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Original article

# The Relationship Between Polypharmacy and Frailty in Older Adults: Which Frailty Assessment Tool Shows the Relationship Best?

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**Abstract.** Frailty syndrome is one of the geriatric syndromes that carries an increased risk for adverse health outcomes. This study aims to investigate the relationship between frailty and polypharmacy in the elderly. This cross-sectional study was conducted for a period of 4 months from September 2019 to January 2020. Frailty was assessed by using the Fried Frailty Index (FFI) and SOF (Study of Osteoporotic Fractures) Index. Patients were evaluated for inappropriate medication use by TIME (Turkish Inappropriate Medication Use in the Elderly) criteria. Data analysis was done by using SPSS version 22. The study population was composed of 93 women and 57 men, and the mean age was 73 +/- 9 years. The frequency of polypharmacy was %73 (n=110). Presence of polypharmacy and number of drugs used were related to both FFI and SOF index scores. We found that the FFI score was associated with number of drugs used in regression analysis ($r^2$=0.166, p<0.001). The relationship between multimorbidity and frailty was also demonstrated by FFI(p=0.01). We showed a cut-off value of 6.5 of drug numbers for being frail according to the FFI index in the ROC curve (sensitivity:68%; specificity:62%; p<0.001; CI:95%; AUC:0.693). The frequency of inappropriate medicine use was 38%. In this study, we revealed that frailty was related to polypharmacy. We also found that FFI reveals the relationship between polypharmacy and frailty more precisely than the SOF index. Prospective studies to evaluate the effect of decreasing the number of used drugs on frailty could be useful.

**Key words:** frailty, polypharmacy, potentially inappropriate medicine use, TIME, Fried, SOF

## Introduction

Life expectancy had increased worldwide in the past 100 years, mainly because of advances in health care. The percentage of older adults has been increasing in developing and developed countries (1). In 2050, the proportion of people aged 60 years and over is estimated to be 22% (2). The syndrome of frailty is taking global attention as the population of older adults increases (3). The frailty syndrome is a situation characterized by a decrement in the functionality of multiple physiological systems and increment in the vulnerability to stressors (4). To identify the people who are at risk of being frail and frail several tools have been developed. Fried and colleagues described the FFI in the light of physical phenotype (3). Ensrud and colleagues developed a more feasible frailty index named as SOF index(5).Older adults are prone to take multiple medications because multi-morbidity is more common in them. That condition can be referred to as polypharmacy. The strict cut-off of the number of drugs required to define polypharmacy varies, ranging from more than 4 to more than 10 (6). The frequent occurrence of polypharmacy in elderly individuals may be associated with multimorbidity. Coexistence of more than 2 chronic health problems is called

multimorbidity (7). The use of potentially inappropriate medication (PIM) is defined as drugs that risk of use of them predominates the benefit. The prevalence of PIM use by older adults was found to be between 11.5-62.5% (8).

Frailty and polypharmacy are common geriatric syndromes, and their effect on each other has not clarified yet (9).We purposed to reveal the relationship between frailty syndrome and polypharmacy in people aged 65 or over. In previous studies, the relationship between frailty and multimorbidity has been demonstrated (10). In this study, we tried to determine the prevalence of multimorbidity for our population and with which frailty index would be better to demonstrate its relationship. Also, we aimed to evaluate which frailty criteria predicted polypharmacy more accurately.

## Methods

### *Participants*

This cross-sectional study was carried out for a period of 4 months from September 2019 to January 2020. Outpatients admitted to the geriatric outpatient clinic were included in the study. The Local Research Ethics Committee gave approval for the study. All participants gave informed consent.

### *Exclusion Criteria*

Patients, who were below 65 years of age, and had already diagnosed with any of the geriatric syndromes such as sarcopenia, frailty, malnutrition, polypharmacy, fall, urinary and fecal incontinence were not included in the study. Patients who were in a cancer chemotherapy program or treated for a severe disease were excluded too.

### *Comprehensive Geriatric Assessment*

A cognitive evaluation was done by the standardized form of mini-mental state examination (MMSE), assessment of abilities of daily living (ADL) by Katz index, instrumental activities of daily living (IADL) by Lawton Brody index, risk of fall by Tinetti Balance-Gait Evaluation Scale and psychological status by short form of Yesavage Geriatric Depression scale.

In MMSE, patients were evaluated for six different areas; orientation, attention, registration, language, calculation and recall (11). Patients whose scores were ≤24 accepted for the presence of dementia. Katz index of ADL appreciated patients for personal hygiene, continence, toileting, dressing, feeding, and ambulating. Scores were between intervals of 0 and 6; high scores are considered high self-sufficiency (12). Lawton Brody index was used for evaluating IADL like house cleaning, doing the laundry, marketing, managing medications, cooking, communicating with others, using transportation, and doing financial management; higher scores mean higher independence (13). Tinetti Balance-Gait Evaluation Scale (14) and Timed up and Go Test (TUG) (15) were used for evaluating the falling risk. In the Tinetti Balance-Gait Evaluation Scale, a score of >24 means low risk of fall, 19-23 moderate risk of fall, and <19 high risks of fall (14). Patients took 14 seconds, or longer from the TUG test, were classified as high-risk for falling too (15). GDS scores of 5 and higher eligible for depression (16).

### *Assessment for Sarcopenia*

For defining sarcopenia, muscle strength, mass, and physical performances were assessed. SARC-F (strength, assistance walking, rise from a chair, climb stairs, and falls) test was used to select cases to evaluate muscle strength (17). The handgrip test was performed if the patient had point ≥4 from SARC-F to diagnose probable sarcopenia. The handgrip test was performed by using a hand dynamometer with the dominant hand (18). For female <16 kg (kilograms), for male <27 kg was accepted as probable sarcopenic. A bioimpedance test was carried out to probable sarcopenic patients to assess skeletal muscle mass. Sarcopenia was diagnosed by skeletal muscle mass index. In this study, we used skeletal muscle mass index (SMMI) adjusted to height. SMMI was calculated by dividing skeletal muscle mass to the square of height (19). We evaluated gait speed with a four-meter gait speed test in order to diagnose severe sarcopenia (20).

*Assessment for Frailty Syndrome*

Frailty was assessed by using the Fried Frailty Index (FFI) and SOF (Study of Osteoporotic Fractures) index. FFI is constituted from five criteria: unintentional weight loss, self-reported poor energy, weakness (reduced grip strength), slow gait speed, and low physical activity. People who were positive for three and more FFI criteria were defined as frail. Whom were positive for one or two criteria were described as pre-frail(3). The SOF index evaluates frailty syndrome by using three components (weight loss, inability to rise from a chair five times without using the arms, and reduced energy). Presence of frailty syndrome was by the presence of two or more of the three criteria in SOF index. Patients that positive for 1 criterion were described as pre-frail (5). People not meeting any criteria was confirmed defined as robust in both assessment tools.

*Evaluation of Polypharmacy*

Polypharmacy was evaluated by using the database of the Social Security System. The drugs prescribed in the last 3 months were checked. The number and name of the drugs used were recorded. The use of 5 to 9 drugs was accepted as polypharmacy, ≥10 drugs were accepted as excessive polypharmacy (6). Patients were evaluated for potentially inappropriate medication (PIM) use by TIME (Turkish Inappropriate Medication Use in the Elderly) criteria (21).

*Evaluation of Multimorbidity*

Chronic disease information of the patients was obtained from the database of the Social Security System. Those with more than 2 chronic diseases were accepted as multimorbid (7).

*Statistics*

The variables were analyzed for the normality of their distribution using the Kolmogorov–Smirnov test. Numerical variables were denoted as mean ± standard error (SE). Categorical variables were represented as frequencies. Comparison of two groups were done by independent sample t-test. Chi-square test, correlation analysis, and linear regression model were used to assess the relationship between variables. The IBM SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

## Results

The study population was composed of 93 women and 57 men, and the mean age was 73 +/- 9 years. Forty-five percent of the patients were frail, 49% of the patients were pre-frail, and 6% of the patients were robust, according to FFI. Forty-four percent of the patients were diagnosed as frail, 37% of them were pre-frail, and 19% of them were robust by the SOF index. Polypharmacy and excessive polypharmacy were reported in 73 and 12% of the study population, respectively. Eighty-one percent of the patients were multimorbid. Average number of diseases carried by patients was 2.9±1.2. According to the FFI, 91% of those who are frail and 73% of those who are not frail are multimorbid. Frail status was found to be associated with multimorbidity($p=0.01$). The presence of polypharmacy and the number of used drugs were revealed to be positively related to scores of FFI and SOF Index. SARC-F survey results were also positively related to number of drugs used and polypharmacy. Handgrip strength was negatively related to the presence of polypharmacy. Number of drugs used were found to be negatively related to gait speed. The relationship between frailty and sarcopenia parameters with polypharmacy was shown in table 1. The mean values of the parameters of frailty and sarcopenia were summarized in table 2. We found that the FFI score was independently associated with number of drugs used in linear regression analysis ($r^2=0.166$, $p<0.001$). Results of linear regression analysis were summarized in table 3. Frailty was also revealed to be related to PIM use when evaluated with FFI ($r=0.172$, $p=0.029$). In addition, when the number of drugs, the number of chronic diseases and the use of PIM were considered as independent variables, it was seen that only the number of drugs affected the frailty evaluated by FFI in the linear regression analysis. Results were summarized in table 4. We found a cut-off value of 6.5 of drug

**Table 1.** Relationship between frailty, sarcopenia, and polypharmacy

| | Number of drugs | Presence of polypharmacy |
|---|---|---|
| FFI | **r=0.406**, p<0.001** | **r=0.203**, p=0.014** |
| SOF index | **r=0.284**, p<0.001,** | **r=0.168*, p=0.042,** |
| SARC-F | **r=0.292**, p<0.001** | **r=0.229**, p=0.006** |
| Handgrip strength | p=0.098 | **r=−0.196*, p=0.018** |
| SMMI | p=0.459 | p=0.68 |
| Gait speed | **r=-0.241**, p=0.006** | p=0.36 |

FFI*: Fried Frailty Index
SOF*: Study of osteoporotic fractures
SARC-F*: Strength, assistance walking, rise from a chair, climb stairs, and falls
SMMI*: Skeletal muscle mass index

**Table 2.** Frailty and sarcopenia assessments

| | Presence of polypharmacy (mean±SE) (n=110) | Absence of polypharmacy (mean±SE) (n=40) | p= |
|---|---|---|---|
| FFI score | 2.68±0.13 | 2.02±0.23 | **0.014*** |
| SOF score | 1.5±0.09 | 1.13±0.14 | **0.042*** |
| SARC-F | 4.26±0.33 | 2.5±0.53 | **0.006*** |
| Handgrip strength (kg) | 26.98±1.27 | 33.47±2.8 | **0.018*** |
| SMMI (kg/m$^2$) | 11.03±0.15 | 10.91±0.28 | **0.68** |
| Gait speed (m/s) | 0.51±0.02 | 0.48±0.015 | **0.36** |

FFI: Fried Frailty Index
SOF: Study of osteoporotic fractures
SARC-F: Strength, assistance walking, rise from a chair, climb stairs, and falls
SMMI: Skeletal muscle mass index

**Table 3.** Results of linear regression analysis

| Independent Variables | B | St. Error | Beta | T | P |
|---|---|---|---|---|---|
| FFI score | 1.005 | 0.262 | 0.433 | 3.834 | **<0.001*** |
| SOF score | -0.125 | 0.389 | -0.036 | -0.320 | 0.749 |

FFI*: Fried Frailty Index
SOF*: Study of osteoporotic fractures

**Table 4.** Results of linear regression analysis

| Independent Variables | B | St. Error | Beta | T | P |
|---|---|---|---|---|---|
| Number of drugs | 0.086 | 0.043 | 0.491 | 2.007 | **0.047*** |
| Number of chronic health problems | -0.077 | 0.118 | -0.161 | -0.654 | 0.514 |
| PIM use | 0.125 | 0.098 | 0.101 | 1.277 | 0.204 |

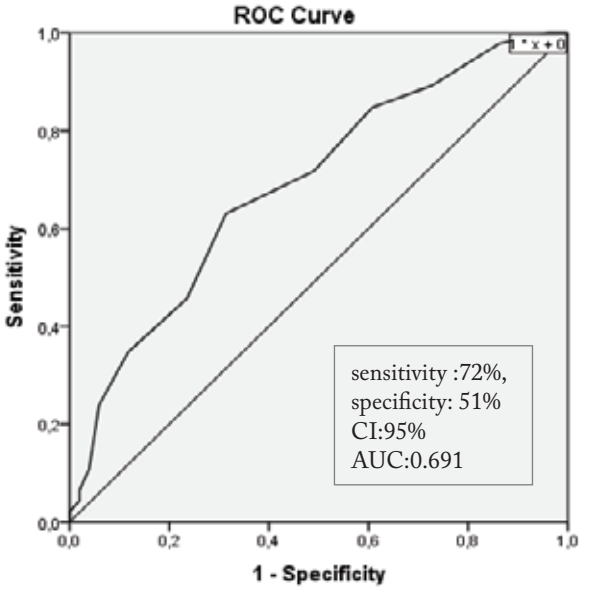


**Figure 1.** Cut-off value of number of drugs for being frail

number for being frail according to FFI (sensitivity 68%; specificity 62%; CI=95%, p<0.001, AUC:0.693) (Figure 1). Results of comprehensive geriatric assessment tests and relationships with polypharmacy were summarized in table 5.

## Discussion

In this study, we revealed that the presence of polypharmacy and the number of drugs used were related to frailty. They were positively related to Fried Frailty and SOF index. Many studies were done to evaluate the relationship between polypharmacy and

**Table 5.** Relationship between comprehensive geriatric assessment and polypharmacy

| | **Presence of polypharmacy (n=110) mean±SD** | **Absence of polypharmacy (n=40) mean±SD** | **p=** |
|---|---|---|---|
| MMSE | 21.91±6.71 | 21.92±7 | 0.081 |
| ADL | 5.16±1.1 | 5.32±1.13 | 0.418 |
| IADL | 4.95±2.77 | 5±2.87 | 0.305 |
| GDS | 11.61±6.69 | 8.97±5.45 | **0.023*** |
| Tinetti total | 26.83±8.04 | 29.5±6.25 | **0.048*** |
| Tinetti balance | 19.8±6.12 | 21.83±4.78 | 0.083 |
| Tinetti gait | 6.97±2.5 | 7.63±2.16 | 0.092 |

MMSE* = Mini-mental state examination
ADL* = Activities of daily living
IADL* = Instrumental activities of daily living
GDS* = Geriatric depression scale

frailty. Fried's criteria, Edmonton Frail Scale, and the FRAIL scale are some of the commonly used frailty assessment tools used in studies (22). Veronese et al. evaluated the relationship between polypharmacy and frailty in their 8-years longitudinal study. They used the SOF index as in our study. They found a cut off value of 7 drugs for being frail (23). We found a cutoff value as 6.5, and because this number has a fraction, we can say the use of 7 or more drugs increases the risk of frailty. Sutorius et al. compared the frailty assessment tool Groningen Frailty Indicator (GFI) with the Edmonton Frail Scale (EFS), the Frailty Index (FI), and comprehensive geriatric assessment tools. A comprehensive geriatric assessment tool PRISMA-7 performed best over two reference standards (24). Esses et al. compared the modified frailty index, risk analysis index, and Ganapathi index to predict 30-day mortality and morbidity in patients that had undergone aortic valve replacement surgery. They found that frailty was a better predictor for mortality than morbidity, and there was no significant difference among any of the three indices (25). Hirai et al. assessed the validity of three frailty evaluation tool -the Kihon Checklist (KCL), the Japanese version of the Cardiovascular Health Study, and the Study of Osteoporotic Fractures – in elderly chronic obstructive pulmonary disease patients. They found that KCL had the strongest correlations with physical, psychological, and prognostic indices (26). Henry et al. evaluated the SOF index and the Cardiovascular Health Study (CHS) index in cardiovascular surgery patients. The SOF index better identified frail patients (27). Our study compared different frailty assessment tools for being related to polypharmacy first-time. We concluded that the FFI index shows the relationship between polypharmacy and frailty better than the SOF index. In our study, we reached the conclusion that the results of the frailty assessment tests were more strongly related to the presence of polypharmacy than the comprehensive geriatric assessment tests. A previous study declared a relationship between the number of drugs used and frailty development and suggested that reducing the number of drugs used could decrease the risk for frailty (23). Polypharmacy can also cause mistakes in drug use or diminish adherence to drugs (28). Furthermore, the side effects of some drugs give rise to frailty. For example, the cholinesterase inhibitors and the osmotic cathartics can cause weight loss and muscle weakness, respectively (29).

Our study is the first study that evaluated the relationship between frailty and PIM use assessed by TIME criteria**.** We found that PIM use was also related to frailty. As in our study, Herr et al. found a significant relationship between PIM use and frailty. They evaluated PIM by according to French criteria for Potentially Inappropriate Medications. They assessed frailty by Cardiovascular Health Study criteria (9). We can think that the relationship between

PIM use and frailty syndrome is related to the relationship between polypharmacy and frailty syndrome. In the study of Herr et al., PIM was found to be effective on frailty independent of polypharmacy, and this was mostly attributed to the use of anticholinergics. In our study, 11% of those using PIM had inappropriate use of anticholinergics. However, we found that the effect of PIM use on frailty is affected by the number of medications.

We also found low Tinetti total scores in patients who were in the polypharmacy group. The relationship between postural imbalance and polypharmacy was shown by many researchers, such as Zia and colleagues (30). We thought that the relationship between polypharmacy and balance disorders might have been affected by inappropriate drug use. According to TIME criteria, neuroleptics, benzodiazepines, antiepileptics, high dose vitamin D, antimuscarinics, anticholinergics and diuretics are some drugs that increase the risk of falls (21). Geriatric depression scale scores were also positively related to polypharmacy. Leszek et al. showed the relation between polypharmacy and depressive emotional status in a previous study, too (31).

The major limitation of our study is the number of patients that evaluated. It could also be better to explain a causal relationship between used drugs and frailty syndrome.

## Conclusion

Frailty and polypharmacy are two of the common geriatric syndromes, and their incidences increase with age. Both of them impair quality of life, increases morbidity and mortality, and financial cost burden(22). Acute or chronic illnesses, inflammation, decreased food intake, decreased mobility, and mood disorders can cause frailty, and it can be a consequence of the aging process. Frailty and polypharmacy seem to be related to each other. More studies could clarify this relationship better.

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**Ethical approval:** Procedures were completed under the institutional ethical standards of the responsible committee on human experimentation and the Declaration of Helsinki(33). Gaziantep University Local Research Ethics Committee approved the study protocol. All the patients gave informed consent.

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**Conflicts of interest:** The authors have no conflicts of interest.

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