

## Association of physical frailty with cognitive function and mood in older adults without dementia and depression

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**Background/aim:** Physical frailty is thought to be related with a decline in cognitive function, mood, and social activities, especially in patients with depression and dementia. It is not clear whether or not physical frailty is associated with an impairment in cognitive function and mood in patients without dementia and depression. In this study, we evaluated the association of physical frailty with cognitive function and mood in geriatric patients without dementia and depression.

**Material and methods:** In this study, 612 patients aged 65 years and over were evaluated. Physical frailty was assessed by using Fried criteria. Furthermore, comprehensive geriatric assessment was performed to each patient.

**Results:** Median age of the patients was 72 years (min-max: 65–93), 58% were female, and 6.5% were frail. Clock drawing ( $p < 0.001$ ), MMSE ( $p < 0.001$ ), and Yesevage geriatric depression scale ( $p: 0.010$ ) test results were worse in frail patients compared to pre-frail and robust ones. Age ( $p: 0.009$ ), being university graduate ( $p: 0.031$ ), three words recall test ( $p: 0.014$ ), activities of daily living (ADL) ( $p: 0.006$ ), instrumental activities of daily living (IADL) ( $p < 0.001$ ), and MNA-SF ( $p: 0.001$ ) scores were determined to be independent related factors of frailty.

**Conclusion:** We have demonstrated that cognitive function and mood might be associated with physical frailty in patients without dementia and depression.

**Key words:** Frailty, cognitive function, mood, dementia, depression

### 1. Introduction

Frailty is common in older age and predicts high risk for health-related problems, including institutionalization, mortality, falls, and hospitalization with consequent negative influences on the quality of life [1–3]. It is a condition caused by a decrease in reserve capacity in systems such as brain, immune system, endocrine, and skeletal muscle in older adults [4–6]. Individuals in the same chronological age may be very different in terms of health and functional status. The concept of frailty has been developed to explain this heterogeneity among older adults [7]. The main and the best known conceptualization of physical frailty is the one suggested by Fried et al., who defined frailty as a biological syndrome resulting from the cumulative decline of different physiological systems [4].

Cognitive impairment indicates reduction in intellectual functions, which ranges from forgetfulness to dementia. The association between frailty and cognition has been mentioned in recent studies. In the study by Avila-Funes et al., patients were divided into two groups as robust and frail. The prevalence of cognitive impairment was higher in the frail group (frail group 22%, robust group 10%), however, patients with dementia and depression were included in this study [1]. Samper-

Ternent et al. examined patients with the mini-mental state examination (MMSE) score after grouping as frail and robust. At the end of the 10 year follow up, cognitive decline was found to be greater in the frail group than in the robust group [8].

Depression is not a normal consequence of aging. Loss of function or independence, persistent bereavement, and serious depression are pathological and should be treated. Untreated depression causes important health problems such as complicated chronic conditions including heart disease, diabetes, hypertension, and stroke. It also increases health care costs [9–11]. Not only depressive disorder, but also depressive symptoms have high influence on sense of well-being, disability, and utilization of health care services in older adults [12–14]. The relationship between frailty and depression has been examined in the literature, but no consensus has been reached. In a review, it was reported that the high percentage of frail older adults have depressive symptoms. It is assumed that similar mechanisms play role in depression and frailty, but these information are insufficient to explain the relationship [15].

We have hypothesized that there may be a vicious cycle between physical frailty, cognitive function and mood in geriatric patients independent from dementia

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and depression. Therefore, the purpose of the present study is to evaluate the relationship between physical frailty, cognitive function, and mood in patients without dementia and depression in community dwelling older persons.

## 2. Material and methods

### 2.1. Participants

The study was designed as cross-sectional study. Patients admitted between June 2014 and September 2016 were evaluated. One thousand and fifty patients admitted to geriatric medicine outpatient clinic consecutively were evaluated and 612 were included after applying exclusion criteria. Patients over 65 years of age who could be appraised with the Fried frailty criteria were included in the study. Patients with the following criteria were excluded from the study: 1) MMSE score < 20; 2) Yesavage geriatric depression scale (GDS) short form > 5; 3) patients with diagnosis of depression and/or dementia; 4) patients with diagnosis of psychiatric disorders including schizophrenia, bipolar disorder, borderline personality disorder; 5) patients using antidepressants, antipsychotics, sleep medications, and dementia drugs. Age, sex, smoking status, alcohol consumption, chronic diseases, number of drugs, whom living with (partner, children, alone), education level, number of falls, fractures in the last year, and unintentional weight loss during the last year, and urinary incontinence were recorded. Height (m), weight (kg), calf, and upper-mid arm circumferences were measured for each participant. The patients were weighed in the outpatient clinic after, fasting, wearing light clothes and taking off their shoes and their height was measured with the shoes removed. Body mass index (BMI) was calculated by dividing the patient's weight (kg) by the square of the height (m<sup>2</sup>).

### 2.2. Cognitive function assessment

Within comprehensive geriatric assessment, cognitive assessment was performed. The cognitive functions of the patients were evaluated by clinical assessment, the MMSE and The Clock drawing test (CDT). The MMSE, developed by Folstein in 1975, is thoroughly used to measure cognitive functions. Generally, the MMSE score higher than 20 points is thought to indicate good cognitive performance [8]. However, due to different literacy and low educational status rates in different countries, there are different cut-off points indicating poor cognitive performance in the literature [16–19]. In this study, the patients with MMSE  $\geq$  20 points and no diagnosis for dementia were included in the study. Three-word recall was also recorded to evaluate patients' immediate memory.

We used the CDT that was initially used by Stahelin et al. Its score ranges from 0 to 6 points and the point < 4 in CDT was accepted to show low cognitive performance [20–22]. CDT score was examined individually for each patient. It was observed that there was no dementia in

patients who got 0 on the test and had a score below 4, and the reason for failure was due to low education level.

After cognitive and clinical assessment, patients who met DSM-V criteria for dementia were excluded from the study. Diagnosis of mild cognitive impairment was made according to Petersen criteria.

### 2.3. Physical frailty assessment

An adapted version of the frailty phenotype of Fried et al. was used to detect physically frail older adults [4]. Fried criteria is well-established in the literature and the most frequently used diagnostic criteria [23]. Weight loss, exhaustion, physical activity, walking speed, and grip strength were the parameters that were evaluated in the Fried criteria. According to these criteria, the patients scoring 3 or more were reported as frail, scoring 1 or 2 points as pre-frail, and scoring 0 as robust.

With a hand-held dynamometer (Takei A5401), three different grip measurements were made by using both hands and the best was recorded. The devices (scale, handgrip) used in the study were calibrated and used under appropriate conditions. The walking speed of 15 feet for each patient was evaluated by the timed up and go test.

### 2.4. Psychological assessment

Depressive symptoms were assessed clinically and by performing Yesavage GDS short form. A score of 6 or greater is considered clinically significant [24]. The patients having < 6 points in this scale and no diagnosis for depression were included for the study.

### 2.5. Comprehensive geriatric assessment parameters

Basic activities of daily living (ADL) and instrumental activities of daily living (IADL) were performed to measure the functional capacities of the patients. ADL was evaluated using the Katz scale which assesses the degree of dependence on 6 basic activities: feeding, sphincter control, transferring, personal hygiene, dressing, and bathing. The subject is classified based on the number of activities on which he/she is dependent to others [25,26]. The Lawton brody scale was used for the evaluation of IADL; this scale assesses eight activities: using a telephone, transportation, shopping, cooking, doing household chores, taking prescribed medications, and financial affairs management [27].

The nutritional status of the patients was appraised with the mini nutritional assessment short form (MNA-sf), where the total score of  $\leq$  11 was described as the risk of malnutrition [28].

### 2.6. Ethics

Informed consent forms were received from all participants in the study and the study protocol was evaluated and approved by the ethics committee (GO 15/36-25).

### 2.7. Statistical analysis

Descriptive statistical results were offered as frequencies and percentage for categorical variables. Continuous variables were tested with histogram and Kolmogorov-Smirnov tests to decide whether or not the parameters

had normal distribution. The skewed variables were presented as median (minimum-maximum). Comparisons of categorical variables between groups were performed by Chi-square or Fischer exact tests where appropriate. The skewed variables were compared between two groups with Mann-Whitney U test. Kruskal-Wallis and Jonckheere-Terpstra tests were used for the analyses between three or more groups for those with skew distribution. Binary logistic regression analysis was used to determine to independently associated parameters for frailty, and values that showed a significant difference in the univariate analysis results of the frail and nonfrail groups and lower than  $p < 0.20$  were included in this analysis. Odds Ratios (OR) with a 95% confidence interval (CI) was calculated for each variable. Statistical significance was evaluated as  $p$  value lower than 0.05. All statistical results were obtained using the "Statistical Package for Social Sciences" (SPSS) v: 22.0 programme.

### 3. Results

Six hundred and twelve patients aged 65 years and older, living in the community were included in this study. The median age of patients were 72 years (range 65–93), 58% were female, 19.2% were university graduates, 65.3% were living with their partners or families. The three most common comorbid conditions were hypertension (67.2%), diabetes mellitus (35.9%), and urinary incontinence (33.2%). The frequencies of comorbid diseases and geriatric syndromes are shown in Table 1.

Among the 612 older patients evaluated 276 patients (45.1%) were classified as robust, 296 patients (48.4%) were classified as pre-frail, and 40 patients (6.5%) were classified as frail. Pre-frail and frail participants were more likely to be older ( $p < 0.001$ ), less educated ( $p: 0.006$ ), had decreased calf circumference ( $p: 0.047$ ), and increased number of drugs ( $p: 0.041$ ) than robust ones. A significant decrease in weight was observed from the

**Table 1.** Comparison of comprehensive geriatric assessment parameters between groups determined by the Fried's frailty index.

	Total (n = 612)	Robust (n = 276)	Pre-frail (n = 296)	Frail (n = 40)	P value
Age, year	72 (65-93)	71 (65-88)	72 (65-90)	78 (65-93)	<0.001
Female, %	355 (58)	153 (55.4)	175 (59.1)	27 (67.5)	0.304
Male, %	257 (42)	123 (44.5)	121 (40.9)	13 (32.5)	0.304
Education level, university graduate, %	116 (19.2)	70 (25.4)	44 (14.7)	2 (5)	0.006
Weight, kg	74 (43-145)	76 (45-145)	73 (43-116)	67 (50-98)	<0.001
BMI, kg/m <sup>2</sup>	27.6 (17-50.1)	27.8 (18.6-50.1)	27.6 (17-44.3)	26.9 (21-40)	0.431
Calf circumference, cm	36 (17.9-52)	36.7 (17.9-51)	36 (23.5-52)	34.5 (24-46)	0.047
Hypertension, %	411 (67.2)	172 (62.3)	207 (69.9)	32 (80.0)	0.031
Diabetes mellitus, n (%)	220 (35.9)	100 (36.2)	104 (36.2)	16 (40.0)	0.827
Osteoporosis, n (%)	143 (23.4)	61 (22.2)	72 (24.3)	10 (25.0)	0.808
Coronary artery disease, n (%)	91 (14.9)	38 (13.8)	46 (15.5)	7 (17.5)	0.745
Chronic obstructive pulmonary disease, n (%)	34 (5.6)	12 (4.3)	18 (6.1)	4 (10)	0.297
Hyperlipidemia, %	189 (30.9)	94 (34.1)	87 (29.4)	8 (20.0)	0.147
Congestive heart failure, %	21 (3.4)	7 (2.5)	10 (3.4)	4 (10)	0.053
History of falls, %	150 (24.5)	47 (17.0)	89 (30.1)	14 (35)	0.001
Fracture, n (%)	72 (12.1)	29 (10.9)	36 (12.4)	7 (18.4)	0.410
Urinary incontinence, %	203 (33.2)	78 (28.3)	104 (35.1)	21 (52.5)	0.006
Number of drugs	4 (0-17)	3 (0-17)	4 (0-13)	5 (0-10)	0.041
Katz ADL score	6 (0-6)	6 (5-6)	6 (0-6)	5 (0-6)	<0.001
Lawton IADL score	17 (0-17)	17 (7-17)	17 (7-17)	13 (0-17)	<0.001
CDT score	6 (0-6)	6 (0-6)	6 (0-6)	3 (0-6)	<0.001
MMSE score	28 (20-30)	29 (20-30)	28 (20-30)	27 (21-30)	<0.001
Three words recall	3 (0-3)	3 (0-3)	2 (0-3)	2 (0-3)	<0.001
MNA-sf, score	14 (0-14)	14 (2-14)	13 (0-14)	11 (6-14)	<0.001
Yesavage GDS score	0 (0-5)	0 (0-5)	0.5 (0-5)	1 (0-5)	0.010
15 ft walking time, s	4.5 (1.5-28.5)	4.03 (1.5-6.7)	4.82 (1.9-25.2)	8.78 (3.9-28.5)	<0.001
Handgrip, kg	22.8 (6.7-52.4)	27.8 (14.4-52.4)	19.9 (7.7-48.6)	14.0 (6.7-31.8)	<0.001

\* The skew variables were presented as median (minimum-maximum). Categorical variables were given as numbers and percentages.

\* BMI: body mass index, ADL: activities of daily living, IADL: instrumental activities of daily living, CDT: clock drawing test, MMSE: mini-mental state examination, MNA-sf: mini nutritional assessment short form, GDS: Geriatric depression scale.

robust to the frail group ( $p < 0.001$ ). In the frail group; the Katz ADL ( $p < 0.001$ ), Lawton Brody IADL ( $p < 0.001$ ), CDT ( $p < 0.001$ ), MMSE score ( $p < 0.001$ ), and MNA-sf ( $p < 0.001$ ) scores were lower and Yesavage GDS score ( $p: 0.010$ ) was higher compared to the nonfrail group.

Median hand grip strength was 22.8 kg (range 6.7–52.4) and median 15 feet walking time was 4.5 s (range 1.5–28.5). Frail group was powerless ( $p < 0.001$ ) and walked slower ( $p < 0.001$ ) compared to the nonfrail ones. In Table 1, demographic characteristics, comorbid diseases, and comprehensive geriatric assessment of the patients were given according to the degree of frailty.

After logistic regression analyses, age (OR: 1.093, 95% CI: 1.022–1.169,  $p: 0.009$ ), being university graduate (OR: 0.020, 95% CI: 0.001–0.703,  $p: 0.031$ ), ADL (OR: 0.448, 95% CI: 0.252–0.796,  $p: 0.006$ ), IADL (OR: 0.760, 95% CI: 0.665–0.869,  $p < 0.001$ ), MNA-sf (OR: 0.721, 95% CI: 0.599–0.869,  $p: 0.001$ ), and three words recall (OR: 0.531, 95% CI: 0.320–0.880,  $p: 0.014$ ) scores were determined to be independent factors related to frailty. The parameters included in the regression analysis were age, weight, congestive heart failure, urinary incontinence, hypertension, hyperlipidemia, history of falls, sleep duration, number of drugs, ADL score, IADL score, CDT score, three words recall, and MNA-sf. The parameters independently associated with frailty are shown in Table 2.

#### 4. Discussion

This study aimed to examine the association between physical frailty, cognitive function, and mood in community-dwelling older patients without dementia and depression. MMSE, CDT, Yesavage GDS, and three words recall tests' results were shown to be worse in frail patients than in nonfrail ones in univariate analyses. Moreover, three words recall test was found to be an independent correlate for frailty in regression analysis. This study demonstrated that there is a relationship between physical frailty and cognitive function and mood in older adults regardless of having dementia or depression. The frequency of frailty in patients with depression and dementia has been shown in previous studies. In our study, although the patients with these diagnoses were excluded from the study, it was shown that the scores of the scales assessing cognition and mood were poor in the frail group. By showing these results, this study adds to the existing literature on physical frailty and its relationship with other common syndromes of the older adults.

Despite the exclusion of the diagnosis of depression in this study, depressive symptoms detected in Yesavage GDS were found to be increased in the frail group than the nonfrail subjects. The bidirectional relationship between mood and frailty has been explored in some studies, but not well documented. Ormeland and colleagues have shown that frailty is a stronger predictor for depressive symptoms [29]. Gayman and colleagues have found that frailty deteriorated depressive symptoms [30]. Similarly,

**Table 2.** Parameters independently associated with frailty.

	OR	95% CI	p value
Age	1.093	1.022–1.169	0.009
Educational status, university graduate	0.020	0.001–0.703	0.031
ADL score	0.448	0.252–0.796	0.006
IADL score	0.760	0.665–0.869	<0.001
MNA-sf	0.721	0.599–0.869	0.001
Three words recall	0.531	0.320–0.880	0.014

\*All the parameters those had p value lower than 0.20 when compared between frail and nonfrail patients in univariate analysis were included in regression analysis. The parameters included in the regression analysis were age, weight, congestive heart failure, urinary incontinence, hypertension, hyperlipidemia, history of falls, sleep duration, number of drugs, ADL score, IADL score, Clock drawing test score, three words recall, and mini-nutritional assessment-SF. Backward elimination method was used for binary logistic regression analysis. The last model (step 13) was presented in this table. This regression model had omnibus test result as chi-square 93,206 and  $p < 0.001$ . Also, this model had p value as 0.935 for Hosmer–Lemeshow test and Nagelkerke R square was 0.469.

\* ADL: activities of daily living, IADL: instrumental activities of daily living, MNA-sf: mini nutritional assessment short form.

Collord and colleagues have indicated that the severity of frailty has a negative influence on late-onset depressed mood [31]. However, in these studies patients with a diagnosis of depression have not been excluded. In our study, patients with a diagnosis of depression were excluded from the study, and geriatric depression scale scores were found to be higher in the frail group.

The review by Mezuk and colleagues described the positive correlation between frailty and depression in detail [32]. The results summarized in this systematic review support the hypothesis that frailty and depression are comorbid geriatric syndromes in a subgroup of older individuals; at the same time, frailty is also a risk factor for the development and persistence of depressive symptoms. The same common symptoms and risk factors may also explain why frailty could sustain depressive symptoms and leads subjects to new symptoms of depression [33]. In the majority of these studies, the diagnosis of dementia and depression was not excluded. In two studies excluding the diagnosis of dementia but not depression, depressive symptoms were associated with frailty, but it was not associated with the pre-frail group and was shown to be weakly related, respectively [34,35]. So, we can say in the light of our and similar studies that there is a positive correlation between frailty and depressive symptoms irrespective of having diagnosis of depression and dementia. In daily practice, when a geriatric patient with frailty is seen, depressive symptoms should be checked to rule out or early detect the diagnosis

of depression. Therefore, the frailty assessment should be routinely involved in the assessment of a geriatric patient.

Cognitive impairment was more presumably to be present among pre-frail and frail older persons than their robust peers. This is in compromise with cross-sectional studies which show a higher prevalence of cognitive impairment within physically frail older persons [36–38]. The association between frailty and cognitive impairment is controversial in the literature. Although studies show that frailty may be an indicator of mild cognitive impairment and dementia, there appears to be a correlation between the initiation of frailty and cognitive decline. These two situations may be sharing the same physiopathological mechanisms [1,39–41]. That's why the assembling of frailty and cognitive impairment can increase an individual's vulnerability and deepen the deterioration in cognitive status [36,37].

The connection between frailty and cognitive impairment risk may be accounted by common etiopathogenetic mechanisms. Cognitive decline that frailty contributes may be addressed in many different pathways [39,42]. Cognitive decline is a course that starts with small changes in a few domains and progresses in many domains slowly. In some dementia types which cortices, the substantia nigra, and the striatum are often changed, accumulation of neural plaques and neurofibrillary tangles is involved in the etiology of the decline. It has been shown in some studies that changes in these regions of the brain are associated with alterations in the components of frailty such as slow gait and weight loss. These findings and the outcomes of our study demonstrate that alteration in the neural system may be predictive for frailty [43–45]. Further studies are needed to explain this precise relationship.

Another mechanism that may explain the relationship between cognitive dysfunction and frailty is the inflammatory process. Proinflammatory cytokines increase during stress reactions, and interleukin-1 and tumor necrosis factor levels increase in diseases that trigger inflammatory reactions. Interleukin-6 increases with the aging process, and these increased cytokines accelerate the catabolic process resulting in diminished lean body mass and muscle, leading to frailty. Furthermore, peripheral pro-inflammatory cytokines increase the central proinflammatory cytokine levels leading to neurotoxicity and cognitive impairment. It is stated that inflammatory reactions contribute to physical frailty and cognitive dysfunction in the direction of this knowledge [46–49].

In our study, it was observed that the age of the patients increased with the increase in the degree of frailty. The association of pre-frailty and frailty with age is consistent with the findings of previous studies [50,51]. Physiological changes in many systems when aging and their consequent interactions with pathological mechanisms make aging a predisposing factor for frailty [6]. According to the results of our study, the relationship between the level of education and frailty was determined

with higher frailty prevalence rates among lower educated people. Hoogendijk and colleagues found similar results and concluded in their study that public health strategies about struggling with frailty should also include focusing on patients' education levels. The knowledge regarding high prevalence of frailty in low educational level improved this strategy [52]. Arguments have shown that longtime education in early life may enhance the development of cognitive reserve throughout the life process [53,54]. All patients underwent comprehensive geriatric assessment in our study and ADL, IADL, and nutritional status were detected to be independently related parameters with frailty. Similarly, some studies in the literature have shown that there is a relationship between frailty and basic activities of daily life and instrumental activities of daily life [6]. We know that frailty has multi-dimensional aspects. Physiologic, cognitive, behavioral, and physical reserves of the geriatric patients are negatively affected by frailty. Therefore, all the parameters in comprehensive geriatric assessment may be affected by frailty. In this study, evaluation of patients with good general condition who were admitted to the outpatient clinic was reflected to the results as low prevalence of frailty. It cannot be generalized to the whole geriatric population because of the lack of nursing home residents among the patients enrolled.

The major limitation of this study is having a cross-sectional design. We could not determine causality between frailty, cognitive function, and depressive symptoms due to the cross-sectional design of the study. The strengths of our study are excluding patients with depression and dementia and including a large number of patients. The results of this study revealed that frailty is associated with depressive symptoms and cognitive dysfunction even in the patients without depression or dementia diagnosis, in a very large sample. In some studies, in the literature, it was seen that the MMSE score was taken as a cut off 20. In our study, when the patients were examined one by one with their education level, it was decided to determine the MMSE score as 20.

In conclusion, the relationship between physical frailty and cognitive function and depressive symptoms was shown in this study. Prevention of frailty and intervention of reversible factors have become important in order to minimize the consequences. There is a need for future work to elucidate this issue clearly. Frailty should be evaluated comprehensively. In patients with physical frailty cognition and mood should always be assessed and precautions should be taken on time. Increasing awareness on all aspects of frailty should be an aim for healthcare policies and further studies showing impact of frailty on healthcare costs will further emphasize its importance.

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