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CONTENTS

ORIGINAL RESEARCH

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Eur J Geriatr Gerontol 2026;8(2):56-65

Immature Granulocyte Percentage in Post-Menopausal Sarcopenic Individuals: A Potential Novel Biomarker?

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Abstract

Objective: Sarcopenia is an age-related muscle disorder marked by loss of muscle mass, strength, and function. Post-menopausal women face an increased risk due to alterations in hormones and metabolism. In addition, systemic inflammation has been proposed as a key contributor in this population. Although standard inflammatory markers, such as interleukin-6 and tumor necrosis factor-α, are not readily available, the percentage of immature granulocytes (IGr%), easily obtained from routine blood tests, may serve as an indicator of inflammation. To investigate the association between IGr% and sarcopenia in post-menopausal women and identify related clinical and laboratory factors.

Materials and Methods: This study was designed as a retrospective observational analysis. The study included post-menopausal women who attended the Geriatrics and General Internal Medicine outpatient clinics between May and August 2024. Assessment of sarcopenia included the strength, assistance with walking, rising from a chair, climbing stairs, and falls questionnaire, handgrip strength, bioelectrical impedance analysis, and a 4-meter gait speed test. Basic activities of daily living (ADL) were measured with the Katz ADL scale, instrumental activities were assessed with the Lawton IADL scale, and nutritional risk was assessed with the nutritional risk screening (NRS-2002). Laboratory parameters included IGr%, C-reactive protein (CRP), albumin, and white blood cell count (WBC).

Results: Among 198 participants (mean age: 59 years), 43.9% had probable or confirmed sarcopenia. Sarcopenic women were older ($p < 0.001$), had lower lumbar bone density ($p = 0.024$), had more comorbidities ($p = 0.001$), and had greater functional dependency ($p = 0.001$). Sarcopenic individuals showed a significantly higher IGr% in univariate analysis ($p = 0.046$), while no significant differences were observed among other inflammatory markers, such as CRP, WBC, neutrophils (NEUTs), lymphocytes (LYMPH), the NEUT-to-LYMPH ratio and the platelet-to-LYMPH ratio (all $p > 0.05$). Multivariate analysis revealed that older age [odds ratio (OR): 1.058, 95% confidence interval (CI): 1.022–1.096; $p = 0.002$] and albumin (OR: 0.891, 95% CI: 0.773–0.981; $p = 0.023$) were independent predictors of sarcopenia.

Conclusion: Although IGr% was higher in sarcopenic individuals in univariate analysis, it did not remain an independent predictor after adjustment. However, as a readily available, cost-effective parameter from the routine complete blood count, IGr% may serve as an early biomarker reflecting low-grade systemic inflammation in sarcopenia, a finding that warrants confirmation in larger, prospective, multicenter studies.

Keywords: Aging, immature granulocyte percentage, postmenopause, sarcopenia

Introduction

Sarcopenia, a common progressive muscle condition, is associated with adverse health outcomes, including falls, bone fractures, disability, and increased mortality. Over the past decades, the concept and diagnostic criteria of sarcopenia have evolved. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) proposed that the condition be diagnosed on the basis of reduced muscle mass combined with

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either low muscle strength or impaired physical performance (1). Later, the EWGSOP2, introduced by the same group, released revised guidelines that refined the definition and diagnosis of sarcopenia in older adults. The 2019 update marked a major shift by integrating muscle function into the diagnostic algorithm, moving away from earlier approaches that focused primarily on low muscle mass. In this framework, muscle function—particularly reduced muscle strength—is emphasized as the central and initial diagnostic indicator (2). In this algorithm, individuals with low muscle strength are classified as having "probable sarcopenia"; the presence of low muscle mass or impaired muscle quality confirms the diagnosis, and the presence of impaired physical performance categorizes the condition as "severe sarcopenia" (2). The group further advises the use of population-specific reference data for determining diagnostic cut-off values. Consequently, Turkish-specific reference values are defined in the literature (3).

Although sarcopenia is commonly associated with aging, emerging data suggest it may develop earlier than previously thought (4). Low muscle mass, weakness, and poor physical performance, hallmarks of sarcopenia, correlate with higher morbidity and mortality rates in the geriatric population; moreover, sarcopenia is directly linked to quality of life and healthy aging, even in individuals under the age of 65. The sarcopenic phenotype encompasses a multifactorial etiology that extends beyond chronological age (2). Because of hormonal changes, post-menopausal women are especially vulnerable to sarcopenia.

During menopause, defined as the permanent cessation of menstruation for at least 12 consecutive months due to ovarian failure or surgical removal of the ovaries (e.g., bilateral oophorectomy) (5), estrogen levels decline sharply. This estrogen deficiency, in combination with age-related decreases in bone mineral density (BMD) and muscle mass, as well as increased inflammation and adiposity, significantly contributes to the development and progression of sarcopenia in this group (6). Although the World Health Organization states that menopause occurs between 45 and 55 years (7), the average age at menopause in Türkiye is reported to be 47 years (8,9). This suggests that Turkish women may enter the period of increased vulnerability to sarcopenia relatively early, underscoring the importance of early preventive strategies in this population.

The mechanisms underlying sarcopenia remain under investigation, but core elements appear to be oxidative stress, neuromuscular dysfunction, endocrine disorders, malnutrition, physical inactivity, and, prominently, inflammation (10). The literature indicates that the inflammatory response is associated with loss of muscle mass and impaired physical function; accordingly, inflammatory biomarkers have been proposed as valuable tools for understanding the diagnosis, prognosis, and pathogenesis of sarcopenia (11). However, the routine clinical availability of specific cytokines, such as interleukin (IL)-6, IL-1, and tumor necrosis factor (TNF)-α, is limited due to cost-effectiveness issues. Therefore, the percentage of immature granulocytes (IGr%), readily available from a complete blood count (CBC), has become a valuable indicator of systemic inflammation (12).

In the bone marrow, IGr% identifies early myeloid precursor cells, including promyelocytes, myelocytes, and metamyelocytes. Typically, these cells are not found in the peripheral blood; however, inflammation, infection, or bone marrow stimulation can cause them to appear in the bloodstream (13). Findings suggest that IGr% levels could serve as a valuable biomarker for both inflammatory and infectious conditions (14). Moreover, elevated IGr% levels are associated with various non-infectious conditions, including diabetic kidney disease, myocardial infarction, stroke, rheumatic disorders, and metastatic cancer (15-18).

Given the revised EWGSOP2 definition of sarcopenia, investigating the relationship between sarcopenia and IGr% in post-menopausal women is particularly important. This study aimed to evaluate sarcopenia status, analyze routine CBC parameters, examine the association between IGr% and sarcopenia, and identify clinical and laboratory factors associated with post-menopausal sarcopenia. We hypothesized that higher IGr% levels would be associated with sarcopenia, reflecting subclinical systemic inflammation in this population.

Materials and Methods

This study was a retrospective observational analysis. Post-menopausal women attending the Geriatrics and General Internal Medicine outpatient clinics between May and August 2024 provided the data. The study received ethical approval from Marmara University's Local Ethics Committee (decision number: 09.2025-25-0174, date: 21.03.2025).

Patients whose last menstrual period had occurred less than one year earlier, and those with a cardiac pacemaker or limb prostheses, which preclude measurement by bioelectrical impedance analysis (BIA), were excluded from the study. In addition, participants with active infection and C-reactive protein (CRP) levels above 10 mg/L, those receiving active antibiotic or steroid therapy, and those with a diagnosis of malignancy were also excluded. A CRP cut-off of <10 mg/L was applied to exclude participants with active infection or systemic inflammation, minimizing potential confounding effects on the assessment of sarcopenia-related parameters.

Patient data, including sociodemographics, comorbidities, medical and medication histories, and laboratory results, were collected during routine outpatient visits. Menopausal history, including age at menopause and type of onset (physiological or

surgical), was also recorded. Measurements of calf, waist, and hip circumferences were also recorded.

Strength, assistance with walking, rising from a chair, climbing stairs, and falls is an easy-to-use, self-report screening tool for sarcopenia that assesses five key functional components. Each question is scored on a 0–2 point scale, depending on how difficult the question is for the respondent. In total, 10 points were recorded as the maximum score and 0 points as the minimum. Scores of 4 or higher indicate that individuals are at risk of sarcopenia (19). Muscle strength assessment involved measuring handgrip strength using a hand-held dynamometer (Jamar®). Participants, seated with their dominant elbow flexed at 90°, were asked to squeeze the device with maximal effort. The highest result from the three test runs informed the analysis. The procedure was repeated three times, and the best measurement was noted. Values below 22 kilograms (kg) were considered low and indicative of probable sarcopenia (3).

Muscle mass was estimated using BIA, a non-invasive technique that measures the resistance of body tissues to a weak electrical current. The Tanita BC-532 device was employed in this analysis. Using BIA, fat-free mass was calculated and then multiplied by 0.566 to determine skeletal muscle mass (SMM) (20).

The skeletal muscle mass index (SMMI) was calculated as SSM divided by body mass index. Participants with an SMMI value below 0.823 kg/(kg/m²)—the established cut-off for Turkish women—were classified as having low muscle mass (3). The 4-meter gait speed test measured physical performance. (21). A gait speed of <0.8 m/s was used to indicate diminished muscle function (21). Patients who met the criteria for sarcopenia and also demonstrated low physical performance were categorized as having severe sarcopenia. In this study, individuals classified as having probable, confirmed, or severe sarcopenia were grouped under the umbrella term "sarcopenia" for analytical purposes.

The functional status of the participants was evaluated using standardized assessment tools. Basic activities of daily living (ADL) were measured using the Katz ADL scale (22), while instrumental activities were assessed using the Lawton IADL scale (23). Participants were grouped as independent, partially dependent, or dependent based on these assessments. Nutritional status was determined with the Nutritional Risk Screening tool (NRS-2002). An NRS-2002 total score of 3 or higher signifies that the individual is either at risk for malnutrition or already malnourished, indicating the need for nutritional support (24). Additionally, participants were asked about any falls they had experienced within the previous year and their fear of falling.

Laboratory parameters included white blood cell count (WBC), IGr%, CRP, and serum albumin level.

Hematological Analysis: CBC analyses were performed on the Mindray BC-6800 Plus (Mindray Bio-Medical Electronics Co., Shenzhen, China), a fully automated hematology analyzer. This device uses SF-Cube fluorescent flow cytometry for cellular analysis (25). Measurements are based on three primary signals: side fluorescence light, abnormal lymphocyte (LYMPH) scatter, and side scatter light. These signals are used to assess structural characteristics, such as cell volume, nucleic acid content, and granularity (26).

The device automatically calculates IGr% parameters: IGr% and IGr% count (absolute number of IGr%s). Reference ranges for IGr%s were defined according to Sysmex technical reports and reference interval studies conducted in healthy donors (e.g., n ≈ 156). When Sysmex XE/XN series automated hematology analyzers were used, the reported upper limits were approximately 0.5% for IG% and 0.03 × 10^9/L for IG count (27). Therefore, these values were adopted as the upper reference limits in the present study. The measurement is performed by identifying specific cell populations using the device's algorithms, which can distinguish early-stage neutrophils (NEUTs), such as myelocytes, metamyelocytes, and promyelocytes (28). SF-Cube technology enables the reliable classification of these cells based on their three-dimensional morphological characteristics (29).

SF-Cube technology integrates three distinct signals generated when cells are exposed to laser light. This technology simultaneously analyzes parameters such as nuclear density, granule content, and cell volume, generating a multidimensional profile of each cell (30). As a result, the detection of rare cell populations, such as IGr%s, becomes both more specific and more sensitive (31).

Statistics

Normality of the variables was evaluated through graphical inspection methods (probability plots and histograms) and the Kolmogorov-Smirnov test. Categorical data were summarized using counts and proportions (n, %). Group comparisons for categorical outcomes were carried out using the chi-square test or Fisher's exact test when appropriate. Continuous variables following a normal distribution were reported as mean ± standard deviation (SD), and differences between groups were examined using the independent-samples t-test. When continuous variables were not normally distributed, medians (with minimum and maximum values) were used, and comparisons were performed using the Mann-Whitney U test. Binary logistic regression was used to investigate associations between variables.

Variables that were significant in univariate analyses were entered into the regression models. Potential multicollinearity among predictors was evaluated using Pearson correlation coefficients, with values exceeding 0.8 considered suggestive

of multicollinearity. The relationship between sarcopenia and potential predictors was examined using multivariable logistic regression analysis. Based on clinical relevance and prior literature, age, serum albumin level, and osteoporosis status were included as independent variables. The ENTER method was used to simultaneously enter all variables into the model. In the regression models, the effect of each independent variable was expressed by the unstandardized regression coefficient (B). The coefficient (B) in the logistic regression model represents the change in the log-odds of the outcome associated with a one-unit increase in the predictor. The exponential coefficient, Exp(B), was presented as the odds ratio (OR). Statistical significance was defined as $p < 0.05$, and 95% confidence intervals (CIs) were calculated. All analyses were performed using IBM SPSS Statistics version 26.0 (Armonk, NY, USA).

Results

One hundred ninety-eight post-menopausal women participated in the study. The mean participant age was 59.4 ± 10.0 years; 33.8% were older than 65 years. Menopause occurred at a mean age of 46.5 ± 5.2 years, with 84.8% of participants experiencing physiological menopause. Hypertension (53.5%), osteoporosis (28.3%), and diabetes mellitus (26.3%) were the most frequent comorbidities. Among the patients, 33% reported a fear of falling, while 25% had a history of falls. ADL independence was reported by 92% of participants in the functional assessment; IADL independence was reported by 78% of participants. Of the participants, 87 (43.9%) showed sarcopenia (Table 1).

As Table 2 shows, post-menopausal women with sarcopenia were significantly older (mean ages, 56.5 vs. 63.1 years; $p < 0.001$), had a higher number of chronic diseases, and used a greater number of medications ($p = 0.001$). Osteoporosis and hypertension were also more common among these individuals ($p = 0.028$ and $p = 0.016$, respectively). In addition, these individuals showed significantly lower femoral neck T-scores [-1.10 (-3.40–1.20) vs -1.50 (-3.40–1.20); $p = 0.042$) and L1–L4 BMD scores (1.054 (0.603–1.522) vs 0.990 (0.668–1.457); $p = 0.024$], along with increased dependence in ADL, both basic and instrumental ($p = 0.001$ and $p < 0.001$, respectively). Sarcopenic individuals also showed a higher IGr% ($p = 0.046$); no significant differences were observed for other inflammatory markers, including CRP, WBC, NEUT, LYMPHs, NEUT-to-LYMPH ratio (NLR), and platelet-to-LYMPH ratio (PLR) (all $p > 0.05$).

Multivariate analysis revealed that older age (OR: 1.058, 95% CI: 1.022–1.096; $p = 0.002$) and albumin (OR: 0.891; 95% CI: 0.773–0.981; $p = 0.023$) were independent predictors of sarcopenia. Increasing age was a significant predictor of sarcopenia, with approximately a 6% increase in risk per year. Sarcopenia showed no significant association with IGr% or osteoporosis in multivariate logistic regression analysis (OR: 6.429; 95% CI: 0.651–63.536; $p = 0.111$ and OR: 1.715; 95% CI: 0.906–3.532; $p = 0.094$) (Table 3).

Table 1. Demographic characteristics of participants (n = 198).

	Total n = 198, n (%)		**Total n = 198, n (%)**
Age*	**59.4 ± 10.0**	**BMI (kg/m²)**	**29.6 ± 5.9**
Age group <65 Years ≥65 Years	 131 (66.2%) 67 (33.8%)	Sarcopenia classification [based on SMMI (kg/kg/m²)] No sarcopenia Sarcopenia • Probable sarcopenia • Sarcopenia • Severe sarcopenia	 111 (56.1%) 87 (43.9%) • 79 (39.9%) • 7 (3.5%) • 1 (0.5%)
Number of chronic diseases*	2 (1–6)	Age at menopause*	46.5 ± 5.2
Number of medications*	3 (1–11)	Type of menopause Physiological Surgical	 168 (84.8%) 30 (15.2%)
Hypertension	106 (53.5%)	Hormone usage Never used Currently using Discontinued	 181 (91.4%) 9 (4.5 5) 8 (4.1%)
Diabetes mellitus	52 (26.3%)	L1-L4 BMD*	1.028 (0.603–1.522)
Osteoporosis	56 (28.3%)	Albumin (g/dL)*	43 (28–49)
Osteoporosis treatment	23 (11.6%)	C-reactive protein, mg/L*	2.8 (0.11–9.9)
Fear of falling	71 (35.9%)	Hemoglobin(×10³/µL)*	13.1 ± 1.2
History of falls	53 (26.8%)	Platelet (×10³/µL)*	252.5 (37.9–554)
History of fractures	42 (21.2%)	Leucocyte (×10³/µL)*	6.7 (3.4–14.0)

Table 1. Continued

	Total n = 198, n (%)		Total n = 198, n (%)
Age*	**59.4 ± 10.0**	**BMI (kg/m²)**	**29.6 ± 5.9**
Functionality–IADL Dependent Partially-dependent Independent	 18 (9.1%) 25 (12.6%) 155 (78.3%)	Neutrophil (×10³/μL)*	3.8 (1.0–10.9)
Functionality–ADL Dependent Partially-dependent Independent	 2 (1.0%) 13 (6.6%) 183 (92.4%)	Lymphocyte (×10³/μL)**	2.2 (0.4–5.8)
Polypharmacy	40 (20.2%)	Immature granulocyte%	0.10 (0.0–1.50)
NRS-2002 score Risk of malnutrition Normal	 175 (88.4%) 23 (11.6%)	Immature granulocyte (×10³/μL)*	0.01 (0.0–0.14)
Slow gait speed (<0.8 m/s)	19 (9.6%)	Immature granulocyte neutrophil ratio	0.003 (0.0–0.04)
Presence of sarcopenia risk (according to SARC-F score)	37 (18.7%)		
Right-hand grip strength-according to Turkish standards (<22 kg)	87 (43.9%)		
SMMI [kg/(kg/m²)]*	0.816 ± 0.140		

*Values are expressed as mean ± standard deviation and median (minimum-maximum).
BMI: Body mass index, SMMI: Skeletal muscle mass index, BMD: Bone mineral density, ADL: Activity of daily living, IADL: Instrumental activity of daily living, NRS-2002: Nutritional risk screening-2002, SARC-F: Strength, assistance with walking, rise from a chair, climb stairs, and falls.

Table 2. Characteristics of participants based on sarcopenia.

	No sarcopenia (%), (n = 111)	Sarcopenia (%), (n = 87)	p-value
Age*	**56.5 ± 8.1**	**63.1 ± 10.9**	**<0.001**
Age group <65 years ≥65 years	 86 (77.5%) 25 (22.5%)	 45 (51.7) 42 (48.3)	**<0.001**
Number of chronic diseases*	2 (0–6)	3 (0–6)	**0.001**
Hypertension	51 (45.9%)	55 (63.2%)	**0.016**
Osteoporosis	24 (21.6%)	32 (36.8%)	**0.028**
History of falls	24 (21.6%)	29 (33.3%)	0.092
History of fractures	21 (18.9%)	21 (24.1%)	0.474
Osteoporosis treatment	12 (10.8%)	11 (12.6%)	0.860
Number of medications*	2 (0–11)	3 (0–11)	**0.024**
Age at menopause*	46.1 ± 5.2	46.9 ± 5.3	0.336
Type of menopause Physiological Surgical	 94 (84.7%) 17 (15.3%)	 74 (85.1%) 13 (14.9%)	0.942
Hormone usage Never used Currently using Discontinued	 103 (92.8%) 6 (5.4%) 2 (1.8%)	 78 (89.7%) 3 (3.4%) 6 (6.9%)	0.179
BMI (kg/m²)	30.4 ± 6.1	30.0 ± 5.8	0.916
Femoral neck T-score*	-1.10 (-3.40–1.20)	-1.50 (-3.40–1.20)	**0.042**
L1-L4 BMD*	1.054 (0.603–1.522)	0.990 (0.668–1.457)	**0.024**
Albumin (g/dL)*	43 (36–48)	42 (28–49)	**0.001**
Leucocyte (×10³/μL)*	6.4 (3.4–12.5)	6.7 (3.7–14.0)	0.814

Table 2. Continued

	No Sarcopenia (%), (n = 111)	Sarcopenia (%), (n = 87)	p-value
Age*	**56.5 ± 8.1**	**63.1 ± 10.9**	**<0.001**
Neutrophil (×10³/µL)*	3.6 (1.7–8.8)	4.0 (1.0–10.9)	0.628
Lymphocyte (×10³/µL)**	2.3 (1.1–4.1)	2.2 (0.8–5.8)	0.106
Hemoglobin (×10³/µL)*	13.0 ± 0.9	12.6 ± 1.2	**0.024**
Platelet (×10³/µL)*	241 (37.9–505)	254 (42–507)	0.883
Immatur granulocyte (×10³/µL)*	0.01 (0.0–0.07)	0.01 (0.0–0.14)	0.106
Immature granulocyte,%	0.1 (0.0–0.7)	0.1 (0.0–1.5)	0.046
Immature granulocyte neutrophil ratio	0.003 (0.0–0.04)	0.003 (0.0–0.02)	0.226
C-reactive protein, mg/L*	2.9 (0.3–9.5)	2.2 (0.11–9.9)	0.437
Functionality – ADL Dependent Partially-dependent Independent	 0 (0.0%) 2 (1.8%) 109 (98.2%)	 2 (1.0%) 11 (6.6%) 74 (92.4%)	**0.001**
Functionality – IADL Dependent Partiallyd-dependent Independent	 3 (2.7%) 9 (8.1%) 99 (89.2%)	 15 (17.2%) 16 (18.4%) 56 (64.4%)	**<0.001**
NRS-2002 score Risk of malnutrition Normal	 12 (10.8%) 99 (89.2%)	 11 (12.6%) 76 (87.4%)	0.690

*Values are expressed as mean±standard deviation and median (minimum-maximum).
BMI: Body mass index, BMD: Bone mineral density, ADL: Activity of daily living, IADL: Instrumental activity of daily living, NRS-2002: Nutritional risk screening-2002.

Table 3. Multivariate logistic regression analysis of the factors that affect sarcopenia.

	p	Exp (B)	Odds ratio (95% CI)	
			Lower	Upper
Age	**0.002**	1.058	1.022	1.096
Presence of osteoporosis	0.094	1.715	0.906	3.532
Albumin (g/dL)	**0.023**	**0.891**	**0.773**	**0.981**
Immature granulocyte %	0.111	5.644	0.651	63.536

Variables included in the multivariable logistic regression model were selected based on statistical significance in univariate analyses and clinical relevance. Age, serum albumin level, osteoporosis status, and immature granulocyte percentage (IGr%) were simultaneously entered into the model using the ENTER method.
CI: Confidence Interval, dL: Deciliter, g: Gram.

Discussion

Sarcopenia's underlying processes are not fully understood, but it is recognized as a multifactorial condition. Among these, inflammation is considered to play a pivotal role. This study examined the association between sarcopenia and IGr%, a potential marker of systemic inflammation, among post-menopausal women evaluated in outpatient clinics. Significantly higher IGr% levels were observed in the sarcopenic group in the univariate analysis of the current study. In contrast, other inflammatory parameters such as CRP, WBC, NEUT, LYMPH, NLR, and PLR showed no significant group differences. While no significant differences were observed in other inflammatory markers, higher IGr% levels in the sarcopenic group suggest that this parameter may capture early inflammatory activity associated with sarcopenia.

In this study, 39.9% of post-menopausal participants were classified as probable sarcopenia, whereas 4% met the criteria for confirmed sarcopenia. By comparison, two studies conducted on post-menopausal women in Switzerland reported probable sarcopenia rates of 12.3% and 18.5%, respectively (32,33). Meanwhile, a study conducted in India that used the handgrip strength protocol recommended by the Asian Working Group for Sarcopenia 2019—which defines low grip strength as <18 kg—reported a probable sarcopenia prevalence of 45.3% (34). Such variability underscores that differences in diagnostic cut-off values, ethnic and demographic characteristics, and methodological approaches can markedly influence sarcopenia prevalence estimates across populations. Therefore, direct comparisons between studies should be interpreted with caution when reference standards or assessment protocols

differ. Our findings provide context-specific epidemiological data and further emphasize the need for standardized, population-appropriate diagnostic frameworks to enhance the accuracy of sarcopenia detection and enable more reliable comparisons across cohorts.

Several factors may account for the relatively higher prevalence observed in our cohort. First, our study utilized population-specific cut-off values for handgrip strength, as proposed by Bahat et al. (3) (22 kg for women), which likely increased the sensitivity of sarcopenia detection and consequently elevated the prevalence rate. Indeed, if the EWGSOP2-recommended cut-off of 16 kg had been applied, the prevalence of sarcopenia in our cohort would have been 10.1%. Second, our cohort consisted exclusively of post-menopausal women referred to an outpatient clinic, a population that may have a higher burden of metabolic or functional decline compared with community-dwelling samples. Although 92% of participants were functionally independent in ADL, this does not necessarily preclude early or subclinical sarcopenia, since declines in muscle strength may precede overt functional impairment. Similarly, Bahat et al. (3) reported that sarcopenia was associated with low nutritional status rather than with functional decline, suggesting that functional deterioration may emerge later in the disease course (35). Taken together, these findings underscore the importance of employing population- and sex-specific reference values to ensure accurate sarcopenia identification and to avoid underestimation in at-risk clinical groups.

The prevalence of sarcopenia was significantly higher in individuals aged 65 years and older. A prior study reported a markedly increased risk of sarcopenia with advancing age, with prevalence rates of 1.4%, 4.9%, and 12.5% in the 60-69, 70-79, and 80+ age groups, respectively (5). The risk of sarcopenia increases with age due to declines in SMM and muscle strength. Progressive muscle dysfunction results from this physiological process, which encompasses primary aging and the effects of chronic diseases. Early detection and prevention of sarcopenia are vital due to its increasing prevalence with age, especially among older adults and those with multiple conditions. Increasing evidence highlights the importance of developing age-specific diagnostic tools and health policies that are tailored to older adults.

Osteoporosis and sarcopenia together define the relatively new medical concept of osteosarcopenia. Although each condition has been studied extensively in isolation, epidemiological data on osteosarcopenia are limited (36). Research in the United Kingdom found sarcopenia in half of post-menopausal women with osteoporosis (37). The results of our study likewise confirm the possibility of these two conditions co-occurring. Sarcopenia occurred in 36.8% of people with osteoporosis, and conversely, 57% of sarcopenic individuals also had osteoporosis. Moreover, the sarcopenic group showed substantially reduced femoral neck T-scores and lumbar spine BMD, suggesting an increased risk of osteoporosis. Regarding prior falls or fractures, there were no statistically significant differences between the groups. Our results are consistent with the study by Zanchetta et al. (38), which reported decreased femoral neck BMD and a higher incidence of falls in the past year among sarcopenic women, but no significant difference in fracture rates. The relatively young study population could explain the lack of a statistically significant difference in fall and fracture rates. Our results indicate that osteosarcopenia is prevalent in post-menopausal women, underscoring the need for integrated bone and muscle health assessments in clinical settings. The close physiological relationship between muscle and bone is evidenced by their shared mechanical loading, biochemical pathways, and genetic controls.

Notwithstanding the unclear pathogenesis of sarcopenia, many studies associate its progression with dysregulated inflammation, resulting in loss of muscle mass and impaired physical performance. Muscle protein breakdown and inhibition of protein synthesis, driven by proinflammatory cytokines, are believed to contribute to sarcopenia. Inflammatory biomarkers may aid early diagnosis and prognosis of sarcopenia in this context (11). However, a consensus in the literature on the specific biomarkers or pathophysiological mechanisms driving the inflammatory processes of sarcopenia is currently lacking. Zhao et al. (10) found that higher levels of NLR, PLR, and systemic immune-inflammation index were significantly associated with a greater likelihood of sarcopenia in middle-aged and older adults. The findings suggest that regular monitoring of systemic inflammatory markers may be an effective strategy for screening and managing sarcopenia. In a similar vein, a Turkish study explored the SI as a potential biomarker in sarcopenia screening and management (39). The study by Can et al. (40) demonstrated an association between sarcopenia and inflammatory markers, including erythrocyte sedimentation rate, CRP, and adiponectin.

In addition, many studies have identified links between sarcopenia and elevated levels of proinflammatory cytokines, particularly TNF-α and IL-6 (41). However, measuring these cytokines in everyday clinical settings is rarely practical due to cost, technical difficulty, and the demands of laboratory infrastructure. Therefore, employing more practical, accessible, and cost-effective inflammatory biomarkers for sarcopenia screening and evaluation is vital.

CBCs readily measure IGr%s, providing an accessible laboratory parameter. Bone marrow regulates IGr% production in response to inflammation (13). In hospitalized patients who develop sepsis, IGr%s have been reported to be among the earliest biomarkers to rise (42). In a retrospective study of 84 patients with acute pancreatitis, IGr% levels were significantly higher in severe cases

and were suggested to be associated with prognosis. Similarly, another retrospective analysis found that both IGr% and IGr% count were markedly elevated in patients with complicated appendicitis compared with those with uncomplicated disease (43,44). Additionally, a recent study demonstrated that IGr% levels at admission could serve as an innovative, cost-effective, and readily accessible biomarker with predictive value in patients with coronavirus disease-2019 (45). Collectively, these findings highlight the potential of IGr% as an early diagnostic indicator and a prognostic biomarker across a range of acute inflammatory conditions.

Studies show that elevated IGr% levels occur not only in infections but also in various systemic inflammatory conditions, such as diabetic nephropathy, acute myocardial infarction, stroke, rheumatologic diseases, and metastatic cancers (15-18). In rheumatologic and autoinflammatory diseases, IGr%s hold potential as indicators of inflammation. In familial mediterranean fever, elevated IGr% levels during attack-free periods compared with those of healthy individuals reflect subclinical inflammation and may serve as predictive markers for future attacks (46). In patients with rheumatoid arthritis, IGr% levels are rapid, accessible, and cost-effective markers for assessing disease activity; peripheral blood IGr% levels also have potential value for prognostication and prediction of response to anti-TNF therapy (47). In addition, IGr%s, as quantified by both absolute IGr% count and IGr%, have consistently demonstrated robust sensitivity and specificity for identifying metastatic involvement in breast and colon cancers. In breast cancer, IGr% levels accurately predicted axillary metastases that were clinically occult but pathologically confirmed, whereas in colon cancer, both the IGr% count and percentage effectively discriminated metastatic from non-metastatic cases in the preoperative setting (18,48). These findings position IGr%s as readily accessible, cost-effective biomarkers that reflect early inflammatory responses and tumor-associated immune dysregulation and offer potential for monitoring acute and chronic inflammation. This dual functionality underscores its utility for patient stratification, early detection of metastasis, prognostic assessment across various malignancies, and evaluation of low-grade chronic inflammation that may contribute to sarcopenia in post-menopausal women.

In this study, none of the standard inflammatory indicators, including WBC, NEU, LYM, PLR, NLR, and CRP, demonstrated a statistically significant association with sarcopenia. Interestingly, IGr% were significantly higher among sarcopenic individuals in the univariate analysis; however, this association was no longer significant in the multivariate model adjusted for confounders. This finding aligns with previous reports indicating that systemic inflammation contributes to sarcopenia pathogenesis in post-menopausal women, yet the specific inflammatory pathways and their measurable biomarkers remain inconsistent across studies. Cesari et al. (49) showed that elevated blood IL-6 concentrations were linked to low muscle strength and poorer physical performance among older adults, underscoring the involvement of inflammatory pathways in age-related muscle decline. In contrast, a meta-analysis conducted by Bano et al. (50) in 2017 reported no significant difference in IL-6 levels between individuals with sarcopenia and their non-sarcopenic counterparts. These findings suggest that the detectable inflammatory profile in sarcopenia may differ across populations and study settings, potentially reflecting heterogeneity in underlying biological mechanisms or methodological factors. In this context, IGr% may serve as an early-phase indicator of subclinical inflammation, potentially preceding increases in traditional markers such as CRP or NLR. Although its independent predictive value was not confirmed in our sample, the observed elevation supports its possible role in the early detection of inflammation-related muscle deterioration. Future large-scale, longitudinal studies are warranted to validate these findings and clarify whether IGr% offers incremental predictive value beyond standard inflammatory markers in the stratification of sarcopenia risk.

Study Limitations

This study is pioneering in its evaluation of the relationship between IGr% and sarcopenia, significantly advancing current research. Furthermore, limiting participants to post-menopausal women allows for focused sarcopenia awareness campaigns within this population. This study may enhance our understanding of age-related muscle loss and women's health concerns following menopause. The generalizability of the findings to other populations is limited due to the study's single-center design and the exclusive use of Turkish participants. Furthermore, the exclusive inclusion of post-menopausal female participants restricts the applicability of the results to male populations. The cross-sectional study design prevents the determination of causality between IGr% levels and sarcopenia. Additionally, the relatively young mean age of our study population (59 years) should be taken into consideration when interpreting the findings. Most sarcopenia research and biomarker validation studies target older adults (≥65 years), in whom age-related muscle decline and inflammatory alterations are more pronounced. Therefore, the results of our study may not be directly generalizable to geriatric cohorts. Consequently, larger, more diverse, multicenter studies are required to establish causality.

Conclusion

The IGr%, an easily obtainable parameter from routine CBC testing, may be a promising biomarker for sarcopenia, reflecting early low-grade systemic inflammation. While these findings highlight its potential usefulness in clinical risk assessment, further validation through large-scale, prospective, multi-center studies is necessary before its routine clinical application can be recommended.

Ethics

Ethics Committee Approval: The study received ethical approval from Marmara University's Local Ethics Committee (decision number: 09.2025-25-0174, date: 21.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.Y., N.Ş.D., A.Y., E.Ü., E.D.K., Z.B.Y., Ç.A., B.C., A.T., Concept: Y.Y., N.Ş.D., A.Y., E.Ü., E.D.K., Z.B.Y., Ç.A., B.C., A.T., Design: Y.Y., N.Ş.D., A.Y., E.Ü., E.D.K., Z.B.Y., Ç.A., B.C., A.T., Data Collection or Processing: Y.Y., N.Ş.D., A.Y., E.Ü., E.D.K., Z.B.Y., Ç.A., B.C., A.T., Analysis or Interpretation: Y.Y., N.Ş.D., E.Ü., B.C., A.T., Literature Search: Y.Y., N.Ş.D., A.T., Writing: Y.Y., N.Ş.D., A.T.,

Conflict of Interest: One author of this article, Aslı Tufan, is a member of the editorial board of the European Journal of Geriatrics and Gerontology. However, he did not take part in any stage of the editorial decision of the manuscript. The other authors declared no conflict of interest.

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ORIGINAL RESEARCH

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Tandem Stance Test Performance is Independently Associated with Overall Mortality Risk in Middle-Aged and Older Adults

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Abstract

Objective: The tandem stance test (TST) is a simple, non-invasive measure of static balance, but its independent prognostic value for all-cause mortality in the general population remains unclear. This study aimed to evaluate the prospective association between TST performance and all-cause mortality.

Materials and Methods: We analyzed data from 11973 participants aged ≥45 years (51.8% female; mean age 59.0 ± 9.2 years) enrolled in the China Health and Retirement Longitudinal Study (CHARLS) at baseline in 2011, with follow-up through 2020. TST was categorized as "success" or "failure". Cox proportional hazards (PHs) models assessed the association between TST outcomes and mortality, adjusting for age, sex, smoking, comorbidities, and income. Sensitivity analyses employed semiparametric PHs models for interval-censored data due to incomplete death dates in some waves.

Results: Overall, 22.9% failed the TST; failure was associated with older age, female sex, greater comorbidity burden, and higher mortality (17.8% vs. 11.0%; $p < 0.001$). In fully adjusted Cox models, TST failure predicted increased mortality risk (hazard ratio (HR): 1.261, 95% confidence interval (CI): 1.128-1.410; $p < 0.001$). Subgroup analyses showed consistent associations across sex, smoking, comorbidity, and most income strata, but not among participants ≥70 years or with high income. Semiparametric models confirmed the robustness of the results (adjusted HR: 1.329, 95% CI: 1.157-1.527; $p < 0.001$).

Conclusion: TST failure is associated with all-cause mortality in middle-aged and older adults. As a quick, scalable tool, TST holds promise for early risk stratification in clinical and public health settings, warranting validation in diverse populations.

Keywords: Tandem stance test, mortality, CHARLS, balance, semiparametric models

Introduction

Balance plays a key role in maintaining overall physical vitality and functional autonomy,drawing from a blend of vision, inner ear, and body-sense signals processed by the central nervous system (1-4). A rapid decline in balance ability after age 50 is one of the main causes of falls; approximately 30%-60% of community-dwelling older adults experience falls yearly, accounting for two-thirds of accidental deaths (5-7).

Although balance assessments, such as posturography tests (8), were not routinely conducted in the physical examination of older adults, recent evidence indicates their potential association with mortality; for example, was associated with an 84% increased risk of all-cause mortality in middle-aged and older adults (9). Nevertheless, the single-leg stance is more demanding than the semi-tandem or tandem positions, requiring greater neuromuscular control. Patients with vestibular dysfunction or diminished muscle strength frequently exhibit compromised postural control, rendering the single-leg stance maneuver difficult to perform and thereby limiting its applicability in these populations.

The tandem stance test (TST) involves aligning one foot directly anterior to the other. Similar to the single-leg stance, this posture significantly reduces the body's base of support, thereby increasing the challenge of maintaining balance. TST can be used independently or as an integral component of commonly used balance assessment tools, such as the short physical performance battery (SPPB) balance scale and the clinical gait

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and balance scale (10-13). Previous studies have shown that TST duration is positively correlated with gait speed (14) and is a predictor of falls within six months in older adults (8).

Recent studies have demonstrated that inability to complete the TST is associated with prevalent cardiovascular disease, cognitive impairment, and frailty (15-17). Thus, TST may offer a rapid, low-cost means of detecting multisystem dysfunctions that themselves are established predictors of mortality (18-21). Nonetheless, to our knowledge, whether TST performance is independently associated with all-cause death remains elusive. To address this gap, we aim to evaluate the association between TST failure and subsequent all-cause mortality in middle-aged and older adults.

Material and Methods

Study Population

The China Health and Retirement Longitudinal Study (CHARLS), coordinated by Peking University, is a nationwide prospective survey targeting Chinese adults aged 45 and above (22). Using a multistage, stratified design, CHARLS enrolled participants from 150 counties across 28 provinces at baseline in 2011. Follow-up waves were completed in 2013, 2015, 2018, and 2020 to capture longitudinal changes in health status, socioeconomic status, and demographic characteristics. Approval for the study was granted by the Biomedical Ethics Review Committee of Peking University (IRB approval number: IRB00001052-11015, date: 05.06.2011), and written informed consent was obtained from all participants before enrollment.

A total of 17705 participants were initially enrolled at baseline, of whom 5732 were excluded due to: 1) missing TST data (n = 4913); 2) age less than 45 years at enrollment (n = 263); and 3) loss to follow-up immediately after baseline survey (n = 556). Missing data were handled using listwise deletion. Consequently, 11973 participants were included in our prospective longitudinal analyses (Figure 1).

Assessment of TST

To date, no universally standardized cutoffs for TST have been established. Prior investigations have variously proposed 10-, 30-, or 60-second thresholds for this balance assessment (8,10,11,14,23). In CHARLS survey, TST performance was classified using predefined age-stratified criteria according to sponsor's protocol: participants aged ≥70 years who sustained the stance for less than 30 seconds and those aged <70 years who held it for less than 60 seconds were classified as "Fail" (Questionnaire PE001: determines which of the following tests the subject should perform based on the subject's age? 1) 30-second tandem stance balance test (subjects 70 years or older); 2) 60-second tandem stance balance test (subjects under 70 years old).

Statistics

Baseline demographic, lifestyle, clinical, and socioeconomic variables were obtained from the CHARLS 2011 wave. Vital status and mortality data were collected during follow-up waves (2013, 2015, 2018, and 2020) through standardized exit interviews. While mortality status was confirmed in all waves, exact dates of death were only documented in the 2013 wave and in a subset of the 2020 wave. For deaths reported in 2015 and 2018, the precise dates were unavailable. For participants who died, the survival time was calculated as the interval from the 2011 wave date to either the known date of death or, if the exact date was unknown, the median interview date of the wave in which their death was recorded.

In summarizing descriptive data, continuous measures were reported as means with standard deviations (SD) (mean ± SD), whereas discrete factors were detailed through frequencies and proportions. Survival curves for participants with TST "success" and "fail" outcomes were estimated using the Kaplan-Meier method. Additionally, the associations between variables and mortality risk were evaluated using Cox proportional hazards (PHs) regression. R software (4.1.1) was used for statistical analysis, with significance assessed at the 0.05 level (two-tailed).

Sensitivity Analyses

Given that the exact death dates in some waves were unknown, we reanalyzed the data using an interval-censored method. Survival times were treated as interval-censored, bounded between the date of the last interview confirming the participant was alive and the date of the subsequent interview confirming death. Interval-censored survival times were analyzed using semiparametric PH models implemented in the icenReg package (24). The hazard function was modeled as $h(t|X_i) = h_0(t) \exp(\beta^T \cdot X_i)$, where $h(t|X_i)$ denotes the hazard rate at time t, h0(t) is the unspecified baseline hazard, X_i is the covariate vector, and β is the vector of log hazard ratios (HR) estimated from the data. Bootstrap resampling (B = 100 samples) was employed to compute robust standard errors and confidence intervals (CI).

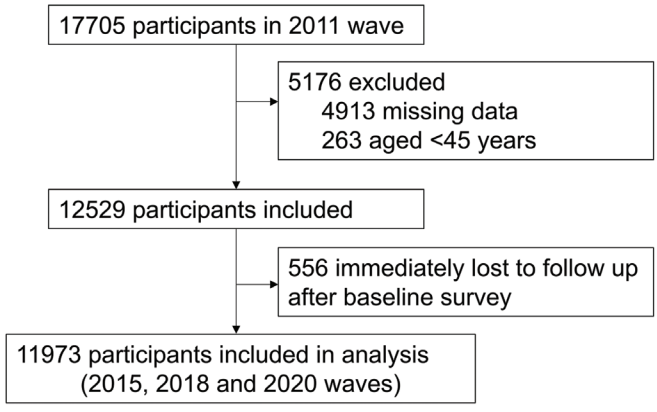

Figure 1. Study diagram.

This approach avoids biases inherent to methods assuming exact or right-censored event times, ensuring valid inference for interval-censored data (24).

Results

A total of 17705 participants were interviewed between 2011 and 2020, of whom 11973 were included in our analyses (Figure 1). The mean ± SD age of the participants was 59.0 ± 9.2 years, and 51.8% were female. No adverse events occurred during TST testing, and 2746 (22.9%) participants failed to complete the TST (Table 1). The proportion of TST failure responders increased with age, was 14.9% among those 45-49 years, and almost half (48.8%) at ≥80 years (Supplementary Figure 1). Specifically, individuals who failed the TST were, on average, older (61.8 years vs. 58.2 years, $p < 0.001$), more likely to be female (63.3% vs. 48.3%, $p < 0.001$), and had a higher prevalence of comorbidities (74.8% vs. 66.0%, $p < 0.001$), including hypertension, diabetes, and heart disease. Additionally, the TST "fail" group included a greater proportion of non-smokers (65.5% vs. 57.8%, $p < 0.001$) and individuals with "poor" income (14.6% vs. 11.8%, $p = 0.001$). Notably, the higher proportion of non-smokers in the TST "fail" group may be attributed to the significantly greater prevalence of smoking among males than females (74.9% vs. 8.3%, $p < 0.001$). Furthermore, the mortality rate was significantly higher among those who failed the TST (17.8% vs. 11.0%,$p < 0.001$). These findings indicate a robust association between TST performance and key sociodemographic and health-related factors.

During the nine-year follow-up (2011–2020), 1507 (12.6%) participants died (Table 1). The Kaplan-Meier survival curves demonstrate a significant difference in all-cause mortality between the TST "success" and "failure" groups (Figure 2). Over the follow-up period, individuals in the TST "fail" group exhibited a consistently lower survival probability than individuals in the TST "success" group ($p < 0.001$), suggesting that impaired TST performance is associated with an increased risk of mortality. The Cox PHs analysis demonstrated a significant association between TST failure and elevated all-cause mortality risk (unadjusted HR: 1.503, 95% CI: 1.348-1.674, $p < 0.001$; Table 2). This relationship persisted in an age- and gender-adjusted model (HR: 1.267, 95% CI: 1.133-1.417, $p < 0.001$) and in a fully adjusted model incorporating age, gender, smoking status, comorbidities, and income (HR: 1.261, 95% CI: 1.128-1.410, $p < 0.001$).

Table 1. Demographic and clinical characteristics of study participants according to tandem stance test.

Variable		Tandem stance test		p-value
	Total (n = 11973)	Success (n = 9227)	Fail (n = 2746)	
Age, years, mean (SD)	59.0 (9.2)	58.2 (8.9)	61.8 (9.6)	<0.001
Gender, n (%)				
Female	6198 (51.8%)	4460 (48.3%)	1738 (63.3%)	<0.001
Male	5775 (48.2%)	4767 (51.7%)	1008 (36.7%)	
Smoking, n (%)				<0.001
No	7132 (59.6%)	5332 (57.8%)	1800 (65.5%)	
Yes	4841 (40.4%)	3895 (42.2%)	946 (34.5%)	
*Comorbidity, n (%)				
No	3824 (31.9%)	3133 (34.0%)	691 (25.2%)	<0.001
Yes	8149 (68.1%)	6094 (66.0%)	2055 (74.8%)	
Income, n (%)				
Poor	1486 (12.4%)	1085 (11.8%)	401 (14.6%)	0.001
Relatively poor	3841 (32.1%)	3011 (32.6%)	830 (30.2%)	
Average	6342 (53.0%)	4901 (53.1%)	1441 (52.5%)	
Relatively high	281 (2.3%)	213 (2.3%)	68 (2.5%)	
Very high	23 (0.2%)	17 (0.2%)	6 (0.2%)	
Death, n (%)				
No	10466 (87.4%)	8208 (89.0%)	2258 (82.2%)	<0.001
Yes	1507 (12.6%)	1019 (11.0%)	488 (17.8%)	

*Comorbidity includes hypertension, dyslipidemia, diabetes or high blood sugar, cancer or malignant tumor, chronic lung diseases, liver disease, heart disease, stroke, kidney disease, digestive disease, emotional, nervous, or psychiatric problems, memory-related disease, arthritis or rheumatism, and asthma.
p-values were calculated by Student's t test, or χ^2 test, as appropriate.
SD: Standard deviation.

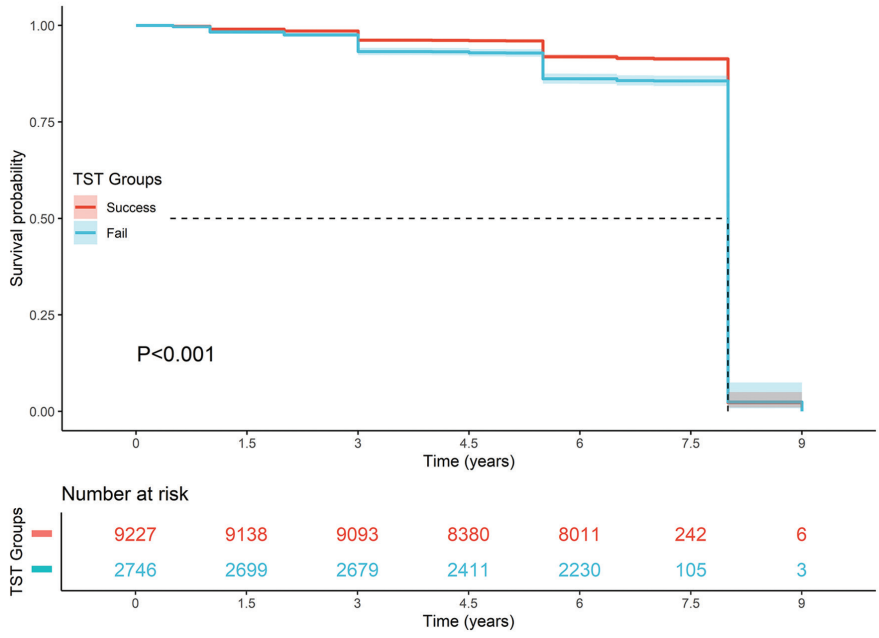

Figure 2. Kaplan-Meier survival curves for participants aged ≥45 years, stratified by TST performance. The log-rank p-value is shown. The dotted horizontal line denotes a survival probability of 0.5. TST. The number at risk decreases sharply toward the end of follow-up, due to cohort attrition and conservative imputation of event times (using the median interval between follow-up waves), resulting in few participants being retained in the final 2020 survey wave.

TST: The tandem stance test.

Table 2. Associations of TST with all-cause mortality in middle-aged and older adults.

TST Outcome	Events/participants (%)	Mortality HR (95% CI)	p-value*
Model 1 - unadjusted			
Success	1019/9227 (11.0%)	1 (reference)	
Fail	488/2746 (17.8%)	1.503 (1.348-1.674)	<0.001
Model 2 - adjusted for age and gender			
Success	1019/9227 (11.0%)	1 (reference)	
Fail	488/2746 (17.8%)	1.267 (1.133-1.417)	<0.001
Model 3 - adjusted for age, gender, smoking, comorbidity and income			
Success	1019/9227 (11.0%)	1 (reference)	
Fail	488/2746 (17.8%)	1.261 (1.128-1.410)	<0.001

*Cox proportional hazards modelling.
HR: Hazard ratio, CI: Confidence interval.

Subgroup analyses revealed that TST failure was associated with increased all-cause mortality across most strata (Figure 3). The association was significant among participants aged <70 years (HR: 1.450, 95% CI: 1.248-1.685), but not among those ≥70 years (HR: 1.153, 95% CI: 0.985-1.349). Both females and males exhibited elevated risks. Similar patterns were observed among non-smokers (HR: 1.498), smokers (HR: 1.658), those with comorbidities (HR: 1.394), and those without comorbidities (HR: 1.737).The association remained significant across most income levels, including "poor", "relatively poor", and "average", except for the highest income categories. These results support the robustness of TST performance as a mortality predictor across diverse populations.

Due to imprecise documentation of the timing of death for selected participants, a sensitivity analysis was performed using an interval-censoring technique, consistent with the prior protocol (24). The semiparametric PHs model showed a significant association between TST failure and an increased risk of all-cause mortality (unadjusted HR: 1.708, 95% CI: 1.506-1.938, $p < 0.001$) (Table 3). This association was significant after adjustment for age and gender (HR: 1.354, 95% CI: 1.178-1.555, $p < 0.001$) and remained significant in the fully adjusted model incorporating age, gender, smoking status, comorbidity, and income(HR: 1.329, 95% CI: 1.157-1.527, p <0.001).

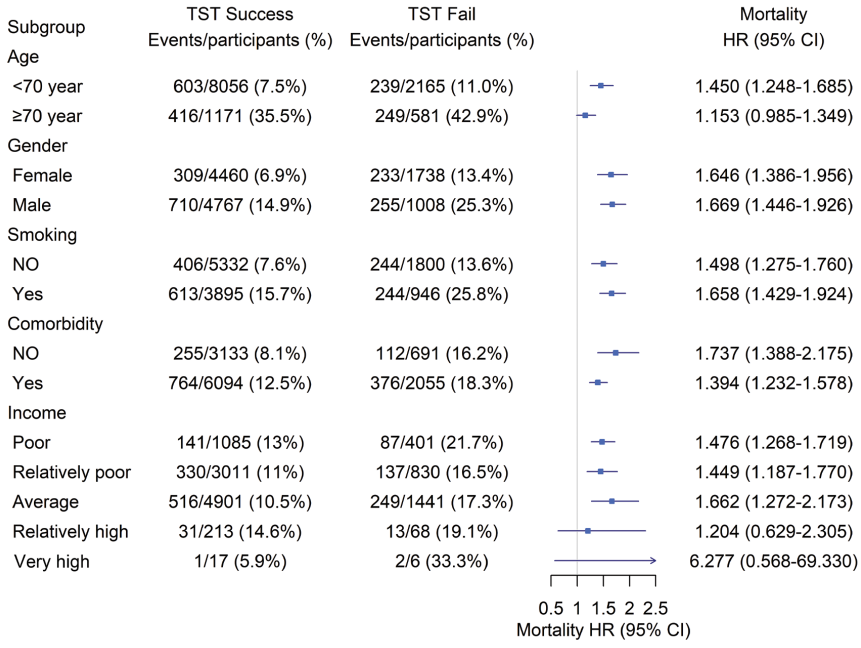

Figure 3. Subgroup analysis of the association between TST failure and all-cause mortality. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using unadjusted Cox proportional hazards models. TST, tandem stance test.

TST: The tandem stance test.

Table 3. Associations of TST with all-cause mortality in middle-aged and older adults in interval-censored regression models.

TST Outcome	Events/participants (%)	Mortality HR (95% CI)	p-value*
Model 1 - unadjusted			
Success	1019/9227 (11.0%)	1 (reference)	
Fail	488/2746 (17.8%)	1.708 (1.506-1.938)	<0.001
Model 2 - adjusted for age and gender			
Success	1019/9227 (11.0%)	1 (reference)	
Fail	488/2746 (17.8%)	1.354 (1.178-1.555)	<0.001
Model 3 - adjusted for age, gender, smoking, comorbidity and income			
Success	1019/9227 (11.0%)	1 (reference)	
Fail	488/2746 (17.8%)	1.329 (1.157-1.527)	<0.001

*Semiparametric proportional hazards modelling.
HR: Hazard ratio, CI: Confidence interval.

Discussion

In this large, prospective cohort study, we observed a significant association between TST failure and increased all-cause mortality over a nine-year follow-up (HR: 1.503, 95% CI: 1.348-1.674; Table 2). This association remained robust after adjusting for key confounders, including age, gender, smoking status, comorbidities, and income (HR: 1.261, 95% CI: 1.128-1.410). Our findings were consistent across most subgroups, except among participants aged 70 years or older and participants in the highest income categories. Our results build on prior evidence linking physical performance measures, such as the SPPB (including side-by-side stance, semi-tandem stance, and TST) and the 10-second single-leg stance to mortality risk (9,11). As a core component of the SPPB, the TST demonstrated comparable predictive value, suggesting that it may serve as an effective surrogate. Compared to the SPPB, TST is simpler, quicker, and elicits higher participant compliance, making it well-suited for large-scale screening. In contrast, the 10-second single-leg stance is more challenging; previous studies indicate that most individuals older than 70 years cannot perform it (9). In the CHARLS cohort, nearly half of the participants under 80 years of age successfully completed TST (Figure S1), highlighting its greater feasibility and acceptability among older adults. Recent findings suggest a relationship between poor performance on

the semi-TST and greater mortality risk in middle-aged and older adults (25). Our findings provide compelling additional evidence underscoring the relationship between balance and mortality. In summary, our study demonstrated that TST is a simple, non-invasive measure of balance, offering a practical and valuable tool for assessing mortality risk in middle-aged and older adults.

An intriguing observation from our subgroup analyses was the lack of a notable correlation between TST failure and mortality among participants aged 70 years or older (Figure 3). Notably, an age-stratified definition of TST failure was employed in the CHARLS protocol: inability to sustain the stance for ≥60 seconds among those aged <70 years versus ≥30 seconds among those ≥70 years. This approach, while pragmatically tailored to age-related declines in neuromuscular capacity, introduces measurement heterogeneity that may attenuate the observed association in the older subgroup (HR: 1.153, 95% CI: 0.985-1.349; Figure 3). Specifically, the lower threshold for older adults could classify a subset of individuals with moderate impairments as "successful", thereby diluting the contrast between groups and reducing statistical power to detect differences in mortality risk. Our findings suggest that adopting a uniform criterion, such as a 60-second threshold for all ages, may improve the predictive utility of TST, which merits further investigation.

The link between TST failure and increased mortality risk likely involves multisystem physiological decline. Impaired balance, as reflected by TST failure, may serve as a sentinel marker of age-related pathologies, including sarcopenia, neurodegenerative changes, and peripheral neuropathy (26-29). Such deficits elevate the risk of falls (30,31), accelerate frailty progression (26,32),and compromise functional independence (33,34) -all pathways that may culminate in premature mortality. The rapid age-dependent increase in TST failure (48.8% among participants ≥80 years, Figure S1) may mirror the trajectory of neuromuscular aging, suggesting that balance impairment is a sensitive indicator of cumulative health deterioration.

Our investigation is characterized by several advantages, including the incorporation of a large, nationally representative panel drawn from CHARLS and followed for nine years, providing robust evidence of a temporal relationship between TST performance and mortality. Standardized data collection protocols and comprehensive adjustment for confounders enhance the reliability of our findings. Additionally, the consistency of results across Cox PHs models and sensitivity analyses using interval-censored methods underscores the robustness of the association.

Study Limitations

Despite the strengths of this study, several limitations must be acknowledged. First, the absence of exact death dates for some participants may introduce imprecision in survival estimates. However, a sensitivity analysis using interval-censored methods addressed this issue and corroborated the primary findings. Second, unmeasured or inadequately measured factors, e.g., history of falls, physical activity levels, education, body mass index, cognitive function, and nutritional status, may have influenced our results. Higher education and healthier lifestyles are typically associated with better balance and lower mortality risk, whereas poor nutrition, obesity, or cognitive impairment may impair balance and increase mortality risk. Furthermore, the lack of correction for multiple comparisons in our subgroup analyses may increase the risk of Type I error. Future studies should incorporate interaction tests to confirm subgroup-specific effects. Finally, the study's reliance on a cohort from mainland China may limit the transferability of its findings to other demographic or geographic contexts. Validation in diverse cohorts is required to evaluate the broader applicability.

Our studies indicate that TST complements established frailty indices and fall risk assessments by providing an additional dimension of functional evaluation. Owing to its simplicity and scalability, TST is particularly suited to primary care and resource-limited settings where comprehensive performance batteries are impractical. Future research should examine its integration into multidimensional geriatric assessments and its potential to enhance risk stratification when combined with existing screening tools.

Overall, our analysis demonstrates an independent association between TST failure and increased all-cause mortality in middle-aged and older populations in China. This simple balance test offers a practical means of identifying at-risk individuals, with potential applications in clinical and public health settings. Although additional studies are required to validate these results across varied populations and clarify the underlying mechanisms, our findings highlight the value of TST as an indicator of general health and survival.

Ethics

Ethics Committee Approval: The study was approved by the Biomedical Ethics Review Committee of Peking University (approval number: IRB00001052–11015, date: 05.06.2011).

Informed Consent: Written informed consent was obtained from all participants before their inclusion in the study.

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary Figure. https://d2v96fxpocvxx.cloudfront.net/beb8919b-f013-4ea1-b1c8-40332e840fe1/content-images/6b065a03-f1c8-4d16-804a-00ccdf67b67f.pdf

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ORIGINAL RESEARCH

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The Associations Between Triglyceride-Glucose Related Indices and Biological Ageing Acceleration in American Adults: Evidence from NHANES 1999-2018

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Abstract

Objective: Biological ageing represents a major public health concern. Triglyceride-glucose (TyG)-related indices, which integrate glucose and lipid metabolism and reflect insulin resistance, have been proposed as potential indicators of metabolic dysfunction. The present study investigated whether TyG-related indices were associated with biological ageing acceleration and explored the mediating roles of inflammation and oxidative stress.

Materials and Methods: Twelve thousand five hundred seventy participants whose age ≥18 years were obtained from the National Health and Nutrition Examination Survey cycles spanning 1999 to 2018. Biological age was calculated using the Klemera–Doubal method. Weighted logistic regression and mediation analyses were conducted to evaluate associations between TyG-related indices and inflammation, oxidative stress, and biological ageing acceleration.

Results: Increasing levels of all TyG-related indices were significantly associated with higher odds of biological ageing acceleration. Individuals in the highest quartile had elevated odds of accelerated biological ageing relative to those in the lowest quartile, with odds ratios (95% confidence intervals) of 2.68 (2.39-3.01) for TyG, 3.66 (3.25-4.12) for TyG-waist circumference, 3.69 (3.28-4.16) for TyG-waist-to-height, and 3.40 (3.03-3.81) for TyG-body mass index. Mediation analyses suggested that inflammatory and oxidative stress markers, including white blood cell count and GGT, accounted for approximately 9.4% and 16.2% of the association between TyG and biological ageing acceleration, respectively.

Conclusion: These findings demonstrate significant associations between TyG-related indices and biological ageing acceleration. Because of the cross-sectional design of National Health and Nutrition Examination Survey, causal inferences should be made cautiously, and further longitudinal studies are necessary to confirm these relationships. Nonetheless TyG and its related indices may serve as simple, practical markers for early metabolic risk classification and prevention of age-related health decline by identifying individuals with increased metabolic and inflammatory burden.

Keywords: Triglyceride-glucose index, TyG-related indices, obesity, biological ageing, NHANES

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Introduction

Ageing is a multifactorial biological process characterized by progressive declines in structural integrity and physiological function, ultimately increasing susceptibility to disease and mortality (1). At the molecular level, ageing involves cumulative alterations in genes, metabolism, and cellular homeostasis, resulting in impaired repair capacity and organ dysfunction (2-4). Recent evidence highlights that biological ageing acceleration—the difference between biological and actual age—serves as an important determinant of chronic disease risk, frailty, and premature mortality (1,5-7). Therefore, identifying metabolic and inflammatory pathways that contribute to accelerated biological ageing is a critical step toward developing effective prevention strategies.

As a simple and reliable alternative indicator, the triglyceride-glucose (TyG) index is increasingly used to evaluate insulin resistance and cardiometabolic health. This measure, determined based on levels of fasting triglycerides and glucose, indicates impaired insulin sensitivity and contributes to metabolic abnormalities such as hyperglycemia and dyslipidemia (8,9). Evidence in the literature links the TyG index to the development of type 2 diabetes and cardiovascular disease and to an increased risk of all-cause mortality (10-12). Several composite indices that integrate the TyG index with obesity indicators, including TyG-body mass index (BMI), TyG-waist circumference (WC), and TyG-waist-to-height ratio (WHtR), have emerged to improve predictive validity and exhibit enhanced performance in assessing metabolism-related risks (13,14).

Biological ageing is a multifactorial phenomenon characterized by the progressive loss of functional integrity, largely driven by chronic inflammation, oxidative stress, and metabolic dysregulation (15,16). Persistent low-grade inflammation, often associated with visceral adiposity and insulin resistance, accelerates molecular damage and functional decline (17). Excessive generation of reactive oxygen species and mitochondrial dysfunction contribute to cellular senescence and telomere shortening—one of the molecular hallmarks of ageing (18,19). Emerging evidence also suggests that metabolic stress influences epigenetic ageing, as reflected by DNA methylation clocks, reinforcing the interplay between metabolism, inflammation, and biological ageing (20). Research directly examining the correlation between metabolic indicators and biological ageing remains limited; however, metabolic dysfunction and obesity are closely associated with the ageing process (21-24). These processes suggest that metabolic, inflammatory, and oxidative stress–related pathways may jointly influence the pace of biological ageing. Therefore, TyG-related indices cannot only reflect metabolic disorders but also serve as accessible indicators of accelerated biological ageing.

However, evidence directly linking TyG-related indices to biological ageing remains limited. Despite these insights, few population-based studies have simultaneously explored the correlation between TyG-related indices and biological ageing acceleration and evaluated the underlying mediating roles of inflammation and oxidative stress. The novelty of this study is that it investigates these associations in a large, nationally representative U.S. sample using National Health and Nutrition Examination Survey (NHANES) data and quantifies the indirect pathways linking metabolic dysregulation to accelerated biological ageing. Given their simplicity and availability from routine laboratory tests, TyG-related indices may provide a clinically viable and cost-effective tool for identifying individuals at high risk of accelerated ageing, thereby guiding the development of prevention strategies in clinical and public health settings. We hypothesized that elevated TyG-related indices would be positively associated with accelerated biological ageing, and that this relationship would be partially mediated by inflammation and oxidative stress.

Materials and Methods

Population and Inclusion Criteria

We analyzed combined data from ten NHANES cycles spanning 1999 to 2018. A total of 101316 participants participated in the survey during the specified timeframe. Figure 1 shows that the final study population comprised 12,570 participants aged 18 years or older. Exclusion criteria were as follows: (1) age below 18 years or pregnancy; (2) missing data on TyG and obesity

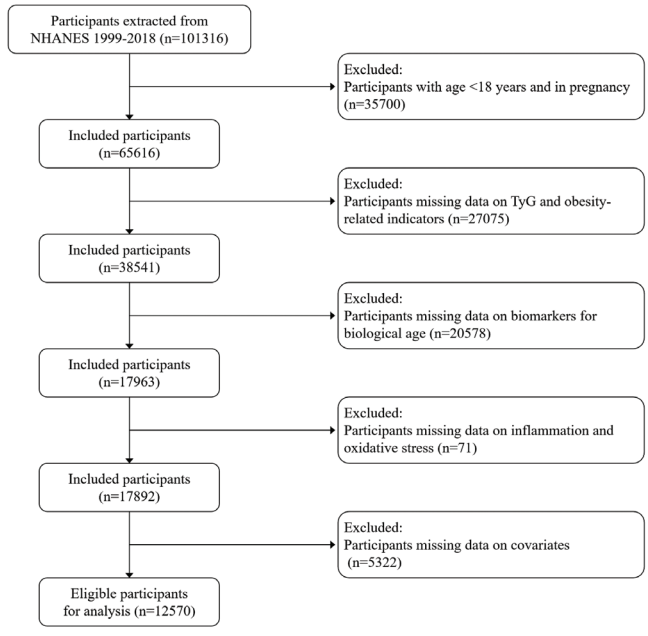

Figure 1. Diagram depicting the participant recruitment process.

TyG: Triglyceride-glucose.

markers; (3) missing data on biomarkers of biological age; (4) missing data on inflammation and oxidative stress; (5) missing covariate data. Of the 101,316 individuals initially enrolled in NHANES 1999–2018, 35,700 were excluded for being under 18 or pregnant; 27,075 were excluded for missing TyG or obesity-related indicators; 20,578 were excluded for missing biological ageing biomarkers; 71 were excluded for missing inflammation or oxidative stress markers; and 5,322 were excluded for missing covariates, leaving a final sample of 12,570 participants.

Assessment of TyG-Related Indices

The TyG index integrates triglyceride and fasting glucose levels measured in participants' blood samples. During physical assessments at the mobile health screening center, participants' waist circumference, height, and body weight were measured. Assessment of indicators of inflammation and oxidative stress is presented in Supplementary Method S1. The formulas for calculating TyG and its combined obesity indices are presented in Supplementary Method S2.

Assessment of Biological Age and Ageing Acceleration

Biological age was expressed as Klemera-Doubal Method Biological Age (KDM-BA), following the method proposed by Klemera and Doubal (25), and was determined using systolic blood pressure in conjunction with seven blood-based biochemical indicators illustrated in Table 1. The R package "BioAge" was employed to assess participants' biological age. Within this package, the reference dataset is derived from non-pregnant individuals aged 30–75 years in NHANES III. The algorithm's settings are tailored for male and female participants to ensure accuracy. The KDM-BA of participants aligns with the age at which their physiology is approximately typical. The KDM-BA is the result of multiple regression analyses of each biomarker on actual age in the reference population. The equation used for the calculation is illustrated in Supplementary Method S3. As the KDM-BA algorithm relies on regression parameters derived from non-pregnant adults aged 30–75 years in NHANES III, potential cultural and ethnic biases may exist when extrapolating these parameters to broader populations.

Biological ageing acceleration was defined as the excess of biological age over chronological age. It was quantified as the residual obtained from a linear regression of chronological age on biological age, with positive residuals indicating accelerated ageing.

Ethical approval was obtained from the NCHS Ethics Review Board (ERB) (protocols number: #98-12, #2005-06, #2011-17, and #2018-01, date: 18.12.2024). All individuals volunteered to participate in the study and provided written informed consent for participation and follow-up.

Table 1. Participants' characteristics (n = 12,570).

Characteristic	Median (IQR) or n (%)
Age, years	50.00 (36.00, 65.00)
<45	4948 (39.4)
45-59	3124 (24.9)
60-74	3131 (24.9)
≥75	1367 (10.9)
Gender, n (%)	
Male	6297 (50.1)
Female	6273 (49.9)
Race and ethnicity, n (%)	
Hispanic	3192 (25.4)
Non-hispanic	8617 (68.6)
Other	761 (6.1)
Educational level, n (%)	
<9 years	1398 (11.1)
9-11 years	1810 (14.4)
12 years	2987 (23.8)
>12 years	6375 (50.7)
Marital status, n (%)	
Married or living with partner	7896 (62.8)
Widowed, divorced or separated	2750 (21.9)
Never married	1924 (15.3)
Family PIR	2.35 (1.24, 4.29)
<1.3	3375 (26.8)
1.3-3.5	5027 (40.0)
>3.5	4168 (33.2)
Energy intake (kcal)	1924.00 (1466.00, 2506.00)
Smoking, n (%)	6012 (47.8)
Drinking, n (%)	9242 (73.5)
BMI (kg/m^2)	27.92 (24.40, 32.20)
Waist circumference (cm)	97.80 (88.00, 108.40)
Height (cm)	167.60 (160.40, 175.30)
Weight (kg)	78.90 (67.30, 92.80)
Triglyceride (mg/dL)	110.00 (76.00, 161.00)
Plasma glucose (mg/dL)	100.00 (92.80, 110.00)
TyG	8.60 (8.20, 9.10)
TyG-WC	852.95 (738.10, 972.00)
TyG-WHtR	5.10 (4.40, 5.80)
TyG-BMI	243.60 (206.10, 287.50)
Biological ages	
KDM-BA	43.18 (30.74, 57.70)
KDM-BA acceleration	-1.82 (-9.41, 6.54)

Table 1. Continued.	
Characteristic	**Median (IQR) or n (%)**
Components of biological ages	
SBP (mmHg)	122.00 (111.00, 135.00)
Albumin (g/dL)	4.20 (4.00, 4.40)
Alkaline phosphatase (U/L)	69.00 (56.00, 84.00)
Blood urea nitrogen (mg/dL)	13.00 (10.00, 16.00)
Total cholesterol (mg/dL)	193.00 (167.00, 221.00)
Creatinine (mg/dL)	0.84 (0.70, 1.00)
C-reactive protein (mg/dL)	0.21 (0.08, 0.47)
Glycated hemoglobin (%)	5.50 (5.20, 5.80)
Indicators of inflammation and oxidative stress	
White blood cell count (1000/μL)	6.50 (5.40, 7.80)
SII	476.80 (340.33, 672.18)
GGT (IU/L)	21.00 (15.00, 32.00)
Total bilirubin (mg/dL)	0.70 (0.50, 0.80)
Uric acid (mg/dL)	5.40 (4.50, 6.40)
Major diseases	
Hypertension, n (%)	4488 (35.7)
Diabetes, n (%)	1486 (11.8)
Stroke, n (%)	466 (3.7)
CVD history, n (%)	1099 (8.7)
Liver condition, n (%)	478 (3.8)
Cancer or malignancy, n (%)	1208 (9.6)

Continuous variables are presented as medians and interquartile ranges, while categorical variables are described using raw frequencies and percentages.
IQR: Interquartile range, BMI: Body mass index, TyG: Triglyceride-glucose, WC: Waist circumference, WHtR: Waist-to-height ratio, KDM-BA: Klemera-Doubal method for biological age, PIR: Poverty income ratio.

Statistics

We selected the two-day dietary sample weights and followed NHANES' prescribed approach to generate individual sample weights that appropriately reflect the U.S. population. To examine the differences between participants with and without biological ageing acceleration, categorical and continuous variables were examined using the chi-square and rank-sum tests, respectively. Binary logistic regression was used to estimate odds ratios (ORs) for the association between TyG-related indices and biological ageing acceleration. For each TyG-related index, subjects were grouped into four quartiles with approximately equal sample sizes; the lowest quartile (Q1) served as the reference group. Trend tests were conducted by assigning to each quartile the median of the corresponding index and entering these medians as continuous variables into logistic regression models. Dose-response curves (linear or non-linear) for associations with biological ageing acceleration were assessed using restricted cubic spline (RCS) regression after adjusting for all potential confounders. Detailed definitions and measurements of all covariates are described in Supplementary Method S4.

We hypothesized that there were both direct (average direct effect) and indirect (average causal mediation effect) effects between TyG-related indices of obesity and biological ageing acceleration. The indicators of oxidative stress and inflammation served as mediators in mediation models. The proportion mediated (PM) was computed using the formula: PM = indirect effect/total effect. We sampled each mediation model 5000 times to minimize bias due to sampling error. Interpretation of mediation effects assumes temporal precedence of exposure, mediator, and outcome, and no unmeasured confounding among them. As the present analysis is based on cross-sectional data, these results should be interpreted cautiously.

To ensure robustness, we performed stratified analyses comparing the highest (Q4) and lowest (Q1) quartiles of TyG and its combined obesity indices, and examined the interaction between stratification variables and exposure factors using likelihood ratio tests. Furthermore, to test the robustness of the findings, a series of sensitivity analyses were conducted. First, we repeated the analyses among participants with available data on frailty, sarcopenia, and physical activity, respectively, additionally adjusting for these variables alongside the covariates included in the main models. Secondly, because information on tumor malignancy was not available, we repeated the primary analyses after excluding participants with a self-reported tumor history. All sensitivity analyses were conducted using the same modeling approach as in the primary analyses. All analyses were based on complete cases. Data analyses were carried out in R (version 4.4.1). Statistical significance was defined as two-sided $p < 0.05$.

Results

Participants' Baseline Characteristics and Biological Ages

Table 1 summarizes participants' baseline characteristics. Overall, the median age was 50.0 years (interquartile range, 36.0–65.0 years); 68.6% were non-hispanic, and 50.1% were male. 50.7% had received education beyond 12 years. As indicated in Supplementary Table S1, 43.6% of individuals exhibited KDM-BA acceleration. Significant group differences were observed for age, gender, marital status, education, family poverty income ratio, dietary energy intake, alcohol use, smoking, and chronic diseases ($p < 0.05$), whereas no significant difference was observed for race/ethnicity ($p > 0.05$). Furthermore, Supplementary Tables S2 and S3 show substantial differences in TyG-related indices and indicators of inflammation and oxidative stress between groups ($p < 0.05$). For details on biological ages and KDM-BA acceleration by quartiles of TyG-related indices at baseline, see Supplementary Table S4.

Table 2. Binary logistic regression analysis of TyG-related indices in relation to biological ageing acceleration.

	Crude model		Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
TyG								
Q1	1.00		1.00		1.00		1.00	
Q2	1.26 (1.14–1.39)	<0.001	1.38 (1.25–1.54)	<0.001	1.41 (1.27–1.56)	<0.001	1.37 (1.23–1.52)	<0.001
Q3	1.55 (1.41–1.72)	<0.001	1.81 (1.63–2.01)	<0.001	1.84 (1.66–2.04)	<0.001	1.71 (1.54–1.90)	<0.001
Q4	2.66 (2.40–2.95)	<0.001	3.19 (2.85–3.57)	<0.001	3.27 (2.92–3.66)	<0.001	2.68 (2.39–3.01)	<0.001
p for trend	/	<0.001	/	<0.001	/	<0.001	/	<0.001
TyG-WC								
Q1	1.00		1.00		1.00		1.00	
Q2	1.40 (1.26–1.56)	<0.001	1.67 (1.49–1.86)	<0.001	1.67 (1.49–1.86)	<0.001	1.58 (1.42–1.77)	<0.001
Q3	1.95 (1.76–2.16)	<0.001	2.45 (2.20–2.74)	<0.001	2.45 (2.20–2.74)	<0.001	2.18 (1.95–2.44)	<0.001
Q4	3.61 (3.26–4.01)	<0.001	4.67 (4.17–5.23)	<0.001	4.71 (4.21–5.29)	<0.001	3.66 (3.25–4.12)	<0.001
p for trend	/	<0.001	/	<0.001	/	<0.001	/	<0.001
TyG-WHtR								
Q1	1.00		1.00		1.00		1.00	
Q2	1.43 (1.29–1.59)	<0.001	1.71 (1.53–1.90)	<0.001	1.70 (1.52–1.89)	<0.001	1.62 (1.45–1.81)	<0.001
Q3	2.11 (1.91–2.34)	<0.001	2.61 (2.34–2.92)	<0.001	2.60 (2.33–2.91)	<0.001	2.32 (2.07–2.59)	<0.001
Q4	3.85 (3.46–4.28)	<0.001	4.78 (4.26–5.36)	<0.001	4.78 (4.26–5.36)	<0.001	3.69 (3.28–4.16)	<0.001
p for trend	/	<0.001	/	<0.001	/	<0.001	/	<0.001
TyG-BMI								
Q1	1.00		1.00		1.00		1.00	
Q2	1.40 (1.26–1.55)	<0.001	1.55 (1.39–1.72)	<0.001	1.54 (1.38–1.71)	<0.001	1.46 (1.30–1.62)	<0.001
Q3	1.97 (1.77–2.18)	<0.001	2.21 (1.99–2.47)	<0.001	2.20 (1.97–2.45)	<0.001	1.94 (1.74–2.16)	<0.001
Q4	3.89 (3.50–4.32)	<0.001	4.32 (3.87–4.82)	<0.001	4.32 (3.87–4.82)	<0.001	3.40 (3.03–3.81)	<0.001
p for trend	/	<0.001	/	<0.001	/	<0.001	/	<0.001

Crude model: unadjusted. Model 1 controlled for demographic and socioeconomic factors. Model 2: additionally adjusted for dietary energy intake, alcohol consumption and smoking. Model 3: further adjusted for major chronic conditions (hypertension, diabetes, stroke, cardiovascular disease, liver disease, and cancer/malignancy).
IQR: Interquartile range, BMI: Body mass index, TyG: Triglyceride-glucose, WC: Waist circumference, WHtR: Waist-to-height ratio, KDM-BA: Klemera-Doubal method for biological age, PIR: Poverty income ratio.

Relationships Among TyG-Related Indices and Biological Ageing Acceleration

Table 2 shows the relationships between TyG-related indices and biological ageing acceleration. Significant positive correlations were observed between all TyG-related indices and biological ageing acceleration after adjustment for covariates. In the fully adjusted model (Model 3), comparison of the highest (Q4) with the lowest (Q1) quartile of TyG-related indices showed a significant increase in odds: ORs [95% confidence intervals (CIs)] were 2.68 (2.39–3.01) for TyG, 3.66 (3.25–4.12) for TyG-WC, 3.69 (3.28–4.16) for TyG-WHtR, and 3.40 (3.03–3.81) for TyG-BMI.

Curvilinear Relation Analysis

As shown in Figure 2, RCS models were employed to flexibly model the dose–response relationships between TyG-related indices and biological ageing acceleration. Three obesity-related TyG indices, including TyG-WC, TyG-WHtR, and TyG-BMI, exhibited roughly linear associations with accelerated ageing after adjustment for multiple variables (p for non-linearity >0.05), whereas the TyG index exhibited a pronounced non-linear association (p for non-linearity = 0.002). Specifically, the risk of accelerated biological ageing increased gradually with higher TyG values and rose steeply beyond the upper range of TyG values, indicating a potential threshold effect.

Relationships Among TyG-Related Indices and Inflammation and Oxidative Stress

We observed that all TyG-related indices exhibited positive associations with white blood cell levels, systemic immune-

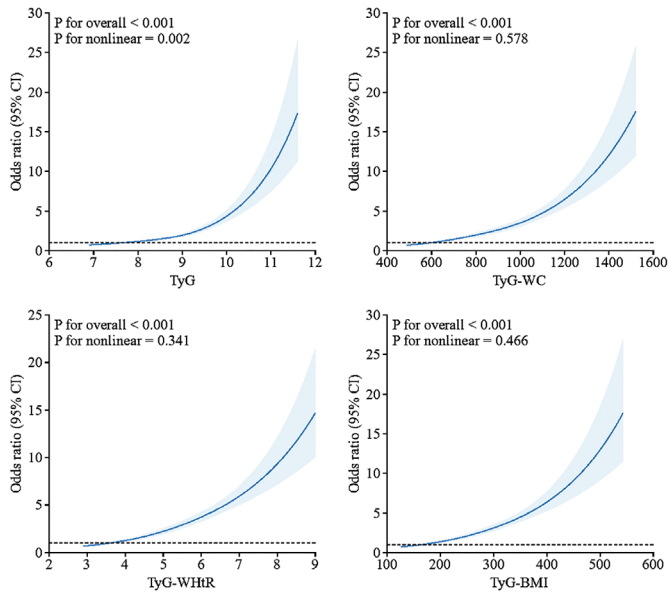

Figure 2. After adjustment for all covariates, restricted cubic spline analysis was used to visualize associations; the central estimate and the 95% confidence interval are shown as a solid blue line and a shaded area, respectively.

BMI: Body mass index, TyG: Triglyceride-glucose, WC: Waist circumference, WHtR: Waist-to-height ratio.

inflammation index (SII), gamma-glutamyl transferase (GGT), and uric acid in ordinal multivariable logistic regression analyses (Supplementary Table S5). For example, participants with TyG in Q4 exhibited significantly elevated white blood cell counts, SII, GGT, and uric acid compared with those in Q1, and the ORs (95% CI) were 2.94 (2.75–3.13), 1.45 (1.36–1.55), 4.38 (4.10–4.68) and 3.35 (3.13–3.58), respectively. Similar relationships were also observed in TyG-WC, TyG-WHtR, and TyG-BMI. Conversely, all TyG-related indices were inversely related to total bilirubin levels.

Relationships Between Inflammation and Oxidative Stress and Biological Ageing Acceleration

As illustrated in Supplementary Table S6, white blood cell count, SII, GGT, and uric acid were significantly and positively associated with biological ageing acceleration ($p < 0.05$). Compared with the reference (Q1), the ORs (95% CI) in Q4 were 1.82 (1.63–2.03), 1.33 (1.20–1.47), 2.22 (1.99–2.48) and 2.65 (2.35–2.98), respectively. In contrast, total bilirubin (Q4: OR: 0.53, 95% CI: 0.48–0.59) was inversely associated with biological ageing acceleration ($p < 0.05$).

Mediation Analyses

Figure 3 illustrates the mediating effects of inflammation and oxidative stress on the associations between TyG-related indices and biological ageing acceleration. Specifically, white blood cell count significantly mediated the relationships with TyG (PM = 9.4%), TyG-WC (PM = 6.5%), TyG-WHtR (PM = 6.4%), and TyG-BMI (PM = 6.1%) ($p < 0.05$). Additionally, GGT and uric acid exhibited strong mediating effects on the relationships between TyG-related indices and biological ageing acceleration ($p < 0.05$). In contrast, the SII and total bilirubin exhibited relatively weak mediation effects, as shown in Supplementary Figure S1.

Stratified Analyses and Interaction Analyses

The correlations of TyG-related indices with biological ageing acceleration across different subgroups are illustrated in Supplementary Figure S2. Upon stratification of participants, the positive association between TyG-related indices and biological ageing acceleration remained consistent across all subgroups. In addition, interaction analyses demonstrated significant effect modification of TyG-related indices by age, hypertension, history of CVD, and diabetes. Notably, the strength of the correlations between TyG-related indices and biological age acceleration gradually decreased with increasing participant age. In particular, participants without hypertension had higher odds of accelerated biological ageing. Similar associations were observed in participants with and without a history of CVD or diabetes.

Sensitivity Analysis

In Supplementary Table S7, the results remained robust after additionally adjusting for frailty and sarcopenia. Taking the extreme quartiles of the TyG index as an example, the adjusted ORs were 2.14 (1.80–2.54) and 3.41 (2.38–4.92), corresponding to Model 1 (with frailty adjustment) and Model 2 (with additional sarcopenia adjustment), respectively (both $p < 0.001$). After excluding the individuals with tumors, the associations between the TyG-related indices and biological ageing acceleration remained robust (Supplementary Table S8). Similarly, the other three indices revealed progressively elevated ORs across quartiles in all models (all $p < 0.05$). In addition, the results remained robust after further adjustment for physical activity (Supplementary Table S9).

Discussion

This large-scale cross-sectional analysis provides new evidence of a correlation between TyG-related indices and accelerated biological ageing. To our knowledge, this is one of the first studies to systematically evaluate TyG and its obesity-related indices in relation to biological ageing acceleration and to explore the mediating effect of oxidative stress and inflammation.

Although previous studies have extensively investigated associations of TyG and its related indices with metabolic diseases, cardiovascular outcomes, and mortality (11,26,27), evidence regarding their relationship with biological ageing remains limited. Our findings extend prior research by demonstrating that TyG-related indices—simple, routinely

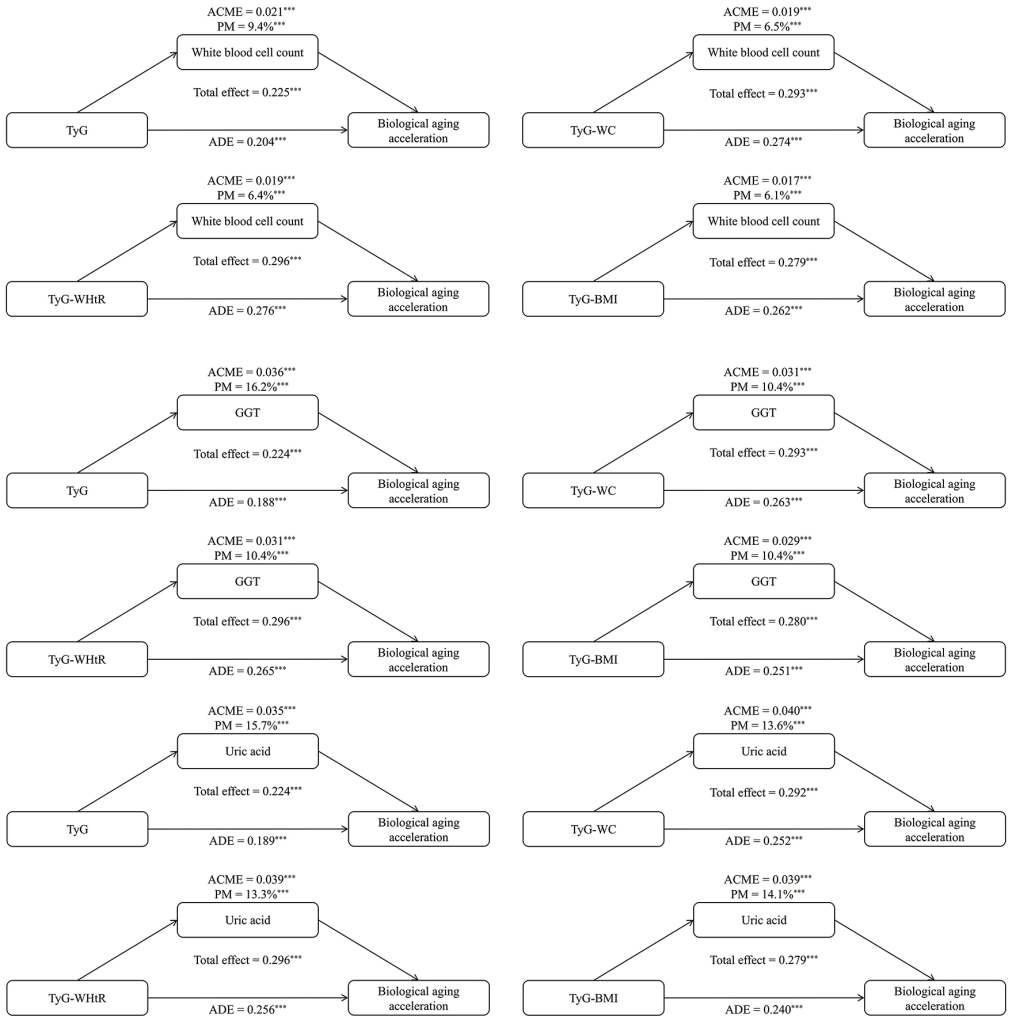

Figure 3. Proportions of mediation by inflammation and oxidative stress markers in the relationships between TyG-related indices and biological ageing acceleration adjusting for all covariables.

ACME: Average causal mediation effect, ADE: Average direct effect, BMI: Body mass index, GGT: Gamma-glutamyl transferase, PM: Proportion mediated, TyG: Triglyceride-glucose index, WC: Waist circumference, WHtR: Waist-to-height ratio.

obtainable indicators of insulin resistance (28)—are also strongly correlated with accelerated biological ageing. This result is consistent with growing evidence that metabolic impairment plays a central role in the ageing process. For instance, insulin resistance and visceral adiposity are known to induce oxidative stress and chronic low-grade inflammation, which accelerate cellular senescence and epigenetic ageing through increased production of reactive oxygen species and mitochondrial dysfunction (29,30). Furthermore, metabolic stress may disrupt DNA methylation homeostasis, thereby promoting epigenetic drift and advancement of biological age (20,31). One study reported that higher TyG index levels were linked to α-Klotho (32), which is known to function as an anti-ageing protein. α-Klotho has been demonstrated to slow the ageing process through multiple mechanisms, including inhibition of insulin and IGF-1 signaling and mitigation of oxidative stress and inflammation (33,34), which supports the biological plausibility of our results. We also found consistent positive associations between obesity-related TyG indices and acceleration of biological ageing, aligning with previous studies showing that central obesity and metabolic dysfunction are associated with epigenetic ageing and telomere shortening (35,36). Our results corroborate these mechanistic insights, suggesting that TyG-related indices may capture broader aspects of metabolic and inflammatory burden relevant to biological ageing.

To further explore the biological mechanisms that likely involve the interplay among insulin resistance, inflammation, and oxidative stress, we conducted mediation analyses and found that inflammation and oxidative stress partially mediated the relationships between TyG-related indices and biological ageing acceleration. These findings align with well-established biological mechanisms whereby insulin resistance and

adiposity promote oxidative stress and inflammation, which in turn accelerate molecular ageing processes. Previous studies have demonstrated positive correlations between TyG and inflammatory biomarkers such as C-reactive protein and SII (37-39), supporting our mediation results. The observed associations may reflect chronic low-grade inflammation induced by TyG-related metabolic dysregulation and adiposity (40). Similarly, oxidative stress markers significantly mediated the relationships between TyG-related indices and biological ageing acceleration. Elevated oxidative stress damages DNA and cellular structures, leading to telomere attrition and increased vulnerability to age-related disorders (41,42). Obesity-related excess reactive oxygen species and inflammatory adipokine release further amplify these effects (43).

In addition, we identified significant effect modification of TyG-related indices by age, hypertension, a history of CVD, and diabetes. Compared with older adults, younger individuals with elevated TyG-related indices had a higher risk of accelerated biological ageing. This may be because most older adults suffer from various chronic diseases related to biological ageing and are already in an adverse metabolic state characterized by high TyG-related indices, which may accelerate biological ageing. In stratified analyses, the positive association between TyG and biological age acceleration was more evident among participants without hypertension or a history of CVD. Several mechanisms may explain this pattern. Individuals with these conditions often receive treatments such as angiotensin-converting enzyme inhibitors, ARBs, β-blockers, or statins, which have metabolic and anti-inflammatory benefits (44,45), and may mitigate the detrimental effects of TyG. In addition, pre-existing vascular and metabolic damage in diseased individuals may lead to a “ceiling effect” whereby further metabolic disturbances exert limited additional influence on aging biomarkers. In contrast, among those without hypertension or CVD history, elevated TyG levels more directly reflect early-stage insulin resistance, lipid toxicity, and mitochondrial dysfunction, promoting oxidative stress and inflammation that accelerate biological ageing. Similarly, the positive association between TyG-WC and acceleration of biological ageing was more evident in participants without diabetes. This may reflect differences in medical management and disease stage. Individuals with diabetes often receive glucose- and lipid-lowering therapies and adopt healthier lifestyles, thereby mitigating insulin resistance and inflammation (46).

These results underscore the potential clinical and public health value of TyG-related indices as accessible, low-cost markers for the early recognition of populations at risk of accelerated biological ageing. Given their availability in routine health examinations, adding TyG-related indices to metabolic health assessment frameworks could facilitate early risk stratification and preventive interventions. Nevertheless, certain limitations of this work must be acknowledged. Despite extensive covariate adjustments, causal inference remains constrained by cross-sectional designs and cannot fully rule out residual confounding. Secondly, KDM-BA, while widely used as a biomarker of biological ageing, represents only one of several available ageing metrics and may not fully capture the multidimensional nature of the ageing process. Thirdly, because the data were derived from an American population, generalizability to other ethnic or regional groups may be limited. In addition, certain covariates were self-reported, which might introduce measurement bias. The associations observed merit further investigation through prospective and interventional research to elucidate causality, mechanisms, and the cross-population applicability of TyG-related indices serving as aging biomarkers.

Conclusion

Significant associations were found between TyG-related indices and accelerated biological ageing in this cross-sectional study. Increasing levels of TyG-related indices were positively correlated with acceleration of biological ageing, and these correlations were partly mediated by inflammation and oxidative stress. Based on these findings, TyG-related indices could be considered early markers for identifying individuals susceptible to accelerated biological ageing. This large-scale study is one of the earliest studies to examine the relationships between TyG-related indices and biological age acceleration in a nationally representative U.S. population and also to incorporate inflammation and oxidative stress as potential mediating pathways. Prospective and interventional studies are necessary to verify these observations and to elucidate the causal pathways connecting metabolic dysfunction, inflammation, oxidative stress, and biological ageing.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the NCHS Ethics Review Board (ERB) (protocols number: #98-12, #2005-06, #2011-17, and #2018-01, date: 18.12.2024).

Informed Consent: All individuals volunteered to participate in the study and provided written informed consent for participation and follow-up.

Footnotes

Authorship Contributions

Concept: H.Z., F.J., Y.G., Z.X., Design: H.Z., F.J., L.L., T.G., Data Collection or Processing: X.X., Analysis or Interpretation: H.Z., X.X., Literature Search: Y.G., L.L., T.G., Writing: H.Z., Z.X.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary Methods: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/d5a2a03d-3f81-4245-8d1b-bda74bb1b7de.pdf

Supplementary Figures: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/b57eecc9-a7e7-40f7-a61b-05c6a55b4a64.pdf

Supplementary Tables: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/a57fd6e6-9d78-4428-92f5-058f9f036e08.pdf

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ORIGINAL RESEARCH

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Frailty Enhances Prognostic Accuracy Compared to CURB-65 in Community-Acquired Pneumonia

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Abstract

Objective: Assessing the severity of community-acquired pneumonia (CAP) and selecting the appropriate care site is crucial for efficient management. Increased frailty is associated with poorer outcomes in both medical and surgical conditions. The objective of the study was to investigate how frailty affects the prognosis of CAP when assessed using frailty scales in combination with CURB-65.

Materials and Methods: The severity of the CAP was assessed utilizing the CURB-65 score and the pneumonia severity index (PSI). We assessed frailty using the FRAIL (F) score and the clinical frailty scale (CFS). New scores (CURB-65-F, CURB-65-CFS) were calculated by augmenting the CURB-65 score with patients' frailty status, and a comparative analysis of patients' mortality was conducted.

Results: One hundred twenty eight subjects (91 males) with a mean age of 60.10 ± 3.98 years were included in the study. While CURB-65-F and CURB-65-CFS had comparable effects on 30-day mortality compared with CURB-65 ($p = 0.001$, HR = 2.245; $p = 0.001$, HR = 2.374; $p = 0.005$, HR = 2.291, respectively), they were superior at 6 months [$p < 0.001$, hazard ratio (HR) = 1.813; $p = 0.001$, HR = 1.797; $p = 0.014$, HR = 1.635, respectively]. Receiver operating characteristic curves evaluating the discriminatory power to predict all-cause mortality, with scores and categories analyzed independently, showed that CURB-65-CFS and CURB-65-F had greater areas under the curve [area under the curve (AUC) = 0.690, 95% confidence interval (CI): 0.590–0.789; AUC = 0.687, 95% CI: 0.586–0.787 respectively] compared with CURB-65 (AUC = 0.614, 95% CI: 0.501–0.726).

Conclusion: In conclusion, using frailty scores to assess an individual's frailty may assist clinicians in more accurately estimating the mortality risk associated with CAP and in determining the site of care, with easy and rapid application at the bedside.

Keywords: Infection, severity, risk, prognosis, lung, scoring

Introduction

Community-acquired pneumonia (CAP), defined as a lung infection acquired outside the hospital, is one of the major causes of morbidity and mortality worldwide (1). The Global Burden of Disease Study revealed that lower respiratory tract infections caused 2,337,697 deaths (4.4% of all deaths) and 65,982,807 hospital admissions globally, across all age groups, from 1990 to 2016 (2). Ramirez et al. (3) reported 30-day and 1-year mortality rates of 13.0% and 30.6%, respectively, among patients hospitalized with CAP. Furthermore, a systematic review of readmission rates after hospitalizations for CAP showed that 20.1% of individuals were readmitted within 30 days and 46.0% within 1 year (4).

The selection of the site of care primarily depends on the severity of the CAP. Given mortality and readmission rates, it is crucial to identify appropriate individuals for hospitalization, mitigate

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hospitalization-related complications, and avoid unnecessary resource utilization. To this end, the most commonly used predictive models are the confusion-urea-respiratory rate-blood pressure (CURB)-65 score and the pneumonia severity index (PSI). CURB-65 is a simple 6-point tool applicable at the point of care that relies on confusion, urea level, respiratory rate, blood pressure, and age (>65 years) (5). Although it is effective in identifying patients at risk of death, it has reduced sensitivity in classifying patients at high risk of requiring admission to the ward or the intensive care unit (ICU), as it relies solely on severe clinical findings and age (6,7). On the other hand, PSI is a comprehensive, guideline-recommended tool that effectively distinguishes between low- and high-risk patients and demonstrates significant discriminative ability (8). Including information on patients' comorbidities, physical findings, and laboratory measures enables the PSI to comprehensively assess illness severity (9). However, the inclusion of 20 questions limits its practical application in daily settings.

Frailty is characterized by physical disability, difficulty with activities of daily living, increased vulnerability to adverse outcomes, and deterioration of cognitive function attributable to age (10,11). Individuals with increased frailty are more susceptible to negative impacts related to medical and surgical conditions (12-14). Recent studies indicate that frailty is strongly correlated with pneumonia severity and mortality risk (15,16). A study using data from 177,991 patients in the Japan Gerontological Evaluation Study showed that frailty was correlated with pneumonia incidence and hospitalization, even among functionally independent, community-dwelling individuals (17). To differentiate frail patients from non-frail patients, numerous screening tools have been developed to facilitate care planning and to determine the need for comprehensive geriatric evaluation (18-20). FRAIL (F) and the clinical frailty scale (CFS) are instruments that may be administered in a few minutes at the bedside, facilitating rapid evaluation in routine clinical practice.

The existing prediction tools for assessing the severity of CAP and determining the site of care primarily focus on chronological age and lack the capacity to assess patient frailty. Our aim was to investigate the impact of frailty on the prognosis of CAP using frailty scales in combination with CURB-65.

Methods and Materials

Study Population

We conducted a prospective observational study to examine the clinical data, laboratory results, and prognosis of patients with CAP. The study was conducted from October 2022 to October 2024 at Hacettepe University Hospital, a tertiary care center. The CURB-65 score and PSI were calculated at the time of admission. Additionally, we assessed the patients' frailty using the CFS and F scales. We recorded the site of care as outpatient, ward, or ICU (Figure 1).

Inclusion and Exlusion Criteria

Patients older than 18 years who were admitted to the emergency department and diagnosed with CAP were included in the study. We excluded individuals admitted in cardiopulmonary arrest; those who died within the first 24 hours after admission; patients diagnosed with CAP in another health facility and referred for further assessment; individuals receiving oral or parenteral antibiotic therapy as outpatients or inpatients and admitted due to treatment failure; patients diagnosed with pneumonia 48 hours or more after admission; those whose pneumonia diagnosis was not confirmed; and individuals under the age of 18.

Laboratory

On admission, we recorded the results of the complete blood count, renal and liver function tests, and acute-phase.

Assessment of Pneumonia

CAP was diagnosed in patients presenting with symptoms indicative of pneumonia, such as fever, cough, purulent sputum, fatigue, and dyspnea, and with pneumonic infiltrates detected on chest X-ray or thoracic computed tomography. We assessed the severity of pneumonia using the two most commonly used tools, CURB-65 and PSI. CURB-65 consists of three physical

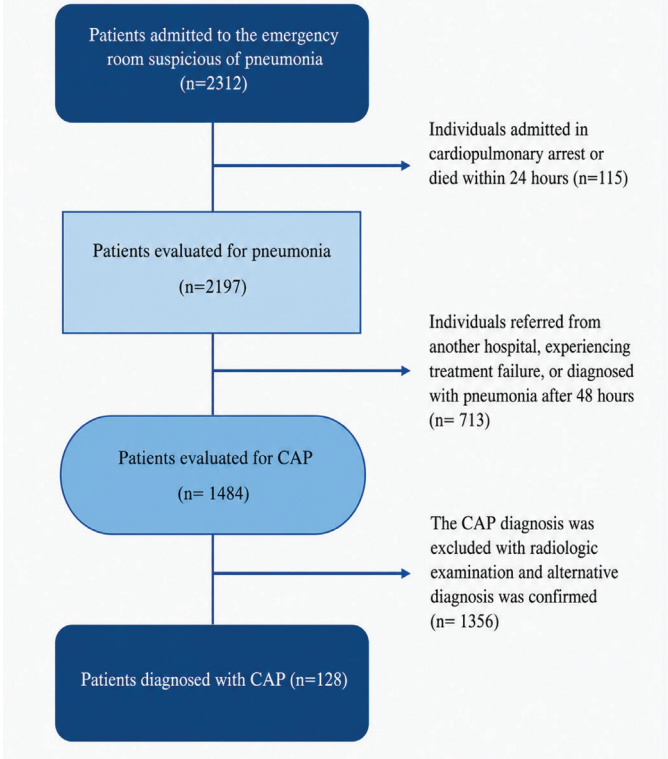

Figure 1. Patient selection flowchart.

CAP: Community-acquired pneumonia.

examination findings: confusion, respiratory rate >30/min, and systolic blood pressure <90 mm Hg; one laboratory measure: urea >20 mg/dL; and age >65 years. PSI is a more comprehensive test, including demographic information (age and gender), comorbidity data, laboratory measures, physical examination findings, and radiologic findings (Supplementary Table 1).

Frailty Assessment

Patient frailty was assessed using Turkish-validated versions of two widely used scales (21,22). The same geriatrician performed frailty assessments on all patients following confirmation of the CAP diagnosis. The F is an effortless tool that can be administered at the point of care. The decision depends on the patients' responses to yes-no questions regarding fatigue, difficulty climbing stairs, difficulty walking, presence of five or more chronic illnesses (including hypertension, diabetes, cancer, chronic lung disease, heart attack, congestive heart failure (CHF), angina, asthma, arthritis, stroke, and kidney disease), and weight loss (18,23). Each "yes" response was assigned 1 point, and a total above 2 points was classified as "frail" (Supplementary Table 2) (24).

Similarly, the CFS is easy to use at the point of care for frailty assessments. Conversely, it is based on clinical judgment, and patients are rated on a scale from 1 (very fit) to 9 (terminally ill). The higher scores indicate increased frailty. It is also dichotomized, with 1–4 points classified as non-frail and 5–9 points classified as frail (20,25) (Supplementary Table 3). Frailty status was determined based on the baseline clinical status assessed two weeks before admission.

Calculation of CURB-65 Plus Frailty Scores

First, we calculated CURB-65 and PSI scores to assess disease severity in the patient. We then divided the subjects into two groups: frail and non-frail. We considered patients frail if they scored 3 or more points on the F scale and 5 or more points on the CFS scale; we assigned +1 point to frail patients. We then calculated 7-point CURB-65-F and CURB-65-CFS scores separately. As is known, patients who receive 1 or more points on CURB, and those who receive 2 or more points on CURB-65, are considered at risk. We added one point for frail patients; therefore, a score of three on CURB-65-F and CURB-65-CFS was deemed high risk.

Follow-Up

We recorded total ward and ICU lengths of stay for hospitalized patients. Additionally, we assessed the patients' survival status for up to 6 months. We used the hospital database and the Ministry of Health's death notification system to ascertain survival status.

Ethical Approval

The study protocol complied with the Declaration of Helsinki and received approval from Hacettepe University Non-Interventional Clinical Research Ethics Committee (research number: GO 22/1168, decision number: 2023/02-38, date: 07.02.2023). Informed consent was obtained from all participants.

Statistical Analysis

Statistical analyses were performed using SPSS version 23. The variables were assessed using visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk tests) methods to determine whether they were normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables. We presented descriptive analyses using medians and ranges (minimum–maximum) for non-normally distributed or ordinal variables. We employed Pearson's test for normally distributed parameters and Spearman's test for non-normally distributed or ordinal parameters to estimate correlation coefficients and assess their significance. The univariate effects of gender, age, and other related factors were investigated using the log-rank test. The Kaplan-Meier survival estimates were calculated. The possible factors identified by univariate analyses were subsequently entered into a Cox regression analysis with backward selection to determine independent predictors of survival. Among correlated factors that had similar effects on survival, only those that were clinically significant were included. We assessed the proportional hazards assumption and model fit using Schoenfeld and Martingale residuals. The Hanley and McNeil approach was employed to compare the areas under the curves (AUCs). A p-value of less than 0.05 was considered statistically significant.

Results

Of the 128 patients included, the mean age was 60.10 ± 3.98 years; 91 (71.1%) were male. Of the individuals, 43 (33.5%) were current smokers, 41 (32.0%) were former smokers, and 44 (34.4%) were never smokers. The most common comorbidities were chronic obstructive pulmonary disease (COPD) (62, 48.4%), hypertension (58, 45.3%), coronary artery disease (CAD) (40, 31.3%), and diabetes mellitus (DM) and malignancy (each 36, 28.1%) (Tables 1 and 2).

The majority of patients had more than one symptom on admission: 122 (95.3%) had fatigue, 121 (94.6%) had cough, and 119 (93.0%) had dyspnea. The median CURB-65 score was 1 (range 0–4), the median PSI class was 4 (range 1–5), and 79 (61.7%) and 62 (48.4%) individuals were classified as low risk by CURB-65 and PSI, respectively. The median scores for both CURB-65-F and CURB-65-CFS were 2 (range 0–5). CURB-65-F classified 92 patients (71.9%) as low risk, whereas CURB-65-CFS classified 88 patients (68.8%) as low risk. A total of 115 individuals (89.8%) were hospitalized: 71 (55.5%) were in the ward and 44 (32.4%) were in the ICU (Table 3).

Table 1. Demographics and vaccination status according to groups.

Total patients: 128

	CURB-65		CURB-65-F		CURB-65-CFS		Total
	Low risk (79, 61.7%)	High risk (49, 38.3%)	Low risk (92, 71.9%)	High risk (36, 28.1%)	Low risk (88, 68.8%)	High risk (40, 31.3%)	
Age	56.8 ± 14.7	70.1 ± 9.1	57.9 ± 14.2	72.2 ± 8.4	57.5 ± 14.3	71.6 ± 8.4	60.1 ± 3.98
Gender (male)	56, 70.9%	35, 71.4%	66, 71.7%	25, 69.4%	62, 70.5%	29, 72.5%	91, 71.1%
Smoking status	Current: 25, 31.6% Former: 27, 34.2% Never: 27, 34.2%	Current: 16, 32.7% Former: 17, 34.7% Never: 16, 32.7%	Current: 31, 33.7% Former: 30, 32.6% Never: 31, 33.7%	Current: 10, 27.8% Former: 14, 38.9% Never: 12, 33.3%	Current: 28, 31.8% Former: 30, 34.1% Never: 30, 34.1%	Current: 13, 32.5% Former: 14, 35.0% Never: 13, 32.5%	Current: 41, 32.0% Former: 44, 34.4% Never: 43, 33.6%
Pneumococcal vaccine	32, 40.5%	30, 61.2%	40, 43.5%	22, 61.1%	38, 43.2%	24, 60.0%	62, 48.4%
Flu vaccine	2, 2.5%	1, 2.0%	2, 2.2%	1, 2.8%	2, 2.3%	1, 2.5%	3, 2.3%
COVID-19 vaccine	69, 87.3%	47, 95.9%	81, 88.0%	35, 97.2%	78, 88.6%	38, 95.0%	116, 90.6%

CURB: Confusion-urea-respiratory rate-blood pressure, COVID-19: Coronavirus disease-2019, F: FRAIL, CFS: Clinical frailty scale.

CURB-65, CURB-65-F, and CURB-65-CFS were correlated with the presence of certain diseases, including DM, hypertension, CAD, CHF, and COPD. A moderate correlation was observed between length of hospital stay and CURB-65-F ($p = 0.026$, $r = 0.196$) and CURB-65-CFS ($p = 0.034$, $r = 0.188$); no statistically significant correlation was observed with CURB-65. CURB-65, CURB-65-F, and CURB-65-CFS were strongly correlated with the PSI ($r = 0.695$, $p < 0.001$; $r = 0.817$, $p < 0.001$; $r = 0.814$, $p < 0.001$, respectively) (Table 4).

Cox regression analysis was used to determine the effect of CURB-65, CURB-65-F, and CURB-65-CFS on mortality using both overall and categorized scores. While the effect of CURB-65 on 30-day mortality [p: 0.005, hazard ratio (HR): 2.291, confidence interval (CI): 1.290-4.069] was comparable with CURB-65-F and CURB-65-CFS (p: 0.001, HR: 2.245, CI: 1.382-3.648; p: 0.001, HR: 2.374, CI: 1.373-3.767, respectively), CURB-65-F ($p < 0.001$, HR: 1.813, CI: 1.310-2.511) and CURB-65-CFS (p: 0.001, HR: 1.797, CI: 1.292-2.500) were superior to CURB-65 ($p = 0.014$, HR: 1.635, CI: 1.103-2.422) at the 6th month. When we categorized the patients as low- and high-risk according to each tool, the effects of CURB-65-F and CURB-65-CFS were more prominent than those of CURB-65 ($p = 0.002$, HR = 7.991, CI = 2.114-30.197; $p = 0.006$, HR = 6.539, CI = 1.734-24.664; $p = 0.022$, HR = 4.704, CI = 1.247-17.740, respectively) at 30 days and at 6 months ($p = 0.002$, HR = 3.553, CI = 1.562-8.083; $p = 0.004$, HR = 3.305, CI = 1.492-7.775; $p = 0.038$, HR = 2.391, CI = 1.048-5.458, respectively) (Tables 5 and 6).

Finally, we used ROC curves to assess the discriminatory power of CURB-65, CURB-65-F, CURB-65-CFS, and PSI to predict all-cause mortality by analyzing scores and categories independently. The tool with the greatest AUC was PSI (AUC = 0.716, 95% CI: 0.622-0.811), followed by CURB-65-CFS (AUC = 0.690, 95% CI: 0.590-0.789), CURB-65-F (AUC = 0.687, 95% CI: 0.586-0.787), and CURB-65 (AUC = 0.614, 95% CI: 0.501-0.726). On the other hand, when we categorized as low or high risk, CURB-65-F (AUC= 0.633, 95% CI: 0.521-0.745) and CURB-65-CFS (AUC= 0.630, 95%CI: 0.519-0.742) were superior to PSI and CURB-65 (AUC= 0.624, 95%CI: 0.518-0.731, and AUC= 0.582, 95%CI: 0.470-0.694, respectively) (Figure 2, Tables 7 and 8).

Discussion

Being one of the major causes of death and the leading infectious cause of death, CAP is a major public health issue (3,26). Therefore, it is crucial to rapidly diagnose and accurately manage the CAP. Following the diagnosis of CAP, clinicians face another challenge: deciding where, how, and for how long to treat it. CURB-65 is the most widely used clinical prediction tool due to its applicability at the point of care; however, it has limited sensitivity for identifying high-risk patients because it is based solely on chronological age (5). On the other hand, the PSI can differentiate between low- and high-risk patients, but the fact that it consists of 20 items makes it impractical in daily practice (8,27). Our tool, which adds frailty assessment to CURB-65, enables improved differentiation between low- and high-risk patients while preserving the advantage of rapid point-of-care examination.

Older age, chronic lung and heart diseases, DM, smoking, and excessive alcohol use were identified as risk factors for CAP (1,28). Furthermore, reports indicate a higher incidence of CAP in males (29). Our findings, which show a predominance of men and of patients with common comorbidities, are consistent with the literature and indicate that the study was grounded in real-world data. In contrast, our study group showed a markedly higher hospitalization rate (89.8%) than reported in the existing literature (30–42.7%) (3,30,31). This may be because our center is

Table 2. Comorbidities according to groups.

Total patients: 128							
	CURB-65		CURB65-F		CURB65-CFS		Total
	Low risk (79, 61.7%)	High risk (49, 38.3%)	Low risk (92, 71.9%)	High risk (36, 28.1%)	Low risk (88, 68.8%)	High risk (40, 31.3%)	
Diabetes mellitus	17, 21.5%	21, 42.9%	23, 25.0%	15, 41.7%	20, 22.7%	18, 45.0%	38, 29.7%
Hypertension	27, 34.2%	31, 63.3%	31, 33.7%	27, 75.0%	30, 34.1%	28, 70.0%	58, 45.3%
Coronary artery disease	20, 25.3%	20, 40.8%	25, 27.2%	15, 41.7%	23, 26.1%	17, 42.5%	40, 31.3%
Hyperlipidemia	3, 3.8%	5, 10.2%	4, 4.3%	4, 11.1%	4, 4.5%	4, 10.0%	8, 6.3%
Congestive heart failure	10, 12.7%	16, 32.7%	12, 13.0%	14, 38.9%	11, 12.5%	15, 37.5%	26, 20.3%
Atrial fibrillation	6, 7.6%	10, 20.4%	6, 6.5%	10, 27.8%	6, 6.8%	10, 25.0%	16, 12.5%
COPD	33, 41.8%	29, 59.2%	41, 44.6%	21, 58.3%	38, 43.2%	24, 60.0%	62, 48.4%
Asthma	9, 11.4%	5, 10.2%	11, 12.0%	3, 8.3%	10, 11.4%	4, 10.0%	14, 10.9%
Dementia	-	2, 4.1%	-	2, 5.6%	-	2, 5.0%	2, 1.6%
Cerebrovascular disease	1, 1.3%	6, 12.2%	1, 1.1%	6, 16.7%	1, 1.1%	6, 15.0%	7, 5.5%
Malign disease	19, 24.1%	17, 34.7%	20, 21.7%	16, 44.4%	20, 22.7%	16, 40.0%	36, 28.1%
Chronic renal disease	3, 3.8%	6, 12.2%	5, 5.4%	4, 11.1%	3, 3.4%	6, 15.0%	9, 7.0%
Chronic liver disease	2, 2.5%	1, 2.0%	2, 2.2%	1, 2.8%	2, 2.3%	1, 2.5%	3, 2.3%
Peripheric vascular disease	-	1, 2.0%	-	1, 2.8%	-	1, 2.5%	1, 0.8%
Connective tissue disease	1, 1.3%	3, 6.1%	2, 2.2%	2, 5.6%	2, 2.3%	2, 5.0%	4, 3.1%
Osteoporosis	1, 1.3%	2, 4.1%	1, 1.1%	2, 5.6%	1, 1.1%	2, 5.0%	3, 2.3%
Depression	1, 1.3%	3, 6.1%	3, 3.3%	1, 2.8%	3, 3.4%	1, 2.5%	2, 1.6%
Peptic ulcer	1, 1.3%	1, 2.0%	1, 1.1%	1, 2.8%	1, 1.1%	1, 2.5%	2, 1.6%
AIDS	-	-	-	-	-	-	-
Charlson CI	3.4 ± 2.7	5.8 ± 2.2	3.5 ± 2.6	6.4 ± 2.1	3.4 ± 2.6	6.3 ± 2.1	

AIDS: Acquired immunodeficiency syndrome, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, CURB: Confusion-urea-respiratory rate-blood pressure, F: FRAIL, CFS: Clinical frailty scale.

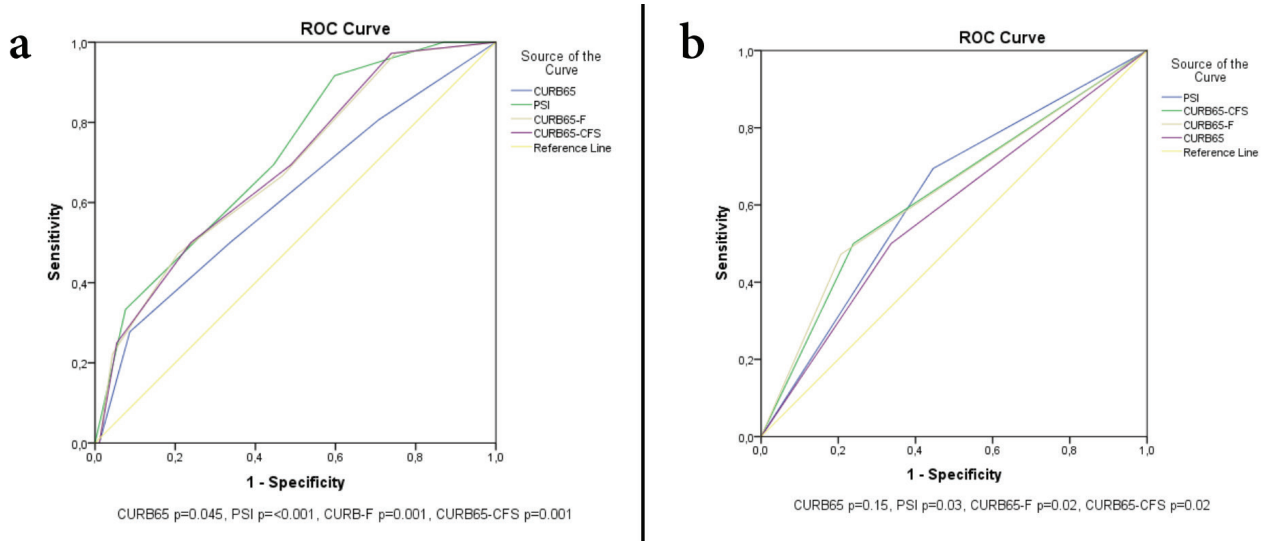

Figure 2. (**a**) ROC curves for CURB-65-F, CURB-65-CFS, and established tools CURB-65 and PSI for predicting all-cause mortality during the study period. (**b**) ROC curves for categorized (as low and high risk) CURB-65-F, CURB-65-CFS, CURB-65, and PSI for predicting all-cause mortality during the study period (represented by adding "c" at the end of the names).

CFS: Clinical frailty scale, CURB: Confusion-urea-respiratory rate-blood pressure, ICU: Intensive care unit, ROC: Receiver operating characteristic, F: FRAIL, PSI: Pneumonia severity index.

a tertiary care hospital, and patients who are too severe to be treated at local health centers are usually admitted. Moreover, high-risk patients with multiple comorbidities who were under our center's monitoring may have preferred to seek care at our hospital.

The American Thoracic Society and the Infectious Diseases Society of America recommendations endorse the PSI over CURB-65 for determining the site of care, since the PSI more reliably predicts 30-day mortality and identifies low-risk individuals (8,32). However, the fact that it comprises 20 parameters limits its usability in everyday practice. The practical one, CURB-65, is feasible in daily practice, but because it focuses solely on chronological age, it may underestimate risk in younger patients at elevated risk and overestimate risk in older patients at low risk (6). New tools have been proposed to increase the predictive power of CURB-65, but adding new parameters requires additional effort to collect data, thereby reducing the tool's usefulness (6,33). In this study, we found that adding a frailty assessment to the CURB-65 enhanced the evaluation of patient severity, outperforming the CURB-65 alone and approaching the accuracy of the PSI. It has been established that people with comorbid chronic diseases are at increased risk of frailty (11). As is well known, PSI includes several questions regarding the patient's chronic diseases. Given the association between comorbidities and frailty, we believe that adding a frailty assessment to the CURB-65 may better reflect the comorbidities of individuals assessed by the PSI.

Table 3. Clinical findings and laboratory results.

Hemoglobine	12.39 ± 0.65
WBC (10^3/µL)	13.23 ± 1.05
Neutrophyle (10^3/µL)	10.08 ± 0.87
Creatinine (mg/dL)	0.91 ± 0.11
BUN (mg/dL)	22.57 ± 3.95
ALT (U/L)	34.1 ± 8.0
AST (U/L)	40.2 ± 11.9
LDH (U/L)	275.4 ± 33.8
Sedimentation rate (mm/h)	36.9 ± 6.3
C-reactive protein (mg/L)	27.6 ± 6.0
Procalcitonin (ng/mL)	1.56 ± 0.93
Cough n, %	121, 94.5%
Sputum n, %	100, 78.1%
Dyspnea n, %	119, 93.0%
Fever n, %	49, 38.3%
Fatigue n, %	122, 95.3%
Palpitation n, %	41, 32.0%
Confusion n, %	11, 8.6%
Hypoxemia n, %	94, 73.4%
CURB-65 score	1 (0-4)
CURB-65 categorical (low risk) n, %	79 (61.7)
PSI class	4 (1-5)
CURB-65-Frail	2 (0-5)
CURB-65-CFS	2 (0-5)
CURB-65 categorical	Low risk: 92, 71.9%, (<3 points) High risk: 36, 28.1%, (≥3 points)
CURB-65-CFS categorical	Low risk: 88, 68.8%, (<3 points) High risk: 40, 31.3%, (≥3 points)
Site of care	ICU: 44, 33.4% Ward: 71, 55.5% Outpatient: 13, 10.2%

ALT: Alanine transaminase, AST: Aspartate Transferase, BUN: Blood urea nitrogen, CFS: Clinical frailty scale, CURB: Confusion-urea-respiratory rate-blood pressure, ICU: Intensive care unit, LDH: Lactate dehydrogenase, PSI: Pneumonia severity index, WBC: White blood cell, F: FRAIL.

CAP is associated with both short- and long-term mortality (3,34). Therefore, determining the site of care is crucial, because the aim is to manage all low-risk patients outside the hospital without patients at high risk of death who require more intensive care. CURB-65 and PSI were shown to predict 30-day mortality (5,9,27). Higher scores on both assessment tools are associated with increased mortality risk, and increasing scores prompt clinicians to admit patients to a ward or ICU. Additionally, a higher PSI class was shown to be associated with long-term mortality. In their study of mortality following pneumonia, Johnstone et al. reported a mortality rate of 12% at 30 days, 28% at 1 year and 53% at the end of the study, with a mean follow-up period of 3.8 years. In the analysis of the association of PSI with post-discharge deaths, it was observed that 15% of the patients in PSI classes 1-2 died after discharge, whereas 82% of the patients in PSI class 5 died (35). We followed patients for mortality for up to 6 months and found that CURB-65-F and CURB-65-CFS were comparable to CURB-65 during the first two months but superior to CURB-65 in the subsequent months. Furthermore, we observed that when we dichotomized patients into low- and high-risk groups across all tools, the superiority of CURB-65-F and CURB-65-CFS became more pronounced. Considering the relationship between frailty and mortality (36), we suggest that adding a frailty assessment to CURB-65 may better predict long-term mortality in patients with CAP.

Various tools, including CURB-65, expanded CURB-65, PSI, SMART-COP, and A-DROP, have been proposed for assessing CAP severity using clinical and laboratory data, specifically to predict 30-day mortality (6,9,37-39). PSI has been also suggested as a predictor of 6-month mortality (40). Additionally, certain frailty scales were evaluated to predict mortality risk associated with CAP. (15,41). Jabeen et al. (41) reported that the Frailty Index was inferior to PSI but superior to CURB-65 for predicting 30-day mortality in CAP. Similarly, Zhao et al. (15) study revealed that the F scale was strongly correlated with CURB-65 and with an increased risk of death in older adults. Consistent with current knowledge, our results indicated that assessment of patient

Table 4. Correlation of severity scores with other comorbidities, length of stay and pneumonia severity index.

	CURB-65		CURB-65-F		CURB-65-CFS	
Variables	**p**	**r**	**p**	**r**	**p**	**r**
DM	0.003	0.264	0.006	0.242	0.002	0.266
Hypertension	<0.001	0.331	<0.001	0.322	<0.001	0.307
CAD	0.002	0.276	0.006	0.243	0.004	0.252
Hyperlipidemia	0.015	0.214	0.017	0.210	0.016	0.212
CHF	<0.001	0.388	<0.001	0.376	<0.001	0.385
AF	0.004	0.253	0.001	0.302	0.001	0.308
COPD	**0.059**	**0.167**	**0.029**	**0.194**	**0.035**	**0.186**
Asthma	0.484	-0.062	0.243	-0.104	0.277	-0.097
Dementia	**0.089**	**0.151**	**0.054**	**0.171**	**0.066**	**0.163**
Cerebrovascular disease	0.014	0.217	0.006	0.242	0010	0.227
Malign disease	**0.164**	**0.124**	**<0.001**	**0.311**	**0.004**	**0.255**
Chronic renal disease	0.023	0.200	0.020	0.205	0.008	0.234
Chronic liver disease	0.800	0.023	0.295	0.093	0.377	0.079
Peripheric vascular disease	0.392	0.076	0.268	0.099	0.307	0.091
Connective tissue disease	0.124	0.137	0.085	0.153	0.118	0.139
Osteoporosis	0.205	0.113	0.220	0.109	0.254	0.102
Depression	0.330	0.087	0.543	0.054	0.650	0.040
Peptic ulcer	0.881	0.013	0.814	-0.021	0.922	0.009
Hospitalization duration	0.320	0.089	0.026	0.196	0.034	0.188
PSI	**<0.001**	**0.728**	**<0.001**	**0.817**	**<0.001**	**0.814**
PSI class	**<0.001**	**0.695**	**<0.001**	**0.779**	**<0.001**	**0.785**

PSI: Pneumonia severity index. CFS: Clinical frailty scale, CURB: Confusion-urea-respiratory rate-blood pressure, DM: Diabetes mellitus, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, AF: Atrial fibrillation.

Table 5. Cox regression analysis shows the effects of CURB-65, CURB-65-F, and CURB-65-CFS scores on mortality.

Survival	Number of Events	CURB-65			CURB-65-F			CURB-65-CFS		p
		HR	CI	p	HR	CI	p	HR	CI	
1th month	11	2.291	1.290-4.069	0.005	2.245	1.382-3.648	0.001	2.374	1.373-3.767	0.001
2nd month	14	1.867	1.129-3.088	0.015	1.912	1.256-2.911	0.003	1.884	1.227-2.893	0.004
3rd month	18	1.738	1.115-2.710	0.015	1.884	1.300-2.731	0.001	1.842	1.264-2.684	0.001
4th month	19	1.763	1.144-2.716	0.010	1.917	1.336-2.751	<0.001	1.869	1.295-2.698	0.001
5th month	21	1.729	1.146-2.608	0.009	1.917	1.361-2.700	<0.001	1.858	1.312-2.631	<0.001
6th month	23	1.635	1.103-2.422	0.014	1.813	1.310-2.511	<0.001	1.797	1.292-2.500	0.001

One of the following parameters was included in the multiple regression analysis model: Age, gender, CURB-65, CURB-F, and CURB-CFS.
PSI: Pneumonia severity index. CFS: Clinical frailty scale, CURB: Confusion-urea-respiratory rate-blood pressure, DM: Diabetes mellitus, CAD: Coronary artery disease, CI: Confidence interval, HR: Hazard ratio, F: FRAIL.

frailty is essential for determining the site of care and predicting mortality, and that combining frailty scales with CURB-65 is more informative than CURB-65 alone. Using the FRAIL scale or CFS, physicians who already perform the CURB-65 assessment in emergency departments or outpatient clinics can evaluate patients' frailty levels with a few questions and, if the patient is frail, add one point to the CURB-65 score more accurately predict mortality.

Study Limitations

There are some limitations to our research. As mentioned above, our center functions as a tertiary care facility and typically accepts patients with more severe conditions, which is reflected in the hospitalization rates reported in the results. This limits the representativeness of the entire population, even though the study is based on real-life data. Additionally,

Table 6. Cox regression analysis shows the effects of categorized CURB-65, CURB-65-F, and CURB-65-CFS scores on mortality.

Survival	Number of Events	CURB-65			CURB-65-F			CURB-65-CFS		p
		HR	CI	p	HR	CI	p	HR	CI	
1th month	11	4.704	1.247-17.740	0.022	7.991	2.114-30.197	0.002	6.539	1.734-24.664	0.006
2nd month	14	2.391	0.829-6.996	0.107	4.128	1.428-11.930	0.009	3.336	1.157-9.624	0.026
3rd month	18	2.239	0.883-5.678	0.089	3.853	1.516-9.796	0.005	3.157	1.245-8.005	0.015
4th month	19	2.473	0.994-6.152	0.052	4.283	1.717-10.684	0.002	3.492	1.403-8.687	0.007
5th month	21	2.425	1.021-5.760	0.045	4.257	1.787-10.138	0.001	3.438	1.447-8.167	0.005
6th month	23	2.391	1.048-5.458	0.038	3.553	1.562-8.083	0.002	3.405	1.492-7.775	0.004

One of the following parameters was included in the multiple regression analysis model: Age, gender, CURB:-65, CURB:-F, and CURB:-CFS.
PSI: Pneumonia severity index. CFS: Clinical frailty scale, CURB: Confusion-urea-respiratory rate-blood pressure, DM: Diabetes mellitus, CAD: Coronary artery disease, CI: Confidence interval, HR: Hazard ratio, F: FRAIL.

Table 7. ROC analysis results.

	Area under curve	%95 confidence interval	p
Continuous			
CURB-65	0.614	0.501-0.726	0.045
PSI	0.716	0.622-0.811	**<0.001**
CURB-65-F	0.687	0.586-0.787	**0.001**
CURB-65-CFS	0.690	0.590-0.789	**0.001**
Categorical			
CURB-65	0.582	0.470-0.693	0.15
PSI	0.624	0.518-0.731	**0.03**
CURB-65-F	0.633	0.521-0.745	**0.02**
CURB-65-CFS	0.630	0.519-0.742	**0.02**

PSI: Pneumonia severity index. CFS: Clinical frailty scale, CURB: Confusion-urea-respiratory rate-blood pressure, ROC: Receiver operating characteristic, F: FRAIL.

Table 8. Comparison of AUCs.

	PSI	CURB-65-F	CURB-65-CFS
Continuous			
CURB-65	0.17	0.34	0.32
PSI	-	0.68	0.71
CURB-65-F		-	0.97
Categorical			
CURB-65	0.59	0.53	0.55
PSI	-	0.91	0.94
CURB-65-F		-	0.97

AUC: Area under curve, PSI: Pneumonia severity index, CURB: Confusion-urea-respiratory rate-blood pressure, F: FRAIL, CFS: Clinical frailty scale.

since the vast majority of patients were hospitalized, we were unable to compare inpatients and outpatients with respect to severity using established assessment tools. We acknowledge that the frailty scales employed were validated in older adults, while our study includes younger adults, which may limit the generalizability of the findings. Furthermore, the predominance of males in the population limits generalizability. Our analysis revealed a considerable age disparity between low-risk and high-risk groups. This pertains to age as a factor in frailty. Consequently, the proposed new scoring systems have considered chronological age and integrated frailty. On the other hand, prospectively collected data, including both clinical and laboratory information, serve as one of the major strengths of the current study. Examining frailty using two different scales facilitated a comparative analysis and enabled us to determine whether one of them is superior.

Conclusion

In conclusion, we are aware that clinical findings, admission measurements, laboratory results, comorbidities, and frailty are associated with morbidity and mortality in CAP. Nonetheless, obtaining all this data for every individual is neither feasible nor practical. Consequently, many tools exhibit specific limitations, including inapplicability to older or younger individuals, inability to identify high-risk patients, dependence on laboratory settings, or lack of usability in everyday practice. We believe that using CURB-65 together with frailty measured by F or CFS will allow us to determine the site of care and to predict mortality more accurately while maintaining bedside applicability.

Ethics

Ethics Committee Approval: The study protocol complied with the Declaration of Helsinki and received approval from Hacettepe University Non-Interventional Clinical Research Ethics Committee (research number: GO 22/1168, decision number: 2023/02-38, date: 07.02.2023).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.K., H.Ç., S.C., Concept: O.K., S.C., M.G.H., Design: O.K., A.B., M.E. Data Collection or Processing: H.Ç., D.A., A.İ., Analysis or Interpretation: O.K., S.C., A.İ., A.B.,

M.G.H., C.B., M.E. Literature Search: O.K., H.Ç., D.A., Writing: O.K., A.İ., A.B., E.Ö., M.G.H., C.B., M.E.

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ORIGINAL RESEARCH

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Might the Haemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score Be Associated with Prefrailty and Frailty in Older Adults without Cancer: A Cross-Sectional Study?

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Abstract

Objective: Frailty is related to both malnutrition and systemic inflammation. The aim of this study was to explore the relationship between the haemoglobin, albumin, lymphocyte, and platelet (HALP) score and different stages of frailty in community-dwelling older adults.

Materials and Methods: A total of 439 patients admitted to our geriatric outpatient clinic from January 2023 to June 2024 were included in the analysis. All participants underwent a comprehensive geriatric assessment, and frailty status was determined according to the Fried frailty phenotype. Patients were then categorized into three groups—frail, prefrail, and robust. The HALP score was calculated for each participant and compared across these three groups.

Results: The mean age of the study population was 76.12 ± 6.74 years; 71.3% were female. The frail group had a higher mean age, a higher proportion of females, and higher frequencies of dementia, recurrent falls, geriatric depression, polypharmacy, malnutrition, and probable sarcopenia compared with the prefrail and robust groups ($p < 0.05$). The median HALP score was significantly lower in the frail and prefrail groups than in the robust group (frail: 34.9 vs. 48.3, $p < 0.001$; prefrail: 38.6 vs. 48.3, $p = 0.005$). In the logistic regression analysis, after adjustment for potential confounding factors, the association remained statistically significant in both the frail and prefrail groups, compared with the robust group ($p < 0.05$).

Conclusion: The HALP score is associated with both prefrailty and frailty and may serve as a risk-stratification marker in older adults.

Keywords: Aging, frailty, geriatric syndrome, inflammation, nutrition

Introduction

Frailty is an important geriatric syndrome. Its frequency increases with age, increasing older individuals' vulnerability to stressors due to age-associated declines in function and reserve across multiple physiological systems (1,2). Frailty is associated with adverse outcomes, including disability, recurrent falls, prolonged hospital stays, and mortality in older adults (2). It has also been reported that frail individuals have lower incomes and more comorbidities than non-frail older adults (3). In this respect, screening for frailty is important in geriatric practice, and several assessment tools are available for this purpose. Of these, the most commonly used is the Fried frailty scale. According to the Fried frailty phenotype, frailty is a clinical syndrome identified when three or more of the following criteria are present: unintentional weight loss, diminished grip strength, exhaustion, decreased walking speed, and reduced physical activity (4). Patients meeting one or two of these criteria are classified as prefrail. In the literature, the frail and Fried scales are among the most commonly used tools for frailty screening, and several scoring systems have been developed to predict frailty in accordance with these scales (5). The pathophysiology of frailty is complex, involving multiple organ systems. Changes in the immune system and inflammation are frequently emphasised in its pathophysiology (1). In addition to inflammation, the pathophysiology of frailty involves mitochondrial dysfunction, dysregulated nutrient sensing, cellular senescence, oxidative

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stress, and neuroendocrine imbalance (6). Chronic inflammation may lead to frailty by increasing growth factor inhibition and catabolism in response to non-infectious triggers (6). Malnourishment is closely associated with frailty (7). From a mechanistic perspective, frailty is a multidimensional geriatric syndrome driven by chronic inflammation, immune dysfunction, and malnutrition, all of which contribute to reduced physiological reserve and increased vulnerability to stressors. Haemoglobin reflects tissue oxygenation and chronic inflammatory burden; anaemia has been consistently associated with decreased physical performance and frailty in older adults (8). Serum albumin is a marker of protein-energy status and systemic inflammation, and low albumin levels indicate catabolic states that promote muscle loss and functional decline (9). Lymphocyte count reflects immune competence, and age-related immunosenescence, characterized by lymphopenia, has been linked to increased severity of frailty (10). Platelets are active participants in inflammatory and oxidative pathways; altered platelet activation has been implicated in endothelial dysfunction and adverse outcomes commonly observed in frail individuals (11). Thus, the haemoglobin, albumin, lymphocyte, and platelet (HALP) score integrates haematologic, nutritional, and immunological components, capturing key biological pathways underlying frailty.

The HALP score serves as a straightforward and clinically relevant biomarker integrating indicators of nutritional status and inflammation (12). It has emerged as a novel biomarker for predicting adverse clinical outcomes across a range of diseases. It has also been suggested to be associated with certain malignancies and with cardiovascular mortality (12). However, there is currently no evidence in the literature examining the relationship between the HALP score and frailty.

Inflammatory markers may be helpful in predicting frailty (13). No study in the literature has shown that the HALP score, an inflammatory marker, predicts frailty. This retrospective study aimed to determine whether an association exists between the HALP score and frailty status. We hypothesized that lower HALP scores would be associated with more advanced frailty stages in community-dwelling older adults.

Materials and Methods

Study Design

This retrospective, cross-sectional study included 439 older adults who were evaluated at the geriatric outpatient clinic of Balıkesir University Hospital between January 2023 and June 2024. A Comprehensive Geriatric Assessment (CGA), including a frailty assessment, was performed for all participants. The patient selection process and reasons for exclusion are summarized in the study flow diagram (Figure 1).

Inclusion Criteria

Patients aged >65 years who had previously undergone a CGA as part of routine clinical care and who did not meet the exclusion criteria were retrospectively identified and included in this cross-sectional study.

Exclusion Criteria

The exclusion criteria included: severe anemia (haemoglobin level <7 g/dL); critical valvular heart disease; acute or chronic kidney failure (stage 4 or 5); advanced cardiac or hepatic failure, or both; malignancy; severe coronary or peripheral artery stenosis; acute exacerbations of rheumatologic or connective tissue diseases; clinically active infection; a history of cerebrovascular disease, myocardial infarction, or lower extremity fracture within the past month; evidence of acute dehydration; electrolyte imbalances such as hyponatremia, hypernatremia, or hypercalcemia; acute hemorrhage; immobility due to severe osteoarthritis or neuromuscular disease; and acute changes in mental status (7). In addition, patients with moderate to severe cognitive impairment (Clinical Dementia Rating Score ≥2), advanced Parkinson's disease (Hoehn and Yahr stage ≥2), and those with essential tremor associated with impaired activities of daily living were excluded from the study, as these conditions could compromise compliance with, and the reliability of, handgrip strength and gait speed assessments. Participants receiving iron supplementation (IV or oral), steroid use, or both were also excluded.

Patient Characteristic

Age, sex, education level, and comorbidities were evaluated. Geriatric syndromes such as polypharmacy (>5 medications), dementia, probable sarcopenia, geriatric depression, urinary

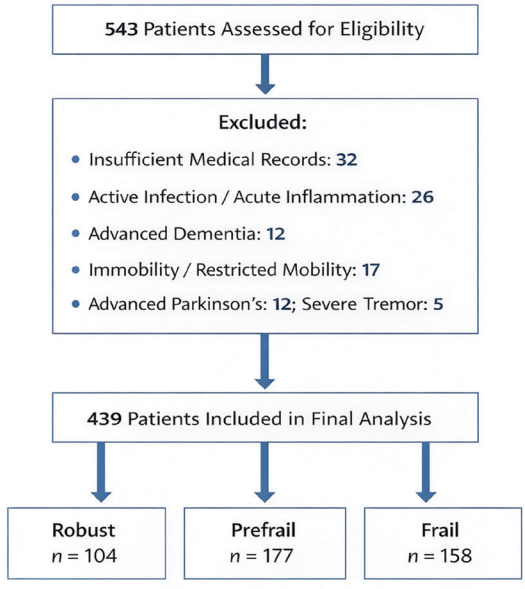

Figure 1. Flowchart of the study population and frailty categorization.

incontinence, recurrent falls within the past year, essential tremor, and malnutrition were also assessed using patients' medical records. Diagnoses of major neurocognitive disorder or dementia were established according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria (14). Probable sarcopenia was determined according to the European Working Group on Sarcopenia in Older People 2 criteria (15). Nutritional status was assessed via the mini nutritional assessment–short form (16), categorizing participants as malnourished or at risk (0–11 points) or well-nourished (12–14 points). A CGA was performed in all participants and included the Yesavage Geriatric Depression Scale, the Tinetti Performance-Oriented Mobility Assessment, the Timed Up-and-Go Test, and evaluations of basic and instrumental activities of daily living (BADL and IADL) (17–21).

Laboratory Findings

Patients' blood samples were routinely collected in the fasting state at 08:00. The haemoglobin level, platelet count, lymphocyte count, glucose level, albumin level, estimated glomerular filtration rate (eGFR), and the levels of vitamin D, folate, ferritin, thyroid-stimulating hormone, and vitamin B12 were obtained from the patients' laboratory records. All these biochemical tests were performed on Diagnostic Modular Systems auto-analysers (Roche E170 and P-800). Serum 25-hydroxyvitamin D was measured by radioimmunoassay (7). Laboratory measurements and CGA were performed on the same day.

HALP Score

The HALP score was calculated using the following formula: [haemoglobin (g/L) × albumin (g/L) × lymphocytes (/L))/platelets (/L)] (22).

Frailty Phenotype

Frailty was evaluated using Fried's physical frailty scale (4). This scale comprises five components: weakness, slowness, low physical activity, exhaustion, and unintentional weight loss (3). Based on their frailty scores, patients were categorized into three groups: robust (0 points), prefrail (1–2 points), and frail (3–5 points).

Ethical Issues

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Balıkesir University (approval number: 2024/10/01, decision number: 2024/208, dated: 03.12.2024).

Statistical Analysis

Categorical variables were presented as percentages (%) and continuous variables as mean ± standard deviation. The patients were divided into three groups according to their frailty status: robust, prefrail, and frail. For each of the three categories, continuous and categorical variables were compared between the two dichotomous groups. In categorical variables', the chi-square test was performed for comparison between these groups. Continuous variables were first evaluated for normality using the Kolmogorov–Smirnov test, and homoscedasticity was assessed. Because not all continuous variables were normally distributed, the Mann–Whitney U test, a non-parametric test, was used to compare two groups; these variables are presented accordingly. The Kruskal-Walli's test was performed to compare the three groups. Binary logistic regression was used to assess the association of the prefrail and frail groups with the robust group. Model 0 was unadjusted for contributing factors. Model 1 was adjusted for demographic featrues including age and gender. Model 2 was adjusted for the covariates included in Model 1, plus comorbidities and geriatric syndromes. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics (version 22.0; Armonk, NY: IBM Corp.).

Results

A total of 439 older adults (mean age 76.12 ± 6.74 years; 71.3% female) were included. The frail group was older and had a higher proportion of females compared with the prefrail and robust groups, whereas no demographic differences were observed between the prefrail and robust groups ($p > 0.05$). Parkinson's disease, geriatric depression, dementia, recurrent falls, probable sarcopenia, polypharmacy, malnutrition, and essential tremor were more common among frail individuals ($p < 0.05$). The prefrail group also showed higher frequencies of essential tremor, depression, malnutrition, and probable sarcopenia than the robust group ($p < 0.05$). Haemoglobin, albumin, and eGFR levels were significantly lower in the frail group ($p < 0.05$). Functional and mobility scores were lower in both the frail and prefrail groups than in the robust group ($p < 0.05$; Table 1).

The mean HALP scores in the frail group were significantly lower than those in the robust and prefrail groups ($p < 0.001$ and $p = 0.001$, respectively). Additionally, the HALP score in the prefrail group was lower than that in the robust group ($p = 0.005$; Table 2).

In logistic regression analysis, after adjusting the HALP score for demographic characteristics, comorbidities, geriatric syndromes, and laboratory findings, a statistically significant difference in the HALP score was observed between frail patients and the robust group ($\beta = -0.040$, OR = 0.96, 95% CI = 0.93–0.95; $p = 0.003$; Model 2). Similarly, after adjusting for the same confounding factors, the prefrail group showed a significant association compared with the robust group ($\beta = -0.018$, OR = 0.98, 95% CI = 0.96–0.99; $p = 0.030$ in Model 2) (Table 3). Decreased HALP scores were associated with prefrail and frail older patients compared with robust patients. No evidence of multicollinearity was observed in the regression models for the frailty scale, with variance inflation factor values ranging from 1.04 to 1.12.

Table 1. Comparisons for demographic features, comorbidities, geriatric syndromes, laboratory findings and comprehensive geriatric assessment parameters in terms of frailty status.

	Robust n = 104	Prefrail n = 177	Frail n = 158	*Pall groups	Probust→frail	Probust→prefrail	Prefrail→frail
Demographic features							
Age (mean ± SD)	73.2 ± 5.2	75.1 ± 6.6	78.4 ± 6.7	**<0.001**	**<0.001**	0.074	**0.001**
Gender (female; %)	64.2	67.2	78.0	**0.031**	**0.028**	0.652	**0.024**
Education year (mean ± SD)	6.80 ± 3.82	5.50 ± 3.90	4.26 ± 3.23	**<0.001**	**<0.001**	0.089	0.208
Comorbities and geriatric syndromes (%)							
Hypertension	79.1	70.6	71.2	0.386	0.212	0.183	0.907
Cardiovascular disease	26.9	19.2	23.2	0.332	0.547	0.192	0.363
Chronic lung disease	12.4	18.6	14.9	0.207	0.416	0.258	0.519
Diabetes mellitus	31.3	44.6	41.2	0.170	0.156	0.060	0.443
Parkinson disease	1.5	2.8	16.4	**<0.001**	**<0.001**	0.549	<0.001
Dementia	9.0	16.9	44.9	**<0.001**	**<0.001**	0.116	<0.001
Recurrent falls (in a year)	28.4	36.2	59.9	**<0.001**	**<0.001**	0.251	<0.001
Essential tremor	14.9	30.5	33.3	**0.012**	**0.004**	**0.014**	0.569
Urinary incontinence	46.3	55.9	62.1	0.148	0.060	0.177	0.275
Geriatric depression	26.9	41.2	67.8	**<0.001**	**<0.001**	**0.038**	**<0.001**
Polypharmacy	58.2	64.4	74.6	**0.024**	**0.013**	0.372	**0.038**
Malnutrition	6.0	23.2	61.0	**<0.001**	**<0.001**	**0.002**	**<0.001**
Probable sarcopenia	3.0	34.5	79.5	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Laboratory findings (mean ± SD)							
Hemoglobin (g/L)	129.1 ± 15.24	126.3 ± 14.92	121.5 ± 18.17	**<0.001**	**0.001**	**0.020**	**0.034**
Lymphocyte count (109/L)	2.06 ± 0.59	1.88 ± 0.69	1.75 ± 0.91	**<0.001**	**<0.001**	**0.032**	**0.009**
Platelet count (109/L)	241.68 ± 63.95	259.84 ± 110.65	260.52 ± 90.01	0.484	0.271	0.572	0.412
Glucose (mg/dL)	111.22 ± 31.28	124.27 ± 52.96	121.54 ± 45.87	0.154	0.132	0.567	0.983
eGFR (mL/min/1.73 m^2)	68.87 ± 14.04	70.92 ± 17.67	63.14 ± 19.48	**<0.001**	**0.047**	0.463	**0.004**
Albumin (g/L)	42.5 ± 2.43	41.4 ± 3.12	40.9 ± 2.45	0.789	**<0.001**	0.225	**<0.001**
TSH (mIU/L)	1.67 ± 1.07	1.71 ± 126	2.36 ± 6.09	0.263	0.895	0.717	0.940
Vitamin B12 (ng/L)	329.91 ± 248.77	354.74 ± 276.50	430.07 ± 352.03	0.119	0.118	0.605	0.084
Folate (mcg/L)	9.50 ± 3.98	8.98 ± 4.55	8.94 ± 4.98	0.722	0.098	0.544	0.852
25-hydroxy vitamin D (mcg/L)	24.28 ± 16.78	21.25 ± 13.09	21.37 ± 14.87	0.308	0.116	0.364	0.888

*Pall groups: comparison for between frail, prefrail and robust group.
eGFR: Estimated glomerular filtration rate, GDS: Geriatric depression scale, MNA-SF: Mini nutritional assessment-short form, POMA: Performance-oriented mobility assessment, SD: Standard deviation, TSH: Thyroid stimulating hormone, TUG: Timed up and go, HALP: Haemoglobin, albumin, lymphocyte and platelet.

Table 2. Comparison for HALP score within robust, prefrail and frail groups.

		p < 0.001		
		p = 0.005	p = 0.001	
		Robust	**Prefrail**	**Frail**
HALP score	Mean	50.79	42.06	35.07
	Standard deviation	21.90	19.17	14.58
	Median	48.30	38.63	34.92
	Interquartile range	27.10	21.50	21.29

HALP: Haemoglobin, albumin, lymphocyte and platelet.

Table 3. Examining the relationship between HALP score in frail and prefrail groups compared to robust group in logistic regression analysis.

		Frail vs. Robust				Prefrail vs. Robust			
		β	OR	95 % CI	p	β	OR	95 % CI	p
HALP score	Model 0	-0.031	0.96	0.95–0.98	**<0.001**	-0.020	0.98	0.96–0.99	**0.007**
	Model 1	-0.028	0.97	0.95–0.98	**<0.001**	-0.019	0.98	0.96–0.99	**0.011**
	Model 2	-0.040	0.96	0.93–0.98	**0.003**	-0.018	0.98	0.96–0.99	**0.030**

Model 0- Unadjusted,
Model 1- Adjusted for age and gender,
Model 2- Model 1 plus the presence of Parkinson's disease, dementia, recurrent falls, essential tremor, geriatric depression, polypharmacy, probable sarcopenia.
HALP: Haemoglobin, albumin, lymphocyte and platelet, CI: Confidence interval, OR: Odds ratio.

Discussion

The HALP score was significantly lower in both frail and prefrail patients than in robust older adults in this study. Importantly, this reduction persisted even at the prefrail stage after adjustment for demographic variables, comorbidities, geriatric syndromes, and laboratory findings.

The prevalence of anaemia, defined by reduced red blood cell count or haemoglobin concentration, increases with advancing age (23). Anaemia in older adults can be categorised into the following groups: nutritional anaemia, anaemia due to bleeding, anaemia of chronic disease, anaemia due to haematological malignancy, hereditary anaemia, and unexplained anaemia. Age-related inflammation is associated with anaemia in the elderly; ageing processes such as genomic instability, mitochondrial reactive oxygen species, proinflammatory cytokines, adverse environmental factors, and chronic diseases contribute to this inflammation (24). Additionally, malnutrition, eating disorders, and loss of appetite can lead to anaemia in older adults. Anaemia in this population is associated with increased hospitalisation, falls, dementia, and functional dependence; decreased quality of life; and development of frailty (25). Furthermore, the literature has highlighted a potentially strong association between haemoglobin concentration and frailty (25).

Albumin levels are influenced by patients' nutritional status and metabolic demands (26). Low albumin levels are seen in patients with poor nutritional status and inflammation (27); hence, albumin is considered a negative acute-phase reactant. Increased proinflammatory cytokines, particularly in the context of low albumin levels, are known to significantly contribute to the development of cancer cachexia (26). As a result, it is unsurprising that muscle strength or mass may also be affected in these patients. Inadequate nutritional intake raises the risk of oxidative stress, chronic diseases, impaired immune response, osteoporosis, fracture, peripheral arterial disease, and frailty in older adults (28). Furthermore, malnutrition shares common pathophysiological mechanisms with frailty. The literature also highlights the importance of nutritional support in slowing or preventing frailty (28).

Lymphocytes and platelets are essential mediators of immune function. Decreased lymphocyte levels and increased platelet levels indicate impaired immunity and increased risk of infection (29). Lymphocytes play a key role in the initiation and progression of atherosclerosis (12). For example, lymphopaenia has been associated with inflammation, malnutrition, peripheral congestion, and sympathetic activation in individuals with heart failure (30), while lymphocytes are crucial for immunosurveillance, tumour detection, and destruction in patients with cancer (26). Additionally, a decreased lymphocyte count may be a determinant of unfavourable outcomes in systemic inflammatory diseases (31). The Total lymphocyte count declines with age due to immunosenescence, increasing susceptibility to infections in older adults (32). Thus, changes in lymphocyte counts may be particularly significant in frail individuals. A recent review indicated that low lymphocyte counts may be associated with frailty and its severity (32).

Platelets play an essential role in the progression of acute and chronic diseases, particularly cardiovascular disease, and platelet count generally decreases with age (33). However, the effect of age on platelet function or molecular changes remains unclear (33). A small study examining the relationship between frailty and platelets found greater platelet aggregation and activation in frail individuals (34). Additionally, platelet oxidative stress is thought to increase the risk of cardiovascular disease in frail individuals (35).

The HALP score is a simple, inexpensive, and reliable marker reflecting the combination of inflammation and nutritional status (36). It is a relatively new marker used to assess clinical outcomes and disease progression across a range of conditions. The importance of the HALP score in predicting prognosis was first highlighted in patients with gastric carcinoma (22). Since then, the HALP score has gained attention as a marker of mortality in numerous malignancies and in stroke patients (12). A higher HALP score has been associated with lower mortality in patients with solid tumours or acute ischaemic stroke (30), whereas a low HALP score has been associated with a poorer immunonutritional status (29). In summary, the association of the HALP score with inflammatory conditions is well established. Thus, the lower HALP scores observed among frail individuals in our study suggest that malnutrition and inflammation play a significant role in the aetiopathogenesis of frailty (6,9).

Currently, few studies have evaluated the effectiveness of the HALP score in predicting geriatric syndromes among community-dwelling older adults. In a study of a specific patient population, the HALP score was identified as a risk factor for post-stroke cognitive impairment (31). Another study found that a low HALP score was associated with sarcopenia in patients with intrahepatic cholangiocarcinoma (37). Our findings suggest that the HALP score is associated with prefrailty and frailty according to the Fried criteria, particularly among individuals without malignancy, constituting the first such evidence in the literature.

The pathophysiological mechanisms of frailty remain unclear. However, aging or a low-grade inflammatory status is an important condition in the development of frailty (10). In mouse models, some changes at the genetic, epigenetic, cellular, and systemic levels may play an important role in the development of frailty (38). At the genetic level, deficiencies in the genes Nrf2, which has an important role in the inflammatory pathway, and interleukin (IL)-10, known as an anti-inflammatory cytokine, accelerated frailty in mouse models (38). In addition, chronic inflammation plays a pivotal role in the development of frailty (6). In particular, the production of proinflammatory cytokines, with IL-6 at the forefront, and of chemokines that upregulate IL-6 plays an important role in frailty (38). Oxidative stress, mitochondrial dysfunction, neuroendocrine dysregulation, and inflammation also contribute to the anorexia of aging, indicating the relationship between frailty and malnutrition (38,39). Therefore, the early predictive power of the HALP score may be important because of these mechanisms. An important finding of this study is that the HALP score was already significantly lower in the prefrail group than in robust older adults, even after adjustment for confounding factors. This suggests that deterioration in immunonutritional status may begin at the prefrailty stage, before overt frailty becomes clinically apparent. Given that prefrailty represents a potentially reversible state, the observed early decline in HALP may reflect subclinical inflammation, early malnutrition, or immune dysregulation, all of which may precede functional decline. Therefore, HALP may capture biological vulnerability at a stage when preventive interventions could still be effective.

Inflammaging, defined as chronic, low-grade inflammation associated with aging, increases the risk of mortality and morbidity (40). C-reactive protein and IL-6 are at the forefront of inflammation in the elderly (40). It is known that inflammation is also associated with malnutrition in older adults (41). Nutritional assessment can predict frailty (42). As a result, frailty and malnutrition share common pathophysiological mechanisms and are closely related. Because the HALP score provides information relevant to nutritional assessment, low HALP scores in frail older individuals support an association with both malnutrition and inflammation.

Study Limitations

This study has several important methodological limitations that should be acknowledged when interpreting the findings. First, its retrospective, cross-sectional design precludes causal inference regarding the association between the HALP score and frailty status. Second, although we adjusted for multiple demographic, clinical, and geriatric confounders in multivariable models, residual confounding cannot be excluded. In particular, factors such as hydration status, the acute-phase response, medication use, and subclinical inflammation may influence hemoglobin and albumin levels, and thereby affect the HALP score independently of frailty. Third, our strict exclusion criteria, including patients with advanced chronic kidney disease, malignancy, severe anemia, acute infection, and major cardiovascular or neurological conditions, may have resulted in selection bias and may have limited the generalizability of our findings to the broader older adult population. Consequently, the observed associations may not fully represent medically complex or hospitalized older adults. Fourth, although frailty was assessed using the Fried phenotype and a CGA was performed, formal neurocognitive testing, such as the Mini-Mental State Examination was not available, which limits the interactions among cognitive impairment, HALP score, and frailty. Finally, as laboratory measurements were obtained at a single time point, intra-individual biological variability and transient changes in

hematologic or nutritional parameters could not be accounted for. Therefore, HALP should be interpreted as a risk stratification marker rather than a definitive diagnostic or causal biomarker of frailty.

Conclusion

The HALP score appears to be a simple and inexpensive biomarker associated with frailty and may be useful for risk stratification in clinical settings; however, its predictive value should be confirmed in prospective longitudinal studies.

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ORIGINAL RESEARCH

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Reducing Polypharmacy and Inappropriate Medication Use in Elderly Individuals: Effects on Sleep Quality, Anxiety, and Quality of Life

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Abstract

Objective: This study aimed to evaluate the impact of reducing polypharmacy and inappropriate medication use on sleep quality, anxiety levels, and quality of life (QOL) in older adults. The primary objective was to investigate whether reducing the number of medications deemed potentially inappropriate leads to improvements in outcomes, such as sleep quality, anxiety, and QOL.

Materials and Methods: This prospective study enrolled sixty-five participants from a geriatric outpatient clinic, aged 65 and older, who were using five or more medications. Participants were followed for 6 months, during which inappropriate medication use was reduced. Assessments of sleep, anxiety, and QOL were performed repeatedly.

Results: After 6 months, significant improvements in sleep quality were observed ($p < 0.01$). Regression analysis showed that a reduction in the number of medications had independent effects on QOL and anxiety ($p < 0.01$).

Conclusion: The study found that reducing the number of medications, particularly inappropriate medications, significantly improved sleep quality in elderly patients. Furthermore, a reduction in the number of medications was identified as an independent risk factor for both QOL and anxiety. This highlights the importance of managing polypharmacy in the care of older adults.

Keywords: Anxiety, inappropriate medication use, polypharmacy, quality of life, sleep quality

Introduction

Medications are essential in treating older adults, who account for the highest share of prescription drug spending (30-40%). Due to multiple chronic conditions (multimorbidity), this population often uses several medications (polypharmacy), increasing the risk of potentially inappropriate medication (PIM) use (1).

Polypharmacy refers to the concomitant use of five or more medications. Since the geriatric population often has multiple health conditions, the use of five or more medications may be insufficient to adequately manage or treat these disease (2). Polypharmacy has been associated with various adverse outcomes, including adverse drug reactions (ADRs), falls, frailty, hospitalizations, and mortality (3).

One of the significant health issues faced by the geriatric population is the prescription of PIMs. PIMs are drugs that should not be given in the geriatric patient group due to their high risk of adverse reactions (4).

Increased medication use also raises the likelihood of exposure to PIMs, in which the potential harms outweigh the benefits for the individual. Deprescribing is supervised withdrawal of inappropriate medications conducted by a healthcare professional. The goal of this practice is to manage polypharmacy and improve health outcomes (5).

In Türkiye, the Turkish Geriatrics Academy has developed the Turkish inappropriate medication use in the elderly (TIME) to assist healthcare professionals in writing optimal prescriptions (6).

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The TIME criteria guide clinical practice by identifying commonly prescribed but PIMs in older adults. While the main goal of our study was to reduce polypharmacy, medications were evaluated both quantitatively and qualitatively. The deprescribing process was conducted based on the TIME criteria, primarily focusing on discontinuing or substituting inappropriate medications. This approach aimed to reduce the number of drugs while improving treatment quality. Additionally, the study examined changes in patients' general characteristics after six months and explored the relationship between the number of medications and both sleep quality and psychosocial parameters.

Materials and Methods

Study Design and Participants

This study was approved by the Gaziantep University Ethics Committee (approval no: 2023/308, date: 20.09.2023) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients included in the study.

This was a prospective observational study. Our study included 65 patients aged 65 years or older who were on five or more medications and who presented to the geriatric outpatient clinic at our university hospital between 01.10.2023 and 01.10.2024. Before applying standardized, validated measurements and questionnaires, all participants were asked to complete a questionnaire assessing their characteristics and sociodemographic data. The deprescribing process was conducted by a team of physicians. Each patient's medications were reviewed using the TIME criteria to identify PIMs. These were prioritized for discontinuation; clinically unnecessary but appropriate medications were also reduced based on individual judgment. All changes were explained to the patient or caregiver, and the process was closely monitored.

Patients were invited for a follow-up visit approximately six months later, during which the same assessor re-administered all standardized and validated assessments. All participants gave informed consent. A priori power analysis using G*Power 3.9.1 (Cohen's $d = 0.5$, $\alpha = 0.05$, power = 95%) indicated a required sample size of 45. With 65 participants, the study had sufficient power to detect medium or larger effects.

Inclusion and Exclusion Criteria

Patients who were under 65 years of age or who were using fewer than five medications were excluded. Those with severe inflammatory conditions, critical illness, cognitive impairments affecting communication, and comorbidities impairing muscle function, walking, or balance were also excluded. Patients diagnosed with specific sleep disorders, such as restless legs syndrome or obstructive sleep apnea, were also excluded.

Evaluation of Inappropriate Medication Use

In our study, we used the TIME criteria to evaluate inappropriate medication use (6). Medications used inappropriately were discontinued according to these criteria. Patients were advised to report any new prescriptions from other outpatient clinics to prevent the introduction of inappropriate medications between evaluations. Participants were informed that the study aimed to assess the health effects of reducing medications, noting that, while some participants may benefit, results could vary among individuals.

Sleep Quality Assessment

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (7). The PSQI examines seven categories when measuring sleep quality: overall quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medication use, and daytime functioning. The total score from these categories ranges from 0 to 21, with a score above 5 indicating poor sleep quality (8).

Assessment of Depression

The geriatric depression scale, which includes 30 questions, was used to assess depressive symptoms. A total score of ≥14 is considered indicative of depression according to the scale (9,10).

Assessment of Anxiety

The beck anxiety inventory (BAI), developed by Beck, Brown, Steer, and Epstein in 1988, is a 21-item clinical test that measures anxiety levels. The patient is prompted to rate the symptoms "in the previous week, including today". Scores range from 0 to 63. Ulusoy et al. (11) tested the validity of the BAI on Turkish patients and found high internal consistency.

Assessment of Quality of Life

Quality of life (QOL) was assessed using the three-level EQ-5D instrument (EQ-5D-3L), which includes two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The descriptive system evaluates five dimensions—mobility, self-care, daily activities, anxiety/depression, and pain/discomfort. Caregivers' responses generate a five-digit code representing their overall health status. In the EQ-VAS, caregivers rate their perceived health on a scale from 0 to 100 (12). The Turkish version of this scale has been validated in patients with cardiovascular disease (13).

Assessment of Activities of Daily Living and Instrumental Activities of Daily Living

Patients were assessed using the Katz activities of daily living (ADL) rating scale for activities such as personal hygiene, urinary and fecal control, toilet use, dressing, feeding, and walking. High scores were considered as a high degree of independence (14).

The Lawton-Brody scale assessed instrumental ADL like house cleaning, laundry, shopping, medication management, meal preparation, communication, transportation, and financial management; higher scores reflect greater independence (15).

Statistical Analysis

Statistical analyses were performed using IBM SPSS, version 24.0 (IBM Inc., Armonk, NY, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess data normality. Normally distributed data were analyzed with parametric tests, and non-parametric tests were used otherwise. Descriptive measures included the mean, median, and standard deviation (SD). The paired-samples t-test was used to compare means, and the Wilcoxon test was applied to non-normal data. To minimize false positives in multiple PSQI subcomponent analyses, the Bonferroni correction was applied. Because there were seven subcomponents, the significance threshold was set at $p < 0.0071$. Only results below this value were considered statistically significant.

The relationship between binary and categorical variables was analyzed using McNemar's test. In this study, simple linear regression analyses were performed for each outcome (QOL, sleep, anxiety, among others) at the second assessment, with the number of medications at that time as the sole independent variable. Thus, multicollinearity was not a concern. The independent variable in all models was the total number of medications used at the end of 6 months. Each row in the table represents a separate simple linear regression model. All dependent variables are values measured at the second follow-up (6 months). Statistical significance was defined as $p < 0.05$.

Results

This prospective study included 80 patients aged 65 and older who used five or more medications; however, 15 patients were lost to follow-up, resulting in a final sample of 65 (Figure 1). Data were collected at baseline and six months later. Of the participants, 33.8% were male and 66.2% female, with an average age of 70.75 ± 5.46 years (males 72.86 ± 7.09, females 69.67 ± 4.11). The most common comorbidities were hypertension (83.1%), diabetes mellitus (72.3%), hyperlipidemia (67.7%), coronary artery disease (35.4%), and osteoporosis (23.1%), highlighting the prevalence of cardiometabolic diseases among these comorbidities.

Socio-demographic characteristics are summarized in Table 1. The number of patients using PIM decreased significantly from 29.2% to 3.1% between evaluations ($p < 0.05$) (Table 2). The most frequently discontinued drugs were long-acting sulfonylureas, tricyclic antidepressants, proton pump inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), and diuretics.

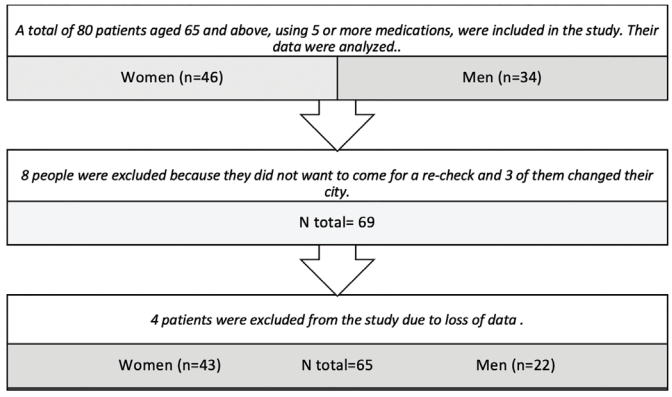

Figure 1. Flow diagram of the patients included in the study.

Table 1. Socio-demographic and general characteristics of the patients.

		Frequency	Percent (%)
Gender	Male	22	33.8
	Female	43	66.2
Marital status	Married	51	78.5
	Widowed/divorced	14	21.5
Education level	Illiterate	22	33.8
	Primary School	29	44.6
	Middle School	7	10.8
	High School	4	6.2
	University	3	4.6
Living with	Alone	7	10.8
	With family members	58	89.2
Smoking	No	58	89.2
	Yes	7	10.8
Alcohol	No	65	100.0
Exercise	No	57	87.7
	Yes	8	12.3

The mean number of medications used dropped from 8.03 (SD = 2.83) to 7.06 (SD = 1.99) post-intervention. The median remained 7 both before [interquartile range (IQR): 5-19] and after (IQR: 4-14) the intervention, but the narrower IQR indicates a significant reduction in some cases ($p < 0.05$). Significant improvements were observed in PSQI subcomponents, including sleep latency, habitual sleep efficiency, and sleep disturbances ($p < 0.01$). After applying the Bonferroni correction for the PSQI subcomponents (significance set at $p < 0.0071$), the PSQI global score also decreased significantly ($p < 0.01$) (Table 3). Although EQ-5D Index and visual analog scale scores increased, these changes were not statistically significant.

The regression analysis used data from the 6-month follow-up after the intervention. The number of medications currently used by patients was the independent variable, while clinical outcomes measured at 6 months were the dependent variables. Regression analysis showed that the number of medications was significantly negatively associated with QOL scores and significantly positively associated with anxiety scores ($p < 0.05$) (Table 4). These findings suggest that deprescribing may improve QOL and reduce anxiety in older adults.

Discussion

In our study, data collected after 6 months showed a significant reduction in both the number of medications used and the number of inappropriate medications used. Improvements were also observed in sleep subscores, including habitual sleep efficiency, sleep latency, and sleep disturbance, along with an overall improvement in the main sleep score. Regression analysis indicated that the number of medications had an independent

Table 2. The relationship between the first and second control data of variables.

Variable	Category	Measurement 1 (n, %)	Measurement 2 (n, %)	p-value
Fall history	No	50 (76.9%)	47 (72.3%)	0.607
	Yes	15 (23.1%)	18 (27.7%)	
Urinary incontinence	No	40 (61.5%)	42 (64.6%)	0.791
	Yes	25 (38.5%)	23 (35.4%)	
Inappropriate medication	No	46 (70.8%)	63 (96.9%)	**0.001**
	Yes	19 (29.2%)	2 (3.1%)	

The McNemar test was used to determine whether there is an association between the first and second control of dichotomous categorical data. A p-value of < 0.05 was considered statistically significant.

Table 3. Comparison of the first and second data of the patients.

Variables	First assessment (n = 65)	Second assessment (n = 65)	p
	Mean ± SD	Mean ± SD	
Number of falls[1α]	0.0 (0-6)	0.0 (0-2)	0.030
Number of drugs[2]	8.03 ± 2.82	7.06 ± 1.99	**<0.01**
Katz score[3α]	6 (3-6)	6 (5-6)	1.000
Lawton brody score[4]	6.78 ± 1.71	7.14 ± 1.07	0.107
EQ-5D index score[5]	0.640 ± 0.25	0.65 ± 0.20	0.693
EQ-5D visual analogue scale[5]	60.92 ± 16.36	62.77 ± 16.13	0.313
Depression score[6]	13.03 ± 6.91	12.65 ± 6.90	0.448
Anxiety score[7]	14.20 ± 10.67	13.22 ± 9.29	0.267
Subjective sleep quality[8]	1.40 ± 0.78	1.28 ± 0.54	0.145
Sleep latency[8]	1.95 ± 1.03	1.58 ± 1.01	**<0.01**
Sleep duration[8]	0.86 ± 0.98	0.62 ± 0.70	0.62
Habitual sleep efficiency[8]	0.92 ± 0.95	0.58 ± 0.72	**<0.01**
Sleep Disorder[8]	1.51 ± 0.61	1.26 ± 0.50	**<0.01**
Use of sleeping drugs[8α]	0.0 (0-3)	0.00 (0-3)	0.739
Daytime dysfunction[8α]	0.00 (0-3)	0.00 (0-3)	0.554
Pittsburgh total score[8]	7.40 ± 3.34	6.02 ± 2.80	**<0.01**

*Significant at 0.05 level. [1]Number of falls in the last 6 months. [2]Number of medicines used. [3]Katz Index of independence in activities of daily living. [4]Lawton-brody instrumental activities of daily living scale. [5]EQ-5D health-related quality of life questionnaire. [6]Geriatric depression scale. [7]Beck anxiety inventory. [8]Pittsburgh Sleep Quality Index total score and subheading scores.
SD: Standard deviation.

Table 4. Analysis of variables independently affected by the number of drugs used.

Dependent variables			95% confidence interval for B		p
	B	Std. error	Lower bound	Upper bound	
[α]Lawton brody score[1]	-0.065	0.067	-0.200	0.069	0.337
[α]EQ-5D index score[2]	-0.038	0.012	-0.063	-0.013	**<0.01**
[α]EQ-5D visual analogue scale[2]	-2.290	0.979	-4.246	-0.334	**<0.01**
[α]Depression score[3]	0.810	0.425	-0.039	1.658	0.061
[α]Anxiety score[4]	1.671	0.549	0.575	2.768	**<0.01**
[α]Pittsburgh total score[5]	0.197	0.176	-0.155	0.548	0.268

*p < 0.05 according to simple linear regression analysis.
[α]Second assessment.
[1]Lawton-brody instrumental activities of daily living scale. [2]EQ-5D health-related quality of life questionnaire. [3] Geriatric depression scale. [4]Beck anxiety inventory. [5]Pittsburgh Sleep Quality Index total score.
B: Beta weight, CI: Confidence interval.

negative effect on QOL scores and an independent positive effect on anxiety scores. We found that sleep quality improved after deprescribing.

Medications can affect sleep in different ways, and even medications prescribed to treat insomnia can sometimes have unwanted side effects. A study by Lande and Gragnani (16) found that as the number of medications prescribed increased, the percentage of deep sleep decreased markedly, while the percentage of light sleep increased. Furthermore, the proportion of REM sleep decreased, while the onset of the deep sleep phase was delayed (16).

Aging causes changes in sleep structure, and numerous studies show that older individuals are more susceptible to sleep disturbances. It is natural to expect changes in sleep structure with increasing age, but age alone does not cause insomnia. However, the ability to sleep decreases with age and this can be caused by different factors related to aging (17).

Polypharmacy is associated with adverse outcomes such as increased mortality, falls, ADRs, prolonged hospital stays, and rehospitalization shortly after discharge (17). Increasing the number of medicines increases the risk of harm and adverse effects (18).

Aging has been associated with multiple diseases and polypharmacy. Sleep disorders are common among the elderly. Another factor that may increase the risk of sleep disorders among older adults is medication use. Polypharmacy can lead to an increased risk of sleep disorders among older patients (19).

In geriatric patients, sleep is an important indicator of overall health and a significant dimension of QOL. Sleep quality affects individuals' daily activities and can have notable impacts on cognitive, physical, and psychological domains. Poor sleep quality can lead to noticeable effects such as unhealthy eating habits, burnout, tension, or fatigue (20).

Decreased sleep quality in older people can lead to insomnia, irritability, fatigue, depression, muscle tremors, pain and reduced mental and functional abilities (20). The literature reveals that chronic diseases and the number of medications used are associated with sleep disorders in elderly individuals (21). In our study, we observed a significant improvement in sleep quality scores six months after reducing the number of medications used. This finding was consistent with the literature.

Polypharmacy affects 20% of elderly patients in primary care and 37% of the general elderly population. People aged 65 years and older typically take 4.5 to 8 medications daily. Polypharmacy often leads to potentially inappropriate prescriptions, increasing risks of nonadherence, drug interactions, and side effects. This is linked to higher rates of hospitalizations, fractures, morbidity, and mortality (22).

Medications can reduce symptoms, treat and prevent diseases, with the ultimate aim of contributing to years of quality life for patients. However, polypharmacy has been associated with multiple adverse health outcomes. For example, increased morbidity and mortality associated with polypharmacy may reduce QOL. Furthermore, age-related changes in pharmacokinetics and pharmacodynamics may make older individuals more susceptible to adverse effects of drugs (23). In our study, the number of medications used decreased significantly at the second follow-up compared with the first. Although patients' QOL scores improved, the change was not statistically significant, possibly due to the sample size, which, if increased, might have yielded significant results. Regression analysis showed that the number of medications was a negative predictor of QOL scores, suggesting that fewer medications may be associated with better QOL.

PIMs are drugs that carry more risks than benefits for older adults. Their use can lead to longer hospital stays and various health complications. PIMs also increase the risk of drug–drug interactions and ADRs. Specifically, they can cause prolonged sedation, higher fall risk, and greater chances of upper gastrointestinal bleeding in the elderly (24).

Many commonly used criteria for identifying inappropriate medications in older adults list numerous anticholinergic drugs. These medications can cause various ADRs such as falls, confusion, malnutrition, acute urinary retention, and constipation. These effects are especially harmful for frail elderly patients and those with geriatric syndromes (25). Anticholinergic medications are used to treat conditions such as Parkinson's disease, psychotic disorders, depression, overactive bladder, asthma, and allergies; they are also used to induce mydriasis. Many psychotropic drugs—such as antipsychotics, antidepressants, mood stabilizers, and anxiolytics—also have anticholinergic effects. In older adults without dementia, cognitive decline is often linked to age-related brain changes, but medication-related anticholinergic effects may also contribute (26). In our study, reducing the number of patients using PIM from 19 to 2 represented a significant success. The most commonly discontinued drugs were long-acting sulfonylureas, tricyclic antidepressants with anticholinergic effects, proton pump inhibitors, NSAIDs, and diuretics because of risks such as hypoglycemia, falls, cognitive decline, and kidney damage. Although high-anticholinergic drugs were avoided, the anticholinergic burden was not quantitatively measured, which is a limitation. Future research using anticholinergic burden scales could better assess the impact of anticholinergic burden on sleep and anxiety.

Anxiety is common among elderly patients and often co-occurs with other chronic conditions. This situation can be associated with increased polypharmacy and the use of inappropriate medications (PIMs) in order to effectively treat the accompanying chronic health issues (27).

The safety of population-specific medication use in older patients, particularly in geriatrics and psychiatry, is receiving increasing attention. There is increasing evidence of polypharmacy and PIM use in older people with diagnoses of anxiety disorders and depression (28). In our study, after we reduced the number of medications and inappropriate drug use, we examined their relationship with anxiety. Although both the medication count and inappropriate medication use decreased significantly, the reduction in anxiety scores was not statistically significant. Regression analysis revealed that the number of medications used was an independent positive predictor of anxiety scores. This study applied basic linear regression without adjusting for covariates; however, using more advanced methods like multivariate regression could offer deeper insights and guide future research. Discontinuing unnecessary and PIMs may help reduce anxiety levels, consistent with existing literature.

Strengths of the Study

This study has several strengths. Its prospective design enabled the assessment of causal links between medication reduction and health improvements. The use of validated scales for sleep quality, anxiety, depression, and QOL increases the reliability of the results. Conducting the study in a real-world geriatric outpatient clinic in a university hospital highlights the practical impact of deprescribing interventions. Notably, the rate of inappropriate medication use decreased significantly from 29.2% to 3.1% within six months, demonstrating the feasibility and effectiveness of targeted medication reviews among older adults.

Study Limitations

In our study, recruiting patients from a single center may limit the generalizability of the results to the broader population. Additionally, some patients either relocated or declined to attend follow-up visits, which reduced the sample size and may have affected the significance of certain data. Furthermore, missing data led to the exclusion of some patients, decreasing the total number of participants.

The absence of a control group limits the ability to attribute observed improvements solely to the deprescribing intervention, as external factors such as time, increased healthcare interactions, or seasonal variations may have influenced the results. Thus, the findings should be interpreted cautiously, and stronger study designs are needed to establish causality. Additionally, the lack of systematic assessment of key clinical variables such as cognitive status (e.g., Mini-Mental State Examination or Montreal Cognitive Assessment scores) restricts the analysis of potential cognitive effects. Future studies should include these measurements for a more comprehensive evaluation. Moreover, regression analyses were performed without adjusting for covariates, relying only on unadjusted associations; therefore, some results may be affected by confounding factors. Future research should incorporate multivariate modeling to control for these influences.

Conclusion

Reducing the number of drugs used, and especially the number of inappropriate drugs, is important for the country's economy, health system, patients' health and well-being. In our study, participants who experienced a statistically significant reduction in the number of medications had higher sleep quality. We have demonstrated in our study how important discontinuing the unnecessary use of even a single drug is for the country's economy, health system, and patients. More studies should be conducted to obtain more meaningful data.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Gaziantep University Clinical Research Ethics Committee (approval number: 2023/308; date: 20.09.2023).

Informed Consent: Written informed consent was obtained from all patients included in the study.

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Footnotes

Authorship Contributions

Concept: E.S.A., P.K., Design: E.S.A., P.K., Data Collection or Processing: E.S.A., P.K., Analysis or Interpretation: E.S.A., P.K., Literature Search: E.S.A., P.K., Writing: E.S.A., P.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH

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Beyond Chronological Age: Clinical Determinants and Geriatric Vulnerability of 30-Day Mortality in Older Adults with Carbapenem-Resistant Enterobacterales Bloodstream Infections

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Abstract

Objective: Carbapenem-resistant Enterobacterales bloodstream infections (CRE-BSIs) are associated with increased mortality, particularly among older adults. This study aimed to evaluate clinical severity, treatment-related factors, and geriatric vulnerability parameters associated with 30-day mortality in patients aged ≥65 years.

Materials and Methods: Patients aged 65 and older who were diagnosed with a BSI caused by CRE between 2016 and 2025 were included in this retrospective cohort study. Demographic, clinical, microbiological, and treatment-related data were collected. Geriatric vulnerability was assessed using the Hospital Frailty Risk Score (HFRS), the Geriatric Nutritional Risk Index (GNRI), polypharmacy, and functional dependency. To determine the factors associated with 30-day mortality, a Cox regression analysis was performed.

Results: Of the 177 patients included in the study, the 30-day mortality rate was 35.6%. The multivariate analysis revealed that a higher Pitt Bacteremia Score [adjusted hazard ratio (HR) = 1.24, 95% confidence interval (CI) 1.12-1.37, $p < 0.001$], a higher HFRS score (aHR = 1.12, 95% CI 1.04-1.21, $p = 0.002$), and a delay in appropriate treatment (≥72 hours) (aHR = 2.01, 95% CI 1.25–3.24, $p = 0.004$) was independently associatedwith increased mortality. GNRI was inversely associated with mortality (aHR = 0.96, 95% CI 0.93–0.99, $p = 0.008$). Chronological age and antimicrobial treatment type were not independently associated with mortality in the multivariable analysis.

Conclusion: Mortality in older adults with CRE-BSIs may be largely explained by infection severity and biological vulnerability rather than chronological age. Frailty and impaired nutritional status appear to be important determinants of outcome, while delayed initiation of appropriate therapy remains a critical modifiable factor.

Keywords: Carbapenem-resistant Enterobacterales, bloodstream ınfections, frailty, mortality, aged

Introduction

Carbapenem-resistant Enterobacterales (CRE) infections have become a significant public health concern on a global scale due to their increasing prevalence, limited treatment options, and high mortality rates. The Centers for Disease Control and Prevention (CDC) classifies CRE among urgent antimicrobial resistance threats, and current guidance from the Infectious Diseases Society of America highlights the substantial mortality burden associated with CRE bloodstream infections (CRE-BSIs) (1,2).

Older age is consistently associated with poor clinical outcomes, including an increased mortality rate, in patients with CRE-BSIs (3-5). Consistently, multicenter epidemiological studies from Türkiye have demonstrated that infections in this population are more frequently associated with more severe clinical presentation and an increased need for intensive care unit (ICU) admission (6).

However, chronological age alone may not adequately reflect biological vulnerability in older adults. Aging is a heterogeneous

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process, and clinical outcomes in older adults are influenced not only by age but also by multidimensional factors such as comorbidity burden, malnutrition, polypharmacy, functional dependency, and reduced physiological reserve. These factors are conceptualized within the framework of frailty, a syndrome characterized by increased vulnerability to stressors and poorer clinical outcomes, including infections (7-9).

Although several studies have investigated predictors of mortality in CRE-BSIs among older adults, most have primarily focused on infection severity and treatment-related variables. Whether geriatric vulnerability beyond chronological age influences outcomes in CRE-BSIs remains unclear. The objective of this study was to identify the factors associated with 30-day mortality in older adults with CRE-BSIs, with a particular focus on geriatric vulnerability that extends beyond a patient's chronological age.

Materials and Methods

This retrospective observational study was conducted at a tertiary-care academic center. Patients aged 65 and over who were hospitalized between January 1, 2016, and December 31, 2025, and who were diagnosed with CRE-BSIs were screened for eligibility. Patients meeting these criteria were included in the study, whereas patients with polymicrobial bacteremia detected in blood cultures, patients with recurrent CRE-BSIs (only the first episode was considered), patients whose blood culture isolates were deemed contaminants, or patients with incomplete or inaccessible clinical data were excluded.

Demographic, clinical, microbiological, geriatric, and treatment-related data were retrospectively obtained from the hospital information management system. The following variables were collected: age, sex, and body mass index. The Charlson Comorbidity Index (10) was used to assess the comorbidity burden. Additional variables included immunosuppressive therapy, history of solid organ transplantation, and history of hematopoietic stem cell transplantation. Geriatric vulnerability was evaluated using the Hospital Frailty Risk Score (HFRS) (11), nutritional status using the Geriatric Nutritional Risk Index (GNRI) (12) and polypharmacy defined as the use of five or more medications, and functional dependency prior to hospitalization.

Clinical and infection-related variables included ICU acquisition, hospital length of stay prior to BSI, presence of sepsis or septic shock according to Sepsis-3 criteria (13), Pitt Bacteremia Score (PBS) (14), calculated on the day of blood culture collection, need for mechanical ventilation, and source of infection defined according to CDC criteria (15).

Blood culture specimens were processed using the BacT/ALERT 3D system (bioMérieux, Craponne, France) according to standard laboratory protocols. Following a positive result, samples were subjected to Gram staining and then inoculated onto appropriate culture media. The inoculated plates were incubated at 37 °C for 24-48 hours for microbial growth. Bacterial identification was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Antimicrobial susceptibility testing was carried out with automated systems (VITEK® 2, bioMérieux; or BD Phoenix®, Becton Dickinson), and the results were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing criteria (16).

CRE-BSIs was defined as the isolation of an Enterobacterales strain showing non-susceptibility to at least one carbapenem agent from blood cultures (2). Frailty was evaluated using the HFRS, calculated based on ınternational classification of diseases, tenth revision (ICD-10) diagnostic coding (11). Because HFRS primarily reflects hospital-based frailty, additional parameters, including nutritional status, polypharmacy, and functional dependency, were evaluated to better capture multidimensional geriatric vulnerability. Nutritional status was assessed using the GNRI as described by Bouillanne et al. (12). Polypharmacy was defined as the regular use of at least five medications.

Treatment-related variables included empirical and targeted antimicrobial therapy and the time to initiation of appropriate therapy. Delayed targeted therapy referred to initiation of an antimicrobial agent with confirmed in vitro activity ≥72 hours after blood culture collection. Thirty-day mortality, defined as death within 30 days of the first positive blood culture, was used as the primary outcome.

Ethical approval was obtained from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval no: 416, date: 05.03.2026). The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice standards. Informed consent was not required due to the retrospective observational nature of the study.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation or median interquartile range (IQR), depending on data distribution. Categorical variables are presented as counts and percentages. Group comparisons between survivors and non-survivors were performed using the Student's t-test or Mann-Whitney U test for continuous variables, and the chi-square or Fisher's exact test for categorical variables. No formal sample size calculation was performed due to the retrospective nature of the study. Missing data were handled using complete-case analysis. Univariable Cox proportional hazards regression was used to explore associations with 30-day mortality. Variables deemed clinically relevant or showing a p-value <0.10 were subsequently entered into the multivariable model. Collinearity was evaluated using the variance inflation factor (VIF), and variables with VIF >5 were excluded. The proportional hazards assumption was evaluated using Schoenfeld residuals and was met for all variables in the final model.

Survival probabilities were estimated using the Kaplan-Meier method, and group differences were compared with the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) are presented.

All statistical tests were two-sided, with a significance threshold of $p < 0.05$. P-values were reported in accordance with journal guidelines. Statistical analyses were conducted using IBM SPSS Statistics (version 29.0).

Results

A total of 177 older adults with CRE-BSIs were included in the study. The median age was 74 years (IQR 68-81); 57.1% (n = 101) were male. No missing data were identified for variables used in geriatric vulnerability assessment, including HFRS, GNRI, polypharmacy, and functional dependency. During the 30-day follow-up, 63 patients (35.6%) died, while 114 (64.4%) survived. Although non-survivors tended to be older, the difference did not reach statistical significance. Baseline demographic, clinical, and microbiological characteristics are summarized in Table 1.

Table 1. Baseline characteristics of geriatric patients with carbapenem-resistant Enterobacterales bloodstream infection according to 30-day mortality.

Variable	Overall, n = 177 (%)[1]	Survived, n = 114 (64.4%)[1]	Death, n = 63 (35.6%)[1]	p-value[2]
Patient-related factors				
Age, median (IQR)	74 (68-81)	73 (67-80)	76 (70-83)	0.09
Male sex,	101 (57.1)	63 (55.3)	38 (60.3)	0.52
BMI, median (IQR)	26.1 (22-30)	26.4 (23-30)	25.7 (21-31)	0.41
Comorbidities				
CCI, median (IQR)	5 (3-7)	4 (3-6)	7 (5-8)	<0.001
Immunosuppressive therapy	43 (24.3)	20 (17.5)	23 (36.5)	0.006
SOT	14 (7.9)	6 (5.3)	8 (12.7)	0.08
HSCT	10 (5.6)	3 (2.6)	7 (11.1)	0.03
Geriatric vulnerability factors				
HFRS, median (IQR)	7 (411)	5 (39)	11 (7-14)	<0.001
GNRI, median (IQR)	95 (88102)	98 (92104)	89 (83-95)	<0.001
Polypharmacy ≥5 drugs	98 (55.4)	55 (48.2)	43 (68.3)	0.01
Functional dependency	66 (37.3)	30 (26.3)	36 (57.1)	<0.001
Clinical characteristics				
ICU-acquired BSI	71 (40.1)	36 (31.6)	35 (55.6)	0.003
Length of hospital stay before BSI, days, median (IQR)	10 (6-17)	9 (6-15)	12 (7-20)	0.08
Sepsis	118 (66.7)	66 (57.9)	52 (82.5)	0.001
Septic shock	39 (22.0)	11 (9.6)	28 (44.4)	<0.001
PBS, median (IQR)	4 (2-7)	3 (1-5)	7 (5-9)	<0.001
Mechanical ventilation	46 (26.0)	18 (15.8)	28 (44.4)	<0.001
Infection source				0.64
Primary BSI	48 (27.1)	30 (26.3)	18 (28.6)	
UTI	42 (23.7)	29 (25.4)	13 (20.6)	
Pneumonia	39 (22.0)	23 (20.2)	16 (25.4)	
Catheter-related BSI	21 (11.9)	15 (13.2)	6 (9.5)	
Intra-abdominal infection	17 (9.6)	11 (9.6)	6 (9.5)	
SSTI	10 (5.6)	6 (5.3)	4 (6.3)	
Microbiological characteristics				0.72
Klebsiella pneumoniae	109 (61.6)	72 (63.2)	37 (58.7)	
Escherichia coli	34 (19.2)	23 (20.2)	11 (17.5)	
Other *Enterobacterales* spp.	34 (19.2)	19 (16.7)	15 (23.8)	

Table 1. Continued.

Variable	Overall, n = 177 (%)[1]	Survived, n = 114 (64.4%)[1]	Death, n = 63 (35.6%)[1]	p-value[2]
Treatment related characteristics				
Targeted therapy delay ≥72 h	74 (41.8)	33 (28.9)	41 (65.1)	<0.001
Targeted antimicrobial therapy				0.016
- Polymyxin-based-regimen	122 (68.9)	71 (62.3)	51 (81.0)	
- Ceftazidime-avibactam	55 (31.1)	43 (37.7)	12 (19.0)	

[1]Data are presented as n (%) or median interquartile range (IQR), 25th-75th percentiles [2]Statistical comparisons were performed using the chi-square test, Wilcoxon rank-sum test, or Fisher's exact test, as appropriate.
BMI: Body mass index, BSI: Bloodstream infections, CCI: Charlson Comorbidity Index, GNRI: Geriatric Nutritional Risk Index, HFRS: Hospital Frailty Risk Score, HSCT: Hematopoietic stem cell transplantation, ICU: Intensive care unit, IQR: interquartile range, PBS: Pitt Bacteremia Score, SOT: Solid organ transplantation, SSTI: Skin and soft tissue infection, UTI: Urinary tract infection.

Empirical antimicrobial therapy most frequently included carbapenems (37.3%, n = 66), followed by piperacillin-tazobactam (29.4%, n = 52), third-generation cephalosporins (21.5%, n = 38), and cefepime (11.9%, n = 21). No patients received ceftazidime-avibactam (CAZ-AVI) or polymyxin-based regimens during the empirical phase.

After susceptibility results became available, all patients were switched to targeted therapy: polymyxin-based regimens in 68.9% (n = 122) and CAZ-AVI in 31.1% (n = 55).

Table 2 summarizes the univariable Cox regression results. CAZ-AVI therapy was associated with lower mortality than polymyxin-based regimens (HR = 0.58, 95% CI 0.34-0.98, p = 0.04), whereas age was not a significant predictor of mortality.

A multivariable Cox model was constructed, including clinically relevant variables and those with $p < 0.10$ in the univariable analysis, namely infection severity (PBS), geriatric vulnerability (HFRS and GNRI), treatment delay, antimicrobial therapy type, and chronological age. Polypharmacy and functional dependency were excluded from the final model due to collinearity with the HFRS, as demonstrated by correlation analysis and the VIF.

In the adjusted model, higher PBS (aHR = 1.24, 95% CI 1.12-1.37, $p < 0.001$) and higher HFRS (aHR = 1.12, 95% CI 1.04-1.21, p = 0.002) were independently associated with increased mortality. In contrast, GNRI showed an inverse association with mortality (aHR = 0.96, 95% CI 0.93-0.99, p = 0.008); lower values, indicating poorer nutritional status, predicted higher mortality. Delayed initiation of appropriate targeted antimicrobial therapy (≥72 h) (aHR = 2.01, 95% CI 1.25-3.24, p = 0.004) significantly predicted mortality. Chronological age and antimicrobial treatment type were not independently associated with mortality after adjustment.

Survival was analyzed using the Kaplan-Meier method according to frailty status. Patients were categorized into three groups based on HFRS (low <5, intermediate 5-10, high >10). Thirty-day survival rates were 82%, 67%, and 41% for the low, intermediate, and high-frailty groups, respectively. Survival differed significantly across groups (log-rank $p < 0.001$). The corresponding survival curves are shown in Figure 1.

Discussion

In this study, infection severity, frailty, nutritional status, and delayed initiation of appropriate therapy were associated with 30-day mortality in older adults with CRE-BSIs, whereas chronological age and antimicrobial treatment type were not. These findings suggest that prognosis in this population may be explained by biological vulnerability and acute illness severity rather than age alone.

Infection severity, as reflected by the PBS, was a strong independent predictor of mortality. This finding aligns with

Table 2. Determinants of 30-day mortality identified by univariable and multivariable Cox regression.

Variable	Univariable HR (95% CI)[1]	p-value[2]	Multivariable aHR (95% CI)[1]	p-value[2]
Age (per year)	1.02 (0.99-1.05)	0.12	1.01 (0.98-1.04)	0.31
PBS (per point)	1.31 (1.20-1.44)	<0.001	1.24 (1.12-1.37)	<0.001
HFRS (per point)	1.17 (1.09-1.26)	<0.001	1.12 (1.04-1.21)	0.002
GNRI (per point)	0.95 (0.92-0.98)	<0.001	0.96 (0.93-0.99)	0.008
≥72 h delay in targeted therapy	2.47 (1.58-3.87)	<0.001	2.01 (1.25-3.24)	0.004
Ceftazidime-avibactam therapy*	0.58 (0.34-0.98)	0.04	0.69 (0.37-1.28)	0.24

[1]95% confidence intervals (CIs) were calculated for hazard ratios. [2]p-values were derived from Cox proportional hazards regression models. *The reference category for antimicrobial therapy was a polymyxin-based regimen. Cox regression analyses were performed to assess predictors of 30-day mortality. Variables with clinical relevance or with p <0.10 were included in the multivariable model, whereas polypharmacy and functional dependency were excluded due to collinearity with HFRS.
HR: Hazard ratio, aHR: adjusted hazard ratio, CI: Confidence interval, PBS: Pitt bacteremia score (per point), HFRS: Hospital Frailty Risk Score (per point), GNRI: Geriatric Nutritional Risk Index (per point).

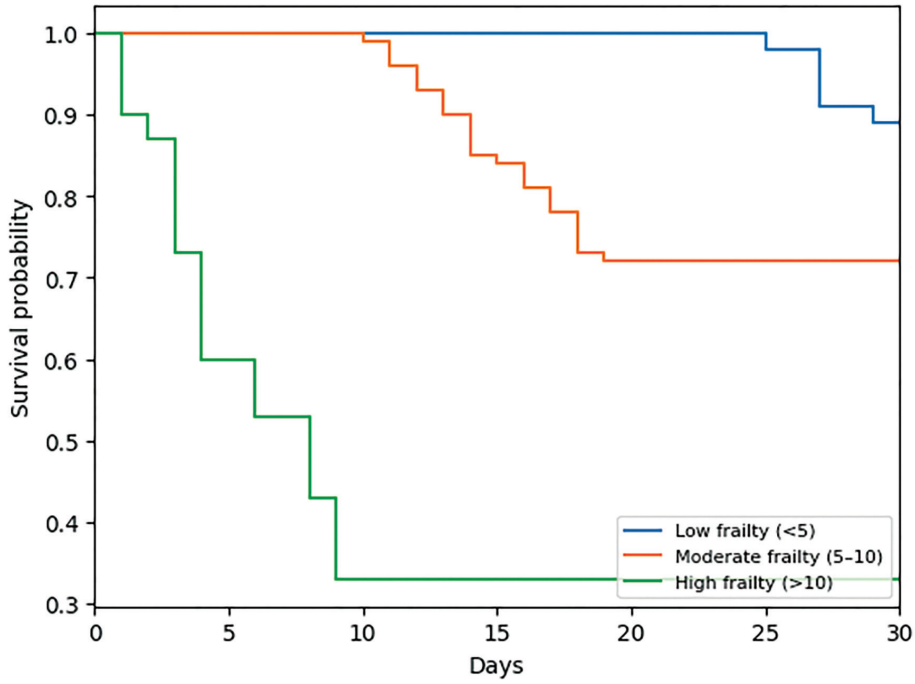

Figure 1. Kaplan-Meier survival analysis by HFRS frailty groups (log-rank $p < 0.001$).

HFRS: Hospital Frailty Risk Score.

previous studies showing that the severity of acute infection is a key determinant of outcomes in CRE-BSIs (3). Similar associations have been reported in older adult cohorts, where higher severity scores correlate with increased mortality (4,5). Overall, these results reinforce the central role of acute physiological derangement in determining prognosis.

Frailty, assessed using the HFRS, was also independently associated with mortality. Frailty is characterized by reduced physiological reserve and increased susceptibility to stressors, and is associated with adverse outcomes across a range of clinical settings (7-9). Our findings extend this concept to CRE-BSIs, suggesting that frailty is a critical determinant of outcomes beyond traditional infection-related parameters. Previous studies in infectious diseases have identified frailty as an independent predictor of mortality (17). These findings may support the integration of frailty assessment into the clinical evaluation of older adults with CRE-BSIs.

In addition to HFRS, nutritional status assessed by the GNRI was associated with mortality. Lower GNRI values, reflecting poorer nutritional status, were linked to a higher risk of death. This association is biologically plausible, as malnutrition impairs immune function and reduces the ability to respond to severe infections (12). These results highlight the role of nutritional vulnerability as a key component of geriatric risk stratification and support prior evidence linking malnutrition to adverse infection outcomes.

Although polypharmacy and functional dependency were more prevalent among non-survivors in descriptive analyses, they were excluded from the multivariable model because of collinearity with HFRS. Therefore, while these parameters likely reflect increased vulnerability, their independent contributions could not be established in this study.

Chronological age was not independently associated with mortality after adjustment. This finding underscores the heterogeneity of the older adult population and suggests that age alone is an insufficient marker of risk. Instead, parameters reflecting biological aging, such as frailty and nutritional status, appear to provide more meaningful prognostic information.

In univariable analysis, CAZ-AVI therapy was linked to lower mortality; however, this effect was not sustained after adjustment for confounders (18). This may reflect confounding by indication, as patients receiving polymyxin-based regimens likely had more severe disease. Therefore, the observed benefit may be attributable to differences in baseline characteristics rather than to a direct treatment effect.

Delayed initiation of appropriate targeted therapy remained an independent predictor of mortality, highlighting the importance of timely effective treatment in CRE-BSIs (2,3,19). However, this finding should be interpreted cautiously given the potential for immortal time bias inherent to retrospective time-to-treatment analyses. These findings also support the potential role of multidisciplinary approaches, including geriatric consultation

and antimicrobial stewardship programs, in facilitating earlier initiation of appropriate antimicrobial therapy in vulnerable older adults.

This study has several important strengths. It specifically addresses a high-risk geriatric population and incorporates a multidimensional assessment of vulnerability, including frailty, nutritional status, and infection-related parameters. This comprehensive approach provides a more nuanced understanding of factors influencing mortality in older adults with CRE-BSIs.

Study Limitations

Several limitations should be acknowledged. First, the single-center retrospective design may limit generalizability and may be subject to residual confounding.

Second, although HFRS is a practical tool, it is retrospectively derived from ICD-10 coding data and may not fully capture all dimensions of frailty or provide real-time bedside clinical assessment during hospitalization (11). Therefore, prospective studies incorporating bedside frailty assessment tools such as the Clinical Frailty Scale may provide a more accurate evaluation of frailty and contribute more robust evidence to the literature.

Third, due to its real-world retrospective nature, molecular characterization of CRE isolates, including carbapenemase production and genotyping, could not be performed systematically, precluding evaluation of the impact of specific resistance mechanisms on outcomes. However, the inclusion of complementary parameters such as GNRI partially mitigates this limitation. Although time-to-event analysis was used, potential immortal time bias related to time-to-treatment variables cannot be fully excluded. Because patients classified as having delayed appropriate therapy were required to survive long enough to receive treatment after the predefined threshold, the magnitude of the observed association between treatment delay and mortality may have been overestimated.

Conclusion

Mortality in older adults with CRE-BSIs appears to be influenced more by infection severity and biological vulnerability than by chronological age. Frailty and impaired nutritional status emerged as key determinants of outcome, while delayed initiation of appropriate therapy remained a critical modifiable risk factor. These findings support a shift from age-based to vulnerability-based risk assessment, emphasizing the need for early targeted treatment, multidisciplinary geriatric evaluation, and antimicrobial stewardship strategies to improve outcomes in this high-risk population.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval no: 416, date: 05.03.2026). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Informed Consent: Informed consent was waived due to the retrospective observational design of the study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: R.D., A.M., Concept: R.D., A.M., Design: R.D., A.M., Data Collection or Processing: R.D., Analysis or Interpretation: R.D., Literature Search: R.D., Writing: R.D., A.M.,

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ORIGINAL RESEARCH

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Association Between Achievement of Nutritional Goals and Refeeding Syndrome in Patients Receiving Enteral or Parenteral Nutrition

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Abstract

Objective: The aim of this study was to compare the frequency of refeeding syndrome (RS) in achieving nutritional goals in patients planned to receive enteral nutrition (EN) or parenteral nutrition (PN) treatment, and to compare outcomes between patients aged older and younger than 60 years.

Materials and Methods: This retrospective study included patients who received EN or PN and were followed up at Hacettepe University Faculty of Medicine Adult Hospital between January 2023 and December 2024. Patients were grouped as achieving ≥70% or <70% of the target in clinical nutrition therapy (NT). A serum phosphorus level <2.5 mg/dL was considered RS.

Results: A total of 723 patients were evaluated, comprising 350 (48.4%) females and 373 (51.6%) males, with a median (interquartile range) age of 62.3 (17.0) years. Based on the rate of goal attainment, 432 patients (59.7%) achieved <70% of the target in clinical NT. RS was significantly more frequent in patients who achieved ≥70% of the target (p = 0.035). In the EN group, RS was more common among patients who met ≥70% of the target (p = 0.023). The multivariate regression analysis results showed that after adjusting for age, sex, body mass index, chronic obstructive pulmonary disease, length of hospital stay and type of NT, achieving ≥70% of the target increased the risk of developing RS (odds ratio :1.86, 95% confidence interval: 1.051-3.316, p = 0.03).

Conclusion: The higher risk of RS in patients who achieve the target in clinical nutrition, especially among those receiving EN, appears to be a barrier. While caloric goals are being achieved, patients receiving clinical NT should be monitored with respect to RS.

Keywords: Enteral nutrition, hypophosphatemia, older adults, parenteral nutrition, refeeding syndrome

Introduction

Malnutrition (MN) is defined as a condition involving changes in body composition, particularly a reduction in fat-free mass, and a decrease in body weight due to inadequate nutrient intake, which leads to deterioration in physical and mental functions and worsened clinical outcomes, according to the European Society for Clinical Nutrition and Metabolism (ESPEN) (1). Early identification of MN contributes to the reduction of healthcare costs, morbidity, and mortality (2,3). Refeeding syndrome (RS) is a severe electrolyte or fluid imbalance that occurs in malnourished patients when nutrition therapy (NT) (oral, enteral, or parenteral) is initiated too aggressively after a period of inadequate nutrition (1). RS was first identified in the 1940s among starved prisoners of war who developed complications after refeeding (4). In the literature, the overall prevalence of RS has been reported across a wide range due to variations in

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diagnostic criteria and differences in patient populations (5). More specifically, multicentre randomized studies conducted on hospitalized acute medical patients have shown that the incidence of RS during NT in malnourished individuals ranges from 8% to 14.6% (6).

RS is primarily driven by an insulin surge following carbohydrate intake, leading to intracellular shifts of phosphate, potassium, and magnesium (7). Following MN, high-calorie nutritional intake may lead to electrolyte imbalances (particularly hypophosphatemia, hypokalemia, and hypomagnesemia), decreased vitamin levels (particularly vitamin B1, thiamine), fluid imbalances, and salt retention. These conditions may present with cardiac and neurological side effects, impaired organ function, and, in severe cases, death and prolonged hospital stay (6). Hypophosphatemia, a hallmark feature of this syndrome may result in a wide range of clinical manifestations, including rhabdomyolysis, haemolysis, respiratory failure, musculoskeletal impairments, and reduced cardiac contractility (8).

A number of factors heighten the risk of RS. Individuals with a body mass index (BMI) under 16 kg/m^2, those who have lost more than 15% of their body weight unintentionally within the past 3-6 months, those who have experienced prolonged inadequate intake, or those who begin NT with already reduced phosphate, potassium, or magnesium levels are considered particularly vulnerable. Additional risk factors include a history of alcohol misuse or the use of certain medications such as insulin, chemotherapy, antacids, or diuretics (9).

Clinical guidelines recommend early initiation of nutrition in critically ill and malnourished patients (10). However, rapid progression to full caloric intake increases the risk of RS (11). Studies have shown that aggressive refeeding, particularly during the first 72 hours, correlates with higher morbidity (12). Given that a gradual increase in caloric intake could mitigate the risk of RS-related complications, risk stratification and individualized caloric advancement protocols are crucial. The aim of this study was to compare the frequency of RS in patients receiving enteral nutrition (EN) or parenteral nutrition (PN), with particular emphasis on success in achieving individualized nutritional goals. By evaluating the incidence of RS and its relationship to nutritional outcomes in each group, it is hoped to contribute to evidence-based guidance in the selection and management of NTmodalities.

Materials and Methods

The study protocol complied with the principles of the Helsinki Declaration. The study was approved by Hacettepe University Health Sciences Research Ethics Committee (approval no: 2025/11-35, date: 20.05.2025). As this was a retrospective study, no written informed consent was obtained from participants.

This retrospective study included 723 patients who received EN or PN therapy and were followed up at Hacettepe University Faculty of Medicine Adult Hospital from January 2023 to December 2024. The patients were categorized based on the proportion of their targeted nutritional intake achieved: those who attained ≥70% of their nutritional goals and those who achieved <70%. The <70% and ≥70% thresholds were selected in accordance with current recommendations and previous studies as pragmatic markers of nutritional goal achievement (13-15). RS was defined as a serum phosphorus level <2.5 mg/dL occurring within the first 5 days following the initiation of EN or PN. Routine blood electrolyte levels were monitored daily, allowing for the timely identification and documentation of any decrease in phosphorus levels to <2.5 mg/dL. This systematic approach ensured that all occurrences of RS following the initiation of NTwere accurately captured. Patients receiving EN were then compared with those receiving PN. Under the supervision of a dietician, individual nutritional targets were set according to the clinical characteristics and metabolic requirements of each patient. In the absence of indirect calorimetry, caloric goals were determined using a weight-based approach of 25-30 kcal/kg/day, consistent with current recommendations (9,13). In accordance with these recommendations supporting the gradual advancement of NT, the achievement of nutritional goals was assessed within the first 5 days after the initiation of NT (16,17). Both the EN and PN groups were further subdivided into groups based on their success in nutritional targets (achieving ≥70% or <70%).

Patients were excluded from the study if they were younger than 18 years, had primary hyperparathyroidism, were taking insulin or diuretics, were undergoing continuous haemodiafiltration for acute kidney failure during NT, or had incomplete data.

Data on each patient's MN assessment results, nutritional therapies, age, sex, educational status, marital status, occupation, living arrangements, and chronic diseases were extracted from patient files in the hospital records system.

Nutritional Assessment

Nutritional status was assessed using the Nutritional Risk Screening (NRS-2002). This is a validated screening tool for MN in adults, which is recommended for use in hospitalized patients to ensure that NT is initiated promptly, thereby helping to prevent potential complications (18-20). The NRS-2002 scale begins with an initial screening comprising four questions. If any of these questions are answered with "yes," indicating a significant deviation from normal, a final screening is performed. This final screening assesses the severity of nutritional impairment and of disease. Each parameter is scored on a scale from 0 to 3. During the validation process, a total score of 3 or more indicates that the patient would benefit from an NT plan (19). Patients with an NRS score of ≥3 were classified as high NRS. Anthropometric data were collected as part of a routine nutritional assessment,

with standardized measurements of weight and height obtained using a digital scale and stadiometer. BMI was calculated as weight divided by height squared (kg/m^2).

Statistical Analysis

Data obtained in the study were analyzed using SPSS v.25.0 (Statistical Package for the Social Sciences). Categorical variables were presented as number (n) and percentage (%). Continuous variables were expressed as mean ± standard deviation values for normally distributed data or as median and interquartile range (IQR) values for non-normally distributed data. Conformity of the data to normal distribution was assessed using the Kolmogorov-Smirnov or Shapiro-Wilk tests and histograms. Between-group comparisons of categorical variables were performed using the chi-square test or Fisher's exact test. The Student's t-test was used to compare two groups of normally distributed continuous variables, and the Mann-Whitney U test was applied to non-normally distributed continuous variables. Relationships between variables were examined using Pearson correlation for normally distributed variables and Spearman correlation for non-normally distributed variables. Variables were initially assessed using univariate analyses comparing patients who developed RS with those who did not. Only variables with a p-value <0.05 in univariate analysis were subsequently entered into the multivariate binary logistic regression model. Binary logistic regression analyses using a backward-selection method were performed in the two groups and were adjusted for confounding variables based on the univariate analysis. A value of $p < 0.05$ was accepted as the level of statistical significance.

Results

Evaluations were made of a total of 723 patients comprising 350 (48.4%) females and 373 (51.6%) males with a median (IQR) age of 62.3 (17.0) years. In the whole sample, 33.2% received EN, and 10.8% developed RS. According to the rate of goal attainment, 432 (59.7%) of the patients achieved <70%, and 291 (40.3%) achieved ≥70% of the target in clinical NT. The comparisons of clinical characteristics and metabolic complications between groups achieving <70% and ≥70% of the target in clinical NT are summarized in Table 1. RS developed in 38 (8.8%) of the patients achieving <70% of the target and in 40 (13.7%) of the

Table 1. Comparisons of the clinical characteristics and metabolic complications between the groups achieving <70% and ≥70% of the target in clinical nutrition therapy.

		Achieving <70% of the target (n = 432)	Achieving ≥70% of the target (n = 291)	p
Age, years, median [IQR]		63.9 [16.3]	60.0 [17.7]	**0.003**
Sex, female, n (%)		215 (49.8%)	135(46.4%)	0.37
BMI, kg/m^2, median [IQR]		23.4 [6.1]	22.1 [8.0]	**0.001**
Nutrition type, enteral, n (%)		130 (30.1)	110 (37.8)	**0.031**
NRS score, median [IQR]		5.0 [2.0]	5.0 [1.0]	**0.031**
Follow up period, days, median [IQR]		11.0 [14.0]	20.0 [23.0]	**<0.001**
Department/unit, n (%)	**Medical ward**	203 (47.0%)	146 (50.2%)	0.078
	Surgical ward	115 (26.6%)	85 (29.2%)	
	ICU	114 (26.4%)	60 (20.6%)	
Comorbidities				
Presence of ≥1 comorbidity, n (%)		304 (70.4%)	181 (62.4)	**0.026**
Diabetes mellitus, n (%)		111 (25.7%)	58 (19.9)	0.14
Hypertension		157 (36.3%)	77 (26.5%)	**0.005**
Coronary arterial disease, n (%)		63 (14.6)	34 (11.7)	0.26
Heart failure, n (%)		23 (5.3)	21 (7.2)	0.30
COPD, n (%)		39 (9.0%)	12 (4.1%)	**0.012**
Chronic renal disease, n (%)		21 (4.9)	18 (6.2)	0.44
Metabolic complications (electrolyte imbalance)				
Hypernatremia		11 (2.5)	5 (1.7)	0.46
Hypokalemia		3 (0.7)	4 (1.4)	0.45
Hyperglycemia		3 (0.7)	1 (0.3)	0.65
Hypophosphatemia		38 (8.8)	40 (13.7)	**0.035**

The variables are presented as number (percentage), median [IQR] or mean ± standard deviation) values. Bold indicates $p < 0.05$.
COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, ICU: Intensive care unit, NRS: Nutritional risk screening, IQR: Interquartile range.

patients achieving ≥70% of the target (p = 0.035). No significant differences were found between the groups with respect to other electrolytes.

Comparisons of clinical characteristics and metabolic complications between in patients receiving EN and PN are summarized in Table 2. No significant difference was found between the EN and PN groups in terms of electrolyte disorders.

The comparisons of metabolic complications between patients achieving <70% and ≥70% of the nutritional target, according to the EN and PN subgroups, are summarized in Table 3. Of the patients receiving EN, the incidence of RS was higher in those who achieved ≥70% of the nutritional target (p = 0.023). In the PN group, no significant differences were found between groups defined according to rates of target achievement. The clinical characteristics and metabolic features were also compared between geriatric and non-geriatric patients, defined as adults aged ≥60 years and <60 years, respectively (Table 4). The non-geriatric group achieved ≥70% of the nutritional target significantly more frequently than the geriatric group (p = 0.006).

The results of the multivariate regression analysis showed that after adjusting for age, sex, BMI, chronic obstructive pulmonary disease (COPD), length of hospital stay and type of NT, achieving ≥70% of the nutritional target increased the risk of developing RS [odds ratio (OR): 1.86, 95% confidence interval (CI): 1.051-3.316, p = 0.03]. Other risk factors for RS development were identified: BMI and the presence of COPD (OR: 0.93, 95% CI: 0.882-0.987, p = 0.015; OR: 2.85, 95% CI: 1.181-6.898, p = 0.02, respectively). The results of the regression analysis are shown in Table 5.

Discussion

The results of this study showed that the rate of RS was higher in patients who achieved ≥70% of the energy goals compared to those who achieved <70%. The development of RS was found to be significantly related to achieving ≥70% of the target independently of age, female gender, BMI, COPD, length of hospital stay and type of NT. This finding suggests that a more aggressive approach to meeting nutritional goals in high-risk patients may be associated with an increased risk of RS.

Previous studies have identified several factors associated with RS, including the amount of energy administered through PN or EN (15,21-24). In a retrospective study that examined hospitalized adults receiving PN, it was indicated that higher energy delivery was independently associated with the development of RS (21). Marvin et al. (15) reported a significantly higher incidence of RS in patients who received more than 70% of their daily energy requirements from PN within the first 24 hours of initiation. From the results of recent studies, RS is thought to result particularly from higher caloric targets and carbohydrate-rich feeding, which triggers increased insulin secretion (22,23). Similarly, reaching

Table 2. Comparisons of the clinical characteristics and metabolic complications in patients receiving EN and PN.

	Patients receiving PN (n = 483)	Patients receiving EN (n = 240)	p
Age, years, median [IQR]	62.0 [22.0]	70.5 [20.0]	**<0.001**
Sex, female, n (%)	235 (48.7%)	115 (47.9%)	0.85
BMI, kg/m², median [IQR]	22.9 [6.4]	22.9 [7.5]	0.49
Presence of ≥1 comorbidity,n (%)	302 (62.5%)	183 (76.6)	**<0.001**
Hypernatremia	9 (1.9)	7 (2.9)	0.42
Hypokalemia	3 (0.6)	4 (1.7)	0.17
Hyperglycemia	1 (0.2)	3 (1.3)	0.10
Hypophosphatemia	49 (10.1)	29 (12.1)	0.44

The variables are presented as number (percentage), median [IQR] or mean ± SD values. Bold indicates p < 0.05.
EN: Enteral nutrition, PN: Parenteral nutrition, IQR: Interquartile range, BMI: Body mass index, SD: Standard deviation.

Table 3. Comparisons of the metabolic complications between patients achieving <70% and ≥70% of the target in the EN and PN groups.

	Patients receiving EN (n = 280)			Patients receiving PN (n = 483)		
	Achieving <70% (n = 130)	Achieving ≥70% (n = 110)	p-value	Achieving <70% (n = 302)	Achieving ≥70% (n = 181)	p-value
Hypernatremia	4 (3.1)	3 (2.7)	1.00	7(2.3)	2 (1.1)	0.34
Hypokalemia	2(1.5)	2(1.8)	1.00	1(0.3)	2 (1.1)	0.55
Hyperglycemia	2 (1.5)	1 (0.9)	1.00	1 (0.3)	0 (0)	1.00
Hypophosphatemia	10 (7.7)	19 (17.3)	**0.023**	28 (9.3)	21 (11.6)	0.41

The variables are presented as number (percentage), median [IQR] or mean ± SD valuess. Bold indicates p < 0.05.
EN: Enteral nutrition, PN: Parenteral nutrition, IQR: Interquartile range, SD: Standard deviation.

the energy goals in the current study was associated with an increased risk of RS.

Age has also been identified as a contributing factor to the development of RS, with incidence rising with age. A systematic review has shown that RS can occur in older adults regardless of the rate of refeeding (20). In the current study, older adults (≥60 years) were less likely to achieve nutritional targets compared with younger adults. This finding was consistent with age-related physiological barriers such as the anorexia of aging, reduced appetite, early satiety and slower gastrointestinal motility (25). These changes limit caloric and protein intake, making it more difficult for older adults to meet therapeutic goals. Advanced age also increases vulnerability to RS due to diminished physiological reserves and a high prevalence of chronic MN. Therefore, clinicians must initiate NT cautiously with slower caloric advancement and close electrolyte monitoring, although reaching the full target can be further delayed (26). Although no significant difference in RS incidence was observed between the geriatric and non-geriatric populations in the current study, ageing remains a substantial barrier to achieving nutritional goals because of impaired intake capacity and the need for conservative refeeding strategies.

A low BMI and the presence of COPD were identified as additional risk factors for RS. Consistent with many previous studies and various guidelines, these findings also showed that lower BMI is a risk factor for RS (15,27). In a study investigating the impact of COPD on RS risk, malnourished patients with COPD who received hypocaloric nutrition were found to have a lower risk of RS and more favourable outcomes (28). In COPD patients, the combination of chronic under-nutrition, systemic inflammation, metabolic alterations, and electrolyte depletion makes them particularly susceptible to RS. Hypoxia contributes to altered glucose and lipid metabolism, and metabolic adaptations during starvation exacerbate electrolyte depletion. Rapid reintroduction of nutrition can lead to significant metabolic shifts when insulin is reactivated (28,29). Many COPD patients,

Table 4. Comparisons of the clinical characteristics and metabolic features between geriatric and non-geriatric patients (adults aged ≥60 and <60 years).

	Geriatric group (n = 439)	Non-geriatric group) (n = 284)	p
Age, years, median [IQR]*	72.0 [12.0]	46.0 [20.0]	**<0.001**
Sex, male, n (%)	234 (53.3%)	139 (48.9%)	0.252
BMI, kg/m², median [IQR]	23.66 [7.03]	21.48 [6.92]	**<0.001**
Nutrition type, enteral, n (%)	177 (40.3%)	63 (22.2%)	**<0.001**
Achieving ≥70% of the target	159 (36.2%)	132 (46.5%)	**0.006**
Presence of ≥1 comorbidity, n (%)	345 (78.8%)	140 (49.3%)	**<0.001**
Diabetes mellitus, n (%)	122 (27.8%)	47 (16.5%)	**0.001**
Hypertension	196 (44.6%)	38 (13.4%)	**<0.001**
Coronary artery disease, n (%)	89 (20.3%)	8 (2.8%)	**<0.001**
Heart failure, n (%)	39 (8.9%)	5 (1.8%)	**<0.001**
Chronic renal disease, n (%)	33 (7.5%)	6 (2.1%)	**0.002**
COPD, n (%)	45 (10.3%)	6 (2.1%)	**<0.001**
Hypophosphatemia	50 (11.4%)	28 (9.9%)	0.517

*Age is presented as median [Q1-Q3] for the geriatric group (72 [67-79] years) and the non-geriatric group (48 [38-55] years). Bold indicates $p < 0.05$.
BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, IQR: Interquartile range.

Table 5. The binary regression analysis results of risk factors for Refeeding syndrome

	Odds ratio	95% CI	p
Sex, female	0.872	0.501-1.518	0.629
BMI	0.933	0.882-0.987	**0.015**
Follow-up period, days	0.990	0.973-1.006	0.223
COPD	2.854	1.181-6.898	**0.020**
Age, years	1.006	0.989-1.023	0.513
Type of nutrition therapy, enteral	0.885	0.482-1.623	0.692
Achieving ≥70% of the target	1.867	1.051-3.316	**0.033**

Bold indicates $p < 0.05$.
BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CI: Confidence interval.

particularly those in advanced stages, have reduced caloric intake for extended periods because of dyspnea while eating, fatigue, or depression; this meets one of the key RS risk criteria (i.e., little or no nutritional intake for more than 10 days). This supports the hypothesis that NT in COPD patients carries a higher risk of RS and should be managed carefully. As these patients are at high-risk of MN due to their underlying disease and altered catabolism, NT should be tailored to mitigate catabolic effects and prevent overfeeding (30).

According to the current study findings, RS in the EN group was more frequently observed among patients who achieved ≥70% of their nutritional target, whereas no significant difference was found in the PN group. RS has been reported in EN at rates more than two-fold higher than in PN (31). Regardless of the method used to estimate calorie targets (e.g., Harris-Benedict equation, kcal/kg, etc.), the importance of avoiding overfeeding has been emphasised (31). Incretins are hormones secreted from the gut in response to food intake that enhance insulin secretion from the pancreas (32). During EN, increased incretin activity may amplify the insulin response, resulting in accelerated electrolyte shifts and an increased risk of RS. The incretin effect, first described in the 1960s, refers to the greater insulin secretion observed when glucose is administered orally rather than intravenously. This phenomenon is attributed to the production of enteral hormones such as gastric inhibitory polypeptide and glucagon-like peptide-1, which enhance insulin secretion from pancreatic β-cells (33). Therefore, careful adjustment of the glycemic content and feeding rate is especially important in EN (34). Further research is needed to clarify the clinical significance and optimal management of NT via enteral or parenteral routes. It is important for clinicians to assess the risk of RS and take appropriate preventive measures.

One recommended practices is to initiate energy intake at a maximum of 50% of the planned target (500-1000 kcal/day). Starting at 20 kcal/hour on the first day, energy intake should be gradually increased over the course of a week until full nutritional requirements are met and the patient is metabolically stable (10). In addition, the American Society for Parenteral and EN (ASPEN) recommends starting NT at a reduced caloric intake (approximately 10 kcal/kg/day) for patients at high-risk of RS, with careful monitoring and gradual increases over several days (4). NICE recommends providing no more than 50% of the estimated target energy and protein requirements during the first two days of feeding in seriously ill or injured individuals receiving tube feeding or PN (22). It is known that critically ill patients are more frequently exposed to overnutrition than to undernutrition (35). In a study comparing restricted and continuous standard calorie intake during the management of RS in critically ill adults, a protocol for restricted calorie intake was shown to be a suitable option in terms of avoiding RS (12). Another study conducted on intensive care unit (ICU) patients reported that higher mortality was observed in those receiving high caloric intake (≥66%), while moderate caloric intake (33-65% of the target) was associated with the most favourable outcomes (36). Although various guidelines have been published, there is no definitive evidence identifying a specific feeding rate and target calories, which would reliably prevent the development of RS (4,10,37). While no significant association with RS was found among ICU patients in the current study, ≥70% of the energy target was identified as a risk threshold in the overall population. Although current nutritional guidelines consistently recommend initiating energy delivery at a reduced rate and gradually increasing to meet target requirements, healthcare professionals seem to lack awareness regarding the risks associated with RS. The most important preventive or protective measures are adequate assessment of high-risk patients and proper treatment planning and follow-up. It is vital that the refeeding protocol be adapted to suit each patient's clinical condition, rather than simply focusing on their calorie target. Thus, it is imperative to implement a controlled hypocaloric nutritional intake strategy in order to mitigate the risk of RS (38). This approach is essential and must be administered by a multidisciplinary team of healthcare professionals.

Study Limitations

The majority of previous studies have incorporated hypophosphatemia, either as a defined cutoff or as a relative decrease from baseline, as a component of their definitions (the range varied from phosphate <1 mmol/L (below the normal range) to <0.32 mmol/L, or as a decrease from baseline >30% or >0.16 mmol/L). However, relying exclusively on hypophosphatemia to identify risk may lead to misclassification, as there are many other potential causes of reduced serum phosphate levels. Although the ASPEN consensus recommendations propose a broader definition of RS based on proportional decreases in serum phosphorus, potassium, and/or magnesium levels following nutritional replenishment, there is currently no universally accepted diagnostic definition of RS (5,39). Notably, ESPEN guidelines do not provide specific diagnostic cutoffs or formal diagnostic criteria for RS. Instead, hypophosphatemia has consistently been described as the hallmark biochemical abnormality of the syndrome and has been widely used in observational studies and systematic reviews as an operational definition. Furthermore, a systematic review demonstrated substantial heterogeneity among published definitions, with most studies incorporating hypophosphatemia either as an absolute threshold or as a relative decline from baseline (5). Given the retrospective design of the currrent study and the limited availability of all ASPEN diagnostic components, hypophosphatemia (serum phosphorus <2.5 mg/dL) was used as a pragmatic surrogate marker for RS (8). An important limitation of this study was that the retrospective design prevented a comprehensive assessment of several potential confounding

factors associated with RS, including malignancy burden, infection or sepsis status, ICU-related interventions, baseline serum phosphate levels, and the use of corticosteroids, alcohol, antacids, or chemotherapeutic agents. Therefore, residual confounding cannot be excluded. Another limitation of the study was that, had it been designed prospectively, the incidence of RS over time could have been evaluated more objectively, and there would have been an opportunity to observe RS that patients developed during the follow-up period. Because the study was retrospective, detailed data on specific nutritional formulations, macronutrient composition, and stepwise caloric advancement protocols were not systematically recorded in patient files, since EN and PN decisions were made at the discretion of the treating clinical team in accordance with current guidelines. The effect of feeding rate on RS development could not be evaluated separately. Nevertheless, all RS cases were assessed within the first 5 days after the initiation of NT, a period recognized as the highest-risk window for RS.

One of the strengths of this study was the large sample size and the use of electronic medical records for data collection, which together ensured data accuracy and reliability. The onset of RS was reported while electrolyte concentrations were monitored daily during the follow-up period. This allowed RS to be detected as soon as it developed. In many studies, patients receiving EN or PN have been analyzed separately. However, the inclusion of both groups in the current study's patient population allowed a more objective and comprehensive comparison. The use of the NRS in all patients was another strength of this study. Rather than using BMI, weight loss, or dietary intake history in isolation, combining these individual variables into a single NRS score provides a practical and accessible tool for identifying patients at risk of RS due to MN.

Conclusion

The main finding of this study was that the risk of RS was higher in patients receiving NT with higher energy targets (≥70% of the goal). RS was seen to be significantly associated with achieving ≥70% of the target independently of age, female gender, BMI, COPD, length of hospital stay and type of NT. Given that the risk appears particularly relevant in EN, further large-sample studies are needed to define optimal initiation and progression protocols specific to enteral NT routes. While achieving caloric goals is fundamental in NT, a cautious and personalized approach is required to avoid RS. Awareness, prevention, and vigilant monitoring can allow for safe advancement in NT without compromising patient safety. Further prospective studies are needed to validate these findings and establish optimal feeding strategies to prevent the development of RS.

Ethics

Ethics Committee Approval: The study protocol complied with the principles of the Helsinki Declaration. The study was approved by Hacettepe University Health Sciences Research Ethics Committee (approval no: 2025/11-35, date: 20.05.2025).

Informed Consent: As this was a retrospective study, no written informed consent was obtained from participants.

Footnotes

Authorship Contributions

Concept: E.S.A., P.K., Design: E.S.A., P.K., Data Collection or Processing: E.S.A., P.K., Analysis or Interpretation: E.S.A., P.K., Literature Search: E.S.A., P.K., Writing: E.S.A., P.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH

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Calf Circumference and Short-Term Prognosis in Older Patients Receiving Palliative Care

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Abstract

Objective: To evaluate the association between calf circumference and short-term prognosis in older adults receiving palliative care and to investigate the independent prognostic value of calf circumference.

Materials and Methods: This retrospective, observational study included older adult patients who were admitted to a palliative care unit from January 2024 to December 2025. Demographic characteristics, comorbidities, laboratory parameters, and calf circumference measurements were extracted from hospital records. The primary outcome was mortality within three months. Survivors and non-survivors were compared using appropriate statistical tests. Variables showing a p-value below 0.10 in the univariate analysis were incorporated into a multivariable logistic regression model. Receiver operating characteristic (ROC) analysis was conducted to evaluate the discriminative ability of calf circumference and to identify its optimal cut-off value for predicting mortality.

Results: One hundred forty seven patients (median age: 79 years) were included; 72 (49.0%) died within 3 months. Non-survivors were older and had significantly lower calf circumference, higher Charlson Comorbidity Index scores, elevated C-reactive protein concentrations, and reduced albumin levels. In multivariable logistic regression, calf circumference remained independently associated with mortality: each 1-cm increase was associated with a 15.5% reduction in mortality risk. ROC analysis showed an area under the curve of 0.707. A calf circumference cut-off of ≤34 cm yielded 48.6% sensitivity and 86.6% specificity for predicting mortality.

Conclusion: Calf circumference is independently associated with 3-month mortality in geriatric patients receiving palliative care. As a simple, inexpensive measurement that is applicable at the bedside, it may provide valuable prognostic information and support risk stratification in this vulnerable population.

Keywords: Calf circumference, palliative care, mortality, older adults, prognostic factor

Introduction

As life expectancy increases worldwide, older population is rapidly growing, and consequently, chronic diseases, multimorbidity, and functional dependence are becoming more common (1). Older patients, especially those receiving palliative care, are at high-risk for adverse outcomes due to their high comorbidity burden, frailty, immobilization, and malnutrition (2). Identifying readily applicable prognostic indicators of short-term mortality in this group is crucial for guiding clinical decision-making and improving patient management.

Malnutrition and sarcopenia are significant determinants of mortality and morbidity in elderly individuals (3). Sarcopenia, defined as a progressive decrease in muscle mass and muscle function due to aging, is associated with loss of physical performance, falls, hospitalizations, and an increased risk of death. Under palliative care, muscle loss becomes more pronounced due to chronic inflammation, malnutrition, immobilization, and comorbidities (4).Therefore, accurate assessment of skeletal muscle mass may provide valuable prognostic information and contribute to mortality risk stratification in older adults receiving palliative care.

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However, assessing muscle mass in palliative care patients presents several challenges. A significant number of these patients are bedridden and have severe functional limitations and multiple comorbidities. Therefore, assessment tools, including dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA) handgrip strength testing or walking speed measurement, are often not feasible due to the final stages of their illness and to their bedridden status (4,5). Clinical practice requires readily applicable, cost-effective, and objective measurements, especially at the bedside.

Calf circumference is a simple and reliable anthropometric measurement used to assess muscle mass and nutritional status in older adults (6,7). Calf circumference has been reported to correlate with appendicular muscle mass and can be used to screen for sarcopenia (8,9). Furthermore, low calf circumference is associated with frailty, functional dependence, hospitalization, and mortality (10,11). Because it is rapid, noninvasive, and suitable for bedside use, calf circumference is a practical assessment tool, particularly for patients with palliative care needs.

However, studies investigating the prognostic value of calf circumference in older patients receiving palliative care are limited. The relationship between calf circumference and short-term mortality, particularly in older adults receiving palliative care, remains insufficiently elucidated. This study aimed to evaluate the association between calf circumference and short-term prognosis and mortality among patients aged ≥60 years who were followed in a palliative care service.

Materials and Methods

Ethical approval was obtained from the Gazi University Ethics Committee (approval no: 2026-1008, date: 04.06.2026), and the study was conducted in accordance with the Declaration of Helsinki. Given the retrospective nature of the study, informed consent was waived.

Study Design and Population

This retrospective observational study was carried out in the palliative care unit of a secondary-level hospital and assessed patients admitted between January 2024 and December 2025. Patients admitted to the palliative care department were primarily those with advanced chronic illnesses requiring supportive care, including severe sequelae of cerebrovascular disease, end-stage dementia, and advanced malignancies. Of the 189 patients, those under 60 years of age and those with missing calf circumference measurements or incomplete 3-month outcome data were excluded. In addition, patients with lower-limb amputation and severe peripheral edema were excluded to avoid bias in calf circumference assessment, resulting in a total of 147 patients.

Data Collection

Demographic data, clinical characteristics, comorbidity burden, and laboratory parameters were extracted from hospital records. Charlson Comorbidity Index (CCI) was calculated to quantify the comorbidity burden (12). Laboratory variables included hemoglobin, mean corpuscular volume (MCV), alanine aminotransferase (ALT), aspartate aminotransferase, blood urea nitrogen (BUN), creatinine, C-reactive protein (CRP), albumin, neutrophil and lymphocyte counts.

Calf circumference was assessed and expressed in centimeters as a marker of nutritional status and muscle mass. Calf circumference was measured at the point of maximum calf girth using a nonelastic tape measure while the patient was seated with the knee flexed to 90°. Measurements were performed in the supine position when sitting was not feasible. The main outcome measure was 3-month mortality, defined by survival status within 90 days following hospitalization (survivor vs. non-survivor). Mortality data were obtained from the national death notification system and hospital electronic records.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as counts and percentages. Normality of continuous variables was assessed using the Kolmogorov-Smirnov test and histogram inspection. Normally distributed data are expressed as mean ± standard deviation, and non-normally distributed data as median (minimum-maximum). Student's t-test and the Mann-Whitney U test were used for parametric and non-parametric comparisons, respectively. The chi-square test was used for categorical variables. A p-value <0.05 was considered statistically significant.

Binary logistic regression analysis was performed for variables with $p < 0.10$ in univariate analyses to identify factors independently associated with mortality. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Multicollinearity was assessed using the variance inflation factor and correlation analysis. Albumin was not included in the multivariable model because both albumin and calf circumference reflect nutritional status, and including highly correlated nutritional markers in a relatively small sample size could result in model instability and redundancy. Similarly, among the remaining variables that were significant in the univariate analyses, only those considered both most clinically relevant and independently contributing to the multivariable model were retained to avoid overfitting and to preserve model stability given the relatively small cohort. Model fit was evaluated using the Omnibus test of model coefficients, Nagelkerke R^2, and the Hosmer-Lemeshow goodness-of-fit test. A p-value <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was conducted

using MedCalc software to evaluate the discriminative ability. The optimal cut-off value was determined using the Youden index.

Results

A total of 147 patients (60-98 years) were included. Of these, 75 (51.0%) were survivors, and 72 (49.0%) were non-survivors. Regarding the primary indications for admission to the palliative care unit, 69 patients (46.9%) had severe sequelae of cerebrovascular disease, 44 patients (29.9%) had end-stage dementia, and 16 patients (10.9%) had advanced malignancy. The remaining 18 patients (12.2%) were admitted for other advanced chronic diseases, such as end-stage organ failure and neurodegenerative diseases.

Non-survivors were significantly older than survivors ($p < 0.001$). Calf circumference was significantly lower in non-survivors ($p < 0.001$). The CCI was higher in non-survivors ($p = 0.020$). CRP levels were significantly higher in non-survivors ($p < 0.001$), whereas albumin levels were significantly lower ($p = 0.035$). Creatinine, ALT, neutrophil count, and lymphocyte count also differed significantly between groups, whereas length of hospital stay, hemoglobin, MCV, and AST did not differ significantly between groups (Table 1).

In the unadjusted analysis, calf circumference was significantly associated with mortality. Calf circumference remained independently associated with mortality in the multivariable logistic regression model. For each 1-cm increase in calf circumference, the odds of mortality decreased by 15.5% (OR = 0.845, 95% CI: 0.762-0.937, $p < 0.001$). Higher CRP levels were independently associated with increased mortality risk ($p = 0.005$). Age, CCI, and BUN were not significant predictors in the adjusted model (Table 2). The protective effect of calf circumference remained robust following adjustment for age, comorbidity burden, inflammatory markers, and renal function.

ROC curve analysis demonstrated that calf circumference had a moderate ability to predict mortality (area under the curve =0.707). The optimal cut-off point determined by the Youden Index was ≤34 cm, with a sensitivity of 48.6% and a specificity of 86.7%. Positive and negative predictive values were 77.8% and 63.7%, respectively (Table 3), and the ROC curve was presented in Figure 1.

Discussion

This study demonstrates that calf circumference is independently associated with 3-month mortality among elderly patients receiving palliative care. Patients who died within three months had significantly lower calf circumferences than survivors, and each 1-cm increase in calf circumference was associated with a 15.5% decrease in mortality risk after adjusting for age, comorbidity burden, inflammatory status, and renal function. Moreover, a calf circumference threshold of ≤34 cm had high specificity in identifying patients at increased risk of short-term mortality. These findings suggest that calf circumference may serve as a simple and clinically useful adjunctive prognostic marker for risk stratification in older adults receiving palliative care, rather than as a standalone predictor of mortality.

Table 1. Demographics and baseline characteristics of the patients.

Parameters	Total (n = 147)	Survivors (n = 75)	Non-survivors (n = 72)	p-value
Age, years	79 (60-98)	76 (60-95)	83 (66-98)	**<0.001**
Sex, female, n (%)	77 (52.4%)	33 (44.4%)	44 (61.1%)	0.070
Length of stay, day	14 (1-288)	16 (1-288)	13 (1-159)	0.778
Calf circumference, cm	36 (22-44)	37 (27-43)	35 (22-44)	**<0.001**
CCI	5 (1-10)	5 (1-9)	5 (2-10)	**0.020**
Hb (g/dL)	11.2 (6.3-16.5)	11.7 (7.2-16.5)	11.1 (6.3-15.5)	0.260
MCV	88 (59.6-108.2)	89.5 (65.2-108.2)	88.4 (59.6-107.5)	0.614
ALT (U/L)	15 (2-126)	17 (2-126)	12 (2-94)	**0.002**
AST (U/L)	22 (5-186)	24 (9-186)	21 (5-109)	0.502
BUN (mg/dL)	22.4 (6.5-99.5)	19.6 (6.5-99.5)	24 (6.5-98.4)	**0.050**
Cr (mg/dL)	0.8 (0.15-4.9)	0.7 (0.1-4.9)	0.9 (0.3-4.5)	**0.031**
CRP (mg/L)	35.5 (0.2-259)	13.6 (0.2-167)	54 (1.3-259.6)	**<0.001**
Alb (g/L)	2.9 (1.5-4.1)	3.0 (1.4-4.2)	2.8 (1.6-4)	**0.035**
Neut, 10^9/L	6.5 (2.1-18.2)	5.8 (2.1-16.4)	7.2 (2.7-18.2)	**0.007**
Lymph, 10^9/L	1.4 (0.3-5.2)	1.5 (0.5-5.2)	1.2 (0.3-4.4)	**0.026**

Data were presented as numbers and percentages for categorical variables, mean ± SD for normally distributed continuous variables, and median (min-max) for non-normally distributed continuous variables.
SD: Standard deviation, Hb: Hemoglobin, MCV: Mean corpuscular volume, CRP: C-reactive protein, Alb: Albumin, BUN: Blood urea nitrogen, Cr: Creatinine ratio, AST: Aspartate aminotransferase, ALT: Alanine transaminase, CCI: Charlson Comorbidity Index.

Table 2. Multivariate analysis of the calf circumference on mortality.

Models	Independent variables	OR	95% CI	p-value
Model 1 (unadjusted)	Calf circumference	0.815	0.741-0.898	**<0.001**
Model 2	Calf circumference	0.845	0.762-0.937	**<0.001**
	CCI	1.037	0.826-1.301	0.757
	Age	1.048	0.996-1.103	0.072
	CRP	1.012	1.003-1.020	**0.005**
	BUN	0.997	0.975-1.019	0.791

Binary logistic regression analysis using variables with $p < 0.10$ in univariate analyses were entered into a multivariable model to identify factors independently associated with mortality. Multicollinearity was assessed using the variance inflation factor (VIF) values and correlation analysis. All VIF values ranged between 1.12 and 1.33, indicating no evidence of multicollinearity. The Omnibus test of model coefficients was significant ($\chi^2 = 127.835$, $p < 0.001$), demonstrating that the model was statistically meaningful. The Nagelkerke R^2 was 0.311, indicating that the model explained approximately 31.1% of the variance in mortality. The Hosmer-Lemeshow goodness-of-fit test indicated good model calibration ($\chi^2 = 8.998$, $p = 0.342$). Variables entered into the model included calf circumference, age, CCI, CRP, and BUN.
OR: Odds ratio; CI: Confidence interval, BUN: Blood urea nitrogen, Cr: Creatinine, CCI: Charlson Comorbidity Index, CRP: C-reactive protein.

Table 3. ROC curve of parameters in the prediction of mortality in older palliative care patients.

Parameters	Cut-off	AUC	SE	p	95% CI	Sensitivity	Specificity	+PV	-PV
Calf circumference	≤34	0.707	0.042	<0.001	0.626-0.779	48.6%	86.6%	77.8%	63.7%

AUC: Area under the curve, SE: Standard error, CI: Confidence interval, PV: Predictive value.

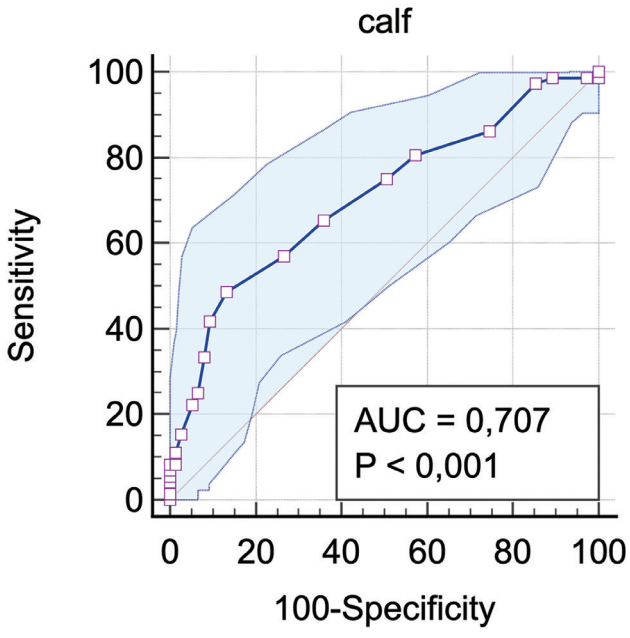

Figure 1. ROC curve analysis of calf circumference for predicting mortality in older palliative care patients (AUC = 0.707, 95% CI: 0.626-0.779, $p < 0.001$).

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval.

The prognostic significance of calf circumference is biologically plausible because it reflects both skeletal muscle mass and nutritional reserves (13). Older adults receiving palliative care are particularly vulnerable to sarcopenia due to chronic inflammation, reduced oral intake, immobilization, multimorbidity, and catabolic processes associated with advanced disease (14).

Our results are consistent with those of previous studies that demonstrate a relationship between calf circumference, a surrogate marker of muscle mass, and survival (15). In a cohort of advanced cancer patients receiving palliative care, it was reported that anthropometric measurements, including calf circumference, were closely associated with nutritional status and survival outcomes (4). The authors emphasized that simple bedside measures may offer valuable prognostic information when more sophisticated assessments of body composition are not feasible. Similar to their findings, our results support the usefulness of calf circumference as a readily available indicator of poor prognosis in patients receiving palliative care. More recently, Back et al. (16) investigated patients receiving home enteral nutrition and found that lower calf circumference was associated with higher mortality risk. Their results highlight the importance of preserving muscle mass and nutritional status in clinically vulnerable populations.

In a cohort of older adults, calf circumference demonstrated a predictive validity for mortality comparable to that of the Mini Nutritional Assessment and Appendicular Skeletal Muscle Mass Index, and demonstrated superior predictive performance compared with conventional markers such as bosy mass index and serum albumin (17). Moreover, higher calf circumference was independently associated with a lower risk of mortality during follow-up. Although we did not directly compare calf circumference to other sarcopenia or nutritional assessment methods in our study, the observed independent association of lower calf circumference with increased 3-month mortality is consistent with these findings. Taken together, the available evidence suggests that calf circumference may serve as a practical surrogate marker of nutritional and muscle status, particularly in palliative care settings where comprehensive body composition assessments are often difficult to perform.

The optimal cut-off value of ≤34 cm identified in the present study is notably consistent with prior research assessing calf circumference as a predictor of mortality (18). In a previous investigation, a calf circumference threshold of approximately 34.5 cm was recognized as a predictor of mortality among older adults, a finding that aligns closely with our own (18). Furthermore, a recent study corroborated that a lower calf circumference (30.6 cm) is independently associated with increased mortality risk, thereby reinforcing its utility as a prognostic anthropometric marker (17). Conversely, a lower calf circumference cut-off of 33 cm has been proposed for the identification of sarcopenia according to the European Working Group on Sarcopenia in Older People criteria (19). This discrepancy is anticipated, as our cut-off was established to predict short-term mortality rather than to diagnose sarcopenia; therefore, optimal calf circumference thresholds may vary depending on the specific clinical outcome sought. Although the identified cut-off demonstrates high specificity, its relatively low sensitivity suggests that calf circumference alone is insufficient as a screening tool for short-term mortality. Instead, it may be more suitably employed as an adjunct prognostic marker to complement routine clinical assessments and other established prognostic indicators in older adults receiving palliative care.

Inflammation is another important mechanism linking reduced calf circumference to mortality. Consistent with previous literature, CRP was independently associated with mortality in our cohort. Chronic inflammation promotes protein catabolism and accelerates skeletal muscle loss, resulting in sarcopenia and cachexia (20,21). Therefore, the coexistence of elevated inflammatory markers and reduced calf circumference may identify a subgroup of patients with a particularly poor prognosis. Future studies should investigate whether combining anthropometric and inflammatory parameters could improve prognostic accuracy in palliative care settings. CRP remained independently associated with mortality in the adjusted model. This aligns with previous research showing that systemic inflammation significantly influences adverse outcomes in patients in palliative care (22,23).

While age and comorbidity burden were associated with mortality in unadjusted analyses, only calf circumference and CRP remained independently associated after adjustment. This indicates that short-term outcomes among older palliative care patients may depend more on biological reserve and inflammation than on age or on cumulative comorbidities alone. Calf circumference could thus offer valuable clinical insights beyond conventional demographic and disease-related prognostic factors.

Study Limitations

This study is subject to certain limitations. The retrospective design and single-center setting may limit the generalizability of the findings, and the sample size was relatively small. In addition, the study population comprised patients with diverse underlying conditions requiring palliative care, including advanced dementia, cerebrovascular disease, malignancy, and end-stage organ failure. Although this heterogeneity reflects real-world palliative care practice, disease-specific differences may have influenced prognosis and limit the applicability of our findings to individual diagnostic groups. The inclusion of some patients with hemiplegia may have affected calf circumference measurements owing to unilateral muscle atrophy.

Conclusion

Finally, direct measures of muscle mass and function, such as DXA, BIA, handgrip strength, or gait speed, were not available. Because muscle strength and physical performance were not assessed, sarcopenia could not be diagnosed according to contemporary consensus criteria. Therefore, our findings should be interpreted as reflecting the prognostic value of calf circumference rather than the presence of sarcopenia itself. In addition, calf circumference was assessed only at admission, and longitudinal changes in muscle mass during follow-up could not be evaluated.

Calf circumference was independently associated with 3-month mortality among older adults receiving palliative care. As a simple, inexpensive, and bedside-applicable measurement, calf circumference may provide complementary prognostic information and support risk stratification when used alongside routine clinical assessment in this vulnerable population.

Ethics

Ethics Committee Approval: This study was approved by Gazi University Ethics Committee (approval no: 2026-1008, date: 04.06.2026) and conducted in accordance with the Declaration of Helsinki.

Informed Consent: Due to the study's retrospective nature, informed consent was waived.

Footnotes

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ORIGINAL RESEARCH

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The Association Between the Primitive Reflexes and Falls in Older Adults Without Neurodegenerative Disease

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Abstract

Objective: Falls, a major public health concern, may lead to morbidity and mortality among older adults. While the re-emergence of primitive reflexes (PRs) reflects a loss of cortical inhibition and is generally associated with neurodegenerative conditions, the relationship between PRs and falls in older adults without neurodegenerative disease has yet to be investigated in detail. This study aimed to evaluate the association between PRs and falls in older adults without neurodegenerative disease.

Materials and Methods: A retrospective cross-sectional study was conducted involving 668 older adults without neurodegenerative disease. Demographics, comorbidities, medications, and laboratory parameters were obtained from patients' medical records. The presence of specific PRs (palmomental, snout, glabellar, and grasp) and a history of falls in the last 12 months were evaluated in such patients.

Results: Of the 668 participants, 241 (36.1%) reported a history of falls. Each of the palmomental, snout, and glabellar reflexes was more prevalent in the fallers group compared with non-fallers ($p < 0.001$, $p = 0.020$, $p = 0.020$, respectively). In logistic regression, the association between falls and both the palmomental reflex and the glabellar reflex remained significant. [Odds ratio (OR): 1.877, 95% confidence interval (CI): 1.162-3.033, $p = 0.010$ and OR: 2.363, 95% CI: 1.130-4.943, $p = 0.022$].

Conclusion: The palmomental and glabellar reflexes are associated with falls in older adults. Eliciting these simple, non-invasive clinical signs may significantly aid in early fall risk stratification and preventive care.

Keywords: Palmomental reflex, glabellar reflex, snout reflex, grasp reflex, risk factors

Introduction

Falls represent a major public health concern, as well as a geriatric syndrome, with incidence increasing significantly with advancing age (1). Approximately one-third of older adults experience at least one fall per year (2). Falls may not only lead to fractures, prolonged hospital stays, increased healthcare costs, a marked decline in functional independence, and a reduced quality of life (3,4) but are also associated with mortality in the geriatric population (1). Given these life-threatening complications, identifying conditions associated with fall risk is crucial for implementing effective preventive and therapeutic strategies in geriatric care.

Falls among older adults are associated with numerous physiological, behavioral, and environmental factors, as well as age-related changes. Furthermore, a multitude of risk factors are detected for falls, such as a previous history of falls, sarcopenia, balance/gait impairment, polypharmacy, vision impairment, and dementia (5). Additionally, primitive reflexes (PRs), which were inhibited during the first year of life as the cerebral cortex matures and takes control of postural reactions, may re-emerge with advancing age (6,7). The re-emergence of PRs generally suggests a loss of cortical inhibition (7). While isolated reflexes, such as the palmomental reflex (PMR), may occasionally be observed in healthy individuals as a sign of physiological aging, the presence of numerous or strong reflexes—particularly the

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grasp reflex—is significantly associated with advanced dementia and brain pathology (7-11). The re-emergence of these reflexes in conditions of impaired cortical integrity may be suggestive of a decline in the ability to process environmental hazards or maintain balance during complex movements (12), which, in turn, raises the question of whether PRs could be related to falls.

Consequently, this study aimed to investigate the relationship between specific PRs—the palmomental, snout, glabellar, and grasp reflexes—and falls among older adults.

Materials and Methods

Study Design and Participants

This retrospective cross-sectional study was conducted at the geriatrics outpatient clinic. The inclusion criteria were age ≥60 years and availability of complete medical records. Patients with a pre-existing diagnosis of dementia (major neurocognitive disorder according to the diagnostic and statistical manual of mental disorders (13) were excluded. Patients with Parkinson's disease, Parkinson-plus syndromes, a history of stroke, malignancy, or acute illness (e.g., acute cerebrovascular events, sepsis, acute coronary syndrome, or organ failure) were also excluded. The final study population consisted of 668 older adult patients who met these criteria. Ethical approval was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval no: 2025/45-09, date: 29.12.2025). Written informed consent was waived due to the study's retrospective design.

Data Collection

Demographic, clinical, and laboratory data were extracted from patients' medical records. Recorded demographic and clinical variables included age, sex, number of medications, and the presence of specific clinical conditions such as urinary incontinence. Comorbidity burden was quantified using the Charlson Comorbidity Index (CCI) (14). Medication history was reviewed specifically for use of antihypertensives, antidiabetics, antidepressants, and antipsychotics. Routine laboratory parameters, including hemoglobin, vitamin B12, thyroid-stimulating hormone, 25-hydroxyvitamin D levels, and estimated glomerular filtration rate (eGFR), were extracted from the patients' files. A patient was categorized into the "fallers" group if they had a documented history of at least one fall, an individual coming to rest at a level lower than their current position without the application of any external force, within the past 12 months (15).

Assessment of Primitive Reflexes

Stimulation of the thenar eminence was utilized to elicit the PMR, with a positive reaction indicated by the twitching of the ipsilateral mentalis muscle (16). The snout reflex was assessed by tapping the closed lips at the midline; lip puckering or protrusion was considered positive (17). The glabellar reflex was tested by repetitive tapping of the glabella; persistent, non-habituating blinking was accepted as positive (18). The grasp reflex was provoked by stroking the palm, and involuntary finger flexion was recorded as a positive response (17). All primitive reflex examinations were performed by a single senior clinician.

Statistical Analysis

Data analysis was performed using Statistical Package for Social Sciences version 25.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Descriptive statistics are presented as mean ± standard deviation for continuous variables and as percentages (%) for categorical variables. Group comparisons (fallers vs. non-fallers) were conducted using the Independent Samples t-test or the Mann-Whitney U test for continuous variables, depending on their distribution. Categorical variables were compared using the chi-square test. Variables that differed significantly between non-fallers and fallers (age, sex, years of education, CCI, number of medications, hemoglobin, eGFR, antidiabetic and antidepressant use, urinary incontinence, and each of PMR, snout reflex, and glabellar reflex) were included in a model to identify independent predictors of falls. Logistic regression analysis was performed using a stepwise backward selection procedure. Statistical significance was set at $p < 0.05$. Model adequacy and explanatory power for each independent primitive reflex model were evaluated using the Hosmer-Lemeshow goodness-of-fit test, Cox & Snell R^2, and Nagelkerke R^2 statistics.

Results

A total of 668 participants were included in the study. Of these, 427 (63.9%) reported no history of falls, while 241 (36.1%) reported at least one fall.

As shown in Table 1, participants in the fallers group were significantly older (75.85 ± 7.92) than those in the non-fallers group (73.22 ± 7.85; $p < 0.001$). The frequency of female participants was significantly higher among fallers than among non-fallers (76.8% vs. 60.2%, $p < 0.001$). Additionally, the fallers group had significantly fewer years of education compared to the non-fallers group (7.91 ± 4.65 vs. 8.77 ± 4.65; $p = 0.030$). Regarding clinical characteristics, the fallers group had a higher CCI ($p = 0.030$) and a significantly higher number of medications (5.32 ± 3.35 vs. 4.11 ± 3.06, $p < 0.001$). Laboratory parameters showed that fallers had significantly lower hemoglobin ($p < 0.001$) and eGFR ($p = 0.040$) levels. Additionally, the use of antidiabetics ($p = 0.029$) and antidepressants ($p < 0.001$) was significantly more frequent among fallers. The prevalence of urinary incontinence was notably higher in those who fell (57.2% vs. 41.4%, $p < 0.001$). Furthermore, PRs, including the

PMR (31.1% vs. 18.5%, $p < 0.001$), snout reflex (12.8% vs. 7.2%, $p = 0.020$), and glabellar reflex (12.3% vs. 6.9%, $p = 0.020$), were significantly more common in the fallers' group.

To evaluate the independent predictive value of PRs for fall risk, binary logistic regression analyses using a backward elimination approach were conducted. The final model for the PMR, selected at step 6, demonstrated adequate goodness-of-fit (Hosmer-Lemeshow $\chi^2 = 12.022$, $p = 0.150$) and descriptive strength, as indicated by a Cox & Snell R^2 of 0.115 and a Nagelkerke R^2 of 0.150. In this final step, the presence of the PMR remained a statistically significant independent predictor of increased fall risk [odds ratio (OR) = 1.877; 95% confidence interval (CI): 1.162-3.033; $p = 0.010$] (Table 2). Similarly, the model assessing the glabellar reflex completed its estimation at step 8. In the final adjusted model, the glabellar reflex was identified as a significant independent risk factor, and its presence more than doubled the odds of falling (OR = 2.363; 95% CI: 1.130–4.943; $p = 0.022$) (Table 3). Model summary statistics yielded a Cox & Snell R^2 of 0.100 and a Nagelkerke R^2 of 0.138; however, the Hosmer-Lemeshow test indicated a suboptimal overall model fit at this step ($\chi^2 = 18.012$, $p = 0.021$). Conversely, stepwise regression for the snout reflex, which was finalized at step 7, did not identify the reflex as a significant independent predictor. Prior to its exclusion at step 6, the step 5 model demonstrated adequate fit

Table 1. Characteristics of participants according to fall status.

	Non-fallers (n = 427)	Fallers (n = 241)	p**
Age, years*	73.22 ± 7.85	75.85 ± 7.92	**<0.001**
Female sex (%)	60.2	76.8	**<0.001**
Education years*	8.77 ± 4.65	7.91 ± 4.65	**0.030**
Charlson Comorbidity Index*	3.93 ± 1.78	4.18 ± 1.71	**0.030**
Number of medications*	4.11 ± 3.06	5.32 ± 3.35	**<0.001**
Hemoglobin, g/dL*	13.08 ± 1.61	12.36 ± 1.56	**<0.001**
eGFR, mL/min/1.73 m^2*	76.09 ± 17.83	72.71 ± 19.53	**0.040**
Vitamin B12 pg/mL*	379.88 ± 291.02	391.07 ± 295.44	0.797
TSH mIU/L*	2.11 ± 2.34	2.00 ± 3.68	0.338
25-hydroxy vitamin D ng/mL*	23.49 ± 29.68	23.90 ± 14.25	0.163
Antidiabetic use (%)	24.9	32.8	**0.029**
Antihypertensive use (%)	67.1	71.8	0.213
Antidepressant use (%)	24.2	40.7	**<0.001**
Antipsychotic use (%)	4.0	7.5	0.054
Urinary incontinence (%)	41.4	57.2	**<0.001**
Palmomental reflex (%)	18.5	31.1	**<0.001**
Snout reflex (%)	7.2	12.8	**0.020**
Glabellar reflex (%)	6.9	12.3	**0.020**
Grasp reflex (%)	6	9.4	0.104

* Mean ± SD.
**Statistically significant p-values ($p < 0.05$) are shown in bold characters.
eGFR: Estimated glomerular filtration rate, SD: Standard deviation, TSH: Thyroid-stimulating hormone.

Table 2. Adjusted logistic regression model for palmomental reflex and fall risk.

	OR	95% CI	p*
Palmomental reflex	1.877	1.162-3.033	**0.010**
Sex	1.700	1.077-2.686	**0.023**
Hemoglobin	0.837	0.729-0.960	**0.011**
Urinary Incontinence	1.434	0.955-2.152	0.082
Antidepressant usage	1.600	1.033-2.478	**0.035**
Number of medications	1.095	1.024-1.170	**0.008**

*Statistically significant p-values ($p < 0.05$) are shown in bold characters.
Multivariate logistic regression analysis was performed to identify independent predictors of falls (age, female sex, education years, Charlson Comorbidity Index, number of medications, hemoglobin, eGFR, antidiabetic and antidepressant, urinary incontinence and palmomental reflex).
CI: Confidence interval, OR: Odds ratio, eGFR: Estimated glomerular filtration rate.

Table 3. Adjusted logistic regression model for glabellar reflex and fall risk.

	OR	95% CI	p*
Glabellar reflex	2.363	1.130-4.943	**0.022**
Sex	1.862	1.173-2.956	**0.008**
Hemoglobin	0.848	0.737-0.974	**0.020**
Number of medications	1.143	1.069-1.223	**<0.001**

*Statistically significant p-values ($p < 0.05$) are shown in bold characters.
Multivariate logistic regression analysis was performed to identify independent predictors of falls (age, female sex, education years, Charlson Comorbidity Index, number of medications, hemoglobin, eGFR, antidiabetic and antidepressant, urinary incontinence and glabellar reflex).
CI: Confidence interval, OR: Odds ratio, eGFR: Estimated glomerular filtration rate.

(Hosmer-Lemeshow $\chi^2 = 14.146$, $p = 0.078$), with a Cox & Snell R^2 of 0.109 and a Nagelkerke R^2 of 0.150. At this pre-exclusion stage, the adjusted effect of the snout reflex was not statistically significant (OR = 1.578; 95% CI: 0.788-3.160; $p = 0.198$), leading to its subsequent removal from the final equation.

Discussion

This retrospective, cross-sectional study demonstrates that the PMR and the glabellar reflex are associated with falls in older adults without neurodegenerative disease. Accordingly, the re-emergence of these PRs may suggest a subclinical compromise in postural control in this demographic.

Re-emergence of PRs, brainstem-regulated movements, may indicate the onset of neurodegenerative processes and dementia; however, they can also be observed in cognitively healthy individuals, signaling processes beyond cognitive impairment (7). It is widely acknowledged that the frontal regions regulate balance by planning body movements and postural responses, particularly in variable conditions that require conscious movement control (19). Accordingly, a recent study has reported that lesions in the frontal white matter are associated with poorer balance, slower gait speed, and a higher risk of falling (20). Moreover, modifiable lifestyle factors, particularly physical activity, may prevent not only the re-emergence of PRs but also falls (21,22). Among all PRs, of which re-emergence frequency increases with age, the PMR is one of the earliest to appear and the most prevalent, observed even in cognitively intact individuals (23-26). The presence of the PMR may predict the insidious onset of a neurodegenerative process. For example, a positive PMR has been reported to show reduced functional connectivity in frontal regions even without structural atrophy in patients with Alzheimer's disease (AD) (27). Accordingly, in a case-control study, Gabelle et al. (28) suggested that the PMR could be an early clinical sign of AD due to the likely frontal amyloid load at an early stage of the disease. Crucially, this underlying disruption in frontal networks is accompanied by impaired motor control mechanisms, which directly increase the risk of falling (20,25,29). Consistent with this pathophysiological link, Tinetti et al. (30) demonstrated an association between PMR and falls in 336 community-dwelling patients aged 75 years or over. Consistent with these findings, PMR was also the most prevalent PR among patients with falls in our study population. Furthermore, the study demonstrated that PMR and the glabellar reflex could be independent predictors of falls in older individuals. The glabellar reflex, which is considered a frontal release sign reflecting frontal lobe and executive dysfunction, as in the PMR, tends to re-emerge later than PMR and has increased prevalence in dementia and extrapyramidal syndromes (9,31). The frequency is particularly higher than that of the PMR in conditions affecting the extrapyramidal system (32). Considering that the risk of falls is increased in extrapyramidal system disorders, particularly due to postural instability and gait disturbances (33), evidence linking the glabellar reflex to falls is limited, unlike that for the PMR (30).

The study found between falls and the grasp reflex. In regression analysis, the relationship between the snout reflex and falls was no longer statistically significant. While the grasp reflex is the most strongly linked to frontal lobe dysfunction and cognitive decline, the snout reflex is the most commonly observed PR in patients with dementia (7,25). Accordingly, excluding patients diagnosed with dementia from the study may have prevented the examination of the relationship between falls and these reflexes.

To the best of our knowledge, this is one of the first studies to demonstrate that the re-emergence of PRs, PMR and the glabellar reflex, is independently associated with falls in older patients without previously diagnosed neurodegeneration. A major strength of this study is its large sample size and the specific exclusion of patients with pre-existing dementia, Parkinson's disease, Parkinson-plus syndromes, and cerebrovascular disease. Furthermore, our regression model was comprehensively adjusted for significant confounding factors.

Study Limitations

Our study has several limitations. First, its retrospective cross-sectional design precludes establishing a definitive causal relationship between the PRs and falls. Second, the history of falls was obtained from patient recall over the previous 12 months and from medical documentation, both of which inherently carry the risk of recall bias or underreporting. Third, although patients with

dementia and neurodegenerative diseases were excluded, data on other important fall-related variables—such as frailty status, gait speed, balance performance, sarcopenia, and objective cognitive assessments (2,34)—were unavailable in our dataset, as the re-emergence of PRs may partly reflects underlying subclinical frailty or motor impairment. Lastly, the single-center nature of this study may restrict the generalizability of our findings.

Conclusion

This study demonstrated that both the PMR and the glabellar reflex are associated with falls in older adults without neurodegenerative disease. Our findings suggest that these PRs may serve as clinical indicators of compromised executive control of gait and postural stability. Moreover, PR evaluation may be used as a simple, low-cost bedside tool for fall risk stratification in geriatric practice. However, longitudinal studies are needed to further assess the predictive reliability of the presence of PR or its subsequent loss as clinical markers of future fall risk.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval no: 2025/45-09, date: 29.12.2025).

Informed Consent: Written informed consent was waived due to the study's retrospective design.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.S.O., F.S.D., A.T.I., Concept: M.S.O., A.T.I., Design: M.S.O., A.T.I., Data Collection or Processing: M.S.O., Analysis or Interpretation: M.S.O., F.S.D., Literature Search: M.S.O., Writing: M.S.O., F.S.D., A.T.I.

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SYSTEMATIC REVIEW

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The Effects of Gamified Exercise on the Physical Health of Older Women: A Systematic Review

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Abstract

This systematic review aims to determine the effects of gamified exercise on the physical health of older women. A search of PubMed, Scopus, Web of Science, Cochrane, EBSCO, Google Scholar, and TR Dizin databases was conducted between July 1 and August 1 2025. Studies published in 2021 or later that investigated game-based interventions and employed randomised controlled or quasi-experimental designs were included. In line with the inclusion criteria, only studies involving women aged 65 years or older were reviewed, resulting in the inclusion of seven studies in the final analysis. Game-based exercises improved lower-extremity strength, balance, and postural control and reduced signs of fatigue and pre-frailty. Virtual-reality and Wii-based training demonstrated significant functional gains and were safe in older women. No additional benefit was found from transcranial stimulation. Overall, exercise games effectively improved physical and cognitive outcomes. Game-based activities are an effective and motivating approach to improving physical function in older women and may be considered a complementary intervention in geriatric rehabilitation.

Keywords: Older women, game-based exercise, physical function, geriatric rehabilitation

Introduction

The rapid increase in the elderly population worldwide is redefining the priorities of healthcare systems. Women, in particular, constitute a significant proportion of the elderly population due to their longer life expectancy and to biopsychosocial factors (1). Biopsychosocial factors include biological processes such as hormonal changes, loss of muscle and bone mass, and increased prevalence of chronic diseases; psychological factors such as depression, anxiety, loneliness, and loss of motivation; and societal factors such as changes in social roles, social isolation, caregiver burden, and economic dependency (2-4). The combination of these factors accelerates the loss of physical capacity and negatively impacts quality of life in older women (5). Therefore, it is important to develop low-cost, accessible, and comprehensive interventions that support the health of older women.

Game-based activities are increasingly used as innovative interventions to promote physical, cognitive, and psychosocial health among older adults. Physical games (e.g., boccia, movement games), cognitive games (e.g., Jenga, chess, Sudoku, puzzles), and digital games e.g., exergaming, Wii, virtual reality (VR) games] can offer multiple benefits. The literature reports that game-based exercise improves balance, mobility, and physical performance in older people (6-8). However, existing studies tend to focus on the older population as a whole, and little data are available specifically on older women. However, women are a group at particular risk, as they are more likely to experience health problems, require more carers, and live alone in the postmenopausal period (9).

According to the existing literature, no previous systematic review has focused solely on the effects of gamified exercise interventions in older women, highlighting a critical gap in the current evidence base. This systematic review aims to develop

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evidence-based practice by demonstrating the effectiveness of game-based interventions for improving balance, mobility, and physical performance in older women.

Materials and Methods

Establishment of the Problem

The seven studies included in this systematic review were selected based on the following PICOS criteria: Population (P): women aged 60 years or older. Intervention (I): Game-based activities such as physical games (digital games, exergaming, Wii, VR-based games). Comparison (C): Individuals who received no intervention or participated in different activities (e.g., standard exercise, educational programmes, or passive activities). Outcomes (O): Physical function, mobility, balance, walking, and physical performance. Study design (S): Randomised controlled trials published in English and Turkish in 2021 and later.

Evidence Sources and Retrieval Strategies

For this systematic review, a literature search was conducted between July 1 and August 1, 2025. To retrieve international publications, the keywords "game and older women/game and elderly women", "Nintendo Wii", "Nintendo Switch", "video game," "exergame", "physical function", "mobility", "balance", "gait", "motor function", and "physical performance" were used. The databases searched included Web of Science, Scopus, PubMed, Cochrane, and EBSCO (Medline, CINAHL, PsycINFO). Additionally, Google Scholar and the TR Dizin database were searched to identify studies published in Türkiye.

Study Inclusion and Exclusion Criteria

The inclusion criteria for this systematic review were: participants were exclusively women aged 60 years or older; the intervention included game-based activities (digital games); the comparison group received no intervention or participated in another activity; at least one physical health indicator (such as mobility, balance, walking, muscle strength) was assessed as an outcome; the research design was randomised, controlled, or quasi-experimental; and the study was published in 2021 or later and in English or Turkish. The exclusion criteria were as follows: studies that consisted only of men or in which data on women were not reported separately; non-game-based interventions; qualitative studies; case reports; observational studies; reviews; conference abstracts; editorial articles; publications before 2021 or written in languages other than English and Turkish; and publications for which the full text could not be accessed.

Data Extraction

The researchers developed a standard data extraction tool for data collection, which was used in this study. This tool was designed to collect basic information about the studies. It includes the author(s)' name(s) and year of publication, the study location and duration, the research design, sample size, demographic characteristics of the groups, the type and method of the game-based intervention applied, and the main findings.

Results

A total of 3,952 data records were identified through database searches. Of these, 1,617 were duplicate records, 1,429 were categorised as unsuitable by automated tools, and 625 were excluded for other reasons. The remaining 281 records were screened on the basis of titles and abstracts, resulting in the exclusion of 225 records that did not meet the eligibility criteria. Fifty-six full-text articles were screened for eligibility; 49 were excluded (including descriptive studies, protocols, case reports, and qualitative studies). Ultimately, seven studies were included in this review (Figure 1).

Working Characteristics

Table 1 summarises the methodologies of the included studies. All studies were conducted among community-dwelling elderly women, and interventions were implemented in various clinical settings. Intervention durations ranged from 4 to 12 weeks, with sessions planned at a frequency of 2–3 times per week. The gamified exercise systems used included Nintendo Wii Fit Plus, Xbox Kinect, Beat Saber, Audioshield, immersive VR headsets, and applications combined with transcranial direct current stimulation (tDCS).

Control groups usually participated in conventional training programmes (proprioceptive exercises, home exercises, kinesiotherapy), whereas in some studies, only exergaming groups were included for comparison. Overall, studies have shown that exergaming applications can have positive effects on balance, postural control, physical function, and muscle strength in older women, but some studies have found that they are not superior to conventional exercises and instead show similar effects.

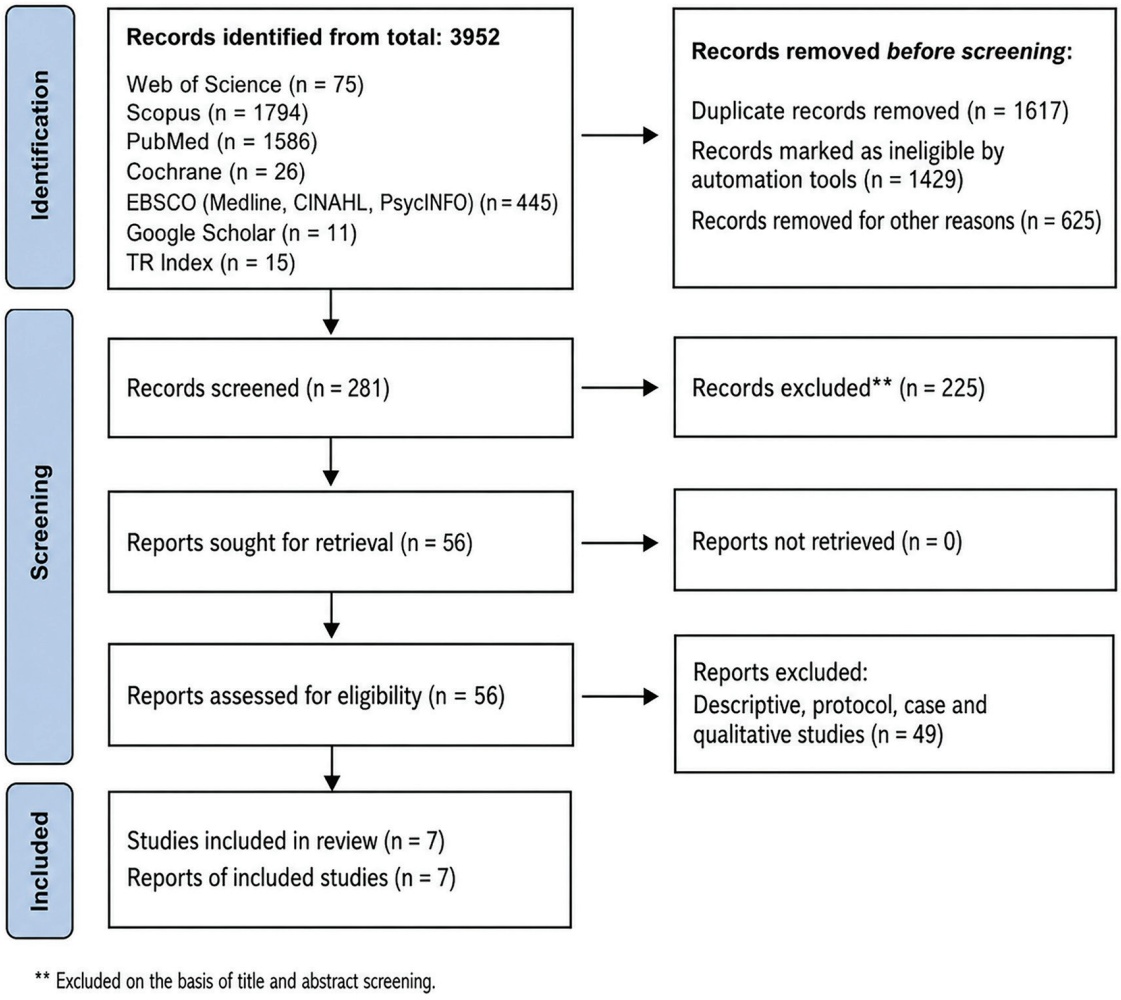

Figure 1. PRISMA flow diagram (10).

Table 1. Characteristics of the included studies.

Author (year) / country	Study year	Intervention characteristics	Sample size	Mean age	Measurement tool/ diagnostic test	Results / key findings
Filho et al. (11) (2022), Brazil	2017–2018	Exercise games (Nintendo Wii Fit Plus, resistance and balance exercises, twice a week, 12 weeks) + protein or isocaloric support	90 women	PTG: 71.2 years PSG: 73.1 years PTPSG: 71.7 years PTISG: 69.7 years CG: 70.4 years	Knee strength tests, five-time chair rise, timed up and go (TUG), gait speed, handgrip, ultrasound, fried frailty	Exercise games with protein supplementation increased lower extremity strength, reduced fatigue, and reversed pre-frailty status in some participants; improvements were significant within groups but not between groups.
Campo-Prieto et al. (12) (2022), Spain	2022	Immersive virtual reality exercise (10 weeks, three days a week, 6-minute sessions)	12 women	EG: 91.67 years CG: 90.83 years	Tinetti balance and walk test, TUG, usability scale	The virtual reality group significantly improved balance, gait, and total Tinetti scores. TUG scores were maintained. It was found to be safe and applicable in non-generative individuals.
Henrique et al. (13) (2023), Brazil	2023	Kinesiotherapy + exercise game vs. kinesiotherapy alone; 6 weeks, 2 days/week	22 women	EG: 64.3 years CG: 63.8 years	Brain-derived neurotrophic factor, interleukins, tumor necrosis factor, histone acetylation, Montreal cognitive assessment, cognitive tests	Improvements in cognitive performance, brain-derived neurotrophic factors, histone acetylation, and inflammation profiles were observed in both groups.

Table 1. Continued

Author (year) / country	Study year	Intervention characteristics	Sample size	Mean age	Measurement tool/ diagnostic test	Results / key findings
Mascarenhas et al. (14) (2023), Brazil	2023	Conventional proprioceptive exercise vs. Xbox Kinect exercise game vs. control; 8 weeks, 3 days/week	50 women	60–79 years (not mean)	Monofilament test	Both intervention groups increased plantar sensory sensitivity, with significant improvements compared to the control group. No difference was found between the groups.
Yilmaz and Kösehasanoğulları (15) (2024), Türkiye	2022	Wii Fit balance games vs. home exercise; 3 days/ week, 12 weeks	60 women	WEG: 67 years HEG: 68 years	TUG, Berg balance scale (BBS), falls efficacy scale (FES)	TUG, BBS, and FES improved in both groups. The Wii group showed greater improvement on the BBS. Exergaming was found to be superior to home exercise in women with osteoporosis.
Yalfani et al. (16) (2024), Iran	2021	Virtual reality-based exercises (bowling, boxing, tennis, skiing, Beat Saber, Audioshield, etc.; 3 days/week, 30 minutes, 8 weeks)	27 women	VRTG: 68.25 years CG: 67.08 years	Plantar pressure analysis, 30-second chair stand test, TUG	Virtual reality training reduced swaying in all directions and improved 30-second chair rise time, TUG performance, postural control, and overall physical function in older adults.
Corrêa et al. (17) (2024), Brazil	2023	Wii Fit balance games + transcranial direct current stimulation (anodal vs. sham) vs. game only; 4 weeks	57 women	AG: 70 SG: 69 CG: 69	Mini balance evaluation systems test	Mini balance assessment test scores improved in all groups; transcranial direct current stimulation provided no additional benefit, indicating that play training alone was effective.

PTG: Physical training using exergames, PSG: Protein supplementation, PTPSG: Physical training and protein supplementation, PTISG: Physical training and isoenergetic supplementation, EG: Experimental group, CG: Control group, TUG: Timed up and go, BBS: Berg balance scale, FES: Falls efficacy scale, WEG: Wii exercise group, HEG: Home exercise group, AG: Anodal group, SG: Sham group, VRTG: Virtual reality training group.

Discussion

Gamification is an approach designed to increase individuals' motivation and to create positive experiences by adapting mechanisms and elements from games to non-game domains (18,19). In recent years, the use of gamification-based methods in training programmes has increased and appears to enhance motivation (20). Gamified exercises, particularly in older adults, have been reported to increase adherence to exercise and to have potential positive effects on muscle strength, balance, walking speed, and functional capacity. A significant number of randomized controlled trials in our review suggest that exergames may be as effective as traditional exercise (13,14) and superior to home exercise or standard treatment approaches (15). A meta-analysis by Chen et al. (21) also reported that exergames may be comparable to traditional exercise in improving physical function, and a 2022 meta-analysis supports these findings (22). Current literature suggests that exergame interventions could be used as an alternative to traditional exercise and may, in some cases, even improve exercise adherence by enhancing motivation and participation. Factors such as low digital literacy in older individuals, difficulty accessing technology, and differences in motivation may limit the applicability and effectiveness of such interventions. However, inconsistent findings regarding their superiority over traditional exercise suggest that further high-quality randomized controlled trials are needed to clarify their effectiveness and to determine the conditions under which they may be more beneficial.

Our review also suggests that exergaming may have positive effects on lower-extremity muscle strength and functional capacity (11,15,16). Hernandez-Martinez et al. (23) reported that Wii Fit interventions improved lower-limb muscle strength by 34%, balance by 23.6%, and reduced fall risk by 35.1% in older adults over a six-week period, compared with those receiving conventional balance training. Additionally, a meta-analysis by Viana et al. (24) indicated that exergaming can enhance both upper- and lower-limb muscle strength in individuals with various health conditions, although this effect may be limited among middle-aged and older adults. These findings suggest that the effects of exercise games may vary depending on factors such as age, health status, duration of intervention, type of game used, and exercise intensity. Therefore, studies with larger samples, standardised protocols, and long-term follow-up may be needed to more comprehensively evaluate the effectiveness of exergame interventions.

Our study also demonstrates that exercise games can be safely implemented even among older adults. Campo-Prieto et al. (12) reported that VR exercises had beneficial effects on balance and gait in women aged over 90 years. Corrêa et al. (17) showed that Wii Fit balance games alone could improve balance without the need for additional methods such as tDCS. However, conflicting findings have also been reported in the literature. Montero-Alía et al. (25) noted that balance training using Nintendo Wii in individuals over 70 years of age did not have a significant effect on fall risk and balance. Lee et al. (26) reported that VR exercises only provided benefits for balance, but did not produce significant changes in walking, mobility, or fear of falling. These differences may stem from the lack of standardisation in intervention protocols, the variety of games and devices used, variation in application duration and intensity, and heterogeneity in participant characteristics. Additionally, factors such as low levels of digital literacy, limited access to technology, and differences in motivation among older adults may limit the effectiveness and feasibility of such interventions.

Study Limitations

This systematic review has several limitations. Most included studies do not report participants' cognitive status or comorbidities, which could influence outcomes. Additionally, the majority of the studies were designed as short-term interventions (4–12 weeks), making it difficult to draw conclusions about long-term effects. Furthermore, the heterogeneity of intervention types, implementation durations, and assessment scales is another important factor limiting the comparability and comprehensive evaluation of the results.

Conclusion

The reviewed study findings and existing literature suggest that exercise games have the potential to increase exercise participation and support motivation in older adults. The engaging, motivating, and accessible nature of technological applications may facilitate long-term adherence. In this context, exercise games can be considered an effective alternative, particularly for older adults who have difficulty adhering to exercise programs or who are unable to maintain traditional programs.

In summary, exergaming appears to be a safe and effective approach for enhancing balance, muscle strength, and functional performance in older women. These interventions may serve as complementary or alternative options to conventional exercise programs. Nevertheless, further evidence from randomized controlled trials with larger sample sizes, longer follow-up periods, and diverse populations is needed to confirm these results. Furthermore, the availability and sustainability of these interventions in various settings, such as home-based programs, nursing homes, or community centers, should be investigated to obtain more concrete data on their effectiveness in both clinical and real-world settings.

Footnotes

Authorship Contributions

Concept: A.K.S., Y.S.A., Design: A.K.S., Y.S.A., Data Collection or Processing: A.K.S., Y.S.,A., Analysis or Interpretation: A.K.S., Y.S.A., Literature Search: A.K.S., Y.S.A., Writing: A.K.S., Y.S.A.

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PERSPECTIVE

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Cognitive Rehabilitation Adherence Failure in Dementia Patients—A Triad of Patient, Caregiver, and Healthcare Challenges

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Abstract

Cognitive impairment and dementia are age-related conditions with extremely high healthcare needs. Cognitive rehabilitation (CR) is a non-pharmacological intervention and an important component of treatment for patients with dementia. Maintaining continuity is a useful concept in dementia care that may confer psychosocial benefits. Non-adherence to non-pharmacological interventions by patients and their caregivers disrupts the efficacy of CR when combined with pharmaceutical interventions. Adherence to CR is hampered by several factors, including psychological and cognitive barriers; caregiver-related challenges; health system and service delivery barriers; barriers related to knowledge, education, and technology; and socioeconomic and cultural factors.

Keywords: Cognitive rehabilitation, adherence, dementia patients, perspective

Introduction

Cognitive impairment and dementia are age-related conditions with extremely high healthcare needs (1,2) and impacts more than 55 million individuals worldwide. There are expected to be 90 million dementia sufferers by 2040 (3).

The main goal of current pharmacological interventions for Alzheimer disease (AD) is to alleviate symptoms rather than alter disease progression. Cognitive training and stimulation are part of the so-called non-pharmacological therapy, which is a significant part of the treatment of dementia patients (4).

Cognitive function is important in adherence behaviours, as evidenced by empirical research on related populations, including older adults with heart failure, which shows that cognitive domain impairments (attention, executive function, and language) independently predict poorer adherence to complex treatment regimens (5).

A specialized treatment strategy, known as cognitive rehabilitation (CR), aims to enhance cognitive abilities affected by brain impairment or injury. Restoring or compensating for lost cognitive abilities such as memory, attention, executive function, and problem-solving entails thorough assessment, goal-setting, and customized exercises. Both restorative techniques, which concentrate on retraining and enhancing cognitive abilities, and compensatory techniques, which assist people in adjusting to cognitive deficits through the use of tools or alternate techniques, are frequently included in this intervention (6).

To help people better manage their daily tasks and plan their activities, computer-assisted training and assistive technologies, such as Global Positioning System devices and smartphones, are also used. Finding cognitive deficits, establishing quantifiable objectives, offering focused cognitive exercises, practicing skills with progressively harder tasks, and routinely assessing progress are all steps in the process (3).

Since rehabilitation goals are described as "a future state that is desired and/or expected," rehabilitation can be viewed as a practice focused on the future. The problem of temporality in rehabilitation has been discussed in the literature, which links the patient's past and present with a potential future state and reveals a variety of potential futures (7).

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Understanding and optimizing the benefits of these training programs requires adherence (8). Poor adherence reduces the efficacy of regimens because patients who follow their doctors' and their medications' instructions maximize the benefits of therapies (9). One effective principle for providing dementia care is continuity of care. Continuity maintenance is a helpful idea for dementia care that may have psychosocial advantages (10).

The difficulties faced by dementia patients and their families include non-adherence to non-pharmacological interventions by both the patients and their caregivers, despite research demonstrating the efficacy of CRCR in conjunction with pharmaceutical interventions in slowing the disease's progression (11,12). Therefore, understanding the factors that influence patients and caregivers who are reluctant to continue their CRCR programs is essential.

Some research suggests that, among patients with non-communicable diseases, medication non-adherence is associated with cultural sensitivity, forgetfulness, drug side effects, lack of access to medications, and patient beliefs. Feelings of despair, disengagement from social networks, and declines in cognitive functioning that may affect memory were other factors (13-16). Lehmann et al. (17) divided barriers into five main categories: factors related to the healthcare system, disease, medication, patient and caregiver factors, and demographic and socioeconomic factors. However, most research focuses on medication adherence rather than on non-medical interventions or rehabilitation. The following is a brief explanation of some reasons why rehabilitation may be discontinued.

Due to a complex interaction of cognitive, psychological, and practical barriers, people with dementia and their caregivers frequently show reluctance toward CR and may discontinue participation in such programs.

Several key elements or categories that can be used to classify the obstacles and contributing factors to nonadherence to CR in patients with dementia. A list of obstacles and elements to improve clarity and flow is provided below:

Psychological and Cognitive Barriers

Depression, apathy, and hopelessness: These factors often accompany dementia. Many patients feel that challenging CR exercises remind them of their deficits, which can increase frustration or a sense of defeat in them. Avoidance and withdrawal are influenced by these "defeatist beliefs," such as the conviction that progress is unattainable. Depression by itself has the potential to be a cause as well as a symptom of disengagement, creating a vicious cycle that deters people from participating in CR (18,19). Grant and Beck (20) describe defeatist beliefs as pessimistic expectations that are based on repeated experiences of cognitive difficulty, such as "I can do this" or "It will fail anyway" These beliefs reduce motivation to participate in rehabilitation, and so cognitive effort is avoided.

Disease progression: Patients with dementia lose cognitive ability, making it harder to engage in CR for an extended period. As functional decline quickens, caregivers may need to rearrange their priorities for care (21,22). Apathy, depression, and agitation are among the behavioural and psychological symptoms that frequently increase with disease progression, further reducing motivation and willingness to engage. These symptoms could make rehabilitation more difficult and unsatisfying, which could cause dissatisfaction and dropout (23).

Immediate effects of medication: Despite evidence demonstrating the advantages of both strategies, people with dementia and those who care for them frequently believe that medication is superior to CR for several reasons. Drugs, particularly memantine and cholinesterase inhibitors, are frequently viewed as "active" therapies that target the underlying biological causes of dementia. Patients and caregivers expect pharmacological treatments to yield more rapid and more noticeable outcomes, such as improved memory or symptom stabilization. The widespread availability of drugs and the emphasis placed by healthcare providers on medication as the first line of treatment serve to support this view (21-23). Because of pharmacotherapy-focused reimbursement models, time constraints, or clinical guidelines, doctors frequently emphasize medication. Short or non-existent discussions regarding CR can lead to underutilization and a diminished sense of its significance (12). In contrast to CR programs, which necessitate consistent attendance, mental effort, and caregiver involvement, medications are simpler to administer and require less continuous effort (24,25). A complex combination of perceived immediacy, educational gaps, cognitive and emotional factors, healthcare practices, and practical convenience contributes to the belief in the superiority of medication. It is crucial to balance expectations and improve adherence through enhanced patient and caregiver education on the beneficial role of CR as a supplemental approach.

Caregiver-Related Challenges

Caregiver burden and relationship dynamics: The strain of overseeing day-to-day care and encouraging involvement in CR can ultimately overwhelm caregivers. Caregivers may stop supporting them or may discourage them from continuing if the intervention adds to their time or stress without obvious benefits. Withdrawal may also result from challenging patient-caregiver dynamics and difficulties implementing home-based programs (26).

Caregiver stress: Stress among caregivers reduces their ability and motivation to support and facilitate therapy, which, in turn, reduces the likelihood that patients with dementia will adhere to CR over time (27,28). Poorer cognitive function

in patients is associated with high caregiver burden, which further complicates adherence to rehabilitation. This cycle can be managed by providing support to caregivers (29). Research indicates that caregivers who are dealing with psychological distress, family stress, and burnout have a lower quality of life and are less resilient, which has an adverse effect on both their ability to provide effective care and the patient's adherence to rehabilitation (27,30).

Health System and Service Delivery Barriers

Resourcing and geographic accessibility of rehabilitation facilities: Individuals with dementia and their caregivers may face challenges accessing post-diagnostic care. Patients may encounter difficulties starting or regularly attending CR programs due to limited access to specialized rehabilitation facilities, particularly in remote or widely separated locations (31). Residents of capital cities also face this issue due to traffic and long commutes, which make it difficult to access care and services. Public transportation may be crucial in enabling rural or capital city residents to receive medical care while maintaining their preferred place of residence (32). The effectiveness of these interventions depends on regular attendance, which is directly hampered by geographic distance. These patients, especially those who require chronic disease management, are further burdened by challenges in care coordination and disparities in quality among healthcare strata (community, secondary, and tertiary levels). Patients must choose between receiving care at neighbourhood clinics or traveling greater distances to the secondary and tertiary hospitals in the city centre. For patients in rural areas who require care from more specialized hospitals, the inconvenience of time and distance creates further obstacles (33). Since caregivers are typically the ones who bring individuals with dementia to rehabilitation facilities, distance, traffic, and transportation issues make them reluctant to continue rehabilitation sessions and instead rely solely on medication for the older adult with dementia. Geographic and resource constraints (e.g., travel and scheduling) create practical barriers and lower the standard of rehabilitation services, which leads to noncompliance among patients with dementia. To increase participation rates, stakeholders could reduce these obstacles by distributing facilities more widely, allocating more resources, and incorporating home-based or remote technologies.

Affordability and insurance policy constraints: CR can be expensive, requiring customized programs, specialized therapists, and, occasionally, long, repeated sessions. Patients may be responsible for increased costs if the cost of their therapy exceeds their insurance benefits, because private insurance coverage varies greatly and frequently imposes copayments, deductibles, and limitations on the number of therapy sessions (34). Mahmood et al. (35) (2023) cite a cost variable as the main reason for non-adherence, along with issues with health literacy and the absence of a caregiver in their narrative review. An additional review that surveyed older adults' people in low- and middle-income nations focused on the financial obstacles older adults encounter when trying to access rehabilitation, including both direct and indirect costs (36). These review articles address older adults' nonadherence to rehabilitation programs due to financial concerns and barriers. These studies demonstrate how socio-economic status, out-of-pocket costs, and associated expenses, such as lodging and transportation, can lower participation rates among older adult populations.

Rehabilitation services are, unfortunately, not fully covered by private insurers in developing countries; instead, they only cover a portion of medical expenses. This is despite medication therapy and other CR services being crucial for older adults, particularly those who have Alzheimer's. Participants frequently stated that issues with affordability are closely related to insurance, particularly coverage limitations (33). Rehabilitation services in LICs are typically insufficient, underdeveloped, or ill-equipped. Therefore, older adult's people avoid using these services due to high costs or lack of insurance coverage (37). Consistent adherence to CR among patients with dementia is significantly hampered by limited affordability due to patient-borne costs and restrictive insurance policies, such as session caps, cost-sharing requirements, and limited coverage. Policies that increase coverage and lower out-of-pocket costs may contribute to better clinical outcomes and adherence (38,39).

Pharmacotherapy priority by the healthcare provider: When the participants were first diagnosed and knew the type of their disease, they reported asking someone else to explain more about the medications and how to take them. Despite the fact that the majority of patients take their medications as directed by medical professionals, some participants reported not taking their medications as directed, feeling let down, and forgetting about it (40). This also applies to rehabilitation therapies; patients frequently forget or arrive late for CR. The majority of seniors consider rehabilitation sessions to be recreational activities and participate at their discretion, not understanding the efficacy of rehabilitation when combined with medication therapy. They are unaware that the effectiveness of rehabilitation depends on the continuity of sessions. CR has been shown in recent meta-analyses to moderately improve occupational performance and quality of life in patients with AD; however, its effects on core cognitive functions (e.g., memory, executive function) are still erratic and weaker (3). Measuring the impact of CR interventions against the backdrop of progressive brain atrophy is challenging, as some studies even show no discernible changes in global cognitive scores after the interventions (21). These gaps indicate that we still do not fully understand CR's broader cognitive efficacy, despite encouraging evidence of its role in enhancing aspects of everyday functioning. An additional issue is the use of technology in CR. Instead of paper-and-pencil

worksheets, CR software is now used because it is more engaging and assesses a broader range of cognitive functions. Technology features that adapt to real-time performance, such as adaptive difficulty, facilitate integration of computerized cognitive training (CCT) and help keep tasks interesting and demanding. Despite the computerization of CCT procedures, the majority of CCT interventions are intended to be delivered in person under the supervision of a qualified expert, such as a therapist or clinician, to guarantee compliance and address technical issues (41). In societies where many older adults lack literacy, and in developing nations where older adults find it difficult to use smartphones, one challenge of adopting new technologies is encouraging older adults to use software in CR sessions and to practice at home with smartphone applications.

Knowledge, Education, and Technology Barriers

Lack of knowledge about rehabilitation: Neurodegenerative dementias do not yet have a cure, although certain pharmaceutical and non-pharmacological treatments may help reduce symptoms, delay the course of the illness, and enhance quality of life (42). In order to reduce disability and enhance the quality of life for patients and caregivers, these interventions are designed to preserve function and participation for as long as possible as the disease worsens, rather than to alter the underlying pathophysiological mechanisms (43). Rehabilitation, according to the World Health Organization (WHO), is a comprehensive strategy to maximize function and lessen the perception of disability. Additionally, according to the organization, rehabilitation is essential for people who are functionally impaired due to aging, as well as for those recuperating from illness or injury. The general public would not be familiar with this more recent definition of rehabilitation, and many of the survey respondents would not have previously considered the potential benefits of rehabilitation for age-related or dementia-related disabilities (44). The word "rehabilitation," according to medical professionals, also suggests that the participant is recuperating from a disease, accident, or injury (such as a stroke). Therefore, even though the programs' content may be the same, health professionals believed that programs labelled as "rehabilitation" were less suitable for individuals with dementia than programs labelled as "reablement". Concerns regarding hope and how to carefully strike a balance between providing hope and avoiding false hope were voiced by both health professionals and individuals with dementia (45).

Misunderstanding of rehabilitation effectiveness: Medical professionals evaluate effectiveness based on clinically meaningful improvements or maintenance in the patient's health and independence. They frequently concentrate on whether rehabilitation meets predetermined clinical objectives, like reducing functional decline or enhancing mobility and safety (46,47). The effectiveness of rehabilitation is interpreted more subjectively and holistically by caregivers, who are frequently family members. They place high importance on noticeable, meaningful improvements in the patient's mood, daily activities, quality of life, and home environment. Crucially, how rehabilitation affects caregivers' personal burden, stress, and emotional health—for example, by lowering the need for continual supervision or improving the handling of difficult behaviours—determines how they perceive the program (48). Effectiveness' in CR is defined as reducing disease progression and patient complications; however, patients and their caregivers define effectiveness as removing all patient complications in two or three sessions. Irrational expectations about the patient's rehabilitation process result from a conflicting understanding of the concepts of treatment and effectiveness. The patient and his or her caregiver decide not to continue the rehabilitation sessions because they do not believe there will be any noticeable short-term changes in the dementia patient's behaviour.

Socio-Economic and Cultural Factors

Low-income and developed countries differences: When it comes to the mechanisms and justifications for discontinuing CR programs for dementia and related conditions, low-income countries (LICs) and developed countries differ significantly. In developed (high-income) nations, psychological and individual factors, such as patient motivation, depression, cognitive impairments that limit participation, and caregiver burden, are more likely to be responsible for withdrawal than system-level access barriers. Comparatively speaking to LICs, developed healthcare systems typically offer more extensive insurance coverage, which lessens financial strain as a withdrawal factor (12,24). It appears that the most frequent obstacles to rehabilitation adherence in LICs are those related to the health system, finances, cultural beliefs and health literacy, transportation, and practical issues (49,50).

Cultural beliefs and health literacy: Cultural norms regarding caregiving and family roles (such as the strong sense of familial duty or "familism" among Latino caregivers) can lead to complicated emotional burdens in addition to influencing willingness and approach to supporting rehabilitation (51,52). Adherence is hampered by low health literacy, which includes a lack of knowledge about dementia, its course, and the justification for treatment. The goals and advantages of CR may be misunderstood by patients and caregivers, who frequently view it as optional or recreational rather than as a vital therapy requiring consistent effort and attendance. Dedication to rehabilitation programs is hampered by this misconception (52,53). Research suggests culturally adapted cognitive therapies (e.g., Cognitive Stimulation Therapy adapted for Māori populations) improve acceptance and effectiveness by respecting cultural values and communication styles (54).

Conclusion

Cognitive decline, lack of insight, psychological distress (such as depression and defeatist beliefs), perceived lack of benefit, caregiver burden, and logistical challenges are the main causes of reluctance and withdrawal from CR among individuals with dementia and their caregivers. Interventions must address these multifactorial barriers by reducing practical obstacles, supporting caregiver well-being, clearly justifying activities, and customizing CR to each person's needs, thereby improving engagement and adherence. Patients with dementia also face challenges related to the disease course, medication management, affordability, and limited care facilities. Restricting services based on age, symptoms, or severity of impairment creates inequities and ethical dilemmas (55).

How can rehabilitative services be made available to those who need them in settings with limited resources that serve a large population of people with dementia? How can we reduce the aforementioned barriers so that CR therapy is as beneficial to older adults with dementia as medication therapy is?

Although WHO has made commendable efforts toward preserving and enhancing the intrinsic capacities of older adults—introducing six functional domains as care priorities within the framework of the Integrated Care for Older People program—and tailored guidelines can be used to improve adherence to CR in patients with dementia, the enforceability and practical implementation of this program, particularly in LICs, remain uncertain. One possible guarantee for program implementation in developing countries could be requiring the submission of reports on implementation stages.

We may be able to overcome individual barriers to some extent by engaging caregivers in the rehabilitation process, using practical strategies, monitoring progress, and sharing positive feedback. However, in order for more seniors and caregivers to have access to these services, we need the support of health decision-makers.

Ethics

Ethics Committee Approval: Since this study is prospective, this section is not applicable to this type of article.

Informed Consent: Not applicable.

Authorship Contributions

Concept: A.A.Z., M.C., Design: A.A.Z., M.C., Literature Search: A.A.Z., M.C., Writing: A.A.Z., M.C.

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