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Cognitive frailty is associated with elevated pro-inflammatory markers and a higher risk of mortality

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Abstract

Background: Cognitive impairment and physical frailty are common among older adults and associated with a higher likelihood of adverse health outcomes. These two conditions frequently co-exist in the same individual as cognitive frailty, yet few studies have examined the impact of such comorbidity on clinical outcomes or underlying biological mechanisms.

Methods: A total of 1,340 older adults (age ≥ 60 years old) from the Bambui Cohort Study of Ageing, with a total follow-up of 10 years, were included in this study. Frailty was defined by the accumulation of deficit framework and cognitive impairment based on scores on the MMSE < 22. In addition, serum IL-6 levels were measured by cytometric bead array assay.

Authors' contribution: BSD was responsible for the study hypothesis, data analyses, draft of the manuscript. MFLC, SVP, JOAF were responsible for the overall study design, data collection, and draft of the manuscript. KCLT, OAMF, ATC were resposible for the study design, biomarkers analyses, and draft of the manuscript. JG and GAK supported the data analyses and interpretation of results and gave significant intelectual contributions to the manuscript. ECC was resposnible for the study hypothesis, data analyses, intelectual contribution and draft of the manuscript. All authors approved the submission of the current version of the manuscript.

Conflict of interest: The authors do not have conflicts of interest to report.

Data Statement

The data has not been previously presented orally or by poster at scientific meetings

Results: Individuals classified with cognitive frailty had significantly higher serum IL-6 levels compared to the robust, cognitively unimpaired group. Those with cognitive frailty (aOR=1.97 [1.18–3.27] and pre-frailty and cognitive impairment (aOR=1.83 [1.24–2.69]) had the highest mortality risk over ten years of follow-up. Higher IL-6 levels were also independently associated with a higher mortality rate (aOR=1.37 [1.23–1.54]).

Conclusions: Our study shows that cognitive Frailty indicates a vulnerability state and of increasing mortality risk. Our findings also suggested that pro-inflammatory abnormalities can be viewed as a central phenomenon underlying common age-related problems (e.g., cognitive impairment and Frailty) and outcomes (e.g., mortality).

Keywords

Cognitive frailty; aging; mortality; IL-6; inflammation

Introduction

Cognitive impairment and frailty are among the most common geriatric syndromes(1, 2). Both conditions directly impact health and society, leading to disability, worse quality of life, higher risk of adverse health outcomes, and elevated direct and indirect costs (3, 4). Frailty is usually conceptualized based on two different frameworks. One framework is the frailty phenotype and is based on impairments in 3 out 5 biological domains: unintentional weight loss (more than 4.5 kg or 5% of one's body weight in the previous year), self-reported fatigue, muscle weakness, low level of physical activity, and slow gait (5). Another framework is based on the deficit accumulation model which considers the frailty syndrome as the result of the accumulation of deficits in multiple organs and physiologic systems as a harbinger of frailty manifestation. The accumulation of deficit model is most commonly defined by the "Frailty Index" which is the result of the number of deficits (numerator) divided by the number of possible deficits examined in one given person (denominator). It ranges from 0 to 1 with higher scores denoting more frailty.(6, 7)

There is a growing body of evidence of frequent co-existence and close association between frailty and neurocognitive disorders, leading to the emergence of the term "cognitive frailty" (CF). This term generally describes individuals with frailty and evidence of cognitive impairment (e.g., MCI or dementia). A longitudinal study, including brain autopsy, found that individuals with Alzheimer's disease had higher odds of being classified as frail than those without dementia (8). A recent meta-analysis showed that individuals classified with CF have higher progression rates of all-cause dementia(9). A study including 761 older adults without cognitive impairment at baseline found that being frail was associated with a 60% greater risk of developing mild cognitive impairment. This association was maintained even after controlling for depressive symptoms and cardiovascular disease(10).

Frailty and cognitive impairment/dementia have been independently linked to increased mortality risk in community-dwelling older adults and nursing home populations in countries with high or low economic development status(11–13). More recent evidence also suggests that individuals classified with CF have increased mortality risk. A meta-analysis showed that individuals classified as CF had significantly higher mortality risk than robust,

cognitively unimpaired older adults (pooled HR = 2.18 [1.6–2.87](14), with estimates for CF being similar or higher that those observed for frailty or cognitive impairment/dementia alone. However, such mortality estimates amoing subjects with CF could have been inflated due to evidence of high study heterogeneity found in the meta-analysis.

Frailty has been viewed as a manifestation of accelerated aging, and its presence can lead or expedite cognitive decline via decreased physical, social, and cognitive engagement caused by the presence of frailty (15). On the other, neurocognitive disorders can independently exacerbate physical decline, and, thus worsen frailty measures(16). The bidirectional association suggests potential shared biological mechanisms between these conditions. However, the potential shared biological mechanisms have not been fully explored. Recent works have focused on evaluating pro-inflammatory processes since they have been independently associated with cognitive impairment/dementia and frailty. In addition, they constitute a significant hallmark or driver of biological aging (e.g., Inflammaging or immunosenescence)(17).

For example, a recent study suggested the involvement of pro-inflammatory markers and abnormalities in cellular processes related to biological aging with CF, defined by the frailty phenotype(5) and scores on the MMSE ≤ 23, TMT-A≥78s, and TMT-B≥106(18). There is also evidence that specific frailty domains, like slow gait, are associated with elevated pro-inflammatory cytokines levels(19).

This study has two main aims. First, we aimed to evaluate if CF is associated with higher pro-inflammatory cytokine IL-6 when compared to robust, cognitively unipaired subjects. We focused on the IL-6 since it is one of the master regulators of the inflammatory response and has been previously associated with cognitive impairment, frailty, and mortality. It is also been consistently involved in accelerated aging processes and constitutes the senescence-associated secretory phenotype in different senescence models(20–22). Second, we aimed to evaluate if CF was associated with higher mortality risk when compared to subjects without CF upon ten years of follow-up.

Methods

Study sample

This study was carried out using the database collected from the baseline of the Bambuí Cohort Study of Ageing, which was conducted in Bambuí city, Minas Gerais (15,000 inhabitants in 1996), Southeast region of Brazil. This original community-based prospective cohort study comprised 1606 (92.2%) of all residents (1742) aged 60 years or more identified by a complete census conducted in the city on January 1st, 1997. Baseline participant interviews and assessments were carried out in 1997. The present analyses included 1,340 individuals who had complete baseline data to calculate the Frailty Index (see below) and available serum IL-6 data. The detailed cohort methodology has been described elsewhere (23).

Frailty index (FI), Cognitive impairment (CI), and Cognitive Frailty (CF) definitions

We included 41 items assessed in the baseline timepoint in the Bambui Cohort Study of Aging (Supplementary Table 1) to build the Frailty index for each individual in this sample. Continuous variables were dichotomized according to published international and Brazilian guidelines to determine their reference value ranges. The Frailty index was calculated based on the number of deficits (numerator) divided by the total number of items assessed (denominator). The FI values ranged from 0.024 to 0.756, with a mean of 0.269±0.085. We used previously published cut-offs to classify each individual into Robust (FI ≤ 0.2, N=330), Pre-Frail (FI between 0.20 and 0.35, N=875), and Frail (FI > 0.35, N=219) categories (24).

We used the mini-mental state examination (MMSE) (25) to measure global cognitive performance in this sample. The MMSE is a widely used cognitive screening tool to identify individuals with cognitive impairment and validated for use in this population. We used a previously validated score of less than 22 to identify subjects with evidence of cognitive impairment(26). A total of 1,100 had no evidence of cognitive impairment (Cognitively unimpaired (CU) group), and 324 had evidence of cognitive impairment (CI group) in the baseline assessment. Baseline demographic and clinical characteristics of the whole sample and based on Frailty index or Cognitive impairment categories are shown in Supplementary Table 2 to 4, respectively.

We further classified participants according to their frailty and cognitive impairment status into the following groups: Robust, CU (N=260), Pre-Frail, CU (N=675), Frail, CU (N=165), Robust, CI (N=70), Pre-Frail, CI (N=200), and Cognitive Frailty (N=54). The baseline demographic and clinical characteristics of these groups are shown in Table 1.

Serum IL-6 measure

Serum IL-6 levels were measured using a cytometric bead array assay by flow cytometry, according to the manufacturer's instructions. The CBA assay comprises 7.5 μm polystyrene capture microbeads, unique on their type-4 fluorescence intensity (FL-4), coupled to a monoclonal antibody (mAb) specific to IL-6. The coefficients of variation intra- and inter-assays were 7–12% and 5–10%, respectively. A second-step reagent comprising a mix of fluorescent-labeled (phycoerythrin-PE) was used, and the concentration of IL-6 was determined by the mean fluorescent intensity (MFI) of the capture microbead. Data were acquired using a FACSVerse flow cytometer (Becton Dickinson, USA), and the BD FCAP Array 3.0 software (Becton Dickinson, USA) was used for sample analysis. The results were based on standard concentration curves and expressed in pg/mL for each biomarker(27). The distribution of the serum IL-6 levels was heavily skewed and followed a non-normal distribution. Therefore, we used a box-cox transformation (with parameter λ=0.01) to normalize the serum IL-6 values.

Mortality Data Source.

Deaths occurring up to June 30th, 2007, were included in this analysis. Deaths were reported by the next of kin during the annual follow-up interview and verified through the Brazilian System of Information on Mortality, available with the permission of the Ministry of Health. Death certificates were obtained for 98.9% of individuals. The endpoint in this analysis was

all-cause death, including deaths due to suicide. Due to the lack of standardized reports of specific death causes in death certificates, we did not evaluate specific causes of death in this study.

Statistical analysis

We carried out a t-test or analysis of variance to evaluate the association between group classifications ("Cognitive Impairment," "Frailty," and "Cognitive Frailty") and baseline demographic, clinical, and IL-6 data. We used Dunnett's test for post-hoc comparison analyses. Chi-square tests were done to evaluate differences in the distribution of dichotomous data in the different group classifications. We carried out Pearson correlation analyses to evaluate the association between frailty index, demographic, clinical, and serum IL-6 levels data. Finally, we used the Cox hazard regression proportional model to calculate the hazard ratio for death in each group classification. The maximal follow-up length of a study participant included in this analysis was 10 years. Also, a formal test of the proportional-hazards assumption based on Schoenfeld residuals was performed. Time-to-event (death) was expressed in days and calculated by the time elapsed between the date of death and the date of baseline assessment.

Results

The prevalence of cognitive Frailty was 3.80% in this population. The frailty index was significantly correlated with IL-6 levels (r=0.10, p=0.0006; n=1340) and depressive symptoms (r=0.29, p<0.0001, n=1340), but not with age (r=0.01, p=0.54, n=1340) or scores in the MMSE (r=−0.04, p=0.12, n=1340) in the whole sample. Serum IL-6 levels were correlated with age (0.15, p<0.0001, n=1340), scores on the MMSE (r=−0.07, p=0.008, n=1340), and marginally significant with depressive symptoms (r=0.05, p=0.05, n=1340). Participants in the CF group were older, had worse cognitive performance, more depressive symptoms, and higher frailty index scores than the Robust, Cognitively Unimpaired (Robust, CU) group (Table 1). They also had a higher frequency of women and lower educational status (Table 1).

We found a statistically significant difference in serum IL-6 levels among cognitive frailty diagnostic groups ($F_{(5,1334)}$=3.87, p=0.001), with participants in the Cognitive Frailty and Frail-CU groups having the highest serum IL-6 levels (Table 1). Furthermore, the difference in serum IL-6 levels remained statistically significant after controlling for the effects of the potential confounding variables: baseline age, depressive symptoms (GHQ-12 scores), sex, educational level ($F_{(5,1325)}$=2.32, p=0.04). In addition, post-hoc Dunnett's tests, with Robust-CU group as reference, showed that serum IL-6 levels were higher in the Frail-CU ($t_{(688)}$=3.17, p=0.007), Pre-Frail-CI ($t_{(458)}$=2.82, p=0.02), and Frail-CI groups ($t_{(312)}$=2.59, p=0.04). We carried out an additional sensitive analysis including an interaction term between Frailty and Cogntive impairment classification groups and we found a significant FrailtyXCognitive impairment interaction on serum IL-6 levels ($F_{(9,1330)}$=2.55, p=0.0067). The baseline demographic, clinical, and serum IL-6 levels analyses in the Frailty or Cognitive Impairment groups are shown in Supplementary tables 2 and 3).

Participants classified as Pre-Frail (unadjusted HR=1.66 [1.26–2.18], z=3.59, p<0.001) and Frail (unadjusted HR=2.07 [1.48–2.88], z=4.29, p<0.001), independent of their cognitive status, had a higher risk of mortality compared to the Robust group. After controlling for the effect of potential confounding variables (baseline age, GHQ-12 scores, MMSE scores, sex, educational level, and serum IL-6 levels), the mortality risk was attenuated for both the Pre-Frail and Frail groups but remained statistically significant (Pre-Frail: HR=1.45 [1.09–1.92, z=2.60, p=0.009; Frail: HR=1.59 [1.13–2.25], z=2.65, p=0.008). The Cox regression model did not violate the proportional hazard assumption (X^2=6.09, df=8, p=0.63) (Figure 1).

Participants classified as having cognitive impairment, independent of the frailty status, also had a higher mortality risk (unadjusted HR=1.85 [1.50–2.28], z=5.78, p<0.001) compared to those without cognitive impairment. The mortality risk was attenuated by the inclusion of potential confounding variables (baseline age, GHQ-12 scores, frailty index, sex, educational level, and serum IL-6 levels) but remained statistically significant (HR=1.27 [1.01–1.60], z=2.05, p=0.04). Therefore, the Cox regression model did not violate the proportional hazard assumption (X^2=6.30, df=7, p=0.50) (Figure 2).

We also evaluated the mortality risk in after classifying subjects into different cognitive frailty diagnostic groups. Subjects in the “Cognitive frailty” had the higher HR for mortality, compared to the “Robust, Cognitively unimpaired” group, independent of potential covariates (Table 2). The Cox regression model did not violate the proportional hazard assumption (X^2=7.67, df=10, p=0.066). It is worth noting that higher serum IL-6 levels were also associated with higher mortality risk in this population, with an increment of 1 standard deviation in the serum IL-6 levels increasing the mortality risk by 37.5% after controlling for potential confounding variables (Table 2).

Discussion

Cognitive impairment and frailty are two significant issues for the growing older adult population. First, we found that the prevalence of CF in this population was 3.8%, in line with previous literature reports, despite the different characterization of frailty and cognitive impairment in different studies. Second, frailty and pre-frailty status were associated with higher pro-inflammatory cytokine IL-6 levels, especially in those with cognitive impairment, showing that their comorbidity is associated with higher pro-inflammatory status and possibly, of accelerated biological aging in older adults. Finally, mortality risk was the highest among individuals with pre-frailty or Frailty and cognitive impairment, independent of potential confounding variables (age, sex, education status, depressive symptoms, and serum IL-6 levels), indicating that these individuals are among those more vulnerable to adverse health outcomes.

Elevated levels of pro-inflammatory cytokines have been linked independently to cognitive impairment and dementia, frailty, and higher mortality risk. The IL-6 is a master regulator of the inflammatory response. However, the lack of resolution of the inflammatory response or under chronic health conditions can lead to the chronic elevation of its levels, triggering a chronic pro-inflammatory state (28). Moreover, IL-6 is a significant component of

the senescence-associated secretory phenotype and can drive, single-handedly, cellular senescence abnormalities (21, 29). Our study is the first to show that subjects with CF have significantly higher IL-6 levels than robust, cognitively unimpaired older adults. Moreover, we found a significant interaction between frailty levels and cognitive impairment on serum IL-6, suggesting that the elevation of IL-6 levels is a common denominator between frailty and cognitive impairment in this population, supporting the hypothesis that pro-inflammatory changes can be mechanistically linked to the emergence of these conditions in older adults.

Pro-inflammatory abnormalities have been consistently found in older adults (30) and are considered one of the hallmarks of biological aging(31). In line with the literature, we found a significant correlation between IL-6 levels, chronological age and the frailty index, and higher levels in those with cognitive impairment and Frailty. Furthermore, high IL-6 levels were also a solid and independent predictor of mortality in this population, with the mortality risk increasing by 37% with an increase of 1 standard deviation of its levels after adjusting for demographic and clinical variables. Thus, our results provide additional evidence to support those pro-inflammatory abnormalities are related to major age-related clinical issues (i.e., frailty and cognitive impairment) and negative health outcomes (i.e., increased mortality). Alternatively, this data can also be viewed from a geroscience perspective where abnormalities in pro-inflammatory response, a significant hallmark of biological aging, can underlie the emergence of common age-related clinical issues and predispose these individuals to increased risk of negative health outcomes commonly associated with aging (i.e., mortality).

A recent meta-analysis showed that the HR of mortality for CF was 2.43 (2.10–2.83) and for pre-frailty plus cognitive impairment was 1.64 (1.26–2.14) over a pooled average follow-up length of 5.3 years. The studies included in the meta-analysis mostly used the Fried Frailty Phenotype to characterize the frail or pre-frail state. In contrast, our study characterized Frailty based on the accumulation of deficit framework (“frailty index”)(6). Like ours, the MMSE was used as the primary tool to define cognitive impairment and did not exclude participants with dementia at baseline. Therefore, our results that CF bears a significantly higher mortality risk are in line with the previous reports in the literature, despite the differences in the frailty characterization.

Our results should be viewed considering the study limitations. First, we relied on the scores on the MMSE to determine the presence of cognitive decline. Although the MMSE has been widely used as a screening tool for cognitive impairment in clinical and community settings, it is not an instrument capable of providing a fine-grained assessment of cognitive performance. Therefore, we may have misclassified some participants that had minor cognitive impairments and were classified as cognitively unimpaired, thus biasing the study results. However, previous studies also used the MMSE solely to define cognitive impairment, and our results on mortality risk are like theirs. Second, we operationalized Frailty based on the deficit accumulation framework, and we included the variables to build up the frailty index based on the availability at the Bambui Aging Study Cohort. Therefore, differences in which items are included in the frailty index can lead to differences in frailty classification and, consequently, in the study results. However, the strategy we used to build

the frailty index is consistent with the original proposal (6) and has been replicated in other studies using independent samples. Third, we analyzed only the IL-6 as a marker of pro-inflammatory activity in this study. However, many other cytokines and immune markers are significant players in the immunological response and inflammatory control, and the measurement of IL-6 only is an oversimplification of a very complex response system. Also, IL-6 levels can be affected by the presence of chronic infectious diseases, which are common in this cohort (e.g., Chagas disease) and chronic use of anti-inflammatory drugs (32, 33). However, these variables were included in the frailty index and thus, incorporated into the analyses. Fourth, we did not include other hallmarks of biological aging, e.g., mitochondrial dysfunction or cellular senescence markers. Finally, we did not include any items part of the frailty index as covariates to avoid circularity in the statistical analyses. However, they have been independently associated with cognitive impairment, mortality risk, or inflammation (e.g., diabetes type 2, high blood pressure, or obesity).

In conclusion, we found that older adults with cognitive Frailty have the highest serum pro-inflammatory cytokine IL-6 and mortality risk over ten years of follow-up. Our findings also suggested that pro-inflammatory abnormalities can be viewed as a central phenomenon underlying common age-related problems (e.g., cognitive impairment and frailty) and outcomes (e.g., mortality). Future studies using different cohorts are needed to confirm the current results, preferentially including a more detailed neurocognitive assessment, a broader measurement of inflammatory markers, and other hallmarks of biological aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1) What is the primary question addressed by this study?

We evaluated if cognitive frailty is associated with increased pro-inflammatory status and higher mortality risk in older adults.

2) What is the main finding of this study?—The finding must be limited to two sentences.

We found that older adults classified as having cognitive frailty have significantly higher levels of the pro-inflammatory cytokine IL-6. Also, we found that the cognitive frailty is an independent risk factor for mortality over 10 years of follow-up in older adults.

3) What is the meaning of the finding?

Cognitive frailty is a potentially modifiable risk factor for premature mortality in older adults.

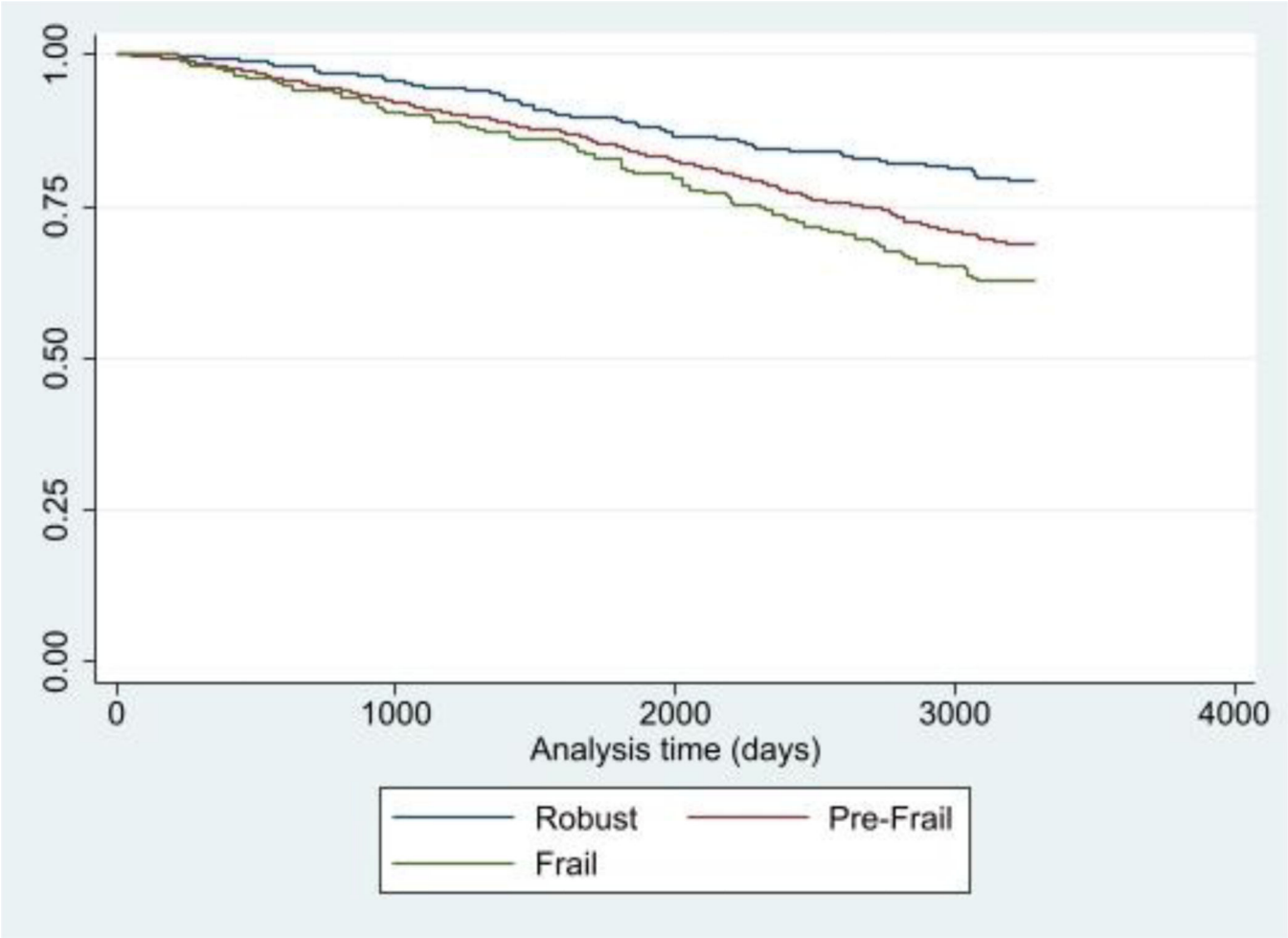

Figure 1 –.
Cox proportional hazard ratio analysis for mortality risk according to frailty status.

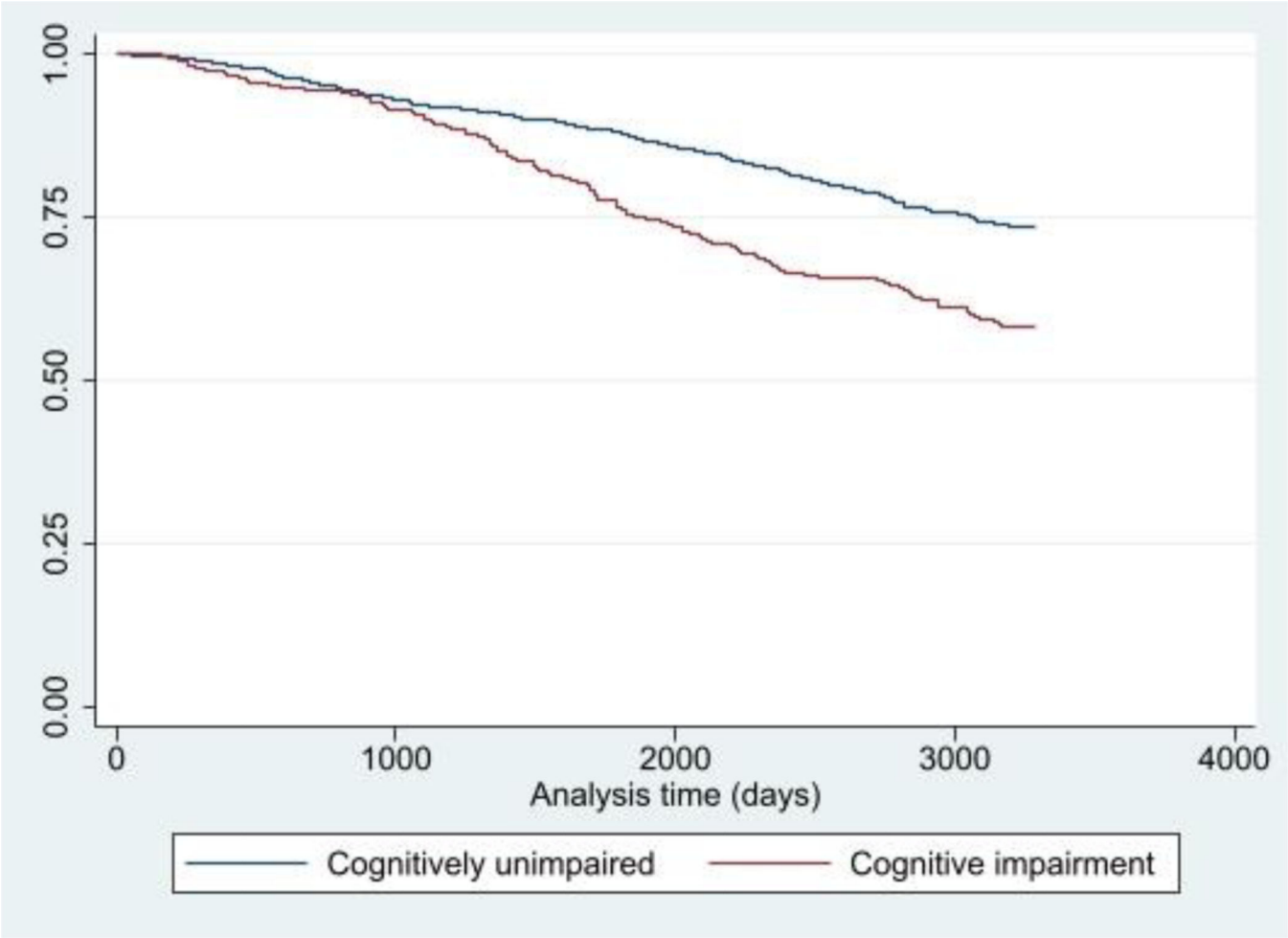

Figure 2 –.

Cox proportional hazard ratio analysis for mortality risk according to cognitive impairment status.

Table 1 –

Demographic, clinical, and serum IL-6 levels data according to cognitive frailty groups.

		Robust, CU (n=260)	Pre-Frail, CU (n=675)	Frail, CU (n= 165)	Robust, CI (n=70)	Pre-Frail, CI (n=200)	Cognitive Frailty (n=54)	Statistics	p-value	Effect size
Age (years)		68.2±6.8	68.5±6.6	68.9±7.2	70.8±7.7	70.6±7.8	71.1±7.4	$F_{(5,1,334)}$=5.01	0.0001	η^2 = 0.02
Sex	Women	17.4%	49.1%	14.3%	3.7%	11.1%	4.3%	$Chi^2_{(5)}$= 34.6	<0.0001	
	Men	20.3%	43.3%	8.0%	6.6%	18.9%	3.0%			
Educational level	>4 years of education	25.6%	53.3%	14.8%	2.3%	3.3%	0.8%	$Chi^2_{(5)}$= 124.0	<0.0001	
	≤3 years of education	14.4%	43.3%	10.3%	6.2%	20.2%	5.5%			
MMSE scores		26.9±2.0	26.6±2.1	26.4±2.0	18.6±3.2	18.5±3.2	18.5±3.2	$F_{(5,1,334)}$=563.9	<0.0001	η^2 = 0.67
GHQ scores		2.3±2.7	3.7±3.4	5.2±3.4	3.4±3.2	4.8±3.6	6.6±3.3	$F_{(5,1,334)}$=27.44	<0.0001	η^2 = 0.09
Frailty Index		0.16±0.03	0.28±0.04[1]	0.41±0.05[1]	0.15±0.04	0.28±0.04[1]	0.40±0.04[1]	$F_{(5,1,334)}$=956.7	<0.0001	η^2 = 0.78
Serum IL-6 (pg/mL)		1.6±2.0	1.7±2.0	2.0±2.3[1]	2.1±2.2	2.2±2.7[2]	2.4±2.6[3]	$F_{(5,1,334)}$=3.87	0.0018	η^2 = 0.014

MMSE: mini-mental state examination; GHQ: general health questionnaire; η^2 = eta-square

Dunnett's post-hoc test (reference group Robust, CU):

Frailty index: 1: p<0.0001

Serum IL-6 levels:

1: p=0.007;

2: p=0.021;

3: p=0.04

Table 2 –

Hazard ratio of mortality according to cognitive frailty groups.

	OR	[95% conf. interval]		z	p- value
Cognitive Frailty					
Robust-CU	Ref				
Pre-Frail-CU	1.43	1.02	2.00	2.1	0.036
Frail-CU	1.56	1.03	2.35	2.11	0.034
Robust-CI	1.23	0.71	2.13	0.75	0.452
Pre-Frai- CI	1.83	1.24	2.69	3.08	0.002
Cognitive Frailty	1.97	1.18	3.27	2.6	0.009
Age	1.07	1.05	1.08	10.33	<0.001
GHQ-12 scores	1.07	1.04	1.10	4.46	<0.001
serum IL-6 levels	1.37	1.23	1.54	5.61	<0.001
Educational level					
≥ 4 years of education	Ref				
<3 years of education	1.12	0.89	1.42	1.00	0.317
Sex					
Women	Ref				
Men	1.49	1.21	1.84	3.78	<0.001