Send Orders for Reprints to reprints@benthamscience.net

Current Aging Science, 2018, *11*, 236-241

RESEARCH ARTICLE

Inflammatory Biomarkers, Depressive Symptoms and Falls among the Elderly in Panama

Gabrielle B. Britton[a,*], Sid E. O'Bryant[b], Leigh A. Johnson[b], James R. Hall[b], Alcibiades E. Villarreal[a], Diana C. Oviedo[c], Ambar R. Pérez-Lao[c], and María B. Carreira[a]

[a]*Neurosciences Center and Clinical Research Unit, Institute of Scientific Research and High Technology Services (INDICASAT AIP), City of Knowledge, Panama;* [b]*University of North Texas Health Science Center, Department of Pharmacology & Neuroscience, Fort Worth, TX, USA;* [c]*Department of Psychology, Santa María La Antigua Catholic University, Panama, Panama*

ARTICLE HISTORY

Received: November 12, 2018
Revised: February 08, 2019
Accepted: February 11, 2019

DOI:
10.2174/1874609812666190215125104

Abstract: ***Background*:** Falls are common among elderly adults, and are predictors of hospitalization, institutionalization and mortality.

***Objective*:** The objective of the present study was to examine the relationship between blood-based markers of inflammation and fall events in a sample of elderly Hispanic adults.

***Method*:** Data were collected from 190 participants enrolled in the Panama Aging Research Initiative study who completed baseline clinical and cognitive assessments. A non-fasting blood sample was obtained. Self-reported falls were classified as no falls, single falls or recurrent (two or more) falls reported in the 12 months prior to baseline evaluations. Serum levels of C Reactive Protein (CRP), T-lymphocyte secreting protein (I-309), interleukin 10 (IL-10), interleukin 6 (IL-6) and interleukin 7 (IL-7) were measured. Global cognition was assessed with the Mini Mental State Examination and depressive symptoms were assessed with the Geriatric Depression Scale (GDS-30). Multinomial logistic regression was used to assess the link between inflammation and fall events.

***Results*:** Depressive symptoms, limitations in Instrumental Activities of Daily Living (IADL), IL-7 and I-309 were significantly related to fall events. Elevated levels of IL-7 increased the likelihood of single and recurrent falls, while increased levels of I-309 were associated only with recurrent falls. Greater IADL limitations and depressive symptoms were associated with an increased likelihood of recurrent falls.

***Conclusion*:** There is a lack of research investigating the relationship between inflammatory biomarkers and fall events. These results provide evidence of risk factors for falls in Hispanic older adults, and could serve to guide public health professionals to establish clinical guidelines to reduce fall risks.

Keywords: Aging, disability, inflammation, depression, Hispanics, Latin America.

1. INTRODUCTION

Falls have a significant impact on health outcomes in the elderly [1]. As the number of falls increases elderly adults experience a greater risk of hospitalization and mortality. Fall-related injuries can result in physical limitations that impact the capacity to perform daily activities independently, place a significant burden on caregivers, and are a leading cause of institutionalization [2]. Moreover, depressive symptoms, which are common among older adults, have been shown also to be associated with falls [3, 4]. Fall events are linked to multiple causes, and so the identification and assessment of factors related to falls could aid in fall prevention [5-7].

Identification of biomarkers that are related to fall events may provide clues into the pathophysiological mechanisms related to falls, which in turn, could lead to novel approaches for identifying individuals at risk for progressing to worse health states. Although several studies have investigated the relationship between inflammatory biomarkers and other age-related conditions, such as cognitive impairment and depression [8], few studies have focused on the relationship between inflammatory markers and falls. Because the immune system undergoes extensive remodeling over the course of aging and has a major impact on an individual's health and survival, an examination of the link between in-

*Address correspondence to this author at the Center of Neurosciences and Clinical Research Unit, Institute of Scientific Research and High Technology Services (INDICASAT AIP), City of Knowledge # 219, Clayton, PO Box 0843-01103, Panama; Tel: +507 5170735; Fax: +507 5070000; E-mail: gbritton@indicasat.org.pa

flammation and falls could shed light on intervention strategies aimed at preventing falls.

Most studies that have examined risk factors associated with falls have been conducted in non-Hispanic white populations, while few have included diverse racial/ethnic minorities [9-11]. Moreover, a significant proportion of the world's aging population lives in developing countries, which will carry a greater share of the burden associated with falls [12]. Despite this, evidence of falls in older adults in developing countries is scarce. The objective of this study was to identify the factors associated with falling in elderly Hispanic adults in Panama. Clinical characteristics, cognitive function, and depressive symptoms, in addition to five inflammatory markers, were assessed in elderly adults who reported no falls, one fall or recurrent falls in order to establish clinical signs of fall risk. Factors that increase with age and may impact this relationship include chronic illness comorbidity, functional limitations, a history of falls, cognitive impairments, depression and physical inactivity [1, 13, 14]. Considering that the aged population is increasing in Panama, as in most developing countries, an increased incidence of chronic medical conditions and other age-related disorders is expected, and thus research to identify the correlates of fall events is timely.

2. MATERIALS AND METHODS

2.1 Participants

Data from this study came from the Panama Aging Research Initiative (PARI) study, an ongoing study of Panamanian aging. The study protocol has been described in detail in previous publications [15, 16]. PARI participants were recruited from the outpatient geriatric services of the largest public hospital of the Social Security (CSS) located in Panama, the capital city of Panama. Inclusion criteria were being at least 65 years of age, willing to participate in baseline and three follow-up interviews over the course of 12-18 months, and provision of informed consent. Exclusion criteria included any physical or medical condition that required current hospitalization or institutionalization or participation in an ongoing clinical study at the time of enrollment. The study protocol was approved by the National Bioethics Committee of the Instituto Conmemorativo Gorgas de Estudios de la Salud and the Institutional Bioethics Committee of the CSS. Participants provided written informed consent in accordance with the principles of the Declaration of Helsinki (1964).

The present report constitutes an analysis of the data from 190 participants who had complete evaluations during the baseline interview and assessment of cognitive function and depressive symptoms. At baseline, each participant underwent a physical exam and clinical interview, and provided information of demographic factors, medical conditions, fall events and functional status. A non-fasting blood sample was obtained. Approximately four months later (M=4.5 months, SD=1.9) participants underwent cognitive testing and assessments of depressive symptoms. Interviewers included physicians, medical students and graduate students. The interviews were conducted in Spanish. Assisted interviews (with a relative, informant or caregiver) were carried out in 12% of cases.

2.2. Variables and Measurement

Participants were asked questions regarding fall events (outcome variable) over the 12 months preceding the baseline interview. We examined the relationship between clinical characteristics and inflammatory biomarkers and the outcome variable, the likelihood (odds ratio) of having experienced a single fall or recurrent falls (two or more) relative to experiencing no falls. Performance in activities of daily living was evaluated through self-report as reported previously [17]. Subjects were asked to indicate whether they had any limitations performing the following seven Basic Activities of Daily Living (BADL): transferring, bathing, dressing, grooming, toileting, feeding, and urinary continence. Limitations in seven Instrumental Activities of Daily Living (IADL) were evaluated: leaving the home independently, preparing a meal, using a telephone, grocery shopping, performing basic house chores, and managing finances and medications. BADL and IADL items were dichotomized as none or at least one. Seven chronic conditions were recorded through self-report: hypertension, coronary heart disease, diabetes, stroke, cancer, chronic lung disease, and arthritis. The number of chronic diseases was coded as a categorical disease indicator of whether a participant reported none or one, two, or three or more conditions (the smallest two categories were grouped due to small numbers). The 30-item Spanish version of the Mini-Mental State Examination (MMSE) was used as a measure of global cognition [18], and scores were adjusted for age and level of education [19]. For regression analyses two MMSE categories were defined: cognitively impaired (< 24) and unimpaired (≥ 24). Depressive symptoms were assessed with the Spanish version of the 30-item Geriatric Depression Scale (GDS-30) [20, 21]. The instrument consists of 30 yes/no items used to identify depression in the elderly, and was applied by the investigator reading the items out loud and registering the participant's responses. For regression analyses participants were classified into one of two categories according to GDS scores. Higher scores indicate a greater possibility of depression. The standard cut-off score of ≥ 11 depressive symptoms was applied to classify depressed individuals [20]. Lastly, participants were asked whether they engaged regularly in physical activity (moderate to intense activity once a week or more), and responses were categorized as yes or no.

2.3. Biomarkers and Assays

Five markers of inflammation were assayed: C-reactive protein (CRP), T-lymphocyte secreting protein (I-309), interleukin-6 (IL-6), interleukin-7 (IL-6), and interleukin-10 (IL-10). Biomarker assays have been described in previous publications [16, 22, 23]. Briefly, non-fasting morning samples were collected with 10 ml serum-separating vacutainer tubes and allowed to clot at room temperature before being centrifuged at 1300 x g for 10 min, aliquoted (1 ml) into polypropylene cryovial tubes and stored at -80°C. Assays were conducted in duplicate *via* a multi-plex biomarker assay platform using electrochemiluminescence (ECL) on the QuickPlex SQ120 Imager from Meso Scale Discovery (MSD;

mesoscale.com) per our previously published protocols [22, 24]. The MSD platform has been used extensively to assay biomarkers associated with a range of human diseases and with greater sensitivity than conventional ELISAs. For each analyte, values that exceeded the limit of detection in > 75% of all the samples for each respective analyte were included in the analyses. These criteria were fulfilled by all analytes in the present study. We recently published ranges and CVs for > 1,000 subjects on these assays [22]. In cases where there were values below the limit of detection, we used imputation to assign a value that was 1% below the lowest detectable value for that analyte (< 1% of cases).

2.4. Statistical Analysis

We first examined relationships between self-reported falls (no falls, single fall, or recurrent falls) and demographic and clinical characteristics using descriptive statistics. We then examined the independent relationships between demographic and clinical characteristics and falls in an age-, sex- and education-adjusted multinomial logistic regression analysis. This strategy examined the association between clinical and functional variables and single and/or recurrent falls, compared to the absence of falls. Age, sex and education were included as covariates based on evidence of their influence on the relationship between predictors and falls [11, 25, 26]. Odds Ratios (OR) and 95% confidence intervals (CIs) are reported. All analyses were conducted using SPSS 21.0.

3. RESULTS

Demographic characteristics of the sample are provided in Table **1**. Thirty-seven percent (*n*= 71) of participants reported at least one fall in the twelve months prior to baseline assessment. Participant ages ranged from 65 to 102 years with a mean age of 78.0 (*SD*= 7.7). Sixty-five percent of participants were female (*n*= 123) and approximately half of the sample (49.5%) completed six years of education (primary) or less. Sixteen percent of the sample (*n*= 17) exceeded the cut-off score of ≥ 11 depressive symptoms and were classified as depressed.

In sex, age and education-adjusted multinomial logistic regression analyses, there were significant associations be-

Table 1. Characteristics of participants who reported no falls, a single fall or recurrent falls.

Characteristic	No Falls (n= 119)	Single Fall (n= 29)	Recurrent Falls (n= 42)	*p**
	Mean/% (SD/n)	Mean/% (SD/n)	Mean/% (SD/n)	
Age, years	77.9 (7.8)	77.7 (6.8)	78.7 (8.2)	NS
Sex, female	63.9% (76)	65.5% (19)	66.7% (28)	NS
Education, years	8.3 (3.8)	8.5 (4.1)	7.0 (3.7)	NS
Marital Status, not married or partnered	54.6% (65)	51.7% (15)	59.5% (25)	NS
BADL	0.31 (0.08)	0.55 (0.15)	0.50 (0.06)	NS
IADL	1.01 (0.14)	1.76 (0.31)[a]	1.50 (0.22)[a]	0.027
Comorbidity	-	-	-	0.002
0-1 Conditions	28.6% (34)	20.7% (6)	16.7% (7)	-
2 Conditions	41.2% (49)	20.7% (6)	21.4% (9)	-
3+ Conditions	30.3% (36)	58.6% (17)	61.9% (26)	-
Physical activity, not active	61.3% (73)	86.2% (25)	66.7% (28)	0.040
Global cognition (MMSE)	25.6 (5.2)	23.6 (4.5)	25.3 (4.5)	NS
Depressive symptoms (GDS-30)	7.1 (0.5)	8.7 (1.3)[a]	8.7 (0.9)[a]	0.041
Biomarkers	-	-	-	-
CRP (ng/ml)	3.34 (0.83)	2.68 (0.56)	5.69 (1.93)	NS
I309 (pg/ml)	3.71 (0.56)	5.10 (0.49)	6.34 (0.60)	0.023
IL-10 (pg/ml)	1.96 (0.45)	1.15 (0.12)	3.50 (1.62)	NS
IL-6 (pg/ml)	6.22 (2.57)	3.90 (1.44)	4.33 (0.75)	NS
IL-7 (pg/ml)	10.30 (0.60)	13.37 (2.00)[a]	12.28 (0.86)[a]	0.037

Data are means (standard deviation) for continuous variables or percentage (number) for categorical variables. *Continuous variables were analyzed with one-way analysis of variance followed by Tukey's post hoc test and categorical variables with chi-square test. [a]Significantly different from individuals who reported no falls. SD = Standard Deviation; NS = Not Statistically significant (p>0.05); BADL = Basic Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MMSE = Mini-Mental State Exam; GDS-30 = Geriatric Depression Scale (30-item); CRP = C Reactive Protein; I309 = T lymphocyte secreted protein; IL-10 = Interleukin 10; IL-6 = Interleukin 6; IL-7 = Interleukin 7.

Table 2. Sex-, age- and education-adjusted multinomial logistic regression analysis examining the relationship between clinical characteristics and inflammatory biomarkers and the likelihood of self-reported falls.

Characteristic	Single Fall OR [95% CI] (Ref: No Falls)	Multiple Falls OR [95% CI] (Ref: No Falls)
Not married/partnered	0.65 [0.12-3.61]	0.48 [0.12-1.90]
BADL (at least one limitation)	0.19 [0.02-1.74]	0.64 [0.14-2.85]
IADL (at least one limitation)	1.45 [0.19-11.07]	4.28* [1.03-17.73]
Comorbidity	-	-
0-1 Conditions	-	-
2 Conditions	1.91 [0.23-15.48]	0.40 [0.07-2.41]
3+ Conditions	0.93 [0.11-8.29]	1.08 [0.22-5.21]
Physical activity, not active	2.30 [0.68-7.70]	0.85 [0.36-2.03]
Global cognition (MMSE)	1.92 [0.72-5.11]	1.11 [0.48-2.57]
Depressive symptoms (GDS-30)	0.82 [0.06-11.41]	2.30* [1.48-11.01]
Biomarkers	-	-
CRP (ng/ml)	1.00 [0.89-1.10]	1.00 [0.65-1.17]
I309 (pg/ml)	1.13 [0.98-1.32]	1.76* [1.10-2.36]
IL-10 (pg/ml)	0.60 [0.18-2.01]	1.00 [0.89-1.12]
IL-6 (pg/ml)	0.98 [0.91-1.06]	1.00 [0.95-1.05]
IL-7 (pg/ml)	1.20** [1.04-1.37]	1.14* [1.01-1.29]

Note: This analysis controls for age, sex and education. OR = odds ratio; BADL = Basic Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MMSE = Mini-Mental State Exam; GDS-30 = Geriatric Depression Scale (30-item); CRP = C Reactive Protein; I309 = T Lymphocyte-Secreted Protein; IL-10 = Interleukin 10; IL-6 = Interleukin 6; IL-7 = Interleukin 7. Significance levels are indicated at $*p < .05$; $**p < .01$.

tween IADL limitations, depressive symptoms, and inflammatory biomarkers with fall events (Table **2**). Participants with increased levels of IL-7 were more likely to have reported single or multiple falls than participants who reported no falls. Likewise, those with increased I-309 levels were more likely to have suffered recurrent falls compared to those who reported no falls. In addition, having at least one IADL limitation and a greater number of depressive symptoms was associated with a greater likelihood of reporting recurrent falls. Chronic illness comorbidity, cognitive impairment, lack of physical activity and CRP, IL-10 and Il-6 levels were not significantly associated with self-reported falls.

4. DISCUSSION

Falls are one of the most common problems among older individuals threatening their independence and increasing morbidity, mortality, hospitalization and institutionalization. In the United States, the Centers for Disease Control and Prevention (CDC) reports that approximately 25% of older adults fall annually [27]. Studies have shown that falls are associated with various factors including muscle weakness, a history of falls, depressive symptoms and impairments in cognition, activities of daily living and balance, among others [1]. Many potential biomarkers are being tested for their association with age-related disease and prospective mortality. Thus, the aim of the present study was to examine the relationship between self-reported falls and various clinical factors and inflammatory biomarkers that have been associated with aging-related conditions. In the present study, we report that depressive symptoms and limitations in instrumental activities of daily living, as well as two inflammatory biomarkers, IL-7 and I-309, were associated with falls.

Among the variables most strongly associated with recurrent falls were limitations in IADL and increased depressive symptoms. Several studies have shown that falls and fall related injuries are associated with functional decline [28] and in many cases are independent predictors of functional decline in community-dwelling older adults [2]. One study found that in younger groups of healthier older adults, those who fall frequently or report injury are at highest risk for functional dependence in activities of daily living [29]. Likewise, in various cross-sectional and longitudinal studies depression has been shown to be a potential risk factor for falls [25, 30, 31]. Our results indicate a strong likelihood of limitations in IADL and depression in recurrent fallers. Participants with limitations in at least one IADL who also reported depressive symptomatology were four and two times as likely, respectively, to report multiple falls than no falls, suggesting that dependent and depressed individuals are at the highest risk for frequent falls.

There is scarce data available regarding the relationship between inflammatory biomarkers and falls. One recent study showed that increased 25- hydroxyvitamin D (S-

25(OH)D), a marker of skeletal devepment, was associated with fewer falls in a cohort of Finnish home-dwelling women [32]. In other studies, a meta-analysis of factors associated with frailty and pre-frailty, which pose the threat of an increased risk of age-related complications including fall incidents, showed that frailty status was associated with significantly higher levels of serum inflammatory biomarkers such as CRP and IL-6 [33]. Similar results were found for plasma concentrations of other inflammatory glycoproteins (transferrin, fibrinogen, and IL-6) and frailty [34]. Together, studies examining frailty suggest that inflammatory proteins may be helpful in the assessment of physical decline as a complement to the clinical evaluation and assessment. Moreover, falls and frailty, although defined differently, share many characteristics, and thus both may provide some insight into age-related disease processes.

In the present study, analysis of the five biomarkers assessed revealed that higher levels of IL-7 and I-309 were significantly associated with a greater likelihood of falls. Previous work has shown that IL-7 and its receptor, IL-7R, are implicated in the differentiation, proliferation, and survival of immune cells, and recent studies have supported the IL-7 pathway as a biomarker of successful aging [35], although results have not been consistent. In general, studies support a critical role for the IL-7 pathway in the homeostasis of the immune system and in the maintenance of healthspan during aging. In one study, longevity was associated with low levels of IL-7R, [35] which limits the number of cells capable of responding to IL-7 [36] and also reduces levels of serum IL-7 [37]. However, the relationship between levels of IL-7R gene expression and ten-year mortality was found to be age dependent; in nonagenarians higher levels of IL-7R were associated with longer lifespan [35]. On the other hand, individuals suffering from autoimmune disease express increased levels of IL-7R complex genes [38, 39]. In sum, the IL-7 pathway appears to be implicated in the rate of aging but in an age- and health-dependent manner. Here we show that fall events are associated with an increase in this serum marker. Further work is needed to clarify the mechanisms that link IL-7 to fall events and to healthspan in general.

To our knowledge, no studies have linked I-309 to fall events in the elderly, although several studies have linked I-309 with Alzheimer's Disease (AD) [16, 24, 40, 41], the most common form of dementia in the elderly. I-309 is a small glycoprotein secreted by activated T cells that belongs to a family of inflammatory cytokines known as chemokines. In recent studies from our laboratory in which we established blood-based biomarker profiles of AD and Mild Cognitive Impairment (MCI) compared with subjects with normal cognition, I-309 was the number one marker in the risk score for both AD and MCI [16], and was found to be significantly elevated in both MCI and AD subjects relative to controls. Moreover, I-309 was among the top 10 markers that overlapped with those from our cross-validated 21 serum-based biomarker panel for AD [24]. Levels of I-309 in cerebrospinal fluid, assessed post-mortem, were also found to be independently associated with the severity of cognitive impairment in AD but not with other neurodegenerative disorders [41]. Because I-309 is associated with the inflammatory response, these findings suggest that falls, like AD, are associated with immune system dysfunction.

This study has several limitations, the most important being the cross-sectional design of the study. Ongoing assessments are being conducted every 18-24 months and the link between baseline measures and risk of future fall events is now being investigated. Another limitation is that the findings cannot be generalized to elderly adults who are institutionalized or hospitalized. More extensive studies, preferably randomized controlled trials with larger sample sizes, will shed light on risk factors associated with fall events.

CONCLUSION

Biomarkers can improve our understanding of and risk for age-associated conditions, changes in health status, morbidity, and mortality. The present study has shown the relationship between inflammatory biomarkers to the incidence of falls in elderly adults. The association of two inflammatory markers, IL-7 and I-309, with single and/or recurrent falls, with depressive symptoms, and with limitations in the capacity to carry out everyday activities stand out as strong predictors of recurrent falls in particular. These findings support a role of inflammatory biomarkers in the likelihood of falls, and emphasize that co-existing medical conditions should be included in assessments looking for potential risk factors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the National Bioethics Committee of the Instituto Conmemorativo Gorgas de Estudios de la Salud and the Institutional Bioethics Committee of the CSS, Panama.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study, the reported experiments on humans were in accordance with the ethical standards of the committee responsible for human experimentation (institutional national), and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/).

CONSENT FOR PUBLICATION

Participants provided written informed consent for this study.

CONFLICT OF INTEREST

The authors report no conflicts of interest. This research was supported by the Melo Brain Project, Secretaría Nacional de Ciencia, Tecnología e Innvovación (SENACYT) of Panama, Universidad Católica Santa María la Antigua (SRUI-CPEI-ID-PSI-2013-2014-002 awarded to GBB and SRUI-CPEI-ID-PSI-2013-2014-004 awarded to DCO) and Sistema Nacional de Investigación (SNI) of Panama (GBB, AEV, MBC and DCO).

ACKNOWLEDGEMENTS

We thank the administration and support staff of the Complejo Hospitalario Dr. Arnulfo Arias Madrid of Caja de Seguro Social for their assistance in conducting this study and the following collaborators from the Panama Aging Research Initiative: Aquiles Aguilar MD, Frank Ferro MD, Patricia González MD, Vanessa González MD, Luis Lee MD, María Mendieta MD, Ribana Molino MD, Astevia Montalván MD, Josué Morales MD, Viterbo Osorio MD, Vivian Vásquez MD and Ramón Zarak MD.

REFERENCES

[1] Rubenstein LZ. Falls in older people: Epidemiology, risk factors and strategies for prevention. Age Ageing 2006; 35(SUPPL.2): 37-41.

[2] Tinetti ME, Williams CS. The effect of falls and fall injuries on functioning in community-dwelling older persons. J Gerontol Ser A Biol Sci Med Sci 1998; 53A(2): M112-9.

[3] Hoffman GJ, Hays RD, Wallace SP, *et al.* Depressive symptomatology and fall risk among community-dwelling older adults. Soc Sci Med 2017; 178: 206-13.

[4] Prizer LP, Smith ML, Housman J, *et al*. Depressive symptomology management and falls among middle aged and older adults. Aging Ment Health 2016; 20(1): 13-21.

[5] Rao SS. Prevention of falls in older patients. Am Fam Physician 2005; 72(1): 81-8.

[6] Stevens JA. A CDC compendium of effective fall interventions: What works for community-dwelling older adults. Second edition. Inj Prev 2010; 1-159.

[7] Sjösten N, Vaapio S, Kivelä SL. The effects of fall prevention trials on depressive symptoms and fear of falling among the aged: A systematic review. Aging Ment Health 2008; 12(1): 30-46.

[8] Singh T, Newman AB. Inflammatory markers in population studies of aging. Ageing Res Rev 2011; 10(3): 319-29.

[9] Nicklett EJ, Taylor RJ, Rostant O, *et al*. Biopsychosocial predictors of fall events among older african americans. Res Aging 2017; 39(4): 501-25.

[10] Nicklett EJ, Taylor RJ. Racial/ethnic predictors of falls among older adults: The health and retirement study. J Aging Health 2014; 26(6): 1060-75.

[11] Hanlon JT, Landerman LR, Fillenbaum GG, *et al*. Falls in African American and white community-dwelling elderly residents. J Gerontol Ser A Biol Sci Med Sci 2002; 57(7): 473-8.

[12] Stewart WJ, Kowal P, Hestekin H, *et al*. Prevalence, risk factors and disability associated with fall-related injury in older adults in low- and middle-incomecountries: results from the WHO Study on global AGEing and adult health (SAGE). BMC Med 2015; 13(1): 147.

[13] Schwartz AV, Hillier TA, Sellmeyer DE, *et al*. Older women with diabetes have a higher risk of falls: A prospective study. Diabetes Care 2002; 25(10): 1749-54.

[14] Shumway-Cook A, Ciol MA, Hoffman J, *et al*. Falls in the Medicare population: Incidence, associated factors, and impact on health care. Phys Ther 2009; 89(4): 324-32.

[15] Villarreal AE, Grajales S, Lopez L, *et al*. Cognitive impairment, depression, and cooccurrence of both among the elderly in panama: Differential associations with multimorbidity and functional limitations. Biomed Res Int 2016; 2016: 7 pages.

[16] Villarreal AE, O'Bryant SE, Edwards M, *et al*. Serum-based protein profiles of Alzheimer's disease and mild cognitive impairment in elderly Hispanics. Neurodegener Dis Manag 2016; 6(3): 203-13.

[17] Villarreal AE, Grajales S, López L, *et al*. Limitations in activities of daily living among dementia-free older adults in Panama. Ageing Int 2018; 43(2): 1-17.

[18] Folstein MF, Folstein S, McHugh P. Mini Mental Test. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-98.

[19] Blesa R, Pujol M, Aguilar M, *et al*. Clinical validity of the "Mini-Mental State" for Spanish speaking communities. Neuropsychologia 2001; 39(11): 1150-7.

[20] Yesavage JA, Brink TL, Rose TL, *et al*. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res 1982; 17(1): 37-49.

[21] Izal M, Montorio I. Adaptation of the geriatric depression scale in spain. Clin Gerontol 1993; 13(2): 83-91.

[22] O'Bryant SE, Edwards M, Johnson L, *et al*. A blood screening test for Alzheimer' s disease. Alzheimers Dement Diag Assess Dis Monit 2016; 3: 1-8.

[23] O'Bryant SE, Mielke MM, Rissman RA, *et al*. Blood-based biomarkers in Alzheimer disease: Current state of the science and a novel collaborative paradigm for advancing from discovery to clinic. Alzheimers Dement 2017; 13(1): 45-58.

[24] O'Bryant SE, Xiao G, Zhang F, *et al*. Validation of a serum screen for alzheimer's disease across assay platforms, species, and tissues. J Alzheimer's Dis 2014; 42(4): 1325-35.

[25] Andresen EM, Wolinsky FD, Miller JP, *et al*. Cross-sectional and longitudinal risk factors for falls, fear of falling, and falls efficacy in a cohort of middle-aged african americans. Gerontologist 2006; 46(2): 249-57.

[26] de Rekeneire N, Visser M, Peila R, *et al*. Is a fall just a fall: Correlates of falling in healthy older persons. The health, aging and body composition study. j Am Geriatr Soc 2003; 51(6): 841-6.

[27] Centers for Disease Control and Prevention. Important facts about falls [Internet]. 2017. Available from: https://www.cdc.gov/homeandrecreationalsafety/falls/adultfalls.html

[28] Jefferis BJ, Iliffe S, Kendrick D, *et al*. How are falls and fear of falling associated with objectively measured physical activity in a cohort of community-dwelling older men? BMC Geriatr 2014; 14: 114.

[29] Sekaran NK, Choi H, Hayward RA, *et al*. Fall-associated difficulty with activities of daily living in functionally independent individuals aged 65 to 69 in the United States: A cohort study. J Am Geriatr Soc 2013; 61(1): 96-100.

[30] Deandrea S, Lucenteforte E, Bravi F, *et al*. Risk factors for falls in community-dwelling older people: A systematic review and meta-analysis. Epidemiology 2010; 21(5): 658-68.

[31] Iaboni A, Flint AJ. The complex interplay of depression and falls in older adults: A clinical review. Am J Geriatr Psychiatry 2013; 21(5): 484-92.

[32] Uusi-Rasi K, Patil R, Karinkanta S, *et al*. Serum 25-hydroxyvitamin D levels and incident falls in older women. Osteoporos Int 2019; 30(1): 93-101.

[33] Soysal P, Stubbs B, Lucato P, *et al*. Inflammation and frailty in the elderly: A systematic review and meta-analysis. Ageing Res Rev 2016; 31: 1-8.

[34] Darvin K, Randolph A, Ovalles S, *et al*. Plasma protein biomarkers of the geriatric syndrome of frailty. J Gerontol A Biol Sci Med Sci 2014; 69(2): 182-6.

[35] Passtoors WM, van den Akker EB, Deelen J, *et al*. IL7R gene expression network associates with human healthy ageing. Immun Ageing 2015; 12(1): 21.

[36] Kim HR, Hong MS, Dan JM, *et al*. Altered IL-7Rα expression with aging and the potential implications of IL-7 therapy on CD8+ T-cell immune responses. Blood 2006; 107(7): 2855.

[37] Banerjee C, Ulloor J, Dillon EL, *et al*. Identification of serum biomarkers for aging and anabolic response. Immun Ageing 2011; 8: 5.

[38] McKinney EF, Lyons PA, Carr EJ, *et al*. A CD8+ T cell transcription signature predicts prognosis in autoimmune disease. Nat Med 2010; 16(5): 586-91.

[39] Bikker A, Hack CE, Lafeber FPJG, *et al*. Interleukin-7: A key mediator in T cell-driven autoimmunity, inflammation, and tissue destruction. Curr Pharm Des 2012; 18(16): 2347-56.

[40] Monson NL, Ireland SJ, Ligocki AJ, *et al*. Elevated CNS inflammation in patients with preclinical Alzheimer's disease. J Cereb Blood Flow Metab 2014; 34(1): 30-3.

[41] Hu WT, Chen-Plotkin A, Arnold SE, *et al*. Novel CSF biomarkers for Alzheimer's disease and mild cognitive impairment. Acta Neuropathol 2010; 119(6): 669-78.