Heliyon 9 (2023) e22245

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Co-existence of malnutrition and sarcopenia and its related factors in a long-term nursing care facility: A cross-sectional study

Noriko Bando [a,b,1], Naomi Nakayama [a,*,1], Kaori Kashiwa [c], Rena Horike [d], Asaka Fujimoto [d], Mitsuharu Egawa [d], Munehiro Adachi [d], Hisae Saji [e], Beni Kira [a,b], Kentaro Nakayama [f], Akira Okayama [g], Satoru Katayama [a]

[a] *Hyogo Medical University, School of Medicine, Sasayama Medical Center, Department of General Medicine and Community Health Science, Tanbasasayama 669-2321, Japan*
[b] *Hyogo Medical University, School of Medicine, Sasayama Medical Center, Department of Clinical Nutrition, Tanbasasayama 669-2321, Japan*
[c] *Hyogo Medical University, School of Medicine, Center for Medical Education, Nishinomiya 663-8501, Japan*
[d] *Hyogo Medical University, School of Medicine, Sasayama Medical Center, Nursing Care Service Division, Tanbasasayama 669-2321, Japan*
[e] *Hyogo Medical University, School of Medicine, Sasayama Medical Center, Department of Rehabilitation, Tanbasasayama 669-2321, Japan*
[f] *Nagoya City University, School of Medicine, Department of Obstetrics and Gynecology 467-8602, Nagoya, Japan*
[g] *Japan Community Health Care Organization Kobe Central Hospital, Department of Orthopedics, Kobe, Japan*

ARTICLE INFO

Keywords:
Sarcopenia
Malnutrition
Co-MS
Aging
Potentially inappropriate medications

ABSTRACT

Objectives: Malnutrition and sarcopenia often co-exist in older patients. This condition, called co-MS, shows a worse prognosis than either condition alone but is often overlooked and under-treated. We aimed to clarify the prevalence of co-MS and its associated factors with a focus on prescription in a long-term nursing care facility in Japan.

Methods: Patients aged >65 years who resided in a long-term nursing care facility in Hyogo, Japan, were recruited for this cross-sectional study, which was conducted from July 1 to July 30, 2022. Sarcopenia and malnutrition were diagnosed using the Asian Working Group for Sarcopenia and Global Leadership Initiative on Malnutrition criteria, respectively. Patients who met both criteria were classified as having co-MS. Potentially associated factors, including age, sex, length of stay, activities of daily living, comorbidity, oral function and hygiene, swallowing ability, and the number and type of prescriptions, were assessed.

Results: The prevalence of sarcopenia was 92 % (72/78). All malnourished patients were sarcopenic (40.3 %) and were classified as having co-MS. Oral function and hygiene, swallowing ability, comorbidity, and the presence of potentially inappropriate medications showed significant associations in univariate analyses. Of particular note, potentially inappropriate medication was an independent factor in the multivariate analysis.

Conclusions: Co-MS is prevalent in long-term nursing care facilities; thus, healthcare workers should pay attention to relevant factors to identify patients at risk of co-MS and to provide appropriate care and intervention.

* Corresponding author. Hyogo Medical University, School of Medicine, Sasayama Medical Center, Department of General Medicine and Community Health Science, 5, Kurooka, Tanbasasayama, Hyogo, 669, Japan.
E-mail address: na-nakayama@hyo-med.ac.jp (N. Nakayama).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2023.e22245
Received 22 June 2023; Received in revised form 6 November 2023; Accepted 7 November 2023
Available online 11 November 2023

1. Introduction

Societal aging is currently occurring in most regions of the world, and the average life expectancy is steadily increasing [1]. This is particularly evident in Japan, where the population transitioned to an aging society (more than 7 % of the total population accounts for older adults) in the 1980s. The older adult population has continued to grow since then, reaching 28.9 % in 2021, the world's highest aging record [2].

Malnutrition and sarcopenia are two important conditions that adversely affect the health of older adults. They are conceptually different conditions but share a common etiology and often overlap in older patients [3,4]. Malnutrition in older individuals can lead to various health problems. The risk of malnutrition increases with age [5], leading to disability, reduced physical function, susceptibility to falls, high mortality, institutionalization, and hospitalization [6–8]. The prevalence of malnutrition varies depending on the environment of investigation, being relatively high (80 %) in acute hospital settings and low (23.4 %) in communities [6]. Moreover, this prevalence is greatly affected by the criteria used for diagnosis [9]. The Global Leadership Initiative on Malnutrition (GLIM) Criteria is a global standard diagnostic algorithm for diagnosing undernutrition that can be used not only in hospitals but also in various healthcare situations [9].

Sarcopenia is a skeletal muscle disease characterized by age-related decreases in muscle mass and muscle strength [10]. Its prevalence varies depending on the study, being relatively low in the community (5–20 %) [11,12] and high in nursing homes (15–85 %) [13–15]. Sarcopenia is associated with various adverse outcomes in older adults [12,13]. Previous reports have shown it to be an independent risk factor for decreases in activities of daily living (ADL), increased falls [10], and mortality [16]. Age-related sarcopenia is classified as primary sarcopenia, whereas sarcopenia caused by malnutrition, inactivity, or diseases is classified as secondary. In general, primary sarcopenia caused by simple aging is rare, and in many cases, aging and other causes co-exist [10].

Malnutrition and sarcopenia are closely related, and malnutrition is one of the factors that can cause sarcopenia [10]. Conversely, sarcopenia contributes to the development of malnutrition by causing dysphagia [8]. Sarcopenic dysphagia is a concept that was first reported in 2012 [17]. Since then, sarcopenic dysphagia has attracted attention, and position papers have been published by Japanese academic societies [8,18]. The definition of sarcopenic dysphagia is dysphagia caused by sarcopenia of whole-body muscles and swallowing-related muscles [19].

Malnutrition and sarcopenia are both conditions that are likely to co-exist in older adults, a condition known as co-MS. In an acute hospital setting in China, approximately 4.9 % of patients were classified as having co-MS, which was associated with a worse prognosis than malnutrition or sarcopenia alone [20]. Results from a post-acute care unit in Spain showed that 14.8 % of senior in-patients who received acute care had co-MS [21]. The prevalence thereof was also reported to be 23.5 % in older patients undergoing rehabilitation in a convalescent ward in Japan and was related to hospital-associated deconditioning and decreased swallowing ability [22].

The prevalence of sarcopenia is higher than that of malnutrition in older patients in various settings [22,23]. Malnutrition and sarcopenia were found in 29.0 % and 62.4 % of patients, respectively, in convalescent rehabilitation hospitals, and 88 % of malnourished patients were sarcopenic [22]. The prevalence of malnutrition and sarcopenia in daycare facilities in Japan is 40.3 % and 87.1 %, respectively, and all malnourished older adults are sarcopenic [23]. Therefore, in older adults in the chronic phase, the prevalence of sarcopenia is higher than that of malnutrition, and sarcopenia is highly comorbid with malnutrition. Similar results were found in a preliminary survey at the site where this study was conducted, with most older adults being sarcopenic and some in a state of co-MS due to comorbid malnutrition. Additionally, no individuals were categorized as solely malnourished, i.e., without sarcopenia. From these previous reports and our preliminary results, it is hypothesized that, among older adults with sarcopenia, a population might be at risk of accompanying malnutrition and progressing to co-MS. In this study, we aimed to clarify the possible factors that may lead to the progression from sarcopenia to co-MS. To this end, we investigated and described the clinicopathological features of co-MS and identified the associated factors by comparing older people with sarcopenia only and those with co-MS in a long-term nursing care facility. Particular attention was paid to the investigation of prescription drugs. This is because polypharmacy and the disadvantages that drugs pose for the elderly are major problems in the field of geriatric medicine. Through an understanding of this aspect, it may be possible to prevent progression to co-MS, which is considered to have a worse prognosis than sarcopenia.

2. Materials and methods

2.1. Study population

This research was conducted as a cross-sectional study at Hyogo Medical University, Sasayama Medical Center, affiliated with a long-term nursing care facility in Hyogo, Japan. We enrolled patients aged >65 years who stayed in the Sasayama Medical Center in July 2022. The study was conducted from July 1 to July 30, 2022. The facility has approximately 90 residents. We included participants aged ≥65 years with the ability to undergo diagnostic evaluation for sarcopenia. Patients who could not be safely evaluated for body composition because of severe dementia were excluded. After the diagnosis of sarcopenia and malnutrition, patients without both conditions were excluded because these patients were few (6/78), and we aimed to investigate the factors associated with developing co-MS from sarcopenia.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by the Ethics Committee of Hyogo Medical University (IRB: 4081). Written informed consent was obtained from all patients for participation in this research and the publication of this paper.

2.2. Diagnosis of sarcopenia, malnutrition, and co-MS

The Asian Working Group for Sarcopenia (AWGS) 2019 criteria were applied to diagnose sarcopenia, which includes muscle mass, volume, and strength, and algorithms for clinical research settings [24,25]. The sarcopenia diagnosis was assessed at the patient's bedside. We used the bioimpedance method for the muscle mass evaluation (Inbody S10; Biospace, Tokyo, Japan). Reduced muscle mass was defined when the skeletal muscle index (SMI) was below the following cutoff values: 5.7 kg/m^2 for women and 7.0 kg/m^2 for men [24,25]. Grip strength, measured using a Smedley hand dynamometer (TTM; Tokyo, Japan), was used as the muscle strength assessment. Reduced muscle strength was defined as a handgrip strength of $<$28 kg and $<$18 kg for men and women, respectively. When decreased muscle mass volume and muscle strength were confirmed, the participants were diagnosed with sarcopenia.

Malnutrition was diagnosed according to the GLIM criteria [26] by well-trained registered dietitians. The GLIM criteria are comprised of two criteria—phenotypic and etiologic—and malnutrition is diagnosed when both are met. Phenotypic criteria include low body mass index (BMI), unintentional body weight loss, and low skeletal muscle mass index (SMI), whereas etiologic criteria include decreased food intake/assimilation and disease burden/inflammation. Regarding phenotypic criteria, Asian-specific cutoff values were adopted for low BMI, which were $<$18.5 kg/m^2 for patients $<$70 years of age and $<$20 kg/m^2 for patients $\geq$70 years of age. Reduced muscle volume was defined using the SMI in the same manner as the diagnosis of sarcopenia described above. For the etiologic criteria, the state of chronic inflammation was assessed by the participants' disease burden, including advanced congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, chronic liver disease, rheumatoid arthritis with elevated inflammatory status (e.g., elevated *C*-reactive protein), and cancer [27]. Weight loss as a phenotypic criterion and reduced food intake or assimilation as an etiologic criterion were evaluated by reviewing medical charts. As for the consideration of weight loss, an objective observation of an unintentional weight loss of $\geq$5 % within six months or $\geq$10 % for a certain period was necessary. Regarding reduced food intake/assimilation, registered dietitians determined the condition as part of a comprehensive nutritional assessment by reviewing patients' clinical symptoms and medical records. Briefly, under the condition of providing individually set adequate nutritional intake requirements, the dietitians reviewed the patient's daily meal intake records and determined whether food intake was reduced. A 50 % reduction in food intake for more than one week or any percentage reduction in intake for more than two weeks was considered reduced food intake. When malabsorptive disorders such as short bowel syndrome and pancreatic insufficiency existed or a chronic GI condition that adversely impacts food assimilation or absorption, such as chronic diarrhea or steatorrhea, was observed, it was considered reduced assimilation. Patients who met the criteria for both malnutrition and sarcopenia were classified as having co-MS.

2.3. Evaluation of prescriptions

Since prescriptions have a large impact on clinical practice in the field of geriatrics, we comprehensively evaluated prescription drugs. Trained physicians evaluated the patients' current medications based on prescriptions recorded in their medical charts. The presence of potentially inappropriate medications (PIMs) and the number of medications were evaluated simultaneously. Patients were defined as being subject to polypharmacy when they were prescribed $\geq$5 different medications simultaneously [28]. PIMs were assessed using the Screening Tool for Older Person's Appropriate Prescriptions for Japanese (STOPP-J) criteria, which are mainly used in Japan [29], and the following drugs were categorized accordingly: antipsychotics (first- and second-generation); antidepressants; hypnotics (barbiturates, benzodiazepines, and non-benzodiazepine receptor agonists); anti-Parkinson drugs; sulpiride; steroids; digitalis; antithrombotic drugs (antiplatelet drugs and anticoagulants); diuretics; α-blockers; β-blockers; first-generation H1 receptor antagonists; H2 receptor antagonists; antiemetic drugs; oral antidiabetic drugs; insulin; overactive bladder medications; laxatives; and non-steroidal anti-inflammatory drugs. The active ingredients and generic names of the drugs were independently reviewed by other physicians to ensure classification accuracy.

2.4. Evaluation of other co-variants

Baseline profiles, including age, sex, and length of stay in the facility, were obtained from medical charts. The severity of the underlying disease was quantified using the Charlson Comorbidity Index (CCI), which measures the number, type, and severity of disease(s) [30].

The Katz-ADL Index is a functional measurement tool that assesses the status of independence in basic daily activities [31]. The Katz-ADL Index is used to assess a person's overall performance regarding six functions of self-care ability: bathing, dressing and undressing, using the toilet, mobility, controlling the bowel and bladder, and food intake. Performance for each activity was evaluated on a 7-point scale as follows: 1, independent in all functions; 2, dependent on help in one activity; 3, dependent in two activities; 4, dependent in three activities; 5, dependent in four activities; 6, dependent in five activities; and 7, dependent in all six activities.

The Food Intake LEVEL Scale (FILS) is a scale that uses 10 levels to evaluate swallowing function [31]. Speech-language-hearing therapists conducted this evaluation. The FILS scores ranged from level 1 (currently no swallowing training due to severe dysphagia or disturbed consciousness) to level 10 (currently eating without problems). Levels 1 to 3, 4 to 6, and 7 to 10 indicate "no oral intake" (i.e., the patients do not eat any food orally due to severe dysphagia or disturbed consciousness), "oral intake and alternative nutrition" (i.e., the patient can eat orally in addition to supplemental enteral or parenteral nutrition), and "oral intake alone," respectively [32]. This has been validated on the Functional Oral Intake Scale, which showed a significant correlation ($r = 0.96$–0.99) [32]. The Revised Oral Assessment Guide (ROAG) was used to assess oral hygiene and function. These were individually assessed by trained dental hygienists [33]. The ROAG includes voice, swallowing, lips, teeth or dentures, oral mucosa, gingiva, tongue, and saliva. Each item is scored on a

scale of 1 (normal) to 3 (severe disability), with the total score ranging from 8 to 24. A total score of 8 indicates normal oral status; 9–12, mild to moderate oral problems; and 13–24, severe oral problems [33].

For the cognitive function assessment, we used the Cognitive Performance Scale (CPS). The CPS is a scale originally developed to evaluate cognitive function in nursing home residents [34]. Trained medical social workers completed the CPS through interviews and medical charts. The CPS assesses a patient's cognitive performance in four domains: short-term memory, ability to make decisions, ability to make oneself understood, and ability to eat. Scores range from 0 to 6, with higher scores indicating worse cognition, and patients are classified into seven categories based on their CPS performance [34].

2.5. Statistical analyses

Data analyses were performed using IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, NY). Continuous variables are reported as mean (standard deviation), and categorical variables are presented as numbers (%). A sample-estimate univariate analysis was performed to examine factors associated with sarcopenia and co-MS. For univariate analysis, each factor was converted into a variable. Continuous variables in a normal distribution were tested using the *t*-test, and those that were not normally distributed were tested by Wilcoxon's ran sum test. CCI, FILS, number of prescribed drugs, and PIMs were converted into two category variables and analyzed using the Fisher's exact test.

In order to determine the risk factors for patients with sarcopenia developing a co-existence of malnutrition, a multivariate logistic regression model was established. In this model, we input "co-existence of malnutrition" as a dependent variable and four clinically relevant factors with available evidence and physiological plausibility—PIMs, CCI, FILS, and number of prescribed drugs—as independent variables and calculated each odds ratio to identify the variables that have a risk of co-existence of malnutrition.

Variables were entered into the regression model simultaneously. All tests of significance were two-tailed, and statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient selection and characteristics

A total of 92 patients aged ≥65 years stayed at Hyogo Medical University, Sasayama Medical Center, affiliated with a long-term nursing care facility during the research period. Among these, seven patients who were unable to provide consent and seven who were unable to perform valid muscle measurements using a body composition analyzer due to limb contractures or severe dementia were excluded. Subsequently, 78 patients underwent diagnostic evaluation for sarcopenia and malnutrition. Among them, six patients were not diagnosed with sarcopenia or malnutrition. Thus, 72 out of 78 patients were diagnosed with sarcopenia, and 29 out of 78 were diagnosed with malnutrition. All the malnourished patients had comorbid sarcopenia. Older individuals with neither malnutrition nor sarcopenia were excluded, whereas those with sarcopenia alone or both malnutrition and sarcopenia (co-MS) were included in the analysis (Fig. 1).

A summary of the clinical characteristics of the study population is shown in Table 1. The mean age was 86.4 years, and the mean length of stay was 303 days, which is relatively long compared with that in acute care hospitals, given that it is a long-term nursing care facility. The mean Katz-ADL Index was 5.07, suggesting that most patients needed assistance to perform their ADL. Additionally, most patients (83 %) had oral health problems based on the ROAG scores. The mean FILS score was 7.61. Participants were divided into two

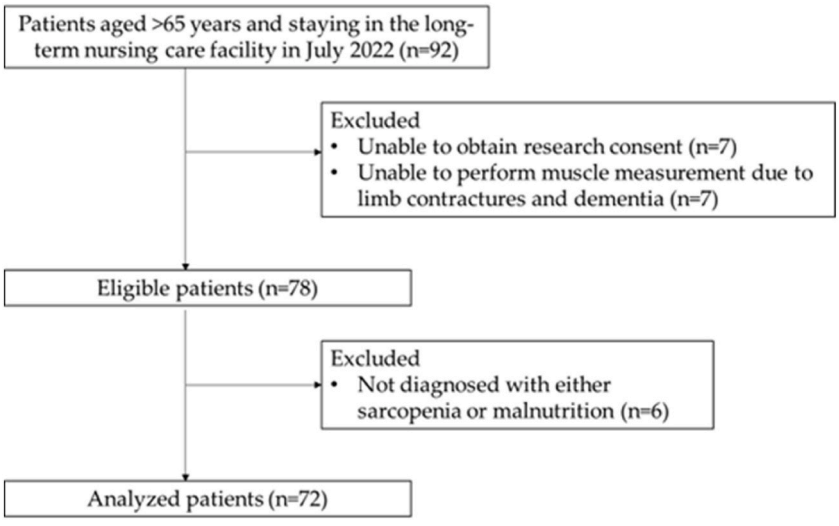

Fig. 1. Flowchart of study participant selection.

Table 1
Characteristics of the study population (n = 72).

Characteristics	Values
Age, years	86.4 (9.64)
Length of stay (days)	303.7 (322.23)
Female sex, n (%)	45 (62.5)
Charlson Comorbidity Index	2.68 (1.71)
FILS score	7.61 (2.10)
<7, n (%)	11 (15.2)
≥7, n (%)	61 (84.8)
ROAG score	11.90 (3.10)
CPS score	4.17 (1.34)
Katz-ADL Index	5.07 (1.97)
Number of prescribed drugs	6.79 (3.63)
<5, n (%)	21 (29.9)
≥5, n (%)	51 (70.1)
Number of PIMs	1.6 (1.64)
0, n (%)	24 (33.3)
≥1, n (%)	48 (66.7)

Data are presented as the mean (standard deviation) unless otherwise noted.
FILS, Food Intake LEVEL Scale; ROAG, Revised Oral Assessment Guide; CPS, Cognitive Performance Scale; ADL, activities of daily living; PIMs, potentially inappropriate medications.

groups, those with FILS scores <7 and those with scores >7, and patients with scores <7 (requiring varying levels of alternative nutrition) were defined as having severe dysphagia [32]. Eleven patients (15.2 %) had severe dysphagia, four of whom were completely fed by gastrostomy without any oral food intake. The mean CPS score was 4.17, and all patients had cognitive decline to a varying extent. The mean number of prescribed drugs was 6.79, and the number of patients who received more than five drugs was 51 (70.1 %), which was considered to be polypharmacy. Forty-eight patients (66.7 %) were administered one or more PIMs.

3.2. Diagnosis of sarcopenia, malnutrition, and co-MS

Study participants were screened using the AWGS 2019 and GLIM criteria; only six were not diagnosed with either sarcopenia or malnutrition. We excluded the six patients without malnourishment or sarcopenia from the study population and included the remaining 72 (92 %) in our analysis. Of the 72 patients with sarcopenia, 29 (40.3 %) were diagnosed with malnutrition by the GLIM criteria (Table 2). As all malnourished patients also had the co-existence of sarcopenia, the prevalence of co-MS was 40.3 % (29/72).

The SMI in men was relatively higher than in women (mean SMI for men and women, 5.53 kg/m^2 vs. 4.14 kg/m^2). Among the GLIM phenotyping criteria for the diagnosis of malnutrition, a decreased SMI was found in all patients (100 %), unlike the other criteria, such as decreased BMI (56 %) and body weight loss (12.5 %). Overall, 22 % of patients had decreased food intake or assimilation, whereas

Table 2
Prevalence of malnutrition, sarcopenia, and co-MS and the result of their diagnostic items in the study population (n = 72).

Characteristic	Value
Sarcopenia, n (%)	72 (100)
GLIM malnutrition, n (%)	29 (40.3)
Co-MS, n (%)	29 (40.3)
SMI, kg/m^2	
Women	4.14 (0.69)
Men	5.53 (0.77)
BMI, kg/m^2	
Women	19.60 (2.86)
Men	20.31 (2.6)
GLIM criteria phenotype, n (%)	
Body weight loss	9 (12.5)
Low BMI	40 (56)
Low SMI	72 (100)
GLIM criteria etiology, n (%)	
Reduced food intake/assimilation	16 (22.2)
Inflammation	17 (23.6)

Data are presented as the mean (standard deviation) unless otherwise noted.
Co-MS, malnutrition and sarcopenia; GLIM, Global Leadership Initiative on Malnutrition; SMI, skeletal muscle index; BMI, body mass index.

23.6 % showed chronic inflammation as an etiology of malnutrition.

3.3. PIMs according to the STOPP-J criteria

PIMs were detected in 48 patients (66.7 %) according to the STOPP-J criteria, and the mean number of PIMs was 1.6 (1.64). Fig. 2 shows the number of patients administered PIMs in each category, and Fig. 3 shows the number of patients taking PIMs in each category among patients with sarcopenia only and those with co-MS. The three most frequently prescribed PIMs according to the STOPP-J criteria were antithrombotic drugs (37.5 %), diuretics (23.6 %), and beta-blockers (16.7 %) (Fig. 2). In contrast, the PIMs that were prescribed significantly more frequently to patients with co-MS than to patients with sarcopenia only were diuretics ($p < 0.001$), steroids ($p = 0.012$), and oral antidiabetic drugs ($p = 0.004$) (Fig. 3).

3.4. Factors associated with co-MS

Table 3 shows the factors significantly associated with co-MS. For the CCI and FILS, we divided the patients into the two groups of severe comorbidity (CCI≥3) and other (CCI<3) and severe dysphagia (FILS<7) and other (FILS≥7), respectively.

Univariate analysis showed that participant comorbid conditions (CCI), swallowing ability (FILS score), oral condition (ROAG score), and presence of PIMs were associated with co-MS ($p < 0.05$). Age, length of stay, cognitive status (CPS score), ADL (Katz-ADL Index), and polypharmacy were not associated with co-MS ($p > 0.05$) (Table 3).

The results of the multivariate logistic regression analysis are presented in Table 4. The presence of PIMs was identified as an independent factor for co-MS (odds ratio = 18.00, 95 % confidence interval: 1.898–170.79, $p < 0.05$).

Patients with co-MS showed a significantly lower BMI and SMI than those with sarcopenia only (Table 5). It is plausible that loss of body weight and low body weight are common in malnourished patients. It is also plausible that malnutrition causes sarcopenia, and a negative energy balance caused by malnutrition can induce muscle catabolism.

4. Discussion

We investigated the clinicopathological features of co-MS and identified the possible associated factors in a long-term nursing care facility in this study. Sarcopenia alone existed in our cohort, but malnutrition alone did not, and malnutrition was always comorbid with sarcopenia. Although not conclusive, this may support our hypothesis that sarcopenia may precede malnutrition and that progression occurs from sarcopenia only to co-MS in a long-term nursing care facility. We also clarified, for the first time, that taking medications classified as PIMs, rather than polypharmacy, is a statistically independent factor associated with co-MS. To the best of our

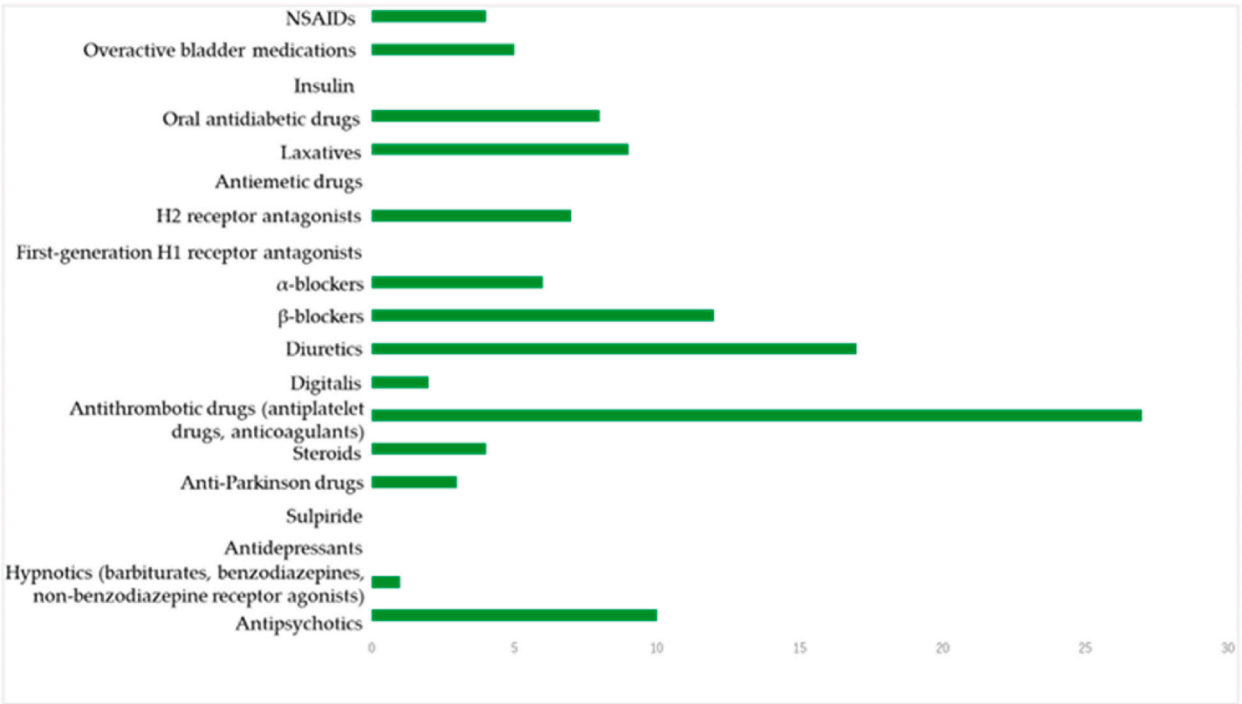

Fig. 2. Number of patients receiving PIM prescriptions by category according to the STOPP-J criteria. PIM, potentially inappropriate medication; STOPP-J, Screening Tool for Older Person's Appropriate Prescriptions for Japanese.

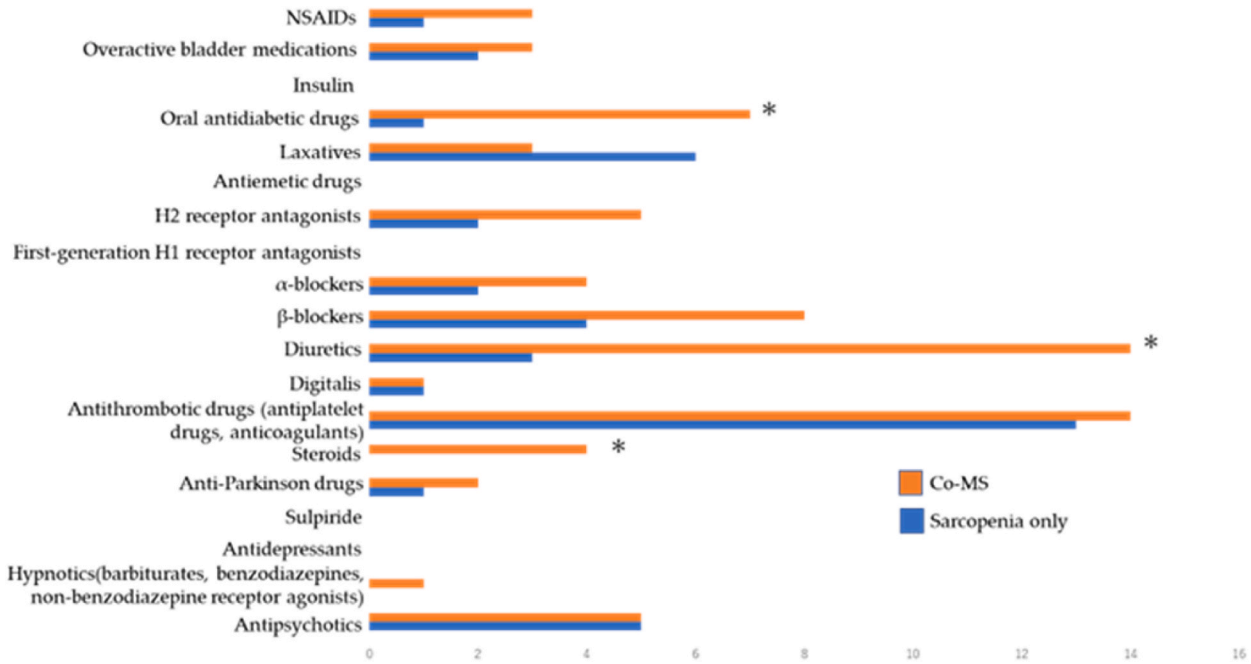

Fig. 3. Number of patients receiving PIM prescriptions by category according to the STOPP-J criteria, shown separately for patients with sarcopenia only and those with co-MS. *Drugs prescribed significantly more frequently to patients with co-MS than to patients with sarcopenia only (p-value<0.05). PIM, potentially inappropriate medication; STOPP-J, Screening Tool for Older Person's Appropriate Prescriptions for Japanese; co-MS, malnutrition and sarcopenia.

Table 3
Factors associated with co-MS according to the univariate analysis.

	Sarcopenia only (n = 43)	Co-MS (n = 29)	p-value
Age	85.79	87.34	0.506
Length of stay (days)	343.04	216.62	0.084
CCI	1.98	3.72	<0.001
<3[a]	28	7	
≥3	15	22	<0.001
FILS score	8.21	6.72	0.003
<7[b]	3	8	
≥7	40	21	0.017
ROAG score	10.51	13.97	<0.001
CPS score	4.02	4.38	0.237
Katz-ADL Index	4.70	5.62	0.051
Number of prescribed drugs			
<5[c]	15	6	
≥5	28	23	0.194
Number of PIMs			
0	23	1	
≥1	20	28	<0.001

Co-MS, malnutrition and sarcopenia; CCI, Charlson Comorbidity Index; FILS, Food Intake LEVEL Scale; ROAG, Revised Oral Assessment Guide; CPS, Cognitive Performance Scale; ADL, activities of daily living; PIMs, potentially inappropriate medications.

[a] CCI<3 indicated mild to moderate comorbidity, and CCI≥3 indicated severe comorbidity.

[b] FILS <7 indicated "no oral intake" and "oral intake and alternative nutrition," and FILS ≥7 indicated "oral intake alone." A FILS score of <7 indicated severe dysphagia.

[c] Number of prescribed drugs ≥5 indicates polypharmacy.

knowledge, this is the first study to investigate the clinical characteristics of co-MS in a long-term nursing care facility.

The prevalence of sarcopenia is influenced by age group and clinical setting. Ethnicity and the diagnostic criteria used also affect prevalence. The prevalence of sarcopenia has been reported to range from 1 to 29 % among community-dwelling older adults [18, 35–40], 14–85.4 % in nursing homes [12–15], and 10–24.3 % in acute hospitals [41,42]. We used the latest Asian-specific diagnostic tool, AWGS 2019, to diagnose sarcopenia in a long-term nursing care setting and demonstrated that the prevalence of sarcopenia was fairly high at 92 %. This is marginally higher than the highest previously reported percentage in nursing homes [12–15] and may be

Table 4
Factors associated with co-existence of malnutrition for patients with sarcopenia according to the logistic regression model.

Variable	OR	95 % CI	p-value
Number of PIMs	18.00	1.898–170.79	0.012
Charlson Comorbidity Index[a]	2.58	0.609–10.927	0.198
FILS score[b]	0.46	0.075–2.909	0.414
Number of prescribed drugs[c]	0.87	0.246–3.079	0.829

Co-MS, malnutrition and sarcopenia; OR, odds ratio; CI, confidence interval; PIMs, potentially inappropriate medications; FILS, Food Intake LEVEL Scale.

[a] CCI<3 indicated mild to moderate comorbidity, and CCI≥3 indicated severe comorbidity.

[b] FILS<7 indicated severe dysphasia, and FILS≥7 indicated none-to-moderate dysphasia.

[c] Number of prescribed drugs ≥5 indicates polypharmacy.

Table 5
Comparison of BMI, SMI, and PA in patients with sarcopenia only and those with co-MS.

	Sarcopenia only (n = 43)	Co-MS (n = 29)	p-value
BMI (kg/m^2)	20.41	18.94	0.045
SMI (kg/m^2)*	−1.38	−1.74	0.039

BMI, body mass index; SMI, skeletal muscle index; co-MS, malnutrition, and sarcopenia.

[a]Difference from sex-specific cutoff values.

explained by the fact that, under the Japanese medical and welfare system, long-term nursing care facilities for older adults, such as the center in our study, are designated as medical facilities. Older patients admitted to these facilities have a higher dependence on daily nursing care and have disease(s) requiring more medical care than do patients in nursing homes, which are categorized as welfare facilities. Therefore, this finding is plausible in that the causes of sarcopenia include inactivity and disease burden.

In the present study, we incorporated GLIM criteria to diagnose malnutrition. The GLIM criteria are consensus-based global standards that can be used in every medical and healthcare setting [43]. All the older patients diagnosed with malnutrition had sarcopenia. In other words, co-MS was present in 40 % of our cohort. This is not surprising because the prevalence of sarcopenia in this study population was quite high (92 %), and malnutrition is one of the causes of sarcopenia due to muscle breakdown from a negative energy balance. It is unclear whether sarcopenia precedes malnutrition or malnutrition precedes sarcopenia in the etiological background of co-MS. It is known that the muscle weakness observed in sarcopenia includes swallowing-related muscles, resulting in a decline in swallowing function called sarcopenic dysphagia [17–19]. This would lead to malnutrition due to reduced food intake. Given that the comorbidity of malnutrition causes further muscle breakdown, it is presumed that both processes form a vicious cycle together. The existence of co-MS and sarcopenia without malnutrition suggests that there may be a high-risk group for progression to co-MS due to malnutrition among older adults with sarcopenia in long-term nursing care facilities. Herein, various clinical features were evaluated and compared between older adults with sarcopenia alone and those with co-MS, and the items associated with co-MS were investigated. We clarified that PIM prescriptions, patient comorbidity as assessed by the CCI, swallowing ability as assessed by the FILS score, and oral condition as assessed by the ROAG score were factors significantly associated with co-MS ($p < 0.05$). ADL assessed using the Katz-ADL Index also showed a tendency toward association ($p = 0.051$) in the univariate analysis. In view of the vicious cycle of sarcopenia and malnutrition, deterioration of swallowing ability and oral function and reductions in ADL may be expected. In contrast, age, length of stay, cognitive function, and polypharmacy were not associated with co-MS in the univariate analysis ($p > 0.05$). Our multivariate analysis showed that taking medications classified as PIMs, rather than polypharmacy, was a statistically independent factor associated with co-MS among older adults with sarcopenia in this study.

The use of PIMs is reportedly associated with unfavorable drug reactions, disability, mortality, hospitalization, institutionalization in long-term care facilities, and excessive medical expenses among older adults [44–46]. For older patients in an acute hospital setting, a systematic review demonstrated that the prevalence of PIMs ranged from 53.2 % to 89.8 % according to the Beers criteria and from 30.4 % to 97.1 % with the STOPP criteria [47]. Another systematic review of nursing homes showed that 16–54 % of residents used PIMs according to the Beers criteria and the Health Plan Employer Data and Information Set [48,49]. It has also been revealed that approximately 26 % of community-dwelling older adults and 49 % of patients living in nursing homes in Europe are exposed to PIMs, as assessed by the Beers criteria [50,51].

The prevalence of PIMs varies according to care settings and criteria. The types of drugs on the market and classification systems may vary across countries; therefore, country-specific criteria should be used in clinical practice [52]. The Japan Geriatrics Society created the "Guidelines for Medical Treatment and its Safety in the Elderly" in 2005 and updated them in 2016 to the latest version, the STOPP-J [30]. PIMs assessed using the STOPP-J criteria are associated with hospitalization and mortality in Japanese patients receiving home-based medical services [53]. In older people with mild cognitive impairment and mild dementia, the prescription of medications that are PIMs according to the STOPP-J criteria is associated with lower verbal fluency scores and lower quality of life [54].

In addition to PIMs, polypharmacy has become widespread in older populations because these patients tend to have various diseases simultaneously. Similar to the problems caused by PIMs, polypharmacy is also significantly associated with adverse outcomes

among older people, such as adverse drug-related events and falling [55,56]. Polypharmacy is observed in 40 % of older outpatients, and the mean number of medications is 5.4 [54]. Polypharmacy is associated with frailty, lower quality of life, and cognitive impairment among older outpatients [54]. A study conducted on older home-care patients reported that polypharmacy was observed in 51.5 % of patients and was associated with malnutrition and multiple comorbidities [57]. In a previous study in Japan, the mean number of medications used per patient (mean age of 77 years) attending an older adult outpatient unit of a university hospital was 4.4 [58].

In the present study, we incorporated the STOPP-J criteria for the evaluation of PIMs because this study was conducted in Japan and all participants were Japanese. Polypharmacy was observed in 70 % of the study population, and the mean number of prescribed drugs was 6.79. In this study population, the proportion of polypharmacy was relatively high, and the mean number of prescriptions was also high compared with previously reported results among older adults in home-care and outpatient clinics. These differences can be attributed to differences among the research participants. As a characteristic of the facility where this research was conducted, patients are more dependent on medical care and have many underlying diseases compared to patients in home-care or outpatient clinics. Indeed, the participants' mean age (86.4 years) and mean CCI (2.6) were relatively high in this study. Unlike in other studies, polypharmacy was not associated with the comorbidity of malnutrition among sarcopenic older adults in our study. However, the reason for this is unclear. Originally, the number of prescription drugs was large in this study. Generally, these prescriptions include many drugs that are not PIMs and are considered to be safer than PIMs, such as expectorants and antiflatulents. As a result, one possibility is that the number of prescriptions will increase, and the number alone will obscure the relationship with the outcome.

Herein, we also found that 66.7 % of older individuals were exposed to PIMs. Since the content of prescription drugs is more important than their number, it is more crucial to scrutinize the content rather than simply reduce the number of prescription drugs to prevent progression to co-MS. When looking at the breakdown of PIMs prescribed to all study participants, antithrombotic drugs were the most common, followed by diuretics, beta-blockers, and antipsychotics. In contrast, among the PIMs, diuretics, steroids, and oral antidiabetic drugs were prescribed significantly more often to older people with co-MS than to those with sarcopenia only. Diuretics are often prescribed for chronic heart failure and chronic kidney disease, which are chronic inflammation-based diseases. Steroids are likewise prescribed for several inflammatory diseases, such as collagen disease. Diabetes is characterized by anabolic disorders caused by insufficient insulin secretion or function. Given that underlying chronic inflammatory diseases cause malnutrition, chronic inflammation is included in the etiological criteria of the GLIM criteria for malnutrition diagnosis (9). Additionally, chronic inflammation has a negative effect on muscle metabolism and causes sarcopenia [10]. The BMI and SMI of older adults with sarcopenia only and those with co-MS were significantly lower than those of older adults with co-MS.

Diuretics and steroids have been reported to have direct negative effects on muscle tissues. Loop diuretics, especially bumetanide and furosemide, have negative effects on muscle myogenesis [59]. They act on the Na–K–2Cl cotransporter, which is highly expressed in skeletal muscle, and inhibit its function in myoblast differentiation [59]. Loop diuretics are commonly prescribed to treat renal and heart failure. Moreover, research from clinical settings has revealed that the use of loop diuretics is associated with muscle wasting in patients with heart failure, regardless of its severity [60]. In this study, all diuretics were prescribed for congestive heart failure, with furosemide being the most common. Although there are patients with conditions that require furosemide, it is worth considering reducing the dosage while monitoring the condition. Of course, if diuretics are not required due to pathological conditions, this would be better, and they should not be prescribed in such cases.

Glucocorticoids (GCs) are anti-inflammatory drugs frequently prescribed for several inflammatory diseases, including rheumatoid and autoimmune diseases. However, despite the excellent anti-inflammatory effects of GCs, they also have various side effects, including muscle wasting, reduced bone mineral density, and glucose metabolism disorders. GCs cause a catabolic reaction in skeletal muscle that may lead to steroid-induced myopathy [61]. A possible mechanism is that GCs may inhibit glucose uptake in skeletal muscle fibers and contribute to the breakdown of muscle proteins. Furthermore, GCs may inhibit protein synthesis in muscle fibers [61]. In this study, although there were various causative diseases of steroid prescription, connective tissue disease, interstitial pneumonia, polymyalgia rheumatica, and an inflammatory disease that causes muscle pain of unknown origin were included. In many cases, it may be difficult to completely stop the use of steroids; however, it is necessary to consider dose reduction, if appropriate.

Epidemiologically, older patients with type 2 diabetes are considered to be at high risk of sarcopenia with a decline in muscle quality and strength [62]. Sarcopenia among older patients with type 2 diabetes is likewise independently associated with all-cause mortality and increased complications of diabetes, such as infection [63]. Several reports have described the negative impact of commonly used antidiabetic drugs on skeletal muscle. For example, although metformin, known as the first-line oral medication for type 2 diabetes, shows beneficial metabolic effects, including an improvement in insulin resistance and hyperinsulinemia, it causes weight loss and a decrease in fat mass [64]. A multicenter longitudinal cohort study of older men with diabetes treated with metformin showed a negative impact on lean body mass [65]. A meta-analysis of randomized controlled trials on the effects of glucagon-like peptide-1 (GLP-1) analogs on body composition also revealed an association of GLP-1 with both weight loss and decreases in muscle mass [66]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors selectively inhibit SGLT2 to reduce proximal tubular glucose reabsorption, increase urinary sugar excretion, and reduce blood glucose concentration. Research shows that the use of SGLT2 inhibitors in patients with diabetes reduces fat mass and lean mass by reducing glucose absorption [67]. To date, no negative effects of dipeptidyl peptidase 4 (DPP4) on body weight or muscle mass have been reported. The negative effects of relatively newer oral antidiabetic agents, such as SGLT2 and GLP-1, on body composition remain controversial. In addition to metformin, older patients sometimes have concomitant heart failure; therefore, SGLT2 is commonly prescribed. DPP4 and GLP-1 are often prescribed to older adults because they have fewer hypoglycemic side effects and are considered safer. In this study, metformin and DPP4, followed by SGLT2, were frequently prescribed. The reason for the low prescription rate of hypnotics categorized as PIMs is the recent tendency to refrain from prescribing these drugs to older adults due to their side effects. For sleep disorders in older adults, relatively new types of

sleeping pills that are not categorized as PIMs, including orexin receptor antagonists and melatonin agonists, are prescribed.

In the current study, 72 of the 78 (92 %) patients were diagnosed with sarcopenia. From this result, we can conclude that most patients in long-term nursing care facilities already have sarcopenia. Since there are no patients with only malnutrition, it is expected, although it has not been proven, that sarcopenia combined with undernutrition leads to co-MS. We should be aware of the possible risk that some of these patients might progress to co-MS due to combined malnutrition. One must also be aware of sarcopenic dysphagia caused by sarcopenia of the swallowing muscles. It should be noted that the progression of sarcopenia may cause dysphagia, which may lead to malnutrition [17–19]. Indeed, the FILS score was associated with co-MS in the univariate analysis, although it was not statistically significant in the multivariate analysis. Not surprisingly, the SMI of patients with co-MS was significantly lower than that of patients with sarcopenia alone. To prevent malnutrition associated with dysphagia, it is important to adjust the form of meals according to swallowing function and individualize nutrition therapy to meet nutritional demands. Specific physical interventions targeting swallowing muscle training, in addition to regular sarcopenia interventions such as whole-body physical therapy, are also essential to prevent co-MS. Many residents of long-term nursing care facilities are expected to have decreased ADL and daily physical activities. Therefore, it is important to make efforts to increase daily physical activities in order to maintain and improve muscle mass and function.

This study has some limitations. First, owing to the cross-sectional nature, we evaluated potentially associated factors based on plausibility and availability (i.e., routinely collected factors in clinical practice). Some factors, such as nutrient intake reports, daily physical activity, and self-perceived level of life satisfaction, were not evaluated but seemed to be related to malnutrition and sarcopenia. Causal relationships between co-MS and potentially associated factors were also not established due to the cross-sectional design. Second, the number of factors in the multivariate analysis was limited due to the number of study participants. Third, the study included only a small number of older individuals from a single institution. Hence, facility-expanded cohort studies are needed to clarify the impact of co-MS on outcomes for older individuals in long-term nursing care facilities.

5. Conclusions

Sarcopenia occurred in most of the older adults in long-term nursing care facilities, and the prevalence of co-MS is relatively high. The presence of PIMs was identified as an independent factor in the co-existence of malnutrition and sarcopenia. Healthcare professionals should be aware of this fact because it is critical to identify patients at risk as early as possible to prevent co-MS. Notably, it is important not to simply reduce the drug but to reduce the use of drugs in consideration of PIMs.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

Data associated with our study has not been deposited into a publicly available repository. Because the authors do not have permission to share data.

CRediT authorship contribution statement

Noriko Bando: Investigation. **Naomi Nakayama:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kaori Kashiwa:** Investigation. **Rena Horike:** Investigation. **Asaka Fujimoto:** Investigation. **Mitsuharu Egawa:** Investigation. **Munehiro Adachi:** Investigation. **Hisae Saji:** Investigation. **Beni Kira:** Investigation. **Kentaro Nakayama:** Validation, Supervision, Conceptualization. **Akira Okayama:** Supervision. **Satoru Katayama:** Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

Abbreviations

ADL	activities of daily living
AWGS	Asian Working Group for Sarcopenia;
BMI	body mass index
CCI	Charlson Comorbidity Index

co-MS	malnutrition and sarcopenia
CPS	Cognitive Performance Scale
DPP4	dipeptidyl peptidase 4
FILS	Food Intake LEVEL Scale
GC	glucocorticoid
GLIM	Global Leadership Initiative on Malnutrition
GLP-1	glucagon-like peptide-1
PIM	potentially inappropriate medication
ROAG	Revised Oral Assessment Guide
SGLT2	sodium-glucose cotransporter 2
SMI	skeletal muscle index
STOPP-J	Screening Tool for Older Person's Appropriate Prescriptions for Japanese

References

[1] United Nations, World Population Prospects, 2019. Available online: https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/files/documents/2020/Feb/un_2019_wpp_databooklet.pdf. (Accessed 5 November 2023).

[2] Homepage of the Japanese Ministry of Internal Affairs and Communications, Japanese Statistics Bureau. Available online: https://www.stat.go.jp/english/data/jinsui/tsuki/index.html (Accessed on 5 November 2023).

[3] T. Cederholm, R. Barazzoni, P. Austin, et al., ESPEN guidelines on definitions and terminology of clinical nutrition, Clin. Nutr. 36 (2017) 49–64, https://doi.org/10.1016/j.clnu.2016.09.004.

[4] A.J. Cruz-Jentoft, G. Bahat, J. Bauer, et al., Sarcopenia: revised European consensus on definition and diagnosis, Age Ageing 48 (2019) 16–31.

[5] D. Volkert, A.M. Beck, T. Cederholm, et al., ESPEN guideline on clinical nutrition and hydration in geriatrics, Clin. Nutr. 38 (2019) 10–47, https://doi.org/10.1016/j.clnu.2018.05.024.

[6] T. Cederholm, I. Bosaeus, R. Barazzoni, et al., Diagnostic criteria for malnutrition - an ESPEN consensus statement, Clin. Nutr. 34 (2015) 335–340, https://doi.org/10.1016/j.clnu.2015.03.001.

[7] L. Söderström, A. Rosenblad, E. Thors Adolfsson, et al., Malnutrition is associated with increased mortality in older adults regardless of the cause of death, Br. J. Nutr. 117 (2017) 532–540, https://doi.org/10.1017/S0007114517000435.

[8] V. Malafarina, J.Y. Reginster, S. Cabrerizo, et al., Nutritional status and nutritional treatment are related to outcomes and mortality in older adults with hip fracture, Nutrients 10 (2018) 555, https://doi.org/10.3390/nu10050555.

[9] D. Sánchez-Rodríguez, E. Marco, N. Ronquillo-Moreno, et al., ASPEN-AND-ESPEN: a postacute-care comparison of the basic definition of malnutrition from the American society of parenteral and enteral nutrition and academy of nutrition and dietetics with the European society for clinical nutrition and metabolism definition, Clin. Nutr. 38 (2019) 297–302, https://doi.org/10.1016/j.clnu.2018.01.017.

[10] J.E. Morley, A.M. Abbatecola, J.M. Argiles, et al., Sarcopenia with limited mobility: an international consensus, J. Am. Med. Dir. Assoc. 12 (2011) 403–409, https://doi.org/10.1016/j.jamda.2011.04.014.

[11] H.P. Patel, H.E. Syddall, K. Jameson, et al., Prevalence of sarcopenia in community-dwelling older people in the UK using the European working group on sarcopenia in older people (EWGSOP) definition: findings from the hertfordshire cohort study (HCS), Age Ageing 42 (2013) 378–384, https://doi.org/10.1093/ageing/afs197.

[12] L.P. Bastiaanse, T.I. Hilgenkamp, M.A. Echteld, et al., Prevalence and associated factors of sarcopenia in older adults with intellectual disabilities, Res. Dev. Disabil. 33 (2012) 2004–2012, https://doi.org/10.1016/j.ridd.2012.06.002.

[13] F. Landi, R. Liperoti, D. Fusco, et al., Prevalence and risk factors of sarcopenia among nursing home older residents, J Gerontol Ser A Biol Sci Med Sci 67 (2012) 48–55, https://doi.org/10.1093/gerona/glr035.

[14] H.E. Senior, T.R. Henwood, E.M. Beller, et al., Prevalence and risk factors of sarcopenia among adults living in nursing homes, Maturitas 82 (2015) 418–423, https://doi.org/10.1016/j.maturitas.2015.08.006.

[15] G. Bahat, B. Saka, F. Tufan, et al., Prevalence of sarcopenia and its association with functional and nutritional status among male residents in a nursing home in Turkey, Aging Male 13 (2010) 211–214, https://doi.org/10.3109/13685538.2010.489130.

[16] F. Landi, A.J. Cruz-Jentoft, R. Liperoti, et al., Sarcopenia and mortality risk in frail older persons aged 80 years and older: results from ilSIRENTE study, Age Ageing 42 (2013) 203–209, https://doi.org/10.1093/ageing/afs194.

[17] Y. Kuroda, R. Kuroda, Relationship between thinness and swallowing function in Japanese older adults: implications for sarcopenic dysphagia, J. Am. Geriatr. Soc. 60 (2012) 1785–1786, https://doi.org/10.1111/j.1532-5415.2012.04123.x.

[18] I. Fujishima, M. Fujiu-Kurachi, H. Arai, et al., Sarcopenia and dysphagia: position paper by four professional organizations, Geriatr. Gerontol. Int. 19 (2019) 91–97, https://doi.org/10.1111/ggi.13591.

[19] H. Wakabayashi, M. Kishima, M. Itoda, et al., Diagnosis and treatment of sarcopenic dysphagia: a scoping review, Dysphagia 36 (2021) 523–531, https://doi.org/10.1007/s00455-021-10266-8.

[20] X. Hu, L. Zhang, H. Wang, et al., Malnutrition-sarcopenia syndrome predicts mortality in hospitalized older patients, Sci. Rep. 7 (2017) 3171, https://doi.org/10.1038/s41598-017-03388-3.

[21] D. Sánchez-Rodríguez, E. Marco, N. Ronquillo-Moreno, et al., Prevalence of malnutrition and sarcopenia in a post-acute care geriatric unit: applying the new ESPEN definition and EWGSOP criteria, Clin. Nutr. 36 (2017) 1339–1344, https://doi.org/10.1016/j.clnu.2016.08.024.

[22] S. Nishioka, T. Matsushita, A. Yamanouchi, et al., Prevalence and associated factors of coexistence of malnutrition and sarcopenia in geriatric rehabilitation, Nutrients 13 (2021) 3745, https://doi.org/10.3390/nu13113745.

[23] A. Shiota, N. Nakayama, Y. Saito, et al., Prevalence and associated factors of malnutrition and sarcopenia in a daycare facility: a cross-sectional study, Healthcare 8 (2020) 576, https://doi.org/10.3390/healthcare8040576.

[24] L.K. Chen, L.K. Liu, J. Woo, et al., Sarcopenia in asia: consensus report of the asian working group for sarcopenia, J. Am. Med. Dir. Assoc. 15 (2014) 95–101, https://doi.org/10.1016/j.jamda.2013.11.025.

[25] L.K. Chen, J. Woo, P. Assantachai, et al., Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment, J. Am. Med. Dir. Assoc. 21 (2020) 300–307, https://doi.org/10.1016/j.jamda.2019.12.012.

[26] G.L. Jensen, T. Cederholm, M.I.T.D. Correia, et al., GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community, JPEN (J. Parenter. Enteral Nutr.) 43 (2019) 32–40, https://doi.org/10.1002/jpen.1440.

[27] C.C. Sieber, Malnutrition and sarcopenia, Aging Clin. Exp. Res. 31 (2019) 793–798, https://doi.org/10.1007/s40520-019-01170-1.

[28] D. Gnjidic, S.N. Hilmer, F.M. Blyth, et al., Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes, J. Clin. Epidemiol. 65 (2012) 989–995, https://doi.org/10.1016/j.jclinepi.2012.02.018.

[29] T. Kojima, K. Mizukami, N. Tomita, et al., Screening tool for older persons' appropriate prescriptions for Japanese: report of the Japan geriatrics society working group on guidelines for medical treatment and its safety in the elderly, Geriatr. Gerontol. Int. 16 (2016) 983–1001, https://doi.org/10.1111/ggi.12890.
[30] M.E. Charlson, P. Pompei, K.L. Ales, et al., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chron. Dis. 40 (1987) 373–383, https://doi.org/10.1016/0021-9681(87)90171-8.
[31] S. Katz, Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living, J. Am. Geriatr. Soc. 31 (1983) 721–727, https://doi.org/10.1111/j.1532-5415.1983.tb03391.x.
[32] K. Kunieda, T. Ohno, I. Fujishima, et al., Reliability and validity of a tool to measure the severity of dysphagia: the Food Intake LEVEL Scale, J. Pain Symptom Manag. 46 (2013) 201–206, https://doi.org/10.1016/j.jpainsymman.2012.07.020.
[33] M.T. Ribeiro, R.C. Ferreira, A.M. Vargas, et al., Validity and reproducibility of the revised oral assessment guide applied by community health workers, Gerodontology 31 (2014) 101–110, https://doi.org/10.1111/ger.12014.
[34] N. Morris, B.E. Fries, D.R. Mehr, et al., MDS cognitive performance scale, J. Gerontol. 49 (1994) M174–M182, https://doi.org/10.1093/geronj/49.4.m174.
[35] F. Landi, R. Liperoti, A. Russo, et al., Association of anorexia with sarcopenia in a community-dwelling elderly population: results from the ilSIRENTE study, Eur. J. Nutr. 52 (2013) 1261–1268, https://doi.org/10.1007/s00394-012-0437-y.
[36] W.J. Lee, L.K. Liu, L.N. Peng, et al., Comparisons of sarcopenia defined by IWGS and EWGSOP criteria among older people: results from the I-Lan longitudinal aging study, J. Am. Med. Dir. Assoc. 14 (2013) e1–e7, https://doi.org/10.1016/j.jamda.2013.03.019.
[37] D. Legrand, B. Vaes, C. Matheï, et al., The prevalence of sarcopenia in very old individuals according to the European consensus definition: insights from the BELFRAIL study, Age Ageing 42 (2013) 727–734, https://doi.org/10.1093/ageing/aft128.
[38] R.A. Murphy, E.H. Ip, Q. Zhang, et al., Transition to sarcopenia and determinants of transitions in older adults: a population-based study, J Gerontol Ser A Biol Sci Med Sci 69 (2014) 751–758, https://doi.org/10.1093/gerona/glt131.
[39] Y. Tanimoto, M. Watanabe, W. Sun, et al., Association between sarcopenia and higher-level functional capacity in daily living in community-dwelling elderly subjects in Japan, Arch. Gerontol. Geriatr. 55 (2012) e9–e13, https://doi.org/10.1016/j.archger.2012.06.015.
[40] S. Volpato, L. Bianchi, A. Cherubini, et al., Prevalence and clinical correlates of sarcopenia in community-dwelling older people: application of the EWGSOP definition and diagnostic algorithm, J Gerontol Ser A Biol Sci Med Sci 69 (2014) 438–446, https://doi.org/10.1093/gerona/glt149.
[41] S. Gariballa, A. Alessa, Sarcopenia: prevalence and prognostic significance in hospitalized patients, Clin. Nutr. 32 (2013) 772–776, https://doi.org/10.1016/j.clnu.2013.01.010.
[42] J. Cruz-Jentoft, F. Landi, S.M. Schneider, et al., Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS), Age Ageing 43 (2014) 748–759, https://doi.org/10.1093/ageing/afu115.
[43] D. Sanchez-Rodriguez, M. Locquet, J.Y. Reginster, et al., Mortality in malnourished older adults diagnosed by ESPEN and GLIM criteria in the SarcoPhAge study, J Cachex Sarcopen Musc 11 (2020) 1200–1211, https://doi.org/10.1002/jcsm.12574.
[44] C.M. Chang, P.Y. Liu, Y.H. Yang, et al., Use of the Beers criteria to predict adverse drug reactions among first-visit elderly outpatients, Pharmacotherapy 25 (2005) 831–838, https://doi.org/10.1592/phco.2005.25.6.831.
[45] V. Hyttinen, J. Jyrkkä, H. Valtonen, A systematic review of the impact of potentially inappropriate medication on health care utilization and costs among older adults, Med. Care 54 (2016) 950–964, https://doi.org/10.1097/MLR.0000000000000587.
[46] N. Wang, J.S. Bell, E.Y.H. Chen, et al., Medications and prescribing patterns as factors associated with hospitalizations from long-term care facilities: a systematic review, Drugs Aging 35 (2018) 423–457, https://doi.org/10.1007/s40266-018-0537-3.
[47] R. Redston, S.N. Hilmer, A.J. McLachlan, et al., Prevalence of potentially inappropriate medication use in older inpatients with and without cognitive impairment: a systematic review, J Alzheimer Dis 61 (2018) 1639–1652, https://doi.org/10.3233/JAD-170842.
[48] S.K. Nothelle, R. Sharma, A.H. Oakes, et al., Determinants of potentially inappropriate medication use in long-term and acute care settings: a systematic review, J. Am. Med. Dir. Assoc. 18 (2017) e1–e806, https://doi.org/10.1016/j.jamda.2017.06.005.
[49] D. Dosa, S. Cai, S. Gidmark, et al., Potentially inappropriate medication use in veterans residing in community living centers: have we gotten better, J. Am. Geriatr. Soc. 61 (2013) 1994–1999, https://doi.org/10.1111/jgs.12516.
[50] L. Morin, M.L. Laroche, G. Texier, et al., Prevalence of potentially inappropriate medication use in older adults living in nursing homes: a systematic review, J. Am. Med. Dir. Assoc. 17 (2016) 862, https://doi.org/10.1016/j.jamda.2016.06.011.
[51] E. Tommelein, E. Mehuys, M. Petrovic, et al., Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review, Eur. J. Clin. Pharmacol. 71 (2015) 1415–1427, https://doi.org/10.1007/s00228-015-1954-4.
[52] F.R. Motter, J.S. Fritzen, S.N. Hilmer, et al., Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria, Eur. J. Clin. Pharmacol. 74 (2018) 679–700, https://doi.org/10.1007/s00228-018-2446-0.
[53] C.H. Huang, H. Umegaki, Y. Watanabe, et al., Potentially inappropriate medications according to STOPP-J criteria and risks of hospitalization and mortality in elderly patients receiving home-based medical services, PLoS One 14 (2019), e0211947, https://doi.org/10.1371/journal.pone.0211947.
[54] V. Bonfiglio, H. Umegaki, M. Kuzuya, Potentially inappropriate medications and polypharmacy: a study of older people with mild cognitive impairment and mild dementia, J Alzheimer Dis 71 (2019) 889–897, https://doi.org/10.3233/JAD-190284.
[55] T. Kojima, M. Akishita, T. Nakamura, et al., Polypharmacy as a risk for fall occurrence in geriatric outpatients, Geriatr. Gerontol. Int. 12 (2012) 425–430, https://doi.org/10.1111/j.1447-0594.2011.00783.x.
[56] T. Kojima, M. Akishita, T. Nakamura, et al., Association of polypharmacy with fall risk among geriatric outpatients, Geriatr. Gerontol. Int. 11 (2011) 438–444, https://doi.org/10.1111/j.1447-0594.2011.00703.x.
[57] H. Komiya, H. Umegaki, A. Asai, et al., Factors associated with polypharmacy in elderly home-care patients, Geriatr. Gerontol. Int. 18 (2018) 33–41, https://doi.org/10.1111/ggi.13132.
[58] Y. Suzuki, M. Akishita, H. Arai, et al., Multiple consultations and polypharmacy of patients at-tending geriatric outpatient unit of university hospitals, Geriatr. Gerontol. Int. 6 (2006) 244–247, https://doi.org/10.1111/j.1447-0594.2006.00355.x.
[59] S. Mandai, S. Furukawa, M. Kodaka, et al., Loop diuretics affect skeletal myoblast differentiation and exercise-induced muscle hypertrophy, Sci. Rep. 7 (2017), 46369, https://doi.org/10.1038/srep46369.
[60] I. Nakano, M. Tsuda, S. Kinugawa, et al., Loop diuretic use is associated with skeletal muscle wasting in patients with heart failure, J. Cardiol. 76 (2020) 109–114, https://doi.org/10.1016/j.jjcc.2020.01.003.
[61] H. Schäcke, W.D. Döcke, K. Asadullah, Mechanisms involved in the side effects of glucocorticoids, Pharmacol. Ther. 96 (2002) 23–43, https://doi.org/10.1016/s0163-7258(02)00297-8.
[62] S.W. Park, B.H. Goodpaster, J.S. Lee, et al., Excessive loss of skeletal muscle mass in older adults with type 2 diabetes, Diabetes Care 32 (2009) 1993–1997, https://doi.org/10.2337/dc09-0264.
[63] Y. Zhang, S. Weng, L. Huang, et al., Association of sarcopenia with a higher risk of infection in patients with type 2 diabetes, Diabetes Metabol. Res. Rev. 38 (2022) e3478, https://doi.org/10.1002/dmrr.3478.
[64] R. Aghili, M. Malek, A.E. Valojerdi, et al., Body composition in adults with newly diagnosed type 2 diabetes: effects of metformin, J. Diabetes Metab. Disord. 13 (2014) 88, https://doi.org/10.1186/s40200-014-0088-z.
[65] C.G. Lee, E.J. Boyko, E. Barrett-Connor, et al., Insulin sensitizers may attenuate lean mass loss in older men with diabetes, Diabetes Care 34 (2011) 2381–2386, https://doi.org/10.2337/dc11-1032.
[66] S. Ida, R. Kaneko, K. Imataka, et al., Effects of antidiabetic drugs on muscle mass in type 2 diabetes mellitus, Curr. Diabetes Rev. 17 (2021) 293–303, https://doi.org/10.2174/1573399816666200705210006.
[67] J. Bolinder, Ljunggren Ö, J. Kullberg, et al., Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin, J. Clin. Endocrinol. Metab. 97 (2012) 1020–1031, https://doi.org/10.1210/jc.2011-2260.