td>
<td>302</td>
<td>Left</td>
<td>No acute lesion</td>
<td>MDI; TDD 36 IU</td>
<td>Haloperidol 3 mg Clonazepam 1.5 mg</td>
<td>39</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>F</td>
<td>20</td>
<td>HTN, dyslipidemia, CKD, DMR</td>
<td>Basal insulin, linagliptin, and gliclazide</td>
<td>9.3c)</td>
<td>118c)</td>
<td>299c)</td>
<td>Bilateralc)</td>
<td>T1 high SI lesions in the putamen on both sides</td>
<td>MDI; TDD 18 IU</td>
<td>Haloperidol 0.75 mg Clonazepam 0.5 mg</td>
<td>47c)</td>
<td>Yes</td>
<td>7.5</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>F</td>
<td>1</td>
<td>HTN, dyslipidemia, CKD, vascular dementia</td>
<td>None</td>
<td>12.7</td>
<td>654</td>
<td>298</td>
<td>Right</td>
<td>N/A</td>
<td>Sliding scale</td>
<td>No</td>
<td>10</td>
<td>No</td>
<td>6.6</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>84</td>
<td>F</td>
<td>35</td>
<td>CKD, DMR</td>
<td>Mixed split insulin and vildagliptin</td>
<td>10.6</td>
<td>393</td>
<td>298</td>
<td>Left</td>
<td>T1 high SI lesion in the right putamen</td>
<td>MDI; TDD 22 IU</td>
<td>Clonazepam 0.5 mg</td>
<td>135</td>
<td>No</td>
<td>7.7</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>83</td>
<td>M</td>
<td>3</td>
<td>HTN, dyslipidemia</td>
<td>Linagliptin and gliclazide</td>
<td>11.0</td>
<td>425</td>
<td>N/A</td>
<td>Left</td>
<td>T1 high SI lesion in the right putamen</td>
<td>MDI; TDD 28 IU</td>
<td>Clonazepam 0.5 mg</td>
<td>172</td>
<td>No</td>
<td>7</td>
<td>112</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>F</td>
<td>2</td>
<td>None</td>
<td>None</td>
<td>11.6</td>
<td>147</td>
<td>N/A</td>
<td>Left</td>
<td>T1 high SI lesions in the basal ganglia on both sides</td>
<td>Sliding scale</td>
<td>No</td>
<td>11</td>
<td>No</td>
<td>7</td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; PG, plasma glucose; MRI, magnetic resonance imaging; HTN, hypertension; CKD, chronic kidney disease; DMR, diabetic retinopathy; MDI, multiple daily insulin injection; TDD, total daily dose; SI, signal intensity; N/A, not available.

a) At 3–6 months from the event.
b) Reported at another hospital.
c) At the first event, this patient underwent brain 18F-FDG PET.
eral abnormalities observed on brain MRI, which showed bilateral hypometabolism in the corresponding lesions (Fig. 1C).

All patients were treated with insulin, with the initial treatment comprising multiple daily insulin injections (total daily dose, 18–36 IU). Two patients were administered sliding-scale insulin injections during their hospitalizations in the emergency and neurology departments and were switched to oral hypoglycemic agents after discharge. Dopamine receptor blockers and benzodiazepines were recommended for four patients. The patients’ symptoms improved gradually after reducing their hyperglycemia, which was stabilized within 3–6 months after the event (Table 1). We could not follow-up on the HbA1c level of one patient who was transferred to another hospital after resolving chorea. The mean duration of hemichorea was 69 days (range, 10–172 days). One patient experienced chorea recurrence 2 months after the first event had resolved. At the time of recurrence, the patient’s glucose level was not aggravated (70–200 mg/dL). The newly developed signs were fever and skin rash without evidence of infection. The patient underwent skin biopsy and laboratory tests and was finally diagnosed with vasculitis. She was transferred to the rheumatology department and treated with immunosuppressants.

DISCUSSION

This report described the clinical presentations and courses of hemichorea in six older patients with T2DM. Their symptoms resolved after achieving adequate glycemic control with insulin and oral hypoglycemic agents. Hemichorea recurred 2 months after the resolution of the initial event in one of the six patients, who was finally diagnosed with vasculitis.

Bedwell6) first described hyperglycemic hemichorea in 1960. The typical pattern of hyperglycemia-induced chorea is unilateral involuntary movement with abnormal neuroimaging in the contralateral basal ganglia.7) However, bilateral involvement appeared as generalized chorea in 11.4% of 54 cases.8) Hyperglycemic hemichorea is more common in women, and older age is a known risk factor.8) The findings in our cases are consistent with those of previous reports and have important clinical implications given the increasing numbers of older patients with diabetes. If patients present with involuntary movement, their glycemic status should be evaluated, and brain MRI should be performed to diagnose hyperglycemic hemichorea. The typical findings on brain MRI of patients with hyperglycemic hemichorea include high signal intensity on T1-weighted images and various signals in T2-weighted images of the basal ganglia and putamen on the side contralateral to the disordered movements.9) Negative findings on brain MRI have rarely been reported,10) which we also observed in one of our patients. Brain computed tomography may show hyperdensity in the same lesion.10)

The suggested pathogenesis of hyperglycemia-related hemichorea involves petechial hemorrhage1) or cerebral ischemia with the depletion of gamma-aminobutyric acid and acetylcholine in the basal ganglia, which results in involuntary movements.11) More directly, FDG PET shows a marked reduction in regional cerebral glucose metabolism in the basal ganglia on the affected side, which provides evidence of the disorder or failure of cerebral glucose me-
We confirmed this phenomenon using $^{18}$F-FDG PET in our patient. To our knowledge, this is the first report of hyperglycemic hemichorea related to bilateral lesions on $^{18}$F-FDG PET.

The most important treatment for hyperglycemic hemichorea is the correction of hyperglycemia. Hemichorea improves over days to weeks after achieving glycemic control alone in most cases; however, additional symptomatic therapy should be considered if symptoms persist or become severe. Such therapy can include dopamine receptor blockers such as haloperidol, benzodiazepine, carbamazepine, or valproate. Recurrence has been reported in a small number of patients, in whom recurrent hyperglycemia or discontinuation of dopamine receptor blockers may be involved. However, the prognosis is generally good, and in our opinion, bilateral presentation might be related to other causes of chorea and poor prognosis.

In conclusion, the prognosis of hyperglycemic hemichorea appears to be good. This condition can be detected based on its typical radiological findings on brain MRI and $^{18}$F-FDG PET. However, other possible causes of abnormal movement such as vasculitis should be considered in cases of bilateral involvement and recurrence after achieving glycemic control.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST
The researchers claim no conflicts of interest.

FUNDING
None.

AUTHOR CONTRIBUTIONS
Conceptualization, SM, HEK, TJO; Data curation, SM, HEK; Investigation, SM, HEK, TJO; Methodology, SM, TJO, CHA; Project administration, SM, HEK; Supervision, TJO, SHC, HCJ; Writing-original draft, SM, TJO; Writing-review & editing SM, HEK, TJO, CHA, SHC, HCJ.

REFERENCES

Apixaban-Induced Skin Purpura

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INTRODUCTION

Owing to the increase in life expectancy, increasing numbers of older patients require hospital care and polymedication. Recently introduced, oral anticoagulants are currently one of the most widely administered pharmacological medications.¹)

Oral anticoagulants are widely administered as therapeutic options for atrial fibrillation (AF), thromboembolic disease prevention and treatment (especially in the postoperative period), acute coronary syndrome, and heparin-induced thrombopenia.²,³) These agents act in the coagulation cascade as direct thrombin inhibitors administered parenterally (bivalirudin or argatroban) or orally (dabigatran) or as direct factor Xa inhibitors administered orally (rivaroxaban, apixaban, edoxaban, and betrixaban). In addition to showing clinical superiority over other anticoagulants, these drugs offer advantages for patients, including the need for fewer controls to adjust the dose and less interaction with food, among others, which has led them to replace classic anticoagulants such as warfarin and acenocoumarol.

CLINICAL CASE

An 89-year-old woman with a history of hypertension, dyslipidemia, and AF was treated with bisoprolol (2.5 mg), apixaban (2.5 mg), ramipril (2.5 mg), and simvastatin (10 mg).

She presented for a consultation because of the spontaneous appearance of purpuric macules in both lower extremities, which had evolved over approximately 15 days. These macules were not pruritic and the patient had no fever, proteinuria, hematuria, or additional symptoms. However, she had started anticoagulant therapy with apixaban 1 month before the diagnosis of paroxysmal AF.

Physical examination (Fig. 1) revealed confluent symmetric petechial lesions in both lower limbs from the dorsal aspect of the foot to the thigh. The lesions were not raised and did not whiten with in vitro pressure. No other abnormalities were noted. An electrocardiogram (ECG) showed AF at 90 bpm, whereas posteroanterior chest radiography showed no alterations.

Laboratory examination revealed a leukocyte count of 11.1 × 10³/µL (12.5% neutrophils), red series, and normal platelet count. Her erythrocyte sedimentation rate was 34 mm/hr, and she showed normal coagulation (plasmin inhibitor [PI], 73%; international normalized ratio (INR), 1.32; activated partial thromboplastin time [APTT], 29.4 seconds), except for fibrinogen levels (560 mg/dL). Biochemical analysis showed normal ion levels and renal function (glutamate pyruvate transaminase [GPT], 23 U/L; total bilirubin [BT], 0.64 mg/dL; gamma-glutamyl transferase [GGT], 186 U/L; alkaline phosphatase [FA], 193 U/L; lactate dehydrogenase [LDH], 234 U/L; C-reactive protein [CRP], 28 mg/L). The patient showed a normal lipid profile as well as normal venous blood gas and complement component 3 and 4 levels. She also showed negative results for antinuclear antibodies, anti-Ro, anti-La, c-ANCA, and p-ANCA. Further, serological tests yielded negative results for hepatitis B, hepatitis C, human immunodeficiency virus (HIV), varicella-zoster virus, and infectious mononucleosis. Finally, results of the QuantiFERON test were negative as well.

Given our clinical suspicion of a drug side effect, the Naranjo algorithm was applied, and the patient’s score was 6, which suggested that an adverse drug had occurred. We suspended the administration of the potentially causative drug, apixaban; performed a skin biopsy; and commenced treatment with low-molecular-weight heparin. The biopsy findings were comparable to those for vasculitis; therefore, a topical corticosteroid was prescribed. After 3 weeks without the drug and with topical corticosteroid treatment, the lesions disappeared (Fig. 2). Furthermore, the altered liver function parameters observed at admission, which were possibly caused by hepatic metabolism of apixaban, normalized. A definitive diagnosis was made on the basis of the results of the biopsy and the clinical improvement after drug withdrawal.

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Assessment of the risks and benefits of treatments for patients is standard process in clinical practice. This involves identifying the best therapeutic option for patients that would result in the fewest side effects. This goal is paradigmatic in the case of anticoagulant therapies, which seek to avoid thrombus formation, with the lowest possible risk for side effects, especially bleeding. New oral anticoagulants show reduced risks for thrombotic events; however, they are not without side effects. Cutaneous side effects are rare, occurring in fewer than 1/100 according to the technical data sheet (apixaban). However, drug interactions must be ruled out by review of basic medication in polymedicated patients such as our patient.

Cutaneous small-vessel vasculitis (CSVV) has been reported in a very few cases after exposure to direct oral anticoagulants (DOACs). A recent review of the literature reported no more than 50 cases; among these cases, 50% reported a time to onset of within 10 days of DOAC exposure. When specified, the predominant type of CSVV reported was leukocytoclastic vasculitis ($n = 31$). The 2012 Chapel Hill International Consensus Conference grouped cutaneous arteritis, primary central nervous system vasculitis, isolated aortitis, and cutaneous leukocytoclastic vasculitis under the term single-organ vasculitis. This entity is associated with a wide spectrum of systemic conditions, neoplasms, infections, and drug hypersensitivities. Histologically, these cases are classified as small-vessel vasculitis ($< 50 \mu m$ in diameter). Localized or systemic damage occurs because of complement action and the release of pro-inflammatory cytokines via the activation of immune complexes, through antigen–antibody interactions in the vascular wall, or by leukocyte activation of ANCA.

We propose that the most appropriate therapy for each patient should be determined on the basis of a series of indicators, namely, the severity of skin involvement, the presence of extracutaneous manifestations, and the evolution time. Treatments may vary from symptomatic treatment to the use of colchicine or corticosteroids. In our patient, drug withdrawal and topical treatment were sufficient.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

REFERENCES


2. Leung LL. Direct oral anticoagulants (DOACs) and parenteral direct-acting anticoagulants: Dosing and adverse effects [Internet]. Waltham, MA: UpToDate; c2021 [cited at 2021 May 10].


Ipsilateral Axillary Adenopathy from mRNA COVID-19 Vaccines

Shyh Poh Teo
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As older people are at risk of complications and death from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections, they are an important target group for coronavirus disease 2019 (COVID-19) vaccination. The mRNA vaccines BNT162b2 by Pfizer-BioNTech and mRNA-1273 by Moderna are potent COVID-19 vaccines that have demonstrated high efficacy and immunogenicity in older people. Older people also tend to have multiple co-morbidities, which increase their risks for adverse events following immunization (AEFI) and complicate the interpretation of AEFI symptoms. Thus, post-marketing active vaccine safety surveillance is important in this population to monitor for evolving and long-term adverse events.

An AEFI that requires recognition by geriatricians is axillary adenopathy, particularly after the administration of mRNA vaccines. The results of a phase 3 trial showed that ipsilateral axillary adenopathy occurred in 11.6% of recipients of the first dose of the Moderna vaccine, which increased to 16.0% after the second dose in those aged 18–64 years. While the Pfizer-BioNTech vaccine study did not solicit adenopathy as an adverse event, unsolicited reports of adenopathy were significantly higher in the vaccine group than in the placebo group (64 vs. 6). Moreover, while adenopathy was reported within 2–4 days for both mRNA vaccines, the average duration was 1–2 days for Moderna vaccine recipients compared to 10 days for Pfizer-BioNTech vaccine recipients.

A systematic review of adenopathy occurring after COVID-19 vaccination reported incidence rates of 44.1%, 25%, and 1.5% for the Pfizer-BioNTech, Moderna, and Oxford-AstraZeneca vaccines, respectively. The median elapsed times for the development of adenopathy were 12 and 5 days following the first and second doses, respectively, and persisted for up to 4 weeks post-vaccination. The higher incidence of mRNA vaccine-associated adenopathy may be due to a higher immunogenic response compared to those for the other COVID-19 vaccine platforms. A case series of ipsilateral axillary swelling or adenopathy after COVID-19 vaccinations based on symptoms and physical examination found that these symptoms closely mimicked those of metastasis and lasted for up to 6 weeks. However, lymph node biopsies confirmed vaccination-related reactive lymphadenopathy.

Patients presenting with unilateral axillary adenopathy should be evaluated for malignancy, particularly breast cancer. Adenopathy may also be incidentally identified on routine imaging studies, such as computed tomography of the thorax or breast magnetic resonance image. Clinicians should enquire regarding recent COVID-19 vaccination, as mRNA vaccines may induce ipsilateral axillary lymph node hyperplasia. Documentation of vaccine administration, such as date and location site, should also be reviewed, as ipsilateral lymphadenopathy in the setting of recent (within 6 weeks) vaccination may indicate a benign entity. For patients with suspected vaccine-associated adenopathy and normal breast imaging, clinicians should consider watchful waiting, with a follow-up ultrasound to ensure resolution of lymphadenopathy performed 8 weeks after the second vaccine dose. This is a way to avoid unnecessary axillary lymph node biopsy. However, in patients with a family history of breast cancer or a suspicion of malignancy such as breast cancer or lymphoma, lymph node biopsies should still be performed.

If possible, routine imaging studies should be performed before vaccination. However, in the setting of the current pandemic, COVID-19 vaccination should not be delayed. Imaging studies should be performed without delay for urgent indications such as acute symptoms or the need for urgent treatment planning, but these procedures may be may be postponed for other indications until at least 6 weeks after the second vaccine dose. Patients with primary cancer, such as breast cancer or upper limb melanoma, should ideally have both vaccine doses administered on the contralateral side.

In conclusion, geriatricians should be aware that ipsilateral axillary adenopathy may represent an AEFI, particularly after the administration of mRNA COVID-19 vaccines. This condition usually occurs several days after vaccination and may last for up to 6...
weeks. Expectant management may be appropriate to ensure resolution, rather than referring to further imaging studies or lymph node biopsies.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST
The author claims no conflicts of interest.

FUNDING
None.

REFERENCES


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Received: June 10, 2021; Revised: July 19, 2021; Accepted: July 21, 2021

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The Korean Geriatrics Society News

Courses and Conferences

The academic events in 2021 of the Korean Geriatrics Society are as follows.
We would like to invite members of the Korean Geriatrics Society and anyone who are interested.

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November 5, 2021
For more information please contact kgskorea1968@gmail.com

[The 68th Annual Meeting of the Korean Geriatrics Society]
November 6-7, 2021
For more information please contact kgskorea1968@gmail.com

Membership Fee Information

Membership Fee

<table>
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<tr>
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<td>KRW 20,000</td>
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<tr>
<td>Other member</td>
<td>KRW 30,000</td>
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Examination date
The examination is held once a year in August.

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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
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c. Certification fee: KRW 200,000
d. Procedure: Confirmation of acceptance → Confirmation of mailing address → Transfer certification fee to AGMR → Certificate is sent by mail
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Enactment December 27, 2013
Revision March 1, 2021

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• All manuscripts must be written in clearly understandable English. Authors whose first language is not English are requested to have their manuscripts checked for grammatical and linguistic correctness before submission. Correct medical terminology should be used, and jargon should be avoided.

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• Drugs and chemicals should be referred to using standard chemical or generic terms. The names and locations (city, state, and country only) of manufacturers of equipment and non-generic drugs should be given.

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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

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<th>Type of article</th>
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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.

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