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Aims and Scope

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

General Information

The official journal title has been *Annals of Geriatric Medicine and Research* since September 2016 which followed the Journal of the Korean Geriatrics Society (1997-2016, pISSN: 1229-2397, eISSN: 2288-1239). It is the official journal of the Korean Geriatrics Society (http://www.geriatrics.or.kr/eng/) and the Korean Society for Gerontology (http://www.korea-biogerontology.co.kr). It is published in English quarterly on the last days of March, June, September, and December. The journal publishes original research articles, case reports, reviews, special contributions, and commentaries. Review board consists of members in 7 different countries. Articles are welcome for submission from all over the world. The contents of this Journal are indexed in Web of Science, Scopus, PubMed, PubMed Central (PMC), EBSCO, DOAJ, Embase, KoreaMed, KoMCI, KCI, DOI/Crossref, and Google Scholar. It is accessible without barrier from Korea Citation Index (https://www.kci.go.kr) or National Library of Korea (http://nl.go.kr) in the event a journal is no longer published.

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Comprehensive Assessment of Lower Limb Function and Muscle Strength in Sarcopenia: Insights from the Sit-to-Stand Test

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The sit-to-stand test is an essential tool used to assess lower limb function and muscle strength in older adults and various patient populations, and also plays a role in sarcopenia screening. Among its forms, the five-time sit-to-stand test (FTSST) is widely used, with previous studies suggesting cutoff values of >10 seconds and >11 seconds for the sitting-to-standing and standing-to-sitting transitions, respectively. The 30-second and 1-minute sit-to-stand tests (30STS and 1MSTS, respectively) also provide comprehensive assessments. While much of the current research on sarcopenia focuses on the FTSST, there is a burgeoning need for an in-depth exploration of the 30STS and 1MSTS. Studies on these tests are vital to refine the criteria for sarcopenia, establish accurate cutoff values, and enhance diagnostic precision and treatment effectiveness. This need highlights the importance of further research into the 30STS and 1MSTS for refining the diagnostic criteria for sarcopenia.

Key Words: Lower extremity, Muscle strength, Older adults, Physical examination

INTRODUCTION

Muscle mass and strength are crucial for maintaining physical health in older adults. Decreased body muscle mass is referred to as sarcopenia.[1)] Sarcopenia is associated with not only a decrease in muscle strength but also a reduction in balance, leading to an increased risk of falls.[1,2)] Fractures resulting from falls can severely limit mobility in older adults and patients.[2)] Mobility is crucial for performing daily activities and significantly impacts overall quality of life.[3)] Additionally, a decline in mobility leads to a decrease in the quality of life of older adults and their patients.[4,5)]

Therefore, proactively identifying and preventing sarcopenia in older adults is crucial. The common methods for screening sarcopenia include surveys, calf circumference measurements, hand grip strength tests, and the sit-to-stand test (STST).[6)] Among these methods, handgrip strength and the STST are used to assess muscle strength. Measuring hand grip strength can be challenging without equipment. However, the STST is a more convenient test that can be easily administered anywhere and requires only a chair, making it highly practical. Additionally, the STST not only assesses lower limb muscle strength but is also a comprehensive tool for evaluating balance and exercise capacity. This test measures the transition from a seated to a standing position and serves as an indicator of basic functional ability in daily activities, akin to a precursor to walking. Therefore, it is a highly versatile testing method, not only for older adults but also for individuals with a variety of diseases.

The five-time sit-to-stand test (FTSST) is commonly used to screen for sarcopenia. Furthermore, in addition to the FTSST, various other STSTs can be used to assess lower limb function and muscle strength. These STSTs enable a more accurate evaluation of lower-limb function and muscle strength tailored to specific situations.[7)] Therefore, this study introduces commonly used STST methods and proposes recommendations for selecting an appropriate STST based on specific situations.

TYPES OF SIT-TO-STAND TESTS

Five-Time Sit-to-Stand Test

The FTSST is a commonly used version of the STST and is one of the assessments included within the Short Physical Performance Battery (SPPB).[8] The FTSST is widely used because it allows easy and rapid measurements using a chair. Moreover, this test is a criterion for assessing sarcopenia in both the Asian Working Group for Sarcopenia (AWGS) 2019 and the European Working Group on Sarcopenia in Older People 2 (EWGSOP-2).[9,10] The FTSST involves rapid standing up and sitting down five times consecutively. In this test, the participants start with their arms crossed over their chest, sitting on a chair without armrests, with their hip and knee joints at 90° (Fig. 1). The participants begin the evaluation once they receive the instructions "ready" and "start." The time required to sit or stand five times is recorded.[8,11] The measurement is performed twice with a 1–2 minute rest interval, with the fastest time used for assessment.[12,13] The results of the FTSST test by age reported in previous studies are presented in Table 1.[14-17]

Thirty-Second Sit-to-Stand Test

The 30-second sit-to-stand test (30STS) is an effective and valid tool used to evaluate lower limb strength in community-dwelling older adults and offers a wider assessment of ability levels compared with the FTSST.[18] Furthermore, the 30STS provides a strong ability to discriminate, particularly in expected differences across age categories and physical activity levels.[18] The 30STS is performed in the same posture as the FTSST. However, it is not a test that involves repeating the sitting and standing motions five times; instead, it records the number of times an individual can sit and stand within 30 seconds.[13,19] The test is repeated twice after the initial attempt, with a rest interval of 1–2 minutes between measurements.[13] The 30STS has been incorporated into function-

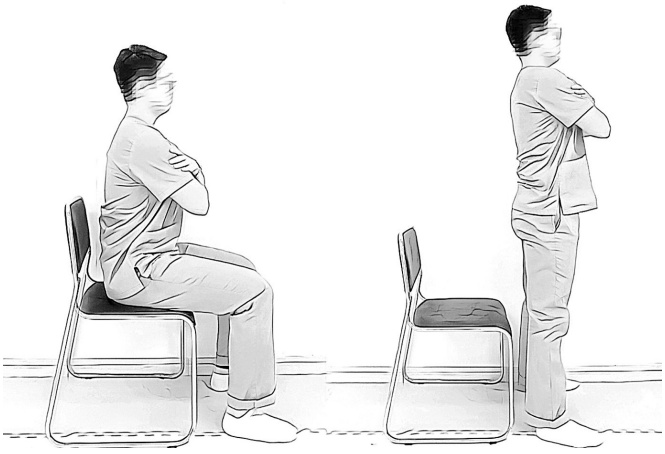

Fig. 1. Sit-to-stand test posture.

Table 1. Reference values for the standard five-time sit-to-stand test (unit: second)

Study	Year	Type of participants	FTSST
Park et al.[17]	2023	Healthy people	20s: M (30) 5.15 ± 1.02, F (30) 5.46 ± 0.95
			30s: M (30) 4.80 ± 1.26, F (30) 5.57 ± 1.26
			40s: M (30) 4.89 ± 0.96, F (30) 5.93 ± 1.43
			50s: M (30) 5.46 ± 1.09, F (30) 6.18 ± 1.19
			60s: M (30) 6.25 ± 1.31, F (30) 7.72 ± 2.46
			70s: M (30) 6.69 ± 1.75, F (30) 7.65 ± 1.83
Bohannon et al.[14]	2010	Community-dwelling people	20s: M/F (36) 6.5 ± 1.2
			30s: M/F (22) 6.1 ± 1.4
			40s: M/F (15) 7.6 ± 1.8
			50s: M/F (20) 7.7 ± 2.6
			60s: M/F (25) 7.8 ± 2.4
			70s: M/F (24) 9.3 ± 2.1
Makizako et al.[16]	2022	Community-dwelling older adults	65–69 y: M (62) 7.2 ± 1.7, F (102) 7.4 ± 2.1
			70–74 y: M (73) 8.1 ± 2.1, F (114) 7.7 ± 2.5
			75–79 y: M (53) 8.2 ± 2.6, F (77) 8.3 ± 2.3
Gao et al.[15]	2021	Community-dwelling older adults	50–54 y: M (911) 9.36 ± 2.79, F (1,031) 10.46 ± 3.17
			55–59 y: M (1,228) 9.86 ± 3.14, F (1,391) 10.91 ± 3.33
			60–64 y: M (1,092) 10.23 ± 3.13, F (1,053) 11.36 ± 3.44
			65–69 y: M (725) 10.61 ± 3.19, F (674) 12.11 ± 3.67
			70–74 y: M (504) 11.75 ± 3.58, F (390) 12.82 ± 4.04
			75–79 y: M (281) 12.52 ± 4.05, F (259) 13.46 ± 3.96

Values are presented as mean±standard deviation.
FTSST, five-time sit-to-stand test; M, male; F, female.

al and balance assessment programs for older adults, such as the Stopping Elderly Accidents, Deaths, and Injuries algorithm developed by the Center for Disease Control and Prevention and the Otago program.[20-22] A previous study including 20 healthy Korean men in their 20s reported an average of 32.37 ± 4.49 repetitions in the 30STS.[23] In a study involving 661 individuals aged 62.6–83.2 years in the Japanese community, the average number of repetitions was 17.26 (95% confidence interval [CI], 15.98–18.55.[24] The reported results of the 30STS by age are presented in Table 2.[23-27]

One-Minute Sit-to-Stand Test

One-minute sit-to-stand test (1MSTS) is conducted in the same manner as the 30STS, but the test time is extended from 30 seconds to 1 minute. The test posture is the same as that for the FTSST and 30STS. The 1MSTS records the number of times an individual can sit and stand within 1 minute[7] and provides auditory notifications when 30 seconds and 15 seconds remain during the test.[28] The test is repeated twice, with a 10-minute rest interval after each test to allow the heart rate and oxygen saturation to return to baseline values before proceeding again.[29] The 1MSTS correlates with the 6-minute walking test (6MWT).[30] A previous study including 20 healthy Korean men reported an average of 62.75 ± 11.09 repetitions in the 1MSTS.[23] In a study involving 30 community-dwelling older women aged ≥ 65 years in Korea, the average number of repetitions was 40.87 ± 8.76.[31] The reported results of the 1MSTS by age are presented in Table 3.[23,31,32]

FACTORS INFLUENCING MEASUREMENT RESULTS

Several factors can influence the measurement results when conducting STST. First, the height of the chair used in STST varies across studies, ranging from 40 cm to 48 cm.[7,29,30,33-36] Chair height is crucial because it influences the biomechanical movements while standing up from a chair.[37] When the chair height is too high, standing is relatively easy, even with an insufficient range of forward trunk flexion.[38] Shifting body weight forward while standing allows for a more comfortable range of movement in the trunk, knees, and ankle joints, thus facilitating the overall biomechanical process.[39] Therefore, standing can occur quickly with minimal muscular effort.[37,39] Given the importance of chair height, ensuring 90° flexion in both the knee and hip joints contributes to objectivity in these measurements and standardizes the test conditions regardless of the chair height.[29]

Second, when conducting the examination, the posture standards for both sitting in a chair and standing upright must be communicated and guidance on hand positioning must be provided. One repetition of sitting and standing is defined as the state in which the lower limbs are fully extended after rising from the chair, with clear contact between the chair and hips when sitting.[35] Additionally, the participants' hands should be well controlled to prevent the use of hands or arms to assist with movement.[35] The use of the hands may involve grasping the knees or chair to assist in standing.

The third consideration is the endpoint criterion. In STST, the

Table 2. Reference values for the standard 30-second sit-to-stand test (unit: times)

Study	Year	Type of participants	30STS
Park et al.[23]	2023	Healthy people	20s: M (20) 32.37 ± 4.49
Lein et al.[26]	2022	Healthy people	20s: M/F (81) 33.00 ± 5.40
Bjerregaard et al.[25]	2021	Greenland population health	55–64 y: M (186) 15.1 ± 5.2, F (234) 12.7 ± 4.4
			65–74 y: M (137) 12.8 ± 5.9, F (152) 10.7 ± 4.3
			75–84 y: M (31) 10.7 ± 4.6, F (37) 9.2 ± 5.4
Sawada et al.[27]	2021	Community-dwelling older adults	65–97 y: M (235) 20.1 ± 5.6, F (443) 18.5 ± 6.4
Nakazono et al.[24]	2014	Community-dwelling older adults	Mean age 62.6–83.2 y
			M/F (661) average 17.26 (95% CI, 15.98–18.55)

Values are presented as mean±standard deviation.
30STS, 30-second sit-to-stand test; M, male; F, female; CI, confidence interval.

Table 3. Reference values for the standard 1-minute sit-to-stand test (unit: times)

Study	Year	Type of participants	1MSTS
Park et al.[23]	2023	Healthy people	20s: M (20) 62.75 ± 11.09
Ritchie et al.[32]	2005	Community-dwelling older adults	55–70 y: M (11) 34.6 ± 6.9, F (9) 26.7 ± 4.9
Park and Shin[31]	2023	Community-dwelling older adults	≥ 65 y: F (30) 40.87 ± 8.76

Values are presented as mean±standard deviation.
1MSTS, 1-minute sit-to-stand test; M, male; F, female.

final endpoint criterion is defined by two aspects: when seated and when in the fully standing position. The endpoint criterion for the fully standing position is based on the SPPB protocol, whereas that for the seated position is a modified version of the SPPB protocol.[11] Specifically, this aspect of the FTSST is crucial because the resulting value is measured within a short duration. The recorded results differ based on the duration taken to complete the test, with variations between the sitting and standing endpoints. A previous study applied a regression equation to 9,383 individuals who underwent the FTSST and were screened for sarcopenia based on the gait speed criterion of < 1.0 m/s established by the AWGS 2019. The results indicated that using the standing endpoint resulted in a screening criterion of 11.1 seconds, whereas using sitting as the endpoint yielded a criterion of 11.7 seconds.[40]

Finally, the use of digital equipment must be considered. When performing the STST, the state of standing from a seated position is monitored using a load cell and a light detection and ranging (LiDAR) sensor on the chair, allowing for the verification of the total number of stand-up and sit-down cycles.[41,42] Although the seated position can be easily measured using the load cell, accurately determining the upright standing posture using both the load cell and LiDAR sensor may pose some challenges. In contrast, if the measurements rely solely on an observer rather than digital equipment, immediate verification of the standing posture is possible; however, accurately confirming the seated posture can be challenging. Therefore, the comprehensive utilization of both approaches allows the most accurate execution of STST. In addition, improving the limitations of digital equipment may lead to more effective measurement methods.

SARCOPENIA SCREENING WITH STST METHODS

Sarcopenia Screening using the FTSST

Among STST methods for sarcopenia screening, the FTSST is widely used. The EWGSOP-2 defines > 15 seconds as the cutoff value for sarcopenia screening using the FTSST,[10] while the AWGS 2019 defines a cutoff of ≥ 12 seconds.[9]

This difference in criteria can be attributed to various factors such as regional variations, population characteristics, and cultural differences. However, an important factor is the difference in gait speed. The EWGSOP-2 and AWGS 2019 set the gait speed criterion for sarcopenia at ≤ 0.8 m/s and < 1.0 m/s, respectively. A previous study reported a negative correlation between chair stand time and gait speed and proposed a cutoff formula for FTSST of -8.41 × gait speed+20.0 (R^2 = 0.34) for sarcopenia screening.[43] The formulas presented in previous studies confirmed that the cutoff values of the FTSST vary slightly depending on the gait speed standard.

A Korean study on sarcopenia screening criteria suggested FTSST cutoff values of > 11 seconds and > 10 seconds for finishing in a seated or standing position, respectively.[6] These criteria, based on previous studies,[6,9] differ from the established standards of the EWGSOP-2 and AWGS 2019. Specifically, they presented criteria based on an endpoint, which was a distinctive feature (Table 4).

Sarcopenia Screening using the 30STS

In addition to the FTSST, the 30STS has also been proposed as a criterion for sarcopenia screening. The Korean Working Group on Sarcopenia Guidelines provide criteria for the 30STS, suggesting cutoff values of ≤ 17 and ≤ 15 repetitions for men and women, respectively.[6] These cutoffs were based on the results of a Japanese study targeting older adults.[27] Analysis of the receiver operating characteristic curves revealed a threshold of ≤ 17 repetitions for men in the 30STS, which showed an area under the curve (AUC) of 0.80, a sensitivity of 75.0%, and a specificity of 71.7%. For women, the cutoff was ≤ 15 repetitions, which showed an AUC of 0.84, a sensitivity of 76.4%, and a specificity of 76.8%.

However, few studies have evaluated the 30STS and 1MSTS and the criteria for sarcopenia. This may be attributed to the limited use of the 30STS and 1MSTS, as the FTSST allows for rapid sarcopenia assessment. Despite these considerations, the 30STS and 1MSTS continue to be widely used for assessing balance in older adults and exercise capacity in individuals with respiratory conditions.[34,44,45] Their superior ability to reflect leg strength compared with the FTSST allows these tests to be applied more broadly be-

Table 4. Sarcopenia screening criteria in each study

Study	FTSST (s)	Gait speed (m/s)	30STS (times)
EWGSOP-2[10]	> 15	≤ 0.8	-
AWGS 2019[9]	≥ 12	< 1.0	-
Korean Working Group on Sarcopenia Guideline[6]	> 10 (standing position)	< 1.0	≤ 17 (male)
	> 11 (sitting position)		≤ 15 (female)

FTSST, five-time sit-to-stand test; 30STS, 30-second sit-to-stand test; EWGSOP-2, European Working Group on Sarcopenia in Older People 2; AWGS, Asian Working Group for Sarcopenia.

yond sarcopenia, serving a diverse range of patients.[18,23,46] This highlights the need for further research to develop more targeted sarcopenia-specific criteria for both the 30STS and 1MSTS to enhance their effectiveness and accuracy in sarcopenia screening.

ASSOCIATION BETWEEN THE STST AND PHYSICAL FUNCTION

The STST is a comprehensive test that assesses overall muscle strength, dynamic balance, and cardiovascular endurance.[47-50] The STST not only assesses the transition from a seated to a standing position but also represents the most fundamental daily activity as the precursor to walking. Successful sitting-to-standing movements require good biomechanical strength in the knee extensor muscles.[51] The STST is a test method strongly associated with lower limb strength. The 30STS shows a high correlation with leg press ($r = 0.71–0.78$),[18] and through hierarchical linear regression analysis, isokinetic knee extensor concentric contraction at 180° (adjusted $R^2 = 0.425$, $p = 0.004$) and eccentric contraction (adjusted $R^2 = 0.427$, $p = 0.004$) were identified as significant independent predictor variables in 30STS.[52] STST is significantly correlated ($r = -0.49–-0.36$) with the thickness of the quadriceps muscle.[53]

In a study measuring physical activity levels, individuals with typical activity levels had FTSST times of 5.93 ± 1.29 seconds, 22.11 ± 3.12 30STS repetitions, and 41.72 ± 7.26 1MSTS repetitions.[54] However, individuals with high-intensity activity levels showed significantly higher results than those with typical activity levels, with FTSST times of 5.13 ± 1.10 seconds, 26.00 ± 4.93 30STS repetitions, and 50.54 ± 10.26 1MSTS repetitions.[54] Another study investigating the correlation between 6MWT distance and 30STS and 1MSTS repetitions in 20 healthy adult men and 20 women in their 20s reported a 6MWT distance of 667 ± 55.9 m, 23.6 ± 4.35 30STS repetitions, and 45.2 ± 9.56 1MSTS repetitions. A significant positive correlation was observed between the 6MWT distance and the STST, with r values of 0.61 for 30STS and 0.64 for 1MSTS, suggesting a moderate correlation.[46] Additionally, older adults with relatively poor FTSST results may have a higher risk of falling.[55] Moreover, previous studies have investigated FTSST cutoff values for individuals with low physical function. The results of a 2-year follow-up revealed that an FTSST duration of 10.8–12.8 seconds could help identify community-based individuals at risk of impaired physical function, which suggests the potential for designing and implementing preventive interventions.[56]

A review of the results of previous studies revealed the numerous associations between the STST and physical function. Therefore, conducting STST assessments in older adults and patients and using these results as a basis for confirming and evaluating physical function is feasible. Among STST methods, the FTSST is commonly used because it allows for rapid examination and provides immediate results regarding lower limb function and strength. While the FTSST is fundamentally the most widely used screening criterion for sarcopenia, using it to assess lower limb strength and function across various age groups may be overly simplistic.[17] Therefore, the 30STS and 1MSTS, with slightly higher difficulty in assessing lower limb function and muscle strength, are feasible not only for older adults but also for individuals of various ages. Moreover, the correlation of the 6MWT with the 30STS and 1MSTS has been verified more extensively than with the FTSST; therefore, the 30STS and 1MSTS would be better to use rather than the FTSST in situations where it is difficult to conduct the 6MWT.[30,46]

CONCLUSION

The STST is a tool that can be easily and conveniently used anywhere to assess physical function and screen for sarcopenia, not only in the older adult population but also in patients with various diseases. Different STSTs have been used in research, and their value is being increasingly recognized. The appropriate application of the STST as proposed in the present study is as follows: FTSST should be used for rapid sarcopenia screening. The 30STS should be additionally performed after the FTSST to assess muscle strength. Furthermore, either the 30STS or the 1MSTS should be used to assess balance, exercise capacity, and leg strength in community-dwelling older adults, patients with respiratory diseases, or those with other medical conditions. Presently, most sarcopenia criteria research focuses on the FTSST, including the proposed cutoff values. However, there is a growing need for more research on the criteria for sarcopenia involving the 30STS and 1MSTS, along with the establishment of corresponding cutoff values.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

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

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Older Adult Patients in the Emergency Department: Which Patients should be Selected for a Different Approach?

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Background: While multidimensional and interdisciplinary assessment of older adult patients improves their short-term outcomes after evaluation in the emergency department (ED), this assessment is time-consuming and ill-suited for the busy environment. Thus, identifying patients who will benefit from this strategy is challenging. Therefore, this study aimed to identify older adult patients suitable for a different ED approach as well as independent variables associated with poor short-term clinical outcomes. **Methods:** We included all patients ≥65 years attending 52 EDs in Spain over 7 days. Sociodemographic, comorbidity, and baseline functional status data were collected. The outcomes were 30-day mortality, re-presentation, hospital readmission, and the composite of all outcomes. **Results:** During the study among 96,014 patients evaluated in the ED, we included 23,338 patients ≥65 years—mean age, 78.4±8.1 years; 12,626 (54.1%) women. During follow-up, 5,776 patients (24.75%) had poor outcomes after evaluation in the ED: 1,140 (4.88%) died, 4,640 (20.51) returned to the ED, and 1,739 (7.69%) were readmitted 30 days after discharge following the index visit. A model including male sex, age ≥75 years, arrival by ambulance, Charlson Comorbidity Index ≥3, and functional impairment had a C-index of 0.81 (95% confidence interval, 0.80–0.82) for 30-day mortality. **Conclusion:** Male sex, age ≥75 years, arrival by ambulance, functional impairment, or severe comorbidity are features of patients who could benefit from approaches in the ED different from the common triage to improve the poor short-term outcomes of this population.

Key Words: Emergencies, Geriatrics, Frail elderly, Triage

INTRODUCTION

Aging populations challenge health and social care systems worldwide.[1] The percentage of people aged ≥ 65 years in European countries is predicted to increase from 16% in 2001 to 21% in 2020.[2] Greece, Finland, Portugal, Germany, and Bulgaria (22%) had the highest forecast percentages, whereas Ireland (14%) and Luxembourg (15%) had the lowest. The group of individuals aged ≥ 80 years comprised nearly 6% of the population in 2020, a two-fold increase compared with 2001 (3.4%).[2] Projections indicate that the percentage of people aged ≥ 80 years in Europe will multiply by 2.5-fold between 2020 and 2100, rising from 5.8% to 14.6%.

Over the past decade, increasing pressure on emergency care has led to crowding in emergency departments (EDs), which represents a major challenge. This has negative consequences for the efficiency, quality, and safety of emergency care.[3,4] ED crowding is partially caused by a growing number of older adults.[5] These individuals often have complex health problems and multimorbidities associated with high rates of health service utilization. This population accounts for an estimated 15%–25% of total ED visits.[6]

Older adult patients experience age-related physiological changes in the immunological, cardiovascular, and respiratory systems, which may hinder the identification of disease severity.[7] Older adult individuals also have a greater probability of atypical disease presentation, comorbidities, cognitive disorders, geriatric syndromes, and polypharmacy.[8] In emergency care, these differences imply a more complex clinical evaluation requiring more staff time; a greater need for complementary tests and consultations with other specialists; longer stays in the ED; and a greater probability of misdiagnosis, hospitalization, and discharge with undetected or untreated problems, leading to a greater risk of medical complications, functional impairment, and poorer health following discharge.[6,9,10] In addition, other factors such as pre-existing functional impairment, cognitive decline, and social issues hamper disposition planning.[11-13]

Older patients also often experience poorer outcomes following ED visits. This is reflected in the hospitalization, return rates, and deaths in older adults compared with those in younger patients. Approximately 10%–23% of older patients return unexpectedly within the first month,[14] and up to 25% of older adults return to the ED within 3 months.[11] Within 3 months of discharge, 12.4% of the older patients die, 18.3% are hospitalized, and 2.6% subsequently enter a nursing home. Within 6 months of discharge after the index ED visit, 43.9% of older adults return to the ED at least once, and 7.5% return ≥ 3 times. Furthermore, approximately 80% of the older adults discharged from the ED have at least one unaddressed health issue.[15] Such high rates of re-presentation and other adverse outcomes after initial ED admission support concerns regarding traditional ED models that do not meet the underlying needs of many older patients.[16]

ED urgency triage aims to prioritize patients based on their clinical urgency, rapidly diagnose potentially lethal illnesses, and reduce the negative impact of treatment delays on prognosis.[17] However, triage tools may allocate urgency less effectively in older populations,[18-20] possibly due to different reference values for vital signs, atypical disease presentations, and the presence of cognitive impairment. Older patients are, therefore, at risk of "undertriage," an assignment of an inappropriately low triage level, resulting in longer waiting times and the risk of adverse outcomes due to harm by delay in treatment.[17] Triage performance is inferior in older patients compared to younger patients and is illustrated by a worse predictive ability for identifying in-hospital mortality risk in older patients.[19,20]

Several geriatric screening tools have been developed to identify vulnerable geriatric patients in the ED.[21-24] These tools are prognostic tools for long-term adverse outcomes, whereas urgent triage tools are primarily designed to assign short-term clinical priority and secondarily to predict short-term mortality. Multidimensional and interdisciplinary assessments of older patients have been shown to increase the likelihood of older people being alive and living in their own homes 12 months after admission. However, this process is time-consuming and ill-suited for busy ED environments.[25]

Considering the above, determining which older patients are at risk of adverse effects related to their age or specific basal circumstances and for whom different or complementary triage models should be applied is critical. Therefore, this study aimed to identify in which older adult patients a different ED approach would be suitable, as well as variables independently associated with poor short-term clinical outcomes not included in common triage systems, based on sociodemographic characteristics, comorbidities, and baseline functional status characteristics in patients aged ≥ 65 years evaluated in the ED.

MATERIALS AND METHODS

Description of the emergency department and elders in need (EDEN) Challenge

The EDEN challenge emanates from the Spanish Investigators in Emergency Situations Team (SIESTA) network,[26] which includes 52 EDs (approximately 20% of Spanish public EDs). These hospitals are representative both territorially (12 of the 17 Spanish regions) and in terms of typology (university, high technology, and regional hospitals). The results of this challenge have recently been

presented.[27] The primary objective is to increase knowledge about the sociodemographic, organizational, baseline, clinical, care, and evolutionary aspects of the population aged 65 years and older who consult Spanish EDs. To this end, we created a multipurpose registry that included all patients who consulted the ED regardless of the reason for consultation.

The inclusion period was April 1–7, 2019 (7 days). No exclusion criteria were applied and EDs wishing to participate were required to include all patients seen during the study period.

Ethical Considerations

The EDEN project was approved by the Clinical Research Ethics Committee of the Clínico San Carlos de Madrid Hospital (Protocol No. HCSC/22/005-E). Because of the characteristics of the study and the time periods for which data collection was planned, the requirement for written informed consent by the patients was waived. The database was used with coded patients to preserve their anonymity. The creation of the EDEN cohort and the work emanating from them followed the ethical principles of the Declaration of Helsinki.

This study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[28]

EDEN-15 Study Design

The EDEN-15 study analyzed patients included in the EDEN cohort. We analyzed six sociodemographic characteristics (age, sex, how the patient arrived at the ED, how the patient was referred to the ED, home accompaniment status, and whether the patient had social support) and five characteristics related to the patient's baseline functional status (dependence according to the Barthel Index, comorbidity according to the Charlson Comorbidity Index, falls in the previous 6 months, and previous diagnoses of dementia and depression). The outcome variables were 30-day mortality, re-presentation, and hospital readmission. For the calculation of re-presentation and hospital readmission, patients who died during hospitalization at the index visit were excluded. These outcomes were calculated based on hospital or ED discharge. Finally, we considered poor outcome as a composite variable, including all events (30-day mortality, re-presentation, and hospital readmission).

Statistical Analysis

The frequencies and percentages of qualitative variables and the median and interquartile range of continuous variables were recorded. Characteristics of alive and dead patients, readmitted patients, and represented after 1 month of follow-up were compared using the chi-square test for categorical variables. Cox proportional hazards regression analyses were performed to assess the accuracy of the different scores to predict 30-day mortality, readmission, and re-presentation. Univariate Cox regression models were used to assess the response variables. All variables with $p < 0.2$ were considered in the multivariate Cox model. Hazard ratios (HRs), 95% confidence intervals (CIs), and p-values were calculated for each category. Differences between groups were considered statistically significant for $p < 0.05$, or if the 95% CI of the HR excluded the value of 1. We also calculated the C-index to study the predictive accuracy of the model, where the null value of the C-statistic was 0.5. To create the scale score, we first assigned a weight to each category of each statistically significant variable, relative to the estimated beta parameter of each survival model. We added the total scores for each patient, with higher scores indicating a greater probability of each outcome.[29] Once the risk score was developed, we divided the scores into three categories. Kaplan–Meier curves were generated for the four outcomes for the different scores. The optimal categorization of each continuous risk score was obtained using the CatPredi function of the R package CatPredi (https://cran.r-project.org/) using a genetic algorithm. Subsequently, the results were internally validated by bootstrapping with 500 resamples, and the C-index was calculated with 95% CI. All statistical processing was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA), SAS for Windows, version 9.4 (SAS Institute, Cary, NC, USA), and R version 4.1.1. The figures were produced using PowerPoint 2016 (Microsoft Corp., Redmond, WA, USA).

RESULTS

During the study period 96,014 patients were evaluated in the 52 EDs participating in the study; among these, 23,338 patients aged ≥65 years—mean age, 78.4±8.1 years; 12,626 (54.1%) women—were finally included (Fig. 1). During follow-up, 5,776 patients (24.75%) had a poor outcome after evaluation in the ED: 1,140 (4.88%) died, 4,640 (20.51%) returned to the ED, and 1,739 (7.69%) were readmitted within 30 days after discharge fol-

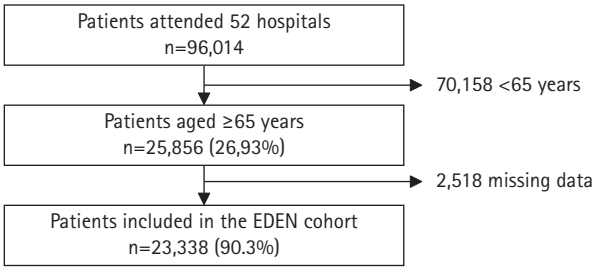

Fig. 1. Flowchart for the inclusion of patients in the EDEN cohort.

lowing the index visit. Table 1 shows the patient characteristics.

Supplementary Table S1 presents the comparative analysis of poor outcomes (mortality, readmission, and re-presentation within 1 month) and the composite poor outcome, including all variables analyzed. The results of the univariate analysis of poor outcomes are shown in Supplementary Table S2. The factors associated with a higher risk for 30-day mortality included age > 84 years (HR = 4.510; 95% CI, 3.822–5.321), living in a geriatric residence (HR = 4.329; 95% CI, 3.257–5.754), ED arrival by ambulance (HR = 5.792; 95% CI, 5.106–6.569), having moderate or severe comorbidities (HR = 4.237; 95% CI, 3.216–5.582 and HR = 10.025; 95% CI, 7.714–13.029, respectively), having moderate or severe impairment (HR = 3.735; 95% CI, 3.225–4.326 and HR = 8.234; 95% CI, 7.078–9.579, respectively), dementia (HR = 3.159; 95% CI, 2.750–3.606), and delirium (HR = 3.035; 95% CI, 2.417–3.877). The factors associated with a higher risk of 30-day readmission were age > 84 years (HR = 1.784; 95% CI, 1.584–2.009), living in a geriatric residence (HR = 1.674; 95% CI, 1.321–2.120), ED arrival by ambulance (HR = 1.711; 95% CI, 1.551–1.888), and having moderate or severe functional impairment (HR = 1.906; 95% CI, 1.716–2.117 and HR = 2.305; 95% CI, 2.009–2.645, respectively). Thirty-day re-presentation was mainly related to male sex (HR = 1.204; 95% CI, 1.136–1.277) and moderate or severe functional impairment (HR = 1.335; 95% CI, 1.250–1.426 and HR = 1.309; 95% CI, 1.188–1.442, respectively).

Table 2 shows the results of the multivariate analysis using univariate survival models for poor outcomes, as well as the models obtained, and the points assigned to each variable. A model including sex (male), age ≥ 75 years, arrival by ambulance, Charlson Comorbidity Index ≥ 3, and having functional impairment, even mild, had a C-index of 0.81 (95% CI, 0.80–0.82) for 30-day mortality. The C-index for the 30-day readmission was 0.66 (95% CI, 0.64–0.67). The model for 30-day re-presentation had a C-index of 0.57 (95% CI, 0.56–0.58) and included male sex, Charlson Comorbidity Index ≥ 3, and functional impairment. A model for the composite outcome had a C-index of 0.61 (95% CI, 0.60–0.62) and included male sex, age > 84 years, arrival by ambulance, Charlson Comorbidity Index ≥ 3, and the presence of functional impairment. A forest plot of the HRs is shown in Fig. 2. Table 3 shows the functioning of risk groups derived from the developed models. In Fig. 3, the Kaplan–Meier curves for the models are presented for each dependent variable for the three patient groups: 0–5, 6–11, and 12–18–case for 30-day mortality; 0–1, 2–3, and 4–8 for 30-day readmission; 0, 1–2, and 2–4 for 30-day re-presentation; and 0–4, 5–8, and 9–14 for poor outcome within 30 days.

Table 1. Characteristics of the patients included (n=23,338)

	Characteristic	Value
Sociodemographic	Age (y)	78 (71–85)
	Sex, female[a]	12,626 (54.1)
	Arrival to ED	
	Own transport	17,291 (74.1)
	Non medicalised ambulance	4,591 (19.7)
	Medicalised ambulance	1,456 (6.2)
	Referral to the ED	
	Initiative of the patient or caregiver	15,998 (68.6)
	From primary care	4,747 (20.3)
	By medical specialist other than primary care	635 (2.7)
	From another hospital	512 (2.2)
	Situation at home[a]	
	Lives alone, does not have professional caregivers	1,685 (12.0)
	Lives with relatives	10,373 (73.9)
	Live with professional caregiver 24 hours	343 (2.4)
	Live with a professional caregiver for a few hours	208 (1.5)
	Lives in residence	1,412 (10.1)
	Has social assistance[b]	1,333 (17.1)
Basal status	Barthel index	
	Independent (100 points)	15,615 (66.9)
	Mild-moderate dependence (60–95 points)	5,480 (23.5)
	Severe dependency (< 60 points)	2,243 (9.6)
	Charlson Comorbidity Index	
	No comorbidity (0 points)	6,114 (26.2)
	Mild comorbidity (1–2 points)	9,505 (40)
	Moderate comorbidity (3–4 points)	4,489 (19.2)
	Severe comorbidity (≥ 5 points)	3,230 (14.6)
	Fall in the previous 6 months	1,627 (7)
	Established diagnosis of cognitive impairment	3,095 (13.3)
	Diagnosis of depression	3,133 (13.4)
Comorbidity	High blood pressure	16,446 (70.5)
	Dyslipidaemia	11,752 (50.4)
	Diabetes mellitus	6,762 (29)
	Chronic lung disease	4,515 (19.3)
	Cancer	3,935 (16.9)
	Heart failure	3,477 (14.9)
	Ischaemic heart disease	3,685 (15.8)
	Chronic kidney disease	2,677 (11.5)
	Stroke	2,850 (12.2)
	Dementia	2,425 (10.4)
	Peripheral vascular disease	2,294 (9.8)
	Connective tissue disease	1,949 (8.4)
	Active smoking	1,372 (5.9)
	Chronic liver disease	890 (3.8)
	Ulcer disease	973 (4.2)
	Alcoholism	585 (2.5)
	HIV infection	74 (0.3)

Values are presented as median (interquartile range) or number (%).
ED, emergency department; HIV, human immunodeficiency virus.
[a]Calculated from 14,021 patients, [b]calculated from 7,773 patients.

Table 2. Multivariate analysis in people over 65 years of age for 30-day mortality, readmission, and re-presentation using univariate survival models

	30-day mortality				30-day readmission				30-day re-presentation				30-day poor outcome			
	HR (95% IC)	p-value	Coeff	Weight	HR (95% IC)	p-value	Coeff	Weight	HR (95% IC)	p-value	Coeff	Weight	HR (95% IC)	p-value	Coeff	Weight
Sex, male	1.302 (1.151–1.473)	< 0.0001	0.264	1	1.31 (1.189–1.444)	< 0.0001	0.160	1	1.157	0.0005	0.146	1	1.173 (1.112–1.238)	< 0.0001	0.16	2
Age (y)																
65–74	Ref.	Ref.	Ref.	0	Ref.	Ref.	Ref.	0	-	-	-	-	Ref.	Ref.	Ref.	0
75–84	1.232 (1.026–1.480)	0.0258	0.209	1	1.092 (0.969–1.230)	0.4171	0.027	1	-	-	-	-	1.027 (0.963–1.095)	0.4171	0.027	-
≥ 85	1.862 (1.552–2.233)	< 0.0001	0.622	2	1.291 (1.131–1.474)	0.0093	0.097	2	-	-	-	-	1.102 (1.024–1.186)	0.0093	0.097	1
Arrival (ambulance)	3.209 (2.794–3.686)	< 0.0001	1.166	6	1.285 (1.154–1.432)	< 0.0001	0.176	6	-	-	-	-	1.192 (1.122–1.267)	< 0.0001	0.176	2
Charlson Comorbidity Index (≥ 3)	1.952 (1.716–2.220)	< 0.0001	0.669	3	2.06 (1.863–2.278)	< 0.0001	0.428	3	1.43 (1.344–1.522)	< 0.0001	0.358	2	1.535 (1.452–1.622)	< 0.0001	0.428	4
Barthel index	-	-	-	-	-	-	-	-	-	-	-	-				
Independent	Ref.	Ref.	Ref.	0	Ref.	Ref.	Ref.	0	Ref.	Ref.	Ref.	0	Ref.	Ref.	Ref.	0
Mild-moderate dependence	1.989 (1.693–2.338)	< 0.0001	0.688	3	1.504 (1.338–1.691)	< 0.0001	0.276	3	1.233 (1.151–1.321)	< 0.0001	0.210	1	1.317 (1.234–1.407)	< 0.0001	0.276	3
Severe dependence	3.174 (2.660–3.787)	< 0.0001	1.155	6	1.785 (1.509–2.112)	< 0.0001	0.441	6	1.201 (1.087–1.327)	0.0003	0.183	1	1.555 (1.423–1.699)	< 0.0001	0.441	5
Dementia (yes)	-	-	-	-	0.724 (0.616–0.851)	< 0.0001	-0.322	1	-	--	-	-	-	-	-	-
C-index (95% IC)	0.81 (0.80–0.82)				0.66 (0.64–0.67)				0.57 (0.56–0.58)				0.61 (0.60–0.62)			
Score c-index (95% IC)	0.81 (0.80–0.82)				0.65 (0.64–0.66)				0.56 (0.55–0.57)				0.60 (0.59–0.51)			
Bootstrap validation c-index (95% IC)	0.81 (0.80–0.82)				0.66 (0.65–0.67)				0.57 (0.56–0.58)				0.60 (0.59–0.61)			
Bootstrap validation score c-index (95% IC)	0.81 (0.80–0.82)				0.65 (0.64–0.66)				0.56 (0.55–0.57)				0.60 (0.59–0.61)			

Multivariate analysis in people over 65 years of age for 30-day mortality, readmission, and re-presentation using univariate survival models.

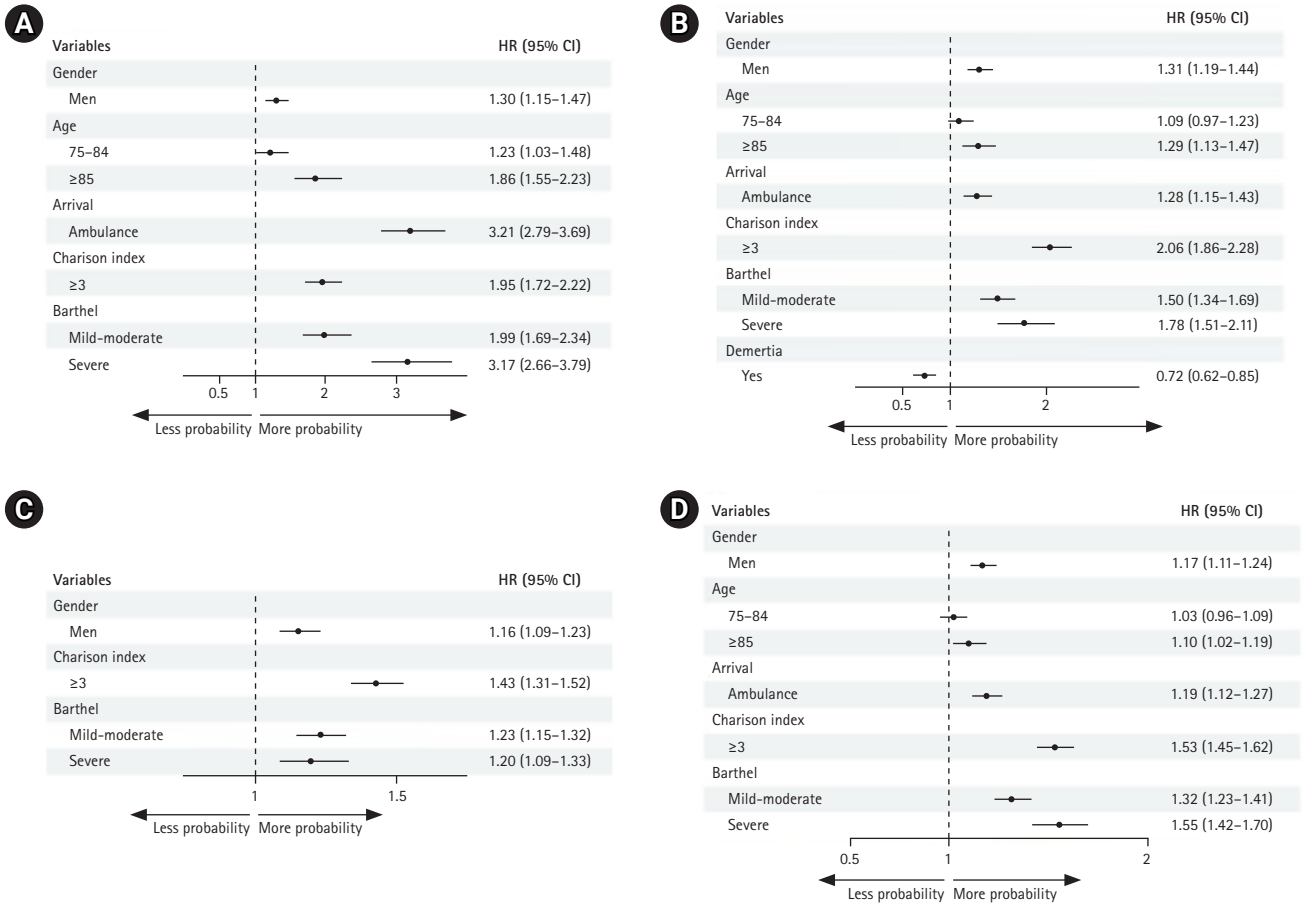

Fig. 2. Forest plot results for the four outcomes: (A) 30-day mortality, (B) 30-day readmission, (C) 30-day re-presentation, and (D) 30-day poor outcome.

Table 3. Risk groups of the four outcomes

		Total	n (%)	HR (95% CI)	p-value
30-day mortality	Score < 6	14,123	181 (0.79)	Ref	Ref
	6 ≤ Score < 12	5,922	418 (1.82)	5.681 (4.772–6.762)	< 0.0001
	Score ≥ 12	2,804	517 (2.26)	15.831 (13.366–18.752)	< 0.0001
	C-index (95% CI)			0.78 (0.76–0.79)	
	Bootstrap C-index (95% CI)			0.77 (0.76–0.79)	
30-day readmission	Score < 2	10,012	390 (1.76)	Ref	Ref
	2 ≤ Score < 4	6,123	530 (2.39)	2.282 (2.002–2.601)	< 0.0001
	Score ≥ 4	6,013	775 (3.50)	3.461 (3.064–2.909)	< 0.0001
	C-index (95% CI)			0.64 (0.62–0.65)	
	Bootstrap C-index (95% CI)			0.64 (0.62–0.65)	
30-day re-presentation	Score < 1	6,661	248 (1.11)	Ref	Ref
	1 ≤ Score < 3	9,814	682 (3.08)	1.901 (1.644–2.198)	< 0.0001
	Score ≥ 3	5,673	765 (3.45)	3.812 (3.303–4.388)	< 0.0001
	C-index (95% CI)	0.56 (0.55–0.57)			
	Bootstrap C-index (95% CI)	0.56 (0.55–0.57)			
30-day poor outcome	Score < 5	13,471	2,564 (11.22)	Ref	Ref
	5 ≤ Score < 9	6,100	1,801 (7.88)	1.665 (1.568–1.769)	< 0.0001
	Score ≥ 9	3,278	1,278 (5.59)	2.406 (2.249–2.573)	< 0.0001
	C-index (95% CI)			0.56 (0.55–0.57)	
	Bootstrap C-index (95% CI)			0.56 (0.55–0.57)	

HR, hazard ratio; CI, confidence interval.

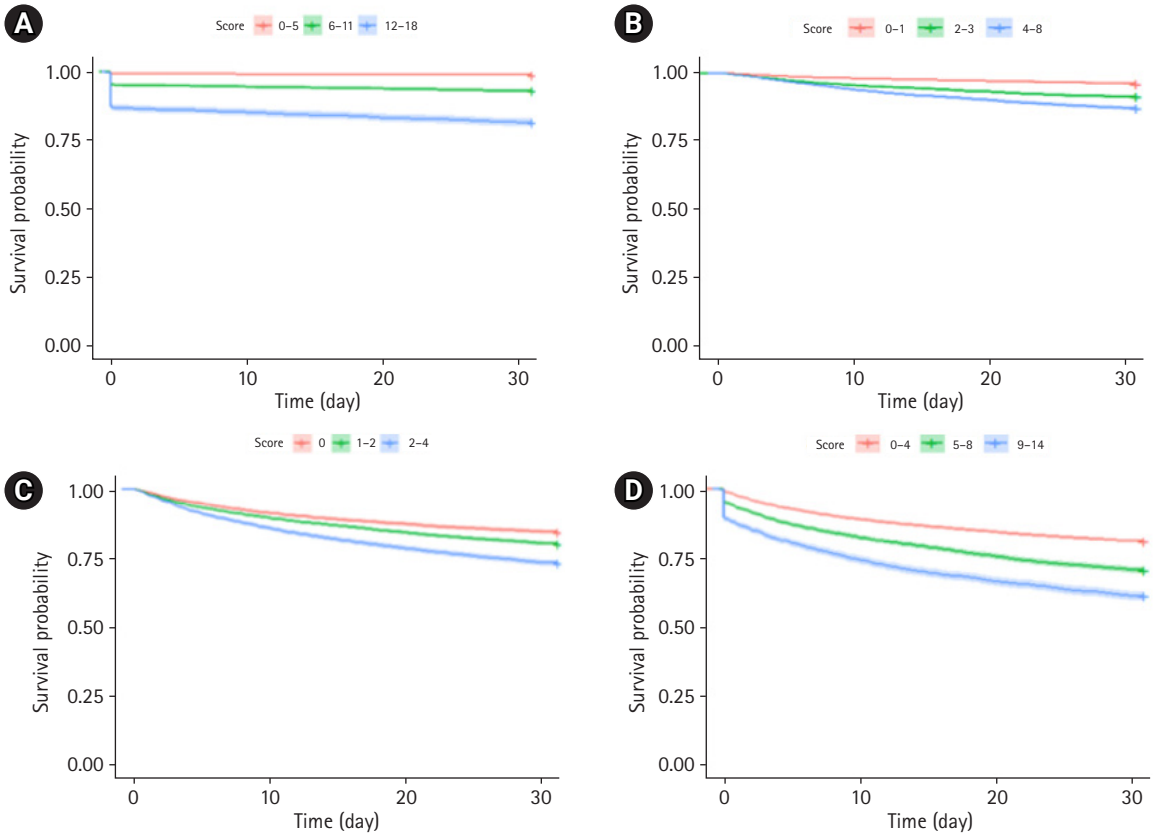

Fig. 3. Kaplan-Meier curves for the variables studied: (A) 30-day mortality, (B) 30-day readmission, (C) 30-day re-presentation, and (D) 30-day poor outcome.

DISCUSSION

In the present study, one in four patients had a poor short-term outcome after being evaluated in the ED, 5% died, one in five patients returned to the ED, and 7% were readmitted within the first month of discharge. To improve these results, new strategies are required during the index visit to identify high-risk patients. A model including male sex, age ≥ 75 years, ED arrival by ambulance, functional impairment, and Charlson Comorbidity Index ≥ 3 could be useful for identifying short-term mortality. In patients meeting these criteria, geriatric screening tools should be used to improve outcomes. The other three risk-scoring models (30-day readmission, 30-day re-presentation, and composite poor outcome) presented relatively low C-index values (0.55–0.65), suggesting their limited predictive accuracy.

Kuriyama et al.[30] evaluated the accuracy of common triage systems used in the ED and showed that accuracy diminishes with increasing patient age. While underestimation of severity in these patients did not significantly increase, misclassification significantly increased with patient age. Gasperini et al.[31] measured the proportion of patients > 65 years of age who were assigned a lower triage level than the real level of care needed, showing undertriage in 7.6% of the patients evaluated, which occurred more frequently in patients aged > 85 years (9.2%) than in those aged 75–84 years (7.5%) and 65–74 years (6.4%). Different reference values for vital signs and atypical presentations of diseases in older adult patients could contribute to undertriage.[32]

Several geriatric screening tools have been developed to identify vulnerable geriatric patients in the ED, including the Identification of Seniors at Risk,[22] Triage Risk Screening Tool,[23] and Acute Presentation of Older Patients.[33] These screening tools could add value, as they improve knowledge and approaches to geriatric patients in the ED.[32] The American College of Emergency Physicians, American Geriatrics Society, Emergency Nurses Association, and Society for Academic Emergency Medicine developed the Geriatric Emergency Department Accreditation (GEDA) program to provide a standardized set of guidelines to effectively improve the care of the geriatric population.[34] These guidelines create a template for staffing, equipment, education, policies, procedures, follow-up care, and performance improvements.

Geriatric education programs based on content and teaching methods, learning outcome effects, and factors promoting or hin-

dering program implementation can improve ED professionals' geriatric knowledge and positively impact their clinical practice.[35] A systematic review[15] including interventions in EDs targeted at reducing ED revisits, hospitalizations, nursing home admissions, and deaths in older patients after initial ED discharge showed that studies varied in their design and outcome measurements, but suggested that the use of a validated risk prediction tool to stratify patients into high- and low-risk groups could lead to improved patient outcomes. Furthermore, interventions that extend beyond simple referral might reduce the rates of adverse outcomes after ED discharge and should be considered. More intensive interventions that followed patients beyond referral and the use of a clinical risk prediction tool were associated with improved outcomes. Our study results could help define which patients could benefit from such specific approaches.

Nevertheless, these strategies are not widely implemented, partly because of their complexity in environments such as the ED, where time is limited.[36] The term geriatric has different definitions over time. Fries et al.[37] defined three groups by dividing the older adult population into young old (65–74 years), middle old (75–85 years), and oldest (> 85 years). The World Health Organization defines the older population starting at 60 years of age.[38] The GEDA guidelines use 65 years as the cutoff for the geriatric population. Nevertheless, hospitals may find that using the age of ≥ 65 years does not match the aim of identifying a high-risk population.

One challenge in the ED is recognizing which patients will benefit from this strategy; therefore, it is crucial to identify patients at risk of poor outcomes, independent of the reason for consultation, using variables available at presentation in the ED. Common triage uses vital signs for classification; however, older adult patients experience age-related physiological changes, leading to a lower heart rate or temperature, and increased stiffness of the arterial wall, which leads to increased blood pressure.[7] Considering these changes, we did not include vital signs in the analysis and used only variables related to the basal status of older adult patients to identify those at risk for poor outcomes that could benefit from the application of multidimensional and interdisciplinary assessments to improve clinical results.

Our study has some limitations. First, the 52 participating EDs were not chosen at random but rather expressed their interest in participating. However, the broad representation both territorially (12 of the 17 autonomous communities were represented) and in terms of typology (universities, high technology, and regional hospitals) means that bias in this regard is probably small. Second, the analysis was not conducted by nosology groups but rather globally. This may indicate that the findings are conditioned by certain processes that may be more prevalent according to the patient's sex or age. Nonetheless, our design captured the entire spectrum of attended patients and was not limited to a single disease or a group of diseases, thus providing an overall picture. Third, this was a secondary analysis of a multi-purpose cohort, and the associations may have been influenced by factors not covered in the cohort design. Therefore, the findings should be considered hypothesis-generating and confirmed by studies specifically designed for this purpose. Fourth, patients in the EDEN cohort were included by episode rather than by patient, and some episodes may have corresponded to the same patient. However, as the inclusion period was very short (7 days), the chance of a repeat visit for a particular patient was low. Finally, the inclusion period was limited to a single week of the year. Pathologies affecting older adult patients may differ depending on the season of the year, especially related to infectious diseases. However, the large number of included patients may have limited the impact of this consideration.

In conclusion, male sex, age ≥ 75 years, ED arrival by ambulance, the presence of functional impairment, or severe comorbidity are features of patients in whom the application of a specific approach different from common triage may be useful in the ED to improve the poor short-term outcomes of this population. While it may be difficult to integrate these variables into the structured triage systems already established in EDs, alerts could be included in the electronic medical histories of EDs to make attending physicians aware of the possible need for a specialized taxonomic approach.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4235/agmr.23.0121.

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Prevalence of Adrenal Insufficiency in Korean Patients undergoing Total Knee Arthroplasty

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Background: This study investigated the prevalence of adrenal insufficiency among patients admitted for total knee arthroplasty (TKA) due to osteoarthritis and identified factors contributing to adrenal insufficiency. **Methods:** We divided the patients into two groups based on the results of preoperative standard-dose short synchronous stimulation tests: group 1 (adrenal insufficiency) and group 2 (normal adrenal function). We also assessed the prevalence of adrenal insufficiency and compared the numbers of patients who received oral steroids, the frequency of previous steroid injection use, and the frequency of systemic symptoms of steroid depletion such as fatigue and loss of appetite between the two groups. Multiple regression analysis was performed to identify factors related to adrenal insufficiency. **Results:** The prevalence of adrenal insufficiency was 60.0% (120/200). Group 1 had higher numbers of previous steroid injections (12.8±10.2 vs. 6.8±7.9) and patients taking oral steroids (18/120 vs. 3/80) ($p<0.001$ and $p=0.011$, respectively). The frequency of systemic symptoms of steroid depletion, such as fatigue and loss of appetite, was also higher in group 1 (94/120 vs. 42/80, $p<0.001$). Recent steroid injections and loss of appetite were associated with adrenal insufficiency ($p=0.002$ and $p=0.009$, respectively). **Conclusion:** The results of this study revealed a high prevalence of adrenal insufficiency in Korean patients hospitalized for TKA due to end-stage osteoarthritis. Recent steroid injections were causally related to the development of adrenal insufficiency. Therefore, adrenal function should be assessed preoperatively to prevent postoperative complications related to adrenal insufficiency.

Key Words: Arthroplasty, Replacement, Knee, Adrenal insufficiency, Prevalence

INTRODUCTION

The prevalence of adrenal insufficiency is approximately 250–400 per million, while that of secondary adrenal insufficiency is 150–280 per million.[1,2] Individuals with advanced osteoarthritis may be at risk of developing adrenal insufficiency because of repeated oral steroid administration or intra-articular steroid injections.[3,4] Individuals with adrenal insufficiency may be able to perform daily activities without showing any symptoms.[5] However, once they are exposed to stressful situations, such as infection, trauma, or surgery, they may experience life-threatening adrenal crisis.[6] The symptoms of adrenal crisis include weakness, nausea, vomiting, and abdominal pain. In surgical patients, it is often difficult to differentiate these symptoms from those of cerebrovascular accidents, ileus, and sepsis.[7] However, untreated adrenal crisis can develop into coma and hypotension, with a high mortality rate.[7,8] As symptoms of adrenal crisis are nonspecific, early diagnosis is difficult unless the underlying adrenal insufficiency is identified in advance.

In particular, older adult patients who undergo total knee arthroplasty (TKA) for severe osteoarthritis are more difficult to manage than other age groups in terms of the incidence rate, symptom ambiguity, and mortality rate.[9,10] As a result, these patients may be

misdiagnosed, and the optimal timing of treatment may be missed. To promptly diagnose adrenal crisis and provide timely and appropriate management, patients must be assessed for adrenal insufficiency before surgery and patients with insufficiency carefully monitored for adrenal crisis symptoms after surgery. However, because the prevalence of adrenal insufficiency is very low, the evaluation of adrenal function before surgery is not routinely performed in practice.

The present study investigated the prevalence of adrenal insufficiency among patients in Korea admitted for TKA who underwent assessment using a standard-dose short synacthen stimulation test and identified the contributing factors associated with adrenal insufficiency.

MATERIALS AND METHODS

Subjects

This prospective cross-sectional study was conducted from March to December 2022 after receiving the approval of the Institutional Review Board of our institution. We recruited all patients hospitalized for TKA for severe arthritis (Kellgren–Lawrence grade 3 or 4).[11] We obtained informed consent from all patients before their study inclusion. The exclusion criteria were rheumatoid arthritis, osteonecrosis, neuropathic arthropathy, and revision total TKA. Patients who refused to participate were also excluded (Fig. 1).

Methods

We surveyed the patients for a history of steroid use as a treatment modality, such as spinal nerve block, intra-articular injection, autoimmune connective tissue diseases, asthma, chronic obstructive pulmonary disease, skin diseases, and a family history of autoimmune diseases. We determined the number of steroid injections in the past 3 months using a questionnaire. We reviewed the medical records of the relevant medical institutions for patients who had received so many steroid injections that they could not accurately recall the number of times they had received them. We also investigated the history of oral steroid administration and daily dose of oral steroids in the past 3 months.

Before hospitalization, we asked the patients about symptoms such as fatigue and loss of appetite that might appear during steroid depletion.[12,13] Fatigue was defined as an average score of ≥4 on the 11-point rating scale in the brief fatigue inventory.[14] We assessed appetite using visual analog scale (VAS) ratings (0–100 mm; 0 = no appetite at all, 100 = very good appetite).[15,16] Loss of appetite was defined as a VAS score for appetite of ≤70.[15] We also assessed whether the patients had been previously diagnosed with adrenal insufficiency. Patients who were taking hydrocortisone discontinued it 24 hours before the short synacthen stimulation test, and those taking prednisone or prednisolone switched to an equivalent dose of hydrocortisone 1–2 weeks before the stimulation test and discontinued it 24 hours before.

On the morning of the day of surgery, the patients underwent a standard-dose short synacthen stimulation test, in which 250 μg of synacthen was intravenously administered immediately after taking a blood sample to measure the basal blood cortisol concentration.[17] We measured blood cortisol concentrations before and 30 and 60 minutes after synacthen administration. A normal basal blood cortisol concentration of ≥ 18 μg/dL was defined as normal adrenal function regardless of the results of the synacthen stimulation test. Adrenal insufficiency was defined as a blood cortisol concentration of < 18 μg/dL at 30 and 60 minutes after synacthen administration. Patients diagnosed with adrenal insufficiency were classified into group 1, while those with normal adrenal function were included in group 2 (Fig. 2). An endocrinologist verified the diagnostic protocol for adrenal insufficiency.

Outcome Assessments

We also assessed the prevalence of adrenal insufficiency. We compared the proportions of patients who had received steroid injections within the past 3 months and the number of steroid injections between the two groups. Similarly, we also compared the proportions of subjects who had taken oral steroids daily in the last 3 months. The correlation between the prevalence of adrenal insufficiency and the American Society of Anesthesiologists (ASA) classification[18] was analyzed. Finally, we compared the frequency of the manifestation of symptoms of steroid depletion between the two groups.

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics

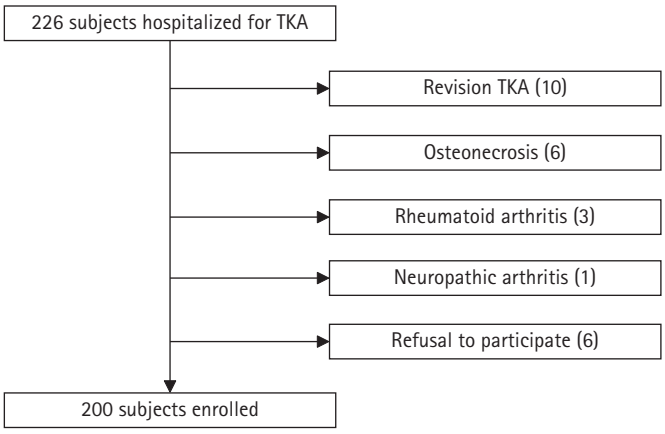

Fig. 1. Flow diagram of the subjects. TKA, total knee arthroplasty.

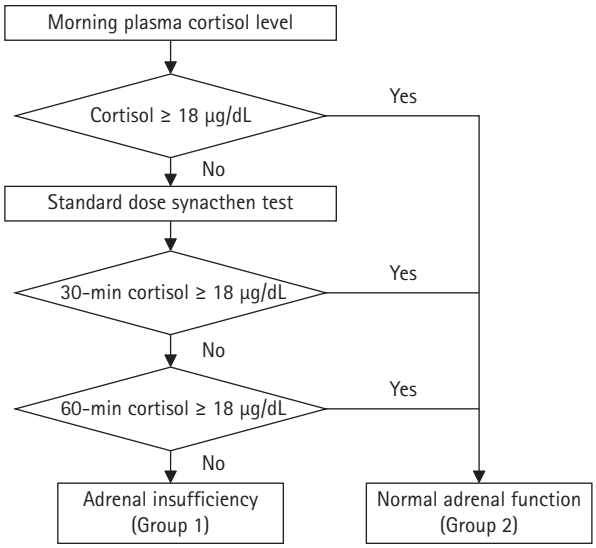

Fig. 2. Flow diagram of the diagnosis of adrenal insufficiency.

for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Means and standard deviations are used to describe the data. Comparisons between the two groups were conducted using the Student t-test for continuous variables and the chi-square test for categorical variables. We performed a multiple logistic regression analysis to identify factors associated with adrenal insufficiency among the variables that showed statistically significant differences between the two groups. Statistical significance was set at $p < 0.05$.

Ethical Statement

Primary approval was obtained from the Institutional Review Board of Kangwon National University Hospital (No. KNUH-2022-01-021-001). Informed consent was obtained from all the study participants. This study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[19]

RESULTS

Among 226 recruited patients, 200 were enrolled in the study. Their demographics according to the groups are presented in Table 1. Forty-seven patients were male and 153 were female. The mean age was 72.8 ± 6.9 years. The mean body mass index was 27.0 ± 3.6 kg/m^2. Of 200 patients, 120 (60.0%) were diagnosed with adrenal insufficiency. None of the patients had been previously diagnosed with adrenal insufficiency. One hundred and one patients underwent unilateral TKA, and 99 underwent simultaneous or sequential bilateral TKA. There was no significant difference in the prevalence of adrenal insufficiency according to the bilaterality of the joint arthroplasty ($p = 0.299$). Two patients in group 2 had preoperative serum sodium levels < 135 mmol/L (122 mmol/L and 132 mmol/L, respectively). No patients in group 1 had a preoperative serum sodium level < 135 mmol/L. The distribution of ASA classifications did not differ significantly between the two groups ($p = 0.491$). The basal plasma adrenocorticotropic hormone (ACTH) and basal and stimulated blood cortisol levels are shown in Table 2.

The mean numbers of steroid injections were 12.8 ± 10.2 in group 1 and 6.8 ± 7.9 in group 2 ($p < 0.001$). In the past 3 months, 77.5% (93 of 120) patients in group 1 and 55.0% (44 of 80) patients in group 2 had received steroid injections, and 14.2% (17 of 120) patients in group 1 and 5.0% (4 of 80) patients in group 2 had taken oral steroids ($p < 0.001$ and $p = 0.038$, respectively) (Table 3). However, of the 62 patients with no history of injection or oral steroid use within 3 months before surgery, 26 (41.9%) were diagnosed with adrenal insufficiency.

The frequency of systemic symptoms of steroid depletion, such as fatigue and loss of appetite, was higher in group 1 ($p < 0.001$) (Table 4). The results of the logistic regression analysis for the variables that differed significantly between the two groups are shown in Table 5.

DISCUSSION

The principal findings of this study were as follows: (1) the overall prevalence of adrenal insufficiency was 60.0% in patients hospitalized to undergo primary TKA for osteoarthritis, and (2) the frequency of steroid injections administered within 3 months before surgery and the loss of appetite, which is one of the symptoms of steroid depletion, were predictive factors of adrenal insufficiency.

Adrenal insufficiency is a rare disease affecting only 2–4 people per 10,000 people in the population.[1,2] Individuals who have not experienced serious stress may continue their daily lives without any significant symptoms. Owing to its low incidence and lack of symptoms under normal circumstances, routine preoperative screening for adrenal function is typically not performed in patients undergoing orthopedic surgery. However, patients with adrenal insufficiency undergoing major surgeries, such as joint replacement, which can cause significant stress, are at risk for adrenal crisis. The probability of mortality is high without proper treatment. The results of the present study revealed a 60% prevalence of adrenal insufficiency, a rate much higher than previously reported. Moreover, none of the patients in this study had previously been diagnosed with adrenal insufficiency.

In this study, patients with adrenal insufficiency had significantly higher rates of injection and oral steroid use than the control group.

Table 1. Demographics of the subjects between the two groups

	Group 1 (n = 120)	Group 2 (n = 80)	p-value
Age (y)	73.4 ± 6.7	71.8 ± 7.2	0.118[a]
Sex			0.077[b]
Male	23	24	
Female	97	56	
Bilaterality of TKA			0.299[b]
Unilateral	57	44	
Bilateral	63	36	
Biochemistry tests			
Blood urea nitrogen	16.9 ± 5.3 (7.0–36.1)	17.4 ± 7.1 (5.5–50.5)	0.544[a]
Creatinine	0.76 ± 0.20 (0.41–1.42)	0.83 ± 0.51 (0.43–4.58)	0.219[a]
Total protein	6.9 ± 0.4 (6.0–7.8)	7.0 ± 0.4 (6.1–8.1)	0.243[a]
Albumin	4.2 ± 0.3 (3.3–4.7)	4.3 ± 0.2 (3.6–4.7)	0.139[a]
Aspartate transaminase	28 ± 12 (16–104)	29 ± 14 (13–100)	0.713[a]
Alanine transaminase	25 ± 12 (8–68)	28 ± 25 (8–156)	0.367[a]
Sodium (Na)	143 ± 2 (137–147)	142 ± 4 (122–147)	0.146[a]
Potassium (K)	4.2 ± 0.4 (3.4–5.7)	4.2 ± 0.3 (3.4–5.3)	0.748[a]
Bone mineral density	-0.7 ± 1.6	-0.5 ± 1.4	0.385[a]
Body mass index (kg/m^2)	27.08 ± 3.68	26.95 ± 3.48	0.921[a]
ASA classification			0.491[b]
1	4	1	
2	97	64	
3	19	14	
4	0	1	
Underlying diseases			0.512[b]
Asthma	10	8	
Chronic obstructive pulmonary disease	1	4	
Connective tissue disease	1	1	
Skin disease	1	0	
Thyroid disease	9	3	
Hypertension	97	59	
Diabetes mellitus	39	31	
Tuberculosis	1	2	
None	12	10	

Values are presented as mean±standard deviation (range).
TKA, total knee arthroplasty; ASA, American Society of Anesthesiologists.
[a]Independent t-test, [b]chi-square test.

Table 2. Basal ACTH, basal and stimulated blood cortisol level

	Group 1 (n = 120)	Group 2 (n = 80)	p-value
Basal plasma ACTH level (pg/mL)	16.88 ± 15.51	24.58 ± 19.97	0.003[a]
Serum cortisol level (μg/dL)			
Before synacthen stimulation	4.08 ± 3.18	7.54 ± 4.49	< 0.001[a]
30 minutes after stimulation	11.31 ± 3.87	17.61 ± 1.95	< 0.001[a]
60 minutes after stimulation	13.39 ± 4.20	20.00 ± 2.05	< 0.001[a]

Values are presented as mean±standard deviation.
ACTH, adrenocorticotropic hormone.
[a]Independent t-test.

Additionally, a history of steroid injections into the joint or spine was a predictive factor for adrenal insufficiency, whereas a history of oral steroid use was not. Of the 200 included patients, 21 had taken oral steroids, including 6 and 15 who were using hydrocortisone and prednisolone, respectively. The hydrocortisone doses were 10–15 mg/day, while those for prednisolone were ≥ 10 mg/

Table 3. The proportion of subjects with a history of steroid use within 3 months prior to TKA in each group

	Group 1 (n = 120)	Group 2 (n = 80)	p-value
Steroid injections			< 0.001[c]
Yes (mean cumulative dosage)[a]	93 (17.9 ± 9.2 mg)	44 (13.4 ± 5.9 mg)	
No	27	36	
Oral steroid administration			0.038[c]
Yes (mean dosage per day)[b]	17 (7.5 mg, 2.5–15.0)	4 (11.3 mg, 2.5–15.0)	
No	103	76	
Steroid inhaler			0.466[c]
Yes	6	6	
No	114	74	

TKA, total knee arthroplasty.
[a]To standardize the potency of various steroid injections, they were converted to an equivalent dose of betamethasone with the same potency for the analysis.
[b]To standardize the potency of various oral steroid preparations, they were converted to an equivalent dose of prednisolone with the same potency for the analysis.
[c]Chi-square test.

Table 4. Systemic symptoms of steroid depletion between the two groups

	Group 1 (n = 120)	Group 2 (n = 80)	p-value
Fatigue	78	37	< 0.001[a]
Loss of appetite	53	15	
None	26	38	

[a]Chi-square test.

day, exceeding the physiological dose. Most of these subjects had a history of using steroids for ≥ 3–4 weeks. Due to the diversity in steroid types, dosages, and durations of use, statistical analysis was not feasible. Previous studies have reported an increased risk of developing adrenal insufficiency in patients taking oral prednisolone at a dose of ≥ 5 mg/day or oral hydrocortisone at a dose of ≥ 15 mg for ≥ 3–4 weeks.[20-22] In this study, the prevalence of adrenal insufficiency in patients using steroid inhalers did not differ significantly compared to that in patients not using inhalers. However, both steroid inhalers and ointments carry a risk of inducing adrenal insufficiency.[23,24]

Temporary adrenal insufficiency caused by short-term steroid treatment is reversible, with recovery of adrenal function after steroid administration.[25] Although this study specifically examined the prevalence of adrenal insufficiency at the time of surgery and did not investigate whether it was permanent or reversible, many patients experienced adrenal insufficiency during the perioperative period. Therefore, paying close attention to postoperative management is crucial in these cases. This study investigated medical conditions that could potentially cause adrenal insufficiency. However, the distribution of these conditions did not differ significantly between the two groups, making it difficult to identify a specific medical condition as the cause of adrenal insufficiency.

The risk of adrenal crisis in patients with adrenal insufficiency is approximately 10 in 100 patient years.[26] The primary clinical features of adrenal crisis are hypotension and hypovolemia. However, the initial symptoms such as anorexia, nausea, vomiting, abdominal pain, fatigue, lethargy, fever, and altered consciousness are often nonspecific.[6] While the prophylactic administration of steroids in patients with adrenal insufficiency can prevent adrenal crises, the postoperative administration of steroids to patients who have undergone artificial joint surgery may be avoided because of concerns about impaired wound healing and an increased risk of infection. Therefore, a strong conviction that these symptoms are due to an adrenal crisis is necessary to actively initiate steroid treatment. The misdiagnosis of patients with sepsis and subsequent delay in steroid administration can worsen their condition. Most cases of untreated adrenal crises result in death.[8,27] Thus, prompt recognition and appropriate treatment of adrenal crises are essential for patient survival. During the study period, five patients with symptoms suggestive of adrenal crisis, including postoperative hypotension, mental changes, and respiratory failure, showed immediate improvement with steroid treatment. The tests for cerebrovascular accidents and pulmonary embolism yielded negative results.

The symptoms of adrenal insufficiency, such as fatigue and loss of appetite, may be nonspecific and may be overlooked in older adult patients with chronic arthropathy. However, the prevalence of these symptoms differed significantly between the two groups in this study. The results of the regression analysis further indicated that a loss of appetite was associated with adrenal insufficiency. Therefore, the surveillance of these symptoms may be helpful in screening for adrenal insufficiency.

This study has several limitations. First, the sample size was small. Considering the known prevalence of adrenal insufficiency, a larger sample size was required in this prospective study. However, a previous pilot study investigating the prevalence of adrenal in-

Table 5. Logistic regression analysis for variables with significant differences between the two groups

	β	SE β	Wald's χ^2	df	p-value	Exp(β)[a]
Total injection within 3 months prior to surgery	0.345	0.112	9.458	1	0.002	1.412
Daily oral steroid within 3 months prior to surgery	0.002	0.267	0.000	1	0.993	1.002
Fatigue	0.405	0.323	1.573	1	0.210	1.499
Loss of appetite	0.938	0.361	6.776	1	0.009	2.556

[a]Odds ratio.

sufficiency in subjects scheduled for TKA also observed a higher prevalence than previously reported. Secondly, this was a time-zero study. This study only investigated the prevalence of preoperative adrenal insufficiency without determining the effect of adrenal insufficiency on surgical outcomes. We did not provide prophylactic steroid supplementation to patients with adrenal insufficiency. Among patients with preoperative adrenal insufficiency, five exhibited symptoms of adrenal crisis shortly after surgery; however, their condition improved immediately after steroid supplementation. Third, synchronous stimulation testing results may yield false negative results or appear normal in cases of mild disease or with recent onset.[28] In mild disease, sufficient adrenal functional cortex may exist to sustain adrenal reserve, enabling a suitable response to the standard dose of synacthen. Similarly, in cases with recent onset, sufficient time may not have elapsed for the adrenal gland to lose its complete function, allowing it to respond to synacthen stimulation. Finally, the number of steroid administrations, an important risk factor for adrenal insufficiency, was investigated based on the patients' recall. While the oral medications taken by the patients at the time of admission were thoroughly examined, the medications they had previously taken orally and stopped before hospitalization may not have been completely investigated. Due to these limitations, it may be challenging to establish a definitive causal relationship between oral steroid use and the occurrence of adrenal insufficiency within the scope of this study. However, our results revealed adrenal insufficiency in most of the patients who did not receive steroid injections. Therefore, surgeons should be cautious when treating patients with end-stage osteoarthritis.

In conclusion, we observed a high prevalence of adrenal insufficiency in Korean patients hospitalized for TKA due to end-stage osteoarthritis. Recent steroid injections were causally related to the development of adrenal insufficiency. Therefore, adrenal function should be assessed preoperatively to prevent postoperative complications related to adrenal insufficiency.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, SWB; Data curation, SWB, YSH; Investigation and Methodology, JHN; Writing_original draft, SWB, YSH, JHN; Writing_review & editing, SWB, YSH, JHN.

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Bidirectional Longitudinal Association between Back Pain and Loneliness in Later Life: Evidence from English Longitudinal Study of Ageing

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Background: This study examined the bidirectional and temporal-ordinal relationship between loneliness and back pain. **Methods:** Data from 7,730 participants in waves 6 (2012–2013), 7 (2014–2015), and 8 (2016–2017) of the national English Longitudinal Study of Ageing were analyzed. Back pain was graded on a scale of 0–10 (0, no discomfort; 10, unbearable pain). Loneliness was measured using the Revised University of California Los Angeles Loneliness Scale. A targeted minimum loss-based estimator was used to examine the bidirectional longitudinal associations between back pain and loneliness. **Results:** No loneliness in waves 6 and 7 (relative risk [RR]=0.76; 95% confidence interval [CI], 0.61–0.94), no loneliness in wave 6 but loneliness in wave 7 (RR=0.58; 95% CI, 0.50–0.68), and loneliness in wave 6 but not in wave 7 (RR=0.69; 95% CI, 0.57– 0.86) were associated with significant risk reductions of back pain in wave 8 compared with the scenario of loneliness in waves 6 and 7. Mild back pain in wave 6 but moderate back pain (RR=0.55; 95% CI, 0.35–0.86) or severe back pain in wave 7 (RR=0.49; 95% CI, 0.34–0.72) showed a significant risk reduction of loneliness in wave 8 compared with severe back pain in waves 6 and 7. **Conclusion:** Loneliness may be a risk factor for back pain, and back pain may be a risk factor for loneliness. The results of this study will inform the development of more effective interventions for loneliness and back pain.

Key Words: Back pain, Loneliness, Longitudinal studies

INTRODUCTION

Back pain is a common cause of physical disability[1-3] and affects a large proportion of the general population.[4,5] A systematic review reported that the prevalence of back pain tends to be higher in older adults than in young adults.[4] Moreover, the healthcare costs associated with back pain are high, particularly in high-income countries, at an estimated $87.6 billion in the United States,[6] €740 million in Sweden,[7] and ¥1.2 trillion ($10.6 billion, €9.3 billion) in Japan.[8] Therefore, back pain prevention and interventions are essential from a public health perspective.

Loneliness is a risk factor for various health outcomes, including physical and cognitive decline, mental illness, and cardiovascular disease,[9,10] It is defined as a state in which individuals experience a deeply felt lack of social contact or belongingness or a sense of isolation.[9] Loneliness is also a risk factor for musculoskeletal pain.[11,12] However, the relationship between loneliness and pain may be bidirectional,[13,14] in which loneliness-induced stress may increase pain, which contributes to loneliness by limiting social interaction.[15,16]

Previous studies examining the longitudinal relationship between loneliness and pain generally analyzed these factors separately, making it difficult to determine the relative importance of the two temporal orders.[13,15] Loeffler et al.[14] demonstrated a bidirectional longitudinal association between baseline loneliness and pain in an older population. Baseline loneliness predicted pain in

the fourth follow-up year, and vice versa. In contrast, Yu et al.[17] did not identify any significant longitudinal interaction between loneliness and pain; that is, pain did not predict future loneliness and vice versa. This discrepancy between studies may be due to the time-varying nature of loneliness and back pain. Loeffler et al.[14] examined the association between baseline exposure and outcome at the fourth follow-up year and, thus, did not account for temporal degeneration of exposure over 4 years. Although Yu et al.[17] adjusted for the time-varying nature of pain, they did not consider the time-varying nature of social isolation. In general, longitudinal observational studies examining the effects of exposures measured only at baseline on the outcome of interest are likely to underestimate time-varying exposures.[18] Loneliness and back pain status can change over time. For example, loneliness increased by 31.7% after 4 years among people aged ≥ 60 years.[19] Another study that compared the prevalence of social isolation in Japan and England reported an increase in prevalence over 6 years.[20] During the coronavirus disease 2019 (COVID-19) pandemic, loneliness was reported to increase in older populations after approximately 6 months because of limited social interactions resulting from physical distance restrictions.[21] Another systematic review reported that the COVID-19 pandemic increased the prevalence and severity of back pain.[22] Additionally, approximately 6% of older individuals who were free from back pain reported new-onset back pain in the fourth year of a follow-up survey among older individuals who were free from back pain.[23] Moreover, exercise therapy reduced back pain severity during the first year of follow-up.[24] Therefore, from the public health perspective, changes in "exposure" status should be evaluated as the outcome of interest. Therefore, to address the limitations of previous studies, the present study examined the bidirectional and temporal relationships between loneliness and back pain using a single nationally representative population survey conducted in England.

MATERIALS AND METHODS

This study conducted two statistical analyses to examine the bidirectional and temporal[25] relationships between loneliness and back pain using back pain (Study 1) and loneliness (Study 2) as the outcome, respectively.

Study Population

Data from waves 6 (2012–2013), 7 (2014–2015), and 8 (2016–2017) of the national English Longitudinal Study of Aging (ELSA) survey were analyzed. The survey began in 2002 and is conducted every 2 years among men and women aged > 50 years residing in England.[26]

The analysis included 7,730 participants who were eligible to be polled in all three waves. Of the 7,730 participants, 942 were excluded because of missing baseline variables—educational attainment (n = 30), equalized household income (n = 123), back pain (n = 6), loneliness (n = 722), longstanding illness (n = 1), arthritis (n = 5), osteoporosis medication (n = 1), and depressive symptoms (n = 54). Participants who responded to the baseline survey but did not respond to waves 7 or 8 and those with missing variables from waves 7 and 8 were also excluded. In Study 1, after excluding 2,900 participants, the main analysis included 4,830 participants (mean age at baseline, 67.2 ± 8.9 years). Similarly, after excluding 3,246 participants, the main analysis in Study 2 included 4,484 participants (mean age at baseline, 67.1 ± 8.8 years) (Fig. 1).

Back Pain

The participants were asked the following questions to gauge their level of back pain: "Are you frequently bothered by pain?" If the participants answered "Yes," they were then asked, "In which parts of the body do you feel pain?" "Back" responses were interpreted as those indicating back pain. The participants were also asked to rate the severity of their pain by answering the following question: "How would you rate your pain if you were walking on a flat surface? Please rate your pain from 0 to 10 for each of the following, where 0 is no pain and 10 is severe or excruciating pain or "as bad as you can imagine" (i.e., the numerical rating scale, [NRS]).[27] As previously described, participants who did not report "back" pain were regarded as having an NRS of 0.[28] The NRS has been previously validated.[27]

As no definitive cutoff value for pain severity has yet been determined,[29] given the clinical utility of assessing the detailed impacts of pain severity on the outcomes, we defined the following categories of back pain: none (NRS 0), mild (NRS 1–3), moderate (NRS 4–6), and severe (NRS ≥ 7) in Study 2. While a previous study reported that an NRS score of 5 or 6 is commonly used as the cutoff value for moderate pain,[29] we used a cutoff score of 6 in Study 1 because it is associated with disability.[30]

Loneliness

Loneliness was measured using a short form consisting of three items from the Revised University of California Los Angeles (UCLA) Loneliness Scale. Each item is rated on a scale of hardly ever (1 point), sometimes (2 points), or often (3 points), with a score of ≥ 6 indicating loneliness.[31] Cronbach's alpha was calculated to assess the internal consistency of the reliability. Its validity has been examined previously.[32]

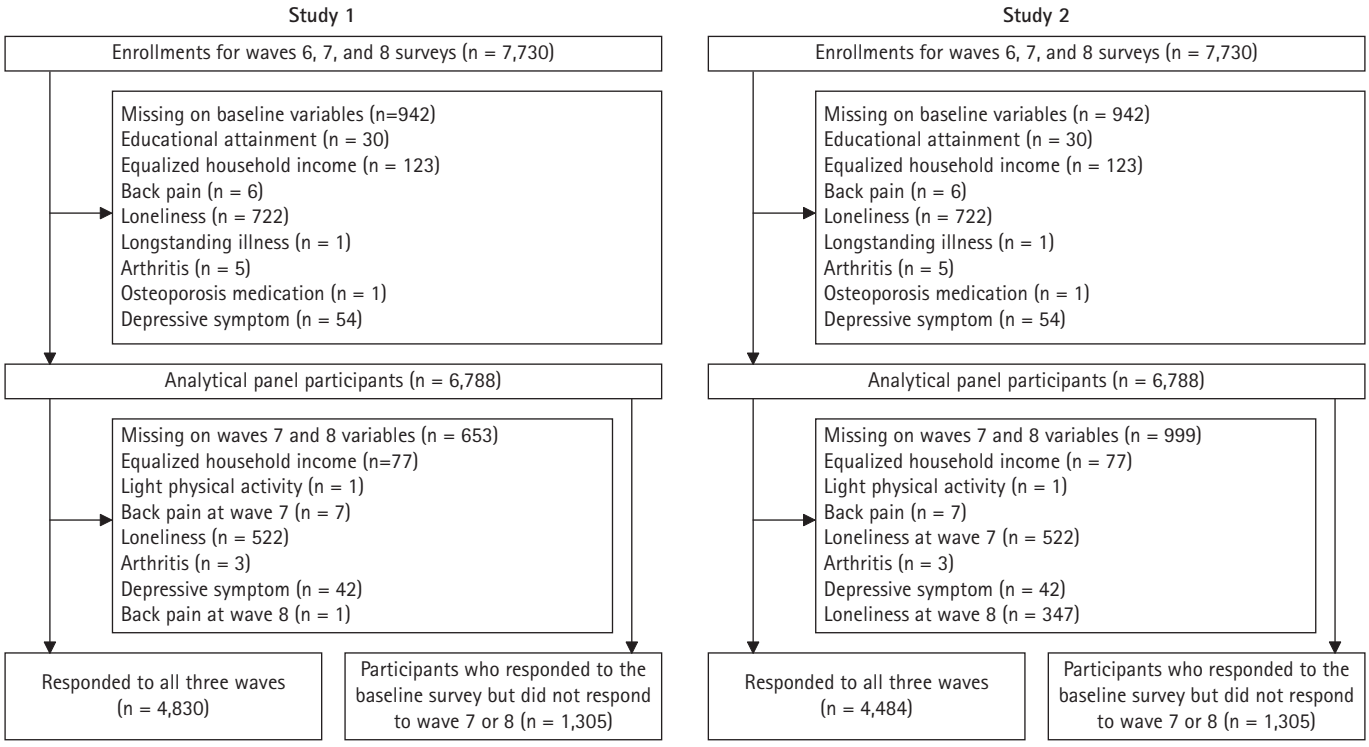

Fig. 1. Participants of Study 1 and Study 2.

Covariates

Age (continuous), sex (binary; male vs. female), educational attainment (continuous), race (binary; white vs. other), equalized household income (continuous), depressive symptoms (binary; no vs. yes; based on the Center for Epidemiologic Studies Depression Scale), exercise at least once weekly (binary; no vs. yes), longstanding illness (binary; no vs. yes), arthritis (binary; no vs. yes), osteoporosis medication (binary; no vs. yes), physical therapy (PT) or occupational therapy (OT) interventions in the past 3 months (binary; no vs. yes), and participation in exercise classes (binary; no vs. yes) were associated with back pain and loneliness and were used as covariates.[14,16,23,33,34] PT or OT and exercise interventions were considered potential confounding factors in Study 1 but not in Study 2 according to previous studies.[23,34-36]

Statistical Analysis

The targeted minimum loss-based estimator (TMLE) was used to assess time-variant exposure to outcome risk.[37] We used the SuperLearner package, an ensemble machine learning method, to select the optimal algorithm for the exposure and outcome models. The candidate estimators for the SuperLearner algorithms are generalized linear models, gradient boosting models, and neural networks.[38-41] Changes in hypothetical exposure in waves 6 and 7 were assessed for their impact on outcome risk in wave 8. These models were compared to calculate the relative risk (RR) and 95% confidence interval (CI). In Study 1, four scenarios were set up based on the presence or absence of hypothetical loneliness in waves 6 and 7. Each estimate was compared with the loneliness scenario for both waves 6 and 7, and the RR for back pain in wave 8 and its confidence interval were calculated. The same analysis was performed using two different sensitivity analyses with different cutoff values for the definition of back pain. The cutoff values were ≥4 and ≥5. In Study 2, 16 scenarios were established based on hypothetical back pain changes in waves 6 and 7. Each estimate was compared with the scenario of severe back pain in both waves 6 and 7, and the RR for loneliness in wave 8 and its confidence interval were calculated. R software (version 4.2.2 for Windows) was used for all statistical analyses. The National Research and Ethics Committee approved all ELSA waves, and all participants provided informed consent—wave 6 (No. 11/SC/0374), wave 7 (No. 13/SC/0532), and wave 8 (No. 15/SC/0526). We applied to the UK Data Service (https://beta.ukdataservice.ac.uk/) to obtain permission to access ELSA data. As all ELSA data were anonymous and freely accessible from the UK Data Service, the need for ethical approval was waived for this study.

This study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[42]

RESULTS

Study 1

Table 1 shows the baseline characteristics of back pain based on the follow-up survey (wave 8). In the follow-up study, participants who reported back pain were older, were more likely to be female, had lower levels of education and income, had more comorbidities, had a history of arthritis, and had lower physical activity levels compared with those who did not report back pain. Moreover, 29.8% of the participants with back pain experienced loneliness at baseline (Supplementary Table S1). The Cronbach's alpha across the UCLA Loneliness Scale in Study 1 was 0.83, indicating good internal consistency.

The results of the TMLE model are shown in Fig. 2. The scenarios with no loneliness in waves 6 and 7 (RR = 0.76; 95% CI, 0.61–0.94; p = 0.013), no loneliness in wave 6 but loneliness in wave 7 (RR = 0.58; 95% CI, 0.50–0.68; p < 0.001), and loneliness in wave 6 but no loneliness in wave 7 (RR = 0.69; 95% CI, 0.57–0.86; p < 0.001) all showed a significant risk reduction of back pain compared with the scenario with loneliness in waves 6 and 7.

The sensitivity analysis results are shown in Supplementary Figs. S1 and S2. Analysis with reclassified cutoff values for moderate/severe back pain revealed a similar trend.

Study 2

Table 2 shows the baseline characteristics according to loneliness in the follow-up survey (wave 8). Based on the follow-up survey, the participants who reported loneliness were more likely to be female, had lower levels of education and income, had more comorbidities and arthritis, and participated less in exercise classes than those who did not report loneliness. Among participants with loneliness at baseline, 8.1%, 10.4%, and 7.7% had mild, moderate,

Table 1. Baseline characteristics of the study participants who responded to all three waves, stratified according to back pain at follow-up (England, 2012–2014–2016)

Characteristic	Back pain at the 4-year follow-up		p-value
	Did not report (n = 4,253)	Reported (n = 577)	
Age (y)	66.5 ± 8.3	68.3 ± 8.6	< 0.001[a]
Sex, female	2,264 (53.2)	403 (69.8)	< 0.001[b]
Ethnicity, White	4,164 (97.9)	561 (97.2)	0.287[b]
Educational attainment (y)	11.6 ± 1.7	10.9 ± 1.5	< 0.001[a]
Equalized household income (British pound)	428.0 ± 561.2	311.9 ± 194.8	< 0.001[a]
Reported loneliness	767 (18.0)	174 (30.2)	< 0.001[b]
Existing longstanding illness	2,099 (49.4)	478 (82.8)	< 0.001[b]
Existing arthritis	1,222 (28.7)	377 (65.3)	< 0.001[b]
No light physical activity at all	319 (7.5)	82 (14.2)	< 0.001[b]
Osteoporosis medication	140 (3.3)	48 (8.3)	< 0.001[b]
Depressive symptom	369 (8.7)	136 (23.6)	< 0.001[b]

Values are presented as mean±standard deviation or number (%).
[a]T-test, [b]chi-squared test.

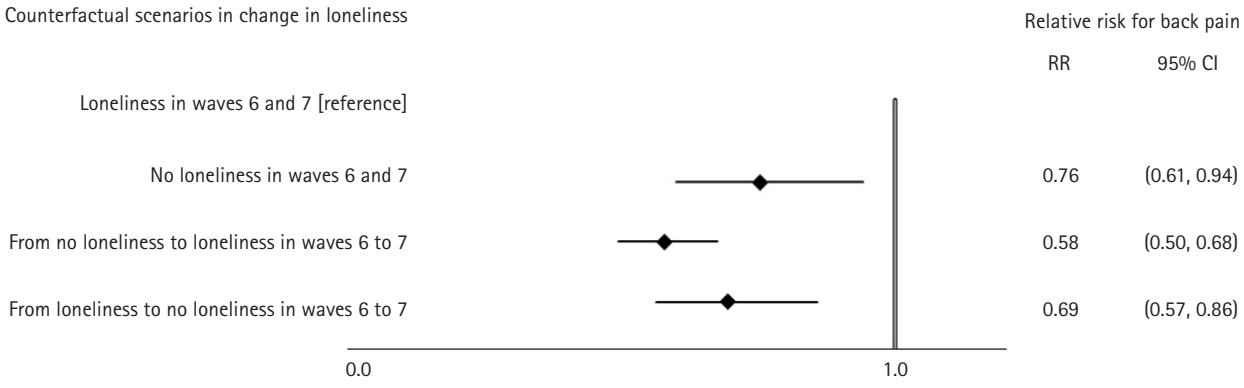

Fig. 2. Results of the targeted minimum loss-based estimator model. The relative risk and 95% confidence interval (CI) for back pain in wave 8 are calculated from the hypothetical scenarios of loneliness changes in waves 6 and 7. Cutoff values for the definition of back pain were ≥6.

Table 2. Baseline characteristics of the study participants who responded to all three waves, stratified according to loneliness at follow-up (England, 2012–2014–2016)

Characteristic	Loneliness at the 4-year follow-up		P-value
	Did not report (n = 3,708)	Reported (n = 766)	
Age (y)	66.4 ± 8.1	66.9 ± 8.7	0.122[a]
Sex, female	1,998 (53.9)	482 (62.1)	< 0.001[b]
Ethnicity, White	3,636 (98.1)	755 (97.3)	0.168[b]
Educational attainment (y)	11.6 ± 1.7	11.2 ± 1.6	< 0.001[a]
Equalized household income (British pound)	430.0 ± 535.4	359.3 ± 586.7	< 0.001[a]
Reported back pain			< 0.001[b]
Mild	202 (5.4)	56 (7.2)	
Moderate	226 (6.1)	80 (10.3)	
Severe	143 (3.9)	75 (9.7)	
Existing longstanding illness	1,874 (50.5)	496 (63.9)	< 0.001[b]
Existing arthritis	1,161 (31.3)	307 (39.6)	< 0.001[b]
No light physical activity at all	267 (7.2)	81 (10.4)	0.073[b]
No participation in exercise classes	3,062 (82.6)	685 (88.3)	< 0.001[b]
PT or OT interventions in the past 3 months	311 (8.4)	90 (11.6)	0.006[b]
Osteoporosis medication	136 (3.7)	36 (4.6)	0.203[b]
Depressive symptom	240 (6.5)	222 (28.6)	< 0.001[b]

Values are presented as mean±standard deviation or number (%).
PT, physical therapist; OT, occupational therapist.
[a]T-test, [b]chi-squared test.

and severe back pain, respectively (Supplementary Table S2). The Cronbach's alpha across the UCLA Loneliness Scale in Study 2 was 0.84, indicating good internal consistency.

The results of the TMLE model are shown in Fig. 3. The scenarios with no back pain in waves 6 and 7 (RR = 0.64; 95% CI, 0.49–0.85; p < 0.005), no back pain in wave 6 but severe back pain in wave 7 (RR = 0.59; 95% CI, 0.48–0.73; p < 0.001), mild back pain in wave 6 but moderate back pain in wave 7 (RR = 0.55; 95% CI, 0.35–0.86; p < 0.01), mild back pain in wave 6 but severe back pain in wave 7 (RR = 0.49; 95% CI, 0.34–0.72; p < 0.001), moderate back pain in waves 6 and 7 (RR = 0.57; 95% CI, 0.35–0.93; p = 0.024), and severe back pain in wave 6 but mild back pain in wave 7 (RR = 0.51; 95% CI, 0.32–0.83; p = 0.007) showed significant risk reductions in reported loneliness compared with the scenario with severe back pain in waves 6 and 7. The scenarios with moderate back pain in wave 6 but severe back pain in wave 7 (RR = 1.30; 95% CI, 1.04–1.62; p = 0.021) showed a significant risk increase in reported loneliness compared with the scenario with severe back pain in waves 6 and 7. No significant differences were observed in the other scenarios.

DISCUSSION

This study analyzed ELSA data to examine the bidirectional and temporal relationships between loneliness and back pain. The results of Study 1 showed that a single period of no loneliness during the two study periods was associated with the risk of back pain at the 4-year follow-up (wave 8). The results of Study 2 showed significant associations with back pain in some scenarios, although it was also a risk factor for loneliness.

The results of Study 1 implied that loneliness could be a risk factor for back pain, which is consistent with the findings of a previous study on the relationship between loneliness and pain.[9,14,15] The relative risk of back pain differed between the no-loneliness scenario in wave 6 and the loneliness scenario in wave 7 (RR of 0.58), and the loneliness scenario in wave 6 but the no-loneliness scenario in wave 7 (RR of 0.69). These results suggest that even when participants experienced loneliness at some point, a period without loneliness could alleviate the onset of back pain because of the reminder effect. Therefore, the early detection and implementation of interventions for loneliness may prevent the onset of back pain. The results from Study 1 also indicated that interventions to prevent persistent loneliness could reduce the burden of feeling disabled and the medical costs associated with back pain diagnosis.

Chronic stress response over-activation can be caused by loneliness, which can lead to pain.[43] Stress and pain are associated because neurotransmitters released by stress affect nociceptors.[44] Long-term exposure to stress reorganizes regions of the brain related to pain,[45] while stress-related metabolic changes affect peripheral nerve function and pain transmission.[46] In addition, neurotransmitters such as serotonin are involved in both depression and pain,[16] and loneliness-related depression may lead to pain. Ac-

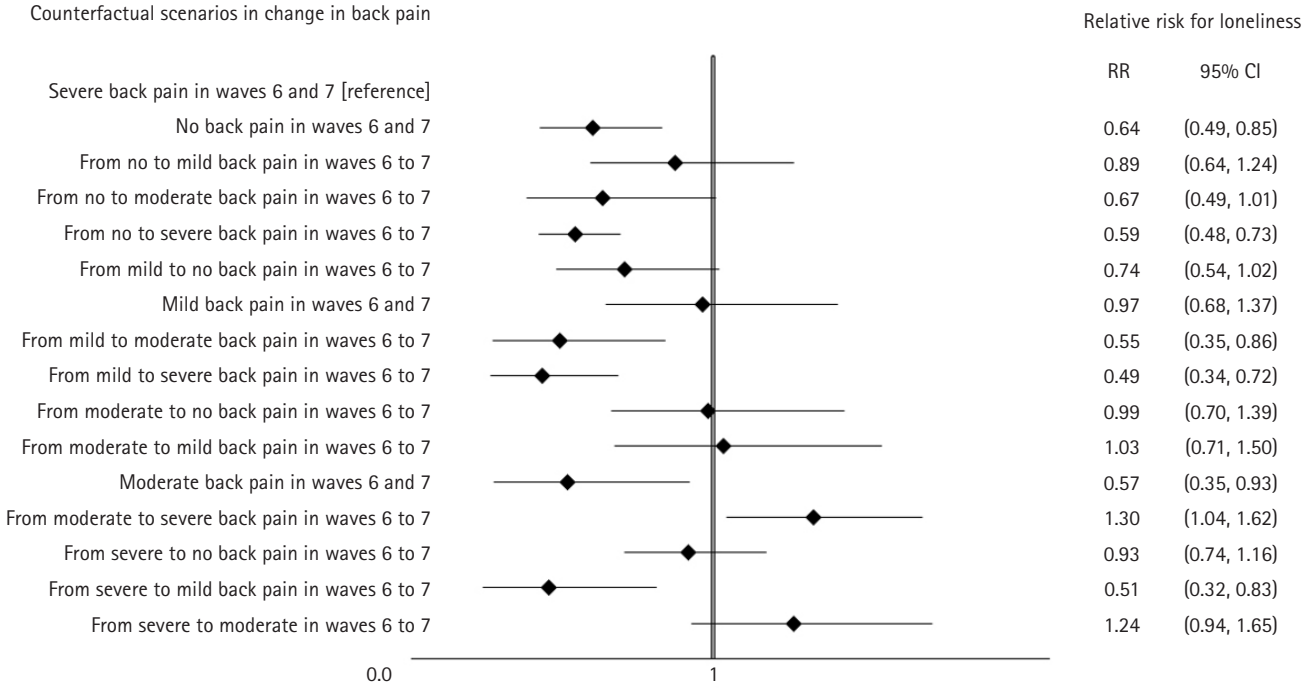

Fig. 3. Results of the targeted minimum loss-based estimator model. The relative risk and 95% confidence interval (CI) for loneliness in wave 8 are calculated from the hypothetical scenarios of back pain changes in waves 6 and 7.

cording to one theory, social isolation affects brain regions that process physical pain.[47] These findings support the association between loneliness and back pain. The results of the present study suggest that loneliness may reduce the burden of disability and increase medical costs associated with back pain.

In contrast, Study 2 identified a significant association between changes in back pain and the prevalence of loneliness. This finding is contrary to those of a report by Yu et al.[17] However, the previous study did not consider the time-varying nature of exposure.[17] Moreover, the definitions of pain and loneliness and the statistical analysis methods used in the present study differ from those used in previous studies. Previous studies examining the association between chronic pain and loneliness generally targeted widespread pain, whereas the present study focused on back pain. In addition, previous analyses did not distinguish between moderate and severe pain, contrary to the present study. Because of these differences, further studies are needed to examine multiple cases using different analytical methods. In the present study, the risk of loneliness tended to decrease in many severe back pain scenarios in waves 6 and 7. For example, the scenarios with no back pain in waves 6 and 7 (RR = 0.64; 95% CI, 0.49–0.85; $p < 0.005$), mild back pain in wave 6 and moderate back pain in wave 7 (RR = 0.55; 95% CI, 0.35–0.86; $p < 0.01$), and moderate back pain in waves 6 and 7 (RR = 0.57; 95% CI, 0.35–0.93; $p = 0.024$) showed significant reductions in reported loneliness compared with the severe back pain scenarios in waves 6 and 7. Back pain decreases with increased social participation,[48] and decreased social participation is a factor contributing to feelings of loneliness.[49] These findings suggest that back pain could be a risk factor for loneliness by limiting social participation. However, the moderate back pain scenario in wave 6 the but severe back pain scenario in wave 7 (RR = 1.30; 95% CI, 1.04–1.62; $p = 0.021$) showed a significant risk increase in reported loneliness compared with the severe back pain scenario in waves 6 and 7. Although no significant differences were observed, a similar trend was observed in the severe back pain scenario in wave 6 but moderate back pain scenario in wave 7 (RR = 1.24; 95% CI, 0.94–1.65; $p = 0.13$). This suggests that moderate-to-severe temporal changes may be risk factors for loneliness. Therefore, future studies are needed to quantitatively evaluate the differences in the impact of back pain severity on social participation.

Poor social relationships and low social acceptance are predictors of chronic pain.[50] In addition, participation in cultural activities such as visiting museums and art galleries can reduce the risk of developing pain in older adults.[34] These findings suggest an association between psychosocial activity and pain. Compared with mild/moderate back pain, severe back pain may have acted as a disincentive for social participation and activity in the present study. Interventions for back pain may not only improve back pain but also improve social interventions, such as increasing social participation and exercise, which are effective interven-

tions for loneliness.

This study has several limitations. First, unknown confounders were possible owing to the longitudinal observational study design rather than a randomized controlled trial. Second, participant dropout may have contributed to a selection bias. This study included only participants with no missing data in waves 6–8. Of the 7,730 participants, 2,900 dropped out in Study 1, and 3,246 dropped out in Study 2. Third, we defined the cutoff back pain values differently between Studies. In Study 1, we defined back pain as NRS ≥6. In Study 2, we defined back pain categories (NRS 0, none; NRS 1–3, mild; NRS 4–6, moderate; and NRS ≥7, severe); however, a clear cutoff value for these categories is lacking.[30] Therefore, a change in the cutoff value could have affected the results. Fourth, we could not distinguish between participants with acute and chronic back pain because of the imprecise recall period. Therefore, the prevalence of back pain may have been underestimated or overestimated. Fifth, the NRS used in this study may represent disabling pain, rather than general back pain at rest. Chronic pain that interferes with daily life ranges from short-term episodes with low degrees of disability to long-term syndromes with multiple physical and psychological symptoms and severe daily living restrictions.[51] From a public health perspective, the reality of disabling pain in older populations must be understood across this spectrum. Sixth, we could not distinguish between participants who answered "often" to all questions at baseline (9 points) but "rarely or never" to all questions in the intermediate wave (3 points) and those who answered "sometimes" to all questions at baseline (6 points) but "sometimes" to two questions in the next wave and "sometimes" to one question in the "very little or none at all" (5 points).

In conclusion, this study analyzed ELSA data to examine the bidirectional and temporal associations between back pain and loneliness. These results suggest that loneliness is a risk factor for back pain. Moreover, mild-to-moderate back pain may reduce the risk of loneliness. Interventions for loneliness are effective in reducing the risk of back pain, while interventions for back pain may reduce the risk of loneliness.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, YS, TS, MT, MM, TI; Data curation, YS, TI; Funding acquisition, TI; Investigation, TI; Methodology, YS, TI; Project administration, YS, TI; Supervision, TI; Writing–original draft, YS; Writing–review & editing: TS, MT, MM, TI.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4235/agmr.23.0136.

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Polypharmacy in Older Patients: A Three-Year Longitudinal Analysis in Primary Care Settings of Aragón, Spain

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Background: Challenges of polypharmacy and the impact of coronavirus disease 2019 (COVID-19) pandemic in older patients require further investigation. This retrospective study analyzed the progression of polypharmacy and anticholinergic burden in older patients in a primary care setting before, during, and after the COVID-19 pandemic. **Methods:** This 3-year cross-sectional study (2019, 2020, and 2021) comprised a dynamic cohort of individuals aged ≥75 years, who attended the Arrabal Primary Care Center in Zaragoza, Spain. Older patients with polypharmacy (≥5 medications) were identified according to their electronic health records. We collected demographic and clinical data, including medication prescriptions, diagnoses, and anticholinergic risks, and performed descriptive and statistical analyses. **Results:** This study included a total of 1,928 patients with a mean age of 83.52±0.30 years. Over the 3-year study period, the mean number of medications prescribed increased, from 9.4 in 2019 to 10.4 in 2021. The prevalence of excessive polypharmacy (≥10 medications) increased from 39% in 2019 to 45% in 2021. The most commonly prescribed drugs were anilides, proton pump inhibitors, benzodiazepine derivatives, and platelet aggregation inhibitors. Women had a higher prevalence of illnesses and anticholinergic drug prescriptions than men. **Conclusion:** The results of this study highlighted an upward trend in polypharmacy and excessive polypharmacy among older patients in primary care settings. Future research should focus on optimizing medication management and deprescribing strategies and minimizing the adverse effects of polypharmacy in this population.

Key Words: Aged, Polypharmacy, COVID-19, Cholinergic antagonists, Primary health care

INTRODUCTION

Population aging has significant implications for public health and healthcare systems.[1)] The proportion of the world's population aged ≥65 years is projected to increase from 10% in 2022 to 16% in 2050.[2)] An increasing population with progressive aging has led to an increase in the number of individuals with chronic diseases. In Europe, these conditions are among the leading causes of illness, disability, and healthcare costs.[3)]

Consequently, older individuals often receive multiple medica-

tions for comorbidities including geriatric syndromes such as dysphagia, delirium, depression, pressure ulcers, frailty, and dependence.[4,5] This situation poses a major challenge as it often leads to polypharmacy in this population.

Polypharmacy and excessive polypharmacy are commonly defined as the concurrent use of ≥ 5 and ≥ 10 medications, respectively.[6-9] Polypharmacy by itself is a geriatric syndrome, and its prevalence varies widely due to differences in study inclusion criteria (age group, definition, health care setting, location), and can range from 4% to > 80%.[10,11] For instance, in a cross-sectional study conducted across 17 European countries and Israel, researchers analyzed data from the sixth wave of the Survey of Health, Aging, and Retirement in Europe (SHARE) database. This study including participants aged ≥ 65 years (mean age 75.1 ± 7.2 years), revealed that the prevalence of polypharmacy (simultaneous use of ≥ 5 medications), ranged from 26.3% to 39.9%.[12] In addition, a cross-sectional study analyzing the electronic medical records of adults in Scotland reported a polypharmacy (4–9 medications) prevalence of 28.6% in adults aged 60–69 years and 51.8% in those > 80 years.[13] In this regard, a study based on data from the National Health Survey 2017 in Spain, which included participants aged ≥ 65 years (mean age 76 ± 7.6 years), reported a polypharmacy and excessive polypharmacy prevalence of 27.3% and 0.9%, respectively.[14]

The frequent occurrence of polypharmacy in the older adult population is concerning as it is associated with an increased risk of drug interactions, adverse drug effects, poor treatment adherence, and potentially inappropriate medication.[15-18] These factors increase the susceptibility of older adults to cognitive and functional impairments, episodes of delirium, falls, hospital admissions, increased healthcare costs, and even mortality.[19-22] Furthermore, certain drugs with anticholinergic activity may have adverse effects in this population, including confusion, dizziness, delirium, mild cognitive impairment, falls, compromised physical function, increased hospitalization rates, and elevated risk of mortality.[23-25]

The increased vulnerability of older adults to complications and higher mortality rates, as evidenced during the coronavirus disease 2019 (COVID-19) pandemic, is attributable to factors including immunosenescence, frailty, underlying diseases, and the concurrent use of multiple medications.[22,26] Additionally, the social isolation, fear of contagion, and loneliness experienced during the pandemic further exacerbated the susceptibility of older patients to adverse outcomes.[27] In their meta-analysis, Pimentel-Tormon et al.[28] reported the effects of the COVID-19 pandemic on the older adult population, including outcomes such as weight loss, increased prevalence of respiratory and heart diseases, and higher rates of depression and anxiety. In response to these new health problems, physicians may have prescribed additional medications to treat these pathologies.[27] Consequently, studies have investigated the relationship between polypharmacy and COVID-19. Poblador-Plou et al.[29] reported that a higher number of medications was associated with worse outcomes, including death, in men with COVID-19. Moreover, a meta-analysis of 14 studies involving 189,870 patients with COVID-19 reported the prevalence of polypharmacy as 34.6%.[30]

Given its impact on the general population, especially older individuals, investigating the effects of the COVID-19 pandemic on polypharmacy and anticholinergic risks within this age group is essential. The pandemic has caused complications and adverse clinical, functional, psychosocial, and mental health outcomes. Unfortunately, current scientific literature offers limited insights into this topic. Therefore, the present study analyzed the evolution of polypharmacy and anticholinergic burden in older patients in a primary care setting before, during, and after the pandemic.

MATERIALS AND METHODS

Study Design

The study was designed in three cross-sectional periods—2019, 2020, and 2021—within a dynamic cohort composed of individuals aged ≥ 75 years who attended the Arrabal Primary Care Center in Zaragoza, Spain, between January 1, 2019, and December 31, 2021. We collected demographic and clinical variables from electronic primary care records from all patients using an Aragon health card at the time of their medical consultation and analyzed these variables of the older patients with polypharmacy (≥ 5 prescribed medications).

Ethical Considerations

This study was reviewed and approved by the Aragon Clinical Research Ethics Committee (Protocol Code PI22/456; approval date on November 2nd, 2022). All procedures contributing to this work complied with the ethical standards of the Aragon Clinical Research Ethics Committee (part of the Government of Aragon's Department of Health) and the principles of the 1975 Declaration of Helsinki, revised in 2008. Data were obtained from the clinical records provided in a non-identifiable format by the Aragonese Health Service. Written informed consent from the participants or their legal guardian/next of kin was not required for this study, in accordance with national legislation and institutional requirements (Law 14/2007, of July 3, on Spanish Biomedical Research). The processing, notification, and transfer of personal data was conducted in accordance with the European Parliament's 2016/679 Regulation (EU) and the 3/2018 Spanish Organic Law on the Protec-

tion of Personal Data and the Guarantee of Digital Rights. This study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[31]

Subjects and Sample Size

The present study included all patients ≥ 75 years of age who were prescribed ≥ 5 medications based on the electronic health records of Arrabal Primary Care Center, a center of the Spanish public health system. Inclusion criteria are individuals aged ≥ 75 years with polypharmacy (≥ 5 prescribed medications).[7-9]

Variables

The following variables were collected.

Demographic data

Age at consultation and sex were collected from the electronic health records.

Clinical variables

1) The total number of drugs prescribed at consultation was recorded to assess whether the patient had polypharmacy (≥ 5 medications) or excessive polypharmacy (≥ 10 medications).
2) The Anatomical Therapeutic Chemical Classification (ATC) system proposed by the World Health Organization was used to identify the drugs prescribed in the study. This system classifies drugs based on their therapeutic effects and characteristics. The system is organized into five levels and includes multiple categories at each level.
3) Diagnoses during consultation were made according to the International Classification of Primary Care 2 (CIAP-2),[32] developed and updated by the World Organization of Family Doctors. The conditions are classified into 17 chapters based on the body systems that represent the problem's location and disease.
4) Comorbidity was measured using the CIAP-2.[32]
5) We assessed anticholinergic risk using the anticholinergic cognitive burden (ACB) scale. This scale includes 88 medications with known anticholinergic activity. The assigned scores ranged from 0 to 3, with 0 indicating no activity and 3 indicating the maximum anticholinergic activity. We categorized ACB in the present study as 0, 1, 2, or 3+.

Statistical Analysis

We analyzed the evolution in terms of diagnosis, anticholinergic risk, and drugs of low therapeutic usefulness in older patients who were prescribed > 5 medications at the Arrabal Primary Care Center between 2019 and 2021.

We used descriptive analysis, with continuous variables expressed as means ± standard deviation, and categorical (nominal) variables reported as percentages of the total sample. Owing to the large sample size, parametric tests were deemed appropriate because in large samples, even if the data distribution is not normal, the statistics tended to be normal.[33] Welch two-sample t-tests were conducted to compare two numerical variables and assess significant differences in the means between the groups. We applied one-factor analysis of variance to examine substantial standard variations across groups for comparisons among more than two numerical variables after log-transformation to ensure that the data conformed sufficiently to normality. Heteroscedasticity in the data was not considered a problem because the designs were well-balanced. We used Fisher exact test to explore the associations between categorical variables. All statistical analyses were performed using R version 4.3 (https://cran.r-project.org/), with significance set at $p < 0.05$. The R packages nortest and PMCMRplus were also used to analyze the data.

RESULTS

We included 1,928 patients aged ≥ 75 years who were prescribed > 5 medications during the study period (2019–2021). The mean age of these individuals was 83.5 ± 0.3 years, and 1,222 patients (63.4%) were females (Table 1). Evaluation of the distribution of patients according to age revealed that 37.3% of the patients were 75–79 years of age (Table 2).

A mean of 9.3 ± 0.15 medications were prescribed during the study period. The mean number of medicines per year among the enrolled patients showed a significant upward trend, with values of 9.4, 9.9, and 10.4 in 2019, 2020, and 2021, respectively ($p = 0.009$).

Table 1. Demographics and clinical characteristics of patients with polypharmacy (n=1,928)

Characteristic	Value
Sex	
Male	706 (36.6)
Female	1,222 (63.4)
Age (y)	83.52 ± 0.3
Number of medications	9.31 ± 0.1
Excessive polypharmacy	
2019	375 (19.5)
2020	390 (20.3)
2021	409 (21.2)
Number of diagnoses per year	
2019	6.22 ± 1.9
2020	6.42 ± 2.2
2021	6.51 ± 2.1

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

Regarding the number of drugs prescribed by sex per year, although we observed an increasing tendency to prescribe more drugs to women than men; however, the variation between sexes was not statistically significant ($p = 0.12$). Specifically, we observed that the number of women taking multiple medications per year remained stable, with rates ranging from 761 to 870, while the figures for men were lower, at around 460 to 497 during the same period (2019–2021). In addition, the analysis of the average number of prescribed drugs according to sex revealed averages of 9.2 and 9.4 medications in men and women, respectively, in 2019, and 9.6 and 9.9 medications in 2021, respectively. The medication use did not differ significantly between the sexes for any of the 3 years ($p = 0.22$, 0.23, and 0.10, respectively) (Fig. 1).

Moreover, examination of the mean number of drugs prescribed by the age range and year of the study showed that despite the observed upward trend, the number of drugs prescribed per patient according to age did not differ significantly ($p = 0.1$, 0.2, and 0.3).

Table 2. Percentages (%) of patients with polypharmacy according to age/sex (n=1,928)

Sex	Age (y)				
	75–79	80–84	85–89	>90	Total
Male	16.55	9.28	7.16	3.63	36.62
Female	20.80	15.35	15.72	11.51	63.38
Total	37.34	24.64	22.87	15.15	100

Fig. 2 shows the annual trends observed in each year.

An average of 12.9, 14.2, 12.9, and 10.5 drugs were prescribed to patients aged 75–79, 80–84, 85–89, and >90 years, respectively. The result of the t-test showed statistically significant differences between groups ($p < 0.01$) (Fig. 3). The sub-analysis comparing the mean numbers of drugs prescribed between patients >90 years and those aged 75–89 years showed no statistically significant difference.

The results of the examination of the prevalence of excessive polypharmacy (≥ 10 medications) revealed an increase over the

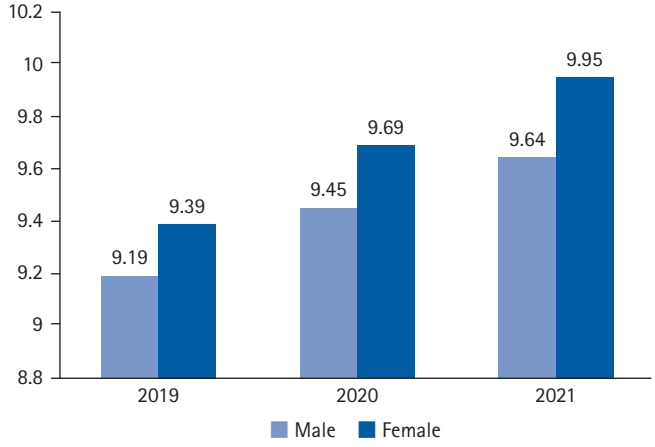

Fig. 1. Average number of medications by sex and year.

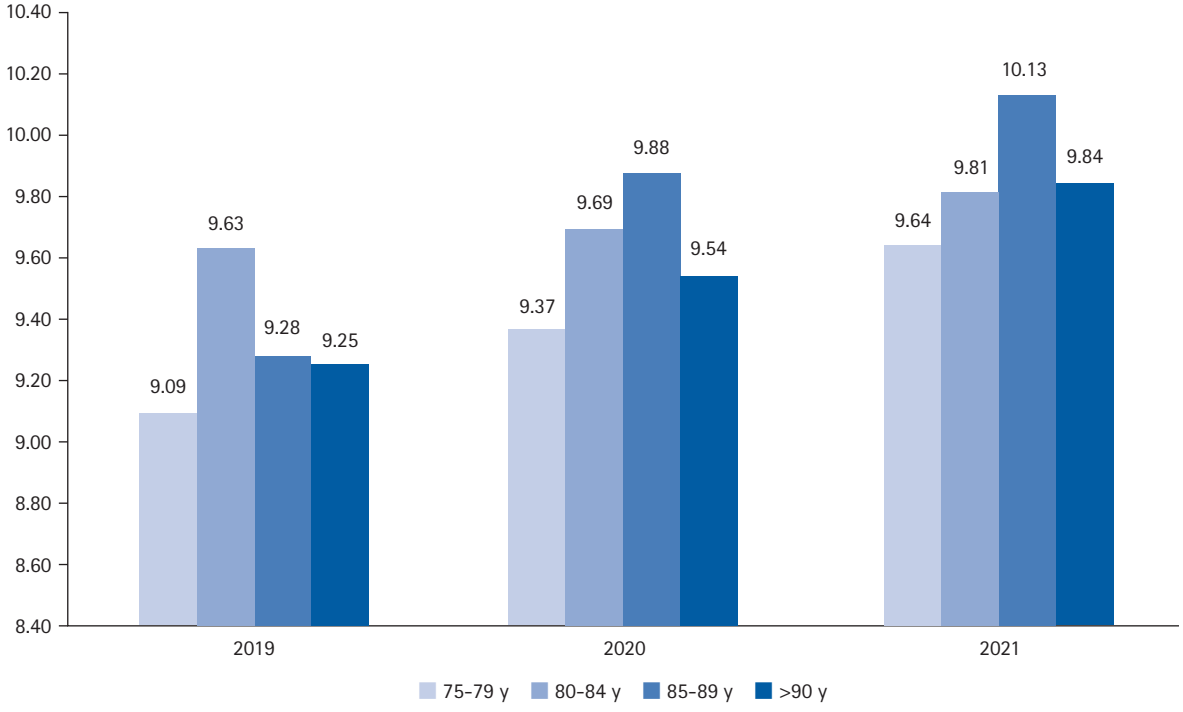

Fig. 2. Average number of drugs by age and year.

3-year period, with 538 (39.4%), 506 (41.5%), and 551 (45.1%) patients in 2019, 2020, and 2021, respectively. Pearson product-moment correlation test identified a high correlation between the year and percentage of patients with excessive polypharmacy ($R^2 = 0.98$); however, this relationship was not statistically significant ($p = 0.07$). The most commonly prescribed drugs during the study period were anilides (paracetamol), proton pump inhibitors (PPIs), acetylic acid, lorazepam, and bisoprolol (Fig. 4).

The analysis of the prevalence of anticholinergic medication use revealed that 46% of the patients were on a drug with a low risk of anticholinergic activity, while 37.5% were prescribed a drug with high anticholinergic risk, a significant difference ($p = 0.006$). Analysis of patients taking at least one anticholinergic drug across age groups showed that 73.7% of individuals aged 75–79 years were prescribed such medications; this percentage increased significantly to 89% among patients aged >90 years ($p = 0.0$) (Fig. 5). Likewise, women were prescribed more anticholinergic drugs than men ($p < 0.01$). The results of the comparative analysis of prescriptions of drugs with anticholinergic risk between patients under and over 90 years of age revealed that such drugs were prescribed to only 10.96% in patients <90 years and 89.5% among those aged >90 years; a statistically significant difference was observed ($p < 0.01$).

As most patients were prescribed several drugs, which could be related to multimorbidity, we also analyzed the mean number of pathologies. The mean number of diseases was significantly lower in men (7.1) than in women (7.4). and showed a statistical difference ($p = 0.007$). In contrast, while the mean number of diagnoses per patient ranged from 6.81 to 7.10 across age groups, the differences were not statistically significant ($p = 0.1$). Additionally, the mean number of pathologies for 2019, 2020, and 2021 were 6.2, 6.4, and 6.5, respectively, and did not differ significantly ($p = 0.2$). The most prevalent diseases in the patients included in the study were arterial hypertension (K86), non-insulin-dependent diabetes

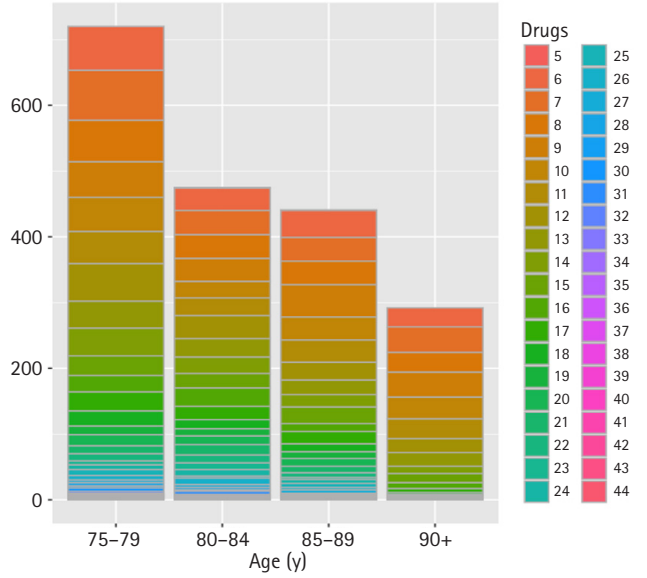

Fig. 3. Numbers of drugs dispensed during the study period according to age groups.

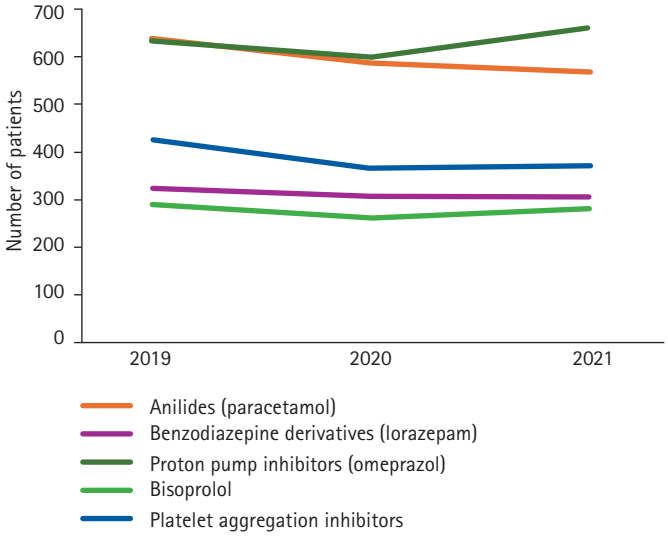

Fig. 4. Most prescribed medication over the 3 years.

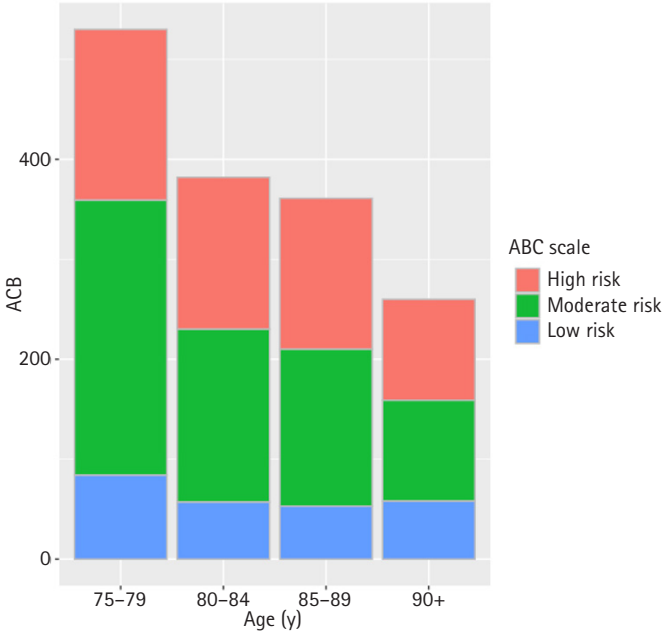

Fig. 5. Anticholinergic risks of the prescribed medications by age groups. ACB scale, anticholinergic cognitive burden scale.

(T90), arterial hypertension (K86), lipid metabolism disorders (T93), and atrial fibrillation (K78).

DISCUSSION

The results of this study revealed a significant increase in the mean number of drugs prescribed over the 3-year study period, from 9.4 in 2019 to 10.4 in 2021. These results should be interpreted with caution as this increase cannot be attributed solely to the impact of the pandemic. Factors other than COVID-19 may have contributed to this increase, as new diseases may have occurred during this period. Moreover, the growing survival rate of the older population also increases the probability of developing multiple chronic diseases. The presence of two or more diseases affects approximately 40% of individuals aged ≥65 years, and this prevalence increases with age, increasing the likelihood of polypharmacy.[12,34]

Considering the high vulnerability of the older population to polypathology and the impact of COVID-19, which has resulted in not only respiratory complications but also cardiac, hematological, and other health problems, a remarkable increase in the prescription of specific drugs designed to address these various medical conditions has been observed.[35-37] Furthermore, the impact of the virus extends beyond the physical realm, with the older population experiencing elevated stress and anxiety levels due to the threat of the virus, pandemic uncertainties, and social isolation measures. Healthcare practitioners frequently prescribe antidepressants and anxiolytics to manage such psychological burdens.[38,39]

We did not identify any research directly comparable to our findings, which underscores the need for further research to improve our understanding of medication patterns and their implications for older patients in primary care settings.

Regarding the characteristics of the included patients, 63.4% of the patients were women. This distribution is consistent with that of previous research that has related female sex to a higher prevalence of polypharmacy.[12,14,40-42] This can be attributed to several factors. First, the demographic structure of the population plays an important role as women tend to have a longer life expectancy than men. Secondly, greater longevity exposes women to a higher likelihood of developing multiple chronic diseases, leading to polypharmacy.[41] Concerning age, in the present study, 720 patients (37.3%) were 75–79 years of age, which is consistent with results reported by Gutiérrez-Valencia et al., in which polypharmacy was more frequent in individuals aged 76–85 years.[14] Contrary to many studies suggesting that polypharmacy increases with age,[13,40] we did not observe this trend in our study. One possible explanation could be that patients attending primary care centers present a relatively younger profile than those usually studied in polypharmacy research.

Our analysis of the number of polypharmacy patients across different age ranges revealed a decline throughout the 3-year study period. However, the number of patients attending health centers also decreased each year. This decline may be attributed to various factors, particularly the COVID-19 pandemic. In 2020 and 2021, many patients could not visit their healthcare facilities for regular care, as they may have followed safety guidelines and stayed home. Additionally, some individuals may have been relocated to alternative living arrangements such as staying with relatives or being admitted to nursing homes. Furthermore, some patients may have died during the study period. These factors may have contributed to the observed decrease in the number of patients receiving polypharmacy over time.

We also analyzed the number of drugs prescribed according to age groups; the average number of drugs dispensed during the study period according to age groups was >12.9 drugs in the 75–89 age group, which decreased to 10.5 in patients over >90 years of age. These results are consistent with those of a study conducted in octogenarians with polypharmacy, in which the number of medications gradually decreased with age.[9] Furthermore, the mean number of drugs prescribed during the study period, 9.3±0.15, is concordant with the findings of a previous study conducted in primary care that identified the associations of comorbidities such as heart failure and ischemic heart disease with higher levels of medication prescription. Specifically, the authors identified a mean of nine medications for patients with heart failure and eight for those with ischemic heart disease.[13] In contrast to our study, other investigations reported lower mean numbers of medications. Hazen et al. reported a mean of eight chronic medications.[43] Additionally, another study on oncology patients reported 7.3±3.4 drugs (range 0–18).[10] These findings highlight the variability in the number of medications prescribed among different patient populations.

In addition, our analysis of the prevalence of excessive polypharmacy among participants over the 3-year period revealed a gradual, although not statistically significant, increase in the number of patients experiencing this geriatric syndrome. Approximately 40%–45% of patients were affected by excessive polypharmacy. Compared with a study of 1,140 octogenarian patients that reported excessive polypharmacy in 16.9% and 20.7% of men and women, respectively, we observed a significantly higher prevalence in our cohort. These similarities with our study are significant because they reiterate the need for physicians to be aware of the potential complications arising from multiple drug interactions. These complications include adverse effects such as drug-drug interactions, in-

creased risk of falls and fractures, cognitive impairment, and decreased functional capacity. Moreover, these findings emphasize the importance of carefully managing polypharmacy to minimize adverse effects and optimize patient outcomes.[9,44,45]

Our sub-analysis of patients aged >90 years compared to the rest of the participants did not reveal a significant difference in the average number of prescribed drugs. In 2021, both groups were prescribed an average of 9.8 drugs. This finding suggests that we may be overlooking the issue of de-prescription in this age group and that measures should be taken to address this issue and ensure appropriate medication management for older adults.

Our study results revealed that the most commonly prescribed drugs were anilides, PPIs, benzodiazepine derivatives, and platelet aggregation inhibitors (excluding heparin). These results are consistent with those of a Spanish study in Barcelona that analyzed the electronic records of 916,619 people aged >65 years. In that study, 49.9% of the participants had polypharmacy, and the same five drugs were identified as the most frequently prescribed. Several studies have confirmed that PPIs and antithrombotic agents are the most commonly used drugs.[4,43] These findings highlight the prevalence of this problem, with a significant number of prescriptions considered inappropriate owing to the unnecessary continuation of PPIs and a lack of appropriate indications. Our results underscore the need for healthcare professionals to exercise caution when prescribing PPIs to older adults, considering the potential risks and benefits, and ensuring that the indications are appropriate.[46] Likewise, this caution is required not only for PPIs but also for every medication prescribed to older patients to avoid the inappropriate use of PPIs in older patients discharged from acute care hospitals.

Our analysis using the anticholinergic risk scale revealed a significant difference between sexes, with a higher prevalence of anticholinergic drug prescriptions among women, which is consistent with previous studies.[47] Sex disparities in anticholinergic prescription patterns may be attributed to various factors, including differences in disease prevalence, healthcare-seeking behaviors, and pharmacokinetic and pharmacodynamic properties.[41,42] Our results showed that 73.7% of patients aged 75–79 years were prescribed drugs with anticholinergic effects. We also observed a significant increase up to 89.4% in patients >90 years. These rates were higher than those reported in a study that was also conducted in the primary care setting, which reported that 25.8% of patients received at least one drug with anticholinergic action.[48] Our results also revealed age-related changes in the use of anticholinergic medications, with a notably higher prevalence among individuals aged >90 years. This finding aligns with the fact that advanced age is often accompanied by multiple pathologies such as cognitive impairment, dementia, Parkinson disease, and incontinence.[5] This contributes to an increased likelihood of patients taking at least one drug with anticholinergic properties as they age.[49] Recent investigations have highlighted the adverse effects of anticholinergic drugs, including an increased incidence of dementia. This emphasizes the importance of close monitoring and controlling the use of anticholinergic medications to reduce short-, medium-, and long-term adverse effects.[50]

In conclusion, we observed an increase in the mean number of drugs prescribed over a 3-year study period in patients aged >75 years. Although partly attributable to the COVID-19 pandemic, this growth underscores the complexity of polypharmacy in older adults, which requires vigilant monitoring and management. This study also revealed sex disparities, with a higher prevalence of polypharmacy in women, and a notable prevalence of anticholinergic medications, especially among those aged >90 years. Further research is required to better understand the underlying factors that contribute to polypharmacy and anticholinergic risk in geriatric patients. All healthcare professionals should prioritize the minimization of drug use and be cautious when prescribing new medications.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, RMB, BOB, AGR, PM; Data curation, PM, IFP, ATL, AGR, VCV; Formal analysis, BOB, RMB, ATL, VCV, PM; Writing-original draft, RMB, BOB, PM; writing-review & editing, PM, BOB, IFP, ATL, AGR, VCV, RMB. All authors have read and agreed to the published version of the manuscript.

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Edentulism and Individual Factors of Active Aging Framework in Colombia

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Background: While edentulism remains a serious public health problem for older adults in Colombia, few analyses have been conducted from the framework of active aging as a part of the positive discourse of aging. This study analyzed complete edentulism and its relationship with determinants including personal, behavioral, and health systems and social services. **Methods:** This study included a total of 19,004 older adults. We used univariate, bivariate, and multivariate logistic regression type scores to investigate the relationships between the variables. The personal determinants included basic (Barthel scale) and instrumental activities of daily living (Lawton scale), public transportation, functional limitations, self-perceived health, and health problems. The behavioral factors included alcohol and tobacco use, mini nutritional tests, and physical activity. The last determinant was the healthcare system, while social services access included dental services. The analysis also included sociodemographic variables. **Results:** The results revealed significant associations for the variables of the three determinants, including the risk of malnutrition (odds ratio [OR]=1.15), functional limitation (OR=1.15), moderate physical activity (OR=1.08), and access to dental services (OR=2.31). Sex, years of education, and race were also risk factors, among other variables. Personal determinants, behavior, and use and access to health services were related to edentulism in older adults. **Conclusion:** These findings support the need to include different analyses of edentulism from multicausality and to understand the oral cavity and the living conditions of aging adults.

Key Words: Aging, Healthy aging, Oral health, Public health dentistry, Geriatric dentistry, Edentulous mouth

INTRODUCTION

The human aging process is individual and multidimensional and is characterized by its heterogeneous presentation, intrinsic nature, and irreversible progression. Aging begins at conception, develops throughout life, and ends with death.[1)] This complex process is accompanied by biological and psychological changes,[2)] which implies the accumulation of needs, limitations, changes, losses, capacities, and opportunities during an individual's lifetime.

Active aging is defined as "the process of optimizing opportunities for health, participation, and security to enhance the quality of life as people age." The active aging model presented by the World Health Organization (WHO)[3)] encompasses six groups of determinants, each including several features, as follows: (1) availability and use of health and social services (e.g., health promotion and prevention, continuous care); (2) behavioral determinants (e.g., exercise and physical activity, drinking and smoking habits, feeding, medication); (3) personal determinants (biology and genetics, psychological characteristics); (4) physical environment (e.g., safe houses, low pollution levels); and (5) social (e.g., education, social care) and (6) economic (e.g., wage, social security) determinants.[4)]

Active aging is a theoretical model used to analyze aging processes and develop policies or programs framed within them.[5] Three conditions must be met for an active aging process: (1) avoiding illness and disability, (2) maintaining high physical and cognitive functional capacity, and (3) actively engaging in life.[6] As aging is a process highly mediated by the social determinants of health, active aging includes variables that explain socioeconomic conditions within its analysis.

Oral health is a part of active aging and is a behavioral determinant; however, few analyses have investigated the relationships between the general determinants of active aging and oral health. One reason for this lack of research could be that active aging is a particularly new concept developed in the 21st century and because geriatric dentistry has not yet developed around the theories of aging, new knowledge and ways of publishing on this topic are needed.[7-9] A conceptual framework about oral health and aging was proposed in 2021 and includes teamwork, minimal intervention, oral functionality, and patient-centered care, with maximal tooth preservation being one of the main goals,[10] particularly because maintaining oral health and keeping the teeth in the mouth are difficult in old age.[11]

One major problem faced by older adults is tooth loss and edentulism, an irreversible condition that can be partial or total, in which individuals lose all of the natural teeth that were present in early life. Edentulism is related to the inability of an older adult to carry out social activities such as talking with peers and participating in support networks.[3] It is also associated with many pathologies and adverse general health events such as cancer, cardiovascular disease, and diabetes.[12,13] Alcohol, tobacco use, and nutrition are also associated with oral health.[14-17] Few studies have evaluated the relationship between the Barthel scale and oral health; however, alterations in dependency could influence the oral health of older adults due to their inability to eat.[18] Variables such as ethnicity, sex, socioeconomic income, level of education,[19] urban-rural regional location,[20] increasing age, social capital, and marital status[19] are also significantly associated.

Socioeconomic, biological, and interpersonal relationships such as those described above make edentulism a public health problem that has been described as the "final marker of disease burden for oral health" [21,22] and remains a challenging problem for healthcare providers worldwide. The prevalence of edentulism varies across populations, ranging from 1.3% to 78.0% in patients aged ≥65 years.[23] The eight industrialized nations in the world, organized as the G8 (Canada, France, Germany, Italy, Japan, Russia, the United Kingdom, and the United States), show considerable differences in the prevalence of edentulism (16.3, 19, 46, and up to 58% in France, Italy, the UK, and Canada, respectively, with no data available for Russia).[24] Colombia has a history of edentulism, and according to the IV National Study of Oral Health in 2014, 32.87% of people aged 65–79 years had total bimaxillary edentulism.[25]

The present study aimed to identify the development of various determinants of the framework of active aging; namely, the behavioral, personal, and health systems and social services associated with edentulism in the Colombian population.

MATERIALS AND METHODS

This study analyzed secondary data from the Health, Well-being, and Aging (Salud, Bienestar y Envejecimiento [SABE]) survey carried out in 2016, which comprises 12 chapters, with national and regional representative samples for the population > 60 years of age. The sample design was adapted and adjusted based on the guidelines established by the National System of Studies and Population Surveys in Health of the Ministry of Health. The estimated sample size was 24,553 individuals from 244 municipalities across all departments (Colombian administrative units) and 23,694 older adults.[26-28]

Of the total respondents, 4,689 were excluded from the oral section because of cognitive impairment identified by the Mini-Mental State Examination.[27,28] This study analyzed data of 19,005 Colombian older adults who responded to questions about oral health conditions. The theoretical framework that was used for the survey recollection process was based on active aging and social determinants.[27,28]

The participants signed a written informed consent form and the study was approved by the Ethics Committee of Universidad del Valle (Cod. 09–014, Cod. 008–2014, and Cod. 011–015). At the time of this study, the dataset was completely coded, and no personal information was identifiable. This special analysis was also approved by the committee (Cod. E010-023). Approval from the Ministry of Health and Social Protection was also requested for the analysis. Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[29]

Study Variables

Edentulism was the outcome variable in this study. It was self-reported and analyzed as having or not having teeth (totally edentulous). The sociodemographic factors included area (rural and urban), age, socioeconomic status, sex (male or female), healthcare system (contributive and subsidized), race (light, medium, and dark), years of education (< 5 or ≥ 6), and categorized income (until US $252.6 and More than US $252.6). The values were converted to US dollars at the time of the national survey (2015

exchange rate: 1 USD = 2.743 pesos), and the socioeconomic strata were categorized according to the National Administrative Department of Statistics (DANE) as 1–2, 3–4, and 5–6. Age was only used in the univariate and bivariate analyses; it was not included in the multivariate model because as age increased, it was directly related to worse health conditions, both general and oral.

The behavioral factors included alcohol consumption, tobacco use, physical activity, and nutritional status. Alcohol and tobacco consumption were evaluated using direct questions on consumption (yes or no). Tobacco use was categorized as non-smoker, former, or current smoker. Nutritional status was evaluated using the validated version of the Mini Nutritional Assessment Test in Spanish, which includes 19 variables such as body mass index, neuropsychological problems, mobility, daily food intake, circumference, and self-perceived health.[14] Accounting for these variables, the scale has three categories: normal (≥ 24 points), at risk of malnutrition (17–23.5 points), and malnourished (< 17 points). Physical activity was measured using two questions regarding vigorous and moderate physical activity, respectively. Each had a dichotomous answer of yes or no.

The personal factors included public transportation use, Barthel scale, self-perceived health, health problems in the last 30 days, Lawton scale, and functional limitations.

Basic activities of daily living were measured using the Barthel scale, which includes several basic domains of functioning, such as urinary and fecal continence and the ability to independently carry out self-care activities such as brushing teeth, going to the toilet, preparing food, moving from one place to another (e.g., moving to a chair), moving around the house, dressing, climbing stairs, and bathing. A Spanish-validated version of the Barthel index was used to generate information.[30] For this study, variables were analyzed in dependent and independent older adults.

Functional status was evaluated using the Lawton scale for instrumental activities of daily living (IADL).[31] The Lawton scale included in this study evaluates six activities (using the telephone, taking medications, managing finances, preparing meals, shopping, and using transportation), with scores ranging from 0 to 6, with lower scores indicating a lower functional status. Inability is defined as low IADL (≤ 5).[26]

Functional limitations were determined according to the responses to the question: "Do you have difficulty walking five blocks (400 m)?" Two categories—with and without limitations—were created. Self-perceived health was analyzed according to the responses to the question "Would you say that your health in the last 30 days has been ...?" The categories were good–very good, regular, bad, and bad–very bad.[32] A question asking if the participant had presented with any health problems in the last 30 days was also used. The last variable included in this group of determinants was the use of public transport, dichotomized as use or non-use.

Health systems and social services were used to indicate access to dental services in the last 12 months. Fig. 1 shows the variables used in this analysis.

Analysis

We performed descriptive analyses by estimating the percentages of all variables. In the bivariate analyses, the chi-squared differences were calculated for the primary outcome (edentulism). Multivari-

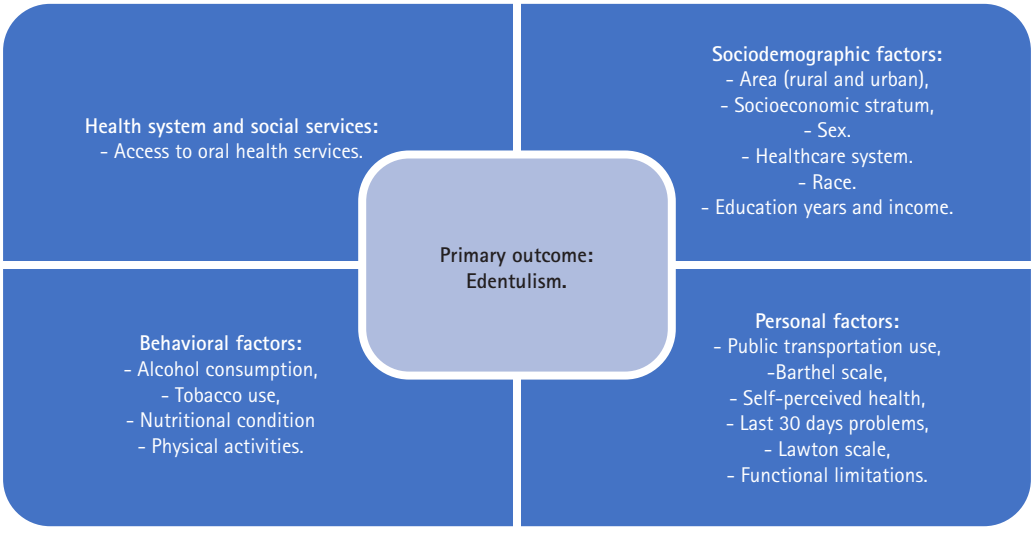

Fig. 1. Variables from active aging framework analyzed with edentulism.

ate analysis was also performed, and odds ratios (ORs) with 95% confidence intervals (CIs) and p-values were calculated and compared between established risk factors for edentulism with each group of behavioral and personal variables. In the case of the health system and social services determinants, we estimated the unadjusted effect because the model included only one variable. We performed multivariate logistic regression analysis to analyze the complete set of variables.

Under the framework of logistic regression analysis, models of this type are premised on the presence of symmetry in the resulting variable (edentulism). Asymmetric binary regression models are desirable when the variables do not have adequate symmetry. Table 1 shows that edentulism was present in approximately 28% of the population. Given the asymmetry of this variable, a Scobit-type regression was selected owing to the extreme probabilities; that is, the predominant presence of one of the response variable values and the inadequacy of symmetric regressions.[33,34] Statistical significance was set at $p < 0.05$. STATA software version 17 (StataCorp LLC, College Station, TX, USA) was used for all the analyses.

The multivariate model included variables with < 10% missing data, except for nutritional screening, which presented a greater loss because it was a construction of variables, and income, which was a sensitive response variable. Model 1 included all determinant

Table 1. Edentulism and sociodemographic, behavioral, and personal factors and health system and social services

Variable		All	Edentulism		p-value
			Yes	No	
Sociodemographic factors	Age (y)				< 0.001
	60–64	6,073 (31.66)	1,073 (36.91)	5,000 (19.66)	
	65–69	4,946 (26.03)	1,280 (23.45)	3,666 (27.07)	
	70–74	3,584 (18.86)	1,210 (22.17)	2,374 (17.53)	
	75–79	2,494 (13.12)	930 (17.04)	1,564 (11.55)	
	≥ 80	1,907 (10.03)	966 (17.70)	941 (6.95)	
	Sum	19,004 (100)	5,459 (100)	13,545 (100)	
	Sex				< 0.001
	Female	10,660 (56.09)	3,696 (67.70)	6,964 (51.41)	
	Male	8,344 (43.91)	1,763 (32.30)	6,581 (48.59)	
	Sum	19,004 (100)	5,459 (100)	13,545 (100)	
	Race (pigmentocracie)				< 0.001
	Light	9,568 (50.35)	3,128 (57.30)	6,440 (47.55)	
	Medium	6,919 (36.41)	1,867 (34.20)	5,052 (37.30)	
	Dark	2,517 (13.24)	464 (8.50)	2,053 (15.16)	
	Sum	19,004 (100)	5,459 (100)	13,545 (100)	
	Area				< 0.001
	Urban	14,040 (73.88)	3,883 (71.13)	10,157 (74.99)	
	Rural	4,964 (26.12)	1,576 (28.87)	3,388 (25.01)	
	Sum	19,004 (100)	5,459 (100)	13,545 (100)	
	Socioeconomic stratum				< 0.001
	1–2	15,251 (80.25)	4,499 (82.41)	10,752 (79.38)	
	3–4	3,600 (18.94)	923 (16.91)	2,677 (19.76)	
	5–6	153 (0.81)	116 (0.86)	37 (0.68)	
	Sum	19,004 (100)	5,459 (100)	13,545 (100)	
	Healthcare system				< 0.001
	Contributive	7,844 (41.31)	2,007 (36.77)	5,837 (43.14)	
	Subsidized	11,144 (58.69)	3,451 (63.23)	7,693 (56.86)	
	Sum	18,988 (100)	5,458 (100)	13,530 (100)	
	Education years				< 0.001
	0–5	13,891 (59.99)	4,473 (85.02)	9,418 (73.72)	
	6–10	4,145 (22.98)	788 (14.98)	3,357 (26.28)	
	Sum	18,036 (100)	5,261 (100)	12,775 (100)	
	Income (US dollar)				< 0.001
	≤ 252.60	13,248 (82.82)	3,944 (88.75)	9,304 (80.54)	
	> 252.60	2,248 (19.46)	500 (11.25)	2,748 (17.18)	
	Sum	15,996 (100)	4,444 (100)	11,552 (100)	

(Continued to the next page)

Table 1. Continued

	Variable	All	Edentulism		p-value
			Yes	No	
Behavioral factors	Alcohol consumption in the last month				< 0.001
	Yes	2,553 (13.44)	468 (8.58)	2,085 (15.40)	
	No	16,439 (86.56)	4,988 (91.42)	11,451 (84.60)	
	Sum	18,992 (100)	5,456 (100)	13,536 (100)	
	Tobacco use				< 0.001
	Non-smoker	9,133 (48.06)	2,819 (51.64)	6,314 (46.62)	
	Former smoker	7,857 (41.35)	2,077 (38.05)	5,780 (42.68)	
	Current smoker	2,012 (10.59)	563 (10.31)	1,449 (10.70)	
	Sum	19,002 (100)	5,459 (100)	13,543 (100)	
	Nutritional condition				< 0.001
	Normal	7,258 (53.82)	1,821 (48.10)	5,437 (56.05)	
	Risk of malnutrition	5,868 (43.51)	1,840 (48.60)	4,028 (41.53)	
	Malnutrition	360 (2.67)	125 (3.30)	235 (2.42)	
	Sum	13,486 (100)	3,786 (100)	9,700 (100)	
Physical activity	Vigorous				< 0.001
	Yes	3,961 (20.85)	897 (16.43)	3,064 (22.63)	
	No	15,040 (79.15)	4,562 (83.57)	10,478 (77.37)	
	Sum	19,001 (100)	5,459 (100)	13,542 (100)	
	Moderate				< 0.001
	Yes	9,978 (52.55)	2,388 (43.78)	7,590 (56.09)	
	No	9,008 (47.45)	3,067 (56.22)	5,941 (43.91)	
	Sum	18,986 (100)	5,455 (100)	13,531 (100)	
Personal factors	Public transportation use				0.344
	Yes	16,392 (86.26)	4,729 (86.63)	11,663 (86.11)	
	No	2,612 (13.74)	730 (13.37)	1,882 (13.89)	
	Sum	19,004 (100)	5,459 (100)	13,545 (100)	
	Barthel scale (basic ADL)				< 0.001
	Dependent	2,998 (15.78)	1,129 (20.68)	1,869 (13.80)	
	Independent	16,006 (84.22)	4,330 (79.32)	11,676 (86.20)	
	Sum	19,004 (100)	5,459 (100)	13,545 (100)	
	Lawton scale (IADL)				< 0.001
	Low IADL ≤ 5 (inability)	3,622 (19.06)	1,227 (22.48)	2,395 (17.68)	
	Lawton = 6 (no Inability)	15,382 (80.94)	4,232 (77.52)	11,150 (82.32)	
	Sum	19,004 (100)	5,459 (100)	13,545 (100)	
	Functional limitation: walking five blocks				< 0.001
	With limitation	13,169 (69.35)	2,144 (39.32)	3,677 (27.16)	
	Without limitation	5,821 (30.65)	3,309 (60.68)	9,860 (72.84)	
	Sum	18,990 (100)	5,453 (100)	13,537 (100)	
	Self-perceived general health				< 0.001
	Very good–good	9,119 (48)	2,429 (44.52)	6,690 (49.40)	
	Regular	8,265 (43.50)	2,495 (45.73)	5,770 (42.61)	
	Bad–very bad	1,650 (8.50)	532 (9.75)	1,083 (8)	
	Sum	18,999 (100)	5,456 (100)	13,543 (100)	
	Health problems in the last 30 days				0.595
	Yes	6,562 (34.55)	1,900 (34.84)	4,662 (34.43)	
	No	12,432 (65.45)	3,554 (65.16)	8,878 (65.57)	
	Sum	18,994 (100)	5,454 (100)	13,540 (100)	
Health system and social services	Access to oral health services				< 0.001
	Yes	3,331 (17.54)	462 (8.46)	2,869 (21.20)	
	No	15,659 (82.46)	4,996 (91.54)	10,663 (78.80)	
	Sum	18,990 (100)	5,458 (100)	13,532 (100)	

Values are presented as number (%).
ADL, activities of daily living; IADL, instrumental activities of daily living.
Chi-squared test was used to calculate significant differences between variables.

and sociodemographic variables. The final model included variables with p-values < 0.1, as they were considered important in the consolidation of the definitive model and discussion.

In terms of the multivariate analysis and as a final model, we removed individual variables that were not significant to determine if any important changes in the measures of association could cause noise in the results. To strengthen the discussion, we retained variables with p-values < 0.09.

RESULTS

Table 1 shows the results of the bivariate analysis with each of the variables considered in the behavioral, personal, health, and social services system determinants. Public transportation and health problems in the last 30 days did not differ significantly between the groups. The other variables showed significant differences between the groups.

Multivariate Analysis

We performed the multivariate analysis using each of the determinants with the edentulism result variable. The results of these models are shown in Tables 2 and 3.

The behavioral determinants of nutritional status for older adults at risk for malnutrition showed an OR of 1.26, p < 0.05, and a confidence interval of risk. This risk did not exist when a person was already malnourished. Not performing vigorous (OR = 1.26) or moderate (OR = 1.41) physical activity was a risk factor for edentulism, while alcohol consumption and smoking were not. We observed a protective relationship in older adults who were former smokers (OR = 0.81; p < 0.05).

Analysis of personal determinants showed that the Barthel scale (OR = 1.22) and Lawton scale OR = 1.13), functional limitations (OR = 1.47), and health problems in the last 30 days (OR = 0.88) were significantly associated with tooth loss, while public transportation use and self-perceived general health were not. The last group of determinants, a single determinant, health system, and social services, evaluated by access to oral health services, presented a significant relationship, an OR of 2.61 and p < 0.05, which was the only significant finding for this group of determinants.

Subsequently, as a part of the multivariate analysis, we included all variables into a new model and adjusted for sociodemographic variables to establish whether the significance remained contrary to the OR where some of the variables changed the risk. Table 4 describes the model with all the variables.

Regarding personal determinants, the Barthel test, Lawton test, health problems in the past 30 days, and functional limitations re-

Table 2. Logistic regression model of behavioral determinants (n=13,459)

Variable	OR	Coefficient (95% CI)	p-value
Alcohol consumption			
No	1.0	-	
Yes	0.54	(0.38–0.78)	0.001
Tobacco use			
Non-smoker	1.0	-	
Former smoker	0.81	(0.68–0.96)	0.017
Current smoker	0.93	(0.82–1.06)	0.332
Mini nutritional test			
Normal	1.0	-	
Risk of malnutrition	1.26	(1.03–1.53)	0.021
Malnutrition	1.35	(0.95–1.94)	0.092
Physical activity			
Vigorous			
Yes	1.0	-	
No	1.26	(1.04–1.52)	0.016
Moderate			
Yes	1.0	-	
No	1.41	(1.07–1.85)	0.012

OR, odds ratio; CI, confidence interval.
p-value based on logistic regression analysis. We observed significant relationships between variables for all behavioral determinants analyzed as a single determinant.

Table 3. Logistic regression model of personal determinants (n=18,976)

Variable	OR	Coefficient (95% CI)	p-value
Public transportation use			
Yes	1.00	-	
No	0.90	(0.82–0.98)	0.026
Barthel scale (basic ADL)			
Independent	1.00	-	
Dependent	1.22	(1.10–1.36)	0.000
Lawton scale (IADL)			
Independent	1.00	-	
Dependent	1.13	(1.05–1.22)	0.001
Functional limitation: walking five blocks			
With limitation	1.00	-	
Without limitation	1.47	(1.28–1.69)	0.000
Self-perceived general health			
Very good–good	1.00	-	
Regular	1.06	(0.99–1.15)	0.076
Bad–very bad	1.08	(0.96–1.22)	0.174
Health problems in the last 30 days			
Yes	1.00	-	
No	0.88	(0.82–0.95)	0.002

ADL, activities of daily living; IADL, instrumental activities of daily living; OR, odds ratio; CI, confidence interval.
p-value based on logistic regression analysis. We observed significant relationships between variables in all personal determinants analyzed as a single determinant.

Table 4. Multivariate statistical model of behavioral, personal, and access to health services factors, adjusted for sociodemographic variables, and the final model

	Variable	Model 1			Model 2 (final model)		
		OR	95% CI	p-value	OR	95% CI	p-value
Sociodemographic factors	Sex						
	Male	1.00	-		1.00	-	
	Female	1.68	(1.46–1.94)	< 0.001	1.66	(1.53–1.80)	< 0.001
	Area						
	Urban	1.00	-		1.00	-	
	Rural	1.06	(0.97–1.16)	0.135	1.06	(0.98–1.16)	0.122
	Education years						
	≥ 6	1.00	-		1.00	-	
	0–5	1.52	(1.31–1.77)	< 0.001	1.52	(1.36–1.70)	< 0.001
	Income (US dollar)						
	≤ 252.60	1.00	-		1.00	-	
	> 252.60	1.12	(0.97–1.29)	0.102	1.13	(0.98–1.29)	0.076
	Socioeconomic stratum						
	5–6	1.00			1.00		
	3–4	0.74	(0.46–1.17)	0.206	0.74	(0.47–1.17)	0.204
	1–2	0.71	(0.45–1.13)	0.157	0.72	(0.45–1.13)	0.154
	Race (pigmentocracie)						
	Light	1.00	-		1.00	-	
	Medium	0.74	(0.67–0.83)	< 0.001	0.75	(0.69–0.81)	< 0.001
	Dark	0.49	(0.40–0.59)	< 0.001	0.49	(0.44–0.56)	< 0.001
	Healthcare system						
	Contributive	1.00	-		1.00	-	
	Subsidized	1.02	(0.97–1.07)	0.300	1.02	(0.97–1.07)	0.309
Behavioral factors	Alcohol consumption						
	No	1.00	-		1.00	-	
	Yes	0.70	(0.60–0.81)	< 0.001	0.71	(0.62–0.81)	< 0.001
	Tobacco use						
	Non-smoker	1.00	-		-	-	
	Former smoker	1.10	(0.92–1.09)	0.916	-	-	
	Current smoker	1.12	(0.97–1.29)	0.121	-	-	
	Mini nutritional test						
	Normal	1.00	-		1.00	-	
	Risk of malnutrition	1.15	(1.05–1.27)	0.003	1.15	(1.06–1.24)	< 0.001
	Malnutrition	1.10	(0.87–1.39)	0.402	1.09	(0.87–1.37)	0.408
	Vigorous physical activity						
	Yes	1.00	-		-	-	
	No	1.01	(0.91–1.12)	0.750	-	-	
	Moderate physical activity						
	Yes	1.00	-		1.00	-	
	No	1.08	(1.1–1.18)	0.048	1.08	(1.1–1.18)	0.040
Personal determinants	Barthel scale (basic ADL)						
	Independent	1.00	-		1.00	-	
	Dependent	1.11	(0.99–1.24)	0.072	1.10	(0.98–1.22)	0.07
	Lawton scale (IADL)						
	Independent	1.00	-		1.00	-	
	Dependent	1.11	(1.01–1.23)	0.039	1.10	(0.99–1.21)	0.05
	Public transportation use						
	Yes	1.00	-		-	-	
	No	0.92	(0.82–1.04)	0.213	-	-	

(Continued to the next page)

Table 4. Continued

	Variable	Model 1			Model 2 (final model)		
		OR	95% CI	p-value	OR	95% CI	p-value
	Functional limitations						
	Without limitations	1.00	-		1.00	-	
	With limitations	1.20	(1.08–1.33)	0.001	1.19	(1.09–1.30)	< 0.001
	Health problems in the last 30 days						
	No	1.00	-		1.00	-	
	Yes	0.88	(0.80–0.97)	0.010	0.87	(0.80–0.95)	0.002
	Self-perceived health in the last 30 days						
	Very good–good	1.00	-		-	-	
	Regular	1.01	(0.92–1.10)	0.798	-	-	
	Bad–very bad	0.93	(0.79–1.09)	0.386	-	-	
Health system and social services	Access to dentistry service						
	Yes	1.00	-		1.00	-	
	No	2.33	(1.93–2.81)	< 0.001	2.31	(2.02–2.64)	< 0.001

Model 1, complete model (sociodemographic characteristics, personal determinants, behavioral determinants, and healthcare system and social services); Model 2, final model (sociodemographic characteristics, personal determinants, behavioral determinants, and healthcare system and social services); ADL, activities of daily living; IADL, instrumental activities of daily living; OR, odds ratio; CI, confidence interval.
p-value based on logistic regression analysis. We observed significanWe observed significant relationships for sociodemographic factors, sex, years of education, and race, while socioeconomic stratum, healthcare system, and area did not.

mained significant. The associations with public transportation use and self-perceived health in the previous 30 days were not statistically significant. Regarding behavioral factors, mini-nutritional tests and moderate physical activity remained significant. Access to dental services also remained a risk factor for edentulism.

DISCUSSION

This is the first study in Colombia to integrate active aging and its relationship with edentulism into the discourse and use quantitative data to explain these relationships. The sociodemographic variables of sex, skin color, and years of education showed statistical significance in the complete model, while area, health regimen, and stratum did not. All determinants included in this analysis showed a relationship between edentulism and some of the included variables.

Some personal determinants demonstrated relationships with edentulism. The Lawton scale of IADL has not been deeply investigated in the oral health; however, previous studies reported a relationship.[35] Similarly, few studies have investigated the relationship of the Barthel scale with oral health; among these studies, some results are consistent with the findings of the present study, in which a lower Barthel index score was generally related to poorer oral health conditions, in this case, edentulism.[36] This analysis revealed an OR very close to statistical significance for both the Barthel and Lawton scales in the final model and a significant relationship when they acted as independent determinants that were preserved for the Lawton scale after adjusting for sociodemographic variables. Care of the oral cavity is intimately related to the basic activities of daily life; thus, the Lawton and Barthel scales should be included in the analysis of oral health in older adults in the framework of active aging. These findings are consistent with those of the functional limitations variable, which was significant in the independent and final models, meaning that limitations in older adults could impact on oral health, concordant with previous reports.[37] The present study contributes to this line of research on basic and instrumental activities and their relationship with the oral cavity. Few such approaches have been described previously.

Health problems in the last 30 days can be analyzed from different perspectives. A person who reports a health problem could need more support from services, which would imply a potential protective effect against edentulism, as a lack of access to dental support is a risk factor for tooth loss.[38] The determinants of health system and social services demonstrated that lack of access to dental care increased the possibility of being edentulous by approximately 130%.

Access to services is key to avoiding tooth loss.[39,40] Use of public transportation and self-perceived health during the past 30 days were not significantly related to edentulism. Despite these findings, interventional approaches related to tooth loss have suggested including the perception of general health based on reported associations and relationships[41] and the association of general health with tooth loss.[42]

Behavioral factors are also associated with edentulism. In the be-

havioral factor-exclusive model, former smoking status was significant. Smoking shows a strongly dose-dependent association[43]; thus, this relationship requires further analysis in future studies. Alcohol consumption at an early age is related to depression, consistent with the findings in the present study. The consolidation of this variable as a constant factor in all the models in this study was striking. In older adults, findings related to alcohol consumption have been controversial,[44] with some studies reporting findings comparable to those in the present study.[45] Alcohol and tobacco consumption as behavioral factors require further analysis in future studies. Participation in groups and support networks is also important in the aging process; thus, alcohol and tobacco consumption could be accompanied by participation.

Nutritional status is also associated with oral health.[13] The findings showed that being at risk of edentulism increased the risk of malnutrition. Therefore, interventions to prevent malnutrition and tooth loss are needed. Vigorous and moderate physical activities are related to lifestyle, and their relationship with edentulism has been reported previously.[46] The findings of the present study demonstrated the relationship between a healthy lifestyle and tooth loss. Although vigorous physical activity lost significance in the final model, it remained an independent factor. Moderate activity was significant; therefore this variable should be analyzed in association with edentulism in future studies.

This study has several key findings. Among these was the relationship between the three determinants of active aging and dental loss. The presence of good oral health in older adults can be highlighted in a lot of aspects of daily life, specifically their behavioral and personal determinants and access to health services.

Public policy plays a leading role in preserving dental structures. One of the main goals of the WHO and various dental associations is to retain at least 20 teeth by 80 years of age.[47] This is a challenge for Colombian public policy if we continue to treat dentistry separately from geriatrics and gerontology. Innovative concepts and more holistic ways of addressing challenges are required. The complexity framework could be one way to better understand problems in dentistry.[48] The findings in this study provide the most robust analysis of edentulism in Colombia. This study also contributes significantly from the perspective of geriatrics and gerontology because the presence and absence of teeth require different analyses in the 21st century. Current oral health problems must be analyzed from a multicausality perspective.[10] The information in this study will be useful for subsequent theoretical analyses of aging and for the development of more holistic public policies to preserve teeth. A lower prevalence of edentulism is expected in future generations. Previous approaches involved the development and understanding of problems from the perspective of active aging and actions to improve health outcomes.[49]

Active aging is a complex theoretical framework, and the multiple disabilities that become evident due to the interrelation of the various determinants are key to highlighting, in this case, that personal and behavioral determinants and the use and access to health services are related to edentulism in older adults. Based on the findings in the present study, Colombian public policy must recognize the possibility of different public policies and interventions. Dentistry cannot continue to be viewed from an involuted perspective of the oral cavity, and broadening the vision to different scenarios is important.

This study has several limitations that merit discussion regarding their importance in the aging process. The cross-sectional nature of SABE does not allow personal determinants, behavioral determinants, or access to oral healthcare to be established as the cause of the observed tooth loss. While caries and periodontitis are usually considered relevant causes of tooth loss, they were not considered in this study.[50] A full oral cavity examination was not feasible during the study; however, complete dental presence or absence was an easily self-reported variable. A major strength of this study is the robustness of its design. The carefully selected and validated indicators, indices, and questions used in the survey, which were applied to a large representative sample of the Colombian population, yielded more consistent findings. More prospective studies on the active aging framework, its relationship to oral health, and its contribution to well-being are needed.

The results of this study promote the development of a holistic interpretation of oral edentulism among older adults. This population should be included in programs aimed at maintaining optimal oral health.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, BG, AGM; Data curation, BG; Investigation, BG, AGM, IA; Methodology, BG, AGM, IA; Project administration, BG, AGM, IA; Supervision, BG, AGM, IA; Writing–original draft, BG, AGM, IA; Writing–review & editing, BG,AGM, IA.

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Case-Finding for Sarcopenia in Community-Dwelling Older Adults: Comparison of Mini Sarcopenia Risk Assessment with SARC-F and SARC-CalF

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Background: We compared the diagnostic performance of the short five-item and full seven-item Mini Sarcopenia Risk Assessment Questionnaire (MSRA-5 and MSRA-7) against the Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls (SARC-F) and SARC-F with calf circumference (SARC-CalF) scales for sarcopenia in healthy community-dwelling older adults. **Methods:** We conducted a post-hoc cross-sectional secondary data analysis of a prospective cohort study, using data from 230 older adults (mean age 67.2±7.4 years, 92% Chinese, and 73% female) from the "Longitudinal Assessment of Biomarkers for characterization of early Sarcopenia and Osteosarcopenic Obesity in predicting frailty and functional decline in community-dwelling Asian older adults Study" (GeriLABS-2) conducted between December 2017 and March 2019 in Singapore. We performed receiver operating characteristic curve analysis to ascertain the area under the curve (AUC) for sarcopenia diagnosis using the Asian Working Group for Sarcopenia 2019 consensus criteria. We applied the DeLong method to compare the AUCs of the four instruments. **Results:** The MSRA-5 and MSRA-7 demonstrated poor diagnostic performance (AUC of 0.511, 95% confidence interval [CI] 0.433–0.589 and AUC of 0.526, 95% CI 0.445– 0.606, respectively), compared to that in SARC-CalF (AUC of 0.739, 95% CI 0.671–0.808) and SARC-F (AUC of 0.564, 95% CI 0.591–0.636). The SARC-CalF demonstrated significantly superior discriminatory ability compared to that in the SARC-F, MSRA-5, and MSRA-7 (all $p<0.01$). The MSRA-5 demonstrated lower sensitivity (0.464) and specificity (0.597) than in the SARC-CalF (0.661 and 0.738, respectively), whereas the MSRA-7 had higher specificity (0.887) and lower sensitivity (0.145). **Conclusion:** The poor diagnostic performances of the MSRA-5 and MSRA-7 in our study suggest limitations of self-reported questionnaires for assessing general and dietary risk factors for sarcopenia in healthy and culturally diverse community-dwelling older adults. Studies in different populations are needed to ascertain the utility of the MSRA for the community detection of sarcopenia.

Key Words: Sarcopenia, Frail elderly, Diagnosis

INTRODUCTION

Sarcopenia, an age-related, progressive, and generalized skeletal muscle disorder,[1] is associated with adverse health and health utilization outcomes, including falls,[2] health-related quality of life,[3] hospitalization, healthcare costs,[4] and mortality.[5] The Asian Working Group for Sarcopenia (AWGS) 2019 consensus[1] updated the diagnostic algorithm for sarcopenia to emphasize case findings for the early identification of people at risk for sarcopenia in community settings without access to advanced diagnostic equipment.[1] The AWGS 2019 recommends calf circumference, Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls (SARC-F), and SARC-F with calf circumference (SARC-CalF) scales as case findings in community settings.

Three self-report questionnaires have been validated for community case findings of sarcopenia. The SARC-F,[6] a five-item questionnaire, is characterized by low sensitivity and high specificity.[7-9] The SARC-CalF[10] measures calf circumference in addition to the SARC-F, with studies suggesting improved sensitivity. More recently, the Mini-Sarcopenia Risk Assessment Questionnaire (MSRA) was validated in an Italian population of community-dwelling older adults.[11] Unlike the SARC-F and SARC-CalF, the MSRA evaluates self-reported general and nutritional risk factors for sarcopenia. The two versions of the MSRA are the full seven-item version (MSRA-7) and a short five-item version (MSRA-5), omitting the two questions on dairy and protein intake. The original validation study developed the short version after dairy and protein intake items were not associated with sarcopenia.

Compared with the SARC-F, which is a self-reported screening tool with low sensitivity, and the SARC-CalF, which requires calf circumference measurement, the MSRA purports to be a self-reported questionnaire with higher sensitivity that does not require additional measurements. Thus, whether the MSRA is a good screening test in addition to the current repertoire of screening tools warrants investigation. In two Asian studies involving frail older adults from assisted-living facilities and nursing homes,[12] the SARC-CalF demonstrated significantly better diagnostic performance for sarcopenia than in the MSRA-5, MSRA-7, and SARC-F. Three studies examined the use of the MSRA-5 and MSRA-7 among community-dwelling older adults in Poland,[13] China,[14] and Thailand,[15] respectively. In the Polish study, the SARC-CalF had the best diagnostic performance compared to that in the MSRA-5, MSRA-7, and SARC-F. In the Chinese and Thai studies, the MSRA-5 and MSRA-7 demonstrated higher sensitivity but lower specificity than in the SARC-F. In all three studies, the MSRA-5 had a better diagnostic performance for sarcopenia than in the MSRA-7, alluding to possible cultural influences attenuating the utility of the nutritional questions.

To better evaluate the effectiveness of the MSRA as a community case-finding tool for sarcopenia, we must understand its utility in diverse settings. First, studies examining the diagnostic performance of the MSRA-5 and MSRA-7 in healthy community-dwelling older adults, in whom early detection of sarcopenia may arguably be even more critical, are lacking. In previous studies involving community-dwelling older adults,[13-15] the average gait speed was less than the AWGS 2019 recommended cut-off of 1 m/s, suggesting that participants may be less robust despite community-dwelling. A Thai study involving participants recruited from a medical outpatient clinic reported a higher prevalence of sarcopenia (22.7%), with 69.6% of participants having a gait speed of < 1 m/s. Secondly, it is important to ascertain if the attenuated performance of the MSRA-7 vis-à-vis the MSRA-5 applies to other Southeast Asian populations, where the diet does not typically include the regular consumption of dairy products. This provided the impetus for our study, which examined and compared the diagnostic performance of the MSRA-5 and MSRA-7 with the SARC-F and SARC-CalF among healthy community-dwelling older adults in Singapore.

MATERIALS AND METHODS

Study Population

We performed a post-hoc cross-sectional secondary data analysis of the "Longitudinal Assessment of Biomarkers for characterization of early Sarcopenia and Osteosarcopenic Obesity in predicting frailty and functional decline in community-dwelling Asian older adults Study" (GeriLABS-2). The GeriLABS-2 is a prospective cohort study involving cognitively intact and functionally independent community-dwelling adults aged 50 years and older in Singapore. The study design has been previously described.[16,17] Briefly, the inclusion criteria were (1) age 50–99 years at study enrollment, (2) community dwelling, and (3) independence in both basic and instrumental activities of daily living (IADL). The exclusion criteria were cognitive impairment (prior diagnosis of dementia or modified Chinese version of the Mini-Mental State Examination [mCMMSE] score ≤21[18]), inability to walk 8 m independently, or being a resident in long-term residential care. Ethical approval was obtained from the domain-specific review board of the National Healthcare Group (NHG DSRB Reference: 2017/00850). Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[19]

Data Collection

Demographic data, anthropometric measurements (standing height, body weight, calculated body mass index, and calf circumference), and cardiovascular health data were collected. Cognition was assessed using the mCMMSE.[18] Functional status was assessed using the Barthel activities of daily living (ADL) index[20] and the Lawton and Brody IADL index.[21] Physical function was assessed using the Short Physical Performance Battery (SPPB), maximal hand grip strength using a hydraulic hand dynamometer, usual gait speed on the 3-m walk test, and the five-time chair-stand test. Other questionnaires obtained at baseline included the Mini Nutritional Assessment (MNA)[22] and the Frenchay Activity Index (FAI).[23] The AWGS 2019 consensus criteria[1] were used to diagnose sarcopenia. This required the presence of (1) low muscle strength (< 28 kg for men and < 18 kg for women measured using

a hydraulic hand dynamometer (North Coast Exacta Hydraulic Hand Dynamometer; North Coast Medical Inc., Morgan Hull, CA, USA) and/or low physical performance (as measured by usual gait speed < 1.0 m/s on the 3-m walk test) and (2) low muscle mass. As previously described,[17] we measured the height-adjusted appendicular lean mass using dual-energy X-ray absorptiometry (DXA) (Discovery APEX 13.3; Hologic, Bedford, MA, USA). Frailty was assessed using the Fatigue, Resistance, Ambulation, Illness, and Loss of weight (FRAIL) scale, a five-item self-report questionnaire,[24] and the modified Fried phenotypic criteria, a five-item scale comprising both self-report items and objective measurements.[25,26]

MSRA Questionnaire

The Chinese version of the MSRA[27] (Table 1) comprises seven items in two broad categories: (1) general assessment (four questions evaluating participant age, activity level, hospitalization, and weight loss) and (2) dietary assessment (three questions evaluating the consumption of protein and dairy and the number of meals).[11] Items #1–7 are scored and summed up to a total of 0–40 points for the MSRA-7 questionnaire, while Items #1–4 and 7 are scored and summed up to a total of 0–60 points for the MSRA-5 questionnaire. Participants with scores of ≤ 30 or ≤ 45 points are considered at risk for sarcopenia using the MSRA-7 and MSRA-5, respectively.

As the MSRA was not directly administered to the participants at the time of enrolment, appropriate questions available from the baseline data were approximated to the MSRA. Question #3 of the MSRA, which evaluates the activity level of participants, was approximated using the FAI item "In the last 3 months, how often have you walked outside for > 15 minutes?" Question #4, which evaluated a participant's number of daily meals, was approximated using the MNA item, "How many full meals do you eat daily?" Questions #5 and #6, which evaluated a participant's dairy and protein intake, respectively, were approximated using the respective components of the MNA item, which asked participants whether they consumed dairy or protein daily. Question #7, which evaluated a participant's weight loss, was approximated using the MNA item, which asked participants if they had experienced involuntary weight loss during the last 3 months.

Statistical Analyses

All analyses were performed using R statistical software (v4.2.1; https://www.R-project.org). Descriptive statistics were calculated using the gtsummary package (v1.1.6).[28] Receiver operating characteristic (ROC) curve analysis was performed using the plotROC package (v2.3.0),[29] and cut-off points were obtained using the OptimalCutpoints package (v1.1.5).[30] All statistical tests were

Table 1. The Mini Sarcopenia Risk Assessment 7 and 5 items (MSRA-7 and MSRA-5) questionnaires

	Score	
	MSRA-7	MSRA-5
1. How old are you?		
≥ 70 years	0	0
< 70 years	5	5
2. Were you hospitalized in the last year?		
Yes, and more than one hospitalization	0	0
Yes, one hospitalization	5	10
No	10	15
3. What is your activity level?		
I'm able to walk less than 1,000 m	0	0
I'm able to walk more than 1,000 m	5	15
4. Do you eat 3 meals per day regularly?		
No, up to twice per week I skip a meal (for example I skip breakfast or I have only tea or soup for dinner)	0	0
Yes	5	15
5. Do you consume any of the following?		
Milk or dairy products (yogurt) but not every day	0	-
Milk or dairy products (yogurt) at least once per day	5	-
6. Do you consume any of the following?		
Poultry, meat, fish, eggs, legumes, ragout or ham, but not every day	0	-
Poultry, meat, fish, eggs, legumes, ragout or ham at least once per day	5	-
7. Did you lose weight in the last year?		
> 2 kg	0	0
≤ 2 kg	5	10

two-tailed, with $p < 0.05$ considered statistically significant.

ROC curve analysis was performed to ascertain the area under the curve (AUC), using the AWGS 2019 diagnostic criteria as the reference standard. The DeLong method was used to compare the AUCs of the four instruments. The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated. We derived the optimal cut-off points using the Youden Index, which was compared with the validated cut-offs in the original study.

RESULTS

We analyzed the data of 230 participants with a mean age of 67.2 ± 7.4 years, education of 10.8 ± 4.4 years, and mCMMSE score of 26.1 ± 1.7. The participants were predominantly female (73%) and of Chinese ethnicity (86% males, 95% females). The women were younger (mean age 66 ± 7 years) compared to men (mean age 69 ± 8 years) (Table 2). Overall, the participants were functionally independent, with a mean Barthel's score for basic ADL of 98.1 ± 3.3 and Lawton's score for IADL of 22.7 ± 0.5. In this study, 23% and 38% of female and male participants, respectively, met the AWGS 2019 consensus criteria for sarcopenia. The prevalence rates of participants who were classified as robust, pre-frail, and frail were 52%, 44%, and 3.9% for the modified Fried scale and 85%, 15%, and 0% for FRAIL, respectively. The high average gait speed (1.17 ± 0.23 m/s) and low prevalence of frailty (3.9% for Fried and 0% for FRAIL) reflected the relatively robust health of the study participants. The mean SARC-F, SARC-CalF, MSRA-5, and MSRA-7 scores were 0.45 ± 0.74, 3.3 ± 4.5, 58.0 ± 9.0, and 33.0 ± 4.8, respectively.

Table 3 shows the results of comparisons of the diagnostic performances of the sarcopenia case-finding tools with the AWGS 2019 diagnostic criteria. The SARC-CalF demonstrated the highest discriminatory ability compared to the other three case-finding tools, with an AUC of 0.739 (95% confidence interval [CI] 0.671–0.808) (all $p < 0.001$). Conversely, the MSRA-5 and MSRA-7 did not perform well, with AUCs of 0.511 (95% CI 0.433–0.589) and 0.526 (95% CI 0.445–0.606), respectively. The SARC-F had an AUC of 0.636 (95% CI 0.591–0.636). The AUCs of the SARC-F, MSRA-5, and MSRA-7 did not differ significantly ($p = 0.308$ SARC-F vs. MSRA-5; $p = 0.449$ SARC-F vs. MSRA-7; $p = 0.614$ MSRA-5 vs. MSRA-7) (Fig. 1).

Using the Youden index, the SARC-CalF demonstrated the highest sensitivity (0.661) and specificity (0.738). The MSRA-7 had a higher specificity (0.887) but lower sensitivity (0.145), whereas the MSRA-5 had a comparable sensitivity (0.597) but a lower specificity (0.464). The SARC-CalF demonstrated the highest positive likelihood ratio (2.525) and the lowest negative likelihood ratio (0.459). Both the MSRA-5 and MSRA-7 had lower PPV and NPV than those in the SARC-F and SARC-CalF.

Comparison of the validated cut-off points of the four case-finding tools to the Youden cut-off points revealed optimal cut-off points for the MSRA-5, SARC-F, and SARC-CalF that were more inclusive than the validated cut-off points, reflecting the more robust profile of our study participants. For example, participants were considered to be at high risk for sarcopenia if their MSRA-5 score was < 60 using the Youden cut-off point compared to the validated cut-off point of 45.[11] Only the MSRA-7 demonstrated a more stringent threshold, with a Youden cut-off of 25, compared with the validated cut-off point of 30.[11] None of the participants scored > 3 on the SARC-F, which has a validated cut-off point of 4.[6]

Table 4 summarizes the individual responses to the MSRA-5 and MSRA-7 questionnaires analyzed for the presence of sarcopenia according to the AWGS19 diagnostic criteria. Of the seven

Table 2. Baseline characteristics of GeriLABS-2 patients

Characteristic	Male (n = 63)	Female (n = 167)
Age (y)	69 ± 8	66 ± 7
Race		
Chinese	54 (86)	158 (95)
Malay	1 (1.6)	1 (0.6)
Indian	3 (4.8)	7 (4.2)
Eurasian	3 (4.8)	1 (0.6)
Others	2 (3.2)	0 (0)
Years of education	12.6 ± 3.7	10.1 ± 4.4
Number of cardiovascular risk factors	1.90 ± 1.48	1.04 ± 0.97
Weight (kg)	66 ± 10	57 ± 8
Height (m)	1.66 ± 0.07	1.54 ± 0.05
Calculated BMI (kg/m^2)	23.9 ± 3.5	23.9 ± 3.1
Barthel's basic ADLs (0–100)	100.0 (100.0–100.0)	100.0 (95.0–100.0)
Lawton's IADLs (0–23)	23.0 (22.0–23.0)	23.0 (22.0–23.0)
Chinese Modified MMSE (0–28)	26.0 (25.0–27.0)	26.0 (25.0–28.0)
Fried scale		
Not frail	25 (40)	94 (56)
Pre-Frail	33 (52)	69 (41)
Frail	5 (7.9)	4 (2.4)
Calf circumference (cm)	35.37 ± 3.79	34.58 ± 2.94
Gait speed (m/s)	1.16 ± 0.27	1.17 ± 0.21
Total SPPB score (0–12)	12.0 (11.0–12.0)	12.0 (11.0–12.0)
Handgrip strength (kg)	32 ± 7	20 ± 4
Diagnosis of sarcopenia based on AWGS19 Criteria	24 (38)	38 (23)

Values are presented as mean±standard deviation or number (%) or median (interquartile range).
BMI, body mass index; ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery; AWGS19, Asian Working Group for Sarcopenia 2019.

Table 3. Comparison of the four case-finding tools

Variable	AUC (LL, UL)	Type	Score	Sensitivity	Specificity	PPV	NPV	LR	
								Negative	Positive
MSRA-5	0.511 (0.433, 0.589)	Youden	60	0.597	0.464	0.291	0.757	0.868	1.114
		Validated	45	0.194	0.839	0.308	0.738	0.961	1.204
MSRA-7	0.526 (0.445, 0.606)	Youden	25	0.145	0.887	0.321	0.738	0.964	1.284
		Validated	30	0.435	0.595	0.284	0.741	0.948	1.076
SARC-F	0.564 (0.491, 0.636)	Youden	1	0.419	0.708	0.347	0.768	0.820	1.438
		Validated	4	0.000	1.000	0.000	0.730	1.000	NA
SARC-CalF	0.739[a] (0.671, 0.808)	Youden	3	0.661	0.738	0.482	0.855	0.459	2.525
		Validated	11	0.194	0.946	0.571	0.761	0.852	3.613

MSRA-5, Mini-Sarcopenia Risk Assessment Questionnaire 5 items; MSRA-7, Mini-Sarcopenia Risk Assessment Questionnaire 7 items; SARC-F, Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls; SARC-CalF, SARC-F with calf circumference; AUC, area under the curve; LL, lower limit; UL, upper limit; PPV, positive predictive value; NPV, negative predictive value; LL, likelihood ratio.
[a]Significant ($p<0.001$) using DeLong method when compared against SARC-F, MSRA-5 and MSRA-7.

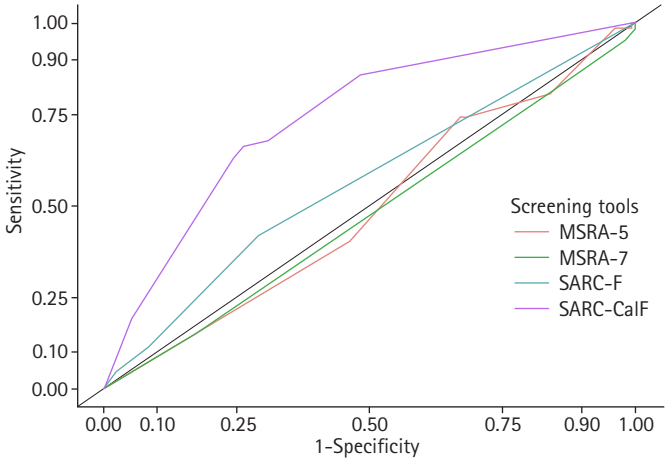

Fig. 1. Receiver operating characteristic curve of the four sarcopenia screening tools. MSRA-5, Mini-Sarcopenia Risk Assessment Questionnaire 5 items; MSRA-7, Mini-Sarcopenia Risk Assessment Questionnaire 7 items; SARC-F, Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls; SARC-CalF, SARC-F with calf circumference.

questions, only Question #1, which evaluates age, differed significantly between those with and without sarcopenia ($p<0.01$). Question #7, which evaluated weight loss, tended towards statistical significance ($p=0.087$). However, Questions #2–6 demonstrated no differences between participants with and without sarcopenia.

DISCUSSION

Early detection via community case-finding is crucial for identifying patients with sarcopenia.[1] Our study findings build upon the existing body of evidence by examining the diagnostic performance of the MSRA among healthy community-dwelling older adults in a Southeast Asian population. Unlike earlier studies in less robust older adults,[12,31] our results suggest that, compared to the SARC-CalF and the SARC-F, MSRA5 and MSRA7 did not perform well in community case detection. Furthermore, the MSRA-5 had lower sensitivity, negative predictive value, and negative likelihood ratio than in the SARC-F or SARC-CalF, suggesting that it is likely to miss participants with sarcopenia. The MSRA-5 had lower specificity, positive predictive value, and positive likelihood ratio than those in the SARC-F or SARC-CalF, suggesting that it will likely result in more false-positive findings. Our study did not replicate the results of earlier studies, in which the MSRA-5 demonstrated better diagnostic performance than in the MSRA-7.[14]

The unsatisfactory diagnostic performance of the MSRA questionnaires in our study indicates the diagnostic limitations of the MSRA questionnaire in healthy populations. Furthermore, the cut-offs validated in the original study differed from the derived cut-offs in our population, with our cut-offs generally lower thresholds for identifying sarcopenia, further corroborating the limitations of the MSRA as a screening tool in more robust older adult populations. This may be attributed to two factors. First, the questions may not directly reflect the risk of sarcopenia. While the SARC-F questions are based on the assessment of muscle strength, physical performance, and calf circumference, which adds a measure of muscle mass, the MSRA questions do not directly evaluate the components of sarcopenia. Instead, they evaluate the general and dietary risk factors that may contribute to the development of sarcopenia. This finding is particularly pertinent in the context of the relatively robust spectrum of older adults enrolled in our study. In our study, most healthy older adults scored well on the MSRA components. For instance, 98% of the participants could walk 1,000 m, while 90% ate protein. The analysis of the individual

Table 4. Comparison of individual questions of MSRA

Characteristic	Overall (n = 230)	Diagnosis of sarcopenia		p-value[a)]
		No (n = 168)	Yes (n = 62)	
SARC-F total score	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.074
SARC-CalF total score	1.0 (0.0–10.0)	0.0 (0.0–3.0)	10.0 (1.0–10.0)	< 0.001
MSRA-5 total score	60 (50–65)	60 (50–65)	60 (52–65)	0.8
MSRA-7 total score	35.0 (30.0–35.0)	35.0 (30.0–35.0)	35.0 (30.0–35.0)	0.5
MSRA Q1 (< 70 y)				0.004
≥ 70 y	84 (37)	52 (31)	32 (52)	
< 70 y	146 (63)	116 (69)	30 (48)	
MSRA Q2 (Hospitalization)				> 0.9
Yes, ≥ 2	0 (0)	0 (0)	0 (0)	
Yes, 1	13 (5.7)	10 (6.0)	3 (4.8)	
No	217 (94)	158 (94)	59 (95)	
MSRA Q3 (Able to walk)				0.6
Walk, < 1,000 m	5 (2.2)	3 (1.8)	2 (3.2)	
Walk, ≥ 1,000 m	225 (98)	165 (98)	60 (97)	
MSRA Q4 (Eats 3 meals)				0.7
No, up to 2x/wk	44 (19)	33 (20)	11 (18)	
Yes	186 (81)	135 (80)	51 (82)	
MSRA Q5 (Dairy)				0.9
Yes, not every day	124 (54)	90 (54)	34 (55)	
Yes, daily	106 (46)	78 (46)	28 (45)	
MSRA Q6 (Protein)				0.8
Yes, not every day	24 (10)	17 (10)	7 (11)	
Yes, daily	206 (90)	151 (90)	55 (89)	
MSRA Q7 (No weight loss)				0.087
Yes, > 2 kg	29 (13)	25 (15)	4 (6.5)	
No or low, ≤ 2 kg	201 (87)	143 (85)	58 (94)	

Values are presented as median (interquartile range) or number (%).
MSRA-5, Mini-Sarcopenia Risk Assessment Questionnaire 5 items; MSRA-7, Mini-Sarcopenia Risk Assessment Questionnaire 7 items; SARC-F, Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls; SARC-CalF, SARC-F with calf circumference.
[a)]Wilcoxon rank sum test, Pearson chi-squared test, and Fisher exact test.

component questions of the MSRA highlights that the MSRA questions may lack discriminatory ability for participants with and without sarcopenia.

Furthermore, in the Southeast Asian context, sociocultural influences on dietary questions may attenuate the utility of the MSRA as a sarcopenia case-finding tool. For instance, the consumption of milk or dairy products is relatively low among older people in Singapore. Up to 54% of older adults in our study did not eat dairy daily, in contrast to > 90% who reported daily dairy intake in the original validation study conducted in Italy,[11)] highlighting the salience of cultural differences in the dietary habits of older adults. The low base rate of dairy intake may attenuate the discriminatory ability of the questions in identifying the risk of sarcopenia in our participant population, who may have nutritional statuses and dietary norms different from those of older adults in Western countries.[32,33)]

The diagnostic performances did not differ between the MSRA-5 and MSRA-7 in this study. This finding is in contrast to three earlier studies that examined the use of the MSRA-5 and MSRA-7 in community-dwelling older adults,[13)] wherein the MSRA-5 demonstrated better diagnostic performance with higher specificity for sarcopenia than in the MSRA-7. The specificity of the MSRA-5 was lower than that of the MSRA-7 in our study, suggesting its diminished ability to rule out false-positive cases. This is likely attributable to the higher cut-off (< 60) for the MSRA-5 in our study population, comprising participants who were younger, more robust, and with less impaired MSRA-5 and MSRA-7 scores. This suggests that excluding dairy and protein intake items from the MSRA-5 may not confer an advantage in diagnostic performance in more robust older adult populations.

In summary, our results highlight the limitations of the MSRA as a sarcopenia case-finding tool in a relatively robust Southeast Asian population. However, these results have certain limitations. First, the selection of a relatively healthy Asian population limits the generalizability of the results to less robust or non-Asian populations. Further studies should be conducted in diverse populations to as-

certain the applicability of our findings to populations with different characteristics. Additionally, the MSRA questionnaires were not administered directly to the participants. Responses were approximated from other questionnaires, which may have impacted the accuracy of the responses obtained and reduced the diagnostic accuracy of the MSRA. Finally, while the original study was a longitudinal prospective cohort study of community-dwelling older adults, this was a cross-sectional secondary data analysis at the time of enrollment. Ongoing studies are exploring the predictive validity of the MSRA as a screening tool and its longitudinal association with the incidence of sarcopenia.

In conclusion, our study demonstrated the diagnostic limitations of the MSRA-5 and MSRA-7 for detecting sarcopenia in relatively healthy community-dwelling older adults in a Southeast Asian population. Among the four case-finding tools for sarcopenia, the SARC-CalF showed the best diagnostic performance in identifying sarcopenia in this population. Compared to the SARC-CalF, the MSRA-5 had comparable sensitivity but lower specificity, whereas the MSRA-7 had comparable specificity but lower sensitivity. The diagnostic performance did not differ between the MSRA-5 and MSRA-7.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, SC, JQC, WSL; Data curation, SC, WSL; Funding acquisition, WSL; Investigation, SC, WSL; Methodology, SC, JQC, ESL; Project administration, SC, WSL; Supervision, WSL; Writing-original draft, SC; Writing-review & editing, JQC, JC, JPL, WSL.

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Does Old Age Comprise Distinct Subphases? Evidence from an Analysis of the Relationship between Age and Activities of Daily Living, Comorbidities, and Geriatric Syndromes

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Background: Older individuals are usually treated as a homogenous group despite evidence that old age consists of distinct subphases. This observational study including 493 older patients aimed to identify differences among age subgroups of older persons. Receiver operating characteristic (ROC) curve analysis was then applied to identify the optimal age cutoff points to distinguish those age groups. **Methods:** Data were collected on the demographics of older patients, their medical and medication histories, dependence on activities of daily living (ADLs), and instrumental activities of daily living (IADLs). Non-parametric tests (Kruskal–Wallis and Mann–Whitney U tests) and ROC curves were used for statistical analysis. **Results:** The 65–79 and ≥80 years of age groups showed distinct frailty status, comorbidity, and dependency in ADLs. The median age to remain completely independent in IADLs was 76–79 years, while the median age for being free from geriatric syndromes was slightly higher (77–80 years) and reached 82 years for the absence of delirium, falls, and swallowing problems. In the ROC analysis, the optimal cutoff ages for the presence of frailty, cognitive impairment, and dependency in ADLs were 80–82 years. **Conclusion:** The 65–79 and ≥80 years of age groups differed significantly in numerous parameters, underscoring the need to address these distinct age groups differently, both for applying medical therapies and interventions, as well as for conducting health research.

Key Words: Aged, Aging, Activities of daily living, Cognitive dysfunction, Comorbidity, Frailty

INTRODUCTION

Old age has been described as a heterogeneous phase comprising distinct subphases,[1] even though it can be conceptualized as a single phase marked by constant quality.[2] For example, Baltes and Smith[1] proposed that age >80 years constitutes a separate life stage. Consistent with this statement, previous studies have demonstrated that people >80 years have significantly worse mobility,[3] an increased risk of physical dysfunction,[1] and more cognitive difficulties compared with younger age groups.[4] However, the various age categorization terminologies employed in different studies limit the comparability of research findings.[2]

For instance, Ouchi et al.[5] argued that the current definition of older persons is no longer consistent with the development of changes in physical function brought on by aging and advocated designating individuals aged 65–74 and >75 years as pre-old and old, respectively. Furthermore, other studies have suggested that the 65–74 and ≥75 years of age groups differ in mental and physical health.[6,7] The analysis of the surveys in these previous studies, initially divided the participants into age groups to explore age-related differences. In contrast, based on similarities in disease profiles and using clustering techniques, Geifman et al.[8] investigated

the feasibility of redefining age ranges and concluded that the 76–98 years of age group was distinct in terms of age-related diseases including Alzheimer disease, dementia, cataracts, and Parkinson disease. Chamberlain et al.[9] found that the median frailty index increased monotonically across the 60–69, 70–79, and 80–89 years age groups, with increasing frailty being associated with higher risks of emergency department visits, hospitalization, and all-cause mortality. The frailty index assesses the decline in physiological reserve and function in multiple organ systems, measured by the accumulation of deficits such as the presence of comorbidities and limitations in activities of daily living (ADLs). Zheng et al.[10] examined cognitive function trajectories in people aged 54–85 years, reporting that at the cohort level, cognitive functioning showed accelerating deterioration with age. Regarding disability in instrumental activities of daily living (IADLs), Sharashkina et al.[11] found that the prevalence of IADL dependence increased significantly with age in adults >65 years. In particular, 82.3% of people over the age of 85 years showed dependence in IADLs, compared to only 33% and 54.2% of those aged 65–74 years and 75–84 years, respectively.

Geriatric syndromes are associated with a variety of other factors in addition to age, including unhealthy lifestyles (smoking and alcohol use), exercise, diet, functional impairment, history of falls, comorbid diseases, medication use, sex, economy, culture, marital status, living conditions, and medical payment.[12-14] Additionally, the common risk factors for geriatric syndromes are causally related.[15] Among these, older age is a common risk factor for geriatric syndromes.[16-18] A literature review of the criteria and risk factors for geriatric syndromes identified age as one of four shared risk factors present in all geriatric syndromes examined.[16] Furthermore, age was the most important risk factor in a study by Ni et al.[14] that examined the factors influencing common geriatric syndromes.

Nevertheless, despite these reported age differences, most studies on older adults have classified and treated them as a homogenous and single group.[19] Because diseases[8] and geriatric syndromes[15] in older adults vary according to age, these populations must be properly classified to make accurate diagnostic and therapeutic decisions and implement appropriate interventions.

In this study, we hypothesized that old age comprises different subphases. Therefore, we conducted this study to determine whether there were differences between age subgroups of older adults in terms of geriatric syndromes (e.g., cognitive impairment, falls, delirium, swallowing problems, polypharmacy, and sociability), comorbidity, and dependency in ADLs (e.g., bathing and dressing) and IADLs (e.g., cooking, housekeeping, shopping, and assistance in administering medications). Additionally, we used receiver operating characteristic (ROC) curve analysis to identify the optimal cutoff points for patient age to differentiate those experiencing cognitive impairment, frailty, and dependency in ADLs from those who do not.

MATERIALS AND METHODS

Sample and Data Collection

We conducted this observational study between September 2020 and December 2021 among patients ≥65 years of age who were consecutively admitted through the emergency department at the General and Oncological Hospital of Kifissia "Agioi Anargyroi." Patients' demographic information (age, sex, marital status, level of education, social interactions, living arrangements), comorbidities, number and type of medications taken, history of falls, delirium, swallowing problems, frailty, and cognitive status, and dependence in ADLs and IADLs were all collected at the time of admission. The first page of the survey included a cover letter explaining the study's purpose and guaranteeing the participants' confidentiality and anonymity in the final data report. After the patients were fully informed, one of the three research team members who collected the data asked them questions; in cases where patients were unable to communicate, their relatives provided written consent. Data regarding comorbidities, functional status, and cognitive status were obtained for the period before the onset of the illness that led to hospital admission. To estimate a score for frailty, cognitive status, comorbidity, and the ability to perform ADLs, the three research team members who collected the data interviewed the patients and/or their caregivers using relevant study measurements. The researchers completed the patient forms in an average of 30 minutes.

Study Instruments

We used the Barthel Index (BI) to assess how well the patients performed ADLs. The BI measures functional independence in ten areas of mobility and personal care on an ordinal scale ranging from 0 to 100, in which a higher score indicates a greater capacity to function independently.[20] BI scores can be divided into four groups: no dependency (BI ≥95), mild-moderate dependency (BI 90–65), moderate-severe dependency (BI 60–25), and absolute dependency (BI ≤20).[21]

The Global Deterioration Scale (GDS) is used to evaluate a patient's cognitive status. The GDS is a seven-point scale, with 1 representing no cognitive decline and 7 representing extremely severe cognitive decline and dementia.[22] We divided the GDS scores into three grades for subgroup analysis: no cognitive impairment (GDS 1), mild-moderate cognitive impairment (GDS

2–5), and severe-very severe cognitive impairment (GDS ≥ 6).[23]

We assessed comorbidity using the Charlson Comorbidity Index (CCI). The CCI evaluates most significant medical comorbidities. Each of the 17 comorbidity categories, including age groups, was assigned a score ranging from 1 to 6. The individual scores of each patient were summed to obtain the total comorbidity score.[24] Frailty status was assessed using both the revised nine-item Clinical Frailty Scale (CFS)[25] and the Frail-VIG Index,[23,26] where VIG is the Spanish/Catalan abbreviation for Comprehensive Geriatric Assessment. The CFS is a judgment-based frailty measure that assigns an overall fitness or frailty score to older adults, ranging from 1 (very fit) to 9 (terminally ill patients).[25] The Frail-VIG Index is a simple tool based on a comprehensive geriatric assessment. It includes 22 questions (20 dichotomous and two scaled) that examine various parameters of frailty syndrome (performance of daily activities; nutrition; cognitive, emotional, and social functioning; the presence of geriatric syndromes; the presence of severe symptoms; and comorbidities).

Research Ethics

This study was conducted according to the ethical principles of the Declaration of Helsinki (revised in 2013). The Institutional Ethical and Scientific Committee of General and Oncology Hospital of Kifissia "Agioi Anargyroi" granted initial ethical approval for the study (Approval No. 1494; date, December 4, 2019). The second approval was obtained from the National and Kapodistrian University of Athens School of Medicine Committee on Bioethics and Deontology (Approval No. 284; date, May 25, 2020).

Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[27]

Statistical Analysis

Categorical data are presented as counts and percentages. We applied the Shapiro–Wilk test to evaluate the normality of continuous variables. All continuous variables were skewed and expressed as medians and interquartile ranges (IQRs). Differences in mean ranks in CFS, Frail-VIG Index, CCI, and BI between age groups (65–69, 70–74, 75–79, 80–84, 85–89, and ≥ 90 years) were assessed using the Kruskal–Wallis test, the non-parametric analog of one-way analysis of variance for skewed data. Dunn's pairwise tests were performed and adjusted using the Bonferroni correction for multiple testing. We also used Kruskal–Wallis tests to assess differences in patient age between categories based on walking aid use, cognitive deterioration, sociability, and dependency in some IADLs (e.g., shopping, cooking). We assessed differences in patient age between groups based on the presence of geriatric syndromes or the need for assistance in the remaining IADLs (assistance with financial matters or in preparing or administering medications) using the Mann–Whitney U test. $p \leq 0.05$ was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM, Armonk, NY, USA).

We used receiver operating characteristic (ROC) curve analysis to determine the optimal cutoff points for patient age to distinguish (1) cases with mild-to-severe cognitive impairment from cases with no cognitive impairment, as measured by the GDS; (2) non-frail patients from patients with frailty, as measured by the CFS; and (3) functionally independent patients from patients with mild to severe dependency, as measured by the BI. The ROC analysis addressed each probability as a cutoff point for age. It estimated the proportion of patients with mild-to-severe cognitive impairment, frailty, or dependency in ADLs correctly classified as positive (true positive rate, sensitivity), and the proportion of patients with no cognitive impairment, frailty, or dependency correctly classified as negative (true negative rate, specificity). The ROC curves plotted the sensitivity (y-axis) against 1–specificity (x-axis). The area under the ROC curve (AUC) was used to discriminate between patients with mild-to-severe cognitive impairment, frailty, or dependency and those with no cognitive impairment, frailty, or dependency. The AUC values range from 0.5 (no diagnostic ability or prediction possible) to 1 (perfect diagnostic ability or prediction) and should be as large as possible. An AUC value of 0.9–1.0 represents outstanding discrimination, 0.8–0.9 excellent, 0.7–0.8 acceptable, 0.7–0.5 poor, and ≤ 0.5 failing discrimination.[28] We applied statistical tests to determine whether the AUC differed significantly from 0.5, which corresponds to an AUC plot of the 45° diagonal line and represents a random classification. We performed the ROC curve analysis and optimal cutoff point selection in the diagnostic tests using the Optimal Cutpoints package in R.[29]

RESULTS

During the study period, 504 patients aged ≥ 65 years were admitted to the emergency department of the hospital. Six patients (three men and three women) were unwilling to participate in the study. Five patients (three men and two women) were unable to communicate and their caregivers (one man and four women) refused to participate in the study. Finally, we enrolled 493 patients in this study. The median age of the patients was 82 years (IQR, 75–88 years). Among these participants, 239 were women (48.5%) and 254 were men (51.5%). The characteristics of the participants are presented in Table 1.

Examining of the differences in frailty status, comorbidity, and dependency in ADLs across the age groups demonstrated minor

Table 1. Participants' characteristics (n=493)

Characteristic	Value
Sex	
Male	254 (51.5)
Female	239 (48.5)
Marital status	
Married	247 (50.2)
Unmarried	14 (2.8)
Divorced	15 (3.0)
Widowed	217 (44.0)
Educational level	
Primary	286 (58.0)
Secondary	126 (25.6)
Technological education institution	49 (9.9)
University	32 (6.5)
Clinical Frailty Scale (CFS)	
Non-frail (CFS 1–3)	129 (26.1)
Pre-frail (CFS 4)	59 (12.0)
Frail (CFS 5–9)	305 (61.9)
Frail VIG index	
Non-frail (Frail VIG index < 0.25)	196 (39.8)
Frail (Frail VIG index > 0.25)	297 (60.0)
Living alone	
Yes	78 (15.8)
No	415 (84.2)
Barthel Index (BI)	
No dependency (BI ≥ 95)	179 (36.3)
Mild-moderate dependency (BI 90–65)	136 (27.6)
Moderate-severe dependency (BI 60–25)	87 (17.6)
Absolute dependency (BI ≤ 20)	91 (18.5)
Global Deterioration Scale (GDS)	
No cognitive impairment (GDS 1)	283 (57.4)
Mild-moderate cognitive impairment (GDS 2–5)	130 (26.4)
Severe-very severe cognitive impairment (GDS ≥ 6)	80 (16.2)
Age (y)	82.0 (75–88)
Medication number	5.00 (3–8)
Charlson Comorbidity Index	5.00 (4–7)

Values are presented as number (%) or median (interquartile range).

differences in three groups of older patients (65–69, 70–74, and 75–79 years); therefore, we categorized them into a single group. After 80 years of age, the age groups showed more significant differences in most cases (Table 2).

Age differed significantly between participants who did and did not require assistance in IADLs and who presented with and without any geriatric syndrome. More specifically, those needing assistance with IADLs differed significantly in age from those who did not. The median ages for assistance from another adult and independence in the examined activities were 82–85 years and 76–79 years, respectively. Moreover, patients with geriatric syndromes differed significantly in median age from those without such syndromes (77–82 years for the absence of geriatric syndromes vs. 83–86 years for the presence of geriatric syndromes) (Table 3).

ROC Analysis

Using the Optimal Cutpoints package in R, patient age displayed acceptable diagnostic accuracy or ability to discriminate between patients with mild-to-severe cognitive impairment and patients without cognitive impairment, with an AUC of 0.718, standard error (SE) of 0.023, z-statistic of 9.387, $p < 0.001$, and 95% confidence interval (CI) of 0.673–0.764. Thus, the probability that the age of a patient drawn at random from the population with a positive condition (mild-to-severe cognitive impairment) was greater than that of another individual drawn at random from the population with a negative condition (no cognitive impairment) was 0.718. Implementing a criterion derived from the generalized Youden index, assuming a 50% prevalence rate of mild-to-severe cognitive impairment in the patient population, and considering that a false negative (FN) outcome was as costly as a false positive (FP) outcome, the optimal cutoff point for patient age was 82

Table 2. Differences in CFS, Frail VIG Index, CCI, and Barthel Index across subgroups of older adults based on age (n=493)

	Age groups						p-value
	65–69 y (n = 63)	70–74 y (n = 51)	75–79 y (n = 76)	80–84 y (n = 103)	85–89 y (n = 114)	≥ 90 y (n = 86)	
CFS score							≤ 0.001
Median (IQR)	4 (2–9)	4 (3–6)	4 (3–7)	6 (3–7)	6 (4.75–7)	7 (6–8)	
Mean rank	214.8[a,b]	195.6[a,b]	200.8[a]	248.3[a,b]	265.3[b,c]	316.0[c]	
Frail VIG Index							≤ 0.001
Median (IQR)	0.16 (0.08–0.36)	0.20 (0.08–0.36)	0.22 (0.09–0.32)	0.28 (0.16–0.44)	0.36 (0.24–0.48)	0.44 (0.32–0.52)	
Mean rank	180.0[a]	186.5[a]	191.7[a]	244.4[a,b]	282.1[b,c]	337.4[c]	
CCI score							≤ 0.001
Median (IQR)	4 (3–8)	5 (4–7)	4.5 (4–6)	6 (5–7)	6 (5–7)	6 (5–7)	
Mean rank	175.7[a]	239.1[a,b]	198.6[a]	272.9[b]	282.7[b]	268.3[b]	
Barthel Index							≤ 0.001
Median (IQR)	100 (70–100)	95 (75–100)	95 (75–100)	85 (45–95)	75 (40–90)	42 (8.75–76.25)	
Mean rank	313.1[a]	310.0[a,b]	307.6[a]	245.9[b,c]	216.1[c]	150.0[d]	

CFS, Clinical Frailty Scale; CCI, Charlson Comorbidity Index; IQR, interquartile range.
Mean ranks were compared by using Kruskal-Wallis post hoc multiple comparison tests. Mean ranks with different letters (superscripts) are significantly different at $p<0.05$.

Table 3. Differences in mean rank for age groups of older adults based on the presence of geriatric syndromes and the dependency on instrumental activities of daily living (n=493)

	n	Age		p-value
		Median (IQR)	Mean rank	
Aid use				
No	241	79 (72.5–85)	198.1[a]	
Walking stick	87	83 (78–88)	259.8[b]	≤0.001
Frame	66	86 (81.75–91.25)	317.5[b]	
Chair or bedridden	99	86 (80–91)	307.8[b]	
Cooking				
Independent	231	78 (71–84)	190.2[a]	
With assistance	58	85 (77.75–88.25)	269.7[b]	≤0.001
Dependent	204	86 (81–91)	304.9[b]	
Housekeeping				
Independent	178	77 (71–82.25)	175.7[a]	
With assistance	94	83 (76–88)	248.6[b]	≤0.001
Dependent	221	86 (81–91)	303.8[c]	
Shopping				
Independent	150	76 (70–81)	161.4[a]	
With assistance	101	82 (75.5–87)	242.3[b]	≤0.001
Dependent	242	86 (81–90)	302.0[c]	
Assistance in preparing or administering medications				
No	238	79 (73–85)	201.2	≤0.001
Yes	255	85 (79–90)	288.8	
Assistance with financial matters				
No	178	77 (70.75–82)	167.1	≤0.001
Yes	315	85 (80–90)	292.1	
Degree of cognitive impairment				
No cognitive impairment	283	79 (72–85)	201.2[a]	
Mild-moderate cognitive impairment	130	86 (79–89.25)	294.5[b]	≤0.001
Severe-very severe cognitive impairment	80	87 (84–92)	332.1[b]	
Delirium				
No	411	82 (75–87)	238.6	0.003
Yes	82	85 (77.75–90)	288.9	
Falls				
No	382	82 (74–87)	235.5	0.001
Yes	111	84 (79–90)	286.6	
Polypharmacy				
No	186	80 (72–86)	213.5	≤0.001
Yes	307	83 (77–88)	267.3	
Swallowing problems				
No	408	82 (74–87)	235.7	≤0.001
Yes	85	85 (79.5–90.5)	301.1	
Socially engaged				
Frequent	116	77 (70–83)	172.2[a]	
Occasional	206	81.5 (75–87)	235.2[b]	≤0.001
Not	171	86 (81–91)	311.9[c]	

IQR, interquartile range.
Mean ranks were compared by using Mann-Whitney and Kruskal-Wallis post hoc multiple comparison tests. Mean ranks with different letters (superscripts) are significantly different at p<0.05.

years. Fig. 1 presents the Youden's metric function values for each age cutoff. This metric, which is used to assess the discriminatory ability of a cutoff point, relies on maximizing the Youden index (sensitivity + specificity – 1). The same age threshold was indicated by the maximum efficiency method for selecting optimal cutoffs, which maximized the efficiency or accuracy. The ROC curve

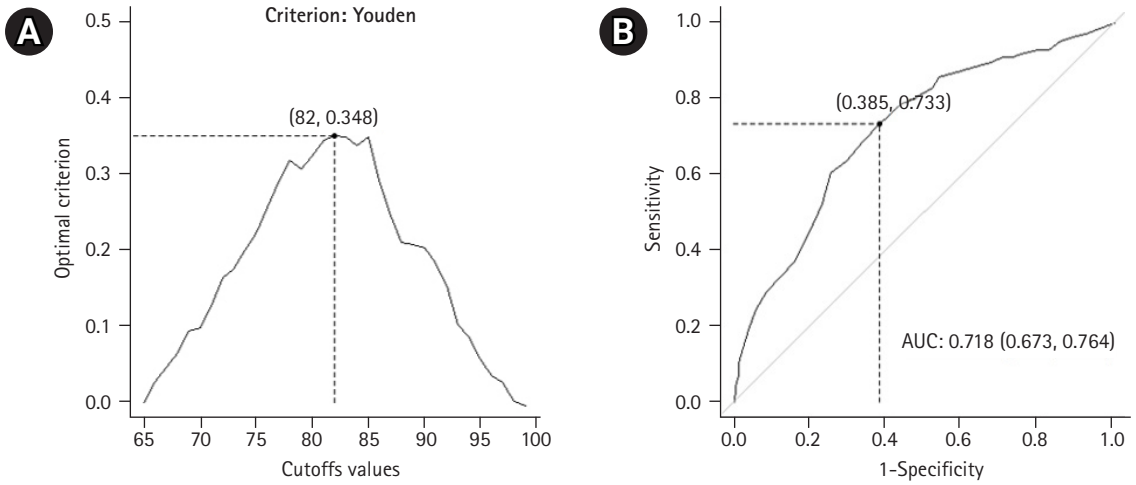

Fig. 1. Receiver operating characteristic (ROC) curve analysis for patients with cognitive impairments: (A) values of the Youden's metric function per age cutpoint (optimal value with coordinates) and (B) ROC curve, together with the optimal cutoff point for age and area under ROC curve (AUC), with 95% confidence interval.

Table 4. AUC, sensitivity, specificity, Youden index (optimal), and optimal cutoff thresholds (with 95% CI) for age distinguishing patients with and without mild to severe cognitive impairment, dependency, and frailty

	AUC (95% CI)	Youden index (optimal)	Optimal cutoff point for age (95% CI)	Sensitivity	Specificity
Cognitive impairment (GDS)	0.718 (0.673–0.764)	0.348	82 (78–85)	0.733	0.615
Dependency (Barthel Index)	0.735 (0.689–0.780)	0.268	82 (79–84)	0.678	0.721
Frailty (CFS)	0.731 (0.683–0.779)	0.151	80 (75–81)	0.712	0.659

GDS, Global Deterioration Scale; CFS, Clinical Frailty Scale; AUC, area under the curve; CI, confidence interval.

is shown in Fig. 1.

Using this cutoff age, we created a 2×2 table that included the disease status (negative, with no cognitive impairment vs. positive, with mild-to-severe cognitive impairment) and the test result (positive, age >81 years; negative, age ≤81 years). Based on patient age, this allowed us to correctly classify 61.5% of patients without cognitive impairment (specificity or true negative rate) and 73.3% of patients with mild-to-severe cognitive impairment (sensitivity or true positive rate) (Table 4).

Furthermore, 69.7% of patients with a negative test result (i.e., age ≤81 years) did not present with mild-to-severe cognitive impairment, while 65.6% of patients with a positive test result (i.e., age >81 years) did present with mild-to-severe cognitive impairment. The probability of a patient with mild-to-severe cognitive impairment having a positive test result was 0.656 (positive predictive value), representing an approximately 16% increase in the probability of the disease in the presence of a positive test. Similarly, the probability of a patient with mild-to-severe cognitive impairment having a negative test result was 0.303 (equal to 1–0.697; negative predictive value), which was associated with an approximately 20% decrease in the probability of disease in the presence of a negative test.

Regarding dependency, implementing a criterion derived from the generalized Youden index, assuming a 55% prevalence rate of mild-to-severe dependency in the patient population, and considering that an FN outcome was as costly as an FP outcome, the optimal cutoff for patient age was 82 years. Fig. 2 presents the Youden's metric function values for each age cutoff. The same threshold was indicated by the MaxEfficiency method for selecting optimal cutoffs that maximized efficiency or accuracy. The ROC curves are shown in Fig. 2. The AUC was 0.735 (SE=0.023, z-statistic=10.150, p<0.001, 95% CI 0.689–0.780).

Accordingly, we used this cutpoint to develop a 2×2 table that included the disease status (negative, with no dependency vs. positive, with mild to severe dependency) and the test result (positive, age >81 years; negative, age ≤81 years). Based on patient age, we correctly classified 72.1% of patients with no dependency (specificity or true negative rate) and 67.8% of patients with mild-to-severe dependency (sensitivity or true positive rate) (Table 4). Furthermore, 64.7% of patients who registered a negative test result (i.e., age ≤81 years) did not present with mild to severe dependency, while 74.8% of patients with a positive test result (i.e., age >81

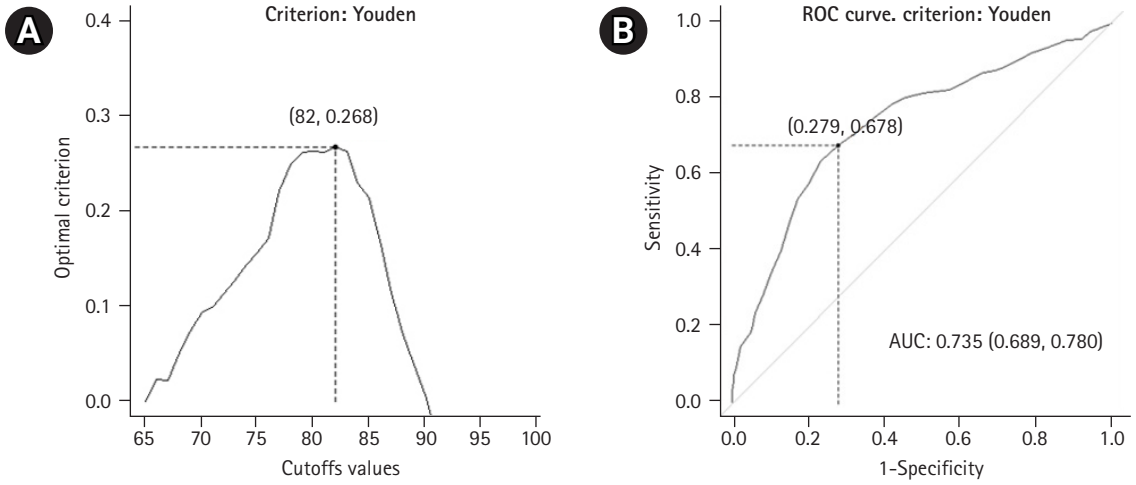

Fig. 2. Receiver operating characteristic (ROC) curve analysis for patients with dependency: (A) values of the Youden's metric function per age cutpoint (optimal value with coordinates) and (B) ROC curve, together with the optimal cutoff point for age and area under ROC curve (AUC), with 95% confidence interval.

years) did, in fact, present with mild to severe dependency. In terms of probabilities, the probability of a patient with mild-to-severe dependency having a positive test result was 0.748 (positive predictive value), representing an approximately 20% increase in the probability of the disease in the presence of a positive test. Similarly, the probability of a patient with mild-to-severe dependency having a negative test result was 0.353 (= 1–0.647, the latter value being the negative predictive value), which was associated with an approximately 20% decrease in the probability of the disease in the presence of a negative test.

Finally, regarding frailty, using a criterion derived from the generalized Youden index, assuming a 60% prevalence rate of frailty in the patient population, and considering that an FN outcome was as costly as an FP outcome, the optimal cutoff for patient age was 80 years. Fig. 3 presents the Youden's metric function values for each age cutoff. We obtained the same threshold using the maximum efficiency method. The ROC curves are shown in Fig. 3. The AUC was 0.731 (SE = 0.024, z-statistic = 9.450, $p < 0.001$, 95% CI 0.683–0.779).

Applying this cutpoint, we created a 2 × 2 table between disease status (negative, non-fr ail patients vs. positive, frail patients) and test result (positive, age > 79 years; negative, age ≤ 79 years). This allowed us to correctly classify 65.9% of patients with no frailty (specificity or true negative rate) and 71.2% of patients with frailty (sensitivity or true positive rate) based on patient age (Table 4). Furthermore, 60.4% of patients with a negative test result (i.e., age ≤ 79 years) did not present with frailty, while 75.8% of patients with a positive test result (i.e., age > 79 years) presented with frailty. The probability of a patient with frailty having a positive test result was 0.758 (positive predictive value), representing an approximately 16% increase in the probability of disease in the presence of a positive test result. Similarly, the probability of a patient with frailty having a negative test result was 0.396 (= 1–0.604), which was associated with an approximately 20% decrease in the probability of disease in the presence of a negative test.

DISCUSSION

The results of our study demonstrated that the age groups of 65–79 and ≥ 80 years of age groups differed in frailty status, comorbidity, and dependency in ADLs. Specifically, we observed that individuals aged 76–79 years included the median age at which individuals remained fully independent in IADLs. The median age for being free of geriatric syndromes was slightly higher, at 77–80 years. Notably, delirium, falls, and swallowing problems were not observed until 84–85 years of age. The results of the ROC analysis indicated an optimal age cutoff for the presence of frailty, cognitive decline, and dependency in ADLs of 80–82 years. However, the possibility of being frail, dependent, or having a cognitive decline in the preceding age group (i.e., 65–79) also exists. This fact does not affect our conclusion, given that frailty, dependency on ADLs, and cognitive decline are also present in middle-aged individuals (50–65 years old).[30-33]

Our findings are consistent with the idea that old age comprises distinct subphases.[1] These subphases were distinguished by an 80-year age limit. Some authors[1,3,4] concur with this age limit; others have reported a cutoff of 75 years.[5-8] This observation is clinically significant. The difficulty of treating older individuals as a homog-

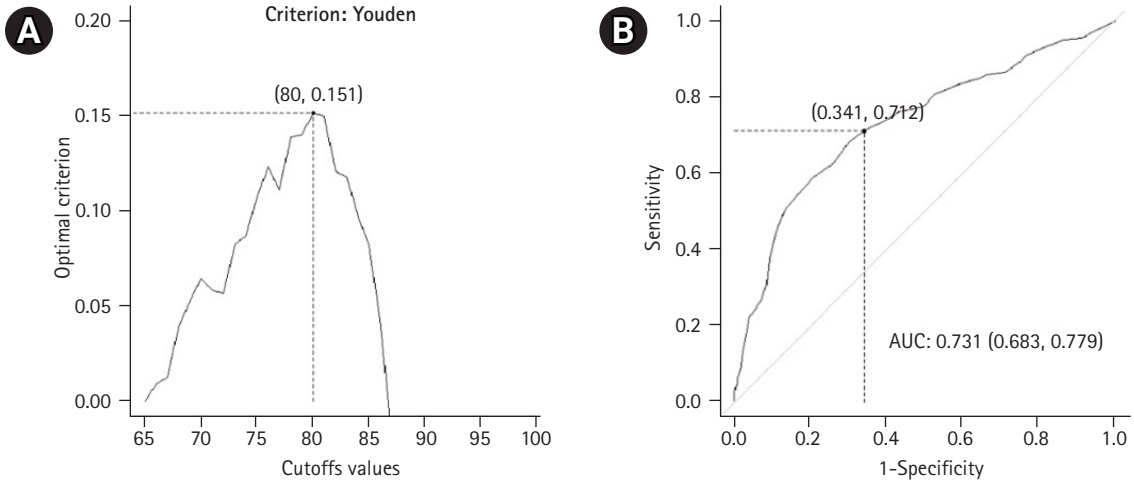

Fig. 3. Receiver operating characteristic (ROC) curve analysis for patients with frailty: (A) values of the Youden's metric function per age cut-point (optimal value with coordinates) and (B) ROC curve, together with the optimal cutoff point for age and area under ROC curve (AUC), with 95% confidence interval.

enous group is reflected in the Australian clinical guidelines. Three of the 20 reviewed guidelines define "older people" by chronological age, while the remaining 17 do not define "older people" at all.[34] Moreover, the 2018 American Heart Association/American Stroke Association guidelines do not suggest an upper age limit for endovascular thrombectomy but recommend considering comorbidities when making relevant decisions.[35] Understanding age-related differences and appropriately categorizing older adults may help in decision-making in the healthcare sector in terms of medication use,[36] cancer screening,[37] organ donation and transplantation,[38] therapeutic interventions,[35,39] and medical research.[40]

Finally, acknowledging that older adults are a heterogeneous group and that the 65–79 and ≥ 80 years of age groups are distinct may help medical staff access patients not primarily based on their age but also by considering their cognitive ability, frailty status, and functional independence. Our results highlight the need for greater attention to diversity in aging, recognizing different ways of aging and different ages. Simplifying the identification of patients > 65 years of age into a single "older people" category encourages inaccurate medical judgments and over- and under-treatment.[41,42] A positive mindset should be cultivated regarding aging as a new stage of life, where healthcare should be personalized according to specific patient needs, preferences, functioning, limitations, and life expectancies. It may be possible to improve older people's access to healthcare, increase the quality of care they receive, and enhance their mental health, by not treating them negatively because they are uniformly perceived as "old." Fighting ageism (i.e., stereotypes, discrimination, and prejudice against older people) can optimize appropriate prescription, improve medication adherence, reduce polypharmacy, apply proper treatments, implement timely interventions, and promote equitable inclusion of older people in research studies and surveillance data.[43,44]

Aging is a process that begins early in life, before 65 years of age, and results in many changes across the body's systems that require special attention and management.[45] Applying proper dietary, behavioral, and pharmaceutical interventions may delay the aging process and increase the healthy lifespan.[46] These preventive interventions may vary depending on age group, and future studies should demonstrate which interventions are appropriate for each age group. For example, interventions to delay frailty should be more suitable for people aged 65–79 years, whereas coping strategies regarding aging and death should be more appropriate for adults aged ≥ 80 years.[47,48]

One strength of this study is our use of a variety of multifaceted criteria, including frailty status, cognitive function, and ADL, to effectively demonstrate the diverse age-related characteristics of older patients. The main limitation of our study is that the study sample consisted of individuals who were consecutively admitted to the hospital through the emergency department. Consequently, our findings regarding the age cutoff points for identifying geriatric syndromes and difficulties in IADLs cannot be generalized to the entire population of older people. Future research should be conducted on a wider range of people in the community. Second, we did not include people from younger age groups (i.e., 50–64 years) for comparison with the 65–80 years of age group to identify any differences in the investigated parameters. Future research in different countries with larger and more representative samples may establish more precise, unambiguous, and definitive age thresholds for the classification of older adults. Nevertheless, these thresholds may differ between countries, as perceptions regarding aging are

culturally sensitive, even though they are not based on strict scientific data but only on personal beliefs. For example, people in Greece believe that youth ends at around 52 years of age and that old age begins at 68, whereas Norwegians think that youth ends around 34 years of age, and British and Turkish individuals believe that old age begins at 59 and 55 years of age, respectively.[49]

In conclusion, notwithstanding these limitations, the current study results add to the existing body of literature by demonstrating the significant differences in several parameters between the 65–79 and ≥80 years of age group. This finding emphasizes the need for different approaches in these two age groups when applying medical therapies and interventions, as well as when conducting health research.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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None.

AUTHOR CONTRIBUTIONS

Conceptualization, IV, FA, PV, DN; Data curation, IV, FA, PV, AK; Formal analysis, FA; Investigation, IV, FA, PV, AK, DT; Methodology, IV, FA, PV, AK, DT; Visualization, FA, DT; Project administration, FA, DN; Supervision, FA, DN; Writing-original draft, IV, FA; Writing-review & editing, IV, FA, PV, DT, DN.

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Long-Term Risk of Reduced Cognitive Performance and Associated Factors in Discharged Older Adults with COVID-19: A Longitudinal Prospective Study

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Background: Increasing numbers of reports have suggested a deterioration in cognitive performance after recovery from coronavirus disease 2019 (COVID-19), however insufficient information is available regarding long-term brain health and risk factors related to reduced cognitive performance in advanced age. We investigated the prevalence of reduced cognitive performance and its associated factors among older adults after COVID-19. **Methods:** This prospective observational study enrolled older individuals (aged ≥65 years) hospitalized for COVID-19. Discharged patients were contacted after an average of 15 months and a brief battery was administered during telephone interviews to assess their mental status. **Results:** Among the 174 patients, 77 (44.3%) showed reduced cognitive performance at follow-up. Multivariate analysis revealed that female sex, education level, and increased Deyo/Charlson Comorbidity Index score, which is an objective indicator of chronic disease burden, were independent risk factors for long-term cognitive performance. Depression and anxiety symptoms, assessed using the Patient Health Questionnaire-2 and Generalized Anxiety Disorder 2-item questionnaire at the end of the study, were not associated with reduced cognitive performance. **Conclusion:** Our findings provide key insights into discharged older adults with COVID-19 at risk of long-term cognitive impairment, and help to ascertain the factors associated with this problem.

Key Words: COVID-19, Cognitive dysfunction, Elderly, Long-term adverse effects

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has adverse effects on the respiratory system in the acute phase; however, increasing evidence suggests that the disease also affects the musculoskeletal, gastrointestinal, neurological, and cardiovascular systems.[1,2] Recently, the long-term symptoms of this disease, termed "post-COVID" syndrome by the World Health Organization, have been characterized as a series of unexplained findings, usually appearing 3 months after the infection onset and lasting for >2 months thereafter.[3,4] Moreover, recent reports have shown that the virus can cause neurological manifestations such as headache, dizziness, confusion, and cognitive dysfunction, although the reasons are not fully understood.[1,3]

The prevalence of poor overall cognitive performance after 3–6 months following hospital discharge varies from 21% to 65%.[5,6] Furthermore, heterogeneous results indicate reduced performance in cognitive functions such as memory, attention, processing speed, problem-solving, planning, reasoning, and visuospatial ability shortly after COVID-19 onset.[7-9] The results of neuropsychiatric assessments performed 3–6 months after infection suggest that cognitive changes may develop during long-term follow-up.[5-10] A longitudinal study of 21 patients in Italy reporting subjectively reduced cognitive performance showed that 52% of the patients had

deficits in at least one cognitive domain at 6 months, a rate that gradually decreased after 18 months.[11] Another recent study reported that the rate of cognitive performance decline accelerated four-fold in patients with reduced cognitive performance compared to the pre-pandemic period.[12]

Findings on the factors associated with reduced cognitive performance following COVID-19 disease are conflicting. Neuroinflammation, hypoxia, and procoagulatory and prothrombotic states may be underlying conditions leading to reduced cognitive performance after COVID-19.[13,14] Furthermore, some studies have highlighted post-intensive care syndrome, which may manifest as the deterioration of cognitive and physical functions in patients surviving intensive care owing to COVID-19.[15-18] Furthermore, hospitalization, delirium, social isolation, depression, and anxiety owing to the loss of loved ones or fear of death may negatively affect cognitive performance.[19,20] Several studies have reported no association between cognition and the length of hospital stay, oxygen demand, comorbidities, or inflammation.[6] However, studies to date have been conducted in the general population and have not focused on older adults who are more vulnerable to permanent neuropsychiatric disorders and reduced cognitive performance.[5-9]

Although evidence suggests that older individuals recovering from COVID-19 are at a greater risk of cognitive dysfunction, information is insufficient regarding the long-term cognitive status and risk factors in this population. Therefore, this prospective study sought to answer the following questions: What is the frequency of long-term decline in cognitive performance after hospitalization for COVID-19 in older adults without previously known cognitive impairment, and which factors affect cognitive performance impairment?

MATERIALS AND METHODS

Design and Participants

This prospective study recruited individuals aged ≥65 years hospitalized for COVID-19 at a tertiary hospital in Ankara, Türkiye, between January and September 2021. All patients tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by reverse transcription-polymerase chain reaction of a nasal swab specimen or had typical computed chest scan images (bilateral multifocal ground-glass opacities) compatible with COVID-19. Strict exclusion criteria were applied at the beginning of the study to include as many cognitively normal individuals as possible. Thus, we asked patients for their own verbal statements about their forgetfulness before the COVID-19 pandemic and confirmed these statements in the national database. All hospitals in our country use a common nationwide database of basic medical records (outpatient visits, surgeries, radiology, prescribed medications, and basic medical histories). Data obtained from patient interviews were compared and, when possible, confirmed using this national database. Patients who had previously complained of forgetfulness, presented to the outpatient clinic with these complaints, were diagnosed with mild cognitive impairment (MCI) or dementia, had been prescribed medication for dementia for any reason, experienced hearing or visual impairment, had incomplete data, had a terminal illness, or were bedridden were excluded from the study. Patients who were dependent on instrumental or daily activities because of cognitive or physical impairment in the pre-COVID-19 period were also excluded because MCI could not be ruled out (Fig. 1).

Patients who recovered and were discharged from the hospital were contacted between September 2021 and October 2022. Additional exclusion criteria were unavailability of telephone contact, lack of consent to participate in the study, presence of delirium, or medical instability owing to any illness such as acute infection or acute exacerbation of a chronic condition. The local ethics committee approved the study (No. 2020-305), which was conducted in accordance with the guidelines of the Declaration of Helsinki. All patients included in the study gave their written and verbal con-

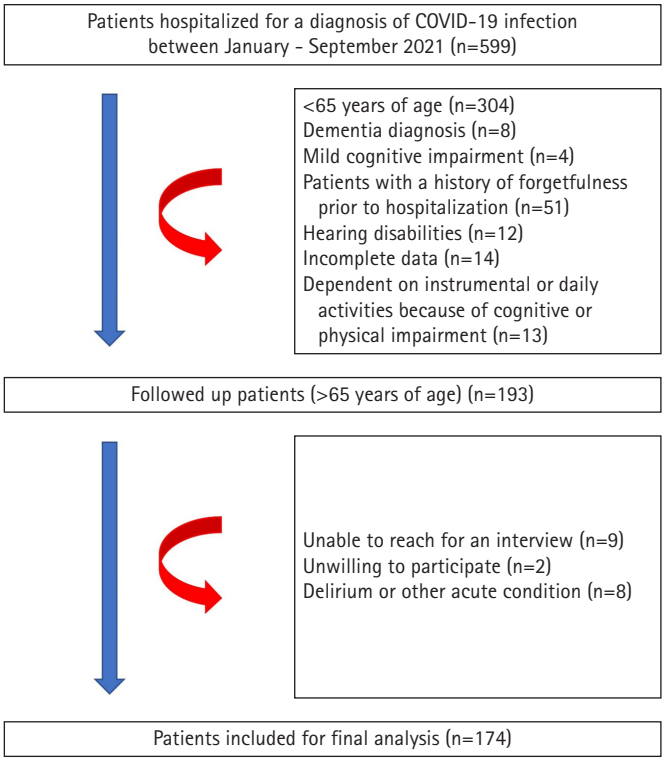

Fig. 1. Study inclusion and exclusion flow chart.

sent to participate in the study. Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[21]

A single trained interviewer conducted a telephone-based visit for 30 minutes at the end of the follow-up period and obtained verbal informed consent from all included participants. The interviews began with an assessment of delirium and medical conditions. Subsequently, a brief battery was used to assess mental status, including the Patient Health Questionnaire-2 (PHQ-2), the Generalized Anxiety Disorder 2-item questionnaire (GAD-2), and the Telephone Cognitive Screening Scale Türkiye (T-CogS-TR). After the interview, cognitive performance was evaluated and recorded as present or not (categorically). Individuals with poor cognitive performance were verbally advised to visit a nearby health institution for further examination.

To calculate the minimum sample size required, the incidence of dementia in the population ≥ 65 years of age was assumed to be 0.5%, whereas after COVID-19 was assumed to be 2.66%.[22] Thus, a total of 161 cases was calculated to be sufficient for maximum type 1 and type 2 errors of 0.05 and 0.20, respectively.

Mental Status Assessment

Mental health was assessed using the T-CogS-TR, PHQ-2, and GAD-2. The T-CogS-TR is a 16-question screening instrument used to identify reduced cognitive performance. This test evaluates cognitive functions including orientation, registration, memory, attention, and language. The overall scores range between 0 and 26 points, with a cut-off score of ≤ 21 points indicating reduced cognitive performance (sensitivity 96.8%, specificity 90.2%).[23] The PHQ-2 is a self-reported depression screening tool that detects and measures depressive symptoms within the past 2 weeks. Two items are rated on a three-point Likert scale, with a cut-off score of ≥ 3 indicating depression (range, 0–6).[24] The GAD-2 is a self-reported instrument used to assess generalized anxiety disorder symptoms within the past 2 weeks. Two items are rated on a three-point Likert scale, with a cut-off score of ≥ 3 indicating anxiety (range, 0–6).[25]

Reduced Cognitive Performance

The outcome variable was reduced cognitive performance at follow-up. The participants were stratified into two groups according to their T-CogS-TR scores: reduced cognitive performance (≤ 21 points) and cognitively healthy (≥ 22 points).[23]

Covariates

The potential confounders included basic demographics (age, sex, marital status, and educational level), medical history (chronic diseases and currently used medications), laboratory parameters (neutrophils, lymphocytes, hemoglobin, C-reactive protein [CRP], D-dimer, glomerular filtration rate [GFR], and lactate dehydrogenase [LDH]), intensive care unit (ICU) admission, delirium, and length of hospitalization. All data were obtained from patient charts and electronic clinical records. An unfavorable clinical outcome was linked to baseline neutrophil count $< 4 \times 10^9$/L, lymphocyte count $< 1 \times 10^9$/L, neutrophil/lymphocyte ratio > 8, CRP > 30 mg/L, D-dimer > 0.5 mg/L, and LDH > 300 U/L.[26,27] Anemia was defined as hemoglobin levels < 12 g/L in women and < 13 g/L in men.[28] Decreased kidney function was described as a GFR < 60 mL/min/1.73 m^2.[29]

The Deyo/Charlson Comorbidity Index (DCCI), which gives a weighted score for each of 17 comorbidities (acquired immunodeficiency syndrome [AIDS], any hematological malignancy, cerebrovascular disease, chronic pulmonary disease, congestive heart failure, dementia, diabetes with complications, diabetes without chronic complications, hemiplegia or paraplegia, metastatic solid tumor, mild liver disease, moderate/severe liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease, and rheumatoid disease) according to the risk of mortality within 1 year, was used to assess the comorbidity level.[30] The concomitant use of five or more drugs was defined as polypharmacy.[31] The anticholinergic burden of drugs was evaluated based on the Anticholinergic Cognitive Burden scale,[32] with high exposure classified as a score ≥ 1.

Statistical Analyses

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to determine the data distributions. The chi-squared test was used to compare categorical variables. Student t-test was used for normally distributed continuous variables, Student t-test was used, whereas the Mann–Whitney U test was used for non-normally distributed variables. The effect size in Student t-test was calculated as the difference between the group means divided by their pooled standard deviation, known as Cohen's d.[33] In non-parametric comparisons, effect size was calculated by dividing the absolute standardized test statistic "z" by the square root of the number of pairs.[33] Phi (φ) was used to indicate the effect size measure in the chi-square test.[33] A univariate Cox regression analysis was performed to examine the association between time and reduced cognitive performance after follow-up. Subsequently, a multivariate Cox regression model was constructed using clinically and statistically significant ($p < 0.1$) variables (age, sex, marital status, educational level, DCCI, D-dimer level, and delirium history). The effects of depressive and anxiety symp-

toms on cognitive impairment at the end of the follow-up period were assessed using univariate binary logistic regression analysis, followed by multivariate adjustments for age, sex, and educational status. The statistical significance level was set at $p < 0.05$.

RESULTS

Basic Characteristics

We enrolled 174 patients (mean age 70.4±6.8 years), with slight female predominance (55.7%). The mean follow-up period was 15.0±3.2 months (range, 11–18 months). At follow-up, 77 (44.3%) participants had cognitive impairment. Compared to patients without reduced cognitive performance, those who developed cognitive impairment were older ($p < 0.001$, $r = 0.315$); predominantly women ($p < 0.001$, $\varphi = 0.398$); unmarried ($p < 0.001$, $\varphi = 0.340$), had a lower educational level (≤5 years) ($p < 0.001$, $\varphi = 0.425$); and had greater current tobacco use ($p = 0.016$, $\varphi = 0.183$), DCCI score ($p = 0.001$, $r = 0.246$), anticholinergic burden ≥1 ($p = 0.003$, $\varphi = 0.229$), D-dimer level ≥0.5 ($p = 0.029$, $\varphi = 0.177$), and delirium history during hospitalization ($p < 0.001$, $\varphi = 0.392$). The number of medications, polypharmacy, other laboratory parameters, ICU admission, length of hospital stay, and follow-up period did not differ between the two groups. The characteristics of all participants are shown in Table 1.

Table 1. Characteristics of the study sample

Variable	Total (n=174)	Cognitive impairment		p-value	Effect size
		Yes (n=77)	No (n=97)		
Demographics					
Age (y)	70.4±6.8	73.0±7.8	68.3±5.0	<0.001*a)	0.315
65–74	133 (76.4)	47 (61.0)	86 (88.7)	<0.001*b)	0.323
75+	41 (23.6)	30 (39.0)	11 (11.3)		
Sex (female)	97 (55.7)	60 (77.9)	37 (38.1)	<0.001*b)	0.398
Marital status (married)	122 (70.1)	42 (56.8)	80 (82.5)	<0.001*b)	0.340
Years of education (≤5)	21 (12.1)	21 (28.4)	0 (0)	<0.001*b)	0.425
Current smoking	45 (25.9)	13 (16.9)	32 (33.0)	0.016*b)	0.183
Comorbidities					
DCCI	3.8±1.5	4.2±1.5	3.5±1.3	0.001*a)	0.246
Drug count	3.8±2.9	4.0±2.6	3.6±3.1	0.100a)	0.124
Polypharmacy	57 (32.8)	28 (38.4)	29 (29.9)	0.367b)	0.068
Anticholinergic burden (≥1)	58 (33.3)	35 (45.5)	23 (23.7)	0.003*b)	0.229
Laboratory parameters					
Neutrophil ($<4\times10^9$/L)	82 (47.1)	42 (54.5)	40 (41.2)	0.081b)	0.132
Lymphocyte ($<1\times10^9$/L)	61 (35.1)	32 (41.6)	29 (29.9)	0.109b)	0.121
N/L (≥8)	31 (17.8)	12 (15.6)	19 (19.6)	0.493b)	0.052
Anemia (female <12 g/dL, male <13 g/dL)	47 (27.0)	22 (28.6)	25 (25.8)	0.680b)	0.031
CRP (>30 mg/L)	95 (54.6)	37 (48.7)	58 (60.4)	0.124b)	0.117
D-dimer (≥0.5 mg/L)	99 (56.9)	50 (74.6)	49 (57.6)	0.029*b)	0.177
GFR (<60 mL/min)	48 (27.6)	23 (29.9)	25 (25.8)	0.548b)	0.046
LDH (>300 U/L)	68 (39.1)	32 (45.7)	36 (44.4)	0.876b)	0.013
Hospitalization characteristics					
ICU admission (yes)	25 (14.4)	8 (10.4)	17 (17.5)	0.183b)	0.101
Delirium (yes)	51 (29.3)	38 (49.4)	13 (13.4)	<0.001*b)	0.392
Length of stay (>7 days)	131 (75.3)	55 (71.4)	76 (78.4)	0.293*b)	0.080
Follow-up time (mo)	15.0±3.2	15.5±2.8	14.5±3.5	0.194a)	0.098
	15 (11–20)	15 (11–19)	15 (12–20)	0.147	0.087

Values are presented as mean±stadnard deviation or number (%) or median (min–max).
DCCI, Deyo/Charlson Comorbidity Index Score; N/L, neutrophil and lymphocyte ratio; CRP, C-reactive protein; GFR, glomerular filtration rate; LDH, lactate dehydrogenase; ICU, intensive care unit.
Missing data: Education (7), CRP (2), D-dimer (22), and LDH (23).
Effect size: some widely used suggestions about the magnitude of the effect of r and phi 0.10 (small effect), 0.30 (medium effect) and 0.50 (large effect) 39.
a)Mann-Whitney U test, b)chi-square test.
*p<0.05 was statistically significant.

Mental Health Status Assessment after Follow-Up

The mean score of all subjects on the T-CogS-TR questionnaire after follow-up was 21.6 ± 3.3. The mean T-CogS-TR scores in patients with and without reduced cognitive performance were 18.7 ± 2.5 and 24.0 ± 1.3, respectively. The group with reduced cognitive performance had more clinically significant depression and anxiety symptoms (p = 0.022, φ = 0.173 and p = 0.001, φ = 0.261, respectively) (Table 2).

Associations between Cognitive Impairment and Clinical Variables

In the univariate Cox regression analyses, age (> 75 years) (hazard ratio [HR] = 1.98; 95% confidence interval [CI] 1.24–3.15; p = 0.004), female sex (HR = 2.57; 95% CI 1.50–4.41; p = 0.001), 1-year decrease in education (HR = 0.84; 95% CI 0.78–0.90; p < 0.001), each point increase in DCCI score (HR = 1.34; 95% CI 1.16–1.56; p < 0.001), D-dimer (≥ 0.5 mg/L) (HR = 2.37; 95% CI 1.33–4.23; p = 0.003), and a history of delirium (HR = 1.90; 95% CI 1.21–2.99; p = 0.006) were associated with the presence of reduced cognitive performance. In the multivariable analysis, female sex (HR = 1.27; 95% CI 1.04–1.56; p = 0.020), 1-year decrease in education (HR = 0.87; 95% CI 0.79–0.94; p = 0.001) and each point increase in DCCI score (HR = 1.34; 95% CI 1.16– 1.56; p < 0.001) were associated with reduced cognitive performance risk (Table 3, Fig. 2). The Hosmer–Lemeshow (H–L) test yielded a chi-square value of 11.913 and was insignificant (p = 0.155), indicating a good fit of the model. The omnibus test confirmed that the model was highly significant (−2LL = 119.161, $\chi^2(2) = 71.449$, p < 0.001).

In the univariate logistic regression analysis, depression (odds ratio [OR] = 2.33; 95% CI 1.12–4.86; p = 0.024) and anxiety (OR = 3.94; 95% CI 1.75–8.89; p = 0.001) symptoms at the end of follow-up were associated with reduced cognitive performance. However, in the multivariate analyses, the associations remained

Table 2. Long-term mental health status after COVID-19 infection

Variable	Total (n = 174)	Cognitive impairment		p-value	Effect size
		Yes (n = 77)	No (n = 97)		
Mood status					
PHQ-2	1 (0–6)	2 (0–6)	1 (0–6)	0.065[a)]	0.139
PHQ-2 (≥ 3)	38 (21.8)	23 (29.9)	15 (15.5)	0.022*[b)]	0.173
GAD-2	1 (0–6)	1 (0–6)	0 (0–6)	0.003*[a)]	0.228
GAD-2 (≥ 3)	34 (19.5)	24 (31.2)	10 (10.3)	0.001*[b)]	0.261
Cognitive status					
T-CogS-TR	21.6 ± 3.3	18.7 ± 2.5	24.0 ± 1.3	< 0.001*[a)]	0.864

Values are presented as median (min–max) or number (%) or mean±stadnard deviation.
COVID-19, coronavirus disease 2019; PHQ-2, Patient Health Questionnaire-2; GAD-2, Generalized Anxiety Disorder-2; T-CogS-TR, Turkish version of the Telephone Cognitive Screen.
Effect size: some widely used suggestions about the magnitude of the effect of r and phi 0.10 (small effect), 0.30 (medium effect) and 0.50 (large effect) 39.
[a)]Mann-Whitney U test, [b)]chi-square test.
*p<0.05 was statistically significant.

Table 3. Associations between cognitive impairment and clinical variables

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (≥ 75 y)	1.98 (1.24–3.15)	0.004*	0.78 (0.37–1.65)	0.521
Sex (female)	2.57 (1.50–4.41)	0.001*	2.13 (1.11–4.13)	0.023*
Marital status (married)	0.47 (0.29–0.74)	0.001*	0.70 (0.37–1.30)	0.256
Years of education (≤ 5)	0.09 (0.02–0.37)	0.001*	1.45 (0.71–2.45)	0.310
Current smoking	0.75 (0.41–1.38)	0.357	-	-
DCCI	1.34 (1.16–1.56)	< 0.001*	1.27 (1.04–1.56)	0.020*
Anticholinergic burden (≥ 1)	1.48 (0.92–2.35)	0.102	-	-
D-dimer (≥ 0.5 mg/L)	2.37 (1.33–4.23)	0.003*	1.49 (0.80–2.78)	0.209
History of delirium (yes)	1.90 (1.21–2.99)	0.006*	1.34 (0.76–2.35)	0.310

DCCI, Deyo/Charlson Comorbidity Index Score; HR, hazard ratio; CI, confidence interval.
Adjusted age, sex, marital status, education, DCCI, anticholinergic burden, D-dimer, delirium.
*p<0.05 was statistically significant.

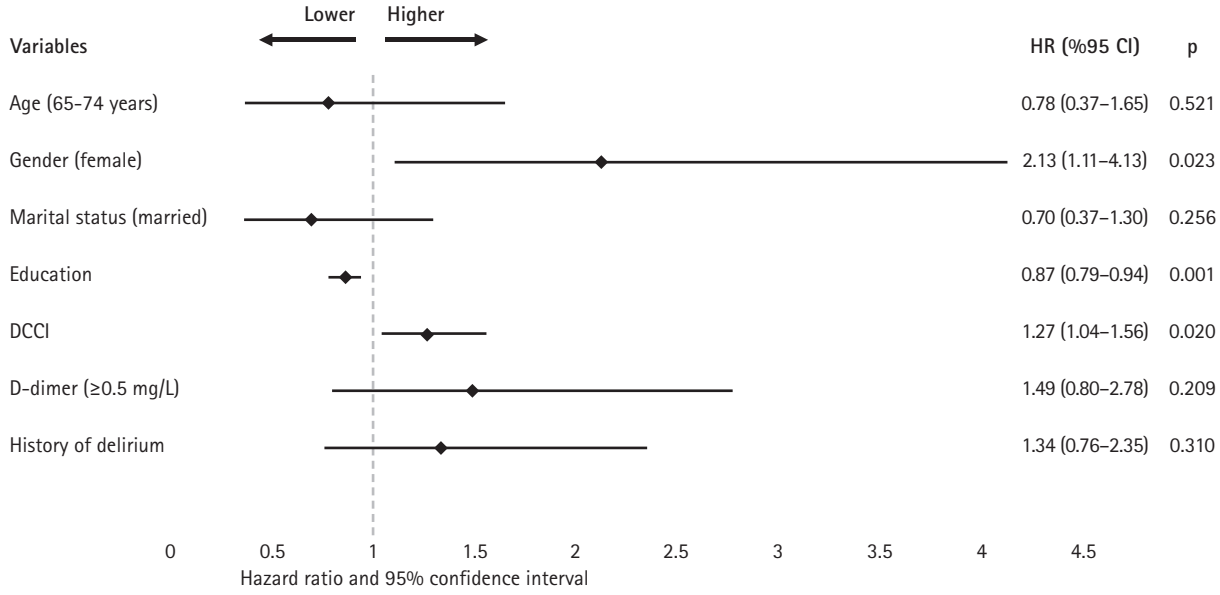

Fig. 2. Multivariate analysis of the relationship between cognitive impairment and clinical variables with the respective adjusted hazard ratios. DCCI, Deyo/Charlson Comorbidity Index Score.

insignificant (OR = 0.83; 95% CI 0.26–2.60; p = 0.752 and OR = 2.15; 95% CI 0.63–7.30; p = 0.220, respectively).

DISCUSSION

The most important finding of this study, and also the answer to our first hypothesis, was that, on average, almost half of the survivors showed reduced cognitive performance 15 months after hospitalization for COVID-19. Regarding our second study question, female sex, comorbidities, and low educational level were important predictors of reduced cognitive performance after adjusting for confounding factors. Contrary to previously described pathophysiological mechanisms,[13,14,19,20] reduced cognitive performance was independent of baseline blood inflammatory marker levels and mood status on mental assessment at the end of follow-up.

Information on cognitive and mental health post-COVID-19 is increasing. Recent studies have reported differing incidences of reduced cognitive performance in the early phase of COVID-19 ranging between 61.5% and 80%.[34] Furthermore, prospective cohort studies have examined the impact of long COVID syndrome on cognition at various time intervals.[5,6,34-38] Reduced cognitive performance ranged from 23% to 65% in studies examining mental health 3–6 months after recovery from COVID-19.[5,6,37] A meta-analysis of 10,530 participants with a mean age of 52 years showed that memory problems varied from 22% to 35%.[35] That study also observed a higher prevalence of cognitive impairment at 6 months than during the first 3 months.[35] At the 1-year follow-up after discharge, the reported prevalence of reduced cognitive performance is between 21.2% and 49.1% in patients with a mean age < 60 years.[37,38] In addition, the incidence of reduced cognitive performance was 12.5% in individuals aged ≥ 60 years and older examined 1 year after discharge.[36] No research has assessed cognition in older adults at > 1 year after recovering from COVID-19. The results of the present study indicated a higher prevalence of reduced cognitive performance in the long-term follow-up (44.3%). The differences in results across studies are most likely owing to sociodemographic, clinical, and methodological differences as well as the timing of cognitive function assessment after acute infection. Our findings extend those of previous studies by demonstrating the persisting prevalence of reduced cognitive performance in cognitively frail older individuals 15 months after discharge. However, the predictors of reduced cognitive performance in long-term COVID syndrome and whether this condition is permanent remain unclear.

Comorbidities, female sex, and a low level of education were predictors of long-term cognitive impairment in our study. Similar to our findings, a large-scale web-based study of 81,337 participants reported a link between comorbidities and reduced cognitive performance in individuals who had recovered from COVID-19.[39] In contrast, another study by Miskowiak et al. observed a mean DCCI score of 2.9 and reported no association between comorbidity and cognitive status after recovery.[6] One possible reason for this difference may be that their study was conducted in a younger population (mean age, 56.2 years) and had fewer participants

(n = 29). Consistent with our results, a study with a small sample size reported that women had a 7.35-fold increased risk of subjective decline in cognitive status 5 months after discharge.[5] A prospective online survey conducted 12 months after recovery found that female sex showed borderline significance for cognitive impairment risk.[38] The Atahualpa cohort study from Ecuador reported no female predominance in reduced cognitive performance at 6 months in individuals recovering from mild symptomatic COVID-19 infection.[40] The reason why female sex emerged as a negative factor in our study may be because men tend to have more severe COVID-19 than women.[41] At the beginning of the study, individuals experiencing more severe conditions may not have been included because they failed to meet the inclusion criteria. Those experiencing more severe conditions may exhibit a greater decline in cognitive performance, possibly owing to inflammatory processes. Therefore, women may have demonstrated a higher incidence of cognitive performance decline in our study. However, further research that incorporates inflammatory parameters is required for a more objective assessment of these differences. Given the impact of education on cognitive function in old age, it is not surprising that we observed an increased risk of long-term reduced cognitive performance with decreasing educational level.[42] Education is associated with long-term cognitive performance.[43,44] The number of formal years of education completed by individuals is positively associated with cognitive function throughout adulthood and predictive of a lower risk of dementia in later stages of life.[45] A study conducted in China showed a decreasing risk for each year of education ($\beta = -0.098$, $p = 0.013$), whereas a study in New York showed that an education level of < 12 years was a significant risk factor for long-term reduced cognitive performance after COVID-19 (OR = 5.21; 95% CI 2.25–12.09).[44] Thus, more research is needed to identify, the risk factors for long-term cognitive decline related to COVID-19. In addition to studies evaluating risk factors, further studies using intermittent testing are needed to determine whether this cognitive decline is permanent. In this context, a prospective study assessing cognitive decline and risk factors in individuals whose cognitive tests were objectively assessed before the COVID-19 pandemic who did and did not develop COVID-19, and who are matched for education and comorbidities would be very valuable.

Mood disorders can be a cause and consequence of reduced cognitive performance; however, the presence of this relationship following COVID-19 remains controversial.[19,20] A cross-sectional study of 153 participants hospitalized for COVID-19 reported that depression was associated with worse cognitive health 3 months after illness.[46] However, one limitation of this study was that it did not examine cognitive complaints using formal screening tools. Consistent with our results, a recent study reported no significant correlation between most cognitive tasks and depression and anxiety scales, whereas cognitive tests showed a statistically significant correlation with a very small effect (percentage of variance < 15%).[47] Another prospective study did not observe a correlation between depression, anxiety, and cognition, suggesting that mood disorders may not lead to reduced cognitive performance.[44,48] We extend these findings by showing them in the long term and isolated older adults. However, the mechanisms underlying the negative effects of COVID-19 on cognition remain unclear. Given the negative effects of depression on cognition, one reason that we did not observe this effect in our multivariate analyses may be the complex relationships among many existing variables, which remain to be elucidated. In addition, although evidence suggests a relationship between serum inflammatory markers in the course of acute COVID-19 illness and reduced cognitive performance in the early period, we did not find any impact of these markers on future reduced cognitive performance.[6]

Post-intensive care syndrome, which manifests as the loss of cognitive and physical functions in patients who survive intensive care, may be responsible for some cognitive impairments caused by COVID-19.[15,17,18] In our study, we observed no differences in cognitive function among patients who survived intensive care. Similarly, a study in Belgium also observed no such difference[49]; however, a cohort study conducted in New York reported that post-intensive care syndrome was common in patients who survived COVID-19.[15,17]

The mechanisms underlying cognitive sequelae after COVID-19 remain unclear.[34] SARS-CoV-2 with neuro-invasion and neurotropism may cause patients to develop delayed neurodegenerative diseases.[14] Transsynaptic transmission of the virus to the limbic structures and deeper parts of the central nervous system could explain the occurrence of neurological symptoms.[14] Furthermore, reduced cognitive performance may be associated with hyperinflammation, hypoxia, and thrombotic events in the central nervous system.[13,14] Whole-brain cortical and hippocampal atrophy, hypoxic-ischemic brain changes, and cerebral small-vessel disease are neuropathological events that develop owing to inflammatory reactions and oxidative stress related to this infection.[35] We did not design the present study to investigate these pathophysiological mechanisms. However, the results demonstrated that cognitive impairment may occur during long-term follow-up, although it is not yet clear by what mechanism.

This study has some limitations. First, the lack of information on comprehensive mental examinations of participants before infection is a common limitation shared with similar studies.[5,6,36-38] To minimize selection bias while forming the study cohort, we used

strict exclusion criteria (e.g., participants who had not been diagnosed with a cognitive disorder, had never taken medication for dementia, or had no limitations in daily and/or instrumental life activities). Second, the participants' cognitive function was assessed using a telephone-based screening tool to decrease the spread of COVID-19. Difficulties exist in performing cognitive tests on phones. Particularly in the older population, individuals may have serious hearing problems and tend to give more superficial answers to questions compared to face-to-face interviews. This makes it difficult to obtain accurate results. Therefore, we did not include patients with severe hearing loss in our study and used a telephone cognitive test whose validity and reliability have been confirmed in a Turkish population.[23] Finally, some risk factors that may affect cognitive status may have been overlooked.

In conclusion, the results of this study provided evidence that older adults discharged following hospitalization for COVID-19 were at risk for long-term cognitive impairment. In addition to the previously established short-term predictors, we identified female sex and comorbidity burden as important risk factors for the long-term development of reduced cognitive performance. Further studies are needed to develop potential therapeutic interventions after COVID-19 among older people at a higher risk for decreased cognition.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, ED, MIN; Data curation, BGYV; Funding acquisition, BGYV; Investigation, ED, BGYV, MIN; Methodology, BGYV, MIN; Project administration, ED; Supervision, MIN; Writing-original draft, ED, BGYV; Writing-review & editing, ED, BGYV, MIN.

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Polypharmacy, Potentially Inappropriate Medications, and Dysphagia in Older Inpatients: A Multi-Center Cohort Study

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Background: Although the relationship between medication status, symptomatology, and outcomes has been evaluated, data on the prevalence of polypharmacy and potentially inappropriate medications (PIMs) and the association of polypharmacy and PIMs with swallowing function during follow-up are limited among hospitalized patients aged ≥65 years with dysphagia. **Methods:** In this 19-center cohort study, we registered 467 inpatients aged ≥65 years and evaluated those with the Food Intake LEVEL Scale (FILS) scores ≤8 between November 2019 and March 2021. Polypharmacy was defined as prescribing ≥5 medications and PIMs were identified based on the 2023 Updated Beers Criteria. We applied a generalized linear regression model to examine the association of polypharmacy and PIMs with FILS score at discharge. **Results:** We analyzed 399 participants (median age, 83.0 years; males, 49.8%). The median follow-up was 51.0 days (interquartile range, 22.0–84.0 days). Polypharmacy and PIMs were present in 67.7% of and 56.1% of patients, respectively. After adjusting for covariates, neither polypharmacy (β=0.05; 95% confidence interval [CI], -0.04–0.13, p=0.30) nor non-steroidal anti-inflammatory medications (β=0.09; 95% CI, -0.02–0.19; p=0.10) were significantly associated with FILS score at discharge. **Conclusion:** The results of this study indicated a high proportion of polypharmacy and PIMs among inpatients aged ≥65 years with dysphagia. Although these prescribed conditions were not significantly associated with swallowing function at discharge, our findings suggest the importance of regularly reviewing medications to ensure the appropriateness of prescriptions when managing older inpatients.

Key Words: Deglutition disorders, Geriatrics, Polypharmacy, Potentially inappropriate medication list

INTRODUCTION

Dysphagia is a serious problem in older people that affects aspiration pneumonia and patient quality of life (QOL).[1-3] Dysphagia is a disorder caused by the disuse of muscles related to swallowing or impairment of the central nervous system.[1] The prevalence of dysphagia varies by setting, with 11%–34% in independent individuals, 29%–47% in inpatients, and 38%–92% in those hospital-

ized for community-acquired pneumonia.[2] Dysphagia is associated with adverse events, including aspiration pneumonia, dehydration, poor nutrition, and low QOL.[1-3] In addition, these adverse events can result in unexpected rehospitalization, prolonged hospitalization, and increased medical costs due to excess medications.[4,5] Similarly, side effects and drug-drug interactions can also cause dysphagia.[6,7]

Polypharmacy resulting from excessive medication use has been a growing concern among older people in recent years.[8-11] Although a consensus definition for polypharmacy is lacking.[11,12] several reviews[8,13-15] have reported that the prevalence of polypharmacy varies widely (10%–90%) owing to age differences, definitions used, chronic conditions, healthcare settings, and geographical settings. Our previous 21-center descriptive study[16] reported a median of six medications (interquartile range [IQR], 4–7) among 467 hospitalized patients aged ≥20 years with dysphagia. Additionally, several reviews[8,10,12,15,17] reported that although the numerical definitions (2–11 medications) and prevalence of polypharmacy (4%–97%) vary among studies, polypharmacy is consistently associated with adverse events. For example, adverse drug events are associated with anticholinergic drugs, pneumonia,[18] and dysphagia.[19,20] A list of potentially inappropriate medications (PIMs) for older people has been established.[21-24] Therefore, polypharmacy and PIMs for older adults are problematic from a health risk perspective.[11]

Although the relationship between medication status, symptomatology, and outcomes has been evaluated, data are limited regarding the prevalence of polypharmacy and PIMs and the association of polypharmacy and PIMs with swallowing function during the follow-up period among hospitalized patients aged ≥65 years with dysphagia. Regarding the association with polypharmacy and clinical outcomes, Matsumoto et al.[25] reported that polypharmacy on admission was negatively associated with dysphagia and nutritional status on discharge among 257 consecutive stroke patients with sarcopenia in a rehabilitation hospital. Second, Maki et al.[26] also reported a significant higher Barthel Index among inpatients in the Japan Medical Data Center claims database aged ≥65 years with acute hip fracture who received ≤5 medications compared with those who received ≥6 medications. Kose et al.[19] reported a negative association between anticholinergics (PIMs) and patient functional state. However, data on the proportion of polypharmacy and PIMs in hospitalized patients aged ≥65 years with dysphagia are limited. In addition, information on the association between polypharmacy and PIMs at admission and swallowing function at discharge is scarce. Identifying these associations could help reduce the risk of prolonged hospitalization, overmedication, and increased healthcare costs.[4,5]

Therefore, this study aimed to (1) describe the proportion of polypharmacy and PIMs in hospitalized patients aged ≥65 years with dysphagia and (2) evaluate the association of polypharmacy and PIMs with swallowing function at discharge. We hypothesized that the proportion of polypharmacy and PIMs on admission would be high and negatively associated with swallowing function at discharge.

MATERIALS AND METHODS

Study Design

We conducted a 19-site cohort study to describe the prevalence of polypharmacy and PIMs in hospitalized patients aged ≥65 years with dysphagia and to evaluate the association of polypharmacy and PIMs with swallowing function at discharge (Supplementary Fig. S1). The results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[27] This study was conducted in accordance with the principles of the Declaration of Helsinki and registered in the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (No. UMIN000038281; Registration date: October 12, 2019). This study was approved by the Institutional Review Board of Yokohama City University Medical Center (No. B190700074; approval date: August 7, 2019). All participants provided written informed consent before enrollment or were given the right to refuse participation on an opt-out form. This study complied with the ethical guidelines for authorship and publication of *Annals of Geriatric Medicine and Research*.[28]

Data Source

The database was derived from a multicenter cohort study that used the Japanese Sarcopenic Dysphagia Database, which primarily aimed to assess the risk and contributing factors associated with sarcopenic dysphagia,[16,29] using the REDCap web-base data-capturing system.[30] In the database, we registered dysphagic patients aged ≥20 years and with a Food Intake LEVEL Scale (FILS) score of ≤8[31] from nine acute-care hospitals, eight rehabilitation hospitals, two long-term care hospitals, and one home-visit rehabilitation team between November 2019 and March 2021 through a standardized questionnaire for data collection.

Study Participants

We included non-consecutive inpatients aged ≥65 years with dysphagia, defined as a FILS score of ≤8[31] in the database. The exclusion criteria were patients aged 20–64 years and outpatients.

Outcome

The primary outcome was the FILS score at discharge. The

FILS[31] is used to evaluate swallowing function based on the patients' level of food intake and the following 10-point observer-rated scale (discrete variable, ranging from 0 to 10): scores of 1–3 indicate various degrees of non-oral food intake; scores of 4–6 indicate various degrees of oral food intake and alternative nutrition; scores of 7–8 indicate various degrees of oral food intake alone; a score of 9 indicates no dietary restriction, but with given medical consideration; and a score of 10 indicates normal oral food intake.

Exposure

We defined polypharmacy as the prescription of ≥5 medications.[12,25] PIMs were identified based on the American Geriatrics Society 2023 Updated Beers Criteria.[21] We collected medication information from electronic medical chart reviews on participant enrollment. Newly prescribed medication information taken within the 4 weeks before admission was excluded as a washout window. Two researchers (S.T. and M.N.) independently searched for and reviewed the medication codes to identify PIMs (Supplementary Table S1) and discussed with H.W. when necessary. The concordance rate between the researchers was 94.0% (141 of 150 individual medication names). We excluded aspirin and anticoagulant agents such as warfarin and rivaroxaban from our PIM assessment because of insufficient clinical information in our database to assess their appropriateness.

Covariates

We collected the following patient data: age (continuous variable); sex (binary variable); primary disease diagnosed (injuries, cerebral vascular diseases, respiratory diseases, cancer and other diseases); Charlson Comorbidity Index (CCI)[32] (continuous variable); FILS at baseline (discrete variable); and general sarcopenia (binary variable), considered a proxy indication of systemic vulnerability, as diagnosed using the 2019 criteria of the Asian Working Group for Sarcopenia.[33] We plotted a directed acyclic graph that was associated with polypharmacy and swallowing function based on previous studies[6,7,10,14,25,34-36] (Supplementary Fig. S2) and discussions with our research team (registered nurses, physical therapists, registered dieticians, pharmacists, and medical doctors).

Statistical Analysis

All analyses were conducted according to polypharmacy exposure. First, we described patient characteristics using standard descriptive statistics of medians and IQRs for continuous variables and numbers (%) for categorical variables. Additionally, we described the medication categories of PIMs based on the 2023 Updated Beers Criteria prescribed at baseline. Second, we used descriptive statistics to summarize and repeated measures two-way ANOVA (time × polypharmacy) for the FILS score at discharge by overall and hospital type as effect modifiers owing to differences in patient characteristics and purpose for hospitalization between the three hospital types.

Third, we conducted a complete case analysis as a base-case analysis, considering that the proportion of missing values was <5%; thus, the effect of selection bias due to missing values was likely to be small[37,38] (Supplementary Fig. S3). Because the FILS score is a finite discrete variable, we applied a generalized linear model with a Poisson distribution and log-link function using Huber-type robust estimators (robustbase package in R)[39] to evaluate the association of polypharmacy and PIMs with FILS score at discharge. In Model 1, we introduced the FILS score at discharge (discrete variable, ranging from 0 to 10) as the dependent variable and polypharmacy, age, sex, CCI, FILS score at baseline, and hospital type as independent variables in the analytical model. In Model 2, we added general sarcopenia as an independent variable to Model 1 to assume that it was an intermediate factor. In Model 3, we added primary diagnosis at hospitalization as an independent variable to Model 2. Additionally, we applied individual PIM categories with proportions >4% as exposure using Models 1–3.

We then conducted a sensitivity analysis. First, we applied a change cut-off value from 5 to 6, which was used as a secondary frequency in a previous systematic review,[12] to assess differences in the results due to changing the cut-off value for polypharmacy. Second, we applied the multiple imputation approach under the missing-at-random assumption to check the results due to changes with multiple imputation. We generated 50 imputed datasets using the multiple imputation by chained equations (MICE) procedure and pooled the results (mice package in R) using the standard Rubin's rule.[40,41] Third, we analyzed the associations using four primary diagnoses (injury, cerebrovascular diseases, respiratory diseases, and cancer) to check for groups with different effect sizes. Finally, for scenario analysis, we excluded participants diagnosed with conditions commonly associated with dysphagia, including esophageal cancer (10th revision of the International Statistical Classification of Diseases and Related Health Problems [ICD-10] codes: C15x), laryngeal cancer (C32x), pharyngeal cancer (C14x), stroke (I630, I631–I636, I638, I639, I600–I611, I613–I616, I619, I629, and G459), Alzheimer's disease (G20), head injury (S00x–S19x), Parkinson disease (G20x), and pneumonia (J15x, J18x, and J690) to evaluate the results in participants without common conditions known to cause dysphagia.[1,42]

We performed data processing and all statistical analyses using R version 4.0.5 for Mac (R Foundation for Statistical Computing, Vienna, Austria)[43] (Supplementary File).

RESULTS

The final analysis included data from 399 patients (Fig. 1). Table 1 shows the demographic and clinical characteristics of the study population. Patients with polypharmacy were more likely to be female, older, have PIMs, have injuries, and have been admitted to rehabilitation hospitals. They were also less likely to have cerebrovascular diseases and be admitted to acute-care hospitals. Of the nine patients with missing medication data, seven were female, five were aged ≥85 years, and nine had sarcopenia. The median follow-up period was 51.0 days (IQR, 22.0–84.0 days).

Table 1 and Supplementary Fig. S4 provide information on polypharmacy and PIMs, respectively. A median of 6.0 medications was prescribed (IQR, 4.0–8.0). Polypharmacy, defined as the use of ≥5 medications and ≥6 medications, was observed in 270 (67.7%) and 231 (57.9%) participants, respectively. Additionally, 224 (56.1%) participants used a median of 1.0 PIMs (IQR, 0.0–1.0). Table 2 presents the medication categories of PIMs at admission.

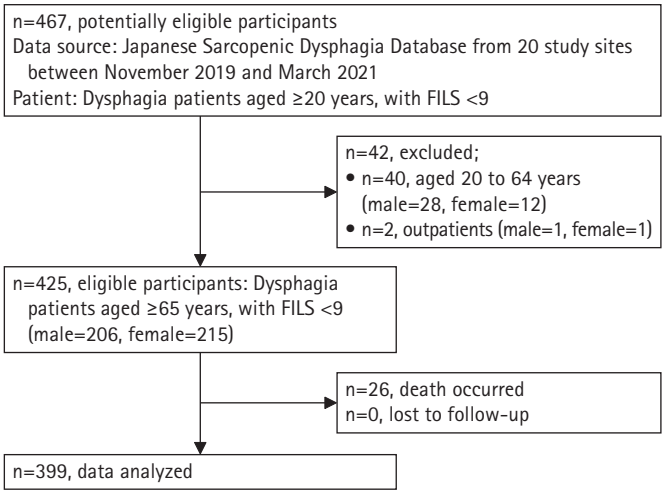

Fig. 1. Study flow. A total of 467 patients were registered in our database. Of these, 42 patients (9.0%) were excluded for the following reasons: 40 patients (8.6%) aged 20–64 years and two outpatients (0.4%). Of the 425 patients (91.0%), 26 patients occurred dead by follow-up period and zero patients had been lost to follow-up. Therefore, 399 patients (85.4%) were analyzed in the study.

Table 1. The demographic and clinical data of patients with and without polypharmacy

Variable	Overall (n=399)	With polypharmacy (n=270)	Without polypharmacy (n=120)	Missing on number of medications used (n=9)
Sex				
Female	211 (52.9)	147 (54.4)	57 (47.5)	7
Male	188 (47.1)	123 (45.6)	63 (52.5)	2
Age (y)	83.0 (78.0–88.0)	84.0 (78.0–88.0)	81.0 (76.0–89.0)	87.0 (84.0–90.0)
65–74	62 (15.5)	36 (13.3)	25 (20.8)	1
75–84	153 (38.3)	100 (37.0)	50 (41.7)	3
≥85	184 (46.1)	134 (49.6)	45 (37.5)	5
BMI (kg/m^2)	20.0 (17.3–22.6)	20.0 (17.3–22.6)	20.2 (17.4–22.5)	19.0 (16.6–19.9)
Primary diagnosis				
Injury, poisoning and certain other consequences of external causes	132 (33.1)	103 (38.1)	27 (22.5)	2
Cerebrovascular disease	114 (28.6)	67 (24.8)	45 (37.5)	2
Diseases of the respiratory system	46 (11.5)	27 (10.0)	16 (13.3)	3
Cancer	16 (4.0)	11 (4.1)	5 (4.2)	0
Other diseases	90 (22.6)	62 (23.0)	26 (21.7)	0
Missing data	1 (0.3)	0 (0)	1 (0.8)	0
CCI score	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (0.0–3.0)	2.0 (2.0–4.0)
General sarcopenia	357 (90.1)	262 (90.3)	112 (88.9)	9
Missing data	2 (0.5)	1 (0.3)	1 (0.8)	0
Number of PIMs				
0	175 (43.9)	85 (31.5)	81 (67.5)	9
1	132 (33.1)	103 (38.1)	29 (24.2)	0
2	80 (20.1)	70 (25.9)	10 (8.3)	0
3	11 (2.8)	11 (4.1)	0 (0)	0
4	1 (0.3)	1 (0.4)	0 (0)	0
Hospital type				
Acute hospital	165 (41.4)	104 (38.5)	60 (50.0)	1
Rehabilitation hospital	194 (48.6)	142 (52.6)	44 (36.7)	8
Long-term care hospital	40 (10.0)	24 (8.9)	16 (13.3)	0

Values are presented as number (%) or median (interquartile range). We defined ≥5 medication usage as polypharmacy.
CCI, Charlson Comorbidity Index; PIMs, potentially inappropriate medications.

The most frequently prescribed PIMs were proton pump inhibitors (PPIs; 45.6%), non-steroidal anti-inflammatory drugs (NSAIDs; 14.9%), antipsychotics (6.4%), and non-benzodiazepines (5.1%).

Table 3 summarizes the repeated-measures two-way ANOVA (time × polypharmacy) results for the FILS score at discharge among patients with and without polypharmacy across all hospitals (Supplementary Fig. S5) and by hospital type. While each factor (time and/or polypharmacy) showed a significant change in

Table 2. Description of medication categories of PIMs based on the Beers Criteria 2023 prescribed at baseline

Category	Overall (n = 399)	With polypharmacy (n = 270)	Without polypharmacy (n = 120)	p-value
Anticholinergics (%)				
First generation antihistamines	0 (0)	0 (0)	0 (0)	NA
Antiparkinsonian agents	0 (0)	0 (0)	0 (0)	NA
Antispasmodics	0 (0)	0 (0)	0 (0)	NA
Antithrombotics	3 (0.8)	2 (0.7)	1 (0.8)	1.000
Cardiovascular (%)				
Peripheral alpha-1 blockers	5 (1.3)	5 (1.9)	0 (0)	0.311
Central alpha agonists	2 (0.5)	2 (0.7)	0 (0)	0.859
Digoxin	7 (1.8)	6 (2.2)	1 (0.8)	0.426
Nifedipine immediate release	2 (0.5)	2 (0.7)	0 (0)	0.859
Amiodarone	4 (1.0)	4 (1.5)	0 (0)	0.426
Central nervous system (%)				
Antidepressants	1 (0.5)	1 (0.7)	0 (0)	1.000
Antipsychotics	25 (6.4)	22 (8.1)	3 (2.5)	0.060
Benzodiazepines	18 (4.6)	18 (6.7)	0 (0)	0.008
Nonbenzodiazepine	20 (5.1)	18 (6.7)	2 (1.7)	0.069
Isoxsuprine	0 (0)	0 (0)	0 (0)	NA
Endocrine (%)				
Estrogens	0 (0)	0 (0)	0 (0)	NA
Sulfonylureas	4 (1.0)	4 (1.5)	0 (0)	0.426
Gastrointestinal (%)				
Metoclopramide	0 (0)	0 (0)	0 (0.0)	NA
Proton pump inhibitors	178 (45.6)	146 (52.1)	32 (27.7)	< 0.001
Pain medications (%)				
NSAIDs	58 (14.9)	48 (17.8)	10 (8.3)	0.024
Skeletal muscle relaxants	0 (0)	0 (0)	0 (0)	NA
Indomethacin	0 (0)	0 (0)	0 (0)	NA

Values are presented as number (%). We defined ≥5 medication usage as polypharmacy.
NSAIDs, non-steroidal anti-inflammatory drugs; NA, not available.

Table 3. Description of outcome according to hospital type

Variable	Overall	With polypharmacy	Without polypharmacy	p-value[a)]
Overall	399	270	120	Polypharmacy (< 0.001)
FILS at baseline	7.0 (4.0–8.0)	7.0 (6.0–8.0)	7.0 (2.0–7.0)	Times (< 0.001)
FILS at follow-up	8.0 (7.0–8.0)	8.0 (7.0–8.0)	8.0 (7.0–8.0)	Time × Polypharmacy (0.411)
Acute care hospital	164	104	60	Polypharmacy (0.040)
FILS at baseline	6.0 (1.0–7.0)	6.0 (1.0–7.0)	4.5 (1.0–7.0)	Times (< 0.001)
FILS at follow-up	7.0 (7.0–8.0)	7.0 (7.0–8.0)	7.0 (6.0–8.0)	Time × Polypharmacy (0.615)
Rehabilitation hospital	186	142	44	Polypharmacy (0.086)
FILS at baseline	7.0 (7.0–8.0)	7.0 (7.0–8.0)	7.0 (6.8–8.0)	Times (< 0.001)
FILS at follow-up	8.0 (7.0–8.0)	8.0 (7.0–8.0)	8.0 (7.0–8.0)	Time × Polypharmacy (0.643)
Long-term care hospital	40	24	16	Polypharmacy (0.364)
FILS at baseline	7.0 (6.0–8.0)	8.0 (6.5–8.0)	7.0 (4.0–7.0)	Times (0.051)
FILS at follow-up	8.0 (6.8–8.0)	7.5 (6.8–8.0)	8.0 (6.8–8.2)	Time × Polypharmacy (0.146)

Values are presented as number or median (interquartile range). We defined ≥5 medication usage as polypharmacy.
FILS, Food Intake LEVEL Scale.
[a)]Using a two-way ANOVA for Times×Polypharmacy.

FILS score, the interaction term (time × polypharmacy) did not significantly change for either the overall participants (time × polypharmacy, p = 0.41) or hospital type.

Table 4 presents the results of the association between polypharmacy and PIMs on admission and the FILS score at discharge. After adjusting for covariates, neither polypharmacy nor PIMs individual category was significantly associated with FILS score at discharge (β = 0.05; 95% confidence interval [CI], -0.04–0.13; p = 0.30) in base-case and sensitive analysis. Regarding the PIMs individual category, NSAID use was not associated with FILS score at discharge (β = 0.09; 95% CI, -0.02– 0.19; p = 0.10). These results demonstrate trends similar to those observed in the sensitivity analysis, where the change cutoff value of polypharmacy and the MICE approach (Table 4).

In the sub-group analysis, participants with cancer (β = 0.39; 95% CI, -0.21–0.99) showed a higher point estimate compared with overall (β = 0.05; 95% CI, -0.04–0.13) and the other subgroup (β = 0.07; 95% CI, -0.10–0.25 in injury; β = 0.05; 95% CI, -0.11– 0.20 in cerebrovascular diseases; β = 0.05; 95% CI, -0.22–0.32 in respiratory diseases) in Model 2 in complete case analysis although no statistically significant differences were observed (Supplementary Table S2, S3). Among cancer patients without polypharmacy (n = 5), two had laryngeal cancer, one had lung cancer, one had stomach cancer, and one had pancreatic cancer.

In the scenario analysis, the results, after excluding participants diagnosed with conditions commonly associated with dysphagia, were generally similar to those of the base case analysis (Supplementary Tables S4, S5).

DISCUSSION

This multicenter cohort study is the first to reveal the proportions of polypharmacy and PIM categories on admission among hospitalized patients aged ≥ 65 years with dysphagia and to evaluate the association of polypharmacy and PIM categories with swallowing function at discharge. In summary, we observed high proportions of polypharmacy and PIMs but no significant association between these prescribing conditions and swallowing function at discharge. These findings suggest that regular medication reviews[8,44,45] for older adults with polypharmacy could help prevent frailty and maintain good body function, activities, participation, and QOL.[6,7]

First, the proportions of polypharmacy and PIMs were 68% and 56%, respectively, among hospitalized patients aged ≥ 65 years with dysphagia. The high proportion of polypharmacy was similar to that in a recent systematic review,[44] which reported a pooled proportion of 71% (95% CI, 57–86) among patients aged ≥ 60 years with frailty as a hospitalized subgroup from 14 studies. The proportion of PIMs in our study is higher than those reported in previous reviews,[34,45] which reported proportions of 9% and 57% among older patients with frailty[45] and cancer,[34] respectively. From a clinical viewpoint, patients with multimorbidity are more likely to have polypharmacy and prescription of PIMs. The risks of polypharmacy and PIMs are likely to increase with comorbidities and complications[13,21] and could be harmful to older people.[11,21]

Table 4. Association of polypharmacy and PIMs with dysphagia at discharge

	Model 1				Model 2				Model 3			
	β	SE	95% CI	p-value	β	SE	95% CI	p-value	β	SE	95% CI	p-value
Base analysis												
-Complete case analysis												
Polypharmacy definition ≥ 5	0.03	0.04	-0.04, 0.13	0.324	0.05	0.04	-0.04, 0.13	0.296	0.05	0.04	-0.04, 0.14	0.263
Sensitive analysis												
Polypharmacy definition ≥ 6	0.03	0.04	-0.04, 0.11	0.386	0.03	0.04	-0.05, 0.11	0.447	0.04	0.04	-0.04, 0.12	0.389
PIMs individual category												
Proton pump inhibitors	0.02	0.04	-0.06, 0.10	0.587	0.02	0.04	-0.05, 0.10	0.537	0.03	0.04	-0.05, 0.10	0.513
NSAIDs	0.09	0.05	-0.02, 0.19	0.103	0.08	0.05	-0.03, 0.18	0.143	0.08	0.05	-0.03, 0.18	0.156
Antipsychotics	0.02	0.08	-0.13, 0.17	0.808	0.01	0.08	-0.14, 0.16	0.877	0.03	0.08	-0.13, 0.18	0.734
Non-benzodiazepines	-0.02	0.09	-0.19, 0.15	0.832	-0.02	0.09	-0.19, 0.15	0.832	-0.02	0.09	-0.19, 0.16	0.844
Benzodiazepines	-0.02	0.09	-0.20, 0.16	0.843	-0.02	0.09	-0.2, 0.16	0.831	-0.02	0.09	-0.21, 0.16	0.796
-Multiple imputation approach												
Polypharmacy definition ≥ 5	0.05	0.04	-0.04, 0.13	0.287	0.05	0.04	-0.04, 0.13	0.293	0.05	0.04	-0.04, 0.14	0.264
Polypharmacy definition ≥ 6	0.03	0.04	-0.04, 0.11	0.357	0.03	0.04	-0.05, 0.11	0.313	0.04	0.04	-0.04, 0.12	0.293

FILS, Food Intake LEVEL Scale; NSAIDs, non-steroidal anti-inflammatory drugs; PIMs, potentially inappropriate medications; β, unstandardized coefficient; SE, Standard error; CI, confidence interval.
Model 1 represents "polypharmacy (without polypharmacy=0, as reference, or with polypharmacy=1) + age + gender + primary diagnosis at hospitalization + Charlson Comorbidity Index + FILS at baseline + hospital type were introduced into the analytical models," Model 2 represents "Model 1 + general sarcopenia were introduced into the analytical models," and Model 3 represents "Model 2 + primary diseases were introduced into the analytical models."

Polypharmacy and PIMs are associated with increased risks of malnutrition, sarcopenia, falls, frailty, dysphagia, and cognitive impairment in older adults.[6,7,10,11,13] Moreover, prescribed medications are often not changed despite improved clinical conditions.[46] As a result, the risk of drug-drug interactions and prescription cascades increases. Therefore, healthcare providers should focus on routinely sorting polypharmacy because PIMs are likely to cause dysphagia as a side effect of drugs.

Second, contrary to our hypothesis, polypharmacy was not associated with swallowing function at discharge among hospitalized patients aged ≥65 years with dysphagia in the base case and sensitivity analyses. Our study showed different results to those of a previous single-center cohort study[25] that reported a negative association between polypharmacy and swallowing function using the Functional Oral Intake Scale (FOIS) at discharge among stroke inpatients with sarcopenia in a convalescent rehabilitation ward. However, another study[36] reported no association between polypharmacy and swallowing function in patients with stroke. Our findings showed a significant impact of time on FILS improvement, with a smaller trend in polypharmacy. According to previous studies,[25,35,36,47] polypharmacy may inhibit the recovery of swallowing function by causing sarcopenia, malnutrition, and impaired activities of daily living. Moreover, these associations were modified using rehabilitation therapy and nutritional support.

Third, each category of PIMs was unrelated to swallowing function at discharge. This result differs from that of a previous study[19] that reported a negative association between increased anticholinergic drug use during hospitalization and swallowing function at discharge among older inpatients with stroke in a convalescent rehabilitation ward. In the present study, none of the patients were prescribed anticholinergic drugs as PIMs on admission, and all had dysphagia. In contrast, in the previous study, the frequency of anticholinergic drug use on admission was 30%, and half of the patients had dysphagia (median FOIS score of 6; IQR, 5–7).[19] One potential cause of these discrepancies is differences in the participants' backgrounds. In addition, our results showed that PPIs, NSAIDs, and antipsychotics were the most frequently prescribed PIMs. The risks of long-term intake have been reported.[21,48] However, we did not examine the association between the change in prescribing PIMs during hospitalization and the improvement of dysphagia because we did not collect medication information at follow-up.[16] Further research is needed to examine the association between changes in the prescription of PIMs during hospitalization and the improvement of dysphagia.

An intriguing finding was that the cancer type could influence the association between polypharmacy and swallowing function at discharge. Contrary to our hypothesis, our results showed that polypharmacy was likely to be positively associated with FILS score at discharge in patients with cancer, although the number of patients was limited (Supplementary Tables S2, S3). Additionally, the proportion of cancer types differed between participants with and without polypharmacy. Given the small sample size, further research on the association between polypharmacy and dysphagia in patients with cancer is needed.

This study had some limitations. First, the measurement error in medication information could have resulted in an underestimation of the frequency of PIMs and their association with the outcome because of zero values (3.9%), missing numbers of medications (2.1%), and missing medication information (7.3%), despite using a standardized questionnaire. Second, the nature of this observational study design could not determine causality because of unmeasured confounding factors. However, this might have had a limited impact on the results because we considered the major confounding factors in previous studies[6,7,10,14,25,34,49,50] (Supplementary Fig. S2) and multidisciplinary team discussions.

In conclusion, the results of this study revealed a high prevalence of polypharmacy and PIMs among hospitalized older adult patients with dysphagia. Although we did not identify an adverse association between polypharmacy and PIMs and subsequent swallowing function during the follow-up period, our findings suggest that regularly reviewing medications for the appropriateness of their prescriptions might help prevent frailty and maintain high body function, activities, participation, and QOL. In this study, the most frequently prescribed medications were PPIs and NSAIDs. Based on the indications for these drugs, the prophylactic use of PPIs to prevent NSAID-induced complications suggests that regular pain monitoring should inform the concurrent discontinuation of both PPIs and NSAIDs once they are no longer required. Additionally, even for PPIs prescribed alone, there is a defined duration of appropriate use, beyond which the risks of long-term intake have been reported. Therefore, the need for ongoing PPI therapies must be reviewed and reassessed to mitigate their potential adverse effects.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, ST, HO, HW, SN, RM; Analysis and interpretation of data, ST, HO, TN, HW; Writing–original draft preparation, ST, HO, TN; Writing–review and editing, ST, HO, TN, HW, MN, AS, SN, RM; Funding acquisition, HW.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4235/agmr.23.0203.

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Phase Angle as a Nutritional Assessment Method in Patients with Hip Fractures: A Cross-Sectional Study

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Background: Phase angle, which is associated with cellular health, has attracted attention as a noninvasive and objective method for nutritional assessment. However, the association between malnutrition and phase angle in older inpatients with hip fractures has not been reported. Therefore, this study investigated this association in older inpatients (aged ≥65 years) with hip fractures and determined the cutoff phase angle for determining malnutrition. **Methods:** This cross-sectional study retrospectively analyzed the data of 96 inpatients with hip fractures who were hospitalized in rehabilitation units after surgery (male, 29.4%; mean age, 82.4±6.2 years). Nutritional status was assessed using the Geriatric Nutritional Risk Index (GNRI), with malnutrition defined as a GNRI ≥98. Bioelectrical impedance analysis was used to measure phase angles. **Results:** The phase angle was associated with malnutrition (B=−1.173; odds ratio=0.310; 95% confidence interval 0.58–0.83; p=0.015). The area under the receiver operating characteristic curve was 0.71. The cutoff phase angle for malnutrition was 3.96° (sensitivity=0.85, specificity=0.63). **Conclusion:** Phase angle could be an indicator of malnutrition in older inpatients with hip fractures. Our findings will help formulate rehabilitation strategies for these patients.

Key Words: Aged, Hospitalization, Nutrition, Rehabilitation, ROC curve

INTRODUCTION

The incidence of hip fractures is increasing worldwide.[1)] Hip fracture is associated with increased hospitalization and rehabilitation costs, a high societal burden given its association with adverse outcomes, including depression and cardiovascular diseases.[1)] In Japan, the cost of treating patients with hip fractures leads to economic burdens on society.[2)] Additionally, older adults with hip fractures have high mortality rates.[3)] Therefore, effective rehabilitation measures are essential for older adults with hip fractures.

Due to insufficient recovery, many older adults with hip fractures require assistance in their daily activities. Specifically, 20%–60% of older adults with hip fractures require assistance for one year after treatment, despite having been independent in daily life before their injury.[4)] Furthermore, >40% of individuals present with new-onset walking disability six months after a hip fracture,[5)] indicating the insufficiencies of strategies to promote recovery in older patients with fractures.

Several factors, including age, sex, and comorbidities, can hinder recovery in patients with a hip fracture,[6)] with malnutrition being a crucial modifying factor.[7,8)] Malnutrition further increases the risk of institutionalization and mortality in older inpatients with hip fractures.[9)] Therefore, the accurate assessment of the nutritional status of older inpatients with hip fractures and the provision of appropriate interventions are essential.

However, the subjective nutritional assessments recommended in inpatient and rehabilitation settings, including the Nutritional Form for the Elderly and Mini Nutritional Assessment Short Form

Version 1,[10] are dependent on changes in weight and food intake. Therefore, their ability to accurately assess patients with severe cognitive impairment may be limited. Additionally, these assessments demonstrate interobserver variability.[11] While objective nutritional assessments, including the Geriatric Nutritional Risk Index (GNRI),[12] are dependent on serum albumin concentration, which is measured using blood tests, blood tests are invasive and may not be performed routinely. Therefore, new objective and routine assessment methods are required.

Phase angle, which can be measured using bioelectrical impedance analysis, is associated with cellular health. The phase angle has recently received attention as a noninvasive and objective method for nutritional assessment.[13,14] Poor nutritional status damages cells, thus decreasing the phase angle; hence, the phase angle can reflect nutritional status. In particular, the phase angle is useful for nutritional assessment in older inpatients.[15]

Bioelectrical impedance analysis is a simple, low-cost, and reproducible tool,[16] and the phase angle is a versatile and practical method that can be used to assess nutrition. Phase angle may be influenced by certain diseases.[17,18] For example, postoperative edema in patients with hip fractures may affect body composition, which, in turn, influences the phase angle.[19] A previous study demonstrated a lower phase angle in patients with hip fractures admitted to rehabilitation units in Japan compared to that of healthy individuals.[20] However, the link between nutritional status and phase angle in older inpatients with hip fractures has not yet been investigated.

Nutritional assessment using bioelectrical impedance analysis may provide useful information for rehabilitation interventions in patients with hip fractures. Therefore, this study assessed the association between the phase angle measured using bioelectrical impedance analysis and malnutrition in older inpatients with hip fractures and ascertained the optimal cutoff phase angle for identifying malnutrition.

MATERIALS AND METHODS

Setting, Design, and Participants

This study was conducted at Tokai Memorial Hospital, Kasugai City, and Saishukan Hospital, Kitanagoya City, both located in Aichi Prefecture, Japan. Both facilities have 50-bed rehabilitation units used for the rehabilitation of patients who have completed treatment or surgery. This cross-sectional study retrospectively collected data from the medical records of hospitalized patients.

We included 103 inpatients with hip fractures aged ≥65 years who were admitted to the rehabilitation unit of Tokai Memorial Hospital between September 2017 and November 2021 or Saishukan Hospital between December 2019 and November 2021. The exclusion criteria were the presence of stroke, spinal cord injury, or other diseases that significantly impaired physical function; an inability to undergo bioelectrical impedance analysis; and missing values for the data required to calculate the GNRI, including height, weight, and serum albumin concentration. Finally, the analysis included 96 participants (Fig. 1).

Procedure

We collected data on age, sex, height, weight, comorbidities, cognitive function, muscle mass, activities of daily living, phase angle, serum albumin level, date of surgery, and the date on which the phase angle and serum albumin level were measured from the patients' medical records. The body mass index was calculated by dividing the weight (kg) by the height (m^2).

Comorbidities were assessed using the Charlson Comorbidity Index (CCI),[21] which is positively correlated with mortality risk. Cognitive function was assessed using the Mini-Mental State Examination (MMSE), a global cognitive function test used in clinical settings,[22] in which a lower score indicates more severe cognitive impairment. The skeletal muscle index (SMI) was calculated based on the skeletal muscle mass of the limbs, as measured using bioelectrical impedance analysis. The SMI was computed by dividing the total skeletal muscle mass of the limbs by the patient's height (m^2). For bioelectrical impedance analysis, both hospitals used InBody S10 devices (InBody Inc., Tokyo, Japan) and performed the measurements according to the manufacturer's instructions. After adequate rest, the InBody S10 was used with each participant in the supine position. The electrodes were attached to the thumb, middle finger, and ankle. All metal objects were removed from the patients to avoid measurement errors. The motor functional independence measure (mFIM) score was used to evaluate activities of daily living. The mFIM assesses self-care and mobility, with higher scores indicating greater independence.

The phase angle was calculated using the resistance and reactance values obtained from the non-fractured limbs and trunk using bioelectrical impedance analysis at a frequency of 50 kHz.[19]

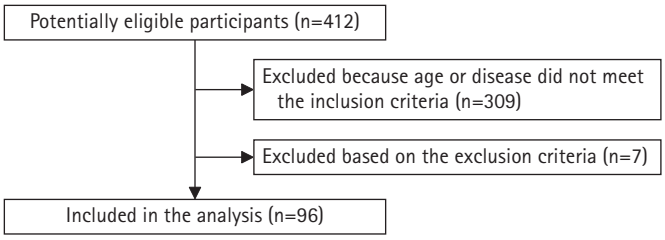

Fig. 1. Study flowchart.

The phase angle represents cellular health, and the higher the value, the better the condition. The phase angle is typically between 8° and 15° and decreases with poor health and disease.[20]

The phase angle was computed using the following equation:

$$\text{Phase angle (°)} = \arctan(\text{reactance} / \text{resistance}) \times (180°).$$

We assessed nutritional status using the GNRI, an objective nutrition-related risk index developed for older adults based on the Nutritional Risk Index. The GNRI is used as a nutritional index for hospitalized adults[12] and is an excellent indicator for older inpatients.[23] In this study, we defined malnutrition as a GNRI of ≤98, as in previous studies.[12] The GNRI was calculated using the following formulas[12]:

GRNI = [14.89 × serum albumin (g/dL)] + 41.7 × [current weight (kg) / ideal weight (kg)],

where,

Ideal weight = height (cm) × 100 × [(height (cm) × 150) / 4] (for men),

Ideal weight = height (cm) – 100 – [(height (cm) – 150) / 2.5] (for women).

Cognitive function assessment, InBody S10 measurement to calculate muscle mass and phase angle, and assessment of activities of daily living were performed by physical and occupational therapists at each facility.

Data Analysis

Patient characteristics are described using descriptive statistics. We analyzed the relationship between malnutrition and other factors using Spearman rank correlation coefficients. To assess the association between the phase angle and malnutrition, we performed a binomial logistic regression analysis with malnutrition as the dependent variable and variables correlated with malnutrition as independent variables.

Subsequently, we performed receiver operating characteristic (ROC) curve analysis to determine the cutoff phase angle for malnutrition and calculated the area under the ROC curve (AUC) as an indicator of model accuracy, in which a value of ≥0.7 indicates acceptable accuracy.[24,25] The cutoff value was the point on the ROC curve closest to 1 for "sensitivity" and closest to 0 for "1–specificity". The statistical analyses were performed using IBM SPSS Statistics, version 28.0 (IBM, Tokyo, Japan). Statistical significance was set at $p < 0.05$.

Ethical Considerations

This study was approved by the Institutional Review Boards of the Tokai Memorial Hospital (Approval No. 2019-004), Saishukan Hospital (Approval No. 059), and Seijoh University (Approval No. 2022C0017). All the study procedures conformed to the principles outlined in the Declaration of Helsinki. The results were reported following the Strengthening the Reporting of Observational Studies in Epidemiology statement. Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[26]

RESULTS

The mean ± standard deviation age of the patients was 82.4 ± 6.2 years, the mean phase angle was 3.96° ± 0.76°, and 76 patients (79.2%) had malnutrition (GNRI of ≤98). The patient characteristics are listed in Table 1.

Spearman rank correlation coefficient revealed significant correlations between malnutrition and SMI ($r = -0.210$, $p = 0.041$) and phase angle ($r = -0.29$, $p = 0.004$) but not between malnutrition and the other variables—age ($r = 0.014$, $p = 0.893$), sex ($r = -0.093$, $p = 0.37$), CCI ($r = 0.046$, $p = 0.654$), MMSE ($r = -0.097$, $p = 0.366$), and mFIM ($r = 0.051$, $p = 0.619$).

Binomial logistic regression confirmed the association of phase angle with malnutrition—crude model (odds ratio [OR] = 0.35, 95% confidence interval [CI] 0.17–0.72) and adjusted model (adjusted by age, sex, and SMI; OR = 0.31, 95% CI 0.12–0.80) (Table 2). The ROC curve analysis revealed an AUC of 0.71 (95% CI

Table 1. Demographic characteristics of the patients (n=96)

Characteristic	Value
Age (y)	82.44 ± 6.18
Sex, male	30 (29.41)
Height (cm)	151.97 ± 47.90
Weight (kg)	47.90 ± 9.16
BMI (kg/m^2)	20.70 ± 3.29
Charlson Comorbidity Index	1.00 (0.0–2.0)
Mini-Mental State Examination[a]	21.48 ± 5.95
SMI (kg/m^2)	5.51 ± 1.01
Motor functional independence measure	50.33 ± 14.96
Phase angle (°)	3.96 ± 0.76
Serum albumin (g/dL)	3.45 ± 0.48
Geriatric Nutritional Risk Index	90.07 ± 9.98
Malnutrition (presence)[b]	76 (79.17)
Days from surgery to bioelectrical impedance analysis	26.97 ± 13.69
Days from surgery blood test	18.91 ± 13.60

Values are presented as mean±standard deviation or number (%) or median (interquartile range).
BMI, body mass index; SMI, skeletal muscle index.
[a]Missing rate: 8 (8.3%).
[b]Malnutrition was defined as a Geriatric Nutritional Risk Index of ≤98.

Table 2. Results of the binomial logistic regression analysis for malnutrition[a)]

	Crude model			Adjusted model		
	B	OR (95 CI)	p-value	B	OR (95 CI)	p-value
Phase angle (°)	-1.065	0.345 (0.165–0.720)	0.005	-1.173	0.310 (0.120–0.796)	0.015
SMI	-	-	-	-0.772	0.462 (0.241–0.887)	0.020

SMI, skeletal muscle index; OR, odds ratio; CI, confidence interval.
Hosmer-Lemeshow test: crude model (p=0432) and adjusted model (p=0.834).
The model was adjusted for age and sex.
[a)]Malnutrition was defined as a Geriatric Nutritional Risk Index of ≤98.

0.58–0.83, p = 0.001). The cutoff phase angle for malnutrition was 3.96° (sensitivity = 0.85, specificity = 0.63) (Fig. 2).

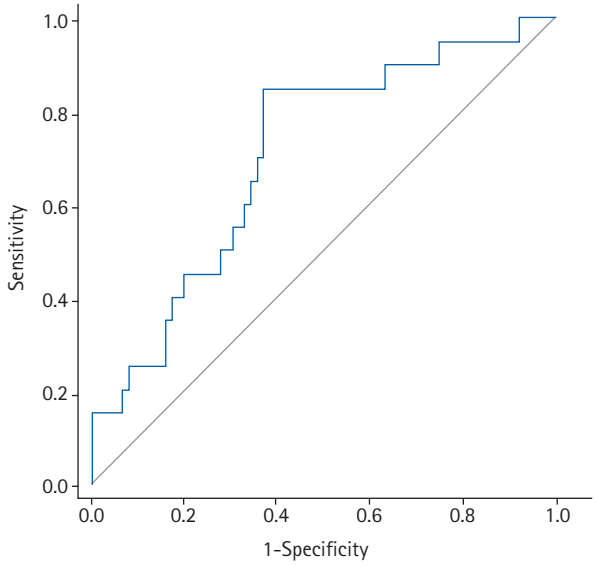

Fig. 2. Receiver operating characteristic curve to estimate the phase angle cutoff for malnutrition. The phase angle cutoff was 3.96° (sensitivity=0.85, specificity=0.63, area under the curve=0.71, 95% confidence interval 0.58–0.83, p=0.001).

DISCUSSION

In this study, the cutoff phase angle for identifying malnutrition in older inpatients with hip fractures was 3.96°. A previous study of inpatients with various diseases reported a mean phase angle on admission of 3.9° ± 0.9°, with cutoff phase angles for malnutrition of 4.03° and 3.65° for men and women, respectively.[27)] This study, which included only patients with hip fractures, yielded similar results. Therefore, the cutoff value in this study showed a certain degree of reliability.

Screening for malnutrition is essential to facilitate prompt nutritional intervention in older inpatients with hip fractures.[9)] Nonetheless, although subjective scales using questionnaires allow for convenient nutritional assessment, their reliability remains questionable.[11)] Although the GNRI is considered a good nutritional assessment index because it incorporates anthropometric factors and serum markers,[28)] blood tests are required to calculate the GNRI and cannot be routinely performed because of the burden they pose on inpatients. Bioelectrical impedance analysis is safe, reproducible, and easy for inpatients, and the results are independent of the examiner's level of experience and skill.[29)] Therefore, our findings overcome the limitations of conventional nutritional assessments and allow for prompt and accurate evaluations.

Nutrition-focused strategies are crucial in the rehabilitation of patients with hip fractures.[7,8)] Moreover, routine nutritional assessments and interventions based on these assessments may be beneficial for the recovery of older adults with hip fractures. However, malnutrition is often not assessed or treated in older adult inpatients.[30)] Therefore, this study, which evaluated a simple method to screen for malnutrition, will help facilitate the development of strategies to promote recovery in older inpatients with hip fractures.

The AUC in this study was 0.71, which was sufficient for diagnostic accuracy, although it was not ideal.[24,25)] Therefore, the ability of the phase angle to identify malnutrition is limited. Considering the relatively high sensitivity for discrimination (0.85), it may be possible to more accurately identify patients with malnutrition by performing a detailed nutritional assessment of those who fall below the phase angle cutoff for screening.

This study has a few limitations. First, we used only the GNRI to assess malnutrition; therefore, nutritional assessments should be performed in conjunction with other assessments. In addition, the GNRI does not demonstrate high accuracy in assessing hypernutrition.[28)] As such, our findings are specific to malnutrition. Nevertheless, the GNRI is a good nutritional indicator[23)] which can be used to assess malnutrition in older patients with hip fractures. Another consideration is that the phase angle is affected by age and sex.[31,32)] Future studies should consider both age and sex to determine more accurate cutoff values. Second, while we performed bioelectrical impedance analysis using the InBody S10 device according to the manufacturer's instructions, we could not confirm whether the procedures described in these instructions were fol-

lowed. Third, as all subjects in this study were postsurgical inpatients and serum albumin levels were affected by surgery, surgery may have influenced the results of this study.[33] In addition, the times between the date of surgery and the bioelectrical impedance analysis and between the date of surgery and the date of the blood tests were not consistent. Performing blood tests and bioelectrical impedance analyses on the same day is likely to yield more accurate results. Nevertheless, the half-life of serum albumin is 20 days,[34] and the interval between the dates of blood tests and bioelectrical impedance analysis was approximately 8 days in this study. Moreover, the results showed a strong association between the GNRI calculated from serum albumin and the phase angle regarding their ability to determine malnutrition, confirming a certain degree of reliability in the accuracy of the calculated phase angle cutoff; therefore, the results of this study may be applicable to clinical practice. Finally, selection bias may have resulted from the exclusion of individuals with missing GNRI values or an inability to undergo bioelectrical impedance analysis. Nonetheless, this study proposes a simple and objective malnutrition index for older inpatients with hip fractures, which has potential for clinical applications.

In conclusion, this study investigated the utility of the phase angle as an objective nutritional assessment index in older inpatients with hip fractures. The results suggest that phase angle is a potentially useful screening tool for malnutrition, with a cutoff value of 3.96° in older individuals. Our findings will contribute to the development of rehabilitation strategies for older adult patients with hip fractures. In other words, if the phase angle is indicative of malnutrition, monitoring it during rehabilitation may prevent or reduce the occurrence of malnutrition and promote recovery in older patients with fractures.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, YK, KN, TN; Data curation, YK, KN; Funding acquisition, YK, TH; Investigation, YK, NK, TN, TH; Methodology, YK, NK, TN, TH; Project administration, YK; Supervision, TH; Writing–original draft, YK; Writing–review and editing, NK, TN, TH.

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Daily Step Count and its Association with Arterial Stiffness Parameters in Older Adults

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Background: Daily step count is a simple parameter for assessing physical activity. However, the potential advantages of setting daily step goals below the traditional 10,000-step threshold remain unclear. The cross-sectional study aimed to determine the relationship between daily step counts and arterial stiffness outcomes in older individuals. **Methods:** Forty-eight older adults recorded their daily step counts over a 7-day period using a pedometer. The participants were classified into two groups based on their daily step count: Group 1 (n = 28) consisted of individuals taking fewer than 5000 steps per day, while Group 2 (n = 20) included those who recorded 5,000 to 9,999 steps per day. To evaluate arterial stiffness parameters, we measured pulse wave velocity (PWV), cardio-ankle vascular index (CAVI), and ankle-brachial index (ABI). Hemodynamic and biochemical parameters were also determined. **Results:** Participants who accumulated fewer daily steps exhibited higher PWV compared to each group. An inverse association was observed between average steps per day and PWV. However, no significant differences were found between daily step counts and CAVI or ABI. **Conclusion:** As individuals increase their daily step count, they may experience a reduction in arterial stiffness. Consequently, the assessment of daily steps has benefits for enhancing vascular health and overall well-being among older individuals.

Key Words: Walking, Vascular stiffness, Pulse wave velocity, Elderly

INTRODUCTION

The global population aged 60 years and older is projected to nearly double by 2050.[1)] While previous research has indicated that increasing physical activity could potentially extend the average lifespan by 0.68 years,[2)] there is a global trend towards increased sedentary behavior and reduced habitual daily physical activity. A decline in physical activity is a significant public health challenge and a primary risk factor for non-communicable diseases, mortality,[3)] and the development of cardiovascular disease (CVD), primarily attributable to its adverse effects on arterial health.[4)]

Several parameters are currently used to assess arterial stiffness, including pulse wave velocity (PWV), cardio-ankle vascular index (CAVI), and ankle-brachial index (ABI). The PWV is considered the gold standard for measuring arterial stiffness, whereas the CAVI provides a blood pressure-independent evaluation. The ABI is widely used to assess peripheral arterial disease (PAD).[5)] However, different measurement methods for assessing arterial stiffness can yield different results. Furthermore, the relationship between optimal physical activity levels and arterial stiffness is controversial, with studies suggesting a negative association,[6)] whereas others have reported no significant association.[7)]

Recent evidence suggests that assessing physical activity levels using wearable step-counting devices to measure daily walking among older adults[8)] can provide valuable insights. Higher daily step counts are associated with increased time spent on higher-in-

tensity activities.[9] Physical activity levels can be categorized according to daily step counts, in which < 5,000, 5,000–7,400, 7,500–9,999, and ≥ 10,000 steps indicate sedentary, low, somewhat active, and active lifestyles, respectively.[10]

The public health message recommends a daily 10,000-step goal,[11] which is associated with a reduced risk of all-cause mortality, cancer, and CVD.[12] Additionally, a higher daily step count is associated with a decreased risk of all-cause mortality in older adults in Japan.[13] Mortality rates decrease gradually, plateauing at approximately 7,500 steps per day.[14] Furthermore, the results of a comprehensive meta-analysis showed that individuals who walk 6,000–9,000 steps per day experience a 40%–50% lower risk of CVD compared with those who walk only 2,000 steps per day.[15] Moreover, individuals who averaged approximately 8,959 steps per day showed a 40.36% lower risk of all-cause mortality compared with those who averaged 4,183 steps per day.[16] However, older adults often encounter challenges in reaching this daily step target due to various factors, including the type of step-counting device, participant demographics, age group, and sample size.[14]

To date, research on daily step counts has produced varying results, and evidence is limited regarding the relationship of daily step counts < 10,000 to arterial stiffness in older adults within this demographic. A previous study on fall risk among older individuals in Thailand established a threshold of ≥ 5,000 steps/day.[17] A prior investigation suggested < 5,000 steps/day as a cutoff for identifying a sedentary lifestyle among older individuals.[11] Hence, this study adopted a walking cutoff of < 5,000 steps/day, following the criteria for older individuals with moderate activity per week, to investigate the association between daily step count and specific parameters related to arterial stiffness, including PWV, CAVI, and ABI, within the context of community-dwelling older adults with a sedentary lifestyle (< 150 minutes of moderate activity per week) from Hatyai Chivasuk's Health Promotion Center. The findings of this study may contribute to the development of effective public health recommendations and targeted interventions that utilize daily step counts.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional study enrolled 48 retired individuals who visited the Health Promotion Center for routine health checkups between December 2018 and March 2019. This health center offers healthcare services to individuals within an urban area in the Hatyai district and nearby communities. A researcher visited the community health center and explained the study's aim and scope to the participants. Potential participants who expressed interest and met the research criteria underwent subsequent evaluations. The inclusion criterion was physical inactivity, defined as < 150 minutes of moderate activity per week based on self-reported data. Moreover, the participants were required to be capable of walking independently without the need for support or mobility aids. None of the enrolled participants were taking medications, including antihypertensive, lipid-lowering, or antihyperglycemic drugs, and were nonsmokers. The exclusion criteria were musculoskeletal issues, such as lower muscle pain and bone fractures, and those with symptoms such as headache, fever, nausea, or vomiting during the examinations. Moreover, older adults with a body mass index (BMI) > 35 kg/m^2 were excluded because of their potential susceptibility to gait and balance issues and an increased risk of falls.[18] Additionally, we excluded participants who had consistently worn their pedometers for a minimum of 5 days for at least 10 hours per day.

Before enrollment, all participants provided written informed consent, following the ethical guidelines outlined in the Declaration of Helsinki. Detailed information regarding the study was provided to all participants, who signed the written informed consent forms before any measurements were obtained. This study was approved by the Research Ethics Committee of the Faculty of Medicine, Prince Songkla University (No. REC 61-157-19-2). Also, This study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[19]

Each participant underwent an initial comprehensive assessment, which included physical measurements, blood sample collection, and pedometer-based evaluations. Subsequently, at the second follow-up visit, seven days after the first visit, the participants were requested to return the pedometer to a researcher. Hemodynamic and arterial stiffness parameters were assessed.

Physiological Parameter Assessment

All anthropometric measurements were performed by trained research assistants. Body weight was measured using a calibrated digital scale, with the participants wearing light clothing. Height was measured using a portable stadiometer while the participants stood barefoot. BMI was calculated as body weight (kg) divided by height in meters squared (m^2). We classified the participants' obesity status using a threshold BMI of > 25 kg/m^2.

Hemodynamic Parameter Assessment

Before collecting blood samples, trained researchers recorded the participants' hemodynamic parameters. The resting heart rate was measured using the right arm (Masimo, Irvine, CA, USA). Blood pressure (BP) was measured using a mercury sphygmomanometer (Riester, Jungingen, Germany). The participants were instructed

to rest quietly in a relaxed position for 10 min before the BP readings were obtained. For comfortable seating and arm placement at heart level on the table, a cuff was wrapped around the arm and positioned approximately 2.5 cm from the elbow. Multiple systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were obtained, and the average of the three measurements was calculated. We calculated pulse pressure (PP) as PP = SBP–DBP, whereas mean arterial pressure (MAP) was calculated as MAP = DBP + 1/3(PP). We defined hypertension as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

Blood Sample Collection

We performed a series of blood analyses, including fasting blood glucose (FBG) levels and lipid profiles. Venous blood was collected after an overnight fast of at least 8 hours and processed immediately. FBG levels were measured using standard glucometer strips (AccuCheck Active; Roche Diagnostic Corporation, Mannheim, Germany). FBG levels were used to assess diabetes mellitus (DM; ≥ 126 mg/dL). Lipid profile assays for low-density lipoprotein (LDL), high-density lipoprotein (HDL-C), triglycerides (TG), and total cholesterol (TC) were conducted by certified nurses using blood drawn in lithium heparin tubes. We classified dyslipidemia based on the following criteria: low HDL-C ≤ 40 mg/dL; high TG ≥ 200 mg/dL; high LDL-C ≥ 160 mg/dL; and high TC ≥ 240 mg/dL.[20]

Daily Step Count Assessment

Daily step counts were monitored using a pedometer (HJA-404; Omron Healthcare Co. Ltd., Tokyo, Japan). During the initial visit, the participants received detailed instructions on how to correctly attach and remove the pedometer. The participants were instructed to wear the pedometer at the waist, specifically over the midline of the right thigh, for 7 consecutive days, encompassing 5 weekdays and 2 weekends. This period extended from morning awakening to bedtime, excluding periods of sleep and water-based activities. The participants were requested to capture a photographic record of their daily step count at the end of each day and subsequently reset the pedometer to zero the next day. The average daily step count over these 7 days was calculated.

The participants' daily step counts were recorded and categorized into two distinct physical activity groups: group 1 (< 5,000 steps/day) and group 2 (5,000–9,999 steps/day). This categorization resulted in the inclusion of 60 participants in the initial assessments. However, valid data were obtained for 48 older adults, as the remaining 12 participants did not meet the inclusion criteria for various reasons, including neglecting to provide photographs of their daily step counts, not wearing the pedometer for at least 5 days, and experiencing reduced step counts due to adverse weather conditions or leg pain.

Arterial Stiffness Assessments

CAVI, PWV, and ABI were measured using a Vasera VS-3000 device (Fukuda Denshi Co. Ltd., Tokyo, Japan). Cuffs were systematically applied to both arms and ankles for BP measurements after a 10-minute rest period in the supine position. The CAVI was automatically calculated. The brachial-ankle pulse wave velocity (baPWV) was obtained to detect brachial and ankle pulse waves and was automatically averaged. Abnormal CAVI values were defined as those ≥ 9.0.[21] Additionally, a PWV ≥ 10 m/s indicated significant alterations in aortic function.[22] The device assessed the ABI of the lower limbs. This involved recording the SBP in the brachial artery at each elbow and the SBP in the posterior tibial arteries at each ankle. We defined PAD as an ABI reading of ≤ 0.90 at rest.[5]

Statistical Analyses

All data were analyzed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Before performing the analyses, we assessed the normality of the variables using the Kolmogorov–Smirnov test. Continuous variables are represented as mean ± standard deviation (for normally distributed data) or median and interquartile range (for non-normally distributed data). Categorical variables are represented as numbers and percentages. We performed intergroup comparisons of continuous variables using an independent t-test for normally distributed data; otherwise, the Mann–Whitney U test was used. We analyzed categorical variables using the chi-squared test. The relationship between daily steps and various clinical parameters was tested using Pearson or Spearman correlations, as appropriate. For sequential data, multiple regression analysis was used to assess the associations between the selected variables adjusted for age, BMI, sex, BP, and lipid profile. The significance level was set at $p < 0.05$.

RESULTS

This study included 48 older adults who completed the test and were physically inactive. The physiological, hemodynamic, and biochemical characteristics of the study participants are represented in Table 1. Regarding the sex distribution, 8.3% of male participants and 91.7% of female participants were divided into two distinct groups based on their daily step counts. Groups 1 and 2 exhibited median daily step counts of 3,678 and 6,578 steps, respectively ($p < 0.001$). Most of the hemodynamic and biochemical characteristics were similar between the two groups; however, individuals with < 5,000 daily steps had a higher SBP than those

Table 1. Baseline characteristics of the study population in the daily step count groups

Variable	Total (n = 48)	Group 1 (< 5,000 steps/day) (n = 28)	Group 2 (5,000–9,999 steps/day) (n = 20)	p-value
Physical characteristics				
Age (y)	66.06 ± 4.764	65.571 ± 4.917	66.750 ± 4.575	0.404
Sex, male	4 (8.3)	3 (10.7)	1 (5)	0.442
Height (cm)	155.58 ± 4.959	154.750 ± 5.720	156.750 ± 3.447	0.171
Weight (kg)	57.70 ± 7.189	57.150 ± 6.558	58.470 ± 8.103	0.536
BMI (kg/m^2)	24.096 ± 2.788	24.124 ± 2.236	24.060 ± 3.483	0.938
Daily step count	4,645 (2,099–9,876)	3,678 (2,099–4,771)	6,548 (5,173–9,876)	< 0.001*
Hemodynamic parameters				
Resting HR (beats/min)	72.250 ± 8.009	72.750 ± 7.863	71.550 ± 8.363	0.614
SBP (mmHg)	132 (94–172)	132 (103–172)	127 (94–139)	0.026*
DBP (mmHg)	75.771 ± 10.199	77.393 ± 10.792	73.500 ± 9.082	0.195
PP (mmHg)	53.188 ± 11.409	55.786 ± 12.583	49.550 ± 8.550	0.061
MAP (mmHg)	93.500 ± 10.687	95.988 ± 10.621	90.017 ± 10.015	0.055
Biochemical parameters				
TC (mg/dL)	234.063 ± 45.237	234.571 ± 47.307	233.350 ± 43.370	0.928
HDL-C (mg/dL)	61.917 ± 15.643	57.679 ± 13.617	67.850 ± 16.684	0.025*
TG (mg/dL)	85 (30–268)	87 (49–268)	85 (30–190)	0.691
LDL-C (mg/dL)	161.006 ± 43.186	161.621 ± 45.516	160.145 ± 40.843	0.909
FBG (mg/dL)	98.50 (85–243)	97.50 (85–130)	102.50 (87–243)	0.205
Clinical parameters				
HT	12 (25)	11 (39.3)	1 (5)	0.007*
Obesity	17 (35.4)	9 (32.1)	8 (40)	0.398
Dyslipidemia	30 (62.5)	19 (67.9)	11 (55.0)	0.272
DM	1 (2.1)	0 (0)	1 (5)	0.417

Values are presented as mean±standard deviation or number (%) or median (interquartile range).
BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HT, hypertension; DM, diabetes mellitus.
*p<0.05. p-values as compared between daily step count groups, were derived from independent t-test or Mann–Whitney U test, or chi-square test, as appropriate.

with higher daily step counts (132 vs. 127 mmHg, p = 0.026). Additionally, the group with a daily step count > 5,000 had a higher HDL-C level (67.850 ± 16.684 vs. 57.679 ± 13.617 mg/dL, p = 0.025). However, there were no statistically significant differences in height, weight, or BMI between the daily step count subgroups (Table 1).

Health assessments revealed that individuals who walked < 5,000 steps per day were more likely to exhibit hypertension, elevated CAVI (≥ 0.9), and increased (PWV ≥ 10) compared to their more physically active counterparts (p = 0.007, p = 0.035, and p = 0.004, respectively) (Tables 1, 2). PWV was significantly higher among participants with lower daily step counts than in the other daily step count group (10.375 ± 2.166 vs. 8.610 ± 1.689 m/s, p = 0.004). Conversely, the CAVI and ABI values did not differ significantly across the daily step count groups (Table 2).

The correlations between baseline characteristics and daily step counts for all participants are represented in Table 3. The physiological parameters were not significantly correlated with daily step counts. However, we observed a positive correlation between HDL-C level and daily step count (r = 0.316, p = 0.029). Correlation analysis revealed an inverse relationship between daily step count and R-CAVI (r = -0.311, p = 0.031) and PWV (r = -0.291, p = 0.045) (Fig. 1A, 1E). Moreover, when additional arterial stiffness parameters were integrated as explanatory variables in multiple regression analysis, PWV exhibited a negative correlation with daily step counts (β = -0.290, p = 0.047) (Table 4).

DISCUSSION

The results of this study provide information on the relationship between the daily step counts of older adults who take < 10,000 steps and various parameters associated with arterial stiffness. A previous study suggested a recommended daily step count goal of 7,000–10,000 steps for older adults.[11] However, our findings revealed a median daily step count of 4,645 (range, 2,099–9,876 steps), below the previously recommended levels. Another study

Table 2. Comparison of arterial stiffness parameters between daily step count groups

Variable	Total (n=48)	Group 1 (<5,000 steps/day) (n=28)	Group 2 (5,000–9,999 steps/day) (n=20)	p-value
R-CAVI	9.137±0.914	9.325±0.812	8.875±1.004	0.093
L-CAVI	9.041±0.925	9.168±0.922	8.865±0.923	0.268
CAVI >9.0	30 (62.5)	21 (75.0)	9 (45.0)	0.035*
R-ABI	1.130 (0.790–1.840)	1.130 (0.860–1.840)	1.085 (0.790–1.700)	0.152
L-ABI	1.100 (0.820–1.710)	1.130 (0.930–1.710)	1.080 (0.820–1.580)	0.064
ABI <0.9	3 (6.3)	2 (7.1)	1 (5.0)	0.627
PWV (m/s)	9.639±2.149	10.375±2.166	8.610±1.689	0.004*
PWV ≥10	20 (41.7)	17 (60.7)	3 (15.0)	0.002*

Values are presented as mean±standard deviation or number (%) or median (interquartile range).
R-CAVI, right cardio-ankle vascular index; L-CAVI, left cardio-ankle vascular index; R-ABI, right ankle-brachial index; L-ABI, left ankle-brachial index; PWV, pulse wave velocity.
*p<0.05. p-values as compared between daily step count groups, were derived from independent t-test or Mann–Whitney U test, or chi-square test, as appropriate.

Table 3. Correlation of physical characteristics, hemodynamic parameters, and biochemical parameters with daily step counts

Variable	Correlation (r)	p-value
Physical characteristics		
Age (y)	0.197	0.181
Height (cm)	0.129	0.380
Weight (kg)	0.004	0.981
BMI (kg/m^2)	-0.200	0.892
Hemodynamic parameters		
Resting HR (beats/min)	0.039	0.790
SBP (mmHg)	-0.263	0.071
DBP (mmHg)	-0.151	0.306
PP (mmHg)	-0.208	0.156
MAP (mmHg)	-0.218	0.137
Biochemical parameters		
TC (mg/dL)	0.095	0.522
HDL-C (mg/dL)	0.316	0.029*
TG (mg/dL)	-0.700	0.638
LDL-C (mg/dL)	0.085	0.566
FBG (mg/dL)	0.051	0.732

BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.
*p<0.05. Values of r represent Pearson or Spearman correlation coefficients, as appropriate.

reported that older adults without chronic diseases and/or smoking habits averaged 6,011±2,089 steps per day.[23] In Japan, older adults who wore accelerometers on their waists recorded a daily step count of approximately 5,412±2,878 steps per day.[24] Additionally, a cross-sectional study involving Japanese community dwellers aged 65–96 years observed an average daily step count of 5,850±169.[25] Several factors contribute to fewer daily steps among older individuals, including differences in devices, age demographics, geographical location, health conditions, and sample sizes.[23,26]

Our analysis revealed an inverse relationship between daily step counts and PWV. Although the correlation coefficient may appear relatively small, it is statistically significant. This finding has significant implications for patient health. The negative correlation suggests an association between increased daily step count and decreased PWV, emphasizing the potential cardiovascular benefits of regular physical activity. The results of a meta-analysis established a significant inverse correlation between daily step count and PWV. Participants with a daily step count of at least 7,500 showed a reduction in carotid-femoral PWV (cfPWV).[9] Furthermore, a previous study involving older Japanese individuals demonstrated that a 17-week pedometer-based physical activity program led to a decrease in baPWV through an increase in daily step count.[27] Earlier studies reported that adding 1,000 steps per day resulted in a 0.1 m/s decrease in cfPWV in adults with type 2 DM or hypertension.[28]

The results of this study demonstrated that individuals who took <5,000 steps per day had a higher likelihood of experiencing arterial stiffness, as assessed by CAVI values >9, compared to that in the other groups. However, our findings failed to establish a significant association between daily step count, CAVI, and ABI. One possible explanation for these findings could be that older adults with an abnormal ABI may have experienced discomfort or limitations in their walking ability, which could have inhibited their participation in our study. Additionally, patients with PAD who took <7,000 steps per day exhibited lower ambulatory function and health-related quality of life compared with those who took 7,000 and 10,000 steps per day.[29]

Accumulating evidence suggests that increasing the daily step count can improve cardiovascular health. Adding an extra 1,000

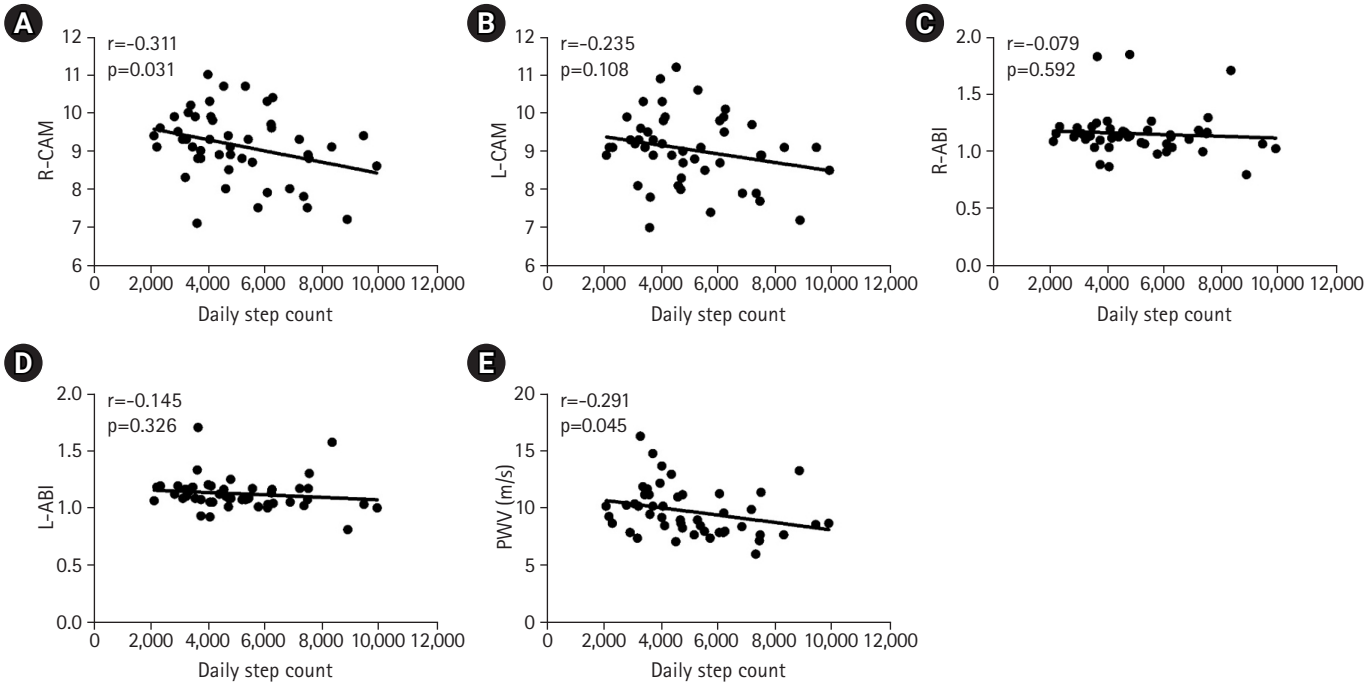

Fig. 1. Correlation between arterial stiffness parameters with daily step count: (A) right cardio-ankle vascular index (R-CAVI), (B) left cardio-ankle vascular index (L-CAVI), (C) right ankle-brachial index (R-ABI), (D) eft ankle-brachial index (L-ABI), and (E) pulse wave velocity (PWV).

Table 4. Multiple linear regression analysis of arterial stiffness parameters with daily step counts

Variable	Unstandardized coefficients		Standardized coefficients	t	p-value	VIF
	B (95% CI)	SE	β			
(constant)	14751.588 (7597.277–21905.898)	3545.104	-	4.161	< 0.001*	-
R-CAVI	-1427.211 (-3042.770–188.347)	800.542	-0.679	-1.783	0.082	7.796
L-CAVI	907.471 (-694.244–2509.186)	793.682	0.436	1.143	0.259	7.836
R-ABI	1197.946 (-4648.968–7044.859)	2897.263	0.121	0.413	0.681	4.607
L-ABI	-3329.470 (-11083.871–4424.932)	3842.462	-0.249	-0.866	0.391	4.433
PWV	-259.509 (-515.049–-3.968)	126.625	-0.290	-2.049	0.047*	1.077

Models were adjusted for adjusted for age, body mass index, sex, blood pressure, and lipid profile.
R-CAVI, right cardio-ankle vascular index; L-CAVI, left cardio-ankle vascular index; R-ABI, right ankle-brachial index; L-ABI, left ankle-brachial index; PWV, pulse wave velocity; B, estimate; β, standardized estimate; SE, standard error; CI, confidence interval; VIF, variation inflation factor.
Dependent variable was daily step counts (R=0.468; Adjusted R^2=0.126; R^2 change=0.219).
*p<0.05.

daily steps is significantly correlated with a reduced overall risk of CVD and all-cause mortality.[30] For adults aged >70 years, each additional 1,000 steps per day is associated with a 13% decrease in the risk of all-cause mortality.[26] Additionally, older women who averaged approximately 4,400 steps/day exhibited significantly lower mortality rates over a 4.3-year follow-up period compared with those who averaged approximately 2,700 steps/day. These health benefits, including anti-atherosclerotic properties and enhanced cardiovascular health, were observed even when daily step counts fell below the conventional threshold of 10,000 steps/day.[15,30] This improvement in vascular health can be attributed to the ability of physical activity to increase blood flow, induce vasodilation, reduce oxidative stress and inflammation, and enhance nitric oxide release.[27]

Our study results demonstrated that individuals who took more daily steps tended to have lower SBP compared with individuals who took fewer daily steps. Additionally, we observed a lower incidence of hypertension among individuals with higher daily step counts. Previous studies have reported lower SBP and DBP in the active group, averaging >4,227 daily steps, compared to those in the inactive group.[31] Similarly, participants categorized as somewhat active and active consistently displayed a lower SBP than

their inactive counterparts.[32] Moreover, individuals with hypertension tended to take fewer daily steps than those with normal BP.[31] However, our study results did not establish a significant relationship between the number of steps and BP parameters. This finding is in contrast to previous reports of significant negative relationships between accumulated daily steps and both SBP and DBP.[31] A pedometer-based walking program requiring either a daily accumulation of at least 10,000 steps[33] or an additional 3,000 steps/day[34] lowered SBP, DBP, or both in overweight Thai participants[33] and patients with hypertension.[34] One explanation for the effect of increasing daily step counts on lowering BP is an improvement in exercise capacity and a reduction in sympathetic nerve activities.[35]

Our study results are consistent with previous studies that reported higher HDL-C levels in women aged 50–60 years with 5,600–9,099 steps compared with those with < 5,600 steps.[36] In addition, these findings revealed an association between the number of steps and HDL-C levels. Consequently, increased HDL-C levels have been associated with stepping-based physical activity, especially those with high intensity.[37] Therefore, increased physical activity levels improve lipid profiles. Lower TG levels were significantly associated with high step volume in multiethnic Asian populations.[37] TC levels improved in participants with > 5,000 steps per day compared with those who took fewer steps, while individuals with ≥ 7,500 steps per day exhibited better LDL-C levels.[32] However, our study results did not establish a significant relationship, possibly due to the low intensity of the activities involved.

Although the statistically significant differences in SBP and HDL levels between the groups did not reach clinical significance at the individual level, it is important to highlight the potentially meaningful implications for cardiovascular health, particularly in the context of the long-term effects on morbidity and mortality. Additionally, the higher HDL levels we observed in individuals with greater daily step counts were consistent with established cardiovascular health indicators. The cumulative effect of increased HDL levels associated with regular physical activity suggests considerable cardiovascular benefits at the population level.

This study has several limitations. First, this was a single-center study with a relatively small sample size. Additionally, the cross-sectional design may restrict our capacity to establish causal relationships among the variables. Furthermore, the participants were not randomly selected from the population, potentially introducing a selection bias. Additionally, participants with specific medical conditions such as systolic dysfunction, atrial fibrillation or flutter, aortic disease, or valvular heart disease may not have been excluded from this study. These conditions can affect arterial stiffness.[38] Finally, we did not exclude patients with psychological conditions, which may have impacted the participants' walking habits. These limitations should be considered and addressed in future studies.

In conclusion, in this study, higher daily step counts were correlated with lower PWV in older adults. Future research should prioritize targeted interventions that focus on motivation, optimal activity intensity, and long-term cardiovascular effects in older adults. Regarding preventive strategies, initiatives such as implementing awareness campaigns on the relationship between daily step count and arterial health, promoting step-monitoring devices, and providing personalized lifestyle recommendations could be effective. Collaborations between healthcare professionals and community leaders can enhance the reach and impact of these preventive efforts.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, SP, TR; Data curation, RS, NH, TR; Investigation, RS, NH, TR; Methodology, SP, NH, PS, TR; Project administration, TR; Supervision, TR; Writing-original draft, SP, NH, TR; Writing-review & editing, SP, RS, NH, PS, TR.

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Impact of Motivation for Eating Habits, Appetite and Food Satisfaction, and Food Consciousness on Food Intake and Weight Loss in Older Nursing Home Patients

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Background: This study analyzed data from the Long-term care Information system For Evidence (LIFE) database to examine the effects of motivation to eat, appetite and food satisfaction, and food consciousness on food intake and weight loss. **Methods:** Of the 748 nursing home residents enrolled in the LIFE database, 336 met the eligibility criteria for this cross-sectional study. Motivation to eat, appetite and food satisfaction, and food consciousness were rated on five-point Likert scales (e.g., good, fair, normal, not so good, and not good). We applied Spearman rank correlation coefficient and multiple regression analyses to analyze the relationships between these three items, daily energy and protein intake, and body weight loss over 6 months. **Results:** The mean participant age was 87.4±8.1 years and 259 (77%) were female. The required levels of care included—level 1, 1 (0%); level 2, 4 (1%); level 3, 107 (32%); level 4, 135 (40%); and level 5, 89 (27%). The mean daily energy intake was 28.2±7.8 kcal/kg. The mean daily protein intake was 1.1±0.3 g/kg. The mean weight loss over six months was 1.2±0.7 kg. We observed strong positive correlations among motivation to eat, appetite and food satisfaction, and food consciousness ($r>0.8$). These three items were significantly associated with higher daily energy intake but not with daily protein intake. Only appetite and food satisfaction were significantly associated with lower weight loss over six months. **Conclusion:** The observed associations of appetite and food satisfaction suggest that these factors may be more important to assess than motivation to eat or food consciousness among older adult residents of long-term care facilities.

Key Words: Anorexia, Nutrition, Protein

INTRODUCTION

Nutrition is important for maintaining and improving function in older adults. A meta-analysis reported malnutrition prevalence rates of 28.7% and 29.4% in long-term and rehabilitation and subacute care, respectively.[1] Malnutrition is common in older adults requiring long-term care, and a malnutrition-disability cycle may occur, in which malnutrition and disability reinforce each other.[2] In patients with stroke and hip fractures requiring inpatient rehabilitation, sarcopenia is common, and activities of daily living (ADL) improve with improved nutritional status.[3-5] Rehabilitation nutrition, which combines both rehabilitation and nutritional care management, is important for maximizing function in older adults.[6-8] Additionally, poor oral health makes it difficult to regain function in rehabilitation.[9,10] Therefore, Japan is promoting the triad of rehabilitation, nutrition, and oral management to improve

functioning and prevent disability in the Japanese long-term care insurance system by 2021. Moreover, the Basic Policy on Economic and Fiscal Management and Reform 2023, a national policy created by the Japanese Cabinet, states that rehabilitation, nutrition management, and oral management should be coordinated and promoted.[11,12] Adequate dietary intake is important because it helps maintain good nutritional status and maintain or improve function.

While appetite is important in nutrition and maintaining function, whether differences in appetite are based on eating motivation, appetite and food satisfaction, and food consciousness remain unclear. Moreover, although aging anorexia is a common and distressing geriatric syndrome, it is underdiagnosed and undertreated in routine clinical care.[13] Appetite loss is associated with increased risks of malnutrition, mortality, and decreased muscle strength, as well as decreased physical performance.[14,15] Anorexia is a diagnostic criterion for cachexia in Asia.[16] Therefore, appetite assessment is necessary in older adults who require long-term care. The Long-term care Information system For Evidence (LIFE) database collects data on nutrition to improve nursing care.[17-20] The data collected by the LIFE include motivation to eat, appetite and food satisfaction, and food consciousness. However, the potential differing effects of these items on dietary intake and nutritional status are unknown.

Therefore, this study analyzed data from the LIFE database to examine the effects of eating motivation, appetite and food satisfaction, and food consciousness on food intake and weight loss.

MATERIALS AND METHODS

This cross-sectional study used data from the LIFE database. The details of the LIFE have been reported previously.[17-20] In brief, the Japanese Ministry of Health, Labor, and Welfare launched the LIFE long-term care insurance service database in April 2021. This database stores information on diseases, physical and cognitive functions, rehabilitation goals and interventions, ADL, instrumental ADL, and nutrition. This database provides feedback to users and facilities and promotes high-quality evidence-based services. In addition, based on the LIFE database, service providers can charge additional fees within the long-term care insurance system. The LIFE data used in this study were stored in the electronic medical record system of Care Connect, Japan. This study used cross-sectional data from 748 nursing home residents enrolled in the LIFE database between April 2022 and March 2023, with consent obtained from the nursing homes.

The inclusion criterion was residents of nursing homes with oral intake only. The exclusion criteria included missing data on oral intake, motivation to eat, appetite and food satisfaction, and food consciousness. The Ethics Committee of Mie University (No. H2022-210) approved the study, which was conducted in accordance with the ethical standards of the Declaration of Helsinki of 1964 and its subsequent amendments. Informed consent and approval requirements were waived.[21] This study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[22]

The LIFE database includes basic patient information such as age, sex, dementia, Barthel Index, and the requirement for a texture-modified swallowing diet. The motivation to eat refers to the willingness to eat three times a day, avoid leftovers, and maintain and improve health and function. The motivation to eat in the past three days was assessed using a five-point Likert scale: good = 1, fair = 2, normal = 3, not so good = 4, and not good = 5. Appetite refers to the desire for food. Food satisfaction encompasses satisfaction and preferences regarding taste, quantity, appearance, aroma, deliciousness, and appropriate temperature. These two items were rated individually, and their average was combined into a single response. Appetite and food satisfaction were the ratings for appetite and food satisfaction for the last 3 days, selected from five levels: much (level 1), some (level 2), usual (level 3), not much (level 4), and not at all (level 5). Food consciousness is an interest in choosing and eating an appropriate diet, including a balanced diet, appropriate portion sizes, and disease-specific diets, such as low-sodium diets for hypertension and low-protein diets for chronic kidney disease. Food consciousness in the last 3 days was rated according to five levels: much (level 1), some (level 2), usual (level 3), not much (level 4), and not at all (level 5). Food consciousness includes energy, nutritional balance, taste, appearance, aroma, ingredients, and quantity. Nurses, care managers, or care workers evaluated and entered these ratings into the database during the study period. Nutrient intake and other nutritional parameters were assessed by a nationally certified, registered dietician in Japan. Although training for the LIFE database was not conducted, registered dietitians possessed nutritional knowledge and skills. The LIFE database entry manual was used for data entry. The relationships between motivation to eat, appetite and food satisfaction, food consciousness, daily energy and protein intake in the last three days, and body weight loss over six months were examined.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). Parametric data are expressed as mean ± standard deviation, while nonparametric data are expressed as medians and interquartile range (IQR). We applied Spearman rank correlation coefficient and multiple regression analyses to investigate the relationships between motivation to eat, appetite and food satisfaction, food con-

sciousness, daily energy intake, daily protein intake, and body weight loss over 6 months. The multiple regression analysis was adjusted for age, sex, presence of dementia, eating independence as assessed using the Barthel Index, and the presence of a texture-modified swallowing diet, which was used to examine the relationship because these factors affect energy intake, protein intake, and body weight loss. Variance inflation factor (VIF) values > 10 were considered indicative of multicollinearity. Statistical significance was set at $p < 0.05$.

RESULTS

Among the 748 patients in the LIFE database, after excluding 15 patients without oral intake, two patients with both oral intake and enteral nutrition, and 395 patients with missing data, a total of 336 patients meeting the eligibility criteria were included in the analysis. Nurses, care managers, and care workers entered data for 100, 224, and 10 patients, respectively.

Table 1 shows the demographic and clinical characteristics of the patients. The mean age was 87.4 ± 8.1 years, and 259 (77%) were female. The median Barthel Index score was 30 (IQR, 10–50). Most of the responses regarding motivation to eat, appetite and food satisfaction, and food awareness were "usual," with no major differences in distribution. Dementia and Alzheimer disease were diagnosed in 212 (63%) and 130 (39%) patients, respectively. The mean daily energy intake, protein intake, and weight loss over 6 months were 28.2 ± 7.8 kcal/kg, 1.1 ± 0.3 g/kg, and 1.2 ± 0.7 kg (n = 106), respectively.

Table 2 shows Spearman rank correlation coefficients. The coefficient value between motivation to eat and appetite and food satisfaction was 0.822, that between motivation to eat and food consciousness was 0.834, and that between appetite and food satisfaction and food consciousness was 0.805, all of which were strongly positively correlated ($p < 0.001$). The Spearman rank correlation coefficients between motivation to eat, appetite and food satisfaction, food consciousness, and daily energy intake showed a weak negative correlation only for appetite and food satisfaction ($r = -0.113$, $p < 0.038$). We observed no significant correlations of motivation to eat, appetite and food satisfaction, and food consciousness with daily protein intake or weight loss over 6 months.

Table 3 presents the results of the multiple regression analysis. After adjusting for age, sex, presence of dementia, eating independence as assessed by the Barthel Index, and presence of a texture-modified swallowing diet, higher motivation to eat, higher appetite and food satisfaction, and higher food consciousness were all significantly associated with more daily energy intake, but not with daily protein intake. In contrast, only higher appetite and food satisfaction were significantly associated with lower weight loss over 6 months. All VIF values in the multiple regression analysis ranged from 1.0 and 1.6. Therefore, our multiple regression analysis did not reveal multicollinearity issues.

Table 1. The baseline demographic data

	Value
Age (y)	87.4 ± 8.1
Sex	
Male	77 (23)
Female	259 (77)
The level of care required	
1	1 (0)
2	4 (1)
3	107 (32)
4	135 (40)
5	89 (27)
Height (cm)	149.3 ± 9.1
Weight (kg)	46.0 ± 9.5
Body mass index (kg/m^2)	20.6 ± 3.6
Barthel Index	30 (10–50)
Eating independence as assessed by the Barthel Index	
Full assistance	63 (19)
Partial assistance	122 (36)
Independence	151 (45)
Dementia	212 (63)
Need for a texture-modified swallowing diet	208 (62)
Motivation for eating habits	
Good	70 (21)
Fair	42 (13)
Usual	187 (56)
Not so good	29 (9)
Not good	8(2)
Appetite and food satisfaction	
Much	50 (15)
Some	47 (14)
Usual	213(63)
Not much	21 (6)
Not at all	5 (2)
Food consciousness	
Much	55 (16)
Some	48 (14)
Usual	184 (55)
Not much	44 (13)
Not at all	5 (2)
Mean daily energy intake (kcal/kg)	28.2 ± 7.8
Mean daily energy intake (kcal)	1,286 ± 293
Mean daily protein intake (g/kg)	1.1 ± 0.3
Mean daily protein intake (g)	51 ± 12
Mean weight loss over 6 months (kg)	1.2 ± 0.7[a)]

Values are presented as mean±standard deviation or number (%) or median (interquartile range).
[a)]n=106.

Table 2. Spearman rank correlation coefficient

	Motivation for eating habits	Appetite and food satisfaction	Food consciousness	Mean daily energy intake	Mean daily protein intake	Mean weight loss over 6 months
Motivation for eating habits	-	0.822*	0.834*	-0.086	-0.024	0.038
Appetite and food satisfaction	-	-	0.805*	-0.113*	0.022	0.102
Food consciousness	-	-	-	-0.090	0.015	0.046
Mean daily energy intake	-	-	-	-	0.851*	-0.175
Mean daily protein intake	-	-	-	-	-	-0.131

*p<0.05.

Table 3. Multiple regression analysis

	Unstandardized coefficient		Standardized coefficient	p-value
	β (95% CI)	SE		
Mean daily energy intake				
Motivation for eating habits	-1.390 (-2.315, -0.464)	0.470	-0.169	0.003
Appetite and food satisfaction	-1.541 (-2.536, -0.545)	0.506	-0.170	0.003
Food consciousness	-1.182 (-2.073, -0.292)	0.453	-0.150	0.009
Mean daily protein intake				
Motivation for eating habits	-0.003 (-0.041, 0.035)	0.019	-0.009	0.872
Appetite and food satisfaction	-0.016 (-0.059, 0.026)	0.022	-0.043	0.451
Food consciousness	-0.016 (-0.055, 0.024)	0.020	-0.045	0.437
Mean weight loss over 6 months				
Motivation for eating habits	0.292 (-0.022, 0.606)	0.158	0.199	0.068
Appetite and food satisfaction	0.425 (0.082, 0.769)	0.173	0.251	0.016
Food consciousness	0.302 (-0.047, 0.651)	0.176	0.185	0.089

CI, confidence interval; SE, standard error.

DISCUSSION

This study examined the effects of motivation to eat, appetite and food satisfaction, and food consciousness on food intake and weight loss. Motivation to eat, appetite and food satisfaction, and food consciousness were associated with daily energy intake but not with daily protein intake. Appetite and food satisfaction were significantly associated with weight loss over 6 months. Motivations to eat, appetite and food satisfaction, and food consciousness were strongly positively correlated.

Regarding the association of motivation to eat, appetite and food satisfaction, and food consciousness with daily energy intake but not with daily protein intake, a previous systematic review reported that appetite scores were not correlated with energy intake in 51.3% of studies, regardless of participant age or sex.[23] Although these factors were associated with daily energy intake, the correlation was weak or insignificant according to the Spearman rank correlation coefficients. Although appetite should be assessed, factors other than appetite may have a greater influence on energy intake. Protein supplementation may suppress appetite; however, a previous meta-analysis reported that it had either a positive or no effect on total energy intake in older people.[24] Moreover, appetite does not necessarily correlate with protein intake in older adults.[25] In older adults with decreased appetite, energy intake is likely to be lower than protein intake; therefore, it may be better to first recommend increased energy intake. However, monitoring protein intake may be important in nursing home residents with good appetite because protein intake does not increase with appetite. If appetite is good but protein intake is inadequate, protein intake should be increased.

Appetite and food satisfaction, but not motivation to eat or food consciousness, were significantly associated with weight loss over six months. Motivation to eat can be improved with interventions.[26] While interventions to improve food consciousness can increase interoceptive sensitivity and exteroceptive expression,[27] these may not be enough to prevent weight loss. Age-related anorexia is also associated with physical frailty and weight loss.[28,29] Food satisfaction is associated with oral frailty in community-dwelling older people.[30] Moreover, oral frailty is a risk factor for physical frailty and may lead to weight loss.[31] Therefore, the assessment of appetite and food satisfaction may be more important than that of the motivation to eat or food consciousness.

We observed strong positive correlations among motivation to eat, appetite and food satisfaction, and food consciousness. Al-

though these are different concepts, the strong correlations suggest much common ground. As the LIFE database has many input items and a high input burden, the number of input items should be reduced if possible. The results of the present study showing strong correlations suggest that if appetite and food satisfaction are recorded, the other two items may not be required.

This study has several limitations. First, not all items related to dietary intake and weight loss were adjusted in the multivariate analysis. The LIFE database contains many items; however, including more items in the multivariate analysis would increase the number of cases excluded because of missing values. Second, many of the patients had dementia and may not have responded appropriately to questions about motivation to eat, appetite, food satisfaction, and food consciousness. Third, the multiple regression analysis included the presence of dementia rather than its severity. The LIFE database lacks data on the severity of dementia; however, it did include the "criteria for determination of the daily life independence level of older adults with dementia," which comprises eight steps. We conducted multiple regression analyses using these criteria instead of the presence of dementia. Nevertheless, the results were similar, and neither the criteria for determining the daily life independence level of older adults nor the presence of dementia was independently associated with energy intake, protein intake, or body weight loss. Fourth, because the LIFE database contained only cross-sectional data, we were unable to perform a longitudinal study, and the causal relationships were uncertain. Future studies should use the LIFE database that contains longitudinal data.

In conclusion, higher motivation to eat, appetite and food satisfaction, and food consciousness were significantly associated with more daily energy intake but not with daily protein intake. Only higher appetite and food satisfaction were significantly associated with lower weight loss over 6 months. Motivation to eat, appetite, food satisfaction, and food consciousness were strongly positively correlated. Further longitudinal studies are needed to examine the relationship of appetite and food satisfaction with weight loss, ADL, oral status, and swallowing function to determine whether some items can be removed from the LIFE database.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, HW; Data curation, HW, SK, RM; Funding acquisition, RM; Investigation, HW; Methodology, HW, RM; Project administration, RM; Supervision, SK, TI, KS, HT; Writing-original draft, HW; Writing-review & editing, SK, TI, KS, HT, RM.

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Elevated Homocysteine Level and Brain Atrophy Changes as Markers to Screen the Alzheimer Disease: Case Series

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Alzheimer disease (AD) is the most common cause of dementia worldwide. Its clinical manifestations include a progressive loss of memory and other cognitive domains, as well as brain atrophy. An elevated homocysteine level (>15 μmol/L), known as hyperhomocysteinemia, is also an attributing risk factor for AD, vascular pathologies, and brain atrophy. Neuroimaging studies including T2-weighted magnetic resonance imaging scans revealed white matter hyperintensities in the periventricular and deep white matter, enlarged ventricles, widened sulci, and decreased white matter mass, which are features of aging, as well as cerebrovascular changes. This case series investigated changes in biochemical marker levels including serum homocysteine, folate, and vitamin B12, and the degree of atrophic variations in cortical-subcortical white matter in AD. The present study hypothesized that serum homocysteine levels might be used as a surrogate marker to screen for AD at an earlier stage.

Key Words: Alzheimer's disease, Brain atrophy, Homocysteine, Vitamin B12

INTRODUCTION

Alzheimer disease (AD) is an age-related progressive neurodegenerative disorder that presents with several neuropsychological impairments, including gradual loss of memory, cognitive decline, mental confusion, and changes in brain atrophy. An elevated homocysteine level (> 15 μmol/L), known as hyperhomocysteinemia,[1] might initiate oxidative stress or changes in DNA methylation, subsequently leading to cortical and subcortical atrophy. Furthermore, it causes neurotoxicity and interferes with neurotransmission in the brain.

Homocysteine is an integral part of the methionine cycle, which involves its remethylation by the methionine synthase enzyme, a process that requires vitamin B12, folate as a cofactor, and 5-methyl tetrahydrofolate (THF) as a methyl donor. Further, S-adenosyl methionine synthase induces methionine to join with adenosine triphosphate to form S-adenosyl methionine (SAM), which requires vitamin B6 and pyridoxal-5'-phosphate (PLP), which is a universal methyl group donor. Due to SAM depletion, it is converted to S-adenosyl-homocysteine, which is further hydrolyzed into homocysteine. Disturbances in homocysteine metabolism may arise from deficiencies in vitamin B12, folate, or other related pathological conditions.[2] Such disruptions have the potential to worsen the condition by contributing to the formation of neuritic plaques, including amyloid plaques and neurofibrillary tangles.[3]

Imaging studies, including magnetic resonance imaging (MRI)-based studies of cortical atrophy, are surrogate methods used to evaluate neurodegenerative changes in the brain or diagnose AD.[4,5] Although aging is an important factor related to brain atrophy, the shrinkage of the cerebral cortex is hastened in the progression from mild cognitive impairment to AD. Furthermore, the evaluation of changes in brain atrophy could help in determining

the severity of AD.[6] White matter hyperintensity (WMH) has been most commonly noted on T2-weighted fluid-attenuated inversion recovery sequences, and are features of aging and cerebrovascular changes.[7]

The results of the present case series demonstrated that hyperhomocysteinemia occurring due to folate and vitamin B12 deficiency may be associated with brain atrophy or the severity of cognitive impairment—Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA). Moreover, we performed an in-depth evaluation of anatomical changes in the brain after MRI of four older adults with cognitive impairment and observed that serum homocysteine levels may be correlated with changes in brain atrophy.

CASE REPORT

Case 1

An 80-year-old woman was brought by her daughter to the geriatric department of JSS Hospital with concerns over her mother's moderate forgetfulness, confusion, and misplacing items at home. Her daughter complained that the patient had acted irritated, anxious, and less interested in communicating with family members and neighbors for the past 6 months. The patient was examined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), criteria followed by a cognitive test. The patient scored 16/30 on the MMSE and 13/30 on the MOCA. Moreover, the patient was moderately affected by psychiatric issues in the Neuropsychiatry Innovatory Questionnaire (NPI) and was able to perform activities of daily living. MRI showed atrophy of the cerebral cortex (prominent sulci), enlarged ventricles, and bilateral temporoparietal atrophy (Fig. 1). Further investigation of the biochemical parameters revealed a significantly increased serum homocysteine level (21 μmol/L; reference range 5–15 μmol/L) and decreased folate level (4.2 ng/mL; reference range 4.6–34.8 ng/mL). However, the patient's vitamin B12 level remained within the normal range (429 pg/mL; reference range 197–771 pg/mL). The biochemical investigations were performed using a Cobas6000 clinical chemistry analyzer (Roche Diagnostics, Indianapolis, IN, USA) following standard operating procedures in the Department of Biochemistry, JSS Hospital, Mysore, India.

Case 2

A 74-year-old woman was accompanied by her son to the geriatric department at JSS Hospital with concerns about her severe forgetfulness of recent events, language problems, and confusion. Her son complained of her irritation, anxiety, and depression that had lasted for 1 year. The patient scored 10/30 on the MMSE and 9/30 on the MOCA and was severely affected by neuropsychiatric issues and inability to perform activities of daily living on functional assessment (IADL). Additionally, MRI showed cerebral cortex atrophy, enlarged sulci and ventricles, reduced gyri volume, and chronic small-vessel ischemic changes. WMHs were observed bilaterally in the frontoparietal cortex (Fig. 2). Biochemical investigation revealed homocysteine, folate, and vitamin B12 levels of 22.5 μmol/L, 3.2 ng/mL, and 194 pg/mL, respectively.

Case 3

A 76-year-old woman was accompanied by her husband to the geriatric department at JSS Hospital with complaints of her forgetfulness of recent events and mild confusion. Her husband complained that the patient had felt anxious and depressed for 3

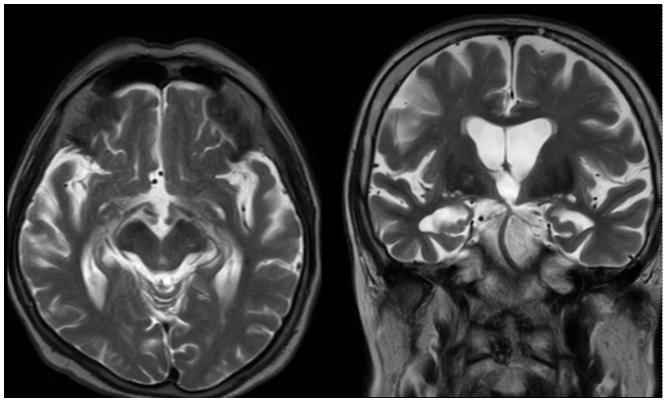

Fig. 1. Case 1 represents bilateral temporoparietal and parietotemporal cortices atrophy as well as enlarged ventricle and widened sulci.

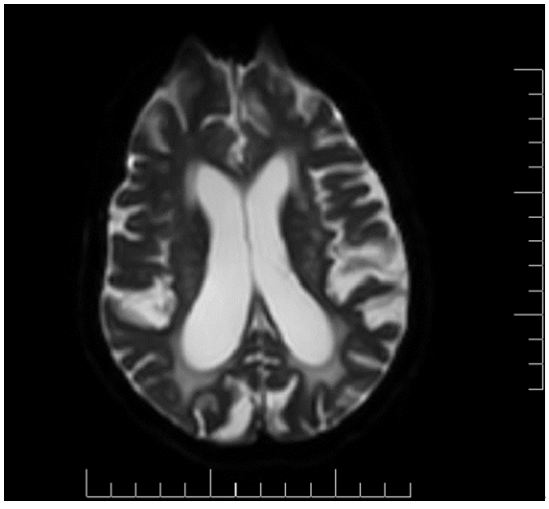

Fig. 2. Case 2 represents progressive enlarged lateral ventricle, sulci, decreased mass of gyri chronic small vessel ischemic changes, and white matter hyperintensities noted in bilateral frontoparietal cortices.

months. She scored 23/30 on the MMSE and 22/30 on the MOCA, was mildly affected on the NPI domains, and was able to perform activities of daily living on functional assessment (IADL). Radiological examination and MRI showed age-related cerebral atrophy with chronic small-vessel ischemic changes. WMHs were observed bilaterally in the frontoparietal cortex (Fig. 3). However, in the analysis of blood serum, her homocysteine, folate, and vitamin B12 levels were measured at 12 μmol/L, 20 ng/mL, and 333 pg/mL, respectively.

Case 4

A 72-year-old man was accompanied by his son to the geriatric department at JSS Hospital complaining of severe forgetfulness in recent events, confusion, and less interest in performing household tasks. On cognitive assessment, he scored 10/30 on the MMSE and 9/30 on the MOCA and had severely affected NPI domains. The functional assessment (IADL) score was 0, indicating dependence on a caretaker to perform activities of daily living. Similarly, MRI showed age-related cerebral atrophy with chronic small-vessel ischemic changes. Multifocal, ill-defined hypodensities were observed in the frontal, parietal, and temporal lobes (Fig. 4). Blood serum investigation showed homocysteine, folate, and vitamin B12 levels of 8 μmol/mL, 17.1 ng/mL, and 1,985 pg/mL, with a significant increase in vitamin B12 level.

DISCUSSION

Evaluation of atrophic changes in the cerebral cortex and their correlation with serum homocysteine levels is necessary to unravel AD severity and etiology. The results of the present study revealed elevated homocysteine levels and decreased folate and vitamin B12 levels in two of the four cases. MRI revealed bilateral temporoparietal cortex atrophy, decreased cerebral cortex mass, prominent sulci, enlarged lateral ventricles, and chronic small-vessel ischemic changes. Similarly, WMHs noted in the bilateral frontoparietal and temporal cortices as well as in the periventricular and deep white matter. A meta-analysis study reported that patients with increased levels of homocysteine and lower folate levels might have increased susceptibility to AD.[8] Another study confirmed decreased vitamin B12 and folate levels but elevated homocysteine levels in patients with AD compared with healthy control subjects.[9,10] Elevated homocysteine levels and reduced MMSE scores are significantly associated with AD dementia and cognitive impairment.[11] Increased homocysteine levels are also associated with AD or vascular-associated dementia progression and also promote the inflammation of blood vessel walls.[12] Temporoparietal atrophy is a sensitive marker to detect the early stage of AD as neurofibrillary tangles start in the medial temporal lobes and further accumulate in the temporoparietal cortices, leading to episodic memory impairment.[13] A recent study reported that WMH is a surrogate marker of AD.[14] Moreover, the severity of cognitive impairment and its progression to AD are in proportion with WMH.[15] Cerebral small-vessel disease, cerebrovascular changes, and AD are strongly correlated, which could be dominant factors at an early stage of AD.[16,17] Prominent lateral ventricles and generalized cerebral atrophy are the most significant features of Alzheimer's dementia and are associated with cognitive impairment.[18,19]

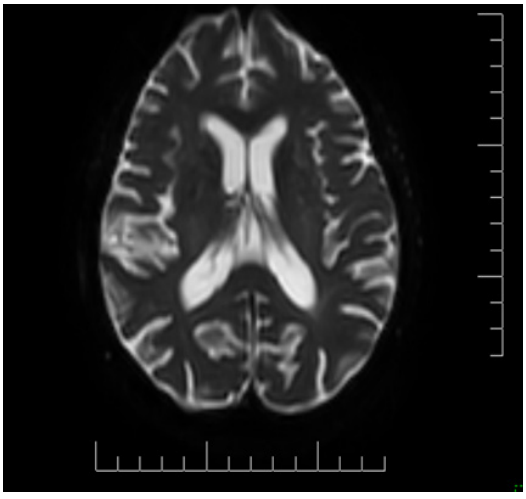

Fig. 3. Case 3 represents age-related cerebral atrophy with chronic small vessel disease. White matter hyperintensities were noted in the frontoparietal cortex and periventricular deep white matter.

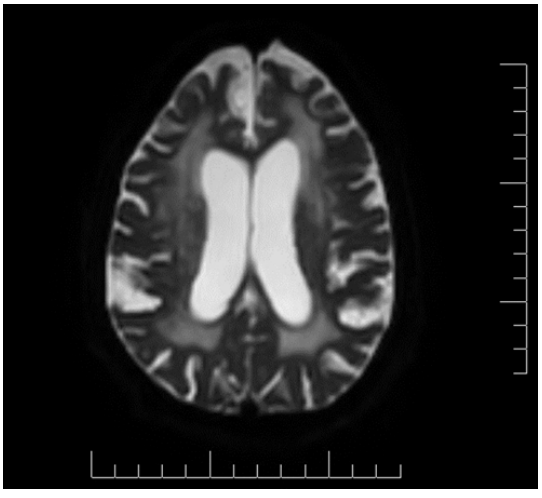

Fig. 4. Case 4 represents progressive enlarged lateral ventricle, sulci, decreased mass of gyri, and chronic small vessel disease. Multifocal ill-defined hypodensities were noted involving bilateral frontal, parietal, and temporal lobes.

Novelty of the Study

This is the first case series of patients clinically diagnosed with AD based on cognitive (MMSE, MOCA), behavioral (NPI), and functional (IADL) tests and MRI scans revealing reduced white matter mass, enlarged sulci, and ventricles to be reported in Southern India, particularly in the older adult population (age 65–85 years). Our study aimed to uncover specific associations between cognitive and functional behavior tests and changes in brain atrophy.

Additionally, the study aimed to identify potential correlations with elevated levels of homocysteine and decreased levels of vitamin B12 and folate. These measures were explored as a screening tool to detect AD at its earliest stage.

Conclusion

The present case series provides experimental evidence suggesting that homocysteine is a neurotoxin and a modified risk factor for neurodegenerative diseases, particularly AD and vascular dementia. Progressively enlarged lateral ventricles with cerebral atrophy and WMHs in different lobes of the cerebral cortex could be used as surrogate markers to screen for AD.

Vitamin B12 and folate deficiencies lead to increased homocysteine levels, which may aggravate brain atrophy and cognitive impairment. Evaluation of serum homocysteine levels and brain atrophy will act as a roadmap for geriatricians and neurologists to screen for AD, which may help in the early identification of pathological processes. Hence, the potential benefits of diet and medications could aid in reducing homocysteine levels and hinder cognitive decline, AD, and atrophy of the cerebral cortex in the older adult population.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

None.

AUTHOR CONTRIBUTIONS

Conceptualization, RPS, CSV; Data curation, CSV, PP; Investigation, RPS, PP; Methodology, RPS, AKY, SP; Project administration, RPS; Supervision, CSV, SJ, PP; Writing-original draft, RPS, CSV; Writing-review & editing, AKY, SD, SJ.

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Enactment December 27, 2013
Revision March 1, 2021

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

- Book chapter:

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

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

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