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# The Influence of Hypophosphatemia on ICU Outcomes in Elderly Critically Ill Patients

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## Abstract

**Objective:** Hypophosphatemia is a critical condition in intensive care settings, often linked to adverse clinical outcomes. Elderly patients, due to factors such as malnutrition, comorbidities, and altered renal function, are vulnerable to this condition. This study aimed to evaluate the incidence, associated factors, and clinical implications of hypophosphatemia in elderly critically ill patients.

**Materials and Methods:** A retrospective cohort study was conducted in a tertiary intensive care unit (ICU) between January 2020 and December 2022. Patients aged  $\geq 65$  years were divided into two groups: hypophosphatemic and non-hypophosphatemic. Hypophosphatemia was defined as a serum phosphate level  $< 2.5$  mg/dL.

**Results:** Among 433 elderly critically ill patients, the incidence of hypophosphatemia was 18.5%. Logistic regression analysis identified cardiac decompensation as the reason for ICU admission [odds ratio (OR): 2.33, 95% confidence interval (CI): 1.09-4.95,  $p=0.028$ ]; absence of renal injury according to the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification (OR: 3.83, 95% CI: 2.19-6.71,  $p<0.001$ ); hypokalemia (OR: 2.61, 95% CI: 1.46-4.69,  $p=0.001$ ); and hypoalbuminemia (OR: 2.61, 95% CI: 1.46-4.67,  $p=0.01$ ) as independent risk factors for hypophosphatemia. Subgroup analysis revealed a higher prevalence of hypophosphatemia of 32.8%, in patients without renal injury according to the RIFLE classification. However, hypophosphatemia was not associated with adverse clinical outcomes, including the requirement of mechanical ventilation, an increased ICU length of stay, or higher mortality, even after excluding patients with renal injury according to the RIFLE classification.

**Conclusion:** Contrary to expectations, this study found that hypophosphatemia incidence is not higher in elderly critically ill patients than in the general ICU population. Although current literature has emphasized the association between hypophosphatemia and negative clinical outcomes, our study did not demonstrate this association, suggesting, hypophosphatemia is an indicator of disease severity rather than a risk factor for mortality.

**Keywords:** Clinical geriatrics, elderly critical ill, geriatric care management hypophosphatemia, intensive care management, mortality, refeeding syndrome

## Introduction

Phosphate is an essential anion for cellular function, including energy production, cell membrane integrity, and muscle function, making its deficiency particularly detrimental in critically ill patients (1-4). Several studies have emphasized the association between hypophosphatemia and adverse clinical outcomes in intensive care unit (ICU) settings. (2-5). The mechanical ventilation (MV) requirement is significantly higher in hypophosphatemic patients, indicating more severe

respiratory compromise (4). Longer ICU and hospital stays in patients with hypophosphatemia compared to those with normal phosphate levels have been demonstrated (2,4). Some studies have shown the link between hypophosphatemia and increased mortality in ICU patients (5). However, recent meta-analyses concluded that hypophosphatemia is an indicator of disease severity rather than an independent risk factor for mortality (1,6).

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Critically ill patients, including postoperative, septic, and trauma patients, are known to be at risk of hypophosphatemia due to decreased intestinal absorption, redistribution of extracellular fluids to intracellular compartments, increased consumption in catabolic phases, increased renal excretion, and iatrogenic complications of renal replacement therapy (RRT) (2-7). The incidence of hypophosphatemia in this patient group varies widely, with some studies reporting rates as high as 28-60% (1). Hypophosphatemia often coexists with other electrolyte abnormalities, such as hypokalemia and hypomagnesemia, complicating the clinical picture. Additionally, low serum albumin levels, indicative of poor nutritional status, are frequently observed in patients with hypophosphatemia (4). Elderly patients are particularly vulnerable to hypophosphatemia due to factors such as malnutrition and associated refeeding syndrome, impaired renal function, and the use of medications like diuretics, steroids, and some antimicrobials that can contribute to phosphate depletion (7-10). Understanding the prevalence and implications of hypophosphatemia in the elderly population is crucial for improving patient outcomes. In the current literature, few studies reveal the clinical consequences of hypophosphatemia, especially in elderly critically ill patients. With this study, we aimed to reveal the incidence of hypophosphatemia, concurrent electrolyte disorders, associated factors, and outcomes in the elderly critically ill population.

## Materials and Methods

### Study Design and Setting

This retrospective cohort study was carried out in the nine-bed tertiary medical ICU at Gazi University Hospital between January 2020 and December 2022. The research protocol was approved by the Local Ethics Committee of Gazi University, Faculty of Medicine, (approval number: 996621, research code number: 2024-1132, date: 09.07.2024). Informed consent was not obtained as the data were collected retrospectively. This study protocol also complied with the Declaration of Helsinki.

### Participants

Critically ill patients were included if they were  $\geq 65$  years old. Patients were excluded if they died within 24 hours, were transferred from other ICUs, or had recurrent ICU admissions. Patients without serum phosphate levels on admission to the ICU were also excluded from the study.

### Data Collection

Epidemiological and laboratory data were retrieved from electronic hospital systems and medical archives. We collected demographic details, including age, gender, ICU admission causes, comorbidities, and clinical severity assessments such as the Glasgow Coma Scale, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment

(SOFA), Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) Score, as well as the infection source in septic patients. Additionally, data regarding the clinical parameters related to ICU admission, RRT requirement, and nutritional support, albumin replacement, length of ICU stay, and ICU mortality rates were documented.

The APACHE II, RIFLE, and SOFA scores were computed within the initial 24 hours of ICU admission to assess the severity of the illness. Hypophosphatemia was defined as a serum phosphate level under 2.5 mg/dL ( $<0.81$  mmol/L) on ICU admission (11). The other electrolyte disorders were also defined according to the lower limit of the reference laboratory of Gazi University Hospital: hypokalemia as a serum potassium level was under 3.5 mEq/L, hypomagnesemia as a serum magnesium level was under 1.3 mg/dL, and hypoalbuminemia as a serum albumin level was under 3.0 g/dL on ICU admission.

### Statistics

Continuous variables were reported as mean  $\pm$  standard deviation or median with interquartile range, depending on their distribution. Categorical variables were summarized as frequencies and percentages. The Mann-Whitney U test was used to compare the medians of continuous variables, and the chi-squared test was used to compare categorical variables. Patients were categorized into two groups based on the presence of hypophosphatemia. Data were compared between both hypophosphatemic and non-hypophosphatemic patients. Due to the higher prevalence of renal injury in non-hypophosphatemic patients according to the RIFLE classification, a subgroup analysis was performed on non-hypophosphatemic patients without renal injury at ICU admission due to the higher prevalence of renal injury, was performed on patients without renal injury based on the RIFLE classification at ICU admission. Variables associated with ICU mortality were also analyzed and provided in a supplementary file. Logistic regression analysis was used to determine independent risk factors for hypophosphatemia and ICU mortality. A p-value of  $<0.05$  was considered statistically significant. All analyses were performed using the SPSS statistical program version 22.0 (IBM Corp., New York, NY).

### Results

Six hundred seventy-nine ICU admissions were detected during the study period. After excluding patients aged under 65, those who stayed less than 24 hours, and those with recurrent ICU admissions, 433 patients were included in further statistical analysis. The baseline characteristics and ICU-related data according to hypophosphatemia on ICU admission are given in Tables 1 and 2. Hypophosphatemia prevalence was 18.5% within the study population. In terms of reasons for ICU admission, cardiac decompensation was observed more frequently in



hypophosphatemic patients, while renal failure was detected at a higher rate in non-hypophosphatemic patients (cardiac decompensation 13.8% vs. 2.6%,  $p=0.02$ , renal failure 28.8% vs. 54.7%,  $p<0.001$ ) (Table 1). According to the RIFLE classification at ICU admission, the risk, injury, loss, and end-stage renal disease categories were higher in non-hypophosphatemic patients ( $p$ -values, respectively 0.045, 0.053, 0.014, and  $<0.017$ ) (Table 1). The two groups had no difference in the requirement for MV, nutritional support, albumin replacement, ICU mortality, length of ICU stay, and length of hospital stay prior to ICU admission (Table 1). When laboratory findings on ICU admission were compared, blood urea nitrogen (BUN), creatinine, potassium, magnesium, and albumin were significantly lower among hypophosphatemic patients (Table 2). Based on the evaluation of risk factors associated with hypophosphatemia on ICU admission using logistic regression analysis, cardiac decompensation as a reason for ICU admission [odds ratio (OR) 95% confidence interval (CI): 2.33 (1.09-4.95)  $p=0.028$ ], absence of renal injury according to RIFLE classification [OR 95% CI: 3.83 (2.19-6.71),  $p<0.001$ ], hypokalemia [OR 95% CI: 2.61 (1.46-4.69),  $p=0.001$ ], and hypoalbuminemia [OR 95% CI: 2.61 (1.46-4.67),  $p=0.01$ ] were defined as independent variables related to hypophosphatemia (Table 3).

In the subgroup analysis evaluating 146 patients without renal injury according to the RIFLE classification on admission to the ICU, hypophosphatemia prevalence was 32.8% within the subgroup population. No statistically significant relationship was found between hypophosphatemia and either the

reasons for ICU admission or comorbidities. Unlike in the overall study population, the subgroup analysis revealed that hypophosphatemic patients without renal injury according to the RIFLE classification had a significantly higher SOFA Score and a longer hospital stay prior to ICU admission ( $p$ -values of 0.015 and 0.016, respectively) (Table 4). In the subgroup analysis, hypophosphatemia was not significantly associated with nutritional support, requirement of MV, ICU mortality, or length of ICU stay ( $p$ -values, respectively 0.528, 0.239, 0.121, 0.140 and 0.393) (Table 4). When laboratory findings on ICU admission were compared, BUN, creatinine, potassium, and albumin were significantly lower among hypophosphatemic patients (Table 5). Based on the logistic regression analysis of factors associated with hypophosphatemia at ICU admission within the subgroup, the SOFA Score [OR 95% CI: 1.069 (0.945-1.210),  $p=0.288$ ], the length of hospital stay prior to ICU admission [OR 95% CI: 1.006 (0.962-1.051),  $p=0.794$ ], hypoalbuminemia [OR 95% CI: 1.597 (0.577-4.417),  $p=0.367$ ] or hypokalemia [OR 95% CI: 1.385 (0.576-3.332),  $p=0.467$ ] were not identified as independent risk factors for hypophosphatemia. Serum creatinine [OR 95% CI, 0.238 (0.074-0.769),  $p=0.016$ ] and pH [OR 95% CI, 230.616 (3.244-16394.30),  $p=0.012$ ] were defined as independent variables related to hypophosphatemia.

Detailed information on the comparison of clinical characteristics and laboratory findings of the overall study cohort based on ICU mortality is also provided in Supplementary Tables 1, 2, and 3 of the supplemental file.

**Table 1. Comparison of baseline characteristics and ICU-related data according to hypophosphatemia on ICU admission in elderly critically ill patients**

	All patients (n=433)	Hypophosphatemic patients (n=80)	Non-hypophosphatemic patients (n=353)	p
<b>Baseline characteristics and ICU admission data</b>				
Age*	77 (71-83)	77 (71-84)	76 (70-83)	0.852
<b>Gender, n (%)</b>				
Female	198 (45.7)	32 (40)	166 (47)	0.266
Male	235 (54.3)	48 (43.4)	187 (53)	
APACHE II Score*	20 (16-27)	21 (16-26)	20 (16-27)	0.800
SOFA Score*	6 (3-9)	6 (3-8)	6 (4-9)	0.305
Glasgow Coma Scale*	13 (8-15)	12 (9-15)	13 (8-15)	0.414
Length of ICU stay (day)*	16 (8-31)	18 (9-33)	16 (8-31)	0.628
Length of hospital stay prior to ICU admission (day)*	2 (0-8)	3 (1-9)	1 (0-8)	0.203
<b>Reason for ICU admission, n (%)</b>				
Sepsis	225 (52)	40 (50)	185 (52.5)	0.621
Renal failure	216 (49.9)	23 (28.8)	193 (54.7)	<b>&lt;0.001</b>
Respiratory failure	243 (56.1)	46 (57.5)	197 (55.8)	0.906
Cardiac decompensation	103 (23.8)	11 (13.8)	92 (2.6)	<b>0.02</b>
Acute GI disorders	46 (10.6)	1 (12.5)	36 (10.2)	0.553

<b>Table 1. Continued</b>				
	<b>All patients (n=433)</b>	<b>Hypophosphatemic patients (n=80)</b>	<b>Non-hypophosphatemic patients (n=353)</b>	<b>p</b>
Acute hepatobiliary disease	38 (8.8)	8 (10)	30 (8.6)	0.667
Acute neurological disorders	54 (12.5)	9 (11.2)	45 (12.7)	0.852
Metabolic disturbances	16 (3.7)	2 (2.5)	14 (4)	0.747
Surgery	13 (3)	1 (1.3)	12 (3.4)	0.477
Trauma	7 (1.6)	0	7 (2)	0.357
<b>Comorbidities, n (%)</b>				
Chronic renal disease	127 (29.3)	10 (12.5)	117 (32.1)	<b>&lt;0.001</b>
Pulmonary disease	156 (36)	34 (42.5)	122 (34.6)	0.190
Cardiac disorders	315 (72.7)	48 (60)	267 (75.6)	<b>0.003</b>
Gastroenterological	23 (5.3)	4 (5)	19 (5.4)	1.0
Neurological	105 (24.2)	25 (31.3)	80 (22.7)	0.114
Rheumatological	43 (9.9)	8 (9.6)	35 (9.9)	0.991
Endocrinological	161 (37.2)	23 (28.8)	138 (39.1)	0.095
Malignancy	149 (34.4)	35 (43.8)	114 (32.3)	0.156
Concomitant shock with septic patients, n (%)	193 (44.6)	36 (45)	157 (44.5)	0.892
<b>Source of sepsis, n (%)</b>				
Respiratory system	90 (20.8)	22 (27.5)	68 (19.3)	0.11
Urinary tract	74 (17.1)	12 (15)	62 (17.6)	0.461
BSI	74 (17.1)	15 (18.8)	59 (16.7)	0.854
Abdominal	22 (5)	3 (3.8)	19 (5.4)	0.579
Soft tissue	12 (2.8)	3 (3.8)	9 (2.5)	0.705
Others	3 (1)	0	3 (1)	1.0
<b>RIFLE stage, n (%)</b>				
Risk	109 (25.2)	13 (16.3)	96 (27.2)	<b>0.045</b>
Injury	64 (14.8)	6 (7.5)	58 (16.4)	0.053
Failure	83 (19.2)	10 (12.5)	73 (20.7)	0.115
Loss	11 (2.5)	3 (3.8)	10 (3.1)	<b>0.014</b>
Endstage	32 (7.4)	1 (1.2)	31 (8.8)	<b>0.017</b>
<b>Nutritional support, n (%)</b>				
Parenteral	34 (7.9)	9 (11.3)	25 (7.1)	0.25
Enteral	250 (57.7)	52 (65)	198 (56.1)	0.161
<b>Requirement of respiratory support, n (%)</b>				
Invasive mechanical ventilation	224 (51.7)	42 (52.5)	182 (51.6)	0.928
Non-invasive mechanical ventilation	98 (22.6)	18 (22.5)	80 (22.7)	0.949
HFNO	22 (5.1)	6 (7.5)	16 (4.5)	0.269
<b>Requirement of RRT, n (%)</b>				
Hemodialysis	110 (25)	10 (12.5)	100 (28.3)	<b>0.003</b>
CRRT	86 (6.9)	13 (16.3)	73 (20.7)	0.348
Albumin Replacement, n (%)	149 (34.4)	30 (37.5)	119 (33.7)	0.570
ICU mortality, n (%)	197 (45.5)	37 (46.3)	160 (45.3)	0.881
*Median (25 <sup>th</sup> percentile-75 <sup>th</sup> percentile). APACHE: Acute physiology and chronic health evaluation, SOFA: Sequential Organ Failure Assessment, ICU: Intensive care unit, BSI: Bloodstream infection, HFNO: High flow nasal oxygen, RRT: Renal replacement therapy, CRRT: Continuous renal replacement therapy, RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease, GI: Gastrointestinal				

**Table 2. Baseline laboratory findings according to hypophosphatemia on ICU admission in elderly critically ill patients\***

	All patients (n=433)	Hypophosphatemic patients (n=80)	Non-hypophosphatemic patients (n=353)	p
Blood urea nitrogen (mg/dL)	42 (27.8-62.3)	28 (19.6-44)	46 (30-60)	<0.001
Creatinine (mg/dL)	1.58 (0.95-2.72)	0.91 (0.6-1.31)	1.76 (1.08-2.92)	<0.001
Sodium (mEq/L)	139 (134-142)	140 (136-144)	138 (134-142)	0.006
Potassium (mEq/L)	4.05 (3.55-4.67)	3.6 (3.3-4.14)	4.14 (3.6-4.8)	<0.001
Chlorine (mEq/L)	103 (99-108)	105 (100-110)	102 (98-107)	0.007
Calcium (mg/dL)	9.1 (8.5-9.6)	9 (8.2-9.5)	9.1 (8.5-9.6)	0.062
Phosphorus (mg/dL)	3.6 (2.8-4.9)	2.05 (1.8-2.3)	4 (3.2-5.3)	0.000
Magnesium (mg/dL)	1.9 (1.7-2.2)	1.8 (1.6-2.3)	2 (1.7-2.2)	0.003
Alanine transaminase (U/L)	23 (13-51)	25 (16-48)	23 (12-53)	0.28
Aspartat transaminase (U/L)	34 (19-71)	36 (22-67)	32 (19-73)	0.84
Lactate dehydrogenase (U/L)	302 (217-468)	280 (199-408)	310 (224-484)	0.04
Total bilirubin (mg/dL)	0.92 (0.59-1.62)	0.84 (0.57-1.47)	0.92 (0.59-1.63)	0.5
Direct bilirubin (mg/dL)	0.28 (0.15-0.7)	0.27 (0.16-0.55)	0.28 (0.15-0.74)	0.98
Albumin (g/dL)	2.6 (2.3-3.0)	2.4 (2.15-2.8)	2.7(2.3-3.1)	0.001
<b>Blood gas sampling</b>				
pH	7.36 (7.29-7.44)	7.42 (7.35-7.47)	7.35 (7.27-7.42)	<0.001
HCO <sub>3</sub> (mEq/L)	20.8 (16.9-25.4)	23.9 (19.7-27)	20 (16.4-25)	<0.001
Lactate (mmol/L)	2 (1.3-3.4)	1.9 (1.3-3.1)	2.1 (1.3-3.5)	0.499
White blood cell count (/μl)	10530 (6910-15700)	10545 (6920-15085)	10530 (6910-15800)	0.931
C-reactive protein (mg/L)	97.2 (42.5-171)	94.6 (44-160)	98 (42-179)	0.67
Procalcitonin (ng/mL)	0.93 (0.28-3.97)	0.7 (0.21-3.37)	0.96 (0.31-3.97)	0.07

\*Median (25<sup>th</sup> percentile-75<sup>th</sup> percentile).  
HCO<sub>3</sub><sup>-</sup>: Bicarbonate, ICU: Intensive care unit

**Table 3. Multivariate analysis of independent risk factors for hypophosphatemia in elderly patients on ICU admission**

	Adjusted OR (95% CI)	p
Cardiac decompensation as a reason for ICU admission	<b>2.33 (1.09-4.95)</b>	<b>0.028</b>
The absence of renal injury according to RIFLE classification	<b>3.83 (2.19-6.71)</b>	<b>&lt;0.001</b>
Requirement of hemodialysis	0.57 (0.26-1.21)	0.142
Hypokalemia	<b>2.61 (1.46-4.69)</b>	<b>0.001</b>
Hypomagnesemia	0.72 (0.13-3.94)	0.704
Hypoalbuminemia	<b>2.61 (1.46-4.67)</b>	<b>0.01</b>

ICU: Intensive care unit, RIFLE: Risk, Injury, Failure, Loss and End-stage Kidney Disease OR: Odds ratio, CI: Confidence interval

**Table 4. Comparison of baseline characteristics and ICU-related data according to hypophosphatemia in elderly critically ill patients without renal injury according to the RIFLE classification on ICU admission**

	All patients (n=146)	Hypophosphatemic patients (n=48)	Non-hypophosphatemic patients (n=98)	p
<b>Baseline characteristics and ICU admission data</b>				
Age*	76 (70-82)	78 (71-84)	75 (70-81)	0.239
<b>Gender, n (%)</b>				<b>0.198</b>
Female	78 (53.4)	22 (45.8)	53 (57.1)	
Male	68 (46.6)	26 (54.2)	42 (42.9)	
APACHE II Score*	18 (14-22)	19 (16-24)	17 (13-22)	0.179
SOFA Score*	4 (2-6)	5 (3-7)	3 (2-6)	<b>0.015</b>

<b>Table 4. Continued</b>				
	<b>All patients (n=146)</b>	<b>Hypophosphatemic patients (n=48)</b>	<b>Non-hypophosphatemic patients (n=98)</b>	<b>p</b>
Glasgow Coma Scale*	14 (9-15)	12 (9-15)	14 (9-15)	0.127
Length of ICU stay (day)*	7 (7-14)	9 (4-21)	7 (4-11)	0.393
Length of hospital stay prior to ICU admission (day)*	2 (0-9)	3 (1-10)	1 (0-6)	<b>0.016</b>
<b>Reason for ICU Admission, n (%)</b>				
Sepsis	56 (38.6)	20 (41.7)	36 (37.1)	0.596
Respiratory failure	96 (66.2)	29 (60.8)	67 (69.1)	0.30
Cardiac decompensation	31 (21.4)	8 (16.7)	23 (23.7)	0.33
Acute GI disorders	18 (12.4)	8 (16.7)	10 (10.3)	0.275
Acute hepatobiliary disease	11 (7.6)	5 (10.4)	6 (5.2)	0.179
Acute neurological disorders	18 (12.4)	5 (10.4)	13 (13.4)	0.608
Metabolic disturbances	4 (2.8)	0 (0)	4 (4.1)	0.302
Surgery	6 (4.1)	1 (2.1)	5 (5.2)	0.382
Trauma	1 (0.7)	0 (0)	1 (1.0)	1.00
<b>Comorbidities, n (%)</b>				
Pulmonary disease	68 (47.2)	22 (46.8)	46 (47.4)	1.00
Cardiac disorders	97 (67.4)	27 (57.4)	70 (72.2)	0.077
Gastroenterological	6 (4.2)	4 (8.5)	2 (2.1)	0.089
Neurological	44 (30.6)	16 (34.0)	28 (28.9)	0.527
Rheumatological	4 (2.8)	0 (0)	4 (4.1)	0.304
Endocrinological	45 (31.3)	10 (21.3)	35 (36.1)	0.072
Malignancy	53 (37.1)	22 (46.8)	31 (32.3)	0.091
Concomitant shock with septic patients, n (%)	43 (29.9)	17 (36.2)	26 (26.8)	0.250
<b>Source of sepsis, n (%)</b>				
Respiratory system	31 (21.2)	14 (29.1)	17 (17.3)	0.186
Urinary tract	19 (13.1)	4 (8.3)	15 (15.3)	0.061
BSI	17 (11.6)	7 (3.5)	17 (17.3)	0.723
Abdominal	19 (13.0)	4 (8.3)	15 (15.3)	1.00
Soft tissue	4 (7.5)	1 (2)	3 (3.0)	0.627
Others	0	0	0	
<b>Nutritional support, n (%)</b>				
Parenteral	12 (8.3)	5 (3.9)	7 (8.1)	0.528
Enteral	85 (59)	31 (66)	54 (55.7)	0.239
<b>Requirement of respiratory support, n (%)</b>				
Invasive mechanical ventilation	70 (48.6)	27 (57.4)	43 (44.3)	0.140
Non-invasive mechanical ventilation	35 (24.3)	12 (25.5)	23 (23.7)	0.811
HFNO	9 (6.3)	3 (6.4)	6 (6.2)	1.00
<b>Requirement of RRT, n (%)</b>				
Hemodialysis	14 (9.7)	4 (8.3)	10 (10.3)	1.00
CRRT	13 (9.0)	4 (8.3)	9 (9.3)	1.00
Albumin replacement, n (%)	46 (32.2)	19 (40.4)	27 (28.1)	0.139
ICU mortality, n (%)	54 (37.0)	22 (45.8)	32 (32.7)	0.121
*Median (25 <sup>th</sup> percentile-75 <sup>th</sup> percentile). APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, ICU: Intensive care unit, BSI: Bloodstream infection, HFNO: High flow nasal oxygen, RRT: Renal replacement therapy, CRRT: Continuous renal replacement therapy, RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease GI: Gastrointestinal.				

**Table 5. Baseline laboratory findings according to hypophosphatemia in elderly critically ill patients without renal injury according to the RIFLE classification on ICU admission\***

	All patients (n=433)	Hypophosphatemic patients (n=80)	Non-hypophosphatemic patients (n=353)	p
Blood urea nitrogen (mg/dL)	28 (19-38.5)	24 (15.7-30.4)	29 (20.7-40)	<b>0.025</b>
Creatinine (mg/dL)	0.85 (0.6-1.07)	0.75 (0.53-0.94)	0.92 (0.65-1.14)	<b>0.004</b>
Sodium (mEq/L)	140 (136-142)	140 (137-143)	139 (135-141)	0.067
Potassium (mEq/L)	3.8 (3.5-4.38)	3.6 (3.3-4.05)	3.87 (3.5-4.5)	<b>0.007</b>
Chlorine (mEq/L)	103 (98-108)	105 (100-110)	101 (98-107)	<b>0.027</b>
Calcium (mg/dL)	9.0 (8.3-9.4)	8.8 (8.3-9.3)	9.0 (8.2-9.5)	0.160
Phosphorus (mg/dL)	3.0 (2.4-3.8)	2.1 (1.9-2.4)	3.5 (3-4.3)	<b>0.000</b>
Magnesium (mg/dL)	1.8 (1.7-2.1)	1.8 (1.7-2.1)	1.85 (1.7-2.1)	0.593
Alanine transaminase (U/L)	22.5 (16-44.5)	19 (12-33)	29 (17-49)	0.121
Aspartat transaminase (U/L)	30 (18-49)	33 (23-55)	29 (17-49)	0.314
Lactate dehydrogenase (U/L)	273 (214-428)	294 (247-401)	269 (211-434)	0.809
Total bilirubin (mg/dL)	0.78 (0.51-1.33)	0.78 (0.54-1.47)	0.77 (0.51-1.33)	0.736
Direct bilirubin (mg/dL)	0.21 (0.13-0.4)	0.25 (0.16-0.48)	0.2 (0.12-0.35)	0.084
Albumin (g/dL)	2.6 (2.3-3.1)	2.4 (2.05-2.8)	2.4 (2.7-3.1)	<b>0.005</b>
<b>Blood gase sampling</b>				
pH	7.41 (7.35-7.46)	7.43 (7.36-7.47)	7.40 (7.32-7.46)	<b>0.017</b>
HCO <sub>3</sub> (mEq/L)	25.1 (20.3-29.3)	25.2 (22.4-28.5)	25 (19.7-30.6)	0.623
Lactate (mmol/L)	1.6 (1.2-2.4)	1.6 (1.3-2.4)	1.6 (1.2-2.4)	0.993
White blood cell count (/μl)	104420 (6410-15640)	10545 (6610-16455)	7500 (15400-10420)	0.659
C-reactive protein (mg/L)	82 (28-174)	97.8 (31-155)	77.7 (24.5-137)	0.330
Procalcitonin (ng/mL)	0.34 (0.14-1.1)	0.37 (0.14-1.36)	0.31 (0.14-1.02)	0.797

\*Median (25<sup>th</sup> percentile-75<sup>th</sup> percentile).HCO<sub>3</sub>: Bicarbonate, RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

## Discussion

Our analysis has several important findings that clarify the incidence and importance of hypophosphatemia in the critically ill elderly population. The hypophosphatemia incidence was 18.5% within the study population. Independent risk factors for hypophosphatemia include cardiac decompensation as a reason for ICU admission, absence of renal injury according to RIFLE classification, hypokalemia, and hypoalbuminemia. The subgroup analysis demonstrated that hypophosphatemia was more prevalent in the absence of concomitant renal injury according to the RIFLE classification, and was associated with a longer hospital stay prior to ICU admission and a higher SOFA score. We also found that hypophosphatemia is not associated with adverse clinical outcomes, such as the requirement of MV, increased length of ICU stay, or increased mortality; even in the subgroup analysis excluding patients with renal injury according to the RIFLE classification.

In our study, which focused exclusively on elderly critically ill patients, we determined the incidence of hypophosphatemia to be 18.5%. After excluding the patients with renal injury based on the RIFLE classification at ICU admission, the incidence of

hypophosphatemia was 32.8%. Several studies have reported hypophosphatemia rates as high as 28-60% in adult critically ill populations (1,4,12). The difference in rates is predominantly due to the study population and the serum phosphate level threshold. (4,6,13). Our study distinguishes itself from previous literature by targeting a specific cohort. As the population ages, elderly patients now account for the vast majority of patients admitted to ICUs (14,15). Elderly patients are particularly vulnerable to hypophosphatemia due to factors such as malnutrition, comorbidities, altered renal function, various medications leading to phosphate depletion, and risk of refeeding syndrome (7-9). Contrary to expectations, this study found that hypophosphatemia incidence is not higher in elderly critically ill patients than in the general ICU population. Although existing literature has demonstrated hypophosphatemia in hospitalized geriatric populations at a rate of 7-14%, this discrepancy can be attributed to the varying cutoffs used for hypophosphatemia (8,16). In this study, the cutoff for hypophosphatemia is 2.5 mg/dL (<0.81 mmol/L) according to the lower limit of reference laboratory, whereas <0.68 mmol/L and 0.77 mmol/L were defined for previous studies, respectively (9,16).

Hypophosphatemia often coexists with other electrolyte abnormalities. Suzuki et al. (13) demonstrated the relationship between hypophosphatemia and other electrolyte disturbances (4). They found that hypophosphatemic patients had lower potassium and calcium concentrations, and a higher incidence of alkalemia. They also reported that in patients without any episodes of hyperphosphatemia, a lower minimum serum albumin level and a lower maximum creatinine level were significantly and independently associated with hypophosphatemia (13). These results were very similar to the results of our study. Our study demonstrates that hypophosphatemia in elderly critically ill patients is associated with lower serum levels of potassium, calcium, magnesium, and albumin, as well as elevated pH and bicarbonate levels. These findings may partly reflect differences in renal impairment between groups. Notably, patients with hypophosphatemia had a significantly lower incidence of renal impairment according to the RIFLE classification, along with reduced BUN and creatinine levels. Subgroup analysis of patients without renal injury supported this trend, showing persistently lower levels of BUN, creatinine, potassium, and albumin in the hypophosphatemic group. Furthermore, multivariate analysis identified absence of renal injury, hypokalemia, and hypoalbuminemia, as independent predictors of hypophosphatemia at ICU admission.

Contrary to previous studies, our findings suggest that admission to the ICU due to cardiac decompensation is an independent factor associated with hypophosphatemia (3,4,10). While earlier research has shown that surgical patients are less likely to develop hypophosphatemia and that patients with hypophosphatemia are more prone to infections and sepsis upon ICU admission, these studies did not establish a significant correlation between hypophosphatemia and underlying diseases (4,10,3). The discrepancy in our results may be attributed to the characteristics of our study population, which primarily consisted of elderly critically ill patients admitted to the ICU for medical, rather than surgical, reasons. Age-related chronic cardiac conditions are commonly observed in this population. Hypophosphatemia occurs in approximately 13% of patients with heart failure and may result from reduced oral intake, ongoing pharmacological treatments, concomitant electrolyte disturbances, and increased sympathetic nervous system activity (17,18). It has been shown to impair cardiac muscle contraction by disrupting adenosine triphosphate synthesis and to induce ventricular arrhythmias, thereby potentially contributing to the development or worsening of heart failure (19,20,21). Although our retrospective design precluded detailed data collection on diuretic regimens, increased renal excretion of phosphorus, potassium, and calcium due to diuretic therapy may also explain the lower levels of these electrolytes observed in hypophosphatemic patients (22).

In the geriatric population, both hypophosphatemia and hypoalbuminemia are commonly associated with malnutrition (8,9,13,16,23). Ensuring adequate caloric intake upon hospitalization, however, can increase the risk of refeeding syndrome and refeeding-associated hypophosphatemia (9,24). Our study aligns with this literature, highlighting hypoalbuminemia and hypokalemia as independent risk factors for hypophosphatemia. Additionally, the subgroup analysis of patients without renal injury according to the RIFLE classification further supports this link, as the hypophosphatemic group exhibited higher prevalence of hypokalemia and hypoalbuminemia, and prolonged hospital stays prior to ICU admission, and prolonged hospital stays. The fact that nutritional risk scores specific to the geriatric population, along with the lack of available data on caloric intake before ICU admission due to the retrospective nature of the study prevents us from demonstrating this relationship. In this respect, designing large-scale, multicenter prospective studies would be beneficial.

The most important result of our study, which differs from the current literature, is that hypophosphatemia is not associated with adverse clinical outcomes, such as prolonged MV duration, increased length of ICU stay, or increased mortality in elderly critically ill patients (3,4,25,26). This discrepancy from the existing literature may be attributed to our exclusive focus on the geriatric population, differences in the defined threshold for hypophosphatemia, as well as the inclusion of patients with hyperphosphatemia in our cohort. Our research recruited patients from the tertiary university medical ICU, providing a more specific and in-depth analysis tailored to this subgroup. In this study, there were two main reasons for including hyperphosphatemic patients. The first was to reveal the exact incidence of hypophosphatemia in the elderly critically ill population. The second was to assess whether hypophosphatemia alone is a risk factor for adverse clinical outcomes in a patient group characterized by high risk of malnutrition and reduced renal function. Nevertheless, in the subgroup analysis excluding patients with renal impairment at admission based on the RIFLE classification, hypophosphatemia was not found to be associated with adverse clinical outcomes in elderly critically ill patients. Previous studies have also demonstrated that the disease severity scores were high in hypophosphatemic patients (12,13). The disease severity scores, such as APACHE II and SOFA Scores, did not differ between hypophosphatemic and non-hypophosphatemic patients in our study population, but the SOFA Score was found to be high in hypophosphatemic patients without renal injury. This finding may reflect that hypophosphatemia indicates disease severity rather than an independent risk factor for mortality (1,2,14).



## Study Limitations

Although the findings of this study have important clinical implications for the management of elderly critically ill patients, it is important to acknowledge several limitations of our research. The major limitation of this study is its retrospective design, which prevents a comprehensive assessment of patients' nutritional status and caloric intake both prior to and during their ICU stay, thereby hindering an objective evaluation of the association between hypophosphatemia and refeeding syndrome. Additionally, the study lacks detailed information on fluid management strategies, diuretic regimens, steroid use, catecholamines, and aminoglycosides, all of which can contribute to hypophosphatemia. Finally, the generalizability of the results is inherently limited by the single-center nature of the cohort.

## Conclusion

Contrary to expectations, we found that hypophosphatemia incidence is not higher in elderly critically ill patients than in the general ICU population. Likewise, it was not correlated with negative clinical outcomes in ICU settings. Admission to the ICU for cardiac decompensation, along with hypoalbuminemia and hypokalemia as independent risk factors for hypophosphatemia, highlights the need for careful evaluation of hypophosphatemia in this population. Additionally, multicenter prospective studies in mixed ICU populations are required to better elucidate the relationship between hypophosphatemia and malnutrition in elderly critically ill patients.

## Ethics

**Ethics Committee Approval:** The research protocol was approved by the Local Ethics Committee of Gazi University, Faculty of Medicine, (approval number: 996621, research code number: 2024-1132, date: 09.07.2024).

**Informed Consent:** Informed consent was not obtained as the data were collected retrospectively.

## Footnotes

### Authorship Contributions

Surgical and Medical Practices: N.B.D., K.İ., B.H., M.T., G.A., Concept: N.B.D., K.İ., Design: N.B.D., K.İ., Data Collection or Processing: N.B.D., K.İ., B.H., Analysis or Interpretation: N.B.D., K.İ., M.T., G.A., Literature Search: N.B.D., K.İ., B.H., Writing: N.B.D., K.İ., M.T., G.A.

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

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Supplementary Table 1. Comparison of baseline characteristics and ICU-related data according to ICU mortality				
	All patients (n=433)	Survivors (n=236)	Non-survivors (n=197)	p
<b>Baseline characteristics and ICU admission data</b>				
Age*	77 (70-83)	77 (71-83)	76 (69-84)	0.437
<b>Gender, n (%)</b>				
Female	198 (45.7)	119 (50.4)	79 (40.1)	<b>0.032</b>
Male	235 (54.3)	117 (49.6)	118 (59.9)	
APACHE II Score	20 (16-27)	18 (15-22)	26 (20-32)	<b>&lt;0.001</b>
SOFA Score	6 (3-9)	5 (3-7)	9 (6-12)	<b>&lt;0.001</b>
Glasgow Coma Scale*	13 (8-15)	14 (12-15)	10 (5-14)	<b>&lt;0.001</b>
Length of ICU stay (day)*	6 (3-15)	6 (3-10)	8 (4-20)	<b>0.003</b>
<b>Reason of ICU admission, n (%)</b>				
Sepsis	225 (52)	81 (34.3)	144 (73.1)	<b>&lt;0.001</b>
Renal failure	216 (50)	109 (46.2)	107 (54.3)	0.085
Respiratory failure	243 (56.1)	123 (52.1)	120 (60.9)	<b>0.06</b>
Cardiac decompensation	103 (23.8)	55 (23.3)	48 (24.4)	0.784
Acute GI disorders	46 (10.6)	22 (9.3)	24 (12.1)	0.331
Acute hepatobiliary disease	38 (8.7)	20 (8.5)	18 (9.1)	0.802
Acute neurological disorders	54 (12.5)	28 (11.8)	26 (13.2)	0.668
Metabolic disturbances	16 (3.7)	9 (3.8)	7 (3.6)	1.0
Surgery	13 (3)	7 (6)	6 (3)	1.0
Trauma	7 (1.6)	4 (1.7)	3 (1.5)	1.0
<b>Comorbidities, n (%)</b>				
Chronic renal disease	127 (29.3)	58 (24.6)	69 (35)	0.972
Pulmonary disease	156 (36.0)	89 (37.7)	67 (34)	0.421

<b>Supplementary Table 1. Continued</b>				
	<b>All patients (n=433)</b>	<b>Survivors (n=236)</b>	<b>Non-survivors (n=197)</b>	<b>p</b>
Cardiac disorders	315 (72.7)	167 (69.5)	148 (75.1)	0.313
Gastroenterological disorders	23 (5.3)	9 (3.8)	14 (7.1)	0.129
Neurological	105 (24.2)	62 (26.3)	43 (21.8)	0.277
Rheumatological	13 (3)	8 (3.3)	5 (2.5)	0.603
Endocrinological	161 (37.2)	90 (38.1)	71 (36)	0.617
Malignancy	149 (34.4)	59 (25)	90 (45.7)	<b>&lt;0.001</b>
Concomitant shock with septic patients, n (%)	194 (44.8)	55 (23.3)	139 (70.5)	<b>&lt;0.001</b>
<b>Source of sepsis, n (%)</b>				
Respiratory system	90 (20.8)	24 (10.2)	66 (33.5)	<b>0.003</b>
Urinary tract	74 (17.1)	36 (15.3)	38 (19.2)	<b>0.016</b>
BSI	74 (17.1)	28 (11.9)	46 (23.3)	0.133
Abdominal	22 (5.1)	11 (4.7)	11 (5.6)	0.212
Soft tissue	12 (2.8)	5 (2.1)	7 (3.6)	0.368
Others	3 (1)	0	3 (1.5)	0.290
<b>RIFLE stage, n (%)</b>				
Risk	109 (25.2)	61 (25.8)	48 (24.3)	0.711
Injury	64 (14.8)	32 (13.6)	32 (16.2)	0.438
Failure	83 (19.2)	33 (14)	50 (25.4)	<b>0.003</b>
Loss	11 (2.5)	10 (4.2)	1 (0.5)	<b>0.014</b>
Endstage	32 (7.4)	12 (5.1)	20 (10.2)	<b>0.045</b>
<b>Nutritional support, n (%)</b>				
Parenteral	34 (7.9)	14 (5.9)	20 (10.2)	0.101
Enteral	250 (57.7)	125 (53)	125 (63.5)	0.031
<b>Requirement of respiratory support, n (%)</b>				
Invasive mechanical ventilation	224 (51.7)	50 (21.2)	174 (88.3)	<b>&lt;0.001</b>
Non-invasive mechanical ventilation	98 (22.6)	64 (27.1)	34 (17.2)	<b>0.013</b>
HFNO	22 (5.1)	11 (4.7)	11 (5.6)	0.655
<b>Requirement of RRT, n (%)</b>				
Hemodialysis	110 (25.4)	42 (17.8)	68 (34.5)	<b>&lt;0.001</b>
CRRT	86 (19.9)	9 (3.8)	77 (39)	<b>&lt;0.001</b>
Albumin replacement, n (%)	149 (34.4)	51 (21.6)	98 (49.7)	<b>&lt;0.001</b>
*Median (25 <sup>th</sup> percentile-75 <sup>th</sup> percentile). APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, ICU: Intensive care unit, BSI: Bloodstream infection, HFNO: High flow nasal oxygen, RRT: Renal replacement therapy, CRRT: Continuous renal replacement therapy, RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease				

	<b>All patients (n=433)</b>	<b>Survivors (n=236)</b>	<b>Non-survivors (n=197)</b>	<b>p</b>
Blood urea nitrogen (mg/dL)	42 (28-61)	39 (24-60)	46 (32-64)	<b>0.005</b>
Creatinine (mg/dL)	1.58 (0.95-2.72)	1.41 (0.93-2.65)	1.76 (0.96-2.84)	0.264
Sodium (mEq/L)	139 (134-142)	139 (135-142)	138 (134-142)	0.333
Potassium (mEq/L)	4.05 (3.55-4.6)	3.99 (3.5-4.65)	4.12 (3.57-4.71)	0.389
Chlorine (mEq/L)	103 (99-108)	103 (99-107)	103 (98-108)	0.740
Calcium (mg/dL)	9.1 (8.5-9.6)	9.1 (8.54-9.5)	9.2 (8.4-9.6)	0.462
Phosphorus (mg/dL)	3.6 (2.8-4.9)	3.5 (2.7-4.5)	3.9 (2.9-5.5)	<b>0.023</b>
Magnesium (mg/dL)	1.9 (1.7-2.2)	1.9 (1.7-2.2)	2.0 (1.7-2.2)	0.195
Alanine transaminase (U/L)	23 (13-51)	20 (12-33)	29 (16-72)	<b>&lt;0.001</b>
Aspartat transaminase (U/L)	34 (19-71)	28 (18-52)	42 (22-105)	<b>&lt;0.001</b>
Lactate dehydrogenase (U/L)	362 (217-468)	265 (202-369)	371 (267-577)	<b>&lt;0.001</b>
Total bilirubin (mg/dL)	0.92 (0.59-1.62)	0.79 (0.55-1.32)	1.13 (0.65-1.95)	<b>&lt;0.001</b>
Direct bilirubin (mg/dL)	0.28 (0.15-0.7)	0.22 (0.13-0.46)	0.41 (0.2-1.06)	<b>&lt;0.001</b>
Albumin (g/dL)	2.6 (2.3-3.0)	2.8 (2.4-3.3)	2.5 (2.2-2.8)	<b>&lt;0.001</b>
<b>Blood gas sampling</b>				
pH	7.36 (7.29-7.44)	7.38 (7.32-7.45)	7.34 (7.25-7.42)	<b>&lt;0.001</b>
HCO <sub>3</sub> (mEq/L)	20.8 (16.9-25.4)	22.4 (18.4-26.5)	19.5 (15-23.8)	<b>&lt;0.001</b>
Lactate (mmol/L)	2 (1.3-3.4)	1.75 (1.1-2.8)	2.3 (1.6-4.8)	<b>&lt;0.001</b>
White blood cell count (10 <sup>3</sup> /μl)	10530 (6910-15700)	10500 (7000-14800)	10700 (6700-16900)	0.537
C-reactive protein (mg/L)	97.2 (42.5-171)	81 (29-154)	117 (71-188)	<b>&lt;0.001</b>
Procalcitonin (ng/mL)	0.93 (0.28-3.97)	0.58 (0.21-3.11)	1.44 (0.41-5.2)	<b>&lt;0.001</b>

\*Median (25<sup>th</sup> percentile-75<sup>th</sup> percentile).  
HCO<sub>3</sub>: Bicarbonate

	<b>Adjusted OR (95% CI)</b>	<b>p</b>
Gender	1.22 (0.65-2.27)	0.538
APACHE II Score	<b>1.09 (1.04-1.15)</b>	<b>0.001</b>
SOFA Score	1.04 (0.93-1.17)	0.455
Sepsis as a reason for ICU admission	<b>2.08 (1.10-3.92)</b>	<b>0.025</b>
Respiratory failure as a reason for ICU admission	1.51 (0.77-2.94)	0.232
Malignancy for comorbidities	<b>2.60 (1.34-5.06)</b>	<b>0.005</b>
The absence of renal injury according to RIFLE classification	1.53 (0.75-3.14)	0.244
Requirement of MV	<b>8.0 (3.89-16.47)</b>	<b>&lt;0.001</b>
Requirement of RRT	<b>3.74 (1.86-7.54)</b>	<b>&lt;0.001</b>
pH	0.19 (0.1-3.18)	0.250
Lactate level	1.02 (0.89-1.16)	0.826
Hypoalbuminemia	<b>2.4 (1.16-4.96)</b>	<b>0.018</b>

APACHE: Acute Physiology and Chronic Health Evaluation ICU: Intensive care unit, MV: Mechanical ventilation, RRT: Renal replacement therapy, SOFA: Sequential Organ Failure Assessment OR: Odds ratio, CI: Confidence interval

# Relationship Between Frailty and Quality of Life and Pain Levels in Older Patients Undergoing Hemodialysis

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## Abstract

**Objective:** Frailty is associated with poorer outcomes in dialysis patients, including higher mortality. The purpose of this study was to investigate the connection between pain levels, frailty, and quality of life in older hemodialysis (HD) patients with chronic kidney disease (CKD).

**Materials and Methods:** This cross-sectional study included 103 patients with CKD undergoing HD. Assessment tools included the Edmonton Frail Scale (EFS), the World Health Organization Quality of Life (WHOQOL-BREF) assessment, and the Geriatric Pain Measure (GPM). Patients who scored <24 on the Standardized Mini-Mental test and >7 on the Hamilton Depression Rating Scale were excluded.

**Results:** The patients' mean age was 68.9±2.4 years, with a male-to-female ratio of 54:49. Significant correlations were found between GPM and WHOQOL-BREF ( $p=0.01$ ,  $r=-0.659$ ), GPM and EFS ( $p=0.02$ ,  $r=0.622$ ), and EFS and WHOQOL-BREF ( $p=0.01$ ,  $r=-0.475$ ). In a generalized linear regression model adjusted for age, comorbid conditions, unemployment, body mass index and education level, GPM was associated with higher EFS scores ( $\beta=1.69\pm0.31$ ,  $p<0.001$ ) and lower WHOQOL-BREF scores ( $\beta=-0.456\pm0.059$ ,  $p<0.001$ ).

**Conclusion:** In older patients receiving HD, pain appears to contribute to worsening frailty and reduced quality of life. Effective pain management should be considered to mitigate frailty in this population.

**Keywords:** Frailty, hemodialysis, older adults, pain, quality of life

## Introduction

An estimated glomerular filtration rate (eGFR), of less than 60 mL/minimum and ongoing kidney dysfunction for at least three months are hallmarks of chronic kidney disease (CKD).

It is more common in older adults and affects between 10% and 14% of the general population (1). Renal replacement therapies including hemodialysis (HD), peritoneal dialysis, and kidney transplantation, are essential for managing CKD. Among these, HD is the most widely used, particularly in emergency settings (2).

Older adults undergoing HD often face significant physical and psychosocial challenges due to age-related physiological decline and multiple comorbidities. According to the World Health Organization (WHO), a person's quality of life is determined by how they view their place in life in relation to their culture, values, and goals (3). The health-related quality of life of HD patients is substantially lower than that of the general population because continuous dialysis therapy exacerbates social barriers, emotional distress, and physical limitations (4,5). Given the increasing number of older adult individuals receiving HD, optimizing their quality of life has become a key clinical priority (6).

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Pain is a common issue among HD patients, particularly in older adults, and is associated with lower adherence to dialysis, poor sleep quality, and psychological distress, including depression and anxiety (7,8). The interaction between pain and mental health is complex, as mood disorders can lower the pain threshold, further worsening the patient's overall well-being. In addition, frailty—a syndrome commonly observed in geriatric patients—is an emerging concern in nephrology. Frailty is characterized by decreased physiological reserves, reduced strength and endurance, and heightened susceptibility to disease-related complications (9,10). It is linked to worse clinical outcomes, including higher mortality, and is much more common in CKD patients receiving HD (11). Multiple factors contribute to frailty, including chronic illness, environmental influences, and genetic predisposition (12).

Given the impact of frailty and pain on health outcomes, it is essential to explore their relationship in older adult HD patients. This study tested the hypothesis that pain contributes to increased frailty and reduced quality of life in this population. The aim was to assess the associations between frailty, pain levels, and quality of life in older adults undergoing HD, with the goal of identifying potential intervention targets to improve patient well-being.

## Materials and Methods

### Procedure and Participants

The required sample size was determined to be 103, using the G\*Power program [ $\alpha = 0.05$ , test power  $(1 - \beta) = 0.95$ ], as informed by the study by Santoro et al. (8).

To collect data, patients receiving dialysis for at least three months were interviewed individually in face-to-face sessions. This cross-sectional study included 103 patients with CKD treated at Dr. Ersin Arslan Training and Research Hospital and Gaziantep University Şahinbey Research and Application Hospital Dialysis Unit between June 27, 2022, and August 31, 2022. Participants aged 65 years or older, who had been receiving dialysis for at least three months, were cognitively oriented, and had not undergone kidney transplantation were included in the study. Individuals who scored below 24 on the Standardized Mini-Mental State Examination (MMSE), scored above 7 on the Hamilton Depression Rating Scale (HDRS), or refused to participate after receiving information about the study were excluded.

All assessments, including MMSE, Edmonton Frail Scale (EFS), WHO Quality of Life (WHOQOL-BREF) and Geriatric Pain Measure (GPM), were conducted in a standardized environment. Tests were administered before dialysis sessions to minimize the impact of treatment-related fatigue and physiological fluctuations.

## Assessment Tools

### Standardized Mini-Mental State Examination

The MMSE, first described by Folstein et al. (13) and standardized by Molloy et al. (14) is used for the quantitative evaluation of cognitive impairment in older adults. Higher scores on this 11-question test, which has a total score range of 0 to 30, indicate stronger cognitive performance. The MMSE assesses orientation, short-term and immediate memory, computation, recall, and language. For both educated and unskilled Turkish populations, the questionnaire's validity and reliability have been verified (15).

### Edmonton Frail Scale

The EFS was developed by Rolfson et al. (16). It evaluates 11 frailty parameters, including cognitive status, general health status, functional performance, functional independence, social support, medication use, nutrition, mood, and continence. The EFS incorporates performance-based items to assess cognitive and functional performance. Cognitive status is evaluated by the Clock test, whereas functional performance is evaluated by the Get-Up-and-Go test.

The EFS scoring system classifies individuals as not frail with scores between 0 and 4 points, apparently vulnerable with scores between 5 and 6 points, slightly frail with scores between 7 and 8 points, moderately frail with scores between 9 and 10 points, and severely frail with scores of 11 or more points. In Türkiye, an investigation into the EFS's validity and reliability was carried out (17).

### World Health Organization Quality of Life Assessment

Better quality of life is indicated by higher scores on this scale, which is used to evaluate overall well-being and quality of life. In this study, a short-form version consisting of 26 questions, derived from the long-form version, was used. The short-form scale is divided into four domains, each scored between 20 and 100 points. The Turkish adaptation of the scale was performed by Eser et al. (18).

### Geriatric Pain Measure

The GPM, a 24-item multidimensional scale, was developed by Ferrell et al. (19). It evaluates five dimensions: withdrawal due to pain, pain intensity, pain with movement, pain with strenuous activities, and pain with other activities. Among the 24 items, 22 are answered with "yes" or "no," while the remaining two are scored on a scale from 0 to 10. The total score is obtained by summing the "yes" responses, with a final score ranging from 0 to 42. Every item's score is converted to a 0–100 scale by multiplying it by 2.38. Pain severity is categorized as follows: mild pain for scores between 0 and 30, moderate pain for scores between 30 and 69, and severe pain for scores of 70 or higher.



Dursun (20) conducted the validity and reliability analysis of the scale in Türkiye.

### Statistics

The Shapiro-Wilk test was used to assess whether numerical variables followed a normal distribution. The Pearson correlation coefficient was applied to evaluate relationships between WHOQOL-BREF, GPM, and EFS. Categorical variables were analyzed using the chi-square test.

A generalized linear regression model was used to examine the associations among GPM, WHOQOL-BREF, and EFS. The normality of the dependent variable was tested using the Shapiro-Wilk test. Before conducting multivariate regression, univariate analyses were performed, and variables with  $p < 0.10$  were considered for inclusion in the model.

The variance inflation factor (VIF) was used to measure multicollinearity, and variables with a VIF greater than 10 were removed from the model. Comorbid conditions, unemployment, body mass index (BMI), and education level were included as covariates in all models. Statistical significance was set at  $p < 0.05$ . All analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

### Results

This study included 103 patients with a mean age of  $68.9 \pm 2.4$  years. The male-to-female ratio was 54:49, and the median duration since the onset of HD was 42 months. The sociodemographic and clinical data of the patient and control groups are summarized in Table 1. Significant correlations were observed between GPM and WHOQOL-BREF ( $p = 0.01$ ,  $r = -0.659$ ), GPM and EFS ( $p = 0.02$ ,  $r = 0.622$ ), and EFS and WHOQOL-BREF ( $p = 0.01$ ,  $r = -0.475$ ). Table 2 displays the findings of the correlation analysis.

Patients were classified based on frailty levels as follows: not frail (5 patients), apparently vulnerable (11 patients), slightly frail (13 patients), moderately frail (20 patients), and severely frail (54 patients).

In a generalized linear regression model, adjusted for age, comorbid conditions, unemployment, BMI, and education level, GPM was associated with higher EFS scores ( $\beta = 1.69 \pm 0.31$ ,  $p < 0.001$ ) and lower WHOQOL-BREF scores ( $\beta = -0.456 \pm 0.059$ ,  $p < 0.001$ ).

No significant correlation was found between EFS/WHOQOL-BREF and duration since CKD diagnosis, duration since HD initiation, or age. However, BMI was significantly correlated with EFS ( $r = 0.214$ ) and WHOQOL-BREF ( $r = -0.475$ ).

### Discussion

The association between frailty, quality of life, and pain levels in CKD patients undergoing HD was examined in this study.

A moderate correlation was found between pain and frailty, as well as between pain and quality of life. The increase in pain scores explained 38.7% and 42.4% of the variation in frailty and quality of life, respectively.

Frailty is associated with poorer outcomes in dialysis patients, including higher mortality, falls, hospitalizations, a lower rate of transplantation, cognitive deficits, and vascular access failure (21,22). Identifying frailty early and taking necessary precautions can improve the quality of life. We could not find a longitudinal study identifying factors that predict frailty among patients with CKD. However, one potential factor predictive of frailty is in older adults and patients undergoing HD (23,24). Therefore, we excluded patients who scored  $< 24$  on the standardized

**Table 1. Descriptive features of the patients**

		Means $\pm$ SD, median (25/75 quartiles)
Age		68.9 $\pm$ 2.4
Duration since the onset of diagnosis (CKD) (months)		61.4 $\pm$ 5.8
Duration since the onset of hemodialysis (months)		42 (24/69)
BMI		27.3 $\pm$ 4.2
Sex	Female	49 (47.6%)
	Male	54 (52.4%)
Marital status	Single	5 (4.9%)
	Married	98 (95.1%)
Level of education	Not literate	23 (22.3%)
	Literate	13 (12.6%)
	Primary school	50 (48.5%)
	High school	11 (10.7%)
	University	6 (5.8%)
The caregiver	Wife or husband	67 (65%)
	Daughter or son	20 (19.4%)
	Other	16 (15.5%)
Comorbidity	Diabetes mellitus	25 (24.3%)
	Hypertension	17 (16.5%)
	COPD	1 (1%)
Smoking status	Yes	13 (12.6%)
	No	90 (87.4%)

CKD: Chronic kidney disease, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, SD: Standard deviation

**Table 2. Correlations between assessment tools**

	EFS	WHOQOL-BREF	GPM
EFS		-0.475**	0.622**
WHOQOL-BREF	*		-0.659**

\*\* $p < 0.01$   
EFS: Edmonton Frail Scale, WHOQOL-BREF: World Health Organization Quality of Life, GPM: Geriatric pain measure

MMSE to eliminate this confounding factor. A cross-sectional study also reported that frailty increases as eGFR decreases before dialysis initiation (25). Lee et al. (26) found that nutritional markers, such as blood urea nitrogen, serum creatinine, and total iron-binding capacity, were negatively associated with frailty status. Other predictors of frailty include age, comorbid conditions, disability, unemployment, higher BMI, and lower education level. In this study, BMI positively correlated with pain but not with age, as all patients were >65 years old. Meanwhile, some studies have found that delayed initiation of dialysis is significantly associated with a lower quality of life (27,28). However, no significant association was found between quality of life and time elapsed since HD initiation. A possible reason for this is that our study population consists of older people who have already been on dialysis for an extended period. After adjusting for age, comorbid conditions, unemployment, BMI, and education level, frailty continued to be associated with higher pain scores. Therefore, pain management in patients undergoing HD should be emphasized further. Pain is the most common symptom that impairs activities of daily living in later life (29) and affects the frailty status of patients receiving dialysis.

We found that pain is not only related to frailty but also has a significant relationship with quality of life in these older patients. Similarly, Samoudi et al. (27) showed that pain has a significant negative effect on the quality of life in patients with end-stage renal disease undergoing HD who had a mean age of 54 years ( $r=-0.590$ ,  $p<0.001$ ) (27). Dantas and Martins (30) reported that the prevalence of pain, which significantly interferes with general activities such as sleep and walking, is higher in the HD group than in the control group.

Frailty is associated with a lower quality of life (31). Similar to previous studies, a significantly positive correlation was found between frailty and quality of life in the present study. This is an expected result, as physical inactivity, diminished strength, and impaired biological functions affect both factors.

### Study Limitations

The sample size and cross-sectional design are limitations of this study. Depression and anxiety are also common in patients undergoing HD (32). Therefore, not excluding depressive disorders with a structured interview is another limitation. However, patients who had an HDRS score of <7 were excluded. Additionally, the scale used to assess quality of life is a limitation, applying a scale specifically for older individuals and the HD population would have strengthened the results. Another limitation is the exclusion of patients with cognitive impairment, which may have introduced bias by limiting the sample to only fit or mildly frail individuals, as cognitive decline is commonly associated with frailty in HD patients.

### Conclusion

In older patients receiving HD, the effect of pain goes beyond simple discomfort, often contributing to a worsening quality of life and eventual frailty. The findings support an association between pain and frailty/quality of life, independent of confounders. Further prospective studies are needed to elucidate the mechanisms underlying the relationship among pain, frailty, and quality of life. Effective management and treatment strategies must be developed immediately.

### Ethics

**Ethics Committee Approval:** The study was approved by the ethics committee of the Gaziantep University Ethics Committee Presidency (decision number: 2021/272, date: 15.09.2021).

**Informed Consent:** Informed consent was obtained from all participants.

### Footnotes

#### Authorship Contributions

Surgical and Medical Practices: A.Z.Ş., N.Ö., Ş.K.Ş., Concept: A.Z.Ş., N.Ö., Ş.K.Ş., Design: A.Z.Ş., N.Ö., Data Collection or Processing: N.Ö., Ç.Ö., Analysis or Interpretation: A.Z.Ş., Ş.K.Ş., Literature Search: A.Z.Ş., N.Ö., Ş.K.Ş., Writing: A.Z.Ş., N.Ö., Ş.K.Ş.

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# The Validation of Pharmaceutical Pictograms Among Turkish Individuals Aged 50 and Over

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## Abstract

**Objective:** Aging is associated with physiological changes that impact medication use and adherence, particularly among older adults. This study evaluates the validity and comprehensibility of pharmaceutical pictograms developed by the International Pharmaceutical Federation for individuals aged 50-79 in Türkiye.

**Materials and Methods:** A cross-sectional survey was conducted with 150 participants visiting a community pharmacy in Ankara. Data were collected through a structured questionnaire assessing socio-demographic characteristics, health literacy, and understanding of 15 selected pictograms.

**Results:** Indicated that 46.6% of the pictograms were valid, with an average prediction performance of 61.01%. Factors such as health literacy and familiarity with medication instructions significantly influenced participants' understanding.

**Conclusion:** The findings suggest a need for culturally appropriate pictograms and enhanced health literacy initiatives to improve medication adherence among older adults in Türkiye.

**Keywords:** Pharmacautical pictograms, older adults, validation, health literacy

## Introduction

Aging is an inevitable and natural process that primarily results in differences in an individual's anatomical structure and physiological functions, as well as in mental capabilities, social relationships, and psychology. With the increasing life expectancy and declining fertility rates across countries worldwide, the proportion of individuals aged 65 and older is rising more rapidly compared to other age groups (1). The United Nations defines countries where the population of older adults exceeds 10% of the total population as "Aged" nations, and it is projected that by 2030, the share of older adults in Türkiye will reach 12.9% (2). The prevalence of chronic diseases also increases with aging (3). One of the natural consequences of this phenomenon is the dramatic increase in medication usage among older adults compared to other age groups (4). In addition to having multiple

chronic conditions, older adults constitute a unique group in medication use due to physiological changes, alterations in the absorption, distribution, metabolism, and excretion of drugs, as well as difficulties in adhering to dosage and administration guidelines (5).

The success of pharmacological treatment depends directly on the adherence of older adults to the prescribed regimen. Adherence to medical treatment is defined as the extent to which a patient's or caregivers' behaviours regarding medication use align with medical recommendations. The increasing incidence of medication non-adherence among older adults leads to various adverse outcomes, including the deterioration of medical conditions, decreased quality of life, increased morbidity and mortality, higher rates of hospital readmission, prolonged hospital stays, and escalating healthcare costs (6). Therefore, it is crucial to optimally present the medications

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to improve patient adherence and achieve the best possible treatment outcomes.

Older adults should always be informed by their doctors and pharmacists about the correct procedures for medication use. However, studies have shown that only 20-60% of verbal medication instructions provided by healthcare professionals are typically remembered (7-9). Therefore, written instructions that patients can easily access and refer to are a critical tool for providing more lasting medication information (10). This is particularly important for older individuals who are more likely to encounter difficulties in recalling instructions. Insufficient understanding or misinterpretation of medication instructions can lead to non-adherence to treatment, less effective therapies, poorer health outcomes, and medication errors (4,11). Older adults, especially those with lower education levels, may lack the necessary reading or language skills to comprehend much or all the written medication information. Furthermore, their ability to read and understand medication information may also be affected by declining visual capabilities. Due to poor visual acuity (e.g., contrast sensitivity) and low literacy, some older adults may need to ask family members or friends to read medication information for them (9).

One way to facilitate patients' understanding of prescribed pharmacotherapy is to support labels and instructions with visual tools such as pharmaceutical pictograms (12,13). Pictograms graphically represent actions (e.g., instilling drops in the eye) in a manner that can be understood regardless of the patient's literacy skills (14). A pictogram is defined as a figurative or metaphorical two-dimensional drawing intended to attract attention and convey information about an object or express an idea (15). Research has demonstrated that pictograms enhance patients' understanding of the proper use of medications, thereby improving adherence (4,13,16-20).

The use of pictograms has garnered increasing attention in recent years, likely due to heightened awareness among healthcare professionals regarding the necessity of providing adequate information to patients, such as older adults, children, and individuals with low literacy levels, who struggle to understand their treatments (21-24). There are two widely used, validated, and comprehensive sets of pharmaceutical pictograms: the United States Pharmacopeia (USP) pictograms and the set of pictograms developed by the International Pharmaceutical Federation (FIP). The FIP pictogram set was developed as downloadable software available on the FIP website. Pictogram projects were initiated in 2004 with the aim of creating a common language between professionals (pharmacists) and patients, resulting in approximately 100 pictograms that were categorized according to various purposes. Furthermore, these pictograms have been tested and validated across different cultures, age groups, and educational levels (15,24,25) and

were last updated in February 2017 to address comprehension issues (26). While FIP's pharmaceutical pictograms are available for use, there has been no study in the literature designed to assess the comprehensibility of these pictograms among older individuals in Türkiye. This study aims to test the validity of the pictograms developed by FIP among individuals aged 50 and over who are likely to benefit the most from their use.

## Materials and Methods

This study is designed as a quantitative descriptive cross-sectional field research, based on the methods of similar pictogram validity studies (4,15,16,25) and the recommendations of Dowse (27), who has conducted research on pharmaceutical pictograms for over 20 years. This study was carried out in accordance with the principles of the Declaration of Helsinki. It has been approved by the Medical and Health Sciences Research Board and the Ethics Committee of Başkent University (approval number: 23/15, date: 18.01.2023) and supported by the Başkent University Research Fund. Informed consent was obtained from all participants.

## Participants

The population of the study consists of individuals aged 50-79 who visited a community pharmacy in the Mamak district of Ankara in April 2023. The sample size was computed as 110 by accepting  $\alpha=0.05$ ,  $Z_{\alpha/2}=1.96$ ,  $p=0.67$  [based on the International Organization for Standardization (ISO) criterion, proportion of citizens who understand the meaning of symbolic images correctly], and margin of error=0.1. The target sample was reached through a convenience sampling method among individuals visiting the community pharmacy in Mamak, Ankara, to obtain prescription or over-the-counter medications. Inclusion criteria for the study were: being between the ages of 50 and 79, being a Turkish citizen, having purchased prescription or over-the-counter medication in the last month, scoring 24 or higher on the Standardized Mini-Mental Test, not being deaf (self-reported), not having more than 3 diopters of myopia, not having more than 2 diopters of hyperopia, and being willing to participate in the study.

## Data Collection

Data for the study were collected using a questionnaire consisting of three sections. Before administering the questionnaire, the Standardized Mini-Mental Test, which has been validated and tested for reliability in Turkish by Güngen et al. (28), was conducted. Participants who scored 24 or above were eligible to complete the questionnaire.

The first section of the questionnaire includes questions regarding the socio-demographic information of the adults (such as age, gender, education level, income level, and occupation). Additionally, to assess the individuals' health literacy levels, the Turkish version of the Single-Item Health Literacy Screening



developed by Morris et al. (29) was employed using a 5-point Likert Scale (30). Questions regarding perceived health status were included through a single-item "perceived health status" measure on a 5-point Likert Scale, as well as questions on the presence of chronic diseases and medication use. Lastly, to evaluate medication adherence, the Morisky Medication Adherence Scale, developed by Morisky et al. (31) in 1986, was used. This scale consists of four yes/no questions and has been validated and tested for reliability in Turkish by Yılmaz and Buzlu (32).

The second section of the questionnaire includes 15 pharmaceutical pictograms selected from the 103 pictograms developed by FIP (Appendix 1). The decision to limit the study to 15 pictograms was based on the consideration that including all pictograms would lengthen the interview duration and increase participant fatigue. This choice aligns with Dowse's (27,33) recommendations for validity studies, which suggest using 15-30 pictograms, as well as the frequent use of 15 pictograms in other validity research. Based on a review of the literature on pictogram validity among older adults in other countries (4,25,34,35), the 15 most evaluated pictograms in other studies were chosen for their potential relevance among commonly used medications for older adults. To assess the predictability and comprehensibility of the pictograms, a survey was developed based on ISO 9186 standards. The purpose of ISO 9186 is to ensure that graphic symbols are understandable to all users. In this test, participants were asked to respond to the question, "What do you think this pictogram means?" for each pictogram.

In the third section of the questionnaire, the pictograms were presented along with their meanings, and participants were asked to evaluate the extent to which the pictograms met their intended meanings. Evaluations were conducted on a 7-point Likert scale, ranging from weak to strong relationships.

**Pilot Study:** A pilot application of the questionnaire forms was conducted to test the comprehensibility of the forms. As a general rule of thumb, that the sample size for a pilot study should be 10 percent of the anticipated sample for the main study (36), a different set of 10 individuals who met the inclusion criteria completed the questionnaire form. Based on the results of the pilot study, the questionnaire forms were revised.

**Data Collection:** Data for the study were collected through face-to-face interviews at a community pharmacy located in the Mamak district of Ankara. The administration of the questionnaire took approximately 25-30 minutes.

### Statistics

The data were analysed using IBM SPSS 27 software, employing validity analysis, descriptive statistics, and hypothesis testing.

**Validity of Pictograms:** Validation studies for pictograms have utilized the parameters of transparency and translucency,

either independently or in combination, to establish pictogram validity (4,25,34). Transparency refers to the understanding of a pictogram without any accompanying text, while translucency refers to the degree of perceived representativeness between a pictogram and its intended meaning (4,25,34). In this study, pictogram validity was similarly established based on transparency and translucency. The transparency parameter was evaluated with the prediction score, and the translucency was evaluated with the semantic proximity assessment.

**Prediction Score:** Open-ended comments from participants regarding their understanding of the pictograms were reviewed by researchers. Each comment was independently assessed for alignment with the intended meanings of the pictograms. Inter-rater reliability was assessed using Fleiss's kappa coefficient and was calculated as 0.876 (95% confidence interval: 0.721-0.987) for 15 pictograms. In the classification made by Fleiss, a kappa value of 0.75 and above was considered to be perfect agreement. Then, the researchers discussed the answers with different ratings. Consensus was sought for inconsistent ratings, and if a consensus could not be reached, the majority rating was accepted as valid. Correct responses were assigned a score of "1", partially correct responses received a score of "0.5", and incorrect responses received a score of "0". The prediction score was calculated as the percentage of correct (both fully and partially) responses obtained for each pictogram (e.g., the "I" pictogram was correctly understood by "x%" of participants). Each pictogram's prediction score was evaluated against the ISO standard comprehension criterion of 67%. Both counts and percentages were computed for prediction scores.

**Semantic Proximity Assessment:** A minimum acceptable level of  $\geq 5$  points were established for evaluating the semantic proximity of the pictograms. Pictograms for which at least 85% of participants rated 5 points or above were considered to align with the intended meanings. Pictograms that met both the 67% prediction score criterion and had a semantic proximity score above 5 were classified as "valid". Pictograms that met only the prediction score criterion were classified as "partially valid", while those that did not meet either condition were classified as "invalid".

**Independent Variables:** The independent variables of the study included socio-demographic characteristics, health literacy levels, characteristics related to health status, medication use characteristics, and medication adherence. For the independent variables, counts and percentages were calculated for categorical variables, and means and standard deviations were calculated for continuous quantitative variables.

**Hypothesis Testing:** The accuracy percentage of a participant's task in predicting the meaning of the pictograms was considered as the prediction performance (e.g., participant "y" successfully



understood an average of "z%" of the pictograms). The mean and standard deviation were computed for prediction performance, and the normality of the distribution was assessed using the Kolmogorov-Smirnov test. To identify factors associated with prediction performance, an Independent Samples t-test was conducted for two-group categorical variables, and One-Way Analysis of Variance was performed for categorical variables with more than two groups.

## Results

The distribution of participants' socio-demographic characteristics is presented in Table 1. Of the participants, 55.4% are male and 44.6% are female. The average age of participants is calculated to be  $57.74 \pm 8.23$  years. Among the participants, 75% are married, while 25% are divorced, separated, widowed, or single. In terms of education, 53.6% of participants have a high school education or lower, while 46.4% have at least an associate's or bachelor's degree. Regarding occupational status, 26.8% are employed in professional occupations, while 29.5% work in unskilled jobs. Additionally, 43.8% of the participants are retirees, homemakers, or unemployed. Notably, 54.5% of participants have an income below the poverty line (Table 1).

The characteristics related to participants' health status and medication use are presented in Table 2. A total of 60.7% of participants rated their overall health status as good. Among

the participants, 54.5% reported having a chronic illness, while 45.5% did not have any chronic conditions. Regarding medication reports, 45.5% of participants possess a medication report, while 54.5% do not. Additionally, 65.2% of participants are aware of the side effects of medications, whereas 34.8% lack such knowledge. When it comes to purchasing over-the-counter medications, 31.3% of participants do so, while 68.8% do not purchase over-the-counter medications. Furthermore, 52.7% of participants frequently or always read the usage instructions, 73.2% understand them, while 26.8% do not (Table 2).

The percentage of participants' understanding of the pictograms (prediction performance) averaged  $61.01 \pm 16.94\%$ . Upon examining the prediction performances of the participants, those who used over-the-counter medications, those who found medication instructions easily, and with high health literacy levels exhibited significantly higher prediction performances ( $p < 0.05$ ) (Table 2).

Table 3 presents the levels of comprehensibility (prediction scores) and semantic proximity assessments for the pictograms. The pictograms with the highest correct responses were P8 ("Do not drink alcohol") at 95.5% and P12 ("Do not crush") at 92.9%. Conversely, the pictograms with the lowest comprehensibility were P3 ("Inject under the skin") at 15.2%, P4 ("Two tablets") at 26.8%, and P6 ("Inhale") at 36.6%. According to Table 3, four pictograms (18.2%) did not meet the ISO' standard of 67%: P3

**Table 1. Distribution of participants according to their socio-demographic characteristics and average prediction performances**

	n	%	Mean $\pm$ SD	p
Gender				
Female	50	44.6	61.86 $\pm$ 16.64	0.634
Male	62	55.4	60.32 $\pm$ 17.28	
Occupation				
Blue collar	33	29.5	61.01 $\pm$ 14.90	0.795
White collar	29	25.9	63.33 $\pm$ 17.62	
Retired	30	26.8	60.67 $\pm$ 15.16	
Not-working	20	17.9	58.85 $\pm$ 19.91	
Having a partner				
Yes	28	75.0	57.5 $\pm$ 15.46	0.207
No	84	25.0	62.18 $\pm$ 17.33	
Age				
50–64	90	80.4	61.77 $\pm$ 16.94	0.336
65–79	22	19.6	57.87 $\pm$ 16.95	
Income				
Below poverty line	61	54.5	59.72 $\pm$ 17.54	0.382
Above poverty line	51	45.5	62.54 $\pm$ 16.22	
Education				
High school or lower	60	53.6	59.27 $\pm$ 16.58	0.246
At least associate/bachelor's degree	52	46.4	63.01 $\pm$ 17.29	
SD: Standard deviation				

("Inject under the skin"), P4 ("Two tablets"), P6 ("Inhale"), and P13 ("Take with food"). In the semantic proximity assessment, the average scores for P4 ("Two tablets") and P13 ("Take with food") fell below 5. Of the 15 pictograms evaluated for meaning prediction and visual semantic relationships, 46.6% (n=7) were found to be valid, 26.6% (n=4) were partially valid, and 26.6% (n=4) were deemed invalid.

## Discussion

The comprehensibility of medication instructions is crucial for improving adherence to medication therapies among older adults. This study utilized a cross-sectional field approach in Ankara to evaluate the validity of pictograms developed by the

FIP among individuals aged 50 and older in Türkiye. The findings of the study indicate two significant conclusions.

First, it was determined that 46.6% of the pictograms were valid, 26.6% were not sufficiently understood, and 26.6% required revision. Studies conducted among older adults in Canada (25) and Poland (34) reported higher validity rates, while lower validity rates were observed in studies in Singapore (4) and the Philippines (35). The notably low validity of the pictograms developed by FIP among Turkish individuals aged 50 and over may stem from several factors. These include generally low educational levels among older adults in Türkiye (with only 7.9% being university graduates according to 2021 TSI statistics), specifically low

**Table 2. Distribution of participants according to their health status and medication use and average prediction performances**

	n	%	Mean ± SD	p
Chronic disease				
Yes	61	54.5	60.54±16.51	0.752
No	51	45.5	61.56±17.59	
General health status				
Good	68	60.7	62.50±18.85	0.250
Not-good	44	39.3	58.71±13.35	
Medication report				
Yes	51	45.5	60.39±17.21	0.725
No	61	54.5	61.53±16.83	
Knowledge of side effects				
Yes	73	65.2	62.28±16.98	0.279
No	39	34.8	58.63±16.81	
Person administering medication				
Self	109	98.2	61.24±16.97	0.288
Others	2	1.8	48.33±11.78	
Purchasing over-the-counter medication				
Yes	35	31.3	66.66±15.75	0.017*
No	77	68.8	58.44±16.93	
Reading medication instructions				
Rarely or never	59	52.7	59.77±15.41	0.417
Frequently or always	53	47.3	62.38±18.55	
Understanding instructions				
Yes	82	73.2	63.25±16.76	0.020*
No	30	26.8	54.88±16.15	
Health literacy				
Low	70	62.5	55.79±18.46	0.011*
High	42	37.5	64.14±15.25	
Medication adherence				
High	34	30.4	58.67±16.08	0.063
Medium	50	44.6	59.12±16.19	
Low	28	25.0	67.50±18.23	
*p<0.05, SD: Standard deviation				

\*p<0.05, SD: Standard deviation

**Table 3. Prediction score and semantic closeness assessment of pictograms**

	Prediction score				Semantic closeness		Validation
	False (%)	Partially correct (%)	Correct (%)	Total correct (%)	≥5 score (%)	Mean ± SD	
P1	14.3	78.6	7.1	85.7	63.4	5.12±1.90	Partially valid
P2	13.4	78.6	8	86.6	65.2	5.16±1.86	Partially valid
P3	84.8	10.7	4.5	15.2	61.6	5.01±2.09	Not-valid
P4	73.2	0	26.8	26.8	59	4.96±2.13	Not-valid
P5	12.5	14.3	73.2	87.5	86.6	6.08±1.30	Valid
P6	63.4	13.4	23.2	36.6	80.4	5.71±1.88	Not-valid
P7	25	2.7	69.6	72.3	83.1	5.95±1.88	Partially valid
P8	4.5	50	45.5	95.5	88.3	6.31±1.31	Valid
P9	29.5	4.5	66.1	70.6	90.2	6.50±1.32	Valid
P10	12.5	0	87.5	87.5	89.3	6.40±1.65	Valid
P11	10.7	1.8	87.5	89.3	91.2	6.46±1.36	Valid
P12	7.1	0.9	92	92.9	92.8	6.54±1.38	Valid
P13	52.7	18.8	28.6	47.4	57.2	4.63±2.50	Not-valid
P14	29.5	0	70.5	70.5	79.5	5.71±2.12	Partially valid
P15	8	8	83.9	91.9	92	6.39±1.42	Valid

SD: Standard deviation

health literacy (37,38), the lack of a standardized pictogram set leading to low familiarity, and the potential cultural inappropriateness of these pictograms.

For example, the two tablets pictogram, which might initially seem straightforward, was often misunderstood by participants. While most correctly interpreted that the tablets were to be taken "orally" and "swallowed", they also failed to grasp the instruction to take "two" tablets. This highlights a common limitation in visual design where numerical information is not explicitly emphasized. Incorporating clearer visual elements, such as prominently displaying two distinct tablets or using numerical symbols alongside the pictogram, could significantly enhance interpretive accuracy. Similar issues have been identified in previous studies, which underscore the importance of precise and unambiguous design in improving user comprehension of numerical instructions (16,39).

Similarly, the pictogram for "Take with food" was frequently misinterpreted by participants as meaning "Eating fish", "Healthy eating", or "Taking medication before/after meals". These misinterpretations could be attributed to the cultural disconnection between the imagery used and local dietary habits. For instance, replacing the fish symbol with a more culturally relevant food item, such as bread or rice, commonly consumed in Türkiye, might improve comprehension. This aligns with findings in the literature that emphasize the importance of integrating local cultural contexts into pictogram design to enhance clarity and effectiveness (4,40).

When examining other pictograms categorized as "invalid", the low prediction score for the "Inject under the skin" pictogram may reflect the physical and cognitive challenges older adults face with injection procedures. Research suggests that older adults may require additional visual or textual clarification to understand complex medical instructions, especially for less familiar procedures (41). Meanwhile, the pictogram for "Inhale" might suffer from a lack of familiarity among those without respiratory issues regarding the use of inhalers. These findings emphasize the critical need to design pictograms that are tailored to the target audience's level of experience and knowledge. Enhancing these pictograms with supplementary text or more recognizable symbols could improve their effectiveness, as studies have recommended, advocating for iterative and user-centered design processes (35,42).

Second, the average prediction performance was found to be relatively low at 61%. However, it was revealed that prediction performance was influenced more by modifiable factors related to medication use—such as health literacy, over-the-counter medication use, and ease of understanding instructions—rather than by socio-demographic characteristics. Numerous studies in the literature indicate that as medication use increases, so does awareness and familiarity with pictograms (4,42,43). Consistent with the findings of this study, a strong relationship between health literacy and pharmaceutical pictogram prediction performance has also been highlighted in other studies on pictogram validity (40,43–46). The emergence of health literacy as a more significant indicator than socio-

demographic characteristics can be considered valuable from the perspective of medication and health policies. This suggests that effective interventions to enhance health literacy may have a substantial impact on understanding medication regimens and adhering to treatment. Improving health literacy could ultimately lead to better health outcomes for older adults, emphasizing the need for targeted educational programs and resources.

### Study Limitations

This study has several limitations. First, the data were collected solely from older adults obtaining medications from a single pharmacy in Ankara, which limits the generalizability of the results. In a country like Türkiye, characterized by high cultural diversity, obtaining data from different regions and socioeconomic groups could contribute to a broader assessment of the validity of the pictograms. Second, while this study included pictograms developed by the FIP, that older adults are most likely to encounter, it is important to note that there are nearly 200 pictograms developed by both FIP and USP. Therefore, the need for validity assessments of additional pictograms should not be overlooked. Finally, this study focused exclusively on the validity of the pictograms; thus, exploring different research designs (such as comparing the effectiveness of text-plus-visual, versus text-only formats) could be beneficial. Such studies would enhance the understanding of the role of pictograms in information dissemination and could provide valuable insights for developing more effective health communication strategies tailored to older adults.

### Conclusion

The findings of this study indicate that medication instructions need to be made more accessible and comprehensible for older adults. In this context, incorporating pictograms into medication instructions when providing healthcare services to older adults in Türkiye and adapting these visuals to local culture could be considered an effective strategy to enhance medication adherence. In societies like Türkiye, where health literacy is low, it is crucial to ensure that the effectiveness of pictograms is optimized by considering cultural appropriateness in their design. Additionally, visual aids should be tailored to accommodate individuals with lower educational levels, thereby improving understanding and adherence to medication regimens.

### Ethics

**Ethics Committee Approval:** It has been approved by the Medical and Health Sciences Research Board and the Ethics Committee of Başkent University (approval number: 23/15, date: 18.01.2023).

**Informed Consent:** Informed consent was obtained from all participants.

### Footnotes

#### Authorship Contributions

Concept: F.Y., B.K., Design: F.Y., B.K., Data Collection or Processing: B.K., Analysis or Interpretation: F.Y., Z.Ö., Literature Search: F.Y., Z.Ö., Writing: F.Y., Z.Ö.












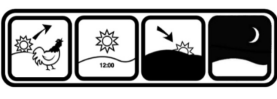



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Appendix 1. Pictograms used in questionnaire form					
No	Pictograms	Meaning	No	Pictograms	Meaning
1		1 drop in the left ear	9		Keep in the fridge
2		1 drop in the right eye	10		Shake
3		Inject under the skin	11		Do not drive
4		2 tablets	12		Do not crush
5		Dissolve 1 sachet in water	13		Take with food
6		Inhale	14		Morning, noon, evening, night
7		Night	15		Seek medical advice
8		Do not drink alcohol			



# The Relationship Between Frailty and Psychosocial Adjustment in Older Adults with COPD

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## Abstract

**Objective:** Frailty in older adults can manifest through various symptoms; reduced oxygen capacity is one of its prominent indicators. As individuals age, the prevalence of chronic obstructive pulmonary disease (COPD), a condition characterized by diminished oxygenation, also tends to increase. COPD and frailty can cause psychosocial adjustment difficulties. The study investigated the relationship between frailty and psychosocial adjustment in older adults with COPD.

**Materials and Methods:** This descriptive-correlational study was conducted with 137 older patients who met the inclusion criteria. Data were collected using a patient identification form, the Psychosocial Adjustment to Illness Scale-self report (PAIS-SR), and the Edmonton Frail Scale (EFS).

**Results:** Participants had a mean PAIS-SR score of  $54.37 \pm 12.91$ . They had a mean EFS score of  $6.79 \pm 3.83$ . Age and COPD stage affected their median PAIS-SR scores ( $p < 0.05$ ). Age, education, occupation, and hospitalization also affected their EFS scores ( $p < 0.05$ ). There is a negative correlation between frailty and psychosocial adjustment. Moreover, the COPD stage and frailty are associated with psychosocial adjustment.

**Conclusion:** The frailer the older COPD patients are, the lower their psychosocial adjustment. Poor psychosocial adjustment is associated with COPD stages and frailty. Age, education, hospitalization, and psychosocial adjustment are predictors of frailty. Older COPD patients with low education levels, advanced disease stages, and frequent hospitalizations should be assessed for frailty and psychosocial adaptation. Evaluating patients may help us detect frail patients with low adaptation levels. In that way, we can meet patients' monitoring and care needs in the early period.

**Keywords:** Adjustment, aging, chronic obstructive pulmonary disease, frailty, geriatric nursing

## Introduction

Chronic obstructive pulmonary disease (COPD), a progressive yet preventable disease, is the fourth leading cause of death (4.7%), with a global prevalence of 10.3% (1,2). In Türkiye, respiratory diseases are the third leading cause of death, with COPD being responsible for 61.5% of deaths due to respiratory diseases (1,3). While there has been a substantial decrease in mortality from other prominent causes of death in recent years, there has been

a rise in mortality due to COPD (2,4). The prevalence of COPD, which is 13.2% at ages 65-69 and 17.9% at ages 75-79, rises with advancing age (5). As the number of risk factors grows and the population continues to age, it is anticipated that the prevalence of COPD will continue to rise in the years ahead (2).

The process of aging often leads to frailty, marked by functional losses in multiple organs or systems and heightened vulnerability to stressors. Frailty involves cognitive, psychological, and social factors (6). According to Buchner and Wagner (6), a primary

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sign of frailty is decreased energy metabolism and O<sub>2</sub> levels due to cardiac or pulmonary disease. Individuals with COPD are also prone to frailty due to the condition's characteristic symptoms of shortness of breath and hypoxia, which are frequently associated with aging (2). Almost one in every three individuals with COPD is frail (32%), which is associated with shortness of breath (7).

Both shortness of breath and comorbidities play a role in the advancement of COPD, rendering the management of the disease more challenging (1). Chronic diseases are stressors that change adaptive capacity (8,9). Some patients consider COPD a devastating condition because COPD is a progressive disease without an effective cure. Progressive pathophysiological changes, medication requirements, and symptoms, (e.g., breathing difficulties) decrease COPD patients' quality of life, resulting in psychological issues (9,10). Research shows that COPD patients often experience death anxiety, which exacerbates their difficulties in adapting socially to the disease and life (9). COPD also leads to frequent hospitalizations and a reduced workforce due to exacerbations, resulting in socioeconomic challenges (1). Older COPD patients with long-term disease and frequent exacerbations exhibit low levels of disease acceptance (11). Therefore, COPD is not only a physical but also a psychosocial condition with biological, psychological, social, familial, and environmental consequences (9,12). Research has shown that COPD patients have poor psychosocial adaptation (9,13,14). Patients with COPD need to adapt to these changes to maintain homeostasis (12).

Psychosocial adjustment is influenced by various factors related to both the disease and its treatment (9,13). Conversely, changes in psychosocial adjustment-whether improvement or decline-can impact the prognosis. Additionally, frailty is common in older COPD patients (5). Uchmanowicz et al. (11) reported that high levels of physical and social frailty reduced the level of disease acceptance. However, the link between frailty and psychosocial adjustment in older COPD patients is unclear. Healthcare professionals should adopt a holistic approach when dealing with individuals with COPD, regularly monitoring their condition and evaluating any problems or challenges they may face. Determining the relationship between frailty and psychosocial adjustment in older adults with COPD and the factors affecting this relationship will guide a holistic approach in the evaluation of care management and treatment. This study was conducted to determine the relationship between frailty and psychosocial adjustment in older individuals with COPD.

## Materials and Methods

### Design and Samples

This descriptive-correlational study population consisted of all patients with COPD admitted to the inpatient and outpatient units of a public hospital in Türkiye between December 2019

and February 2020. The inclusion criteria were 1) aged 65 years and older, 2) having COPD for at least six months, 3) having no mental disorder, 4) having no communication problems, and 5) volunteering. The sample consisted of 137 participants. At the end of the study, a power analysis was performed based on the results of the second regression model. The results indicated a power of 99.9% ( $\alpha=0.05$ ). The independent variables were age, gender, education, and COPD duration, and stage. The dependent variables were psychosocial adjustment and frailty levels.

### Data Collection

The data were collected face-to-face using a patient identification form, the Psychosocial Adjustment to Illness Scale-self report (PAIS-SR), and the Edmonton Frail Scale (EFS). Outpatients were interviewed in the meeting room, while inpatients were interviewed in the patient rooms. Each interview lasted about 25 minutes.

### The Identification Form

Consisted of 20 questions on sociodemographic (age, gender, education, income, etc.) and disease-related factors (alcohol/tobacco use, COPD duration, comorbidities, medications, hospitalizations, etc.). It was developed by the researchers (13,15).

### Psychosocial Adjustment to Illness Scale-Self Report

The instrument consists of seven subscales: 1) healthcare orientation, 2) vocational environment, 3) domestic environment, 4) sexual relationships, 5) extended family relationships, 6) social environment, and psychological distress. The total score ranges from 0 to 138, with lower scores indicating good psychosocial adjustment. The scores below 35 indicate good psychosocial adjustment. The scores between 35 and 51 refer to moderate psychosocial adjustment. The scores above 51 are associated with poor psychosocial adjustment (16,17). Cronbach's alpha score was 0.81 in the present study.

EFS was developed in 2006 (18) and adapted to Turkish by Aygör et al. (19) in 2013. The scale consists of 11 items that assess nine subscales: 1) cognition, 2) general health status, 3) functional independence, 4) social support, 5) medication use, 6) nutrition, 7) mood, 8) continence, and 9) functional performance. The total score ranges from 0 to 17. The degree of frailty is scored as follows: 0-4 points indicate no frailty, while the degree of frailty increases with every 2-point increase. Cronbach's alpha score was 0.74 in the study.

### Statistics

The data were analyzed using the Statistical Package for Social Sciences (SPSS, version 25) at a significance level of 0.05. Descriptive statistical methods, comparison tests, correlation, and regression tests were used for analysis. The results showed that the data were non-normally distributed. Therefore, the

Mann-Whitney U test and the Kruskal-Wallis's test were used for analysis. Tamhane's test was used for post-hoc comparisons. Spearman's correlation coefficients were employed to assess the relationship between numerical variables. Backward analysis was used for regression testing.

### Ethical Considerations

The study was approved by the ethics committee of Düzce University (approval number: 2019/119, date: 25.06.2019). Permission was obtained from the Provincial Directorate of Health (61518654-619). Written consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Results

Participants had a mean age of  $70.51 \pm 5.18$  years. More than half of the patients were 65-69 years of age (52.6%), and 65%

were men. 36.5% of the older patients had primary school degrees; 48.2% of them were retired. Almost a quarter of the participants were smokers, (23.4%) ( $19.69 \pm 10.47$  cigarettes a day. Participants were diagnosed with COPD more than 14 years ago ( $14 \pm 9.16$ ). Fewer than half of the participants had stage II COPD (45.3%). All participants experienced dyspnea, with 54.4% reporting symptoms twice a day. More than 59.1% of the participants had been previously hospitalized for COPD. Additionally, 59.1% of participants had been hospitalized for COPD. Most participants were on respiratory support (75.2%).

Participants had a mean PAIS-SR score of  $54.37 \pm 12.91$ . They had mean PAIS-SR "social environment" and "extended family relationships" subscale scores of  $6.93 \pm 3.1$  and  $3.32 \pm 2.87$ , respectively. 53.3% of the participants had poor psychosocial adjustment (Table 1). Age ( $\chi^2=7.32$ ,  $p=0.026$ ) and COPD stages ( $\chi^2=9.71$ ,  $p=0.021$ ) affected participants' median PAIS-SR scores ( $p<0.05$ ). Participants over 76 years of age had a higher median

**Table 1. EFS and PAIS-SR levels and score of averages**

		Mean $\pm$ SD Median (min.-max.)	Possible range of score (min.-max.)
Edmonton Frailty Scale		$6.79 \pm 3.83$ 6 (0-15)	0-17
PAIS-SR subscales			
Orientation to healthcare		$11.97 \pm 3.28$ 11 (7-20)	0-24
Vocational environment		$7.22 \pm 2.93$ 8 (2-13)	0-18
Domestic environment		$7.96 \pm 3.36$ 8 (0-17)	0-24
Sexual relationships		$9.75 \pm 4$ 9 (1-15)	0-18
Extended family relationships		$3.32 \pm 2.87$ 2 (0-12)	0-15
Social environment		$6.93 \pm 3.11$ 7 (0-17)	0-18
Psychological distress		$7.23 \pm 3.41$ 8 (0-14)	0-21
PAIS-SR total		$54.37 \pm 12.91$ 53 (16-82)	0-138
		n (137)	%
Psychosocial adjustment level (PAIS-SR)	Well adjusted (score of <35)	7	5.1
	Moderately adjusted (35-51 score)	57	41.6
	Poorly adjusted (score of >51)	73	53.3
Frailty level (EFS)	Not frail	48	35
	Apparently vulnerable	21	15.3
	Mildly frail	20	14.6
	Moderately frail	18	13.1
	Severely frail	30	21.9

Min.: Minimum, Max.: Maximum, SD: Standard deviation, PAIS-SR: Psychosocial Adjustment to Illness Scale-Self Report, EFS: Edmonton Frailty Scale

PAIS-SR score than those aged 65-69 years ( $p<0.05$ ). Moreover, participants with stage III COPD had a significantly higher median PAIS-SR score than those with stage I COPD ( $p<0.05$ ) (Table 2).

The participants' EFS mean score was  $6.79\pm3.83$  (Table 1). Almost half of the participants were frail (49.6%), while nearly a quarter of them were severely frail (21.9%) (Table 1).

**Table 2. Comparison of EFS and PAIS-SR scales scores medians according to patients' descriptive and disease characteristics**

	PAIS-SR total score Median (min.-max.)	EFS total score Median (min.-max.)
<b>Age</b>		
65-69 (n=72)	49.0 (16-82)	4.0 (0-15)
70-75 (n=45)	56.0 (34-79)	8.0 (1-15)
76 + (n=20)	61.5 (37-79)	11.0 (5-14)
Test value	$\chi^2=7.325$ ; $p=0.026^*$ Difference: 1-3	$\chi^2=35.963$ ; $p<0.001^*$ Difference: 1-2; 1-3; 2-3
<b>Gender</b>		
Female (n=48)	53.0 (16-79)	5.0 (0-15)
Male (n=89)	53.0 (33-82)	7.0 (1-15)
Test value	$z=-0.127$ ; $p=0.899$	$z=-1.094$ ; $p=0.274$
<b>Marital status</b>		
Married (n=105)	52.0 (16-82)	6.0 (0-15)
Single (n=32)	54.0 (30-79)	8.5 (1-15)
Test value	$z=-0.237$ ; $p=0.813$	$z=-1.879$ ; $p=0.060$
<b>Education status</b>		
Illiterate (n=31)	57.0 (16-79)	9.0 (2-14)
Literate (n=23)	51.0 (34-79)	9.0 (3-15)
Primary school (n=50)	51.5 (33-82)	6.0 (1-14)
High school and higher (n=33)	53.0 (38-77)	4.0 (0-15)
Test value	$\chi^2=2.266$ ; $p=0.519$	$\chi^2=32.244$ ; $p<0.001^*$ Difference: 1-3; 1-4; 2-4; 3-4
<b>Employment status</b>		
Retired (n=12)	54.5 (38-77)	3.0 (1-15)
Officer (n=18)	50.5 (34-76)	4.5 (0-14)
Employee (n=66)	55.5 (30-79)	8.0 (1-15)
Self-employment (n=25)	50.0 (38-82)	6.0 (1-13)
Not working (n=16)	52.5 (16-70)	7.5 (1-12)
Test value	$\chi^2=3.519$ ; $p=0.475$	$\chi^2=12.621$ ; $p=0.013^*$ Difference: 1-3
<b>Income perception</b>		
Less than expenses (n=31)	54.0 (16-82)	7.0 (1-14)
Equal to expenses (n=92)	53.0 (30-79)	6.5 (0-15)
More than expenses (n=14)	52.0 (34-66)	6.0 (1-11)
Test value	$\chi^2=0.678$ ; $p=0.712$	$\chi^2=0.430$ ; $p=0.807$
<b>Smoking status</b>		
Current smoker (n=32)	51.5 (16-79)	4 (1-14)
Non-smoker (n=53)	56.0 (30-79)	7 (1-15)
Ex-smoker (n=52)	51.0 (33-82)	7 (0-14)
Test value	$\chi^2=2.171$ ; $p=0.338$	$\chi^2=3.611$ ; $p=0.164$

Table 2. continued		
	PAIS-SR total score Median (min.-max.)	EFS total score Median (min.-max.)
<b>COPD duration</b>		
1-5 year (n=32)	53.5 (37-82)	7.5 (0-15)
6-10 year (n=27)	50.0 (16-77)	8.0 (1-14)
11-15 year (n=31)	53.0 (30-79)	5.0 (1-14)
16-20 year (n=22)	53.5 (33-79)	4.5 (1-15)
21 and above (n=25)	55.0 (34-79)	9.0 (1-13)
Test value	$\chi^2=1.166$ ; $p=0.884$	$\chi^2=6.753$ ; $p=0.150$
<b>COPD stage</b>		
Stage 1 (n=22)	47.5 (16-76)	5.5 (0-14)
Stage 2 (n=62)	52.0 (30-77)	(1-14)
Stage 3 (n=40)	57.0 (38-82)	(1-15)
Stage 4 (n=13)	53.0 (38-79)	9.0 (1-14)
Test value	$\chi^2=9.712$ ; $p=0.021^*$ Difference: 1-3	$\chi^2=3.518$ ; $p=0.318$
<b>Respiratory distress</b>		
With effort (n=66)	51.0 (16-79)	6.0 (0-15)
All the time (n=71)	55.0 (37-82)	7.0 (1-14)
Test value	$z=-1.266$ ; $p=0.205$	$z=-1.593$ $p=0.111$
<b>Hospitalization</b>		
Yes (n=81)	56.0 (30-82)	8.0 (1-15)
No (n=56)	50.5 (16-79)	4.0 (0-14)
Test value	$z=-1.920$ ; $p=0.055$	$z=-4.063$ ; $p<0.001^*$
<b>Using respiratory support device</b>		
Yes (n=103)	55.0 (16-82)	6.0 (0-15)
No (n=34)	50.0 (37-76)	6.5 (1-14)
Test value	$z=-1.662$ ; $p=0.097$	$z=-0.243$ ; $p=0.808$
* $p<0.05$ , (z): Mann-Whitney U testi, ( $\chi^2$ ): Kruskal-Wallis, Difference: Tamhane's Test. PAIS-SR: Psychosocial Adjustment to Illness Scale-Self Report, EFS: Edmonton Frailty Scale, SD: Standard deviation, Min.: Minimum, Max.: Maximum, COPD: Chronic obstructive pulmonary disease		

Age ( $\chi^2=35.96$ ,  $p<0.001$ ), education ( $\chi^2=32.24$ ,  $p<0.001$ ), occupation ( $\chi^2=12.62$ ,  $p=0.013$ ), and hospitalization history ( $z=-4.06$ ,  $p<0.001$ ) affected participants' median EFS scores. Participants over 76 years of age had a significantly higher median EFS score than those aged 65-69 years. Participants with bachelor's or higher degrees had a significantly lower median EFS score than those with high school or lower degrees. Illiterate participants had a significantly higher median EFS score than those with primary school or higher degrees. Participants with a history of hospitalization had a significantly higher median EFS score than those without a history of hospitalization ( $p<0.05$ ) (Table 2).

There was a weak positive correlation between total EFS and PAIS-SR scores ( $rs=0.337$ ,  $p<0.05$ ). A weak positive correlation existed between total EFS and PAIS-SR "vocational environment" ( $rs=0.314$ ), "domestic environment" ( $rs=0.323$ ), "extended family relationships" ( $rs=0.206$ ), "social environment" ( $rs=0.204$ ),

and "psychological distress" ( $rs=0.248$ ) subscale scores. The results showed that the more severe the frailty, the poorer the psychosocial adjustment (Table 3).

Table 4 shows the effect of sociodemographic characteristics and frailty on psychosocial adjustment. The model using backward elimination was significant ( $F=13.22$ ,  $p<0.001$ ). COPD stages and EFS explained 15.2% of the model. The effect of frailty on PAIS-SR was greater than the effect of COPD stages [ $\beta$  ( $\beta$ )=-0.341].

Two models were developed using backward elimination to assess the effect of sociodemographic characteristics and psychosocial adjustment on frailty (Table 5). Model 1 was significant ( $F=18.654$ ,  $p<0.001$ ). Hospitalization history and psychosocial adjustment accounted for 20.6% of the variance in the model. Psychosocial adjustment had a greater effect on frailty than hospitalization history ( $\beta=0.319$ ). Model 2 was



significant ( $F=24.501$ ,  $p<0.001$ ). Age, education, hospitalization history, and psychosocial adjustment accounted for 40.9% of the model. A one-unit increase in the PAIS-SR score led to an average increase of 0.073 units in the EFS score. Age had a greater effect on frailty than the other variables ( $\beta=0.318$ ).

## Discussion

The study explored the relationship between psychosocial adjustment and frailty in older COPD patients. The participants had poor psychosocial adjustment and were frail to varying degrees. The study results also indicated a negative correlation between psychosocial adjustment and frailty. It was concluded that the psychosocial adjustment of older patients with advanced COPD and those who are frail may be poor.

COPD has adverse effects on an individual's healthcare, psychological well-being, sexual life, relationships, and social surroundings. Because of the systemic impacts of COPD, patients' ability to adapt to psychosocial domains may be affected (14). The participants had poor psychosocial adjustment. Çelik and Özkan (13) found that patients with COPD had poor psychosocial adjustment, mostly affecting their adjustment to healthcare orientation and vocational environment. Yuet et al. (20) documented those patients with COPD had poor psychosocial adjustment, mostly affecting their adjustment to sexual relationships and domestic, vocational, and social environments. Research shows that patients with COPD have poor psychosocial adjustment, mostly affecting their adjustment to sexual relationships, healthcare orientation, and vocational, social, and domestic environments (9,13,20,21). In this study,

**Table 3. The relationship between frailty scale score and psychosocial adjustment scale and sub-dimension scores**

PAIS-SR		Total	Orientation to healthcare	Vocational environment	Domestic environment	Sexual relationships	Extended family relationships	Social environment	Psychological distress
EFS total	Spearman's rho	0.337**	-0.002	0.314**	0.323**	0.064	0.206*	0.204*	0.248**
	p	<0.001	0.131	<0.001	<0.001	0.458	0.016	0.017	0.003

\* $p<0.01$ , \*\* $p<0.05$ .

PAIS-SR: Psychosocial Adjustment to Illness Scale-Self Report

**Table 4. Predictors of the psychosocial adjustment in individuals with COPD**

Model	Coefficient		Standardized coefficient		t	p
	B	Std. Error	Beta			
Constant	40.483	3.259	-		12.423	<0.001
EFS	1.150	0.269	0.341		4.274	<0.001
COPD stage	2.618	1.203	0.174		2.176	0.031

$F=13.222$   $p<0.001$ ; Adjust  $R^2= \%15.2$

EFS: Edmonton Frailty Scale, COPD: Chronic obstructive pulmonary disease

**Table 5. Predictors of the frailty in individuals with COPD**

Variables	Model 1					Model 2				
	Coefficient		Standardized coefficient	t	p	Coefficient		Standardized coefficient	t	p
	B	Std. Error	Beta			B	Std. Error	Beta		
Constant	4.824	1.650		2.925	0.004	4.250	1.666		2.550	0.012
Hospitalization	-2.262	0.602	-0.291	-3.759	<0.001	-1.223	0.544	-0.157	-2.250	0.026
PAIS-SR	0.095	0.023	0.319	4.124	<0.001	0.073	0.020	0.246	3.611	<0.001
Age						1.670	0.388	0.318	4.305	<0.001
Educational status						-0.922	0.261	-0.261	-3.535	0.001
F				18.654					24.501	
p				$p<0.001$					<0.001	
Adjust R2				20.6%					40.9 %	

PAIS-SR: Psychosocial Adjustment to Illness Scale-Self Report, COPD: Chronic obstructive pulmonary disease

COPD mostly affected the participants' healthcare orientation, sexual relationships, and vocational and domestic environments, which is consistent with the literature (9,13,20,22). Limitations in daily activities, functional reliance, and decreased physical activity could have influenced their healthcare orientation.

The stages of COPD, the frequency and duration of symptoms, comorbidities, and the loss of physical strength all have a negative impact on psychosocial adjustment (13,20). With an increase in the severity of COPD, there is a corresponding increase in respiratory difficulty and fatigue, leading to a decrease in activity status. This situation, in turn, results in a decrease in psychosocial adjustment (20). The results showed that COPD stage was a predictor of psychosocial adjustment and that participants with stage III COPD had poorer psychosocial adjustment than those with stage I COPD.

Half of the participants were frail to varying degrees. Researchers also show that the prevalence of frailty ranges from 35% to 50.2% (23-25). The underlying mechanisms linked to COPD, including factors like inflammation and muscle weakness, which contribute to the pathophysiology of frailty can increase the prevalence of frailty by at least twofold in individuals with COPD (15,24,26). Frailty is also a risk factor for COPD exacerbations and progression (15).

Age is also a risk for frailty (24). COPD is also associated with frailty. Aging, chronic inflammation, endocrine dysfunction, and smoking are shared risk factors for both COPD and frailty (11, 27). The result showed that age was a critical predictor of frailty. The literature also shows that age is an important variable for frailty in COPD patients (11,23,27). The findings align with the existing literature.

The results showed that education was a significant variable associated with frailty. There was a negative correlation between education and frailty. Education can mitigate frailty as educated individuals often have better access to information sources, are more adaptable to treatment, and tend to age more actively, which decreases the risk factors for frailty (23,28).

COPD causes repeated hospitalizations in frail patients. Kennedy et al. (29) highlighted a link between frailty and extended hospital stays in COPD patients, while Bernabeu et al. (30) noted that severely frail individuals were about five times more likely to be hospitalized. Frailty was an important risk for rehospitalization in patients with acute exacerbations. Shortness of breath and reduced physical activity resulting from COPD exacerbations as well as the loss of muscle strength due to frailty can contribute to multiple hospitalizations in older adults (11,29,30). Consistent with earlier studies, the findings emphasize that hospitalization is a significant determinant of frailty.

The results indicated a negative correlation between frailty and psychosocial adjustment. The results also showed that frailty was

significantly associated with psychosocial adjustment. Frailty has a greater impact on psychosocial adjustment than COPD stages. Since both COPD and frailty lead to diminished oxygen capacity and share similar risk factors like dyspnea, these factors collectively have adverse effects on adjustment. In line with these findings, Uchmanowicz et al. (11) found that older patients with severe COPD were more prone to frailty and exhibited lower acceptance of their illness. The same study concluded that low disease acceptance was linked to higher levels of frailty, particularly in the physical and social domains. Frailty, coupled with decreased muscle strength resulting from COPD, frequent hospitalizations, reduced mobility, high levels of anxiety, and the fear of death, may collectively impact various aspects of life and hinder psychosocial adjustment (9,20,24,27,30). Zhao et al. (31) found that frailty and depression in individuals with COPD were associated with low disease self-management and limited social support. Low self-management impedes adaptation to healthcare orientation, while inadequate social support can lead to poor adaptation in extended family relationships and social environment areas.

### Study Limitations

This is the first study to unveil the relationship between frailty and psychosocial adjustment and related predictors in older patients with COPD. However, the results are sample-specific and cannot be generalized to all older patients with COPD. Researchers should conduct studies in different centers and different cultures to better understand the link between frailty and psychosocial adaptation.

### Conclusion

The participants had poor psychosocial adjustment. More than half of the participants were frail to varying degrees. Age, education, hospitalization, and psychosocial adjustment were predictors of frailty. The results showed a negative correlation between frailty and psychosocial adjustment. The results also suggested that COPD stages and frailty were associated with psychosocial adjustment. If healthcare professionals implement interventions to promote psychosocial adjustment and reduce frailty, the patients receiving these interventions experience the disease less severely and are hospitalized less frequently. In this context, it is advisable to conduct regular assessments of COPD patients, particularly those who are older, have lower education levels, are in advanced COPD stages, and experience frequent hospitalizations, with a focus on evaluating their psychosocial adjustment and frailty. The assessment will enable healthcare professionals to identify frail patients with low adjustment levels early and meet their follow-up and care needs in the early period. Furthermore, it is essential to expand psychosocial support services for older adults on both clinical and community levels, with the aim of enhancing psychosocial

adjustment. Educational and intervention initiatives are strongly recommended as effective strategies for mitigating frailty and enhancing psychosocial adjustment in older individuals with COPD.

## Ethics

**Ethics Committee Approval:** The study was approved by the ethics committee of Düzce University (approval number: 2019/119, date: 25.06.2019). Permission was obtained from the Provincial Directorate of Health (61518654-619).

**Informed Consent:** Written consent was obtained from all participants.

## Footnotes

### Authorship Contributions

Concept: T.T.K., E.Ö., H.E.D., M.Ç.A., Design: T.T.K., Data Collection or Processing: H.E.D., M.Ç.A., Analysis or Interpretation: T.T.K., Literature Search: T.T.K., E.Ö., M.Ç.A., Writing: T.T.K., E.Ö., H.E.D.

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# Treatment of and Clinical Experience with Breast Cancer in Octogenarians

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## Abstract

**Objective:** Breast cancer is one of most prevalent cancers with high survival rate. As populations age, proportion of individuals aged 80-89, known as "octogenarians", also rises. When determining treatment options for breast cancer in this age group, multiple comorbidities, especially with locally advanced tumors and dementia etc., influence choice of surgical intervention. This study aimed to identify factors affecting such treatment in elderly patients.

**Materials and Methods:** Data from patients ≥80 years of age, admitted between January 2016 and April 2024 and diagnosed with non-metastatic breast cancer, were retrospectively analyzed. Demographic data, laboratory and radiological tests, operative findings, postoperative pathologies, morbidity, mortality, and patient survival times were evaluated.

**Results:** Data from 68 patients [mean (± standard deviation) age, 82.3±2.7 years (range, 80-89 years)] were analyzed. Hypertension was observed in 59 (86.8%) patients and diabetes mellitus in 25 (36.8%), cardiovascular diseases, respiratory conditions, cerebrovascular events in 5 patients (<1%). Breast-conserving surgery was performed in 28 (41.2%) patients and 20 (29.4%) underwent modified radical mastectomy. Axillary node positivity was observed in 28 (41.2%) patients. Sentinel lymph node biopsy was performed in 37 patients (54.4%), and axillary dissection was performed in 25 (36.8%). Estrogen receptor positivity was observed in 63 (92.6%) patients, progesterone receptor positivity in 59 (86.8%), human epidermal growth factor receptor 2 positive positivity in 11 (16.2%), metastases were detected in 10 (14.7%). Hormone therapy was administered to 63 (92.6%) patients, chemotherapy to 52 (76.5%), radiotherapy to 36 (52.9%). Two (2.9%) patients had locally advanced disease, 13 (19.2%) had advanced-stage disease with metastasis, and 53 (77.9%) had early stage disease.

**Conclusion:** In the planning of treatment for this patient population, our clinical observations indicate a potential delay in the initiation of treatment due to cognitive comorbidities. Despite the limited number of patients included in the study, it has been demonstrated that surgical treatment can be safely performed in octogenarians diagnosed with breast cancer.

**Keywords:** Breast cancer, octogenarian, treatment

## Introduction

Breast cancer is the most common cancer among women, and its incidence increases with age. As the global population increases and ages, the proportion of elderly individuals diagnosed with breast cancer will also rise, and breast cancer in this patient population is expected to become a significant public health

issue in the coming years. The global population is aging rapidly, with people over 60 projected to make up 22% of the world's population by 2050 (1), and in Türkiye, the 65+ age group will rise from 10% to over 22% by 2060 (2). Life expectancy has also grown, now averaging 73 years globally and 78 years in Türkiye, contributing to the increasing proportion of older adults (3).

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While an average 65-year-old patient is expected to live for >20 additional years, a 75-year-old patient is expected to live for only an additional 12 years (4).

Although the average age at onset of breast cancer is 61 years, 45% of those diagnosed with breast cancer are  $\geq 65$  years of age. It is estimated that 12% of all breast cancer cases involve women >80 years of age. However, this age group is often excluded from clinical trials and screening programs, leading to frequent delays in diagnosis. As a result, data regarding the diagnosis and treatment for this demographic are quite limited, and this age group often encounters treatment challenges due to the prevalence of comorbid conditions. Serious cardiovascular and cerebrovascular comorbidities have the potential to complicate general anaesthesia in surgical intervention and increase the potential toxic effect of chemotherapy, which may increase the risk of complicating treatment processes (5).

The primary aim in the management of breast cancer among patients of advanced age is to increase survival rates while minimizing undesirable side effects by pursuing effective and well-tolerated treatment options. It is crucial to ensure that these patients receive adequate and appropriate treatment without compromising quality of life (6). This study aimed to identify factors influencing the diagnosis and treatment of older adults with breast cancer and raise awareness to ensure that they receive standard treatment.

## Materials and Methods

A retrospective analysis was performed using data from patients diagnosed and treated for breast cancer at the authors' hospital between January 2016 and April 2024. All procedures adhered to the ethical rules and principles of the Declaration of Helsinki, and the study was approved by the Medical Faculty Clinical Research Ethics Committee University of Health Sciences, Türkiye, İzmir Tepecik Training and Research Hospital (approval number: 2024/03-04 date: 03.04.2024). As the study was retrospective, the ethics committee did not require patients' consent forms. Demographic data, comorbidities, tumor characteristics, surgical interventions, postoperative pathological findings, cancer stage(s), and whether the patients received chemotherapy, radiotherapy, or hormone therapy were recorded. Although severe cardiovascular and cerebrovascular conditions, were highlighted as potential treatment barriers in the introduction, the patient records lacked specific details on these comorbidities.

## Statistics

Data were analyzed using SPSS version 29 (IBM Corp. Armonk, NY, USA). Descriptive statistics are expressed as the number of cases (n), percentage (%), mean  $\pm$  standard deviation (SD), and minimum and maximum values.

## Results

The present study included data from 68 patients, of whom 66 (97.1%) were female, ranging in age between 80 and 89 years, with a mean ( $\pm$  SD) age of  $82.3 \pm 2.7$  years. Procedures were performed on the right side in 33 (48.5%) patients and on the left in 33 (48.5%). Fifty-nine (86.8%) patients had hypertension and 25 (36.8%) had diabetes mellitus cardiovascular diseases, respiratory conditions, cerebrovascular events in 5 patients (<1%), (Table 1). Twenty-eight (41.2%) patients underwent breast-conserving surgery (BCS) and 20 (29.4%) underwent modified radical mastectomy. Axillary positivity was observed in 28 (41.2%) patients. Sentinel lymph node biopsy was performed in 37 (54.4%) patients, while axillary dissection was performed in 25 (36.8%). Tumor size ranged from 0.80 to 20 cm, with a mean tumor size of  $4.0 \pm 2.7$  cm. Among the pathology results, 52 patients (76.5%) had invasive ductal carcinoma, 6 (8.8%) had invasive mammary carcinoma, and 4 (5.9%) had invasive lobular carcinoma. Estrogen receptor (ER) positivity was observed in 63 patients (92.6%), progesterone receptor (PR) positivity in 59 (86.8%), and HER2 positivity in 11 (16.2%). There were 39 patients (57.4%) with a Ki-67 value  $\geq 14$ . Metastasis was observed in 10 (14.7%) patients. Hormone therapy was administered to 63 (92.6%) patients, chemotherapy to 52 (76.5%), and radiotherapy to 36 (52.9%). There were 27 (39.7%) patients with the luminal A molecular subtype and 36 (52.9%) with luminal B subtype. Two (2.9%) patients were in the locally advanced stage, and 13 (19.2%) were in the advanced stage, with metastasis. Fifty-three (77.9%) patients had early stage disease (Table 2). The chi-square test analysis results of the relationship between chronic diseases and chemotherapy toxicities are presented in Table 3. According to the results, no statistically significant relationship was found between hypertension, diabetes, or asthma and chemotoxicity development ( $p > 0.05$ ). However, a statistically significant relationship was identified between heart failure and chemotoxicity development ( $p < 0.05$ ). Among patients diagnosed with heart failure, 2 (40%) also developed chemotoxicity, and this association was found to be statistically significant.

## Discussion

Breast cancer among women  $\geq 80$  years of age exhibits similar characteristics to those encountered in postmenopausal breast cancer, biologically known. However, due to lower screening rates in this age group, breast cancer diagnosis may occur at more advanced stages. Personalized treatments that take into account the individual's general condition, comorbidities, and life expectancy remain a crucial factor in improving both the quality and duration of life. Comprehensive geriatric assessment is an important part of the care of older adults with cancer and it is also important for side effects, complications that may develop during cancer treatment.

Table 1. Characteristics of patients		
	n	%
Age	82.3±2.7 (80–89)	
Genus		
Male	2	2.9
Woman	66	97.1
Side		
Right	33	48.5
Left	33	48.5
Bilateral breast CA	2	2.9
HT	59	86.8
DM	25	36.8
Others (dementia, cardiovascular diseases, respiratory conditions, cerebrovascular events) operation	5	<1
MKC	28	41.2
MRM	20	29.4
Simple mastectomy	13	19.1
BX only	7	10.3
Axilla		
Positive	28	41.2
Negative	40	58.8
SLNB		
Done	37	54.4
Not done	31	45.6
Axillary dissection		
Done	25	36.8
Not done	43	63.2
Size of CA	4.0±2.7 (0.80–20.0)	
Pathology		
Invasive ductal carcinoma	52	76.5
Invasive ductal carcinoma + ductal caesinoma insitu	2	2.9
Invasive lobular carcinoma	4	5.9
Invasive breast carcinoma	6	8.8
Invasive solid papillary carcinoma	1	1.5
Invasive breast carcinoma with mixed type ductal and lobular features	1	1.5
Papillary carcinoma	1	1.5
Papillary neoplasia, left breast	1	1.5
Numerical variables are summarized as mean ± standard deviation, (minimum–maximum). n: Number of patients, %: Percentage value, CA: Carcinoma, HT: Hormone therapy, DM: Distant metastasis, MKC: Mikrokalsifikasyon, MRM: Modified radical mastectomy, BX: Biopsy, SLNB: Sentinel lymph node biopsy		

The health status of elderly patients should be assessed using validated comprehensive geriatric assessment tools to better predict prognosis and treatment-related risks, thereby ensuring more careful treatment decisions. Frailty and its associated challenges in treatment planning are important considerations, as identifying an approach that balances patient quality of life can be particularly challenging for surgeons and oncologists despite often leading to gratifying outcomes for many patients today (7,8).

Efforts should be made to ensure that patients and their family members understand the treatment options, potential side effects of treatment, and the impact of outcomes on quality of to rapid advancements in the field of medicine, human life expectancy is increasing, leading to a rise in the number of malignancies in the elderly recently, elderly patients with breast cancer were not adequately represented in clinical trials; however, more specific research focusing on both localized and metastatic breast cancer in elderly women has been conducted (9).

**Tablo 2. Postop tretment and pathologic findings**

	n	%
<b>ER</b>		
Negative	5	7.4
Positive	63	92.6
<b>PR</b>		
Negative	9	13.2
Positive	59	86.8
<b>C-erbB-2</b>		
Negative	57	83.8
Positive	11	16.2
<b>Ki-67</b>		
<14	29	42.6
≤14	39	57.4
<b>Metastasis</b>		
There is	10	14.7
None	58	85.3
<b>Hormone therapy</b>		
+	63	92.6
-	5	7.4
<b>Chemotherapy</b>		
+	52	76.5
-	16	23.5
<b>Radiotherapy</b>		
+	36	52.9
-	32	47.1
<b>Molecular subtype</b>		
Basal-Like	1	1.5
HER2 (+)	4	5.9
Luminal A	27	39.7
Luminal B	36	52.9
<b>PHASE</b>		
Early stage	53	77.9
Locally advanced stage	2	2.9
Advanced stage + metastatic	13	19.2

n: Number of patients, %: Percentage value, ER: Estrogen receptor, PR: Progesterone receptor, C-erbB-2: Human epidermal growth factor receptor 2, Ki-67: Proliferation marker, HER2: Human epidermal growth factor receptor 2

When deciding on the treatment for breast cancer patients >80 years of age, age alone should not be a prohibitive factor for physicians. Many healthy patients >80 years of age can tolerate traditional treatment and achieve average life expectancy for their age group. After considering all comorbidities, if comprehensive geriatric assessment allows for surgical treatment, it should be implemented. In cases in which early stage cancer is detected, the standard procedure should consist of lumpectomy and radiation therapy. However, in elderly patients with hormone receptor-positive disease, surgery may

not be feasible due to comorbidities. Therefore, endocrine therapy is not only an essential treatment option but also the only available method for patients with low performance status who are not suitable for surgery. Nearly 85% of breast cancer cases in women >80 years of age are hormone receptor-positive. In the present study, the rate was 92.6%. Currently, there are no data regarding the use of chemotherapy in these patients. Many doctors prefer not to use chemotherapy for these patients due to its high toxicity rates. However, the benefits of chemotherapy should not be overlooked in suitable patients, such as those with ER-negative, poorly differentiated, or metastatic tumors (10). The absence of comprehensive follow-up data, due to patients receiving chemotherapy at different centers, limited our ability to assess the relationship between chronic diseases and chemotherapy side-effects.

Elderly women constitute a significant proportion of patients affected by breast cancer. However, treatment decisions for this patient population are complex due to the presence of comorbidities, limited life expectancy, decreased tolerability to treatment, and limited participation in clinical trials. However, with the emergence of new diagnostic and treatment models, life expectancy has also increased. Therefore, considering that their numbers are expected to increase over the years, more attention should be devoted to this age group, and more scientific research is needed. With an aging population, the burden of breast cancer care will continue to increase. Improved survival rates and management of comorbidities mean that older adults diagnosed with cancer can expect longer survival (11,12).

Understanding tumor characteristics and comprehensive evaluation of the physical condition of elderly patients with breast cancer are crucial for the careful selection of treatment options. The treatment of this patient group can often become complicated due to various chronic diseases such as uncontrolled diabetes, hypertension, congestive heart failure, and chronic obstructive pulmonary disease. In cases with multiple comorbidities or high disease severity, less aggressive treatment options may be preferred. However, in patients with or without well-controlled comorbidities, treatment options applicable to younger and postmenopausal patients can be considered. As most elderly breast cancer patients are hormone receptor-positive, treatments such as hormone therapy should be tailored not to the patient's biological age but to their physiological age, to prevent over- or under-treatment, considering factors such as surgery, radiotherapy, and chemotherapy (13).

Even at an advanced age, considering the advantages of morbidity and mortality, standard surgery should be recommended because of the low postoperative complication rates in patients with suitable overall conditions. For women ≥80 years of age with stage 1-2 early-stage breast cancer,

**Table 3. Chi-square analysis results of the relationship between chronic diseases and chemotoxicity development**

		Chemotoxicity development				$\chi^2$	p
		Yes		No			
		n	%	n	%		
Hypertension	Yes	3	60	54	85.7	0.133	0.181
	No	2	40	9	14.3		
Diabetes	Yes	1	25	23	42.5	0.457	0.417
	No	4	75	40	57.5		
Asthma	Yes	1	25	-	-	0.100	0.074
	No	4	75	63	100		
Heart failure	Yes	2	40	-	-	0.120	0.004
	No	3	60	63	100		
$\chi^2$ : Chi-square test, p<0.05.							

$\chi^2$  : Chi-square test,  $p < 0.05$ .

standard surgical treatment has yielded better outcomes specific to breast cancer compared with non-surgical treatment. We can also include stage 3 patients in the group we recommend surgery. In some cases, even in stage 4, surgery, or at least simple mastectomy, can be recommended for local control. Factors that can influence the physician's choice of treatment include age, comorbidities, mental function, and tumor characteristics. This applies not only to BCS, which is less frequently recommended for elderly patients, but also to more aggressive interventions, for which patients are increasingly opting. Patients >80 years of age are often diagnosed with advanced-stage or larger primary tumors; therefore, they can be treated with mastectomy or no surgery. However, this trend has begun to reverse (14). In our study, 53 of 68 patients (77.9%) were diagnosed in the early stage, and 28 underwent BCS. Whether BCS is appropriate for this population can be decided after adequate preoperative evaluation, and the type of surgery should be a joint decision between the oncologist and the patient after due diligence. Chronological age alone is not sufficient for treatment selection, and standardized treatments for younger patients should also be offered to elderly patients deemed suitable to tolerate them. However, if the likelihood of death from other causes is high, aggressive treatment can be avoided (15,16). In our study, surgery was performed in 61 of 68 patients. BCS was performed in 28 (41.2%) patients, modified radical mastectomy in 20 (29.4%), and simple mastectomy in 13 (19.1%). Biopsy alone was performed in 7 patients.

The molecular characteristics of breast cancer in patients  $\geq 80$  years of age are similar to those in younger age groups. Therefore, the evaluation of the prognosis and therapeutic management in elderly patients should be personalized, rather than following general rules, considering the biology of the disease. Although there may be insufficient data regarding the use of chemotherapy in this patient population, chemotherapy should not be disregarded solely because of age. Chemotherapy may be beneficial for healthy elderly patients  $\geq 80$  years of age; however, caution should

be exercised due to the higher incidence of chemotherapy-related toxicities. Typically, cardiac toxicity, arterial thromboembolic events, and worsening cognitive function increase with age. In our study, the presence of hypertension in 59 patients (86.8%), diabetes mellitus in 26 patients (36.8%) and cardiovascular diseases, respiratory disorders, cerebrovascular events in 5 patients (<1%) may be associated with chemotherapy-related toxicity findings. Among patients diagnosed with heart failure, 2 (40%) also developed chemotoxicity, and this association was found to be statistically significant. In our study 8 of the 16 patients who did not receive chemotherapy, severe cardiovascular disease (congestive heart failure, heart attack, arrhythmia) was present at the time of chemotherapy planning. The remaining 8 patients had extensive metastatic disease, chronic renal failure, bilateral carotid artery occlusion, cerebrovascular disease, acute renal failure, etc. and treatment could not be planned. Adjuvant endocrine therapy should be considered in postmenopausal women with stage breast cancer, usually after surgery or radiation therapy. Therefore, the adverse effects of endocrine therapy should be carefully evaluated. Arthralgia, osteoporosis, and vaginal dryness are the common side effects of these agents. However, vaginal bleeding or discharge, "hot flashes", and thrombosis are more common when tamoxifen is administered. Treatment-related side effects can significantly affect patient quality of life. Poorly managed treatment can lead to discontinuation and, consequently, worse outcomes (7,17).

Invasive breast cancers lacking estrogen and PRs and also devoid of overexpression of human epidermal growth factor receptor 2 (HER2) protein are commonly referred to as "triple-negative" breast cancer, which accounts for approximately 10% of all invasive breast cancer cases among elderly women (this proportion was 1.4% in the present study). These patients are at a high risk for local recurrence, disease progression, and breast cancer-related mortality. Triple-negative breast cancer poses a therapeutic challenge, especially in frail, elderly women, as opposed to hormone receptor-positive breast cancer, for which equivalent alternative systemic treatment options are not available (18).

The importance of comorbid diseases increases as their number increases and as mental or physical function(s) decline. A decline in mental and physical function can lead to delays in diagnosis, especially in this age group. In our study, there were 2 patients in the locally advanced stage and 13 in the advanced stage with metastasis. Seven of these patients had neurological diseases (including dementia), all of whom had stage 4 disease. Efforts should be made to ensure that patients and their family members understand the treatment options, potential side effects of treatment, and the impact of outcomes on quality of life. Family members, especially those with neurological diseases, such as dementia play important roles in the diagnostic stage and should be more cautious in this regard (19). A comprehensive geriatric assessment should be performed, and an appropriate treatment plan should be determined based on this assessment (20).

The occurrence of breast cancer in women >80 years of age should not be underestimated. Because national cancer screening programs do not typically cover this age group, diagnosis in this age group relies more on clinical observations than screening. There is no significant difference in the biology of breast cancer between pre- and postmenopausal women and younger women (5). To prevent delays in diagnosis, increasing awareness of breast cancer in the elderly population, especially among relatives of patients with neurological diseases, such as cerebrovascular diseases, dementia, is crucial. Treatment in patients ≥80 years of age should be tailored according to their physiological age and the presence of comorbidities, and age alone should not limit the treatment options. A detailed comprehensive geriatric assessment should be performed and an appropriate treatment plan determined based on this assessment (20).

### Study Limitations

The study's retrospective design, limited number of patients, and lack of detailed examination of some clinical parameters are shortcomings. Rendering the results more reliable and generalisable requires addressing these issues.

### Conclusion

Breast cancer in women over the age of 80 is often underdiagnosed due to their exclusion from national screening programs, with them relying instead on clinical observations. Despite having tumor biology similar to that of younger women, comorbidities such as cardiovascular, respiratory, and cerebrovascular diseases, as well as dementia, frequently lead to delays in diagnosis and treatment. Although our study is limited by a small sample size, our findings demonstrate that surgical treatment can be safely performed in octogenarian patients with breast cancer.

### Ethics

**Ethics Committee Approval:** All procedures adhered to the ethical rules and principles of the Declaration of Helsinki, and the study was approved by the Medical Faculty Clinical Research Ethics Committee University of Health Sciences, Türkiye, İzmir Tepecik Training and Research Hospital (approval number: 2024/03-04 date: 03.04.2024).

**Informed Consent:** As the study was retrospective, the ethics committee did not require patients' consent forms.

### Footnotes

#### Authorship Contributions

Surgical and Medical Practices: S.S., Y.D., S.D., G.Ç., Concept: S.S., Y.D., T.K., G.Ç., Design: Y.D., T.K., S.D., G.Ç., Data Collection or Processing: S.S., Y.D., T.K., S.D., Analysis or Interpretation: S.S., Y.D., T.K., S.D., G.Ç., Literature Search: S.S., Y.D., G.Ç., Writing: Y.D., T.K., S.D., G.Ç.

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# Evaluation of the Prophylactic Effect of Preoperative Ondansetron on Postoperative Delirium in Older Adults Undergoing Orthopedic Surgery: A Double-Blind Randomized Controlled Clinical Trial

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## Abstract

**Objective:** This study aimed to investigate the prophylactic effect of preoperative ondansetron on the occurrence of postoperative delirium (POD) in older adults who are undergoing orthopedic surgery.

**Materials and Methods:** One hundred included patients with American Society of Anesthesiologists (ASA) classification of I and II were randomly divided into two groups: Group A (n=50) and Group B (n=50), who were preoperatively received 2 mL intravenous ondansetron or placebo (saline solution), respectively. Delirium, nausea, itching, and shivering were analyzed between the two groups at 30 minutes, 1, 6, 8, and 24 hours postoperatively.

**Results:** There was no significant difference in terms of sex, age, and ASA class of the patients in the two studied groups. Preoperative ondansetron administration has no impact on POD and itching frequency. In addition, no significant relationship between sex and the occurrence of delirium was observed in the ondansetron group. The frequency of shivering at 30 minutes and nausea at 6 and 8 hours in the postoperative period was significantly decreased in the A group compared with the control group.

**Conclusion:** Ondansetron can still be considered the first line of prevention of postoperative nausea, but does not affect POD, shivering, and itching. However, the study data are not sufficient to draw robust conclusions, and further randomized controlled trials with larger sample sizes are required to validate our results.

**Keywords:** Nausea, older adults, ondansetron, postoperative delirium, pruritis, shivering

## Introduction

Delirium is a common acute cognitive and attentional disorder that is life-threatening and an inevitable clinical state in older adults (1,2). Postoperative delirium (POD) is a common problem in surgical interventions (3,4). This complication usually occurs within five days, especially during the first 24–48 hours postoperatively (5). The incidence rate of delirium in total joint arthroplasty and hip fracture surgery has been reported to range from 5% to 14% and 12% to 56%, respectively (6). It has

been known that advanced age, frailty, pre-existing cognitive impairment, intra-operative blood loss, sleep disruption after surgery, the type of surgery, and poorly controlled pain post-surgery, are the main risk factors involved in development of POD (3,7). POD results in longer hospital stays, which is accompanied by higher hospital costs, increased rates of post-hospital institutionalization, poorer functional recovery, cognitive decline, and increased morbidity and mortality (8). Intervention for prevention and treatment of delirium is the two

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main methods of POD management (3). It has been emphasized that overactivity of the serotonergic system and underactivity of the cholinergic system are prominent among the critical factors in delirium occurrence (9,10). Recently, the majority of investigations concerning the prevention or management of POD have primarily concentrated on the serotonergic system. Ondansetron, a selective 5-hydroxytryptamine 3 (5-HT<sub>3</sub>) receptor antagonist, blocks the action of serotonin (8). In this regard, some experimental trials have indicated that postoperative administration of ondansetron resulted in a decreased occurrence and duration of delirium in the postoperative period, specifically on the 30<sup>th</sup> day after surgery (11,12). To the best of our knowledge, there is no study evaluating the effect of preoperative ondansetron administration on POD prevention. This study aimed to investigate whether preoperative ondansetron administration aids in POD prevention in patients undergoing surgery with spinal anesthesia due to femoral or hip fractures.

## Materials and Methods

### Patients and Design

This double-blind randomized controlled clinical trial was registered in the Iranian registry of clinical trials with registration number IRCT20170515033986N1 (registration date: 16.11.2020). This study was conducted in Urmia, Iran, between November 2020 and June 2021. The patients over 60 years old with American Society of Anesthesiologists (ASA) class I and II, who were candidates for hip and proximal femoral fracture surgery, were enrolled in the study. All participants had a new onset fracture and surgeries were performed within 24-48 hours after, following the institute's protocol for early intervention, aimed at minimizing complications associated with hip fractures.

As frailty affects delirium, the evaluation of frailty was conducted exclusively for patients categorized as robust according to their FRAIL score. Also, a thorough method for assessing cognitive status was implemented prior to enrollment. A comprehensive cognitive assessment was completed by all participants using standardized tools to ensure that the inclusion criteria were met and that no pre-existing cognitive impairments were present. A combination of clinical interviews and validated cognitive screening tools-specifically, the Mini-Mental State Examination and the Montreal Cognitive Assessment -was utilized to evaluate cognitive function. Additionally, the exclusion criteria specifically included any current or past history of neurological disorders, such as dementia, Parkinson's disease, and Alzheimer's disease. This was done to ensure that the study population consisted of individuals with intact cognitive function, thereby allowing for an accurate assessment of the effects of preoperative ondansetron on POD without confounding factors related to cognitive decline.

Other exclusion criteria were a history of alcohol abuse, receiving antidepressant and sedative drugs, hearing, vision, and speech disorders, and surgery duration of more than 3-hours. The sample size required for the study was determined using the following formula. Based on the frequency of delirium in the study of Papadopoulos et al. (11) (15.68% in the ondansetron group and 41.81% in the placebo group) and taking into account the experimental power of 80% and 95% confidence interval, the sample size of 44 people in each group was determined. Considering a 10% chance of dropping out, the final sample size was 50 people in each group.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 [P_1(1 - P_1) + P_2(1 - P_2)]}{(P_1 - P_2)^2}$$

After obtaining the approval of the Ethics Committee of Urmia University of Medical Sciences (approval number: IRCT20170515033986N1, date: 30.05.2018) and patients' informed consent, randomization was performed using Random Allocation Software version 1.0.0 to generate two groups of 50 patients each. Only a single nurse anesthetist possessed knowledge of the two categories and dispensed the 2 mL syringe that contained either the medication or the placebo to the anesthesiologist. After standard hemodynamic monitoring and before spinal anesthesia, the A group received 8 mg (2 mL) of intravenous ondansetron, and the B group received 2 mL of intravenous normal saline (placebo). The participant, anesthesiologist, care provider, investigator, and outcome assessor were blinded to the study groups.

Spinal anesthesia was performed by injecting 10 mg of bupivacaine 0.5%, and 30 micrograms of fentanyl in the L3-L4 or L4-L5 intervertebral space. Delirium, nausea, itching, and shivering were evaluated at 30 minutes, 1<sup>st</sup>, 6<sup>th</sup>, 8<sup>th</sup>, and 24<sup>th</sup> hours postoperatively by the same in-charge anesthesiologist to enhance the reliability of the findings. Delirium was assessed based on a 4-point scale following (13), 0: normal, 1: a restless patient with mild confusion and good cooperation, 2: the patient has memory impairment and is unaware of the place and time but cooperates well, 3: the patient is unaware of the time and does not cooperate, with a possibility of danger due to excessive movements, and 4: the patient is entirely unaware of the place, time, and person, and is very aggressive and delusional.

### Statistics

Quantitative data are presented as mean  $\pm$  standard deviation, and qualitative data are reported as frequency and percentage. A chi-square test (if necessary, Fisher's exact test) was used to compare the frequency of the variables between the two groups. Quantitative data were analyzed using an independent sample t-test. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, IL);  $p < 0.05$  was considered statistically significant.

## Results

A total of 122 hip and anterior femoral fracture patients were admitted to the project between November 2020 and June 2021. Twenty-two patients were excluded from the study: 14 refused to participate, one patient had Parkinson's disease, one patient had Alzheimer's disease, and six patients had a history of drug or alcohol abuse. The remaining 100 patients were randomly divided into two groups (Group A, n=50; Group B, n=50) (Figure 1). As shown in Table 1, there was no significant disparity in terms of age and sex between the two groups. Also, the distribution of ASA classifications and comorbidities in the two groups is shown in Table 1. There were no significant differences in the proportion of ASA I and II patients or in the specific comorbidities that classified patients as ASA II. The results of our study showed the frequency of POD decreased in group A compared with group B, but this decrease was not statistically significant at any time in the study (Table 2). The prevalence of delirium was the same in both sexes, and the effect of ondansetron on delirium was not sex-dependent (Table 3).

The Fisher's exact test showed that the frequency of postoperative itching dose not significantly different between the two groups at any time in the study. As shown in Table 4, the frequency of nausea at 6- and 8-hours post-surgery significantly decreased in Group A compared to Group B. In addition, our results showed a significant decrease in shivering frequency at 30 minutes after surgery in Group A compared with Group B.

## Discussion

The global population is getting older, leading to a higher need for orthopedic surgeries (6). POD is common among older patients undergoing elective surgery, especially orthopedic surgery (1,3,6), which results in longer hospitalizations and increased morbidity and mortality (8). Prevention, timely diagnosis, and appropriate treatment can improve the recognition and risk stratification of delirium and mitigate its unwanted side effects (7). Delirium has now gained recognition as a severe challenge for both patients and medical professionals due to the emergence of discussions in recent years surrounding the specific type of medication that can effectively mitigate the occurrence of delirium (14). Several classes of drugs, such as

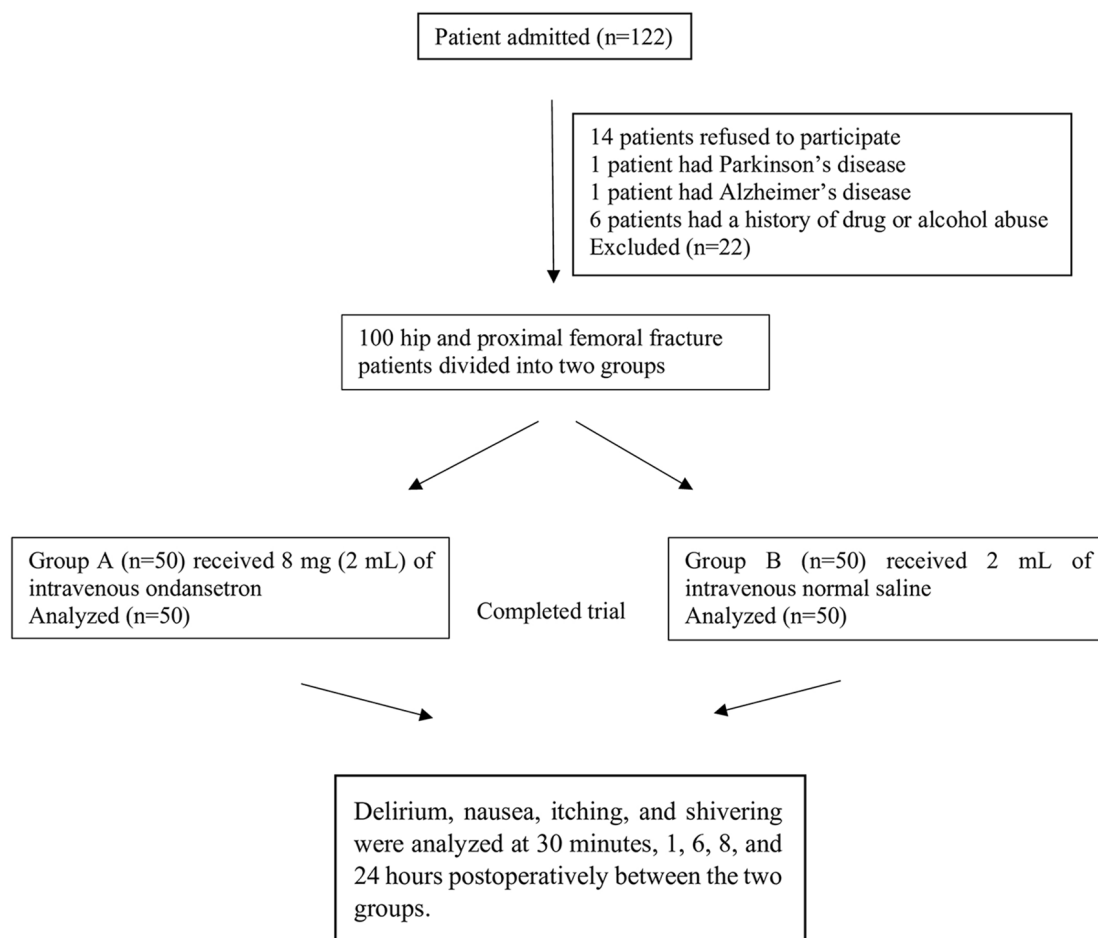


Figure 1. A flow chart of the study

$\alpha$ 2-receptor agonists, atypical antipsychotics, sleep-regulatory drugs, and 5-HT<sub>3</sub> receptor antagonists, have garnered significant interest regarding their potential in preventing or managing delirium (8,11,12,15). However, it remains a topic of ongoing discussion in achieving agreement on this issue, and there is a lack of convincing evidence to support the effectiveness of any particular approach in preventing or treating delirium. The pathophysiology of delirium is related to increased serotonergic activity (8). Ondansetron is a selective serotonin 5HT-3 antagonist, mainly used for postoperative nausea and vomiting control (13). Some experimental trials focused on the effect of postoperative ondansetron administration on the prevention and treatment of POD. However, the results of these studies are controversial (11,12). A retrospective study by Shin et al. (16) was conducted to demonstrate the effect of 5-HT<sub>3</sub> receptor antagonists on the occurrence of POD in older adults who underwent hip fracture surgery. In contrast to our study, another study used ramosetron and palonosetron intraoperatively and found that a 5-HT<sub>3</sub> receptor antagonist may be a preventive strategy for POD (16). Papadopoulos et al. (11) showed that postoperative ondansetron administration for five days in patients undergoing surgical procedures for femoral or hip fractures resulted in a reduced incidence and duration of delirium. A meta-analysis stated that among the candidate pharmacological interventions for the treatment of delirium in critically ill adults, only the  $\alpha$ 2 agonist dexmedetomidine reduces the duration of delirium, while ondansetron does not affect the treatment of delirium (17). To the best of our knowledge, our study evaluated for the first time the effect of ondansetron administration in the preoperative period on POD management in older patients undergoing orthopedic surgery. Our data, inconsistent with other studies, confirmed that ondansetron can still be considered as the first line of prevention of postoperative nausea and vomiting. We also found that

preoperative ondansetron administration has no impact on POD, shivering, and itching frequency in patients undergoing surgery for hip and anterior femoral fracture with spinal anesthesia. This

**Table 1. Patient's demographic characteristics**

Variable	Group A (ondansetron) (n=50)	Group B (placebo) (n=50)	p
Sex (male/female)	(23/27)	(27/23)	0.42
Age (mean $\pm$ SD)	73.66 $\pm$ 13.50	72.02 $\pm$ 10.28	0.49
ASA (I/II)	(14/36)	(11/39)	0.49
Comorbidities (ASA II)			
Hypertension	20	25	0.45
Diabetes mellitus	8	5	0.36
Coronary artery disease	5	8	0.55
Asthma	0	2	0.49
Hypothyroidism	6	4	0.51

SD: Standard deviation, ASA: American Society of Anesthesiologists

**Table 2. Postoperative delirium incidence in groups A and B**

Post-operative time	Group A (ondansetron) (n=50) delirium positive patients n (%)	Group B (placebo) (n=50) delirium positive patients n (%)	p
30 min.	0	0	-
1 h	0	0	-
6 h	9 (18%)	12 (24%)	0.46
8 h	10 (20%)	17 (34%)	0.11
24 h	9 (18%)	10 (20%)	0.79

min.: Minute, h: Hour

**Table 3. Distribution of postoperative delirium among different sex**

Post-op. time	Group A (ondansetron) delirium positive n (%)		Group A (ondansetron) delirium negative n (%)		p	Group B (placebo) delirium positive n (%)		Group B (placebo) delirium negative n (%)		p
	Male	Female	Male	Female		Male	Female	Male	Female	
30 min.	0	0	27 (54)	23 (47)		0	0	23 (47)	27 (54)	
2 h	0	0	27 (54)	23 (47)	-	0	0	23 (47)	27 (54)	-
6 h	4 (33.3)	8 (66.7)	23 (60.5)	15 (39.5)	0.1	4 (44.4)	5 (55.6)	19 (46.3)	22 (53.7)	0.92
8 h	9 (52.9)	8 (47.1)	18 (54.5)	15 (45.5)	0.91	4 (40)	6 (60)	19 (47.5)	21 (52.5)	0.67
24 h	7 (70)	3 (30)	20 (50)	20 (50)	0.26	3 (33.3)	6 (66.7)	20 (48.8)	21 (51.2)	0.4

min.: Minute, h: Hour



**Table 4. Frequency of complications in groups A and B**

Post-op. time	Itching			Vomiting			Shivering		
	A (ondansetron) (n=50)	B (placebo) (n=50)	p	A (ondansetron) (n=50)	B (placebo) (n=50)	p	A (ondansetron) (n=50)	B (placebo) (n=50)	p
30 min.	1 (2%)	0	0.5	4 (8%)	4 (8%)	1	7 (14%)	16 (32%)	0.03
1 h	0	0	-	4 (8%)	7 (14%)	0.33	5 (10%)	9 (18%)	0.24
6 h	0	1 (2%)	0.5	3 (6%)	16 (32%)	0.01	1 (2%)	2 (4%)	0.58
8 h	0	2 (4%)	0.15	1 (2%)	8 (16%)	0.01	2 (4%)	1 (2%)	0.55
24 h	0	0	-	1 (2%)	2 (4%)	0.58	0	0	1

min.: Minute, h: Hour

contradiction in results between different studies may be due to the type of surgery and anesthesia, the type of preoperative risk factors, and the time and dose of ondansetron administration (18–20). After intravenous administration, ondansetron undergoes metabolism and is subsequently eliminated through the urinary system. The elimination half-life of ondansetron following an intravenous dose of 8 mg is likely to be around 3–6 hours; it could extend to 6–8 hours among the older population (21). In Papadopoulos' study, ondansetron was administered daily for five days postoperatively, while in our study a single dose of ondansetron was administered preoperatively. The administration of several doses of ondansetron before the surgery may have a favorable effect on POD management. Furthermore, the anesthetic procedure is different between 2 studies; in our research and Papadopoulos' study, spinal and general anesthesia were used, respectively.

Since there is no worldwide guideline with standardized concepts for POD management, delirium management should consist of a multi-professional consisting of pharmacological, and non-pharmacological approaches (2,22,23). The critical care guidelines first recommend the use of non-pharmacological strategies in both the prevention and management of delirium. One of the types of non-pharmacological plans is individual assessment to identify preoperative delirium risk factors and their underlying causes and to remove them if possible. The factors that are frequently linked to POD include advanced age, pre-existing deficits in the central nervous system, psychiatric illness, alcohol misuse, emergency surgical procedures, and the presence of multiple comorbidities (13), whereas other factors are controversial. The relationship between sex and POD occurrence in various clinical settings has been proven. Some studies reported that men have a higher risk of developing POD after hip and femoral neck fracture (24,25); other studies, consistent with our research, have failed to find a relationship between sex and the POD incidence (26,27).

Frailty and delirium are closely associated, particularly in older adults undergoing surgical procedures. Frailty, characterized by decreased physiological reserve and increased vulnerability to stressors, significantly heightens the risk of POD. The FRAIL scale is a widely recognized tool used for assessing frailty in older adults. Individuals classified as frail (scores of 3 or more) or prefrail (scores of 1–2) had approximately 2.7 times the odds of developing in-hospital delirium compared to those deemed robust (score of 0) after adjusting for various factors such as age and cognitive status (28). Therefore, higher scores, which indicate prefrailty or frailty, were not included in the study due to their correlation with an increased risk of delirium to eliminate its effect.

Furthermore, a meta-analysis by Hua et al. (29) indicated that the ASA classification was identified as an independent risk factor for POD, with an odds ratio of 2,343, suggesting that patients classified as ASA III or higher, are at a greater risk compared to those classified as ASA I or II.

To mitigate this factor and reduce variability, we included only ASA I and II patients in our study. The distribution of ASA I and II patients was balanced between the two groups, with 14 ASA I and 36 ASA II patients in the ondansetron group and 11 ASA I and 39 ASA II patients in the placebo group. However, limiting the study population to lower-risk patients narrows the scope of generalizability, as the results may not fully represent higher-risk populations. Future studies should include patients across all ASA classifications to better understand the impact of ondansetron on delirium prevention. To mitigate this confounding factor, we included patients classified as ASA I and II in our study, with a balanced distribution of 14 ASA I and 36 ASA II patients in the ondansetron group and 11 ASA I and 39 ASA II patients in the placebo group. This approach reduced variability and ensured comparability between groups, thereby strengthening internal validity.

## Study Limitations

This study has some limitations, and the current data are insufficient to draw robust conclusions. First, this study did not assess all the possible risk factors associated with POD other than the factors mentioned in the methods section. Identifying these potential risk factors and the underlying cause(s) can be effective in using the best pharmacological strategies to remove them and finally prevent or treat POD.

Second, the study protocol involved administering only a single dose of preoperative ondansetron, because early surgery was performed for participants undergoing hip fracture surgery. Future studies are recommended to explore the use of varying doses at different intervals prior to surgery.

Third, while our study included only ASA I and II patients to minimize the impact of coexisting comorbidities, this selection limits the generalizability of our findings. The exclusion of older adults with ASA III and IV classifications, who are at a higher risk of POD, restricts the ability to fully evaluate ondansetron's effect across a broader risk profile. Furthermore, we did not analyze the presence of concomitant comorbidities. Although the distribution of these comorbidities was balanced between the two groups, their potential influence on the risk of POD cannot be entirely ruled out. The presence of concomitant comorbidities, even within the ASA II group, may have contributed to the observed outcomes, including the ineffectiveness of ondansetron in preventing POD. Future studies should consider a more diverse patient population, including those with a broader range of comorbidities, to better understand the role of ondansetron in preventing POD.

Fourth, our results are from a small study, and further randomized controlled trials with larger sample sizes are required to validate our results. Additionally, nausea, itching, and shivering were assessed as presence or absence instead of evaluating their intensity, which may have limited our ability to detect more subtle differences between the groups.

## Conclusion

In conclusion, we found that preoperative ondansetron administration has no effect on POD, shivering, and itching frequency in patients undergoing surgery for hip and anterior femoral fractures under spinal anesthesia.

## Ethics

**Ethics Committee Approval:** After obtaining the approval of the Ethics Committee of Urmia University of Medical Sciences (approval number: IRCT20170515033986N1, date: 30.05.2018).

**Informed Consent:** Informed consent, which was approved by the ethics committee, was obtained from all participants before participating in the study.

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## Footnotes

## Authorship Contributions

Surgical and Medical Practices: R.A.B., Concept: N.K., Design: N.K., Data Collection or Processing: R.A.B., Analysis or Interpretation: A.S., Literature Search: A.S., Writing: T.K.

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

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# Using Prognostic Nutritional Index and Systemic Immune-Inflammation Index to Evaluate Short-Term Survival in Hospitalized Octogenarian and Non-agenarian Patients

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## Abstract

**Objective:** This study aimed to investigate the associations between the preoperative Prognostic Nutritional Index (PNI), Systemic Immune-Inflammation Index (SII), and short-term survival in octogenarian and non-agenarian patients who were admitted to the urology department.

**Materials and Methods:** We evaluated 136 octogenarian and non-agenarian patients who were admitted to the urology department. The patient-related data were collected, including demographic and comorbidities. Surgical treatment patterns and outcomes were assessed. Patients' SII and PNI scores were calculated. PNI was calculated as total lymphocyte count ( $10^9/L$ )  $\times$  5 + albumin concentration (g/L). SII was calculated as neutrophil count ( $10^9/L$ )  $\times$  platelet count (109/L)/lymphocyte count (109/L). The cut-off values of PNI and SII were determined through receiver operating characteristic analysis. Overall survival (OS) was estimated by Kaplan-Meier analysis. The log-rank test was used to compare differences between the groups. Univariate and multivariate COX regression analyses were performed to assess the predictive values of PNI and SII for OS.

**Results:** The study population comprised 105 women (77.2%) and 31 men (22.8%), with a median age of 84 years (range, 80-97 years). The most common reason for hospitalization was hematuria, affecting 47 patients (34.6%). A total of 74 patients (54.4%) underwent surgical intervention. The optimal cut-off values for predicting OS were identified as 1243, 42.65, and 32.37 for SII, PNI, and SII/PNI, respectively. Kaplan-Meier analysis also revealed that low PNI was related to poorer OS in octogenarian and non-agenarian patients.

**Conclusion:** Preoperative PNI and SII, based on standard laboratory measurements, may be useful non-invasive, inexpensive, and simple tools for predicting short-term survival of octogenarian and non-agenarian patients admitted to the urology department.

**Keywords:** Octogenarian, non-agenarian, prognostic nutritional index, systemic immune-inflammation index

## Introduction

Currently, life expectancy is increasing and aging populations are growing remarkably. It is thought that life expectancy will increase with each passing year. It is projected that the demographic cohort of individuals aged 80 years and above will expand to exceed 150 million (1). Additionally, this ageing population needs more healthcare services, compared to the younger population. In patients aged over 80, urological diseases occur more frequently, leading to longer hospital stays and higher complication rates compared to younger patients (2). Therefore, it is necessary to adopt a specialized approach when dealing with patients over 80 years of age.

The Prognostic Nutritional Index (PNI) evaluates immune function and overall nutritional health; it is a clinical tool that measures nutritional status in several diseases, such as hepatocellular carcinoma and colorectal cancer (3). The Systemic Immune-Inflammation Index (SII) plays a pivotal role in carcinogenesis and serves as a robust prognostic indicator for various solid neoplasms, including esophageal squamous cell carcinoma, germ cell tumors, and hepatocellular carcinoma (4-6).

Octogenarian and non-agenarian nutritional status and hospitalization are important for life expectancy and overall survival (OS). To our knowledge, no studies have specifically examined the prognostic value of SII and PNI in this population.

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Our study aims to evaluate the prognostic effect of the SII and PNI in relation to short-term survival among elderly patients aged 80 and above.

## Materials and Methods

A retrospective study was conducted on 136 octogenarian and non-agenarian patients who were hospitalized in the urology department of a single center between January 2021 and September 2023, after receiving approval from Medeniyet University Göztepe Training and Research Hospital's Ethics Committee (decision number: 2023/0823, date: 29.11.2023). The patient data set comprised a range of variables, including demographics, comorbidities, diagnoses that led to the patients being hospitalized, the procedures that were performed, the American Society of Anesthesiologists scores of the patients who underwent surgery, the Dindo et al. (7) classification was employed for the assessment of complications, the length of hospital stay, the usage of antiplatelet/anticoagulant therapy, the patients' smoking status, the Katz Index of Independence in activities of daily living, and the WHOQOL-OLD score.

Upon admission to the clinic, the patient's PNI and SII were calculated according to the following methodology:

- The PNI is calculated as follows:  $PNI = [(10 \times \text{albumin (g/dL)}) + (0.005 \times \text{Lymphocyte count})]$
- SII is calculated as follows:  $\text{platelet count} \times \text{NLR (neutrophil count/lymphocyte count)}$

## Statistics

The statistical analysis were conducted using the IBM SPSS Statistics software, version 22. Normally distributed continuous variables are reported as the mean with standard deviation, and non-normally distributed continuous variables are reported as the median with range. T-tests were applied to normally distributed variables, and Mann-Whitney U tests were used for non-normally distributed variables. The optimal cut-off values of the PNI and SII were found by receiver operating characteristic (ROC) curve analysis. We utilized the Kaplan-Meier method to estimate the probability of survival. The independent predictors of survival were determined through a multivariate COX regression model. The independent predictors of PNI and SII were determined using univariate and multivariate logistic regression. Calculations were performed to derive hazard ratios (HR) and 95% confidence intervals (CIs), where a p-value of less than 0.05 was considered statistically significant.

## Results

### Patient Characteristics and Clinical Outcomes

Of the 136 individuals in the study, 77.2% were women (n=105) and 22.8% were men (n=31) (Table 1). Most of these patients (56.6%) were smokers. The most common reason for hospitalization was hematuria, affecting 47 patients (34.6%). The other reasons for hospitalization are postrenal acute kidney injury (AKI) (18.4%), urolithiasis (5.9%), and malignancy (14.7%). A total of 74 patients (54.4%) underwent surgical intervention. The most frequently performed surgical procedure

**Table 1. Patient characteristics and clinical outcomes**

Characteristics	Patients, n (%)
<b>Sex, n (%)</b>	
Male	31 (22.8)
Female	105 (77.2)
Age, median (range)	84 (80-97)
BMI, median (range)	25 (16-38)
<b>Smoking status, n (%)</b>	
Never smoker	59 (43.4)
Current or ex-smoker	77 (56.6)
<b>Lives with, n (%)</b>	
Alone	6 (4.4)
Wife	45 (33.1)
Relative/other	85 (62.5)
Acute renal failure during hospitalization, n (%)	49 (36)
Presence of percutaneous nephrostomy, n (%)	14 (10.3)
Presence of double J-Stent, n (%)	12 (8.8)
<b>Hospitalization</b>	
Elective hospitalization	54 (39.7)
Emergency hospitalization	82 (60.3)

<b>Table 1. Continued</b>	
<b>Characteristics</b>	<b>Patients, n (%)</b>
<b>Hospitalization reason</b>	
Hematuria	47 (34.6)
Post-renal acute kidney injury	25 (18.4)
Urolithiasis	8 (5.9)
Malignancy	20 (14.7)
Other reasons	36 (25.5)
Urinary tract infection during hospitalization, n (%)	60 (44.1)
<b>Surgery of patients with elective hospitalization, n (%)</b>	
n=74	
TUR-P	11 (14.9)
TUR-BT	44 (59.5)
URS	9 (12.2)
RIRS	2 (2.7)
Cystolithotripsy	0 (1.4)
Other surgeries	7 (9.5)
<b>Surgical complication, n (%)</b>	
n=74	
13 (17.6)	
Mortality at hospital, n (%)	5 (3.7)
3-month mortality, n (%)	26 (19.1)
6-month mortality, n (%)	32 (23.5)
12-month mortality, n (%)	41 (30.1)
Systemic Immune-Inflammation Index, median (range)	1178 (172-7248)
Prognostic nutritional index, median (range)	43.5 (20-59)
Mini nutritional assessment-screening, median (range)	11 (6-14)
Mini nutritional assessment-assessment, median (range)	21 (12-27)
WHOQOL-OLD score, median (range)	70 (51-76)
Length of hospitalization, median (range)	5 (1-36)
Follow-up (month), median (range)	9 (1-34)
CCI, median (range)	6 (4-10)
ECOG performance status, median (range)	2 (1-4)
Katz Index, median (range)	4 (1-6)
<b>ASA Score, n (%)</b>	
n=74	
ASA 2	21 (28.4)
ASA 3	53 (71.6)
<b>Clavien dindo classification</b>	
n=13	
Grade 1	10 (76.9)
Grade 2	3 (23.1)
BMI: Body mass index, TUR-P: Transurethral resection of prostate; TUR-BT: Tansurethral resection of bladder tumor; URS: Ureterorenoscopy, RIRS: Retrograde intrarenal surgery, CCI: Charlson Comorbidity Index, ECOG PS: Eastern cooperative oncology group performance status, ASA: American Society of Anesthesiologists	

was transurethral resection of bladder tumor, accounting for 59.5% of cases. A total of 25 patients (18.4%) were hospitalized due to post-renal AKI. Percutaneous nephrostomy was performed in 14 patients (10.3%), while double-J stent was inserted in four patients (2.9%). The intervention was not performed on 5 patients (5.2%).

### Patient Demographics, Characteristics and their Associations with PNI

The association between pre-admission PNI levels and patient demographics and clinical factors is shown in Table 2. Patients

with lower PNI (<42.65) were significantly more likely to be older, have lower body mass index (BMI), ( $p=0.002$ ), higher Electrocardiography Performance Status ( $p=0.002$ ), AKI during hospitalization ( $p=0.001$ ), elective admission ( $p=0.001$ ), and longer hospital stays ( $p=0.001$ ). A significant association was found between pre-hospitalization age ( $p=0.009$ ) and reason for hospitalization ( $p=0.033$ ), but not between pre-hospitalization age ( $p=0.009$ ) and gender ( $p=0.793$ ).



Table 2. Correlation of clinical and demographic characteristics Prognostic Nutritional Index (PNI) levels in patients			
	Low PNI (n=63)	High PNI (n=73)	p
Age (years), mean + SD	86.1±4.5	84.3±3.2	0.009T
Gender, n (%)			
Female	15 (23.8)	16 (21.9)	0.793
Male	48 (76.2)	57 (78.1)	
BMI, mean + SD	24±4.1	26.2±4.0	0.002T
Lives with, n (%)			
Alone	2 (3.2)	4 (5.5)	0.416F
Wife	18 (28.6)	27 (37)	
Other-related	43 (68.3)	42 (57.5)	
CCI, median (minimum-maximum)	6 (4-9)	5 (4-10)	0.364M
ECOG PS, median (minimum-maximum)	3 (1-4)	2 (1-4)	0.002M
Acute kidney injury during hospitalization	33 (52.4)	16 (21.9)	0.001
Percutaneous nephrostomy	8 (12.7)	6 (8.2)	0.391
Double J-stent	3 (4.8)	9 (12.3)	0.121
Hospitalization			
Emergency	50 (79.4)	32 (43.8)	0.001
Elective	13 (20.6)	41 (56.2)	
Reason for hospitalization			
Hematuria	26 (41.3)	21 (28.8)	0.033F
Postrenal AKI	16 (25.4)	9 (12.3)	
Urolithiasis	4 (6.3)	4 (5.5)	
Malignancy	66 (9.5)	14 (19.2)	
Other	11 (17.5)	25 (34.2)	
Urinary tract infection	33 (52.4)	27 (37)	0.071
Hospitalization days	6 (1-36)	3 (1-35)	0.001M
T: T-test, M: Mann-Whitney-U Test, F: Fisher's exact test. BMI: Body mass index, CCI: Charlson Comorbidity Index, ECOG PS: Eastern cooperative oncology group performance status, SD: Standard deviation			

<b>Table 3. Correlation of clinical and demographic characteristics and Systemic Immune-Inflammation Index (SII) levels in patients</b>			
	<b>Low SII (n=63)</b>	<b>High SII (n=73)</b>	<b>p</b>
Age (years), mean+SD	85.1±4.2	85.2±3.8	0.871T
<b>Gender, n (%)</b>			
Female	16 (21.9)	15 (23.8)	0.793
Male	57 (78.1)	48 (76.2)	
BMI, mean + SD	25.9±3.73	24.3±4.5	0.025T
<b>Lives with, n (%)</b>			
Alone	5 (6.8)	1 (1.6)	0.194F
Wife	26 (35.6)	19 (30.2)	
Other-related	42 (57.5)	43 (68.3)	
CCI, median (minimum-maximum)	6 (4-9)	5 (4-10)	0.699M
ECOG PS (minimum-maximum)	2 (1-4)	2 (1-4)	0.279M
Acute kidney injury during hospitalization	21 (28.8)	28 (44.4)	0.058
Percutaneous nephrostomy	4 (5.5)	10 (15.9)	0.047
Double J-stent	10 (13.7)	2 (3.2)	0.031
<b>Hospitalization</b>			
Emergency	37 (50.7)	45 (71.4)	0.014
Elective	36 (49.3)	18 (28.6)	
PNI, mean±SD	47.2±7.2	39±7.4	0.001T

Table 3. Continued			
	Low SII (n=63)	High SII (n=73)	p
<b>Reason for hospitalization</b>			
Hematuria	22 (30.1)	25 (39.7)	0.144F
Postrenal AKI	10 (13.7)	15 (23.8)	
Urolithiasis	4 (5.5)	4 (6.3)	
Malignancy	12 (16.4)	8 (12.7)	
Other	25 (34.2)	11 (17.5)	
Urinary tract infection	30 (41.1)	30 (47.6)	0.445
Hospitalization days	2 (0-13)	1 (0-7)	0.030M

T: T-test, M: Mann-Whitney-U Test, F: Fisher's exact test.  
 BMI: Body mass index, CCI: Charlson Comorbidity Index, ECOG PS: Eastern cooperative oncology group performance status, SD: Standard deviation, PNI: Prognostic Nutritional Index, SD: Standard deviation, min.-max.: Minimum, maximum

### Patient Demographics, Characteristics and their Associations with SII

The demographic and clinical attributes of the patients, as they relate to their pre-hospital SII, are shown in Table 3. Patients with higher SII exhibited higher PNI ( $p=0.001$ ). SII was significantly associated with length of hospital stay ( $p=0.030$ ) but not with age ( $p=0.871$ ) or gender ( $p=0.793$ ).

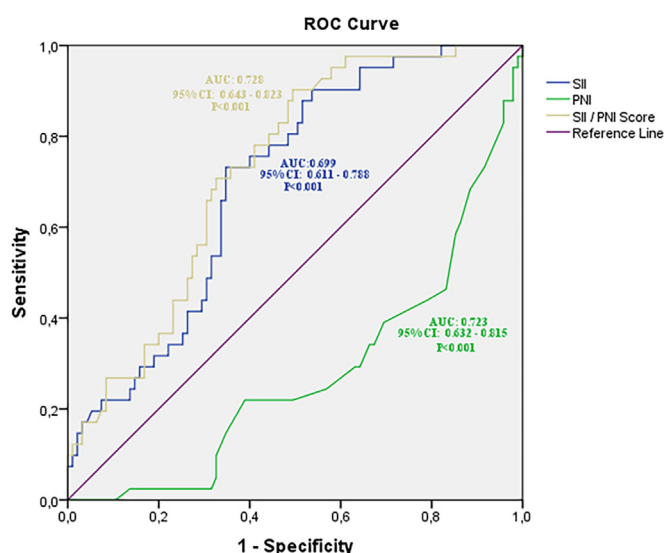
### Optimal Cut-off Points for SII, PNI, and the SII/PNI Ratio

Using ROC curve analysis, we defined the optimal cut-off values for the SII, PNI, and the combined SII/PNI index. The optimal cut-off values for predicting OS were identified as 1243 for SII, 42.65 for PNI, and 32.37 for SII/PNI, respectively. The area under the curve for OS was 0.699, 0.723, and 0.728 for SII, PNI, and SII/PNI, respectively (Figure 1). Percutaneous nephrostomy tubes were placed in patients who had dilated upper systems. Although this improves the short-term survival of these patients, who have a percutaneous nephrostomy tube associated with poorer OS ( $p<0.001$ ) (Figures 2A), it does not affect long-term outcomes. On the other hand, no statistically significant difference in OS was observed between male and female patients ( $p=0.684$ ) (Figure 2B).

### Factors Affecting Patient Survival: A Univariate and Multivariate Analysis

The univariate analysis showed that OS was significantly influenced by Eastern cooperative oncology group performance status (ECOG-PS), percutaneous nephrostomy procedures, reasons for hospitalization, SII, PNI, Katz Index scores, and hospital stay length.

Multivariate COX regression analysis revealed that percutaneous nephrostomy ( $HR=5.013$ , 95% CI=2.485-10.114,  $p<0.001$ ), PNI ( $HR=0.926$ , 95% CI=0.890-0.964,  $p<0.001$ ), and length of hospital stay ( $HR=1.040$ , 95% CI=1.002-1.079,  $p=0.038$ ) were independent predictors of OS, as shown in Table 4.

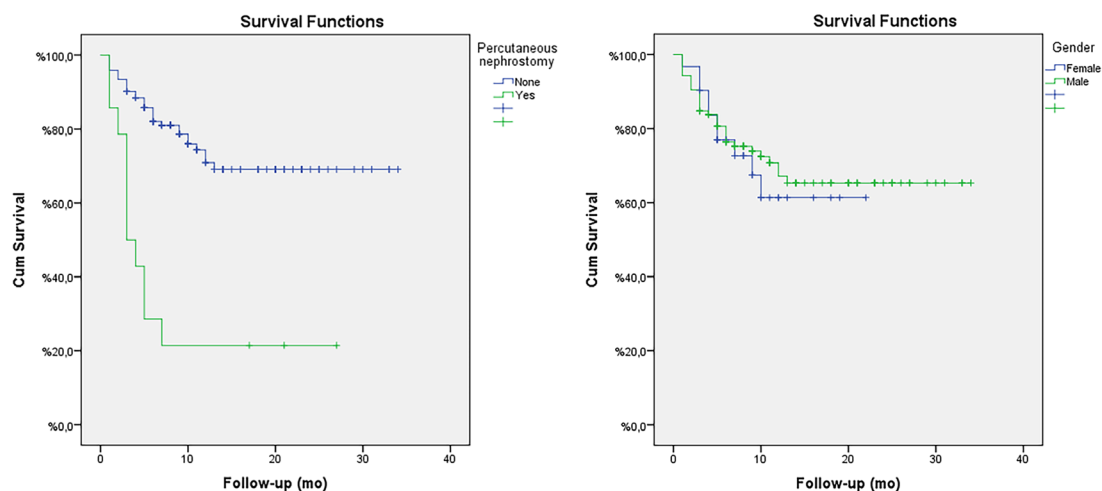


**Figure 1.** Details of the receiver operating characteristics (ROC) analysis of the effect of the SII, PNI and SII/PNI score. The area under the curve (AUC) for (OS) was 0.699, 0.723, and 0.728 for SII, PNI, and SII/PNI, respectively.

PNI: Prognostic Nutritional Index, SII: Systemic Immune-Inflammation Index, OS: Overall survival

### Discussion

The aging population and extended life expectancy have contributed to considerable growth in the number of geriatric patients requiring urological treatment. In the absence of evidence-based guidelines specific to the management of frail elderly patients, case studies can offer valuable insights into the complex diagnostic and therapeutic dilemmas encountered in this population (8). In recent times, there has been a notable increase in interest surrounding the prognostic value of SII and PNI. Additionally, emerging research highlights the role of inflammation in disease initiation, progression, and metastasis, as well as its impact on immune regulation (9-12). The study's



**Figure 2.** (A) Percutaneous nephrostomy tubes improve the short-term survival of these patients, who have a percutaneous nephrostomy tube associated with poorer OS ( $p < 0.001$ ). (B) Kaplan-Meier analyses for OS over 80 years old according to percutaneous nephrostomy (2A) and gender (2B). No statistically significant difference in OS was observed between male and female patients ( $p = 0.684$ ).

OS: Overall survival

Variable	Univariate model	p	Multivariate model	p
	HR (95% CI)		HR (95% CI)	
Age (years)	1.071 (1.000–1.148)	0.051		
Gender (Ref: Female)	0.864 (0.432–1.766)	0.689		
BMI	0.926 (0.855–1.002)	0.056		
Marriage status	1.276 (0.651–2.503)	0.478		
Lives with (Ref: Alone)	1.924 (1.021–3.626)	0.043		
CCI	1.062 (0.841–1.340)	0.613		
Additional malignancy	1.410 (0.553–3.594)	0.472		
ECOG PS	1.777 (1.199–2.633)	0.004		
Antiaggregant status	1.309 (0.708–2.419)	0.390		
Anticoagulant status	0.966 (0.461–2.025)	0.927		
Smoking status	0.633 (0.332–1.210)	0.167		
Percutaneous nephrostomy	4.795 (2.385–9.641)	<0.001	5.013 (2.485–10.114)	<0.001
Double J-stent	0.228 (0.031–1.656)	0.144		
Number of previous hospitalizations	1.012 (0.880–1.165)	0.865		
Number of hospitalizations in the last year	1.266 (0.991–1.616)	0.059		
Reason for hospitalization	0.730 (0.591–0.902)	0.004		
SII	1000	<0.001		
PNI	0.929 (0.896–0.964)	<0.001	0.926 (0.890–0.964)	<0.001
Katz Index	0.724 (0.586–0.894)	0.003		
Mini nutritional assessment-screening	0.798 (0.665–0.956)	0.015		
Mini nutritional assessment-assessment	0.906 (0.819–1.002)	0.055		
WHOQOL-OLD score	0.921 (0.853–0.995)	0.036		
Urinary tract infection	1.256 (0.678–2.326)	0.468		
Hospitalization days	1.063 (1.031–1.096)	<0.001	1.040 (1.002–1.079)	<0.038

BMI: Body mass index, CCI: Charlson Comorbidity Index, ECOG PS: Eastern cooperative oncology group performance status, SII: Systemic Immune-Inflammation Index; PNI: Prognostic Nutritional Index, HR: Hazard ratio, CI: Confidence interval

aim is to examine the clinical utility and predictive power of SII and PNI in hospitalized individuals aged 80 and above, and to analyze their comparative predictive accuracy. Our study results indicates that a high SII and low PNI prior to surgery are independent predictors of short-term survival in patients over the age of 80.

On the other hand, patient-related factors, including systemic inflammatory response (SIR) markers, can also influence cancer progression and prognosis. Malnutrition, indicated by low albumin levels, is linked to increased morbidity, mortality, and impaired response to cancer treatment. It also weakens the immune system, promoting tumor recurrence (13-17). In our study, we found that the low PNI group patients' survival was less than the other group. The mechanisms of SIR are complex and remain controversial. Neutrophils have been linked to the presence of chemokines, growth factors and proteases that regulate angiogenesis. This could potentially influence the tumor's blood supply and growth rate (18-21). It was observed that cancer patients with a SII greater than  $330 \times 10^9$  cells/L exhibited a poorer prognosis compared to those with lower SII scores (22). Elevated SII levels, characterized by increased granulocyte and platelet counts and decreased lymphocyte counts, suggest a weakened immune response and heightened inflammatory state, leading to adverse outcomes. Neutrophils are integral components of innate immunity, playing a crucial role in host defense mechanisms such as antibody-dependent cellular cytotoxicity and phagocytosis (23). The present study revealed that elevated SII was associated with lower BMI, fewer double-J stents, more percutaneous nephrostomy tubes, longer hospital stays, and increased emergency hospitalizations.

A reduction in the number of lymphocytes in the bloodstream may be indicative of an impaired anti-tumor immune response. Additionally, it is established that the inflammatory response associated with the tumor and the cytokines released because of this inflammation can lead to a reduction in blood albumin levels, which may, in turn, contribute to tumor progression (24-25).

The PNI was initially proposed as a means of assessing the immunological and nutritional status of patients who have undergone gastrointestinal surgery (26). It is also known that the lymphocyte count and the blood albumin level have prognostic importance (27). Lymphocytes, another essential component of the PNI, play a pivotal role in cell-mediated immune responses, which can significantly impact tumor recurrence and progression. Additionally, a compromised nutritional status can further contribute to tumor progression by hindering tumor immunity. This immunosuppressed state can lead to suboptimal outcomes in cancer patients. PNI has been shown to be a valuable prognostic marker in various cancers. SI has been linked to tumor progression,

recurrence, metastasis, and poor oncological outcomes (28-29). In our study, lower PNI was associated with increasing age, lower BMI, higher ECOG-PS, emergency hospitalization, urinary tract infection, and a longer hospital stay.

While optimal cutoff values for PNI and SII to predict OS remain elusive, previous research has explored their potential. Mori et al. utilized ROC curve analysis to find PNI cut-offs, reporting 51 for renal carcinoma and 50 for NSCLC, respectively (30). We found that PNI and SII cut-off values of 42.65 and 1243, respectively, are useful to predict short-term survival.

Our study shows that SII and PNI are important markers for older adults. Patients with low SII and high PNI had better outcomes, while those with low PNI and high SII had worse outcomes. Using both SII and PNI improves prediction.

### Study Limitations

It should be noted that this study is subject to several limitations, including its retrospective design, single-center nature, and lack of additional analysis of inflammatory markers, which could have provided further insights into the pathophysiology of the disease.

### Conclusions

This study highlights the prognostic value of the PNI, SII, and SII/PNI ratio in predicting short-term survival among older adults. Multivariate COX regression analysis identified percutaneous nephrostomy, lower PNI, and a longer length of hospital stay as independent predictors of poor OS.

### Ethics

**Ethics Committee Approval:** This study was approved by the Medeniyet University Göztepe Training and Research Hospital's Ethics Committee (decision number: 2023/0823, date: 29.11.2023).

**Informed Consent:** Retrospective study.

### Footnotes

#### Authorship Contributions

Surgical and Medical Practices: İ.H.Z., M.Ç.Ç., Ö.A., Concept: İ.H.Z., M.Ç.Ç., Ö.A., A.K., A.Y., Design: İ.H.Z., M.Ç.Ç., Data Collection or Processing: İ.H.Z., Ö.A., A.K., A.Y., Analysis or Interpretation: İ.H.Z., Ö.A., A.Y., Literature Search: İ.H.Z., M.Ç.Ç., A.K., A.Y., Writing: İ.H.Z., M.Ç.Ç., A.K.

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# Longitudinal Associations of the Yubi-Wakka Test with Sarcopenia: A Two-Year Study Among Thai Older Adults

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## Abstract

**Objective:** Sarcopenia increases risks of adverse outcomes and healthcare costs while reducing independence and quality of life. Early detection allows timely interventions, but advanced diagnostic tools are often inaccessible. The Yubi-Wakka test (finger-ring) test is an easy-to-use and cost-effective screening tool that may serve as a practical alternative. This study examines its association with sarcopenia and its predictive value for new-onset cases in Thai older adults.

**Materials and Methods:** This cohort study followed 460 older adults from the Outpatient Department at Phramongkutklao Hospital. Sarcopenia was diagnosed according to the 2019 criteria established by the Asian Working Group for Sarcopenia. Participants were grouped into "bigger", "just fits", and "smaller" categories according to their Yubi-Wakka (finger-ring) test outcomes. Baseline and longitudinal relationships were analyzed using multinomial logistic regression and Cox proportional hazard models.

**Results:** Participants in the "just fits" group had 3.28 times higher [odds ratio (OR) =3.28, 95% confidence interval (CI): 1.56-6.88] and those in the "smaller" group had 6.91 times higher (OR =6.91, 95% CI: 3.78-12.64) of sarcopenia at baseline compared to the "bigger" group. Over two years, the risk of developing new-onset sarcopenia was 2.1 times higher [hazard ratio (HR) =2.1, 95% CI: 1.40-3.16] in the "just fits" group and 3.3 times higher (HR =3.3, 95% CI: 2.37-4.58) in the "smaller" group.

**Conclusion:** The Yubi-Wakka test or finger-ring test proves to be an effective, low-cost screening tool for sarcopenia, with strong predictive value for both its presence and future onset. Its simplicity makes it highly suitable for resource-constrained environments.

**Keywords:** Aging, clinical geriatrics, geriatric syndromes, geriatrics, sarcopenia

## Introduction

Sarcopenia, characterized by a progressive and generalized decline in skeletal muscle mass (ASM) and strength, is increasingly recognized as a significant health concern, particularly in older adults. The European Working Group on Sarcopenia in Older People identifies low muscle strength as the primary diagnostic criterion, supported by reduced muscle mass and compromised physical performance (1). Similarly, the Asian Working Group for Sarcopenia (AWGS) 2019 recommends diagnostic methods such as handgrip strength for muscle

function, bioelectrical impedance analysis (BIA) or dual-energy X-ray absorptiometry (DEXA) for assessing muscle mass, and gait speed and chair stand tests for evaluating physical performance (2,3). Although these methods are reliable, their reliance on specialized equipment and trained personnel often restricts their availability in resource-limited environments, presenting challenges for broader implementation.

The clinical significance of sarcopenia lies in its association with numerous adverse outcomes, including increased risk of frailty, falls, fractures, hospitalizations, and even mortality (4,5).

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Moreover, sarcopenia contributes to a decline in functional independence, negatively impacting the quality of life and increasing healthcare expenditures (6-11). Early detection is crucial to enable timely interventions, such as resistance training, adequate protein intake, and other therapeutic measures, which have been shown to mitigate its progression (12). However, the unavailability of advanced diagnostic tools in many healthcare settings has highlighted the need for practical, cost-effective screening methods for early risk identification.

To address this issue, several sarcopenia screening tools have been proposed, ranging from questionnaire-based assessments like the SARC-F to physical measurements such as gait speed and grip strength (13). One particularly simple and accessible method is the Yubi-Wakka or finger-ring test. This test involves encircling the maximum circumference of the non-dominant calf with a ring created by forming a circle using the thumbs and index fingers of both hands. Based on the fit of the ring around the calf, individuals are categorized as "bigger" (calf circumference larger than the ring), "just fits" (equal to the ring), or "smaller" (calf circumference smaller than the ring) (14). As an indirect measure of muscle mass, this method is cost-effective, easy to administer, and has been shown to have moderate accuracy for predicting sarcopenia (15). Its simplicity makes it particularly suited for use in community settings or regions with limited healthcare resources.

This study aims to investigate the relationship between initial Yubi-Wakka test findings and subsequent health outcomes among Thai older adults. Specifically, we evaluate its relationship with baseline sarcopenia and new-onset sarcopenia over a two-year period. By assessing the accuracy and predictive value of this simple screening tool, we aim to provide evidence for its broader application in community and clinical settings to improve early detection and risk management of sarcopenia, ultimately enhancing health outcomes in aging populations.

## Materials and Methods

### Setting and Participants

The prospective cohort study invited 460 older adults aged 60 years and above from the family and internal medicine outpatient departments at Phramongkutklao Hospital, Bangkok, Thailand. The participants completed baseline assessments conducted between October and December 2022. Exclusion criteria included individuals with physical or mental limitations that prevented assessment completion, such as severe dementia or being bedridden. Additionally, we excluded individuals with unilateral muscle atrophy due to conditions such as hemiplegia, cerebrovascular accident (stroke), or rheumatological disorders affecting limb symmetry. Participants with contraindications to BIA or conditions such as significant leg edema, which could

affect calf measurements and the Yubi-Wakka test, were also excluded. A longitudinal analysis was conducted, focused on new-onset sarcopenia, using data from annual follow-ups over two years (October 2022 to September 2024). Cross-sectional analysis utilized baseline data.

### Measure

The Yubi-Wakka test assessed calf circumference by asking participants to encircle the largest part of their non-dominant calf with their thumb and index finger while seated, with knees at a 90-degree angle. Results were categorized as "smaller", "just fits", or "bigger" compared to the circle of thumb and index finger (16,17). To enhance measurement consistency and minimize potential bias, the Yubi-Wakka test was self-administered by participants, based on standardized verbal and visual instructions, while trained healthcare professionals closely supervised the process and provided guidance as needed. Although participants performed the test themselves, the presence of healthcare personnel helped reduce variability and improve the reliability of the measurements.

Anthropometric data included standing weight, height, calf circumference (measured while seated using standardized methods), and pedal edema. Sarcopenia was diagnosed following the AWGS 2019 criteria, with thresholds including muscle mass  $<5.7$  kg/m<sup>2</sup> for women and  $<7.0$  kg/m<sup>2</sup> for men, handgrip strength  $<28$  kg for men, and  $<18$  kg for women, or inability to complete a five-time chair stand test within 12 seconds (2).

Measures of body composition, particularly appendicular ASM and body fat, were measured by means of the InBody720 device for BIA after a 12-hour fast and avoidance of water, coffee, or alcohol four hours prior (18). ASM was calculated by summing muscle mass from all limbs, and adjusting for height squared [ASM/height<sup>2</sup> (kg/m<sup>2</sup>)] (2,19).

Muscle strength was measured with a Smedley-type handgrip dynamometer (TKK-5401, Takei Equipment Industries, Japan), using the higher of two readings from the dominant hand (16). Physical performance was measured via the five-time chair stand test, where participants were timed standing up and sitting down five times; inability to complete the task indicated poor performance (20).

Calf circumference was measured with 0.1 cm precision using a non-elastic tape, by averaging the largest circumferences from both calves.

The collected demographic data included sex, age, income, education, physical activity, living arrangements, and chronic conditions, which were recorded via questionnaires. Physical inactivity, for the purposes of this study, referred to not engaging in regular exercise, and previous laboratory tests provided information on serum albumin levels.

For the two-year follow-up assessment, the same measurement protocols were applied to ensure consistency. The same InBody720 device was used for BIA to assess body composition, including ASM. Additionally, the same Smedley handgrip dynamometer and five-time chair stand test were used to reassess muscle strength and physical performance, respectively. This consistency in measurement methods aimed to minimize variability and ensure accurate longitudinal comparisons.

## Statistics

Multiple logistic regression was conducted to assess the association between sarcopenia and Yubi-Wakka test outcomes. Cox proportional hazard modeling was used to analyze new-onset sarcopenia, with the non-onset group as the reference. adjusted odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals (CI) accounting for potential confounders such as age, physical inactivity, and education, while controlling for chronic conditions and body fat percentage. All analytical procedures were executed in IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA), with significance set at  $p < 0.05$ .

## Ethical Considerations

The study was approved by the Institutional Review Board of the Royal Thai Army Medical Department (approval number: IRBRTA1468/2565, date: 04.11.2022) and conducted in compliance with the ethical standards of the Declaration of Helsinki. Prior to participation, all individuals received clear explanations of the study's aims and procedures, and written informed consent was obtained. Participants were assured of the confidentiality of their information and were informed of their right to withdraw from the study at any time without any repercussions.

## Results

### Study Participants

The study analyzed 460 participants, of whom 76 (16.5%) were classified as sarcopenic and 384 (83.5%) as non-sarcopenic. Based on the Yubi-Wakka test, 56.1% were categorized as "bigger", 16.5% as "just fit", and 27.4% as "smaller". Among sarcopenic participants, the majority were in the "smaller" group (56.6%), significantly higher than in the "bigger" (23.7%) and "just fit" (19.7%) groups, ( $p < 0.001$ ). The baseline characteristics of participants grouped by sarcopenia status are shown in Table 1. Sarcopenic participants were older, with a mean age of  $71 \pm 6$  years, compared to  $69 \pm 6$  years for non-sarcopenic participants. Also had fewer years of education [median 6 years, interquartile range (IQR) 6–12] compared to the non-sarcopenic group (median 9 years, IQR 6–16). Physical inactivity was more common in sarcopenic individuals (22.4%) than in those without sarcopenia (7.6%) ( $p < 0.001$ ). In terms of anthropometric measures, sarcopenic participants had lower mean height

( $154 \pm 8$  cm vs.  $159 \pm 8$  cm), weight ( $54.9 \pm 10$  kg vs.  $65 \pm 13.6$  kg), and body mass index ( $23.2 \pm 3.2$  kg/m<sup>2</sup> vs.  $25.7 \pm 4.8$  kg/m<sup>2</sup>). Additionally, their calf circumference was smaller ( $34.0 \pm 2.6$  cm vs.  $36.8 \pm 3.7$  cm). However, there was no notable difference in body fat percentage between the two groups (34.5% vs. 34%). Physical function was significantly poorer in sarcopenic participants, with lower handgrip strength ( $18.7 \pm 5.7$  kg vs.  $24.2 \pm 7.7$  kg) and longer times to complete the five-time chair stand test ( $10.6 \pm 3.0$  seconds vs.  $9.7 \pm 3.3$  seconds). Nutritional status, measured by serum albumin levels, was slightly lower in the sarcopenic group (median 4.2 g/mL, IQR 4.0–4.4) compared to the non-sarcopenic group (median 4.3 g/mL, IQR 4.2–4.4). Regarding chronic conditions, sarcopenic participants had a significantly lower prevalence of chronic renal failure (1.3% vs. 13.3%,  $p = 0.003$ ), while the prevalence of other conditions, such as hypertension, diabetes mellitus, dyslipidemia, and osteoporosis showed no significant differences.

### Longitudinal Analysis of Sarcopenia and the Yubi-Wakka Test

The findings from both the cross-sectional and longitudinal analyses showed the strong relationship between Yubi-Wakka test outcomes and sarcopenia. In the cross-sectional analysis, participants in the "just fits" group had 3.28 times higher odds of sarcopenia (OR = 3.28, 95% CI: 1.56–6.88,  $p = 0.002$ ) compared to those in the "bigger" group, while participants in the "smaller" group had 6.91 times higher odds (OR = 6.91, 95% CI: 3.78–12.64,  $p < 0.001$ ). Stratified by sex, men in the "just fits" group had odds 4.64 times higher (OR = 4.64, 95% CI: 1.16–18.61,  $p = 0.001$ ); and men in the "smaller" group had odds 8.56 times higher (OR = 8.56, 95% CI: 2.77–26.41,  $p = 0.031$ ). Among women, the "just fits" group had odds of 2.56 times (OR = 2.56, 95% CI: 1.07–6.09,  $p = 0.034$ ), while the "smaller" group showed odds of 7.33 times of sarcopenia (OR = 7.33, 95% CI: 3.55–15.14,  $p < 0.001$ ) (Table 2).

In the longitudinal analysis, participants in the "just fits" group demonstrated a 2.1-fold higher risk of developing new-onset sarcopenia (HR = 2.1, 95% CI: 1.40–3.16,  $p < 0.001$ ), while those in the "smaller" group had a 3.3-fold higher risk (HR = 3.3, 95% CI: 2.37–4.58,  $p < 0.001$ ) compared to the "bigger" group. Among men, the "just fits" group had a 1.91-fold increased risk (HR = 1.91, 95% CI: 1.04–3.50,  $p = 0.037$ ), and the "smaller" group had a 3.06-fold higher risk (HR = 3.06, 95% CI: 1.96–4.78,  $p < 0.001$ ). In women, participants in the "just fits" group showed a 2.05-fold greater risk of developing sarcopenia (HR = 2.05, 95% CI: 1.27–3.33,  $p = 0.004$ ), while those in the "smaller" group had a 3.01-fold higher risk (HR = 3.01, 95% CI: 1.96–4.62,  $p < 0.001$ ). These results highlight that participants classified as "just fits" and "smaller" in the Yubi-Wakka test were at significantly higher odds of having sarcopenia and at elevated risk of developing sarcopenia over the two-year follow-up, with similar patterns observed in both men and women (Table 2).

Table 1. Demographic and baseline characteristics of the study participants				
Variables (unit)	Overall	Non-sarcopenia	Sarcopenia	p
No. participants		384 (83.5%)	76 (16.5%)	
Yubi-Wakka (finger ring) test				
Bigger	258 (56.1%)	240 (62.5%)	18 (23.7%)	<0.001
Just fit	76 (16.5%)	61 (15.9%)	15 (19.7%)	
Smaller	126 (27.4%)	83 (21.6%)	43 (56.6%)	
Basic attributes				
Age (years)	69 (6)	69 (6)	71 (6)	
Years of education (years)	9 (6.16)	9 (6.16)	6 (6.12)	
living arrangement (alone)	184 (40.0%)	155 (40.4%)	29 (38.2%)	0.72
Physical activity (inactive)	46 (10%)	29 (7.6%)	17 (22.4%)	<0.001
Anthropometric measurements				
Height (cm)	158 (8)	159 (8)	154 (8)	
Weight (kg)	63.3 (13.6)	65 (13.6)	54.9 (10)	
BMI (kg/m <sup>2</sup> )	25.2 (4.7)	25.7 (4.8)	23.2 (3.2)	
Calf circumference (cm)	36.4 (3.7)	36.8 (3.7)	34.0 (2.6)	
BIA measurements				
ASMI (kg/m <sup>2</sup> )	6.6 (1.1)	6.8 (1.0)	5.8 (1.0)	
body fat rate (%)	34.1 (8.5)	34 (8.8)	34.5 (6.6)	
Physical function				
Handgrip strength (kg)	23.3 (7.7)	24.2 (7.7)	18.7 (5.7)	
5-time chair stand test (sec)	9.9 (3.2)	9.7 (3.3)	10.6 (3.0)	
Nutrition status				
Serum albumin (g/mL)	4.3 (3.9,4.4)	4.3 (4.2,4.4)	4.2 (4.0,4.4)	
Present chronic condition				
Hypertension	344 (74.8%)	289 (75.3%)	55 (72.4%)	0.596
Diabetes mellitus	104 (22.6%)	90 (23.4%)	14 (18.4%)	0.339
Osteoporosis	16 (3.5%)	12 (3.1%)	4 (5.3%)	0.353
Dyslipidemia	400 (87.0%)	339 (88.3%)	61 (80.3%)	0.058
Malignant neoplasm	12 (2.6%)	9 (2.3%)	3 (3.9%)	0.423
Heart disease	8 (1.7%)	7 (1.8%)	1 (1.3%)	0.757
Chronic renal failure	52 (11.3%)	51 (13.3%)	1 (1.3%)	0.003
Values are shown as mean ( $\pm$ standard deviation), median (25 percentile, 75 percentile) or number of participants (%)				
ASMI: Appendicular muscle mass index, BMI: Body mass index, BIA: Bioelectrical impedance analysis				

The Kaplan-Meier curves (Figure 1) illustrate the two-year cumulative survival probabilities according to the Yubi-Wakka test (add space between "Wakka" and "test") (finger-ring) test results at baseline, stratified by the overall population, men, and women. In the overall population, participants in the "bigger" group consistently exhibited the highest survival rates throughout the follow-up period, while those in the "smaller" group showed significantly reduced survival, indicating a higher mortality risk. The "just fits" group displayed intermediate survival

outcomes, positioned between the "bigger" and "smaller" groups. Similar trends were observed in the sex-stratified analyses. Among men, the "bigger" group maintained the highest survival probabilities, whereas the "smaller" group experienced a sharp decline, with the "just fits" group showing survival outcomes in between. Women followed the same pattern, with the "bigger" group demonstrating the most favorable survival rates; the "smaller" group showing the steepest decline; and the "just fits" group displaying intermediate outcomes. Findings consistently

Table 2. Analysis of cross-sectional and longitudinal relationships of the “Yubi-Wakka” test												
			Overall			Men				Women		
	n		95% CI	p	n		95% CI	p-value	n		95% CI	p
Outcome: Sarcopenia												
Cross-sectional analysis												
“Yubi-Wakka” test		OR				OR				OR		
Bigger	18/258	1	(Referent)		4/93	1	(Referent)		14/165	1	(Referent)	
Just fits	15/76	3.28	(1.56-6.88)	0.002	6/24	4.64	(1.16-18.61)	0.001	9/52	2.56	(1.07-6.09)	0.034
Smaller	43/126	6.91	(3.78-12.64)	<0.001	18/65	8.56	(2.77-26.41)	0.031	25/61	7.33	(3.55-15.14)	<0.001
Longitudinal analysis												
“Yubi-Wakka” test		HR				HR				HR		
Bigger	73/258	1	(Referent)		35/93	1	(Referent)		38/165	1	(Referent)	
Just fits	34/76	2.1	(1.40-3.16)	<0.001	10/24	1.91	(1.04-3.50)	0.037	24/52	2.05	(1.27-3.33)	0.004
Smaller	70/126	3.3	(2.37-4.58)	<0.001	38/65	3.06	(1.96-4.78)	<0.001	32/61	3.01	(1.96-4.62)	<0.001
The odds ratios for the “just fit” and “smaller” categories compared to the “bigger” category were calculated based on the baseline prevalence of sarcopenia. Hazard ratios for the risk of sarcopenia in the “just fit” and “smaller” groups, relative to the “bigger” group, were determined for a two-year follow-up period. Participants with baseline sarcopenia or those who missed follow-up assessments were excluded. All ratios were adjusted for baseline factors, including age, education, physical activity, chronic conditions, and body fat percentage												
CI: Confidence interval, HR: Hazard ratio, OR: Odds ratio												

highlight that a smaller calf circumference, as assessed using the Yubi-Wakka test, is linked to an increased risk of mortality, making it a valuable predictor of survival across all participants.

Changes in Sarcopenia Parameters Over Two Years

Over the two-year follow-up period, key sarcopenia-related parameters showed notable declines. Handgrip strength decreased from 23.3±7.7 kg at baseline to 21.5±7.5 kg at follow-up, while calf circumference was reduced from 36.4±3.7 cm to 35.2±3.5 cm. The appendicular ASM Index declined from 6.6±1.1 kg/m² to 6.4±1.0 kg/m². Additionally, physical function deteriorated as indicated by a longer five-time chair stand test duration, increasing from 9.9±3.2 seconds to 11.0±3.5 seconds. The prevalence of sarcopenia also rose from 16.5% at baseline to 22.0% at follow-up, reflecting the progressive decline in muscle health among aging individuals. These findings highlight the importance of early detection and intervention to mitigate sarcopenia progression (Table 3).

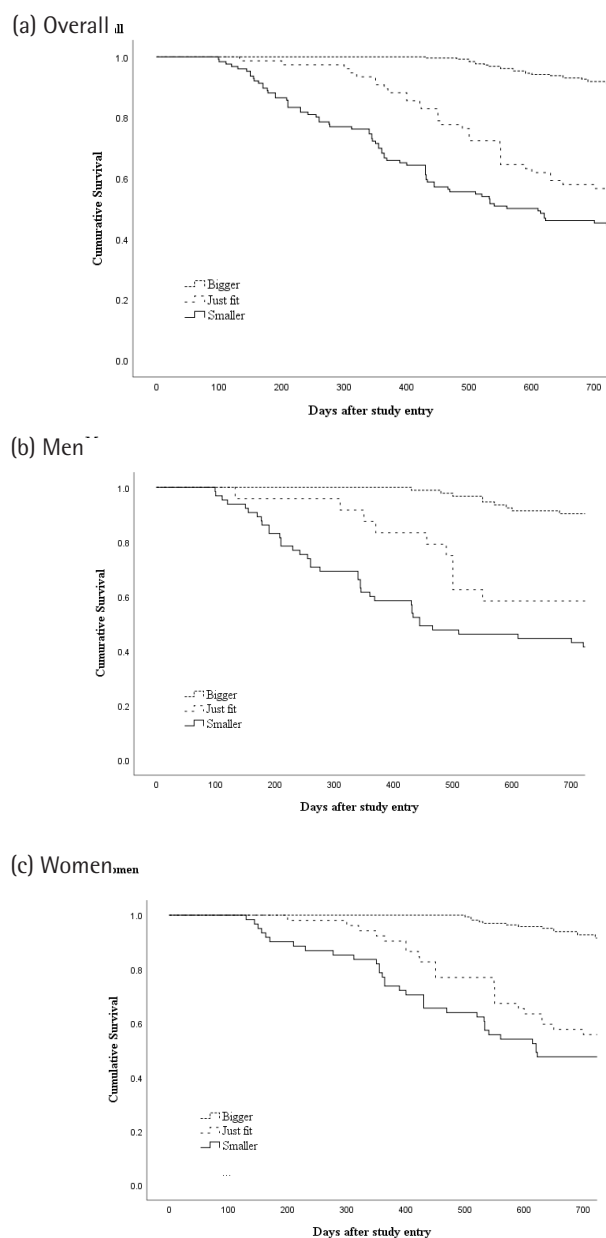
Discussion

This study highlights the clinical utility of the Yubi-Wakka test as an applicable and accessible self-screening tool for sarcopenia among older adults in Thailand. The findings demonstrate that individuals categorized as “smaller” using the Yubi-Wakka test were significantly more likely to have sarcopenia at baseline, and to develop new-onset sarcopenia over the two-year observation period. These results reinforce the potential of the

Yubi-Wakka test in predicting sarcopenia and related adverse health outcomes, particularly in resource constrained settings where more sophisticated diagnostic instruments may not be available.

The cross-sectional analysis revealed that participants in the “smaller” group had nearly sevenfold increased odds of sarcopenia in comparison with those in the “bigger” group. Additionally, those in the “just fits” group also showed increased odds, although to a lesser degree. These findings are consistent with prior research conducted in Japanese populations, which reported that the “smaller” classification in the Yubi-Wakka test demonstrated an association with significantly elevated odds of sarcopenia, as well as a higher likelihood of developing disability and mortality (14). Notably, this study provides new evidence supporting the applicability of the Yubi-Wakka test in a Thai population, addressing a critical research gap in the literature.

The longitudinal analysis further underscores the prognostic value of the Yubi-Wakka test. Over the two-year follow-up interval, participants in the smaller group were more than three times as likely to develop new-onset sarcopenia compared to those in the bigger group. This finding aligns with recent studies suggesting that reduced muscle mass, as indicated by smaller calf circumference, is a strong predictor of sarcopenia progression and its associated complications (21). Importantly, the HR observed in this study highlight the test's potential utility in stratifying risk and guiding early intervention efforts.



**Figure 1.** Kaplan-Meier survival curves illustrating two-year follow-up outcomes based on baseline "Yubi-Wakka" test categories. The graphs depict cumulative all-cause mortality events adjusted for age, shown for (a) the overall cohort for (b) men and (c) women

The association between measurements of calf circumference and performance on the Yubi-Wakka test is particularly noteworthy, as calf circumference is commonly utilized as an indirect measure of muscle mass in both clinical and epidemiological studies (2). The Yubi-Wakka test offers a simple and convenient alternative for estimating calf circumference without requiring specialized equipment. Findings from this study demonstrate a strong correlation between Yubi-Wakka test classifications and actual calf circumference measurements, supporting its effectiveness as a sarcopenia screening tool. Nevertheless, while the Yubi-Wakka test is a feasible and accessible method, direct calf circumference measurement remains the more precise approach (17).

The Yubi-Wakka test serves as an indirect measure of muscle mass through calf circumference, but it does not assess strength capacity or physical function -both of which are crucial elements in the diagnosis of sarcopenia based on established international criteria. Although the test is easy to use and suitable for wide application, it does not reflect functional decline, such as diminished grip strength or slower chair stand performance.

The simplicity and cost-effectiveness of the Yubi-Wakka test make it an appealing instrument for widespread use in community and clinical settings. Unlike advanced diagnostic modalities such as methods like DEXA and BIA, the Yubi-Wakka test requires no specialized equipment or technical expertise, making it particularly suited for use in resource-constrained environments. Furthermore, the self-administrable nature of the test enhances its feasibility for large-scale screening initiatives, potentially improving early detection rates and facilitating timely interventions.

The efficacy of the Yubi-Wakka test has been validated in previous studies using established diagnostic criteria for sarcopenia, including assessments based on BIA. For example, Lawongsa et al. (17) found that the test yielded sensitivity and specificity rates of 85.7% and 71.2% in males, and 87.5% and 80.8% in females, when compared with BIA-defined sarcopenia. These figures are comparable to those obtained using calf circumference, a widely accepted proxy for muscle mass

**Table 3. Sarcopenia parameter changes**

Parameter	Baseline (year 0)	Follow-up (year 2)
Handgrip strength (kg)	23.3±7.7	21.5±7.5
Calf circumference (cm)	36.4±3.7	35.2±3.5
ASMI (kg/m <sup>2</sup> )	6.6±1.1	6.4±1.0
5-time chair stand test (sec)	9.9±3.2	11.0±3.5
Prevalence of sarcopenia (%)	16.5%	22.0%
Values are shown as mean ± standard deviation ASMI: Appendicular muscle mass index		



estimation. Furthermore, the alignment between Yubi-Wakka test classifications and direct calf circumference measurements observed in this study reinforces the Yubi-Wakka test's reliability as a screening method for reduced muscle mass.

In terms of diagnostic accuracy, previous studies have compared the Yubi-Wakka test with other simple screening methods. In the study by Lawongsa et al. (17), the test's performance in terms of sensitivity and specificity was reported as 85.7% and 71.2% in males, and 87.5% and 80.8% in females, respectively, compared to calf circumference, which showed values of 85.7% and 81.8% in males, and 81.3% and 88.0% in females. Similarly, Lin et al. (22) compared calf circumference, SARC-F, and SARC-Calf, reporting that calf circumference had a sensitivity and specificity of 86.7% and 82.4% in males, and 85.5% and 63.3% in females. For SARC-F, sensitivity and specificity were 32.9% and 95.2% in males and 65.5% and 61.1% in females. SARC-calf showed values of 69.9% and 96.7% in males, and 83.6% and 65.6% in females. These findings emphasize that the Yubi-Wakka test demonstrates comparable or favorable diagnostic performance supporting its potential applicability as an initial screening instrument in various clinical and community settings.

In a study, the Yubi-Wakka test was confirmed as a reliable self-screening tool for detecting sarcopenia in Japanese community-dwelling older adults. The research, which involved 1,904 participants, demonstrated that individuals categorized as "smaller" had significantly elevated odds of sarcopenia and demonstrated a heightened risk of functional impairment and mortality (16). Similarly, a cross-sectional study, performed using 230 Thai older adults, revealed that the Yubi-Wakka test had favorable sensitivity and specificity for identifying those at risk of sarcopenia (17).

A novel aspect of this study is the exploration of the Yubi-Wakka test's longitudinal associations with new-onset sarcopenia. While previous research has primarily focused on cross-sectional analyses, this study provides valuable insights into the test's predictive validity over time. These findings align with the recent work of Tanaka et al. (16), which highlighted the significance of longitudinal assessments in comprehending the progression of sarcopenia and evaluating the effectiveness of preventive interventions. Furthermore, the inclusion of additional evidence from systematic reviews and meta-analyses highlights the global burden and significance of sarcopenia, as documented by Beaudart et al. (11) and Shafiee et al. (23). These studies underscore the critical need for effective screening tools to address the widespread prevalence of sarcopenia in aging populations.

Moreover, findings from the health, aging, and body composition study, as discussed by Goodpaster et al. (24), demonstrate the decline in skeletal muscle strength, mass, and quality as key

contributors to functional decline in older adults. This aligns with the present study's results, highlighting the critical role of early detection and intervention. Additionally, the recommendations by Studenski et al. (25) and Rolland et al. (26) further support the integration of simple screening tools like the Yubi-Wakka test into broader sarcopenia management strategies to mitigate its adverse health impacts.

The early detection of sarcopenia through the Yubi-Wakka test offers a critical window for initiating preventive measures aimed at maintaining muscle mass and function. Recommended interventions include progressive resistance exercises, which have consistently been shown to enhance muscle strength, physical performance, and functional independence in older adults (27,28). Ensuring adequate protein intake—especially high-quality protein distributed evenly throughout the day—can help stimulate muscle protein synthesis and mitigate age-related muscle decline (29). Additional nutritional support, such as supplementation with key amino acids like leucine or  $\beta$ -hydroxy  $\beta$ -methylbutyrate, may further contribute to muscle preservation (30,31). Moreover, maintaining optimal vitamin D levels, managing comorbid conditions, and encouraging regular physical activity are essential components of a holistic approach (32). Integrating these strategies into clinical practice following positive Yubi-Wakka screening could improve patient outcomes and reduce the risk of disability among aging individuals.

### Study Limitations

Despite its advantages, the Yubi-Wakka test has several limitations that warrant consideration. It provides only an indirect measure of muscle mass and may be influenced by factors such as subcutaneous fat and edema, potentially affecting its accuracy. While the test demonstrates moderate sensitivity and specificity for predicting sarcopenia, it should be used as a preliminary screening tool rather than a replacement for comprehensive diagnostic evaluations. Additionally, the applicability of our findings may be restricted, as the study population consisted exclusively of older Thai adults. Differences in body composition, habitual activities, and cultural practices across ethnic groups could influence the performance and interpretation of the Yubi-Wakka test. Therefore, it is important to exercise caution when applying these findings to non-Thai populations, and further validation studies in diverse populations are needed. Another limitation is the two-year follow-up period, which may not adequately reflect the long-term impacts of sarcopenia. Extended follow-up studies are necessary to gain deeper insight into its progression and health impacts over time. Moreover, this study did not assess key clinical outcomes such as fracture risk, hospitalization rates, long-term care requirements, or quality of life in individuals with sarcopenia. These factors are



essential for understanding the broader clinical implications of the condition, and future research should aim to incorporate them.

## Conclusion

In conclusion, the Yubi-Wakka test is a valuable self-screening tool for sarcopenia, with demonstrated utility in predicting both baseline and new-onset sarcopenia in older Thai adults. Its simplicity, affordability, and ease of use make it a promising option for widespread implementation in community and clinical settings. Future studies should explore the integration of the Yubi-Wakka test into broader sarcopenia management frameworks and evaluate its impact on health outcomes in diverse populations.

## Ethics

**Ethics Committee Approval:** The study was approved by the Institutional Review Board of the Royal Thai Army Medical Department (approval number: IRBRTA1468/2565, date: 04.11.2022) and conducted in compliance with the ethical standards of the Declaration of Helsinki.

**Informed Consent:** Prior to participation, all individuals received clear explanations of the study's aims and procedures, and written informed consent was obtained.

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## Footnotes

### Authorship Contributions

Concept: K.L., Design: K.L., S.T., K.G., P.S., Data Collection or Processing: K.L., J.T., P.H.O.T., S.T., Analysis or Interpretation: K.L., S.T., K.G., P.S., Literature Search: K.L., Writing: K.L., P.S.

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# The Relationship Between Ultrasonography-Measured Abdominal Subcutaneous Fat Thickness with Sarcopenia/Sarcopenic Obesity and Anthropometric Measurements

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## Abstract

**Objective:** Abdominal subcutaneous fat thickness (ASFT) is an ultrasonography (USG)- based measurement that has been shown to accurately predict segmental or total fat-mass (FM) in previous studies. Since there is limited data on the relationship of ASFT with anthropometric measurements (AM) and sarcopenia, sarcopenic obesity (SO) parameters, we aimed to assess these relationships.

**Materials and Methods:** One hundred thirty-nine geriatric outpatients were enrolled. AMs [calf circumference (CC), mid-arm circumference (MC), hip circumference (HC), waist circumference (WC), and body mass index (BMI)], handgrip strength (HGS) via the Takei grip strength dynamometer, body composition analysis with bioelectrical impedance analysis (BIA) [FM, fat-percentage (FP), fat-free mass (FFM) and phase angle (PA)], thicknesses of rectus-abdominis (RA), external oblique (EO), internal oblique and transversus abdominis (TA) muscles via USG were assessed.

**Results:** The median (interquartile range) age was 71 (67-76) years, and 65.5% (n=91) of participants were female. ASFT was significantly correlated with CC (r=0.315, p<0.001), MC (r=0.432, p<0.001), HC (r=0.354, p<0.001), WC (r=0.199, p=0.019), BMI (r=0.334, p=0.001), FM (r=0.466, p<0.001), FP (r=0.443, p<0.001), PA (r=0.336, p<0.001), RA (r=0.175, p=0.039), EO (r=0.137, p=0.021), and TA (r= 0.209, p=0.014). Regression analysis showed that ASFT was associated with CC, MC, HC, WC, BMI, FM, FFM, PA, HGS, the thickness of RA and EO muscles, and the SO independently of sex, frailty, and age.

**Conclusion:** Our study is the first to comprehensively examine the relationship between the ASFT and body composition analysis of BIA, abdominal muscle thicknesses, and SO. Prospective studies on the role of ASFT in predicting sarcopenia/SO parameters are warranted.

**Keywords:** Sarcopenia, sarcopenic obesity, abdominal subcutaneous fat thickness, ultrasonography, anthropometric measurements, older adults

## Introduction

Sarcopenia is a geriatric giant defined as widespread and progressive loss of skeletal muscle mass, strength, quality, and function (1). The evaluation of body composition in older adults, particularly fat and muscle distribution, has gained

more importance, especially with the recent definition of both sarcopenia and sarcopenic obesity (SO) in the literature (1,2).

Rising obesity rates have become evident as a significant global public health issue (3). Obesity is related to an elevated risk of mortality and morbidity (4). With the rise in life expectancy,

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obesity is likely to become a significant clinical concern for the aging population (5). Obesity and aging contribute significantly to severe health issues, elevating the risk of disease and death. Recently, Barazzoni and Gortan Cappellari (6) explored how obesity affects skeletal muscle mass. SO combines sarcopenia and obesity, a syndrome that is becoming more common among older individuals and is related to adverse clinical outcomes, including mortality (2).

Contrary to previous evidence, particularly in the geriatric population, current studies argue that measuring body mass index (BMI) is insufficient for evaluating conditions associated with various adverse outcomes, such as obesity and SO. Using BMI is still an acceptable practice during the screening stage for conditions such as SO, while acknowledging the significant limitations of BMI in identifying fat distribution and body composition (2,7,8). Besides BMI, anthropometric measurements (AM), particularly waist circumference (WC), are suggested for obesity screening due to their superiority to BMI for predicting obesity-related outcomes (2,9). Moreover, recommendations for body composition analysis via validated tools such as dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA) have become prominent in defining SO and sarcopenia (1,2).

Abdominal subcutaneous fat thickness (ASFT) is a parameter measured from the abdominal region with ultrasonography (USG), and recent studies have shown that it accurately predicts segmental and total fat-mass (FM) measured with DXA (10,11). Unlike DXA, USG is a radiation-free, easily accessible and applicable method, and evaluating ASFT with this method provides advantages. US can also measure muscle mass, which is an important component of the evaluation of sarcopenia and SO (12,13). However, there is limited data on the association between ASFT and sarcopenia parameters, such as muscle strength and mass, other AM.

Since there is no data on the relationship of ASFT with sarcopenia parameters, namely AM, muscle strength [handgrip strength (HGS)], body compositions by BIA, and US-measured abdominal muscle thicknesses, this study aimed to evaluate these relationships.

## Materials and Methods

### Participants

One hundred and thirty-nine geriatric outpatients were included in this 6-month cross-sectional study. Exclusion criteria were defined as any cause resulting in severe lower extremity edema, severe dehydration, the presence of an implant or pacemaker, amputation, or systemic atrophies mainly affecting the central nervous system. Informed consent was gained from the participants. Demographic characteristics of the patients, chronic diseases, drugs and polypharmacy (using five or more drugs) were also recorded.

### Comprehensive Geriatric Assessment

We used validated tools to perform an objective comprehensive geriatric assessment. Functionality was assessed using the Katz activities of daily living (ADL) scale for basic ADL. It assesses the independence of patients in handling daily activities and basic care; the score increases as independence grows. The Lawton Brody Scale for instrumental ADL (14–16). It evaluates independence in instrumental ADLs. Its total score ranges from 0 to 8, and, similar to the Katz scale, higher scores indicate independence in these activities. Cognitive status was screened with the Mini-Mental State Examination (17,18). Mini Nutritional Assessment-short form, was used to evaluate nutritional status (19,20).

### Anthropometric Measurements

After an overnight fast, AM were performed. The BMI was calculated ( $\text{kg}/\text{m}^2$ ). Using a tape measure on the umbilicus level, the WC was determined by the largest diameter of the buttocks. Mid-arm circumference (MC) was measured with the elbow flexed at 90 degrees. The body roundness index (BRI) was calculated using the related formula (21). Online calculators are available for BRI calculation, which allow users to enter height, hip and/or WC measurements (22). All measurements were performed with the online-validated calculation tools.

### Sarcopenia/Sarcopenic Obesity Assessment and Subcutaneous Fat Thickness Measurement

EWGSOP-2 criteria were used to establish the diagnosis of sarcopenia (1). Muscle strength was evaluated via the 5-times Sit and Stand test (5xSST) and HGS using the Takei grip strength dynamometer from the dominant hand, employing previously defined methods (1,23). To determine low HGS, we used two different cut-off points. In the first version, low HGS was defined using the cut-offs determined by EWGSOP-2 for the elderly in Europe:  $<16$  kg for females and  $<27$  kg for males (1). In the second version, we used the specific cut-offs for the Turkish population:  $<22$  kg for females and  $<32$  kg for males (24). Physical performance was evaluated via a four-metre gait-speed test and timed-up and go (TUG) test (1,25).

Total body composition analyses were performed via [BIA-Body Stat Quadscan 4000 bioimpedance analyzer (BodyStat Ltd, Douglas, Isle of Man, British Isles)]. While participants were lying in a supine position, a multifrequency, and tetrapolar technique for BIA was used. Total FM, phase angle (PA) and fat-free mass (FFM) were evaluated. Using the BIA-measured FFM, skeletal muscle mass (SMM) was calculated using the following equation:  $\text{SMM (kg)} = 0.566 * \text{FFM}$ . Low SSM index [ $\text{SMI} = \text{SMM (kg)}/\text{height squared (m}^2\text{)}$ ] was defined as  $<7.4$   $\text{kg}/\text{m}^2$  and  $<9.2$   $\text{kg}/\text{m}^2$  for females and males, respectively (26). Confirmed sarcopenia was defined as probable sarcopenia (two versions of



low HGS with different cut-offs provided as alternative cut-offs) plus low muscle mass (low SMI).

Obesity was defined as high BMI ( $\geq 30$  kg/m<sup>2</sup>) or high WC ( $\geq 102$  and  $\geq 88$  for males and females, respectively), and a total of 99 patients were found to be living with obesity. Among these 99 patients, SO was defined in line with the ESPEN and EASO Sarcopenic Obesity Consensus Statement (2). Two versions of low HGS with two different cut-offs ( $< 16$  kg for females and  $< 27$  kg for males, or  $< 22$  kg for females and  $< 32$  kg for males) were given as different alternatives. Other cut-offs used for the definition of SO were  $\geq 17$  s for 5xSST,  $> 43\%$  and  $> 31\%$  (for females and males, respectively) for FM percentage and  $< 27.6\%$  and  $< 37.0\%$  (for females and males, respectively) for SMM/weight. As suggested in the ESPEN and EASO Sarcopenic Obesity Consensus Statement, obese patients were defined as having a high BMI ( $\geq 30$  kg/m<sup>2</sup>) or high WC ( $\geq 102$  for males and  $\geq 88$  for females), with a total of 99 patients included. In the obese population (n=99), patients with low muscle strength (via HGS or 5xSST) plus high-fat-percentage (FP) plus low SMM/weight were defined as having confirmed SO.

Abdominal muscle and subcutaneous fat thicknesses were assessed using B-mode USG (LOGIQ 200 PRO, General Electric Medical Systems) equipped with a 10-MHz linear-array transducer (5 cm footprint). All examinations were performed by a single radiologist with over 10 years of experience in musculoskeletal ultrasound (US), who was blinded to clinical and laboratory data to avoid measurement bias. Participants were evaluated in the supine position with knees flexed to ensure abdominal muscle relaxation. All measurements were performed at the end of a normal expiration, without breath holding, to minimize variability due to diaphragm movement or muscle contraction. ASFT was measured as the vertical distance from the skin surface to the superficial fascia of the rectus-abdomini (RA) muscle. This measurement was taken 1 cm superior to the umbilicus along the midline (xiphoid–pubic line) with the transducer placed transversely and perpendicular to the skin. Care was taken to apply minimal pressure. RA thickness was measured at the same site—1 cm above the umbilicus—by identifying the anterior and posterior fascia of the muscle in the axial plane. Thickness was defined as the anteroposterior distance between these two echogenic fascial borders, measured on the right side at the mid-belly of the RA. Lateral abdominal muscle thicknesses—including the external oblique (EO), internal oblique (IO), and transversus abdominis (TA)—were measured on the right side of the abdomen at a standardized location: the midpoint between the inferior margin of the 12<sup>th</sup> rib and the anterior superior iliac spine, aligned along the anterior axillary line. With minimal pressure, the transducer was positioned transversely (axial orientation), perpendicular to the skin surface. Each muscle layer was visualized as a distinct hypoechoic band bounded by hyperechoic fasciae. Muscle thickness was defined

as the perpendicular distance between each muscle's superficial and deep fascial borders. Specifically:

- EO: from the subcutaneous fascia to the EO–IO interface,
- IO: from the EO–IO interface to the IO–TA interface,
- TA: from the IO–TA interface to the inner fascial margin (transversalis fascia or peritoneal lining). All measurements were performed three times, and the mean value was recorded. This protocol was established based on widely accepted sarcopenia assessment methodologies and validated protocols from recent literature.

### Statistics

Statistical analysis was executed using SPSS version 27.0 (IBM). We conducted a power analysis to determine the required sample size, based on results from earlier studies (G\*Power 3.1.9.7) (27,28). The sample size with a margin of error of 0.05 (alpha), a power of 90%, and a medium effect size was calculated as 118 participants. Variables were assessed via visual and analytic tools for the normal distribution. Descriptive statistics were given as mean  $\pm$  standard deviation for normally distributed variables, median [interquartile range (IQR)] for variables without normal distribution, and the number of cases and percentage (%) for nominal variables. Depending on whether the data followed a normal distribution, Pearson or Spearman correlations were performed to analyze the relationship between ASFT and the other factors. Due to the non-normal distribution, the logarithmic version of ASFT was computed to attain normal distribution and used in the linear regression analysis to identify independent factors related to ASFT. Using a logarithmic transformation alters values according to the properties of the logarithm. Given its characteristics, the discrepancies between the transformed values diminish relative to those observed in the original values. This transformation compresses the variations between the upper and lower portions. A logarithmic transformation normalizes positively skewed distributions and is called a "log-normal distribution". Linear regression analysis requires a normal distribution for the dependent variable. After applying a logarithmic transformation to the data, the outcome can be considered an estimate. Using a logarithmic transformation in linear regression complicates the interpretation of the results. When the dependent variable necessitates a logarithmic transformation, the interpretation of the regression coefficient changes from signifying a unit change to representing a proportional change. Essentially, the regression coefficient means "a one-unit change in the independent variable produces an increase (or decrease) in the dependent variable by the amount of the regression coefficient". The transformed dependent variable's arithmetic change will be converted into a ratio through the back-transformation of an exponential function (29). Multicollinearity analysis for linear regression showed that a variance inflation factor higher than 5 indicated

high collinearity. All models are created considering collinearity. A p-value less than 0.05 was regarded as statistically significant.

### Disclosure Statement

Each participant in the study gave their informed consent, and the study received ethics approval from the clinical research ethics committee at Hacettepe University's Faculty of Medicine and Hacettepe University Health Sciences Research Ethics Committee (research number: 24/313, decision number: 2024/05-12, date: 05.03.2024). Every procedure carried out in studies involving human participants met the ethical standards set by the institution's or country's research committee, as well as those outlined in the 1964 Declaration of Helsinki and its later updates, or equivalent standards.

### Results

A total of 139 geriatric outpatients enrolled in the study. The median (IQR) of the participants was 71 (67-76) years, and 65.5% (n=91) of them were female. Table 1 provides a summary of the study population's demographic and clinical characteristics. The frequencies of sarcopenia were 8.6% (n=12) in the whole sample; confirmed SO among the patients with obesity (n=99) was 11.3% (n=11).

In the correlation analysis, ASFT was significantly correlated with CC ( $r=0.315$ ,  $p<0.001$ ), MC ( $r=0.432$ ,  $p<0.001$ ), hip circumference (HC) ( $r=0.354$ ,  $p<0.001$ ), WC ( $r=0.199$ ,  $p=0.019$ ), BMI ( $r=0.391$ ,  $p<0.001$ ), BRI ( $r=0.387$ ,  $p<0.001$ ), FM ( $r=0.466$ ,  $p<0.001$ ), FP ( $r=0.443$ ,  $p<0.001$ ), FFM ( $r=-0.183$ ,  $p=0.031$ ), PA ( $r=0.336$ ,  $p<0.001$ ), RA ( $r=0.175$ ,  $p=0.039$ ), IO ( $r=0.137$ ,  $p=0.021$ ), and TA ( $r=0.209$ ,  $p=0.014$ ). No correlation was observed between ASFT and age ( $r=-0.132$ ,  $p=0.120$ ) and HGS ( $r=-0.117$ ,  $p=0.171$ ). All correlations of ASFT with other indicators are shown in Table 2.

Various models were generated in the linear regression analysis to evaluate the independent association between ASFT and sarcopenia parameters, and AMs (Table 3). All models are adjusted for age, sex, and frailty status based on prior evidence of the relationship between ASFT and the related confounders. Our results revealed that ASFT is significantly related to CC, MC, HC, WC, BMI, BRI, FM, FFM, PA, HGS, the thickness of RA, and IO muscles, and SO regardless of age, sex, and frailty. In the logistic regression modeling evaluating the relationship between confirmed sarcopenia and ASFT in the whole sample (n=136), when adjusted for age, sex, and frailty, ASFT was not associated with confirmed sarcopenia for both HGS cut-offs used [for the model low HGS defined as <16 kg for females and <27 kg for males, Odds ratio (OR): 0.94, 95% confidence interval (CI): 0.84-1.06,  $p=0.334$  and for the model low HGS defined as <22 kg for females and <32 kg for males, OR: 0.95, 95% CI: 0.87-1.04,  $p=0.335$ ]. In addition, in the logistic regression model where only obese patients (n=99) were included, factors associated

with SO were evaluated, and ASFT was found to be related to SO, regardless of age, sex, and frailty (for the model low HGS defined as <16 kg for females and <27 kg for males OR: 1.04, 95% CI: 1.01-1.18,  $p=0.025$ , and for the model low HGS defined as <22 kg for females and <32 kg for males OR: 1.11, 95% CI: 1.03-1.20,  $p=0.005$ ).

**Table 1. Summary of demographical and clinical characteristics of the study population**

Age, median (IQR)	71.0 (67.0-76.0)
Female gender, n (%)	55 (64.7%)
Clinical Frailty Score, median (IQR)	3 (3.0-4.0)
Diabetes mellitus, n (%)	43 (30.9%)
Hypertension, n (%)	64 (46.0%)
Coronary arterial disease, n (%)	16 (11.5%)
Atrial fibrillation, n (%)	6 (4.3%)
Chronic pulmonary disease, n (%)	8 (5.8%)
Chronic renal diseases, n (%)	2 (1.4%)
Dementia, n (%)	7 (5.0%)
Hypothyroidism, n (%)	21 (15.1%)
Malignancies, n (%)	14 (10.1%)
Cerebrovascular diseases, n (%)	7 (5.0%)
Number of drugs, median (IQR)	5 (3.0-6.0)
Polypharmacy, n (%)	52 (37.4%)
Katz activities of daily living, median (IQR)	6 (6.0-6.0)
Lawton-Brody Instrumental ADLs, median (IQR)	8 (8.0-8.0)
SARC-f, median (IQR)	1 (0.0-2.5)
Mini-nutritional assessment short form	14 (12.0-14.0)
Gait speed (sec), median (IQR)	4.1 (3.4-5.3)
Timed-up-and-go test (sec), median (IQR)	10 (8.0-14.0)
Chair stand test (sec), median (IQR)	15 (12.0-18.1)
Mini-mental state examination, median (IQR)	28 (25.0-29.0)
Calf circumference, mean $\pm$ SD	35.0 $\pm$ 3.8
Mid-arm circumference, mean $\pm$ SD	29.0 $\pm$ 3.7
Hip circumference, mean $\pm$ SD	106.2 $\pm$ 9.5
Waist circumference, mean $\pm$ SD	97.2 $\pm$ 14.7
Body mass index, mean $\pm$ SD	29.5 $\pm$ 4.6
High BMI ( $\geq 30$ kg/m <sup>2</sup> )	68 (48.9%)
High fat-percentage <27.6% and <37.0% for female (F) and male (M)	61 (43.9%)
Body roundness index, mean $\pm$ SD	5.99 $\pm$ 1.72
Fat-mass, mean $\pm$ SD	27.1 $\pm$ 10.4
Fat percentage, mean $\pm$ SD	35.7 $\pm$ 10.9
Fat-free mass, mean $\pm$ SD	47.4 $\pm$ 10.9
Phage angle, median (IQR)	5.0 (2.7-18.1)
Hand grip strength (HGS), mean $\pm$ SD	21.5 (16.8-27.0)
Low HGS (<16 and <27 for female and male), n (%)	45 (32.4%)



**Table 1. Continued**

Age, median (IQR)	71.0 (67.0–76.0)
Low HGS (<22 and <32 for F and M), n (%)	91 (65.9%)
Low SMMI (<7.4 and <9.2 for F and M), n (%)	15 (10.8%)
Confirmed sarcopenia [low HGS (<16 and <27 for F and M) + low SMMI], n (%)	12 (8.6%)
Confirmed sarcopenia [low HGS (<22 and <32 for F and M) + low SMMI], n (%)	15 (10.9%)
Confirmed sarcopenic obesity [using (low HGS (<16 and <27 for F and M)), n (%)*	11 (9.0%)
Confirmed sarcopenic obesity [using (low HGS (<22 and <32 for F and M)), n (%)*	15 (15.2%)
Subcutaneous fat thickness, mean $\pm$ SD	18.7 $\pm$ 9.8
Rectus-abdominis muscle thickness, mean $\pm$ SD	8.1 $\pm$ 9.4
External oblique muscle thickness, mean $\pm$ SD	3.6 $\pm$ 1.2
Internal oblique muscle thickness, mean $\pm$ SD	5.8 $\pm$ 2.1
Transversus abdominis muscle thickness, mean $\pm$ SD	3.9 $\pm$ 1.4
*Among the 99 patients with obesity. Statistically significant p-values are indicated in bold. IQR: Interquartile range, ADL: Activities of daily living, SD: Standard deviation, BMI: Body mass index, HGS: Handgrip strength, SMMI: Skeletal muscle mass index, F: Female, M: Male	

**Table 2. Correlations of abdominal subcutaneous fat thickness and different indicators**

	Abdominal subcutaneous fat thickness	
	r	p
Age	-0.132	0.120
Clinical frailty scale	-0.146	0.086
Weight	0.247	<b>0.004</b>
Body mass index	0.391	<b>&lt;0.001</b>
Body roundness index	0.387	<b>&lt;0.001</b>
Calf circumference	0.315	<b>&lt;0.001</b>
Mid-arm circumference	0.432	<b>&lt;0.001</b>
Hip circumference	0.354	<b>&lt;0.001</b>
Waist circumference	0.199	<b>0.019</b>
Handgrip strength	-0.117	0.171
SARC-f	-0.074	0.472
Mini-nutritional assessment short form score	-0.089	0.331
Gait speed (sec)	0.128	0.143
Timed-up-and-go test (sec)	0.079	0.365
Chair stand test (sec)	0.033	0.721
Fat-mass	0.466	<b>&lt;0.001</b>
Fat percentage	0.443	<b>&lt;0.001</b>
Fat-free mass	-0.183	<b>0.031</b>
Phage angle	0.336	<b>&lt;0.001</b>
Rectus abdominis muscle thickness	0.175	<b>0.039</b>

**Table 2. Continued**

	Abdominal subcutaneous fat thickness	
	r	p
External oblique muscle thickness	0.080	0.351
Internal oblique muscle thickness	0.137	<b>0.021</b>
Transversus abdominis muscle thickness	0.209	<b>0.014</b>
Statistically significant p-values are indicated in bold.		

## Discussion

ASFT is an important body composition parameter that can be measured easily and accurately, without any radiation exposure. Although the relationship between ASFT and many different AM has been evaluated in different populations, comprehensive studies that evaluate the relationship between sarcopenia and/or SO (defined via current guideline recommendations), body composition analyses determined by BIA, and other AM in older adults are limited in the literature. Our results demonstrated that, even if adjusted for common confounders known to be related to ASFT (age, sex, and frailty) (30,31), ASFT was significantly related to CC, MC, HC, WC, BMI, BRI, FM, FFM, PA, HGS, the thickness of RA and IO muscles, and the confirmed SO. This supports the notion that ASFT may be seen as a potential radiological marker in older adults.

The aging process is characterized by an increase in total FM and a decrease in lean mass (muscle and bone), which occurs even if body weight and BMI remain constant (32). Moreover, there is a change in the distribution of fat tissue. While peripheral subcutaneous tissue decreases, abdominal subcutaneous and visceral fat tissue increases (33). SFT plays an essential role in energy storage and the release of free fatty acids. Upper body/abdominal ASFT is more lipolytic and releases more free fatty acids compared to lower body fat accumulation (34). This may explain the relationship of ASFT and total body FM, as well as AM, to the individual's energy metabolism.

US is a commonly used method for assessing various tissues and the beginning of its usage in fat tissue evaluation dates back to the 1960s (35). Although cross-sectional imaging methods [computed tomography (CT) and magnetic resonance imaging (MRI)] are regarded as the gold standard for assessing many body compositions, including ASFT, there are well-established limitations for these tools, such as radiation exposure and cost-effectiveness (36). US is a cost-effective, radiation-free, and reliable alternative to MRI/CT since it showed promising results for ASFT measurements that significantly correlated with cross-sectional methods (37,38,39). ASFT also successfully predicted the total body FM measured on DXA, another gold standard method for body composition assessment (10,11). Similar to DXA, BIA is a commonly utilized tool to assess body

**Table 3. Results of the linear regression analyses of independent factors associated with subcutaneous fat thickness**

		Abdominal subcutaneous fat thickness	
MODELS*		$\beta$ (95% CI)	p
Model 1	Calf circumference	0.023 (0.012-0.034)	<b>&lt;0.001</b>
Model 2	Mid-arm circumference	0.033 (0.023-0.045)	<b>&lt;0.001</b>
Model 3	Hip circumference	0.010 (0.006-0.014)	<b>&lt;0.001</b>
Model 4	Waist circumference	0.005 (0.002-0.007)	<b>0.002</b>
Model 5	Fat-mass	0.011 (0.008-0.015)	<b>&lt;0.001</b>
Model 6	Fat-free mass	-0.004 [-0.008-(-0.001)]	<b>0.024</b>
Model 7	Phase angle	0.005 (0.002-0.008)	<b>0.002</b>
Model 8	Handgrip strength	-0.007 [-0.013-(-0.001)]	<b>0.024</b>
Model 9	Rectus abdominis thickness	0.005 (0.001-0.010)	<b>0.046</b>
Model 10	External oblique muscle thickness	0.036 (0.004-0.067)	<b>0.026</b>
Model 11	Transversus abdominis muscle thickness	0.027 (-0.013-0.056)	0.079
Model 12	Body mass index	0.015 (0.06-0.024)	<b>0.002</b>
Model 13	Body roundness index	0.050 (0.28-0.078)	<b>&lt;0.001</b>
Model 14	Confirmed sarcopenia [using low HGS (<16 and <27 for F and M) + low SMMI] n (%)	-0.051 (-0.213-0.111)	0.533
Model 15	Confirmed sarcopenia [using low HGS (<22 and <32 for F and M) + low SMMI] n (%)	-0.039 (-0.181-0.102)	0.583
Model 16	Confirmed sarcopenic obesity (using low HGS (<16 and <27 for F and M) (*among 99 obese patients])	0.187 (0.123-0.350)	<b>0.026</b>
Model 17	Confirmed sarcopenic obesity (using low HGS (<22 and <32 for F and M) (*among 99 obese patients])	0.231 (0.087-0.372)	<b>0.002</b>

\*All models are individually adjusted for age, sex and frailty. Statistically significant p-values are indicated in bold.  
CI: Confidence interval, HGS: Handgrip strength, SMMI: Skeletal muscle mass index, F: Female, M: Male

composition by measuring the electrical properties of body tissue and estimating the related parameters (40). Our results showed that ASFT was correlated with the BIA measurements. FM and PA were positively correlated; FFM was negatively correlated with SFT, and these relationships remained significant after adjustment for age, sex, and frailty. The positive correlation of ASFT with total body FM aligns with evidence in the literature revealing the association between ASFT and body fat composition (10,11). The evidence in the literature is contradictory regarding the relationship between PA and total FM. Additionally, no study compares the PA with ASFT. Our results show that ASFT positively correlates with PA, this may be parallel to the evidence on PA's relationship with the general nutritional status and total body weight (41). Our results are also noteworthy, as this is the first study in the literature to show the relationship between body composition parameters measured with BIA and US-measured ASFT.

Defining obesity based solely on BMI has become less preferred since markers such as WC, BRI, and body composition have outperformed BMI in important outcomes, including cardiovascular outcomes (2,42,43). Our results showed that ASFT was positively associated with all obesity-related markers (BMI, BRI, and WC), MC and CC-which are measures related to muscle mass-as well as total body mass. Furthermore, our findings

indicate a positive, modest correlation between ASFT and the thickness of the abdominal muscles. Although ASFT appears to be related to local muscle-related measurements, it was negatively associated with specific measures of muscle strength and total muscle mass (HGS and FFM) when adjusted for age, sex, and frailty. While it is generally recommended to evaluating the decrease in extremity muscle mass when defining muscle wasting conditions such as sarcopenia or malnutrition, there are limited data on the usability of abdominal muscle thickness for determining total muscle mass. Our study's results indicate that ASFT showed a modest positive correlation with abdominal muscle thickness (1,44), similar to other markers indicating total body mass (a combination of muscle and fat). Furthermore, more specific markers of total muscle mass and/or strength FFM [HGS]) exhibited a negative relationship with ASFT, suggesting that abdominal muscle thickness may be more closely related to total mass, particularly in the obese population. Considering the modest relationship in the correlation coefficients, the limited number of patients, and the cross-sectional design, larger studies are warranted to confirm these findings. In addition, even if the association between ASFT and confirmed sarcopenia or physical performance tests (TUG and gait speed) could not be demonstrated, in the subgroup analysis performed in obese patients defined using BMI and WC, high ASFT and SO were found to be related in the linear and logistic regression

models. Although no study directly evaluated the relationship between SO and ASFT, one study investigating the use of the US in the definition of SO also identified an association between increased ASFT and SO (13). In the aforementioned study, SO was defined as solely using BMI to define obesity with a limited number of patients (13). Demonstrating the relationship between SO and ASFT, as defined by the current SO criteria, is consistent with the literature and more objectively supports the relationship between these two variables. Taken together, beyond its relationship with AM, total body mass, body FM, and local muscle masses, ASFT is potentially an important radiological marker of SO in obese older individuals.

### Study Limitations

The primary limitation of the study was the relatively small sample size, the cross-sectional design, which limits assessing causality, and the fact that it was not designed specifically to assess the power of ASFT in predicting SO. Therefore, large-sample prospective studies to evaluate the causality of the relationship between ASFT and other variables, with sex-specific cut-offs of ASFT for SO prediction, are warranted to confirm our findings. Validating US-measured ASFT with gold-standard cross-sectional imaging techniques (MRI or CT) could improve the reliability of this measurement. Although we did not compare the ASFT measurement via the US to a cross-sectional method, our results, demonstrating the relationship between ASFT and adiposity markers from and body composition analyses via BIA, support the evidence in the literature that the US may be a suitable alternative for ASFT measurement. However, prospective studies are still needed to compare ASFT with other gold standard methods. Although factors that may affect BIA measurements and anthropometric assessments, such as edema, BIA measurements and anthropometric assessments were reduced through physical examination and detailed anamnesis, it is possible that factors like dehydration and newly developing anemia were overlooked, even in a small number of patients. This oversight might also be a limitation. The inability to demonstrate very strong correlation coefficients for each parameter with a significant relationship with ASFT was another significant limitation. This limitation might also result from the relatively small sample size of our study. Therefore, studies with much larger samples and including other cross-sectional methods such as BIA, CT, or MRI are required to generalize the results.

### Conclusion

To the best of our knowledge, this is the first study comprehensively evaluating the relationship between ASFT and body composition analysis of BIA, abdominal muscle thicknesses, and SO. Prospective studies on the role of ASFT in predicting SO, in particular, are warranted.

### Ethics

**Ethics Committee Approval:** The study received ethics approval from the clinical research ethics committee at Hacettepe University's Faculty of Medicine and Hacettepe University Health Sciences Research Ethics Committee (research number: 24/313, decision number: 2024/05–12, date: 05.03.2024).

**Informed Consent:** Each participant in the study gave their informed consent.

### Footnotes

#### Authorship Contributions

Surgical and Medical Practices: H.B., A.O.B., Y.Ö., M.G., S.C., M.K., M.H., Z.Ş., C.B., B.B.D., M.C., M.G.H. Concept: H.B., A.O.B., Y.Ö., B.B.D., M.G.H. Design: H.B., A.O.B., Y.Ö., M.C., M.G.H. Data Collection or Processing: H.B., A.O.B., M.G., S.C., M.K., M.H., Z.Ş., C.B., M.G.H. Analysis or Interpretation: H.B., A.O.B., Y.Ö., M.G.H. Literature Search: H.B., A.O.B., Y.Ö., M.K., M.C., M.G.H. Writing: H.B., A.O.B., Y.Ö., M.G.H.

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# Caring for Adult-onset Cystic Fibrosis Diagnosed at the Age of 79: A Case Report

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## Abstract

We present a case of cystic fibrosis (CF) diagnosed at the age of 79, one of the oldest CF cases known to date. Our patient had an unconventional CF genotype, leading to an odyssey of a clinical journey that involved frequent treatment modifications and advanced genetic testing. The course was complicated by multiple prolonged recurrent hospitalizations, requiring extensive geriatrics, and pulmonary multidisciplinary collaborative care. This case illustrates the complexity of caring for geriatric patients with CF, highlighting the following key geriatrics M's: (m)ulti-complexity, (m)obility, (m)edications, and what (m)atters most.

**Keywords:** Adult-onset cystic fibrosis, geriatrics, matters most, multi-complexity, targeted therapies

## Introduction

Cystic fibrosis (CF) is a monogenic disorder caused by mutations of the CF transmembrane *conductance regulator* (*CFTR*) gene encoding an ion channel, characterized by pulmonary infection and other multi-organ dysfunctions (1) associated with thick secretions due to impaired chloride transport. Recently, gene therapy has made a breakthrough in CF treatment. CF, has been rarely reported in older patients during bronchiectasis workup. This case of late-onset CF illustrates the necessity of an appropriate geriatrics approach according to the changing landscape of genetic disorders in older adults.

## Case Report

An 84-year-old female presented to the outpatient geriatrics clinic to establish care for chronic shortness of breath and debility after hospitalization due to pneumonia. Her medical history included advanced adult-onset CF; bronchiectasis; multiple infections, including multidrug-resistant *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* pneumonia;

hypoxic respiratory failure. She had frequent CF exacerbations (6-8 per year), requiring prolonged hospitalizations and home oxygen therapy. Her health was complicated by severe deconditioning, complex polypharmacy with chronic antibiotic suppressive therapy, and iatrogenic pancytopenia.

Our patient was diagnosed with CF at the age of 79, at an outside health system in the setting of progressive bronchiectasis with recurrent pulmonary infections over 15 years. She was previously free of sinopulmonary symptoms. She had no risk factors for lung disease and no family history of genetic disorders. Diagnosis was established via serial sweat tests (70 mmol/L and 63 mmol/L in the following year) and clinical criteria. *CFTR* gene sequencing and deletion/duplication testing at the time of diagnosis showed homozygous variants of the 11TG/7T alleles, which are not the common pathogenic variants. A repeat nasal swab was sent to an outside research-based multi-analysis program and returned with the same genetic profile.

The patient lived with her husband, who was her primary caregiver. The patient encountered significant challenges

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following the CF treatment regimen, which entailed variable daily and weekly multi-drug antibiotic dosing, along with medications for symptomatic management, such as dornase alfa. Hopeful for treatment optimization, the patient underwent multiple bronchoscopies for respiratory fluid sampling. This was part of the *in vitro* research program at an outside institution the cellular response to novel CF-targeted therapies, which yielded negative results. She opted for port-a-cath placement for chronic antibiotic suppressive therapy.

Throughout the patient's remaining clinical course, the geriatrics team provided coordination of care, including consolidating the treatment regimen and educating the patient on CF complications. Geriatrics maintained frequent communication with the pulmonary team, especially to facilitate CF medication changes, follow-up investigations, and coordination of supportive services (such as physical therapy, occupational therapy, skilled nursing, and transportation). Geriatric specialists coordinated regular multidisciplinary meetings to discuss treatment goals, prognosis, realistic expectations, hospice, and quality of life, to find a balance between disease treatment and what matters most. Geriatrics also provided co-management and transition of care during each hospitalization. As the patient's functional status continued to decline with increasing caregiver burden, geriatrics facilitated the transition to a home visiting geriatric program. The patient subsequently had another hospitalization for CF exacerbation, during which she was transitioned to inpatient hospice with terminal extubation, and she passed shortly afterward.

### Consent for Publication

Informed consent for the publication of this case report and any associated clinical details was obtained from the patient's next of kin (her husband, the primary caregiver) and documented in the Electronic Medical Record.

### Discussion

CF is the most common autosomal recessive hereditary disorder in the Caucasian population (2). The condition is diagnosed with either the sweat chloride test coupled with characteristic CF phenotype or the identification of two pathogenic variants of the *CFTR* gene. Different genetic mutations define the mechanism of CFTR protein dysfunction (Class I–VI). Two main types of CFTR modulator therapy are available: 1) potentiators, which are small molecules aiding in opening the chloride channel leading to CFTR activation, 2) correctors, which aid in repairing the CFTR trafficking defects (3). Novel target treatments (modulators) have recently been approved for selected genotypes, such as Phe508del and Gly551Asp. Since many mutations have multiple defects with overlapping mechanisms, a significant amount of work has been geared toward developing novel targeted combinatorial therapeutics (3,4). The triple combination CFTR

modulator drug, ivacaftor/tezacaftor/elexacaftor (Trikafta), including one potentiator and two correctors, has demonstrated superior efficacy for a greater number of CF patients (5).

There are about 2,000 known pathogenic variants in CF, demonstrating genetic heterogeneity. For example, extensive genetic and functional analysis of CFTR in CF patients has identified key regions with disruptions in the polymorphic TG and T tracts (6,7). These molecular lesions are associated with altering the physiological splicing of the *CFTR* gene, resulting in loss of function in the CFTR protein (6), suggesting an important role in CF pathogenesis. Additional research including molecular and functional studies would be helpful to elucidate the roles of other CFTR variants (such as the 11T/7T in our patient) in CF pathogenesis and disease phenotype (8).

Compared to classic cases seen in younger patients, adult-onset CF often presents atypically with milder symptoms due to a lower burden of key mutations (9). Using an extensive etiological work-up in 188 adult bronchiectasis patients, CF was identified in 5% of the patients, often with a lag of >15 years between the bronchiectasis and CF diagnoses (10). Other clinical and laboratory characteristics of adult-onset CF cases with late diagnosis include higher frequency of less severe genotypes, lower sweat chloride levels, and reduced incidence of pancreatic insufficiency and *Pseudomonas aeruginosa* infections (9,11). Importantly, according to data from an Italian registry, about 20% of new CF cases are diagnosed during adult years all the way to the eighth decade of life (12).

### Conclusion

Our case highlights the importance of a low threshold for CF evaluation in older adults with unexplained bronchiectasis, frequent pulmonary infections, and the absence of risk factors for lung disease. This case demonstrates key pillars of geriatric care: close multidisciplinary collaboration (multi-complexity), treatment of physical debility via aggressive rehabilitation and arranging supportive services/equipment (mobility), identifying and simplifying complex treatment regimens (medications), and early advanced care planning to align patient values with treatment goals (matters most). Timely recognition of clinical decline and the need for homebound care and hospice are indispensable to help avoid invasive procedures and treatments.

### Ethics

**Informed Consent:** Informed consent for the publication of this case report and any associated clinical details was obtained from the patient's next of kin (her husband, the primary caregiver) and documented in the Electronic Medical Record.

## Footnotes

### Authorship Contributions

Surgical and Medical Practices: J.L., M.G., Concept: J.L., M.G., Design: J.L., M.G., Data Collection or Processing: J.L., M.G., Analysis or Interpretation: J.L., M.G., Literature Search: J.L., M.G., Writing: J.L., M.G.

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

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# Black Hairy Tongue in a Geriatric Patient with Acute Kidney Injury

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## Dear Editor,

A 68-year-old male patient with a history of hypertension, previous pancreatitis, and radical prostatectomy, due to prostate adenocarcinoma 3 years ago, was diagnosed with lung adenocarcinoma, as a secondary malignancy, and related cranial metastasis during routine follow-up. During his postoperative follow-up in the thoracic surgery department, a decrease in his oral intake, high fever and disorder in renal function tests were detected. The patient was transferred to the nephrology clinic with the preliminary diagnosis of prerenal acute kidney injury and a drug-related kidney injury. He was routinely using nebivolol, indapamide and had a 60 pack-year smoking history (ex-smoker). Urea: 57.2 mg/dL, creatinine: 4.51 mg/dL (2 months ago creatinine: 0.83 mg/dL), glomerular filtration rate (GFR): 12 mL/min./1.73 m<sup>2</sup>, K<sup>+</sup>: 3 mmol/L, Na<sup>+</sup>: 143 mL/L, C-reactive protein: 216 mg/L were detected. In the patient who was receiving antibiotic therapy due to pneumonia in the postoperative period, blackening was noticed in the patient's tongue on the 14<sup>th</sup> day of fluconazole, the 8<sup>th</sup> day of vancomycin and the 14<sup>th</sup> day of imipenem (Figure 1). Antibiotic-related black hairy tongue (BHT) was initially considered. The patient's current antibiotic therapy was stopped, moxifloxacin treatment was initiated. The patient's urinary ultrasonography findings were normal, and improvement in renal function was achieved with intravenous hydration. The patient, whose urine output was sufficient and whose creatinine values regressed to 0.55 mg/dL, showed regression was achieved in the tongue lesion with oral hygiene support after an antibiotic change, and was discharged (Figure 2).

BHT is defined as defective desquamation of filiform papillae and although it may be distressing for the patient, it is generally a transient benign clinical condition. Increased keratinized layering, superimposition of bacterial or fungal infections

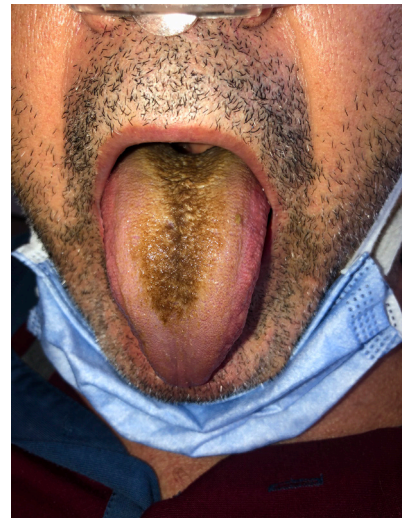


Figure 1. Black hairy tongue observed after 14 days of antibiotic therapy.

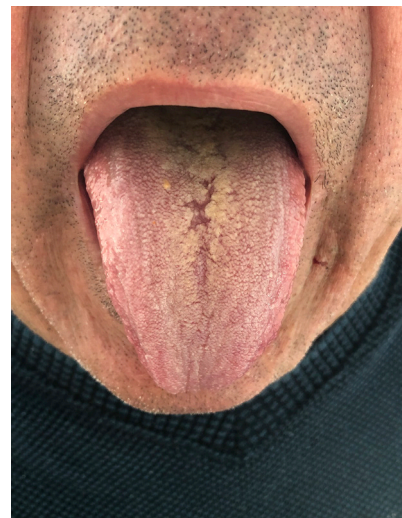


Figure 2. Regression of the black colour after cessation of the potential antibiotics

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have also been implicated. Changes in the chemical and morphological structure of the intraoral milieu are the basic underlying problem. Although global risk factors have not been clearly defined, interestingly, advanced age and kidney damage may be facilitating factors in the development of BHT. Changes in the oral microbiota—especially the tongue coating microbiota—are well described and common in patients with kidney damage. In the study by Luo et al. (1), species such as *Capnocytophaga* and *Leptotrichia* were shown to be positively correlated with erythrocyte glomerular filtration rate in patients. Ezzatt et al. (2) reported that the frequency of dry mouth increased in chronic kidney disease patients undergoing hemodialysis, and approximately half of the patients were found to have increased tongue coating. Chung et al. (3) reported that patients with chronic kidney disease had thicker tongue fur compared to the control group. Oral frailty is a clinical entity of increasing importance in geriatric patients. It is limited not only to its “local” effects but also related to systemic frailty (4). The presence of an oral uremic microenvironment and factors such as decreased saliva secretion, due to direct effects on the salivary glands, and oral dryness, due to restricted fluid intake, may lead to oral hygiene disorders. Increased chewing and periodontal problems, some medications used in the course of kidney damage, and mouth breathing due to acidosis may lead to oral hygiene disorders in elderly and kidney-damaged patients. Underlying kidney injury in geriatric patients, may facilitate the development of BHT.

In addition to etiological factors such as malignancies, markedly poor oral hygiene, intense exposure to tea/coffee and smoking, exposure to different antibiotics has been implicated. Among these, those reported in geriatric patients are ampicillin-sulbactam, co-amoxiclav, metronidazole, moxifloxacin, ceftazidime, piperacillin-tazobactam and linezolid. Liu et al. (5) found a similar appearance after ceftazidime treatment in a peritonitis patient who underwent CAPD. In the literature, cases of BHT due to both imipenem/cilastatin and piperacillin-tazobactam have been reported, albeit rarely, as in our case (6). Interestingly, BHT developed in our patient despite the simultaneous use of fluconazole, which can be used in the treatment of BHT (7). Fluconazole treatment seems to be effective in BHT patients, particularly *Candida* species are involved in the etiology. The lack of response to fluconazole treatment in our patient may be due to the absence of a fungal etiology or the heterogeneous immune suppressive status (due to kidney injury, underlying

malignancy, septic condition). Another point is that BHT regressed in the patient despite the continuation of treatment with moxifloxacin, which has been reported as one of the antibiotics associated with BHT (8). In geriatric patients with kidney injury, the use of some broad-spectrum antibiotics may especially cause BHT.

## Ethics

**Informed Consent:** Informed consent was obtained from the patient.

## Footnotes

## Authorship Contributions

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

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# Use of DeepSeek in Geriatric Caregivers' Simulation Training

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**Keywords:** Artificial intelligence, geriatrics, caregivers, simulation training, clinical competence, DeepSeek

## Dear Editor,

Simulation-based learning (SBL) in medical training refers to the use of technology to recreate medical scenarios in controlled environments (1). This approach allows healthcare providers to practice and improve their skills without the immediate risk of harming patients (2). Repetition in a controlled setting helps develop decision making skills and boosts confidence, thus enhancing patient safety. SBL can be highly beneficial for geriatric caregivers without a medical background in noticing sudden deterioration, early onset of medical emergencies, stroke or myocardial infarct, and detection of red flag signs after fall injury at home etc.

The emphases of SBL are not only on hands-on practice, skills and confidence building, but also immediate feedback, safety awareness and building emotional resilience (3). Recently, DeepSeek has emerged as a groundbreaking tool in artificial intelligence (4). This interactive chatbot could write up various clinical scenarios for pre-hospital care training, allowing caregivers with an opportunity to experience SBL at home with the computers, sets, or even smart phones. By leveraging natural language processing and machine learning, DeepSeek is able to create realistic and interactive scenarios that mimic real-life situations encountered by geriatric caregivers, for example dyspnea, hemiplegia, angina, or even checklist-based questions for assessment after geriatric fall injuries. Debriefing is an essential part of SBL, DeepSeek could cater different learning styles through interactive chat and provide instant feedback, ensuring caregivers can practice and refine their skills in a controlled and supportive environment virtually.

Other than physical health, psychological and mental SBL are also available for caregivers (5). For instance, DeepSeek can simulate a situation where a caregiver needs to assist an elderly patient with dementia who is experiencing behavioral disturbance and agitation. The chatbot guides the caregiver through the steps of calming the patient, providing emotional support, and ensuring their safety. The interactive nature of the training allows caregivers to develop effective communication techniques and empathy, which are crucial for building trust and rapport with elderly patients.

Caregivers often face stress situations that require quick decision making and precise actions. Through simulation training, caregivers can practice these critical skills without the risk of causing harm to real patients. DeepSeek allows a safe space for caregivers to make mistakes, learn from them, and build confidence in their abilities. In addition, the chatbot can response to emergencies such as falls or sudden medical deteriorations as if telemedicine. By repeatedly engaging in these simulations, caregivers become better prepared to handle emergencies calmly and effectively, increasing the likelihood of timely medical attendance in real-life scenarios.

Another aspect of SBL involves medication administration (6). Through the step-by-step guides of verifying prescriptions, calculating dosages, and monitoring for potential side effects, caregivers could receive instant feedback to avoid mistakes. As caregivers gain proficiency in these tasks, their confidence in providing care increases, ultimately leading to better patient outcomes.

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### Step 2: Interactive FAST Evaluation

DeepSeek guides the user through a virtual examination:

#### 1. Face Drooping:

- "Ask your father to smile. Observe his face. Does one side droop or feel numb?"
- **User Input:** "His left smile is weaker."
- **Feedback:** "This is a red flag for stroke. Proceed to the next step."

#### 2. Arm Weakness:

- "Ask him to raise both arms. Does one arm drift downward or feel weak?"
- **User Input:** "His left arm can't stay up."
- **Feedback:** "Arm weakness is another stroke sign. Continue."

#### 3. Speech Difficulty:

- "Ask him to repeat: 'The early bird catches the worm.' How does he respond?"
- **User Input:** "His speech is slurred and jumbled."
- **Feedback:** "Speech issues strongly suggest a stroke. Time to act!"

### Step 3: Time-Sensitive Decision-Making

DeepSeek presents critical choices:

"It's been 5 minutes since symptoms started. What do you do?"

**Options:**

1. Wait 15 minutes to see if symptoms resolve.
2. Drive him to the hospital yourself.
3. **Call emergency services immediately.**

**Correct Answer:** 3. Call emergency services immediately

- **Feedback:** "Correct! Every minute matters. Calling an ambulance ensures faster treatment and safer transport."

### Step 4: Post-Simulation Debrief

DeepSeek provides a summary:

#### 1. Key Takeaways:

- FAST criteria (Face, Arms, Speech, Time).
- Importance of immediate action (time = brain cells saved).

#### 2. Common Mistakes:

- Waiting to see if symptoms improve.
- Transporting the patient without professional help.

#### 3. Real-World Stats:

- "Patients who arrive at the hospital within 3 hours of symptoms have better recovery rates."

### Advanced Simulation Features

To enhance realism, DeepSeek could incorporate:

Message DeepSeek

Figure 1. DeepSeek-V3 chat. A simulation-based learning scenario on acute stroke of an elderly

In short, the use of DeepSeek enhances caregivers' learning experiences, promotes safe practice, improves competence and confidence, and fosters emotional resilience. The integration of driven simulation training could better equip caregivers to meet the complex needs of elderly patients.

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