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Frailty and Cognitive Impairment as Predictors of Mortality in Older Mexican Americans

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Abstract

Objective—Examine the association between frailty and cognitive impairment as predictors of mortality over a 10-year period in a selected sample of older Mexican Americans.

Design—Longitudinal analyses using data from the Hispanic Established Populations for the Epidemiologic Study of the Elderly (1995–96/2004–05).

Setting—Five southwestern states: Texas, New Mexico, Colorado, Arizona, and California.

Participants—Mexican Americans aged 67 and older with complete information on the frailty index and the Mini Mental State Examination (MMSE) (n=1,815).

Measurements—Cognitive impairment determined by a score in the MMSE < 21. Frailty defined as three or more of the following components: 1) weight-loss, 2) weakness, 3) self-reported exhaustion, 4) slow walking speed, and 5) low physical activity level. Sociodemographic characteristics and chronic medical conditions were used as covariates. Mortality was determined using the National Death Index or by proxy.

Results—As MMSE score declined over time, the percent of frail individuals increased in a linear fashion. Frailty and cognitive impairment are independent risk factors for mortality after controlling for all covariates (HR 2.03 95% CI 1.57–2.62; HR 1.26 95% CI 1.05–1.52, respectively). When both cognitive impairment and frailty were added to the model, HR for individuals with cognitive impairment was no longer statistically significant.

Conclusion—The relation between frailty and cognitive impairment needs careful analysis in this population to establish pathways increasing mortality and decreasing quality of life. Our results suggest frailty is a stronger predictor of mortality for older Mexican Americans than cognitive impairment.

Keywords

Frailty; cognitive impairment; mortality; Mexican Americans

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INTRODUCTION

In the last decade, frailty has been established as a concept that helps identify older adults at risk of adverse events [1]. Different sets of criteria have been used to define frailty. Despite their limitations, these criteria have provided a structured starting point for researchers to study older adults at risk while using a common language. Alterations in physical function have been the main focus of widely used constructs that define frailty [2,3]. Today, frailty is a highly relevant clinical entity with a defined phenotype [2]. Frailty is also a predictor of adverse outcomes including mortality [4–6].

Similarly, cognitive impairment is an independent marker of functional decline and mortality, especially in the presence of dementia [7]. Cognitive impairment also leads to loss of independence affecting individuals, families, and impacting the healthcare system [8]. Investigators have suggested that cognitive function is a predictor for becoming frail; however, measurements of cognitive function are not included in most operational definitions of frailty, despite suggestions by several authors in this regards [9–12]. A recent study has reported that cognitive impairment improves the predictive ability of frailty in association with adverse events [13]. Despite this, consequences of the coexistence of frailty and cognitive impairment are not well understood.

The impact of both frailty and cognitive impairment may be particularly dramatic in members of minority or underserved populations including Mexican Americans [14–19]. This is relevant for two reasons: first, the number of older adults from minority groups is rapidly increasing and variations in clinical entities (i.e. frailty and cognitive impairment) will impact care for these adults in the future [20,21]; second, frailty is associated with development of cognitive impairment [22,23] and similarly, cognitive impairment is associated with becoming frail [19,24]. A better understanding of the relationship between frailty and cognitive impairment and their effect on adverse events will lead to improved interventions for older adults, especially those with limited resources [25].

The purpose of this investigation was to examine how frailty status relates to mortality in the presence of cognitive impairment. We studied a large national sample of older Mexican Americans that has been followed for more than 10 years. Our hypothesis was that mortality risk for older frail adults would change in the presence of cognitive impairment.

METHODS

Sample and Procedures

Data are from the Hispanic Established Populations for the Epidemiological Study of the Elderly (Hispanic EPESE) study. The Hispanic EPESE is an ongoing longitudinal study of Mexican Americans aged 65 and older, residing in Texas, New Mexico, Colorado, Arizona and California. The sample and its characteristics have been described elsewhere [26,27]. The original probability-based sample (N = 3050) was representative of approximately 500,000 older Mexicans Americans living in the Southwest in the mid 1990s. The present study uses data obtained between the second and fifth waves (1995 to 2005). Interviews were conducted every two to three years. Information from the baseline interview is not used since the *Physical Activity Scale for the Elderly* (PASE), a component of the frailty index (see below), was only administered at the second wave. The PASE scale is a brief and easily scored instrument to assess physical activity in epidemiological studies of persons age 65 years and older [28,29].

Since frailty includes physical and self-reported performance measures, participants who required assistance by a proxy were not included in our sample. Of the 2,438 individuals

interviewed in the second wave 2,166 were interviewed in person and 272 by proxy. Of the 2,166 individuals interviewed in person, 303 were subsequently excluded due to missing information on the components used to compute the frailty index and 48 due to missing data for other covariates. The final sample consisted of 1,815 individuals who had complete information on the frailty index and covariates at the 2nd wave (hereafter referred to as baseline [1995/96]), and were re-interviewed in the consecutive waves. By the end of follow-up (year 2005–2006) a total of 84 individuals refused to be interviewed, 124 individuals were lost to follow-up, and 690 individuals were confirmed dead through the National Death Index (NDI) and reports from relatives.

Individuals lost to follow-up, those that died and those excluded due to the criteria presented above were compared to our final sample. Excluded individuals were older, had less education and lower MMSE scores ($p<.001$). Excluded individuals also had higher prevalence of diabetes, heart attack, stroke, cancer, hip fracture and disability ($p<0.05$) compared with those included in the study. Finally, a significantly higher percentage of excluded individuals were in the frail category compared to those included in the analysis (18.8% vs. 7.9%; $p<.05$).

Measures

Frailty was assessed using procedures similar to those developed by Fried and colleagues [2] with the exception of physical activity where we used the PASE scale [29] instead of the *Minnesota Leisure Activity Questionnaire* [28]. The five components of the frailty measure include: weight loss, exhaustion, walking speed, grip strength and physical activity. Subjects with weight loss > 10 lbs from the previous interview were categorized as positive for the weight loss criterion. Exhaustion was assessed using two items from the *Center for Epidemiologic Studies - Depression* (CES-D) scale [30]: “I felt that everything I did was an effort” and “I could not get going.” The items asked “How often in the last week did you feel this way?” and were scored on a scale from zero to three depending on the frequency of the symptoms [30]. Subjects answering “2” or “3” to either of these two items were categorized as positive for the exhaustion criterion. Walking speed was assessed over a 16-foot timed walk. Height and gender adjusted time points were used and individuals in the slowest 20 percent were scored as positive for this criterion. Those unable to perform the test were also categorized as positive. Grip strength was assessed with different cut-points for men and women using a Jaymar Hand-held Dynamometer (Model #5030J1- J.A. Preston Corp, Jackson, MI). Subjects unable to perform the grip strength test and those in the lowest 20 percent adjusted for BMI and stratified by gender were categorized as positive for the weakness criterion. Subjects who scored in the lowest 20 percent of the PASE, adjusted by gender, were categorized as positive for the low physical activity criterion.

Individuals with three or more affected components of the frailty measure were considered frail. Individuals with one or two affected components were considered pre-frail and those with zero affected components were considered not frail. This followed the scoring convention developed by Fried and colleagues [2]. A more detailed description of the frailty construct used can be found elsewhere [31,32].

Cognitive impairment was assessed with the *Mini Mental State Examination* (MMSE) [33]. The English and Spanish versions of the MMSE were adopted from the *Diagnostic Interview Scale* (DIS) used in prior Hispanic community surveys [34]. This Spanish version of the MMSE met standard criteria for development of translated tests. The MMSE Spanish version has been successfully used in community surveys of Mexican Americans [35]. Scores range from 0 to 30, with lower scores indicating cognitive impairment. MMSE score was used both as a continuous variable and a dichotomized variable (< 21 for cognitive impairment vs. ≥ 21 for adequate cognitive function). We dichotomized the MMSE score

based on two factors: total score distribution in our population sample at baseline and reports from previous aging research in similar populations [36]. This cut-point has been used in past studies on cognitive impairment among older populations with low educational attainment and low literacy [34,37,38].

Covariates—Sociodemographic variables included age, gender, marital status and years of formal education. The presence of medical conditions was assessed with a series of questions asking individuals if they had ever been told by a physician that they had diabetes, heart attack, stroke, hypertension, arthritis, cancer, or hip fracture.

Statistical analysis

Chi square and analysis of variance (ANOVA) tests were used to examine differences in the distribution of covariates for individuals by status at follow-up. To determine the relationship between cognitive impairment and frailty, unadjusted mean MMSE score and percent of frail individuals were plotted over time. Cox proportional hazard analysis was then used to estimate 10-year mortality as a function of frailty and cognitive impairment at baseline (MMSE < 21 and MMSE ≥ 21). Three Models were estimated to determine the effect of cognitive impairment and frailty on mortality. Model 1 included sociodemographic characteristics, medical conditions and cognitive impairment. Model 2, included sociodemographic characteristics, medical conditions and the three frailty categories (not frail, pre-frail and frail). In Model 3 (full model), sociodemographic characteristics, medical conditions, and both, cognitive impairment and frailty status were included. Survival curves were estimated according to the Kaplan Meier method and the six different groups were compared using log rank test. The first group included individuals with cognitive impairment that were not frail; the second group included individuals with cognitive impairment that were pre-frail; the third group included individuals with cognitive impairment that were frail. Three additional groups were created using the procedure previously explained, for individuals with adequate cognitive function that were in the three frailty categories. Log rank test was used to compare the survival curve for the six groups. All analyses were performed using the SAS System for Windows, Version 9.2 (SAS Institute, Cary, N.C.).

RESULTS

Table 1 shows the characteristics of the sample of older Mexican Americans by mortality status at follow-up. Being male, older, unmarried, and those with hip fracture and those deemed frail, were significantly more likely to be in the deceased group at follow-up. No other significant differences were observed in the remaining covariates between the three groups.

Figure 1 shows the relationship between cognitive impairment and frailty in older Mexican American survivors of our sample. As mean MMSE score declined over time, the percent of frail individuals increased in a linear fashion. There was a 4 point loss in mean MMSE score between wave 2 and wave 5 of the study. In addition, the mean percent of frail older Mexican Americans was more than five times higher in wave 5 compared to wave 2.

Table 2 shows Cox proportional hazard ratios of dying during the 10-year period. In Model 1, individuals with cognitive impairment had significantly higher hazard ratios (HR) of dying compared to those with adequate cognitive function after controlling for all sociodemographic variables and medical conditions (HR 1.26, 95% Confidence Interval [95% CI] 1.05–1.52). In model 2, pre-frail and frail individuals had significantly higher HR of dying compared to non frail individuals, after controlling for all covariates (Pre-frail: HR=1.40, 95% CI 1.18–1.66; Frail: HR= 2.03, 95% CI 1.57–2.62). In model 3, when both

cognitive impairment and frailty status were added in the Model, the HR of dying for individuals with cognitive impairment was not statistically significant (HR=1.19, 95% CI 0.98–1.43), while pre-frail and frail individuals remained at significantly higher risk of dying compared to non frail individuals despite a reduction in the magnitude of the HR (Pre-frail: HR=1.39, 95% CI 1.17–1.64; Frail: HR= 1.97, 95% CI 1.53–2.55).

Following procedures used by other researchers to examine percentage reduction in risk [39,40], we estimated the percentage reduction in mortality risk when frailty and cognitive impairment were used separately in a model compared to when they were together in the model. We wanted to know whether the relation between frailty and mortality and cognitive impairment and mortality would change in the presence of the other condition. The mortality risk attributable to cognitive impairment was reduced by 26.9% when frailty was added to the model. Similarly, mortality risk attributable to being pre-frail was reduced by 2.5%, and to being frail by 5.8%, when cognitive impairment was added to the model.

Figure 2 depicts 10-year mortality for all individuals by frailty and cognitive status at baseline. The six groups resulting from combining the three frailty categories (not frail, pre-frail and frail) and the two cognition groups (cognitive impairment and adequate cognitive function based on the MMSE cut-off of 21) are shown in Figure 2. Individuals with adequate cognitive function that were not frail during the observation period had the lowest mortality rates of all the groups with an absolute mortality rate of 35% after 10 years. Individuals with cognitive impairment that were frail had the highest mortality of all the groups with absolute mortality rates of 100% at 10 years and 70% at 8 years.

Both cognitive impairment and frailty status were independent predictors of mortality in this sample. Frail individuals had higher mortality rates compared to pre-frail and not frail individuals regardless of their cognitive status (Cognitive impairment: absolute mortality rate 70% for frail, absolute mortality rate 45% for pre-frail and 34% for not frail individuals; Adequate cognitive function: absolute mortality rate 58% for frail, 36% for pre-frail and 25% for not frail individuals). Similarly, individuals with cognitive impairment had higher mortality rates compared to individuals with adequate cognitive function regardless of their frailty status.

It is worth noting that when the data are analyzed for the 10-year follow-up period, all individuals deemed frail, regardless of their cognitive status, were dead by the final year of follow-up. Similarly, all pre-frail individuals with cognitive impairment died by the 10^{th} year of follow-up.

DISCUSSION

We examined mortality risk for individuals with frailty and cognitive impairment. As mean MMSE score decreased over time, the percent of frail older Mexican Americans increased. Our study suggests that both frailty and cognitive status increase mortality in older Mexican Americans. Mortality risk of individuals with cognitive impairment changes in the presence of frailty. Similarly, mortality risk of pre-frail and frail individuals changes in the presence of cognitive impairment. Thus, coexistence of frailty and cognitive impairment merit further evaluation in this population.

Previous studies show that frail older adults are at higher risk of dying compared to non-frail and even pre-frail older adults [2,41]. This remains true regardless of ethnic differences and, in some cases, regardless of socioeconomic status [42,43]. Additionally, frail older adults are at increased risk of other adverse events like hospitalization, disability, and institutionalization [9]. Frail older adults also have poorer quality of life compared to non-frail individuals [10,44].

Many studies have reported that individuals with cognitive impairment have higher mortality rates compared to individuals with adequate cognitive function [7]. Studies of patients with dementia show that they have higher rates of hospitalization, suffer more complications during hospitalization and end up with more disability [45]. These adverse outcomes result in higher rates of institutionalization, mortality and poorer quality of life.

Frailty and cognitive impairment are distinct clinical syndromes that share some characteristics. There is evidence that the relationship between cognitive status and frailty is based on shared physiologic pathways, and that the clinical presentation of frailty varies if cognitive impairment is added to the equation [46]. As reported previously, frailty is a dynamic condition and individuals may move between frailty categories over time [47]. We believe that frail individuals with cognitive impairment are likely to have limited ability to recover and move out of frailty.

The frailty phenotype proposed by Fried and colleagues [2] was not only a successful attempt at operationalizing a clinical syndrome that had been observed for some time, but represented an innovative approach that highlighted the importance of identifying clinical phenotypes to improve practice. Cognitive status may affect several of the components of the frailty cycle proposed by Fried et al [2]. For example, gait and muscle alterations as well as decreased physical activity are present in patients with cognitive impairment [48–50].

We prospectively analyzed a large number of individuals from a well-defined and comprehensively studied sample of older Mexican Americans. We also included a wide range of covariates related to both frailty and cognitive impairment. However, our study has some limitations. First, the MMSE is a crude measure of cognitive impairment with limited sensitivity to detect small changes in cognitive status in community living older persons [51,52]. Second, because depression and some cognitive disabilities are also related to brain dysregulation, the association between frailty and cognitive impairment can be mediated by other variables [53]. Finally, the information on medical conditions and comorbidities was based on self-reports. We did not have access to medical records, diagnostic images or serum markers to confirm subject self-reports, however, researchers have reported good agreement between self-reported medical conditions and actual medical diagnoses [46,54].

In conclusion, our investigation demonstrated that frailty and cognitive impairment affect mortality differently when they occur alone and when they are present together. Our findings suggest that both cognitive and frailty status are predictors of mortality in older Mexican Americans. Additional studies are necessary to analyze the shared pathways and common mechanisms influencing cognitive impairment and frailty. Pathways leading to death from frailty and cognitive impairment share some characteristics but are ultimately independent. Clinical phenotypes that include frailty and cognitive status and clarify their relationship will help broaden our understanding of the aging process.

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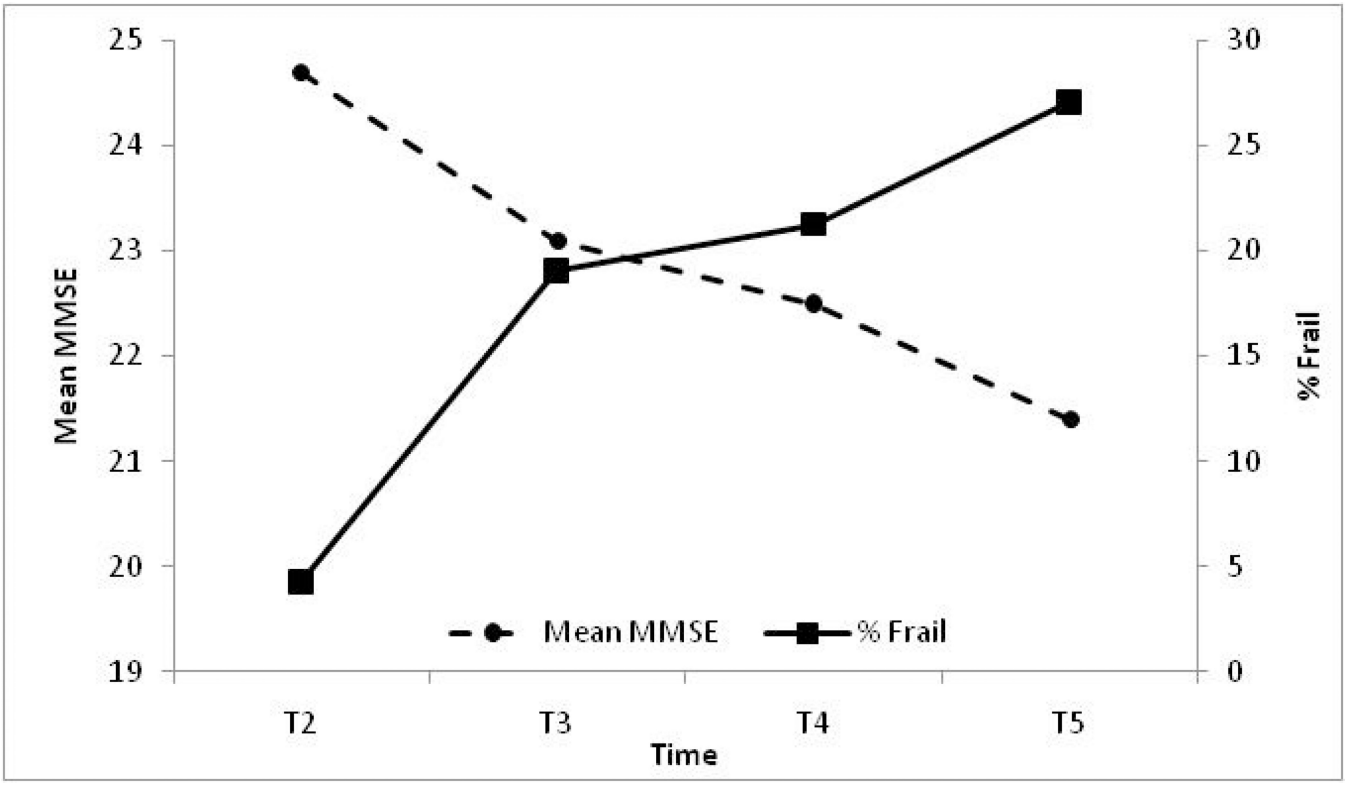

Figure 1.
Relationship between frailty and cognitive impairment in survivors between waves 2 to 5 of the Hispanic EPESE (n=1,127)

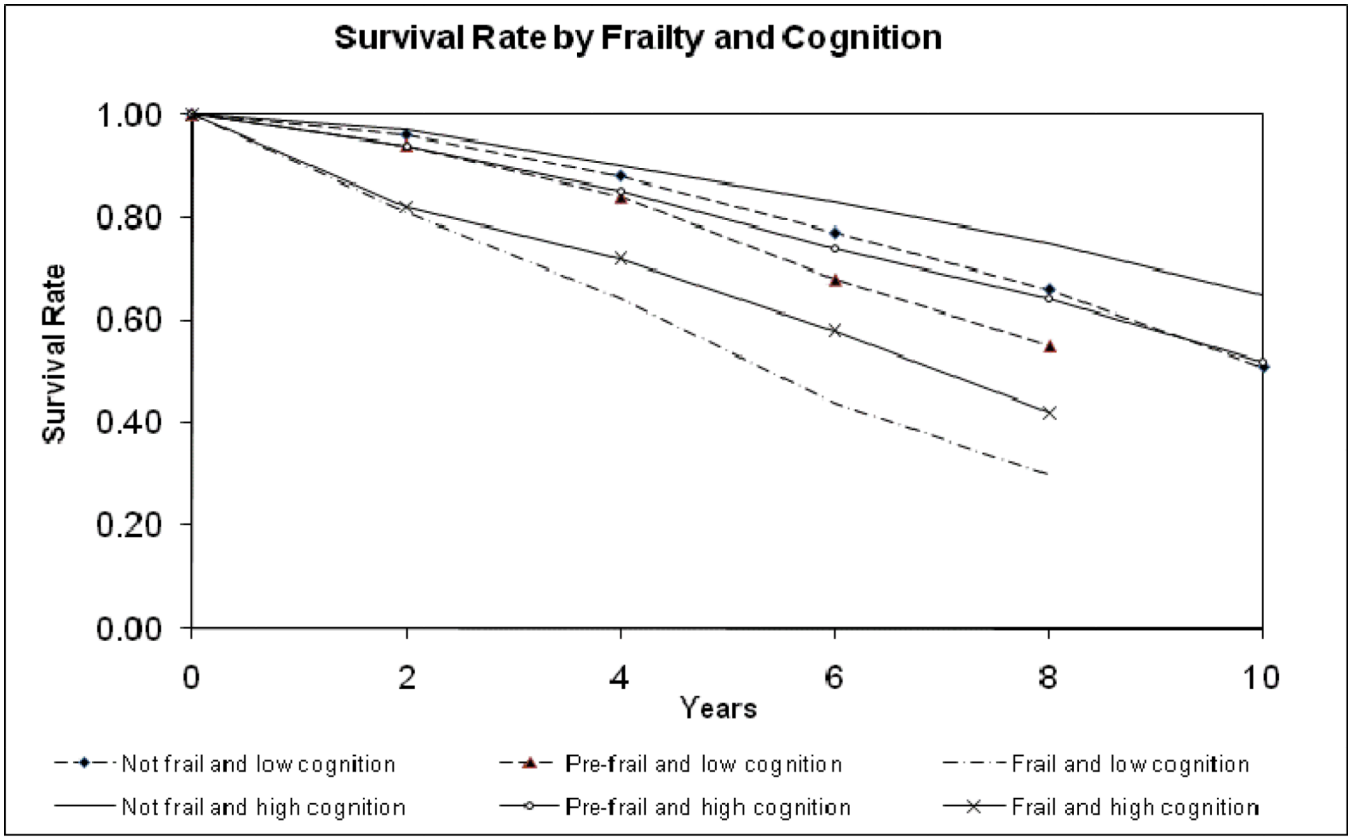

Figure 2.
Survival curve by frailty and cognitive status at baseline (n=1815)

Table 1

Descriptive characteristics of the sample by status at follow-up (n=1815)

	Alive (n=917)	Dead (n=690)	Lost to Follow-up (n=208)	p-value
	n (%)	n (%)	n (%)	
Age, mean ± SD	73.3 ± 5.0	77.1 ± 6.5	73.0 ± 5.0	<0.0001
Gender (female)	573 (31.6)	359 (19.8)	129 (7.1)	0.03
Education, mean ± SD	4.9 ± 3.8	4.8 ± 3.9	5.5 ± 4.3	0.07
Marital Status (married)	542 (29.9)	332 (18.3)	108 (6.0)	0.0005
Diabetes	214 (11.8)	230 (12.7)	41 (2.3)	0.20
Heart Attack	71 (3.9)	71 (3.9)	18 (1.0)	0.25
Hypertension	392 (21.6)	346 (19.1)	94 (5.2)	0.06
Stroke	49 (2.7)	61 (3.4)	10 (0.6)	0.27
Cancer	41 (2.3)	67 (3.7)	9 (0.5)	0.06
Hip Fracture	3 (0.2)	17 (0.9)	2 (0.1)	0.02
Arthritis	424 (23.4)	295 (16.3)	94 (5.2)	0.39
Cognitive Impairment[a]	151 (8.3)	185 (10.2)	30 (1.7)	0.06
Frailty Status				
Non frail	476 (26.2)	238 (13.1)	106 (5.8)	<0.0001
Pre-frail	405 (22.3)	355 (19.6)	91 (5.0)	
Frail	36 (2.0)	97 (5.3)	11 (0.6)	

[a]Cognitive impairment = MMSE < 21; SD = Standard Deviation;

Table 2

Cox proportional hazard models predicting 10-year mortality (N=1815)

	Model 1		Model 2		Model 3	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Age	1.08	(1.07–1.10)	1.08	(1.06–1.09)	1.08	(1.06–1.09)
Gender (female)	0.58	(0.49–0.69)	0.58	(0.49–0.69)	0.59	(0.49–0.70)
Education (continuous)	1.02	(0.99–1.04)	1.01	(0.99–1.03)	1.02	(1.00–1.04)
Marital Status (married)	0.80	(0.68–0.96)	0.79	(0.66–0.93)	0.80	(0.67–0.95)
Diabetes	1.64	(1.40–1.94)	1.62	(1.37–1.90)	1.62	(1.38–1.91)
Heart Attack	1.05	(0.81–1.35)	1.02	(0.79–1.32)	1.02	(0.80–1.32)
Stroke	1.29	(0.99–1.68)	1.20	(0.92–1.57)	1.21	(0.92–1.58)
Cancer	1.69	(1.31–2.20)	1.64	(1.26–2.12)	1.63	(1.26–2.11)
Hip Fracture	1.76	(1.08–2.87)	1.54	(0.94–2.51)	1.55	(0.95–2.53)
Hypertension	1.29	(1.11–1.51)	1.29	(1.10–1.51)	1.30	(1.10–1.51)
Arthritis	0.91	(0.78–1.07)	0.86	(0.73–1.01)	0.87	(0.74–1.02)
Cognitive Impairment[a]	1.26	(1.05–1.52)			1.19	(0.98–1.43)
Frailty Status						
Non frail				1.00		1.00
Pre-frail			1.40	(1.18–1.66)	1.39	(1.17–1.64)
Frail			2.03	(1.57–2.62)	1.97	(1.53–2.55)

[a]Cognitive impairment = MMSE < 21; HR = Hazard Ratio.