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THE RELATIONSHIP BETWEEN ANTICHOLINERGIC LOAD AND FRAILTY STATUS: A CROSS-SECTIONAL STUDY IN ELDERLY INDIVIDUALS

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Abstract

Objectives: Frailty is a significant concern in elderly individuals, and the anticholinergic effects of medications are commonly encountered in geriatric patients. This study aims to explore the relationship between anticholinergic drug burden and frailty status in people aged 65 and older.

Materials and Methods: The study included 1,058 individuals identified as "pre-frail" and "frail" according to the Fried frailty index, who visited a geriatric outpatient clinic at a tertiary reference center. All participants underwent a comprehensive geriatric assessment along with socio-demographic data. The anticholinergic load of the medications used by the participants was measured using the Anticholinergic Cognitive Burden Scale (ACB), with ACB scores of ≥2 considered indicative of a high anticholinergic load. The relationship between frailty status and high ACB burden was analyzed using multivariate analysis.

Results: The study consisted of 672 (56.8%) participants classified as "pre-frail" and 386 (32.6%) classified as "frail". Frailty was more prevalent among older individuals, females, those with lower education levels, and unmarried individuals. Additionally, frail individuals exhibited high ACB scores, multi-morbidity, cognitive impairments, and undernutrition. Multivariate analysis revealed that an ACB score of ≥2 was 2.07 times more likely to be associated with frailty (OR: 1.63, 95% CI: 1.43-2.98, $p < 0.001$).

Conclusion: A high ACB score is significantly associated with frailty compared to pre-frailty. Assessing anticholinergic drug load, a modifiable factor, should be considered as it may positively influence the management of frail patients.

Keywords: Anticholinergic load, frailty, pre-frailty, older adults.

Introduction

The elderly population is rapidly increasing, drawing attention to geriatric syndromes characterized by multifactorial causes and complex clinical symptoms.[1]Frailty," recognized as a decrease in physiological reserves and functions and an impaired ability to cope with stressors, is a geriatric syndrome that tends to increase with age. This condition represents a dynamic process marked by a series of physical, cognitive, and psychosocial changes. According to a meta-analysis by Collard et al., the incidence of frailty in individuals aged 65 and over varies widely, ranging from 4% to 59% depending on the screening tools used.[2]In Turkey, a 2020 study by Naharci et al. found this rate to be 33.1% among community-dwelling individuals.[3]

Commonly used scales to comprehensively assess the multifaceted nature of frailty include the FRAIL Scale, Fried Frailty Index, Clinical Frailty Scale, Edmonton Frail Scale, and Rockwood Frailty Index (FI). The Fried Frailty Index evaluates individuals in five areas: weight loss, decreased physical activity, exhaustion, walking speed, and hand grip strength. Based on these criteria, individuals are classified as "robust," "pre-frail," and "frail".[4]Those in the "pre-frail" stage may show early signs of physical and cognitive decline, decreased stamina, and difficulty maintaining daily activities. In the "frail" stage, these issues are more pronounced, leading to significant functional decline, serious deterioration in quality of life, increased risk of hospitalization, and even death. However, the progression to "frail" can be prevented or delayed with positive interventions for those identified in the "pre-frail" stage.[5]

Medication use is also high among elderly individuals, with almost every individual taking an average of 3 to 8 medications.[6]Anticholinergic drugs, frequently prescribed for conditions such as depression, insomnia, overactive bladder, and chronic obstructive pulmonary disease, exert their effects by inhibiting cholinergic neurotransmission in the peripheral and central nervous systems.[7]These medications can cause numerous undesirable effects, including dry mouth, constipation, blurred vision, urinary retention, cognitive impairment, and an increased risk of falls, particularly in older individuals. Drug-drug interactions and side effects tend to increase due to reduced physiological reserves with advanced age, changes in pharmacokinetic and pharmacodynamic properties, and a decline in cholinergic neurons and receptors.[8]

Many scales have been developed to measure the anticholinergic load, including the Drug Burden Index (DBI), the Anticholinergic Cognitive Burden Scale (ACB), and the Anticholinergic Risk Scale (ARS). [9,10]The ACB is a frequently used, highly practical rating system designed to measure the cumulative anticholinergic potential of a drug regimen.[9]Drugs are evaluated with a categorical scoring system ranging from 0 to 3, where a total score of 1 indicates a “low” anticholinergic effect, and a score of ≥2 indicates a “high” anticholinergic effect.[10]The higher the total score, the greater the anticholinergic effects, especially in older adults who may be more sensitive to these medications.[11]

The potential adverse effects of anticholinergic medications on the health of older adults have raised concerns, particularly regarding their association with frailty. These widely prescribed medications can disrupt the delicate balance of physiological processes in aging individuals. Various studies have investigated the potential relationship between anticholinergic load and frailty in elderly individuals.[3,12,13]Although the tools used to evaluate anticholinergic load and frailty vary, most evaluations compare "robust" and "frail" patients.[14]In 2021, a cross-sectional study by Ruiz et al. using the ACB and FI scales showed a high correlation between the presence of an ACB score of ≥1 and frailty.[12]However, there is limited data on the relationship between anticholinergic load and the "frail" and "pre-frail" groups, and no studies have been conducted directly with the ACB. A 2016 study by Jamsen et al. using the DBI and the Modified Fried Frailty Index found that each unit increase in the DBI score increased the transition from the "robust" group to the "pre-frail" group by 73%, with no significant difference between the pre-frail and frail groups.[13]

Understanding the nuances of the relationship between frailty and anticholinergic medications, which are widely used among older adults, can inform specific interventions and optimize drug therapy management. This can lead to strategies aimed at protecting the health and well-being of individuals, particularly in the transition from the "pre-frail" period to frailty. Our study aims to reveal the subtle relationship between the anticholinergic load measured by ACB and the "pre-frail" and "frail" status in elderly individuals.

Materials and Methods

Study Design and Population

This study is based on a cross-sectional cohort of adults aged 65 years and older enrolled at a tertiary care geriatric clinic. A total of 3,178 different elderly individuals visited the relevant polyclinic between August 2020 and August 2023. Of these, 1,194 patients were excluded due to acute or severe systemic disease, visual or sensorial disability, mood disorders other than depression, delirium, receiving home care services, and having no frail assessment, leaving 1,184 patients for further evaluation (Figure 1). All participants gave written informed consent for the research, and the study was approved by the Health Sciences University Ethics Committee (date and approval number: 2020/03-58).

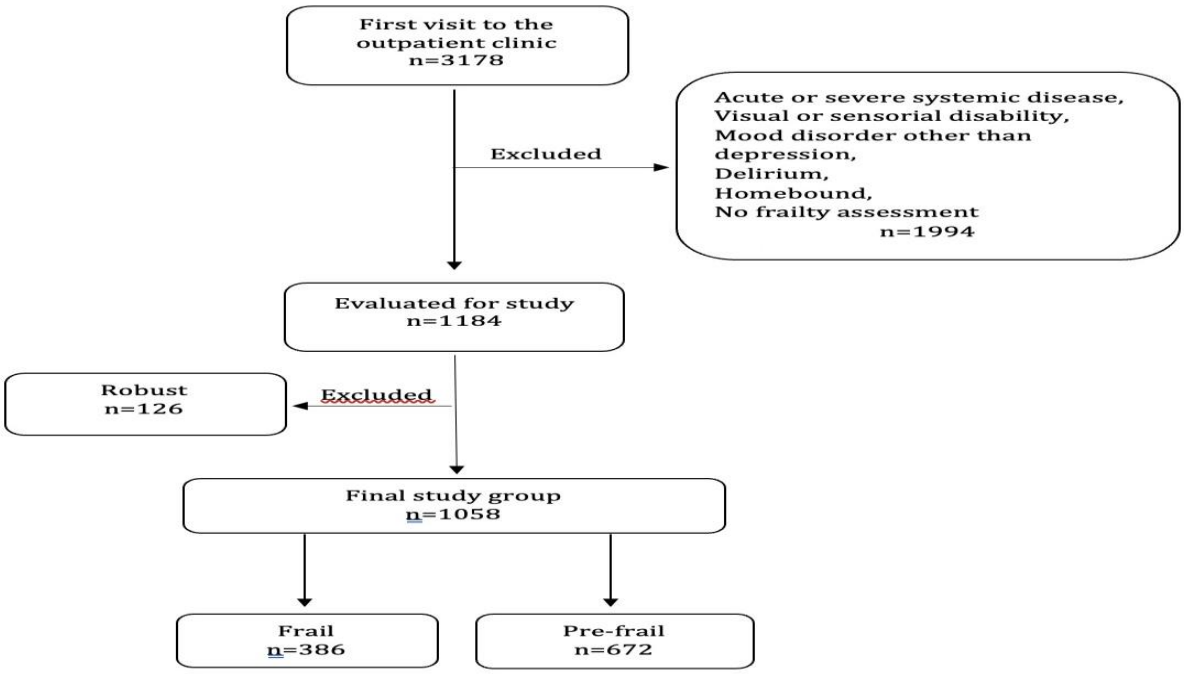

Figure 1. Flow chart of the patient selection process

Measurements

All participants underwent a comprehensive geriatric evaluation. Frailty status was determined according to the Fried Frailty Index.[4] Based on the parameters of weight loss, low handgrip strength, low walking speed, weakness, and decreased physical activity, individuals with a total score of 0 were categorized as “robust,” those with scores of 1-2 as “pre-frail,” and those with scores of ≥3 as “frail.” Of the total applications, 1,058 (89.4%) were evaluated as pre-frail and frail, and 126 individuals categorized as "robust" were excluded from the study (Figure 1). The Anticholinergic Cognitive Burden Scale (ACB) was used to assess patients' anticholinergic burden.[15] Each drug used by the participants was scored between 0 and 3 according to the scale, and the total score of all drugs was recorded.[10] Participants were further categorized into two groups: those with ACB scores of 0-1 (low) and those with ACB ≥2 (high). Nutritional status was assessed using the Mini Nutrition Assessment-Short Form (MNA-SF), with a score ≤11 defined as “malnutrition”.[16]Cognitive assessment was performed using the Mini-Mental State Examination (MMSE)with scores ≤26 indicating cognitive impairment.[17]

Socio-demographic and Medical Characteristics

Socio-demographic data collected included age, gender, marital and educational status, smoking, and alcohol use. Data on comorbidities such as diabetes, hypertension, ischemic heart disease, chronic obstructive pulmonary disease, and Parkinson's disease were obtained from patient history, interviews with relatives, and medical records. The medication history of participants was reviewed, and the number of medications was noted. Multimorbidity was defined as having 2 or more chronic diseases. [18]

Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) (IBM SPSS Inc., IL, Chicago, USA). Numerical variables were presented as absolute numbers and percentages, mean and standard deviation, or median (minimum-maximum). Continuous data were compared using the Student t-test or Mann-Whitney U test. The Kolmogorov-Smirnov test was used to determine the distribution of data. Categorical variables were expressed as percentages and compared using the chi-square test. Frailty status was selected as the dependent variable for all regression analyses. In univariate analysis, statistically significant variables ($p \leq 0.05$) such as age, gender, marital status, cognitive decline, and malnutrition were selected to create a multivariate regression model. The Hosmer-Lemeshow (H-L) test was used to assess model suitability. Odds ratios (OR) and their 95% confidence intervals (CI) were reported from the models. The Phi correlation coefficient test was used to measure the correlation between categorical variables. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 1,058 patients were included in the study, with 672 (63.5%) classified as "pre-frail" and 386 (36.5%) as "frail". The average age of the participants was 78.9 (±6.9) years, and 66.6% were women. More than half of the individuals (57.8%) were married, and 65.4% had received five years of education or less. The median number of medications used was 4, and the rate of patients with any ACB score (≥1) was 37.1%, while 14.8% had a score of 2 or more. The three most common comorbidities were hypertension, diabetes mellitus, and depression. Undernutrition was detected in 21.0% of the patients, functional impairment in 10.0%, and cognitive impairment in 35.1% (Table 1).

Comparing frailty statuses, the "frail" group had a higher average age (80.4 ±6.9 vs. 78.1±6.8), a higher proportion of females (75.1% vs. 61.8%), and a higher rate of individuals with ≤5 years of education ($p<0.001$). The proportion of unmarried individuals was higher in the "frail" group compared to the "pre-frail" group. Those with an ACB score ≥1 were also higher at 45.1% ($p<0.001$). Patients with a "high" anticholinergic load

were 22.5% in the "frail" group and 10.4% in the "pre-frail" group, a significant difference (p<0.001). All evaluated comorbidities were significantly more frequent in the "frail" group, with multi-morbidity present in 76.4% compared to 63.0% in the "pre-frail" group (p<0.001). Under-nutrition and cognitive impairment were also more common in the "frail" individuals (Table 1).

Table 1. Baseline characteristics of participants in terms of frailty states.

Parameters	**Total** (n=1058)	**Frail** (n=386)	**Prefrail** (n=672)	**p**
Age (± SD)	78.9 (±6.9)	80.4 (±6.9)	78.1 (± 6.8)	**<0.001**
Gender, female, n (%)	705 (66.6%)	290 (75.1%)	415 (61.8%)	**<0.001**
Marital status, married, n (%)	611 (57.8%)	181 (46.9%)	430 (64.0%)	**0.001**
Education level, ≤ 5 years, n (%)	692 (65.4%)	299 (77.5%)	393 (58.7%)	**<0.001**
Smoking, n (%)	55 (5.2%)	41 (6.1%)	14 (3.6%)	0.081
Alcohol, n (%)	17 (1.6%)	13 (1.9%)	4 (1.0%)	0.251
Number of drugs, median (range)	4 (3%)	5 (4%)	4 (4%)	**<0.001**
ACB, ≥1, n (%)	393 (37.1%)	174 (45.1%)	219 (32.6%)	**<0.001**
ACB, n (%)				
0-1	801 (85.2%)	299 (77.5%)	602 (89.6%)	**<0.001**
≥2	157 (14.8%)	87 (22.5%)	70 (10.4%)	**<0.001**
Comorbidities, n (%)				
Hipertension	801 (75.7%)	306 (79.3%)	495 (73.7%)	**0.040**
Diabetes mellitus	380 (35.9%)	167 (43.3%)	213 (31.7%)	**<0.001**
Coronary artery disease	284 (26.8%)	118 (30.6%)	166 (24.7%)	**0.039**
Cerebrovasular disease	67 (6.3%)	32 (8.3%)	35 (5.2%)	**0.048**
Chronic obstructive lung disease	109 (10.3%)	55 (14.2%)	54 (8.0%)	**0.02**
Depression	382 (36.1%)	180 (46.8%)	202 (30.1%)	**<0.001**
Multimorbidity, n (%)	717 (67.8%)	294 (76.4%)	423 (63.0%)	**<0.001**
MNA-SF, score, (± SD)	12.4 (1.9%)	11.7(2.1%)	12.8 (1.6%)	**<0.001**
Undernutrition, n (%)	222 (21.0%)	125 (32.8%)	97 (14.5%)	**<0.001**
MMSE, score, (± SD)	26.8 (3.1%)	25.9 (3.4%)	27.3 (2.8%)	**<0.001**
Cognitive impairment, n (%)	371 (35.1%)	198 (51.4%)	487 (72.6%)	**<0.001**

Abbreviation: ACB; anticholinergic cognitive burden, MMSE; mini-mental state examination, MNA-SF; mini nutritional assessment- short form

Multivariate regression analysis, adjusted for age, gender, educational status, marital status, multi-morbidity, under-nutrition, and cognitive impairment, revealed that having a "high" ACB score was 2.07 times associated with being "frail" (OR: 2.07, 95% CI: 1.43-2.98, p < 0.001). The Hosmer-Lemeshow (H-L) test result (Chi-square: 8.506) indicated a high model fit (p=0.386). Other parameters associated with frailty included advanced age, female gender, low education level, multi-morbidity, cognitive impairment, and undernutrition (Figure 2).

The correlation analysis results of Fried subcategories with frailty and ACB≥2 are detailed in Supplementary Table 1.

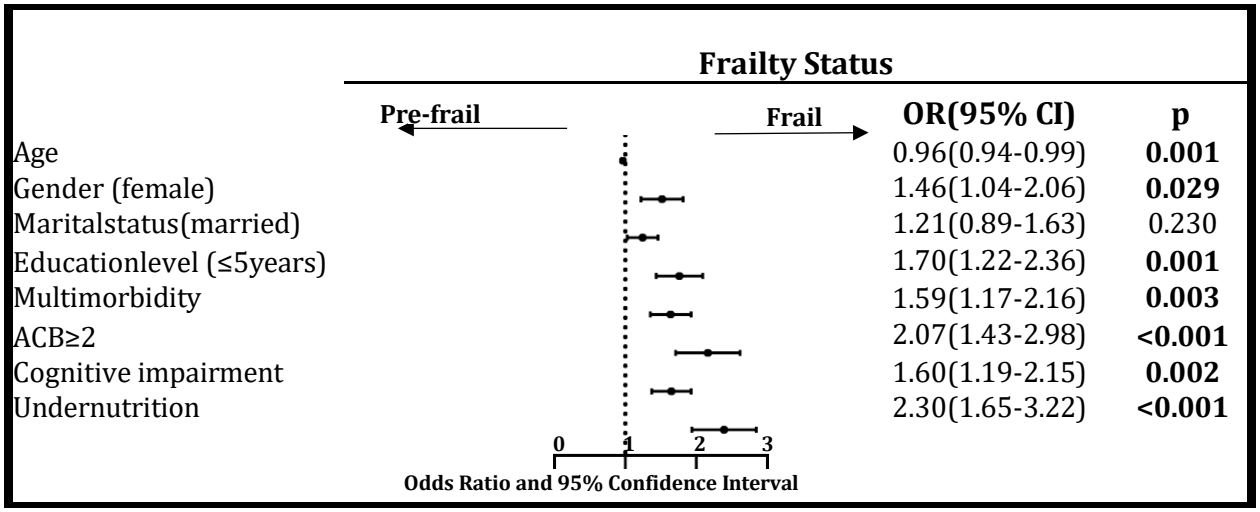

Figure 2. Forest plot of multivariate analysis of parameters related to frailty status.

Abbreviation: ACB; anticholinergic cognitive burden

Discussion

This single-center, cross-sectional study conducted at a tertiary reference center evaluates the parameters affecting frailty compared to pre-frailty. A high ACB score was independently associated with frailty by 2.07 times. Additionally, advanced age, female gender, low education level, multi-morbidity, cognitive impairment, and under-nutrition were other relevant parameters. Notably, 89.4% of the study population was pre-frail or frail, and nearly one in three individuals (37.1%) had any ACB score. This study highlights the relationship between a "high anticholinergic load" and frailty in elderly individuals.

Few studies in the literature separately evaluate the relationship between anticholinergic load and frailty/pre-frailty.[13] To our knowledge, no study compares these two groups using ACB. A study using the Drug Burden Index (DBI) showed that each unit increase in DBI score was 73% higher in the pre-frail group compared to

the healthy group, with no difference between pre-frail and frail groups.[13]This difference may be due to the relatively large number of "healthy" groups in that study and the evaluation of only male patients. Another study assessing 115 inpatients with a higher cut-off point in the ACB score (ACB >3) found that a high anticholinergic load was 2.21 times more associated with frailty compared to the "healthy" group.[19]Ruiz et al. conducted a study among 17,084 male participants, finding that any ACB burden was associated with 4.78 times greater frailty. In our study, an ACB score of 2 or more was 2.07 times more associated with frailty. Our study is significant as it focuses on comparing frail individuals with pre-frail individuals according to ACB score, potentially guiding further studies on this topic.

Other parameters associated with pre-frail and frail states have been evaluated in previous studies, yielding results consistent with our findings. Older age, female gender, and lower education level are more associated with frailty compared to pre-frailty.[20-23]In addition to these immutable factors, modifiable geriatric syndromes such asmalnutrition[20-22,24], and cognitive impairment [20,21,23]are more frequently observed in frail individuals, aligning with our study. While these parameters' association with frailty is expected, identifying the relationship between modifiable factors and frailty can help prevent frailty by improving these conditions, particularly in pre-frail individuals.

The prevalence of frailty and pre-frailty varies depending on the group studied and evaluation methods. In our study, pre-frail or frail individuals constituted 89.4% of the total patients applying to the outpatient clinic. Studies using similar frailty tools support our findings. [21,23] Population screening studies report lower rates, but frail and pre-frail individuals still make up more than half of the population.[20,22] It is important to remember that frailty is a dynamic process. A systematic review and meta-analysis by Kojima et al. showed that 25% of pre-frail patients and only 3% of frail patients returned to 'healthy'.[25]Comparing pre-frail and frail individuals, as we did in our study, can contribute to understanding this dynamic process. Furthermore, nearly one in three patients in our study population had an ACB score, supported by similar studies.[26,27] Both frailty and ACB presence are common problems in the elderly population, making their assessment crucial in geriatric patient evaluations.

Our study has several strengths and limitations. A key strength is the detailed examination of pre-frail and frail groups, which are common in the geriatric population but have different prognoses. Most previous studies found that the parameters distinguishing these two conditions are immutable factors. However, anticholinergic load is particularly important as it is easily modifiable, allowing quick intervention and results. Another advantage is the easy application of the ACB measurement method, facilitating the study's practical application in daily practice. The study's limitations include being single-center and cross-sectional, which limits generalizability. Despite a comprehensive evaluation, there may be variables not examined in this study.

In conclusion, this study showed that a high anticholinergic drug burden in elderly individuals is significantly associated with frailty compared to pre-frail. Understanding the nuances of the relationship between anticholinergic load and frailty levels can optimize drug therapy management and contribute to early strategies in the progression from pre-frail to frail. A larger sample and prospective studies are needed to strengthen our findings on this subject.

Ethical Considerations: The study was approved by the Health Sciences University Ethics Committee (date and approval number: 2020/03-58).

Conflict of Interest: The authors declare no conflict of interest.

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