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Depression and Plasma pTau$_{181}$ Levels Are Associated with Frailty Status in Hispanic Community-Dwelling Older Women

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Abstract

The population of Hispanic older adults is growing along with the burden of chronic diseases. This cross-sectional study aims to assess the factors associated with frailty among community-dwelling Hispanic women aged ≥60 years ($n = 357$) enrolled in the Panama Aging Research Initiative—Health Disparities study of cognitive-functional health of older persons in Panama. Cognitive function was assessed with a neuropsychological test battery. Depression was measured with the Geriatric Depression Scale. Frailty was defined using the Fried criteria and participants were classified as non-frail, pre-frail or frail. A subsample ($n = 281$) provided fasting blood samples for quantification of protein biomarkers. Associations were examined using hierarchical multiple linear regressions. 59.4% and 9.0% of participants ($M = 69.2$ years, $SD = 6.3$) were pre-frail and frail, respectively. Having more depression ($\beta = .28$, $p < .001$) was significantly associated with frailty, even after covariate adjustment. Cognitive function was not associated with frailty. Higher pTau181 levels were associated with increased frailty ($\beta = .13$, $p = .039$), whereas higher α2M levels were associated with decreased frailty ($\beta = -.16$, $p = .004$). These findings advance the search for health indicators and biomarkers of frailty and warrant further studies to decrease the burden of frailty among older Hispanic women.

Keywords

depression, cognitive function, biomarkers, frailty, Hispanic women

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Introduction

Latin America and Caribbean (LAC) countries are experiencing a significant demographic shift as life expectancy rises and birth rates decline. This trend is expected to accelerate in the coming decades, with projections indicating that by 2050, approximately 25% of the LAC population will be 60 years or old (ECLAC United Nations, 2022) resulting in a greater demand for age-appropriate support systems.

Frailty in older persons is associated with greater vulnerability to adverse health outcomes, such as falls, cognitive impairment, disability, hospitalizations, and death (Álvarez-Bustos et al., 2022; Yang et al., 2023). Considerable research has examined frailty prevalence

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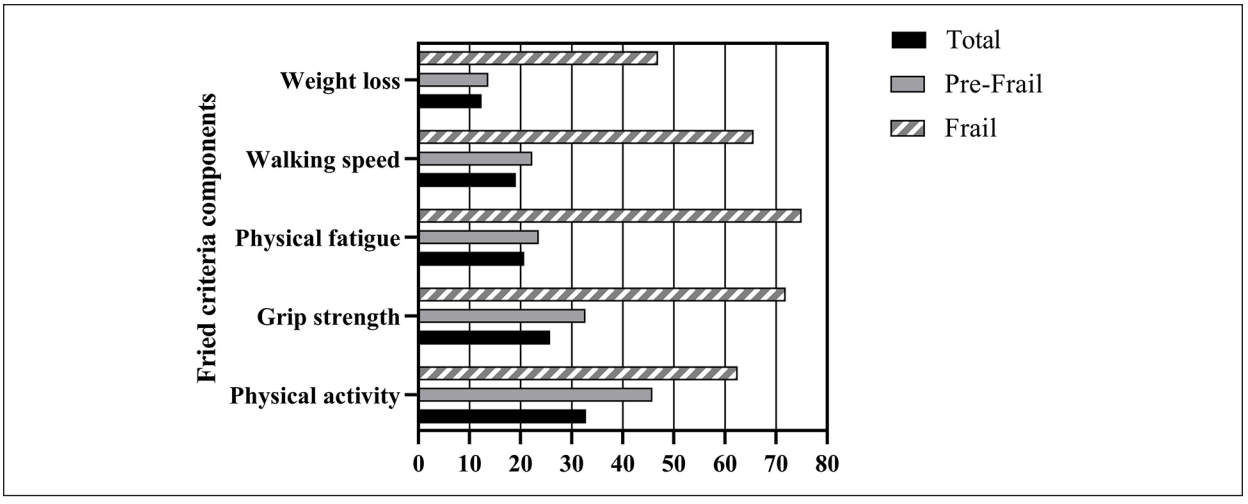

Figure 1. Frequency distribution (%) of the components of frailty criteria according to frailty status.

and associated factors at a population level (Ofori-Asenso et al., 2019), but there is a dearth of frailty research in Hispanic women in LAC. The few studies available have identified country-level differences between risk and protective factors associated with frailty (Santamaría-Ulloa et al., 2023; Vasquez-Goñi et al., 2022) and notably higher mean prevalence rates among community-dwelling adults in South American countries relative to U.S. or European countries (Coelho-Junior et al., 2020; Da Mata et al., 2016).

Frailty is a multifactorial health problem influenced particularly by multimorbidity (Feng et al., 2023; Ogaz-González et al., 2024). In LAC, an estimated 62% (95% CI [49%, 75%]) of adults aged 60 years and older have at least two chronic medical conditions (Huaquiá-Diáz et al., 2021). High rates of depression, obesity and other sociodemographic and lifestyle factors may also contribute to the development of frailty (Ocampo-Chaparro et al., 2019; Prina et al., 2019; Vasquez-Goñi et al., 2022). Moreover, cross-sectional and longitudinal evidence has documented associations between biomarkers and frail states (W. Chu et al., 2023; Picca et al., 2022) and progression to frailty (Liu et al., 2023; Mitchell et al., 2023). However, studies on biomarkers and other aspects of frailty among Hispanic populations in LAC are scarce (Nascimento et al., 2018; Santos Morais Junior et al., 2020).

Among community-dwelling older adults across global regions, frailty and pre-frailty rates consistently have been shown to be elevated among women relative to men (Figure 1) (Alvarado et al., 2008; Gordon et al., 2017; Siriwardhana et al., 2018). In addition, frail women were at increased risk for falls, fractures (Dent et al., 2024), limitations in ability to perform activities of daily living, and institutionalization (Bandeen-Roche et al., 2006). Women were also more prone to develop psychosocial ailments associated with frailty such as depression, anxiety and stress (Whitesides & Lynn, 2021). The main objective of the present report is to fill a gap in the research regarding the correlates of frailty among community-dwelling Hispanic older women, including associated blood biomarkers.

Material and Methods

Participants

Participants were enrolled in PARI-HD, an ongoing, longitudinal, community-based study of the cognitive and functional health of adults aged ≥50 years in Panama. Literate and dementia-free individuals are eligible and are enrolled after providing informed consent. The study protocol [approved by the Institutional Bioethics Committee of the Caja del Seguro Social (P-083-16)], employs a rolling-enrollment design using convenience sampling, with follow-up visits every 18 months. Participants are recruited primarily through social media, word of mouth and community outreach. At each visit, participants undergo clinical interviews, physical and cognitive assessments, and a fasting blood draw. The present report includes cross-sectional data collected between October 2016 and March 2020 from female participants (aged 60 years and older, as per inclusion criteria at the time of enrollment) who completed baseline assessments ($n = 357$). During the same period 78 male participants with complete data were collected, but were excluded from the analysis due to the limited number of samples and given the substantial literature on how frailty more acutely/uniquely affects women.

Clinical Interviews and Scales

The PARI-HD protocol and study instruments have been described previously (Villarreal et al., 2019). Briefly, participants underwent a clinical interview that surveyed chronic conditions and current medications, incidence of falls in the preceding 12 months, current or past tobacco use, difficulties sleeping, and subjective

cognitive impairment. Other measures included waist circumference, body mass index (BMI; kg/m^2) and blood pressure. Cognitive impairment was determined by a neuropsychological test battery that assessed global cognition and seven cognitive domains: (1) attention, (2) executive function, (3) verbal learning, (4) memory, (5) language, (6) visuospatial abilities, and (7) processing speed (Oviedo et al., 2024). Also, depressive symptoms (Yesavage et al., 1982), subjective memory complaints (Youn et al., 2009), subjective health (Badia et al., 1999), independence in activities of daily living (Katz, 1983; Lawton & Brody, 1969), and life satisfaction (Diener et al., 1985) were evaluated.

Frailty was assessed using the Fried criteria (Fried et al., 2001), which includes self-reported weight loss, exhaustion, and physical activity, and objective measurements of grip strength and walking speed. Participants met criteria for weight loss if they reported unintentional loss greater than 4.5 kg in the 12 months prior to the assessment. Exhaustion was surveyed with the following questions: "I felt everything I did was an effort," and "I could not get going," and scored as frail if at least one condition was present for 3 days or more during the previous week. Physical activity was surveyed with the question: "Which of the following best describes your level of physical activity" and three response options: (a) vigorous activity for at least 30 min 3 times a week; (b) moderate activity at least 3 times a week; and (c) rarely active, prefers sedentary activities. Participants who selected the last option met criteria for frailty. Frailty in the grip strength test (Lafayette Hand Dynamometer, Model 78010) was determined according to BMI and corresponding grip strength cutoffs (kg) as follows: BMI $\leq$23.9, 24.0–26.6, 26.7–30.4, $>$30.4 and grip strength cutoffs $\leq$20.5, $\leq$24.4, $\leq$27.6, $\leq$31.7 respectively. Walking speed (m/s) was calculated as the time taken to walk a distance of 5 m at a usual pace and adjusted for height (m). The cut-off points for frailty were as follows: height $\leq$1.58 m and time $\geq$6.31 s (equivalent to 0.79 m/s); height $>$1.58 m and time $\geq$5.91 s (0.85 m/s). Participants unable to complete the handgrip or walking test were scored as frail on these criteria. The overall frailty score comprised a range from 0 to 5. An individual was considered frail if three or more criteria were assessed as positive, pre-frail if one or two were positive, and not frail if none were positive.

A subset of participants (n=281) provided fasting blood samples assayed via a multiplex biomarker assay platform using the ultra-sensitive Simoa (single molecule array) technology platform HD-1 (Quanterix.com). The following plasma proteins were quantified: interleukin 5 (IL-5), pancreatic polypeptide (PP), amyloid-β 40 ($A\beta_{40}$), amyloid-β 42 ($A\beta_{42}$), C-reactive protein (CRP), fatty acid binding protein 3 (FABP3), soluble vascular cellular adhesion molecule 1 (sVCAM-1), tumor necrosis factor α (TNF-α), alpha-2-macroglobulin (α2M), human cytokine I-309 (I-309), interleukin 6 (IL-6), neurofilament light chain (NfL), and phosphorylated tau 181 ($pTau_{181}$).

Statistical Analyses

Statistical analyses were conducted using SPSS 29 (IBM, Armonk, New York, USA) Means and standard deviations were calculated for continuous variables and frequencies and percentages for categorical variables. Univariate and chi-square analyses compared frail, pre-frail, and frail groups for each variable. Hierarchical multiple linear regression, including age, education, income, and number of chronic illnesses as covariates, examined associations between frailty and study variables.

Results

Demographic and Clinical Characteristics

Participants were women with an average age of 69.2 years (SD=6.3) and 15.8 years of education (SD=4.5). BMI measurements (M=27.5 kg/m^2, SD=5.3) indicated that a plurality of participants was overweight (39.8%) or obese (26.9%) with an average of 1.8 chronic illnesses (SD=1.4), of which the most common was hypertension (51.5%). Many participants reported sleep difficulties (38.9%), visual (30.5%) and auditory impairment (14.3%), ever tobacco use (23.8%), and polypharmacy (17.1%). Some participants met criteria for depression (12%) and cognitive impairment (7.3%). Yet, 91.3% of participants rated themselves as "healthy" (M=85.1, SD=14.2) and showed functional independence in activities of daily living (see Table 1). The sum frailty score indicated that 31.7% were not frail, 59.4% were pre-frail, and 9.0% were frail.

Of those participants who provided blood samples (n=281), 14 were excluded from analyses for yielding biomarker values with extreme outliers (i.e., $>$4 standard deviations above the mean) which resulted in a final subsample of 267 participants (see Table 2). Univariate analyses showed significant differences in plasma levels of $A\beta_{40}$ (p=.015), α2M (p=.030), IL-6 (p=.049), NfL ($p<.001$) and $pTau_{181}$ ($p<.001$) across frailty categories.

Hierarchical Multiple Linear Regression Analyses of Factors Predicting Frailty

Hierarchical regression analysis examined the linear associations of depression, subjective health state, and cognitive impairment with the sum frailty score, adjusting for covariates (Table 3). Predictor variables were entered stepwise: covariates, IADL, and BADL were included in Step 1, and depression, subjective health state, and cognitive impairment were entered in Step 2. Step 1 explained a significant portion of the variance [F (6, 346)=13.30, MSE=0.91, R^2=.19, $p<.001$] in frailty, and indicated significant effects for age (β=.16, p=.003), income (β=−.16, p=.003), number of chronic illnesses (β=.21, $p<.001$), and IADL (β=−.15, p=.004). Step 2 explained additional variance [$F\Delta$ (3, 343)=13.28,

Table 1. Demographic and Clinical Characteristics.

Sample characteristic	Total ($n=357$) *n* (%)/*M* (*SD*)	Non-frail ($n=113$, 31.7%) *n* (%)/*M* (*SD*)	Pre-frail ($n=212$, 59.4%) *n* (%)/*M* (*SD*)	Frail ($n=32$, 9.0%) *n* (%)/*M* (*SD*)	*p*-Value
Age (years)	69.2 (±6.3)	67.0 (±5.0)	69.9 (±6.5)	72.5 (±6.9)	<.001
Marital status (% partnered)	160 (44.8%)	52 (46.0%)	91 (42.9%)	17 (53.1%)	.531
Education (years)	15.8 (±4.5)	16.3 (±4)	15.7 (±4.6)	14.3 (±4.8)	.080
Monthly income (USD)[1]	4.1 (±1.8)	4.6 (±1.6)	4 (±1.8)	3.6 (±2.1)	.004
Subjective health state	85.1 (±14.2)	88.6 (±11.1)	84.6 (±14.4)	76.6 (±18.2)	<.001
Body mass index (BMI = kg/m^2)	27.5 (±5.3)	26.6 (±4.1)	27.8 (±5.6)	29.1 (±6.7)	.044
BMI classification					.145
Underweight	8 (2.3%)	0 (0%)	7 (3.3%)	1 (3.1%)	
Normal	109 (30.7%)	39 (34.8%)	62 (29.4%)	8 (25%)	
Overweight	142 (39.8%)	51 (45.6%)	79 (37.4%)	12 (37.5%)	
Obese	96 (26.9%)	22 (19.6%)	63 (29.9%)	11 (34.4%)	
Auditory impairment (% yes)	51 (14.3%)	14 (12.4%)	31 (14.6%)	6 (18.8%)	.647
Visual impairment (% yes)	109 (30.5%)	27 (23.9%)	74 (30.9%)	8 (25.0%)	.094
Difficulty sleeping (% yes)	139 (38.9%)	37 (32.7%)	86 (40.6%)	16 (50.0%)	.157
Ever tobacco use (% yes)	85 (23.8%)	31 (27.4%)	49 (23.1%)	5 (15.6%)	.358
Systolic blood pressure (mmHg)	138.3 (±19.7)	139.6 (±19.4)	137.3 (±19.5)	140.3 (±21.6)	.504
Chronic health conditions (sum)	1.8 (±1.4)	1.5 (±1.1)	1.9 (±1.5)	2.5 (±1.4)	<.001
Diabetes (% yes)	56 (15.7%)	8 (7.1%)	44 (20.8%)	4 (12.5%)	.005
Hypertension (% yes)	184 (51.5%)	57 (50.4%)	104 (49.1%)	23 (71.9%)	.053
Cardiovascular disease (% yes)	39 (10.9%)	8 (7.1%)	24 (11.3%)	7 (21.9%)	.058
Arthritis (% yes)	54 (15.1%)	12 (10.6%)	33 (15.6%)	9 (28.1%)	.049
Osteoporosis (% yes)	142 (39.8%)	40 (35.4%)	90 (42.5%)	12 (37.5%)	.448
Polypharmacy (% ≥ 5 medications)	61 (17.1%)	6 (5.3%)	40 (18.9%)	15 (46.9%)	<.001
Depression symptoms	2 (2.4)	1.2 (1.7)	1.9 (2.4)	4.7 (2.9)	<.001
GDS-15 cut-off (% ≥ 5 symptoms)	43 (12.0%)	5 (4.4%)	24 (11.3%)	14 (43.8%)	<.001
Cognitive impairment (% yes)	26 (7.3%)	4 (3.5%)	16 (7.5%)	6 (18.8%)	.014
Independence in IADL	7.9 (±0.6)	7.9 (±0.2)	7.9 (±0.5)	7.4 (±1.3)	<.001
Independence in BADL	5.8 (±0.4)	5.9 (±0.3)	5.8 (±0.4)	5.6 (±0.5)	.010
Any falls in previous 12 months (% yes)	98 (27.4%)	23 (20.4%)	62 (29.2%)	13 (40.6%)	.050
Overall frailty score	1.1 (±1)	0	1.4 (±0.5)	3.2 (±0.5)	<.001
Weight loss (% frail)	44 (12.4%)	—	29 (13.7%)	15 (46.9%)	<.001
Grip strength (% frail)	92 (25.8%)	—	69 (32.7%)	23 (71.9%)	<.001
Walking speed (% frail)	68 (19.1%)	—	47 (22.3%)	21 (65.6%)	<.001
Physical fatigue (% frail)	74 (20.7%)	—	50 (23.6%)	24 (75%)	<.001
Physical activity (% frail)	117 (32.8%)	—	97 (45.8%)	20 (62.5%)	<.001

Note: *M* = mean; *SD* = standard deviation; USD = U.S. dollars; GDS-15 = Geriatric Depression Scale-15; IADL = instrumental activities of daily living (eight items); BADL = basic activities of daily living (six items).
[1]Monthly income (USD) measured on a Likert-scale (0 = ≤250, 1 = 251–500, 2 = 501–850, 3 = 851–1,200, 4 = 1,201–1,600, 5 = 1,601–2,000, 6 = >2,000).

MSE = 0.87, $R^2\Delta = .08$, $R^2 = .27$, $p < .001$], and yielded significant effects for depression (β = .26, $p < .001$), but not self-rated health or cognitive impairment.

A separate regression analysis explored associations between blood biomarkers and the sum frailty score (Table 4). Predictor variables were entered stepwise as in the previous model. For Step 3, five biomarkers were selected, inductively, based on the results of the univariate analyses: α2M, $A\beta_{40}$, IL-6, NfL, and $pTau_{181}$. Step 1 and Step 2 largely replicated the first analysis, with significant effects for age (β = .13, $p = .034$), number of chronic illnesses (β = .19, $p = .011$), and IADL (β = −.19, $p = .034$) in Step 1, and a significant effect of depression on frailty (β = .27, $p < .001$) in Step 2. The inclusion of Step 3 explained additional variance in frailty [$F\Delta$ (5, 240) = 3.49, *MSE* = 0.85, $R^2\Delta = .06$, $R^2 = .31$, $p < .001$] and revealed significant effects of α2M (β = −.16, $p = .004$) and $pTau_{181}$ (β = .13, $p = .039$).

Table 2. Blood-Based Biomarkers (Plasma).

Analyte (pg/mL)	Total ($n = 267$) *M* (*SD*)	Non-frail ($n = 92$) *M* (*SD*)	Pre-frail ($n = 151$) *M* (*SD*)	Frail ($n = 24$) *M* (*SD*)	*p*-Value
IL-5	0.4 (±0.4)	0.3 (±0.4)	0.4 (±0.4)	0.5 (±0.7)	.411
PP	182.3 (±166.1)	164.0 (±128.5)	192.3 (±184.6)	190.4 (±172.5)	.426
$A\beta_{40}$	166.1 (±55.2)	156.2 (±51.8)	168.2 (±48.7)	192.3 (90.7)	.015
$A\beta_{42}$	8.5 (±2.7)	8.3 (±2.6)	8.6 (±2.6)	8.9 (±3.9)	.556
CRP	4.1E + 06 (±5.2E + 06)	3.4E + 06 (±5.1E + 06)	4.3E + 06 (5.0E + 06)	5.7E + 06 (7.0 E + 06)	.157
FABP3	6.7E + 03 (±2.7E + 03)	6.3E + 03 (±2.1E + 03)	6.8E + 03 (±2.9E + 03)	7.1E + 03 (±3.8E + 03)	.244
sVCAM-1	3.6E + 05 (±9.8E + 04)	3.4E + 05 (±9.0E + 04)	3.6E + 05 (±1.0E + 04)	3.9E + 05 (±11.4E + 04)	.064
TNF-α	3.0 (±0.9)	2.9 (±0.9)	3.1 (±0.9)	3.2 (±1.1)	.093
α2M	1.5 E + 09 (6.6E + 08)	1.6 E + 09 (7.6E + 08)	1.4E + 09 (6.2E + 08)	1.2E + 09 (4.6E + 08)	.030
I-309	24.4 (±13.0)	23.8 (±11.8)	24.6 (±13.7)	25.9 (±13.5)	.746
IL-6	1.0 (±0.6)	0.9 (±0.5)	1.1 (±0.6)	1.2 (±0.7)	.049
NfL	12.7 (±6.5)	11.7 (±4.2)	12.4 (±5.8)	18.2 (±13.0)	<.001
$pTau_{181}$	1.9 (±1.0)	1.7 (±0.6)	2.0 (±1.0)	2.6 (±1.7)	<.001

Note: IL-5 = interleukin 5; PP = pancreatic polypeptide; $A\beta_{40}$ = amyloid-β 40; $A\beta_{42}$ = amyloid-β 42; CRP = C-reactive protein; FABP3 = fatty acid binding protein 3; sVCAM1 = soluble vascular cellular adhesion molecule 1; TNF-α = tumor necrosis factor α; α2M = alpha-2-macroglobulin; I-309 = human cytokine I-309; IL-6 = interleukin 6; NfL = neurofilament light chain; $pTau_{181}$ = phosphorylated tau 181; *M* = mean; *SD* = standard deviation.

Table 3. Hierarchical Multiple Linear Regression Analysis of Demographic and Clinical Factors Associated with Frailty ($n = 353$).

Variables included in the model	*b*	*SE*	β	*t*
Step 1				
Age	0.03**	0.01	.16	3.00
Education	0.001	0.01	.01	0.10
Income	−0.09**	0.03	−.16	−3.04
Number of chronic illnesses	0.15***	0.04	.21	4.11
IADL	−0.25**	0.08	−.15	−2.93
BADL	−0.20	0.12	−.09	−1.69
Step 2				
Age	0.03**	0.01	.16	3.12
Education	0.01	0.01	.03	0.50
Income	−0.06*	0.03	−.11	−2.06
Number of chronic illnesses	0.11**	0.04	.16	3.16
IADL	−0.17*	0.09	−.10	−1.98
BADL	−0.08	0.12	−.04	−0.72
Depression symptoms	0.11***	0.02	.26	4.87
Subjective health state	−0.01	0.004	−.06	−1.17
Cognitive impairment	0.26	0.20	.07	1.32

Note: Criterion variable was the overall frailty (sum) score. Cognitive impairment was coded as 0 = not impaired, 1 = impaired.
*$p < .05$. **$p < .01$. ***$p < .001$.

Discussion

This study assessed the association of demographic, cognitive, clinical, and biological factors with frailty in Panamanian women. We found increased frailty was associated with depression and two plasma biomarkers, $pTau_{181}$ and α2M. Having depression was significantly associated with frailty even after adjusting for age, education, income, comorbidities and degree of functional independence. Similarly, a report including several LAC community-dwelling populations showed that people with depression had greater odds of frailty (Prina et al., 2019), a relationship that was found to be bidirectional (Soysal et al., 2017). A study of Peruvian older adults reported that participants with both frailty and depression and those with cognitive impairment and frailty, were at greater risk for mortality (Vasquez-Goñi et al., 2022). Although recent research points to the role of chronic inflammation as the basic mechanism for a shared pathogenesis between cognitive impairment and frailty (Kochlik et al., 2023; Salvioli et al., 2023), we did not find an association between cognition and frailty in our cohort.

Table 4. Hierarchical Multiple Linear Regression Analysis of Blood-Based Biomarkers Associated with Frailty ($n = 255$).

Variables included in the model	*b*	*SE*	β	*t*
Step 1				
Age	0.02*	0.01	.13	2.01
Education	0.01	0.01	.03	0.41
Income	−0.08*	0.03	−.16	−2.47
Number of chronic illnesses	0.15**	0.05	.19	3.04
IADL	−0.28**	0.09	−.19	−2.99
BADL	−0.14	0.14	−.06	0.99
Step 2				
Age	0.02*	0.01	.13	2.13
Education	0.01	0.01	.04	0.61
Income	−0.06	0.03	−.11	−1.64
Number of chronic illnesses	0.12*	0.05	.15	2.55
IADL	−0.20*	0.09	−.13	−2.16
BADL	−0.07	0.13	−.03	−0.49
Depression symptoms	0.11***	0.023	.27	4.16
Subjective health state	−0.002	0.004	−.03	−0.44
Cognitive impairment	0.17	0.23	.05	0.74
Step 3				
Age	0.12	0.01	.13	2.13
Education	0.007	0.01	.04	0.61
Income	−0.05	0.03	−.11	−1.64
Number of chronic illnesses	0.11*	0.05	.15	2.55
IADL	−0.14	0.09	−.13	−2.16
BADL	0.04	0.13	−.03	−0.49
Depression symptoms	0.10***	0.023	.27	4.16
Subjective health state	−0.004	0.004	−.03	−0.44
Cognitive impairment	0.10	0.23	.05	0.74
α2M	−2.42**	0.001	−.16	−2.88
$A\beta_{40}$	0.001	0.001	.03	0.55
IL-6	0.17	0.10	.10	1.78
NfL	0.01	0.01	.09	1.15
$pTau_{181}$	0.13*	0.06	.13	2.08

Note: Criterion variable was the sum frailty score. Cognitive impairment was coded as 0 = not impaired, 1 = impaired.
*$p < .05$. **$p < .01$. ***$p < .001$.

Univariate analyses showed significant differences among frailty groups in several plasma biomarkers, but after adjusting for covariates, only $pTau_{181}$ and α2M were related to frailty. pTau is a cognitive-related biomarker of intraneuronal accumulation and aggregation, which leads to the formation of neurofibrillary tangles (Sengupta & Kayed, 2022). Similar results of elevated plasma pTau levels in frail individuals have been reported using Fried criteria and other indices of frailty, and for specific domains of frailty including weight loss, grip strength, exhaustion, and inactivity (H. Chu et al., 2024; Zhou et al., 2022). There is substantial evidence linking pTau to the development of various cognitive disorders, including Alzheimer's disease and other neurodegenerative conditions. Possible underlying mechanisms of frailty include endocrine dysregulation related to insulin resistance (Clegg & Hassan-Smith, 2018), which aggravates neurodegenerative development by inhibiting the PI3K/Akt/GSK3β pathway and inducing tau protein hyperphosphorylation (Shen et al., 2024).

We found that α2M, an acute phase protein that is elevated during inflammatory processes, was inversely associated with frailty. One study in rats reported that moderate levels of α2M and fibrinogen were, according to body weight loss and inflammatory status, markers of frailty in aged rats (Mayot et al., 2007), but to our knowledge, there are no other clinical studies that have determined α2M levels and their relationship to frailty. Moreover, other reports of frailty among community-dwelling older people reported significant sex differences in levels of several biomarkers between non-frail, pre-frail, and frail individuals (W. Chu et al., 2023; Yin et al., 2020). Thus, we expected to find a significant association between CRP and IL-6 on the basis of many studies linking these biomarkers with the onset of frailty (Marcos-Pérez et al., 2020; Pothier et al., 2022) and with specific components of Fried's criteria (Gómez-Rubio et al., 2022; Santos Morais Junior et al., 2020).

We found that pre-frailty and frailty affected 59% and 9% of women aged ≥60 years, respectively. The

frequency of pre-frailty was similar to other studies, but frailty was lower than the estimates reported by previous cross-sectional studies that included data from LAC (Aguilar-Navarro et al., 2012; Alvarado et al., 2008; Curcio et al., 2014; Melo Filho et al., 2020; Ocampo-Chaparro et al., 2019; Santamaría-Ulloa et al., 2023). In each of these studies, being female increased the risk of frailty. Likewise, a community-dwelling study in Thailand found sex differences in frailty prevalence, reporting 70% and 17% of prefrail and frail, respectively, among their sample of older women (Semmarath et al., 2019). Notably, a consistently greater percentage of older women are pre-frail relative to frail, indicating the importance of identifying biomarkers as well as other associated factors to enable early interventions that may contribute to delaying or possibly reversing the progression to more frail states.

Our study addresses the gap in data specific to older Hispanic women and frailty in Central America. A systematic review and meta-analysis (Ofori-Asenso et al., 2019) estimated that approximately 1 in 6 community-dwelling older adults are frail, with higher rates of frailty among women than men. Studies performed in LAC countries using the Fried criteria include Mexico (Aguilar-Navarro et al., 2012; Castrejón-Pérez et al., 2017), Brazil (Gomes et al., 2018; Lanziotti Azevedo Da Silva et al., 2015), and Colombia (Gomes et al., 2018; Ocampo-Chaparro et al., 2019), but only the studies in Mexico and one from Colombia reported results by sex.

Our results revealed also that older age and multimorbidity were associated with increased frailty, whereas higher income and greater independence in instrumental activities of daily living were protective factors. In accordance with our results, other studies conducted in LAC reported that factors associated with frailty include older age, being female, having low education, higher comorbidity, poor self-perceived health, functional and cognitive disabilities, and insufficient current income (Curcio et al., 2014; Ocampo-Chaparro et al., 2019; Ogaz-González et al., 2024; Rosero-Bixby & Dow, 2009). Other findings have linked prefrailty and frailty with limitations in performing activities of daily living (Melo Filho et al., 2020). Thus, our results are generally consistent with reports from other LAC regarding demographic, lifestyle, clinical and health determinants of frailty status.

Several study limitations and strengths must be acknowledged. First, we were unable to explore sex differences in frailty due to a limited sample size of men enrolled in the PARI-HD study. However, ongoing efforts to increase male enrollment should mitigate this limitation in the near future. Second, the present analyses did not allow for causal conclusions regarding the factors influencing frailty. Ongoing longitudinal studies should address these questions. The study's strengths are the inclusion of a wide range of variables alongside the Fried criteria and examination of a wide range of plasma proteins.

Conclusion

Our findings indicate cross-sectional associations between frailty and symptoms of geriatric depression and levels of plasma α2M and $pTau_{181}$ in a sample of Hispanic community-dwelling older women. These results point to the benefit of frailty assessments for identifying women at risk and for developing strategies to slow down or reverse its progression. In addition, biomarkers may help to identify people at risk of frailty before clinical manifestations appear.

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Author Contributions

GR: Investigation, Writing – original draft – review & editing. AT: Formal Analysis, Writing – review & editing. DO: Methodology, Writing – review & editing. AV: Writing – review & editing. MC: Writing – review & editing. SRA: Writing – review & editing. EFM: Writing – review & editing. CXH: Writing – review & editing. FW: Writing – review & editing. SOB: Writing – review & editing and GB: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Writing –original draft, Writing – review & editing.

Declaration of Conflicting Interests

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Ethics and Informed Consent Statement

The studies involving humans were approved by Institutional Bioethics Committee of the Caja del Seguro Social (P-083-16). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Data Availability Statement

Raw data were generated for the Panama Aging Research Initiative—Health Disparities (PARI-HD) study, subscribed to the Instituto de Investigaciones Científicas y Servicios de Alta Tecnología (INDICASAT-AIP). Derived data supporting the findings of this study are available from the corresponding author (GB) on request.

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