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RESEARCH ARTICLE

COGNITIVE FRAILTY AND DRUG BURDEN IN NEAR-CENTENARIANS (95 YEARS AND OLDER ADULTS)

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ABSTRACT

Purpose: Cognitive frailty is an emerging concept in geriatric medicine, defined by the coexistence of cognitive impairment and physical frailty without dementia. We planned to investigate the relationship between cognitive frailty and drug burden in individuals aged 95 years and older.
Materials and Methods: This retrospective cross-sectional study included 193 individuals aged ≥95 years receiving care at geriatric outpatient clinics or residential facilities in Turkey. Data on cognitive status, comorbidities, and regular medication use were obtained from medical records. Cognitive frailty was identified based on documented as cooccurrence of physical frailty and cognitive impairment.
Results: Among the participants, 45.1% were identified as cognitively frail. The cognitive frailty group exhibited a significantly lower mean MMSE score (19.8 ± 3.7) in comparison to the control group (24.7 ± 3.1, $p < 0.001$). The mean number of medications was higher among cognitive frailty participants (6.3 ± 2.1) than those without cognitive frailty (4.1 ± 1.8, $p < 0.01$). After adjusting for all variables, increased age (OR: 1.11, 95% CI: 1.03–1.20, $p = 0.006$), higher number of comorbidities (OR: 1.23, 95% CI: 1.05–1.45, $p = 0.014$), and greater number of medications (OR: 1.36, 95% CI: 1.14–1.64, $p = 0.001$) were significantly associated with increased cognitive frailty.
Conclusion: Cognitive frailty is independently associated with a higher drug burden in individuals aged 95 and older. Integrating cognitive and frailty assessments into routine geriatric evaluations may help mitigate the risks of polypharmacy in this vulnerable population.

Keywords: Cognitive frailty, Drug burden, Older adults, Polypharmacy

INTRODUCTION

With the increasing aging population in Turkey and globally, healthcare systems are facing new challenges in managing the complex health profiles of the very old, particularly those aged 95 years and above (1, 2). Among this age group, cognitive frailty—a multidimensional clinical syndrome characterized by the coexistence of cognitive impairment and physical frailty in the absence of dementia—has gained prominence as a critical indicator of vulnerability in geriatric populations (3). Cognitive frailty has been linked to higher risks of falls, disability, hospitalization, and mortality, and has important implications for quality of life and healthcare planning (4, 5).

In the context of aging populations, polypharmacy or drug burden has been frequently reported, particularly in those with multimorbidity and frailty (6, 7). Excessive medication burden in the elderly is associated with increased risk of adverse drug

reactions, medication nonadherence, cognitive decline, and iatrogenic complications (8). While the relationship between cognitive impairment and polypharmacy has been explored in various age groups, data on individuals aged 95 years and older are scarce. Given the physiological and cognitive frailty of this group, even small deviations in medication management or cognitive function may lead to significant clinical consequences (9, 10).

Previous research in Turkish older adults has highlighted the interplay between cognitive frailty, physical frailty, and malnutrition, underlining the multifactorial nature of geriatric vulnerability (11). Current literature appears to lack empirical research examining the potential relationship between cognitive frailty and drug burden among Turkey's oldest-old individuals. To address a gap in the literature, this study examines the association between cognitive frailty and drug burden in adults aged 95 years and over. We hypothesize that those diagnosed with cognitive frailty are more likely to be exposed to drug burden compared to their cognitively robust counterparts.

MATERIALS AND METHODS

This cross-sectional, retrospective observational study was conducted between January 2023 and December 2024 in YASAM and geriatric center in Balıkesir (1, 2). Eligible participants were individuals aged 95 years or older, of any gender, who were under regular follow-up at a geriatric outpatient clinic or integrated home-based care (YASAM) center. Inclusion criteria were defined as follows: Individuals aged 95 years or older, A Mini-Mental State Examination (MMSE) score of 18 or higher, and the ability to ambulate independently. All individuals who met these criteria during the study period were included.

Patients under the age of 95 and under; clinical diagnosis of dementia or severe cognitive impairment (MMSE score <18); acute illness or hospitalization within the previous month; terminal illness; and inability to participate in physical or cognitive assessments due to severe sensory or motor deficits were excluded from the analysis.

Ethical approval for this study was obtained from Balıkesir Atatürk City Hospital Scientific Research Ethics Committee (Date:26.12.2024, Decision No: 2024/12/80). The research was carried out in accordance with the ethical standards outlined in the Declaration of Helsinki. Since anonymized retrospective data were used, the IRB waived the requirement for informed consent.

Data were obtained retrospectively from electronic medical records. Demographic variables including age, gender, and comorbidities were recorded. Medication data included the number of regular medications taken daily for at least one month (12).

A comprehensive geriatric assessment was conducted, encompassing various parameters such as the the Katz Activities of Daily Living (ADL) and Lawton-Brody Instrumental Activities of Daily Living (IADL) scales (13, 14). The nutritional status of the subjects was assessed using the Mini Nutrition Assessment–Short Form (MNA-SF) (15). This examination encompasses factors such as food intake, weight loss, mobility, mental stress, and body mass index. The PHQ-2 questionnaire was utilised in order to evaluate the presence or absence (frequency) of depressed mood and anhedonia (16). Cognitive function was evaluated using the Mini-Mental State Examination (MMSE), a validated instrument frequently applied in both clinical practice and research to assess global cognition (17). Cognitive impairment was defined as an MMSE score between 18 and 23, in the absence of a clinical diagnosis of dementia. The Fried's Frailty Scale was utilised to measure frailty (18). The components of frailty are categorised as follows: weakness, slowness, low level of physical activity, exhaustion, and weight loss (19). The term "cognitive frailty" was defined as the cooccurrence of physical frailty and cognitive impairment (20).

Statical analysis

To summarize the demographic and clinical characteristics of the study, descriptive statistics such as means, standard deviations, frequencies, and percentages were calculated. Furthermore, multivariate regression analyses were conducted where appropriate to adjust for potential confounding factors, including age, sex, number of comorbidities, Katz and Lawton functional scores, PHQ-2 score, MNA score, and number of medications. All statistical analyses were performed utilizing IBM SPSS Statistics for Windows, version 26.0. The threshold for statistical significance was set at a two-tailed p-value below 0.05.

RESULTS

A total of 193 participants aged 95 years and older were included in the study. The mean age of the

Table 1. Demographic and clinical characteristics of participants

Variable	Total (n = 193)	Cognitive Frailty (n = 87)	Control group (n = 106)	p-value	Total (n = 193)
Age, mean ± SD (years)	97.1 ± 2.4	97.8 ± 2.1	96.5 ± 2.5	**0.01**	97.1 ± 2.4
Female, n (%)	121 (62.5%)	57 (65.5%)	64 (60.4%)	0.48	121 (62.5%)
Number of comorbidities	2.7 ± 1.1	3.2 ± 1.1	2.1 ± 1.0	**0.02**	2.7 ± 1.1
Number of medications	5.2 ± 2.4	6.3 ± 2.1	4.1 ± 1.8	**<0.01**	5.2 ± 2.4
Katz Index	4.1 ± 1.8	3.0 ± 1.6	5.2 ± 1.4	**<0.001**	4.1 ± 1.8
Lawton IADL	3.3 ± 2.1	1.9 ± 1.2	4.6 ± 2.0	**<0.001**	3.3 ± 2.1
MNA score	8.7 ± 2.5	7.1 ± 1.9	10.4 ± 2.1	**<0.01**	8.7 ± 2.5
PHQ-2	1.3 ± 0.9	1.4 ± 1.0	1.2 ± 0.9	0.20	1.3 ± 0.9

**Bold value was statistically significant.*

Table 2. Logistic regression analysis of factors associated with cognitive frailty

Variable	OR	95% CI	p-value
Age	1.11	1.03 – 1.20	**0.006**
Female sex	1.08	0.61 – 1.91	0.78
Comorbidities	1.23	1.05 – 1.45	**0.014**
Katz score	0.75	0.63 – 0.89	**0.001**
Lawton score	0.82	0.70 – 0.96	**0.017**
PHQ-2 score	1.09	0.83 – 1.42	0.53
MNA score	0.81	0.70 – 0.94	**0.005**
Medication count	1.36	1.14 – 1.64	**0.001**

**Bold value was statistically significant.*

participants was 97.1 ± 2.4 years, and 62.5% were female. A total of 87 individuals (45.1%) were identified as having cognitive frailty, characterized by an MMSE score less than 24.

The cognitive frailty group had a significantly lower MMSE score (19.8 ± 3.7) compared to the control group (24.7 ± 3.1, $p < 0.001$). The mean number of medications was higher among cognitive frailty participants (6.3 ± 2.1) than those without cognitive frailty (4.1 ± 1.8, $p < 0.01$). The cognitive frailty group also had a higher mean number of comorbidities (3.2 ± 1.1 vs. 2.1 ± 1.0, $p = 0.02$) and lower functional scores on both the Katz Index (3.0 ± 1.6 vs. 5.2 ± 1.4, $p < 0.001$) and Lawton Scale (1.9 ± 1.2 vs. 4.6 ± 2.0, $p < 0.001$). Nutritional status, assessed by MNA, was significantly poorer in the cognitive frailty group (7.1 ± 1.9 vs. 10.4 ± 2.1, $p < 0.01$).

To evaluate the independent predictors of cognitive frailty (MMSE score < 24) among the oldest-old population (≥95 years), a multivariate logistic regression analysis was performed. The model included age, sex, number of comorbidities, Katz and Lawton functional scores, PHQ-2 score, MNA score, and number of medications. After adjusting for all variables, increased age (OR: 1.11, 95% CI: 1.03–1.20, $p = 0.006$), higher number of comorbidities (OR: 1.23, 95% CI: 1.05–1.45, $p = 0.014$), and greater number of medications (OR: 1.36, 95% CI: 1.14–1.64, $p = 0.001$) were significantly associated with increased odds of cognitive frailty. Conversely, better functional status measured by Katz (OR: 0.75, 95% CI: 0.63–0.89, $p = 0.001$) and Lawton scores (OR: 0.82, 95% CI: 0.70–0.96, $p = 0.017$), as well as higher nutritional status (MNA score) (OR: 0.81, 95% CI: 0.70–0.94, $p = 0.005$), were independently associated with lower odds of cognitive frailty. Gender and depressive symptoms (PHQ-2) were not found to be significant in the model.

DISCUSSION

In this study, we investigated the association between cognitive frailty and drug burden among individuals aged 95 years and older in a Turkish geriatric population. Our findings indicate that cognitive frailty is significantly associated with a higher drug burden. Adjusted for age, sex, and comorbidities, cognitive frailty still demonstrated a significant independent association with drug burden.

These results are consistent with previous research highlighting the interplay between cognitive and physical vulnerability in older adults (21, 22). In addition in Turkish older individuals demonstrated a strong relationship between cognitive frailty, malnutrition, and increased clinical complexity (11). Our study extends these findings by focusing specifically on the "oldest-old" group, a population that remains underrepresented in geriatric research. The higher drug burden in this research may reflect increased multimorbidity, but also suggests potential gaps in medication review practices in cognitive frailty individuals.

The relationship between drug burden and both cognitive impairment and frailty warrants careful consideration. The observed negative correlation between MMSE scores and the number of medications further supports the notion that lower cognitive performance is linked to increased medication burden (23, 24). Several mechanisms may explain this association, including reduced self-management abilities, increased dependence on caregivers, and fragmented care across specialties (25-27). Furthermore, polypharmacy itself has been implicated in contributing to cognitive decline, creating a potentially harmful bidirectional relationship (28, 29). Moreover, drug burden may promote or exacerbate frailty through complex pathophysiological pathways, such as drug–drug interactions, cumulative adverse effects, altered pharmacokinetics in older adults, and medication-induced nutritional deficiencies (26, 30). These interrelated processes highlight the need for integrated medication management strategies in cognitively and physically vulnerable populations.

This study has several strengths, including its focus on an extremely old age group and the use of real-world clinical data. However, certain limitations must be acknowledged. First, the retrospective design limits causal inferences. Second, cognitive frailty diagnosis was based on available medical records rather than standardized prospective assessments. Third, the cross-sectional nature of the data precludes examination of temporal relationships or outcomes such as hospitalization or mortality.

Despite these limitations, our findings have important clinical implications. Routine assessment of cognitive frailty and regular medication reviews may help identify individuals at high risk for inappropriate polypharmacy. Integrating cognitive status into medication management decisions could improve safety and outcomes in the oldest-old population (31). Prospective studies are warranted to validate these findings and to investigate intervention approaches addressing both cognitive decline and medication-related risks in oldest old populations.

CONCLUSION

Among individuals aged 95 years and above, cognitive frailty demonstrates a significant association with higher drug burden. This link persists even after controlling for variables such as age, sex, and existing comorbid conditions, indicating that cognitive frailty independently contributes to the increased medication burden observed in the oldest-old population. These results emphasize the critical need to integrate cognitive screening into standard geriatric assessments and pharmacological reviews. Early detection and targeted management of cognitive frailty may play a vital role in minimizing inappropriate drug burden and its related adverse effects, thereby enhancing both clinical outcomes and quality of life for this particularly vulnerable age group.

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Conflict of interests: The authors declare that they have no conflict of interest.

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