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Cognitive Frailty: Frequency and Risk of Adverse Events in Older Individuals

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ABSTRACT

Objectives: To analyze the associated cognitive frailty with falls and clinical admissions in older patients.

Methods: Case-control, analytical, individual-based, observational study based on longitudinal retrospective design. The sample comprised patients older than 65 years old, treated at the outpatient clinic of a geriatric service, who were followed up in the previous period of six months. Cognitive frailty (CF) was used as a dependent variable in the present study. Cognitive impairment was diagnosed based on Clinical Dementia Rating. Frailty was categorized based on the clinical frailty scale. The Chi-square test and Poisson regression model were used to evaluate the association between CF and outcomes.

Results: One hundred and forty-six patients, at a mean age of 81±6 years, were assessed; 69.2% of them were women. Patients with CF presented a higher risk of falls than the control population (p=0.004). However, after the adjusted analysis application, this condition was no longer associated with falls (p=0.32) and hospitalizations (p=0.59).

Conclusion: Patients with CF presented a higher risk of falls than the control population; however, this condition was not associated with hospitalization. These findings confirm the importance of strategies focused on preventing accidents due to falls, which could increase patients' functional dependence on others.

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Introduction

Population aging is a reality worldwide. According to estimates, 25.5% of the Brazilian population will be older than 65 years by 2060 [1]. This process is associated with the emergence of age-related diseases and disabilities, with personal, social, and economic implications.

Dementia and frailty are often observed in individuals older than 75 years; these two conditions are closely related to each other [2]. Recent studies have suggested an association between these conditions and common physiological mechanisms such as chronic inflammation, impaired hypothalamic-pituitary axis stress response, imbalanced energy metabolism, mitochondrial dysfunction, oxidative stress, and neuroendocrine dysfunction [3,4].

The coexistence of physical frailty and cognitive impairment in patients who do not have dementia syndromes was defined as cognitive frailty by the International Academy of Nutrition and Aging (I.A.N.A.) and by the International Association of Gerontology and Geriatrics (I.A.G.G.) [5].

Population-based studies have estimated that the global prevalence of this syndrome ranges from 1% to 4.4% however, according to clinical-based studies, this condition presents a higher prevalence, ranging from 10.7% to 22% [1]. Concomitance between cognitive impairment and frailty reached 10.9% and 13.2% in two different studies conducted in Brazil [6,7].

Cognitive frailty has been associated with increased adverse outcomes in comparison to frailty syndromes and cognitive impairment, in separate. Among other outcomes, patients present reduced quality of life and functionality, as well as an increased number of hospitalizations, institutionalizations, falls and all cause mortality rates [8-12].

Based on a cross-sectional study, patients in the cognitive frailty group recorded significantly higher (48%) incidence of falls than patients in the robust (21%), physical frailty (34.5%), and cognitive impairment (22.2%) groups [10]. Longitudinal study and review have indicated that hospitalization does not correlate to cognitive frailty, but to physical frailty [2,13]. However, another recent meta-analysis has shown that cognitive frailty is a risk factor for all-cause hospitalization events [12].

Despite the growing interest in investigating the association between cognition and frailty, it is necessary to conduct further studies on this topic in developing countries. Therefore, the aim of the current study was to associate cognitive frailty with falls and hospitalizations in older patients followed up at a university geriatric outpatient service.

Method

An analytical, case-control, individual-based, observational study based on the longitudinal retrospective design was carried out with patients with cognitive frailty (case group) and with individuals without cognitive frailty (control group). Participants were paired by age group, sex, weight, and schooling. The sample comprised patients older than 65 years old, treated at the outpatient clinic of a geriatric service of Santa Casa de Misericordia de Vitória philanthropic university hospital, Vitória City - ES, from August 2019 to February 2020, who were followed up in the previous period of six months. Participants who read and signed the informed consent form were included in the study. Patients with dementia of any etiology, with Parkinson's disease, or those who were taking benzodiazepines, antidepressants, and neuroleptics were excluded from the study.

The sample size was calculated by taking into consideration the approximate cognitive frailty rate of 22% recorded in a longitudinal study carried out in France with approximately 300 patients with the neurocognitive disorder who were treated per semester, based on a sample error of 80% (type II error) at 5% significance level (type I error) and 95% confidence level [14]. Calculation results have shown that the approximate sample size in the current study should comprise 141 individuals (case/control) - in total, 146 patients were herein assessed.

Cognitive frailty was used as the dependent variable. Diagnostic criteria for this condition comprised simultaneous incidence of physical frailty and cognitive impairment diagnosed based on a Clinical Dementia Rating (CDR) scale of 0.5, without a concurrent diagnosis of Alzheimer's disease or of other dementia types [5,15].

Rockwood's clinical frailty scale - which addresses several patient-related domains and classifies patients into very fit, fit, managing well, living with very mild frailty, living with mild frailty, living with moderate frailty, living with severe frailty, living with very severe frailty and terminally ill – was used to assess frailty in the investigated population [16]. It was considered frail for those living with very mild frailty, living with mild frailty, living with moderate frailty, living with severe frailty, living with very severe frailty, and terminally ill. The aforementioned scale was included in the comprehensive geriatric evaluation routine of the investigated service. Patients' frailty status was rated by the assistant doctor.

Age, sex, body mass index, marital status (single/divorced, married and widowed), schooling (literate, or not), independence for activities of daily living (Katz scale), functionality for the instrumental activity of daily living (Lawton & Brody scale), diagnosed comorbidities under clinical follow-up (systemic arterial hypertension, diabetes mellitus, congestive heart failure, and osteoporosis), blood pressure measured during medical consultation and routine laboratory tests of the service (blood glucose, vitamin B12, vitamin D, total cholesterol, triglycerides, creatinine, and blood count) were the herein analyzed covariables [17,18].

Mini-Mental State Examination (MMSE) was used for cognitive tracking purposes. Its total score reaches 30 points, and it is stratified by schooling, as follows: illiterate individuals ($\geq$ 20 points); individuals with 1 to 4 years of schooling ($\geq$ 25 points); 5 to 8 years of schooling ($\geq$ 26 points); 9 to 11 years of schooling ($\geq$ 28 points); and more than 11 years of schooling ($\geq$ 29 points) [19].

Lawton & Brody's scale was used to evaluate instrumental activities of daily living; its maximum score reaches 27 points, which corresponds to the highest independence level, whereas the minimum score is 9 points, and it corresponds to the highest dependence level [18]. Lawton and Brody's scale are a reliable instrument used to assess individuals' functional ability to perform instrumental activities of daily living in Brazil [20].

Katz scale comprises six items used to measure individuals' performance in self-care activities [17]. The Portuguese version of the Katz scale of independence in activities of daily living was thoroughly developed and tested [21]. It was considered equivalent to the original version in English. Patients were herein classified into three categories, namely: 0 to 2 compromised domains, 3 and 4 compromised domains, and 5 and 6 compromised domains.

Outcomes corresponded to medical records of at least one fall event in the previous six months and hospitalization in the same period.

Continuous variables were expressed as the mean, standard deviation of the mean, and variability; whereas categorical variables were expressed in percentage (absent or present). A parametric or nonparametric test was used to compare means or medians after the evaluation of continuous sample distribution based on the Kolmogorov-Smirnov test - values $p \leq 0.05$ rejected the null hypothesis of normality. Chi-square and continuous Student t or Mann-Whitney U tests - for parametric and nonparametric data, respectively - were used to compare categorical variables. Independent variables presenting a significance level of $p \leq 0.20$ in the bivariate statistical analysis were included in the Poisson Regression model with robust variance in order to assess the association between the dependent variable and the outcomes, at 95% confidence interval.

$P \leq 0.05$ was considered significant. The Statistical Package for the Social Sciences (SPSS) 27 software, licensed to the EMESCAM (Series: 10101141221) (Escola Superior de Ciências da Santa Casa de Misericordia, Vitória, Brazil), was used to analyze the collected data. The research project was approved by the Research Ethics Committee of the School of Sciences of Santa Casa de Misericordia de Vitória, under number 3.225.605.

Results

One hundred and forty-six patients, at mean age 81±6 (66-98) years, were included in the study; 30.1% (n=44) of them were men and 69.2% (n=102) were women, 57% (n=73) were illiterate and 91.78% (n=134) presented functional independence to perform basic activities of daily living - MMSE reached 21±4. Sample comprised 83 individuals (56.8%) in the control group and 63 individuals (43.2%) with cognitive frailty. Demographic features, blood pressure, comorbidities and laboratory tests of each group are shown in Table 1.

Table 1: Sample Presentation

	Total (n = 146)	Control Group (n = 83)	Cognitive Frailty (n = 63)	p
Age (Years)*	81±6	81±6	82±6	0,26
Sex * Male Female	 30,1% (n = 44) 69,9% (n = 102)	 33,7% (n = 28) 56,3% (n = 55)	 25,4% (n = 16) 74,6% (n = 47)	0,36
Marital status* Single/divorced Married Widowed	 8,2% (n = 12) 56,8% (n = 83) 34,9% (n = 51)	 8,4% (n = 7) 54,2% (n = 45) 37,3% (n = 31)	 7,9% (n = 5) 60,3% (n = 38) 31,7% (n = 31)	0,73
Schooling * Illiterate literate	 57% (n = 73) 43% (n = 55)	 63,1% (n = 41) 36,9% (n = 24)	 50,8% (n = 32) 49,3% (n = 31)	0,21
BMI (Kg/m ^{2})	26 ± 5	27 ± 6	23 ± 5	0,23
Weight (kg	65 ± 1	66 ± 15	63 ± 15	0,26
Hypertension*	83,6% (n =122)	79,5% (n = 66)	90,5% (n = 57)	0,10
Diabetes mellitus *	38,4% (n = 56)	38,6% (n = 32)	38,1% (n = 24)	0,54
Heart failure *	8,9% (n = 13)	8,4% (n = 7)	9,5% (n = 6)	0,57
Osteoporosis*	17,1% (n = 25)	13,3% (n = 11)	22,2% (n = 14)	0,18
SBP (mmHg)**	129 ± 19	130 ± 20	127 ± 6	0,90
DBP (mmHg)**	77 ± 9	78 ± 10	76 ± 8	0,74
Total Cholesterol (mg/dL)*	176 ± 44	176 ± 40	176 ± 49	0,95
Glucose (mg/dL)**	109 ± 29	110 ± 30	109 ± 28	0,80
Triglycerides (mg/dL)**	113 ± 46	116 ±48	107 ± 42	0,41
Vitamin D (mg/dl)*	27 ± 8	27 ± 9	28 ± 8	0,75
Vitamin B12 (mg/dl)**	528 ± 1026	632 ± 1617	404 ± 256	0,89
Hemoglobin (g/dl) *	12,6 ± 2,01	12,7 ± 2,4	12,4 ± 1,2	0,27
Creatinine (mg/dl)*	1,09 ± 0,29	1,10 ± 0,31	1,08 ± 0,26	0,60

*Student's t test **Mann-Whitney U test (non-parametric by the KS test) ***Chi-square test. BMI, body mass index; MMSE, mini mental state exam; SBP, systolic blood pressure; DBP, diastolic blood pressure; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; p, test significance.

The group with cognitive frailty was more dependent on others to perform instrumental activities of daily living than the control group ($p < 0.001$), as shown in Table 2. There was not significant difference in individuals' dependence to perform basic activities of daily living between groups (p=0.06).

Table 2: Functional Evaluation

	Total (n = 146)	Control group (n = 83)	Cognitive frailty (n = 63)	p
KATZ Scale* 0-2 domains 3-4 domains 5-6 domains	 91,8% (n = 134) 2,7% (n = 4) 5,5% (n = 8)	 96,4% (n = 80) 1,2% (n = 1) 2,4% (n = 2)	 85,7% (n = 54) 4,8% (n = 3) 9,5% (n = 6)	0,06
Lawton Scale**	16,9±5,5	18,50±5,31	15,17±5,36	< 0,001
MMSE***	21±4	22±4	2-±13	0,16

Chi-square test; **Mann-Whitney U test (non-parametric by the KS test); ***Student's t test; Katz scale, basic activities of daily living (0-2 domains: independence; 3-4 domains, partial dependence; 5-6 domains, dependence); MMSE, mini mental state examination; p, test significance

Cognitive frailty was significantly associated with fall events (p=0.002); however, it was not associated with hospitalization (p=0.73) (Table 3). Nevertheless, this association did not persist when Poisson Regression without adjustment and adjusted prevalence ratio for Katz scale, Lawton scale, hypertension and osteoporosis (p = 0.32) was applied (Table 4).

Table 3: Outcomes

	Total (n = 146)	Control Group (n = 83)	Cognitive frailty (n = 63)	p
Hospitalizations in six previous months	11,6% (n = 17)	10,8% (n = 9)	12,7% (n = 8)	0,79
Falls in in six previous months	17,8% (n = 26)	9,6% (n = 8)	28,6% (n = 18)	

Chi-square test, p, test significance.

Table 4: Unadjusted and Adjusted Prevalence Ratio for Katz Scale, Lawton Scale, Hypertension and Osteoporosis used to Associate Cognitive Frailty with Outcomes

	Unadjusted OR (95% CI)	Adjusted PR (95% CI)
Hospitalization in the previous six months	1.04 (0.81-1.34) p = 0.73	0.91 (0.67-1.25) p = 0.59
Falls in the previous six months	1.37 (1.12-1.67) p = 0.002	1.16 (0.87-1.46) p = 0.32

Poisson Regression without Adjustment and Adjusted for Lawton scale, Katz scale, Hypertension and Osteoporosis: PR, Prevalence Ratio; (95% CI), 95% Confidence Interval; p, Statistical Significance.

Frailty status of the total sample, control, and cognitive frailty groups are shown in Figure 1.

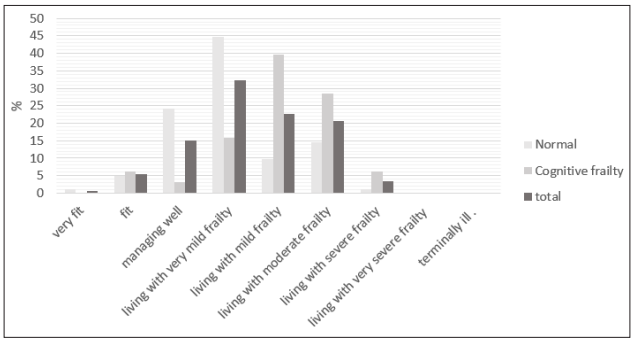

Figure 1: Rockwood's Clinical Frailty Scale: Control, Cognitive Frailty and Total Sample (χ^2 243.148; p < 0,001).

Discussion

Patients with cognitive frailty presented a higher risk of falling than the control group; however, this association was not reported after the analysis was adjusted for Katz score, Lawton score, osteoporosis, and hypertension. Study conducted with the population living in the metropolitan region of Tokyo (Japan) has shown that history of fall events was significantly associated with cognitive frailty; moreover, the incidence of falls in this group was even higher than disability to perform instrumental activities of daily living [10]. This outcome strongly suggests that fall events might be a more serious concern [10,22]. Another Japanese study has shown that cognitive frailty was associated with fall events, as well as with fall-related fractures [8].

Cognitive frailty was not associated with hospitalization. Nevertheless, some studies have shown that this condition is a risk factor for all-cause hospitalization, as well as increases accumulated hospitalization time [12]. A study conducted with an older Chinese population living in Chicago has shown that patients with cognitive frailty were not just likely to undergo more hospitalizations, but they were also more than twice as likely to present one, or more, visits to the emergency department than those without cognitive and physical frailty [23].

Lower ability to perform instrumental activities may have contributed to the larger number of fall events in the cognitive frailty group. This group presented lesser functional independence and lower cognitive function, so it was more susceptible to presenting a reduced ability to predict the risk of daily accidents.

Patients with cognitive frailty presented a lower ability to perform complex activities of daily living. This outcome suggested greater cognitive dependence, although without influence on basic activities, in comparison to the control group. Rockwood and Theou have shown that dementia level often corresponds to physical frailty level. Thus, impaired ability to perform instrumental activities was observed in individuals with cognitive frailty. However, this outcome was not observed for basic activities of daily living, which can be explained by the fact that most patients had mild-to-moderate physical frailty [16].

With respect to functionality, a Malaysian cross-sectional study conducted with 815 patients suggested that a one-point reduction in the Katz scale has increased the risk of cognitive frailty by 2% [9]. Another cross-sectional population-based study has shown that this group had a higher risk of presenting limitations to performing instrumental activities of daily living and dependence [11].

Laboratory test results (glucose, cobalamin, vitamin D, total cholesterol, triglycerides, creatinine, and hematology markers) did not show significant differences between groups. Nevertheless, neuroinflammatory, nutritional, endocrine, cardiovascular, and hematology markers may suggest changes to the cellular immune system and hypothalamic-pituitary-adrenal axis, as well as increased risk of cognitive impairment, frailty, and death [3,4]. Besides, cobalamin is associated with cognitive functions through homocysteine metabolism and methylation reactions; however, the effects of subclinical levels on individuals' cognition remain uncertain [24].

The cognitive frailty group recorded higher comorbidity, hypertension, heart failure, and osteoporosis rates than the control group, although without a statistically significant difference. Clegg et al, have shown that increased frailty was associated with a faster decline rate in several systems, even with cognitive decline [25].

Interventions such as chronic disease control (i.e., dyslipidemia, diabetes, and hypertension), fall prevention, smoking cessation, as well as engaging in an active and socially integrated lifestyle, exercising, and a healthy diet can delay cognitive frailty progression to dementia and prevent adverse events, such as disability, hospitalization, and death [2]. Thus, it is worth adopting an exercising routine and getting nutritional support, since these two aspects may account for reducing the influence of the pathology-disease ratio [26,27]. Accordingly, physical frailty precedes cognitive deficit in some cognitive frailty presentations; therefore, interventions aimed at improving cognitive frailty can avoid the development of cognitive disorders in the long term [2,25].

A recent systematic review has shown that performing dual-task exercises (combining physical activities and cognitive training) has significantly improved individuals' cognitive functions, memory, and functional status [28]. However, other studies have compared multicomponent and dual-task exercises and concluded that both exercise types were effective in improving individuals' physical and gait performance, although without the superiority of the second modality [29].

The current study has some limitations. It was a retrospective study conducted in a single service; therefore, causality became compromised. In addition, data were collected from medical records, which are susceptible to memory bias. Thus, it is necessary to conduct better-designed studies aimed at finding a better definition of cognitive frailty, as well as the means to enable the early prevention of adverse outcomes.

Conclusions

Patients with cognitive frailty presented a higher risk of falling than the control group; however, this association was not observed after adjustments based on Katz score, Lawton score, osteoporosis, and hypertension. Cognitive frailty was not associated with hospitalization. The cognitive frailty group has shown a lower ability to perform complex activities of daily living, a fact that suggested stronger cognitive dependence. These findings have confirmed the importance of developing strategies to prevent accidents due to falls, which could worsen individuals' functional dependence.

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