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Prevalence of Frailty and Association with the Immune Profile Among Older Adults with HIV at a University-Affiliated Hospital

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Abstract

Background: The number of older adults living with HIV (OALHIV) has increased significantly; several similarities have been found between aging and HIV infection. Patients with HIV can present with premature complications that are only observed in chronological aging, this is called Geriatrics Syndromes (GS). The immune profile (e. g. absolute CD4+ T cells/µL count, absolute CD8+ T cells/µL count, and viral load) has become relevant as a predictor of negative outcomes in the context of HIV infection. The association between frailty and the status of immune system in elderly adults with HIV is not clear.

Objectives: To determine the prevalence of frailty and its association with immune profile (IP) (absolute CD4+ T cells/µL count, absolute CD8+ T cells/µL count, and viral load) in OALHIV and attending HIV-AIDS clinics at a university-affiliated hospital in Mexico.

Methods: Cross-sectional study in participants OALHIV, recruited in a two-year period (January 2015 and January 2017). Participants underwent a comprehensive geriatric assessment (CGA) and diagnosis of frailty and IP was obtained. A multivariate linear regression analysis was determined to establish the association between Immunological Profile and Frailty Score (FS).

Results: We included 116 subjects; mean age was 56 years (SD ± 6), women accounted for 20%. Overall, 14% were frail. After adjustment, linear regression analyses showed that baseline IP model did not influenced in variance of the FS.

Conclusions: This study shows that the prevalence of frailty is 14% in the studied population OALHIV. The combination of IP variables cannot account for the variation in the dependent variable (FS).

Keywords: Frailty; HIV; Geriatric Syndrome; Immunological profile

Introduction

The number of older adults living with HIV (OALHIV) has increased significantly since highly effective antiretroviral therapy (HAART) is now readily available. Thus, with the use of HAART, infection has become a chronic disease [1]. The change in the HIV population is so unexpected that the American Society of Geriatrics and the American Academy of HIV had to re-define "elderly". In the context of people with HIV, all patients of 50 years of age and older are considered elderly [2]. The Center for Disease Control (CDC) has projected an increase in OALHIV. In Mexico, almost 20,000 cases have been recorded from 1983 to 2011 in people over 50 years of age (12.5% of the total affected population) [3]. In the US, it is estimated that almost 50% of the HIV-infected population is over 50 year's old [1,2].

Several similarities have been found between aging and HIV infection: DNA damage and impairment of repair ability, neuro-endocrine alterations, and immunosenescence. Patients with HIV have premature complications usually observed in chronological aging, such as, cognitive impairment, disability,

malnutrition and frailty [4-10]. The presence of frailty is an independent factor for morbid-mortality in the HIV infection and although there is currently no specific definition of frailty in OALHIV, it has been accepted as a condition characterized by a decreased physiological reserve and poor response to stressors. One way to assess frailty is through the Frailty Score (FS) proposed by Linda Fried [11,12].

It has been hypothesized that the premature aging of CD4+ T cells in HIV infection may play a fundamental role to the development of the GS observed in OALHIV [13-18].

The aim of this study is to determine the prevalence of frailty and its association with immunological profile (IP) in OALHIV, attending the HIV-AIDS clinics at a university-affiliated hospital in Mexico.

Methods

Participants

One hundred and sixteen patients were included in this cross-sectional study. Participants are all diagnosed with HIV and attending HIV-AIDS clinics at a university-affiliated hospital in Guadalajara, Mexico. All patients were 50 years of age and older. Subjects were identified through the appointment schedule of the outpatient HIV/AIDS clinic. Recruitment occurred between January 1, 2015 and January 29, 2017. Eligible patients had to be 50 years or older with a confirmatory diagnosis of HIV infection. They were all invited to participate in the study and provided written informed consent. All participants were subjected to the comprehensive geriatric assessment (CGA) carried out by trained medical staff. Patients who did not complete the assessment were excluded. The study protocol was reviewed and approved by the Hospital Ethics Committee.

Measures

Frailty

Frailty was defined according to the five components proposed by Fried et al. [12]. Weight loss was defined as self-report of recent and unintentional weight loss (≥ 10 lbs. or more) within a year. Exhaustion was determined by two questions from the CES-D scale: "I felt that everything I did was an effort" and "I could not get going". Slowness was defined by the lowest quintile on timed 4.5-meter walking test, at usual pace, adjusted for sex and height. Weakness was identified by the lowest quintile on grip-strength test adjusted for sex and body mass index. Low physical activity was established according the Physical Activity Scale for the Elderly as recommended. As proposed, participants meeting three or more criteria were classified as fragile, one or two were considered as pre frail, and not frail if none of the criteria met [12]. The frailty score (FS) was summed up in a score ranging from 0 to 5, where a higher score is indicative of more positive criteria.

Correlations

Social and demographic variables included age, gender, and the presence of ten chronic diseases including diabetes, hypertension, dyslipidemia, cancer, myocardial infarction, stroke, chronic obstructive pulmonary disease, cirrhosis, osteoarthritis, and/or chronic kidney disease. All these comorbidities were summed up in a score ranging from 0 to 10 [19]. Time from HIV diagnosis and time on combination antiretroviral therapy (cART), both in years, were considered as continuous covariates. The absolute CD4+ T cells/μL count, absolute CD8+ T cells/μL count, the CD4/CD8 ratio, Viral load (VL) and HIV-clinical stage was determined by retrospective searched in the records of each participant.

Immunological profile

Four immunological variables were investigated as independent variables: absolute CD4+ T cells/μL count, absolute CD8+ T cells/μL count, the CD4/CD8 ratio, and viral load. The scores of the immunological variables used in this study were those recorded at the time of each patient´s HIV diagnosis, this means that they were obtained from the clinical file and in a retrospective manner.

HIV 1-RNA viral load in plasma was measured through the ROCHE Amplicor HIV-1 Monitor™ 1.5 Ultrasensitive PCR techniques. Controlled or undetectable HIV infection was considered if the viral load was ≤ 50 copies/mL, as a low viral load with a count between 51 to 199 copies/mL, and in virologic failure if viral load was ≥ 200 copies/mL during at least six months under treatment.

Statistical analyses

Variables were described using frequencies, proportions and/or means and standard deviations when appropriate. X^2 test or Student's *t* test were used to compare the groups of participants with and without frailty. In order to develop an explanatory model, an unadjusted linear regression analysis was created to identify the immunological variables correlates to frailty scores. Regression diagnostics were performed to investigate any violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity (variance inflation factor and Durbin-Watson test). The choice of independent variables used was based on the review of literature and clinical judgment. In the next step, variables that were statistically significant were included in multivariate regression models with additional adjustment for age, sex and comorbidities. The baseline for 3 immunological variables: absolute CD4+ T cells/μL count, absolute CD8+ T cells/μL count, and viral load were the model of the regression analysis. The scores of these 3 variables contained were added in a range from 0 to the highest score in each of them. For the linear regression only 3 immunological characteristics were used as continuous variables. All statistical tests were performed using 95% confidence intervals (CI). Statistical analyses were conducted using Stata statistical package for Windows® (Stata Corp., Texas, IL., v. 14).

Results

Mean of age was 56 (SD ± 5; range 50 to 84) and 80% of participants were men. Table 1 shows the socio-demographic

Table 1: Prevalence of frailty according to the sociodemographic and clinical characteristics

Variable (total)	*Frailty*		
	Not frail n, (%)	**Pre-frail n, (%)**	**Frail n, (%)**
Sex			
Female (20)	3 (15)	13 (65)	4 (20)
Male (83)	11 (13.3)	62 (74.7)	10 (12)
Age at HIV diagnosis ≥ 50 years			
Yes (43)	6 (14)	28 (65)	9 (21)
No (60)	8 (13)	47 (78)	5 (9)
CD8 T at HIV diagnosis ≥ 25%			
Yes (9)	2 (22)	6 (67)	1 (11)
No (64)	8 (12)	47 (73)	9(15)
Viral loud at HIV diagnosis ≤ 50 copies/mL			
No (56)	8(14)	37(66)	11 (20)
Yes (47)	6(13)	38(81)	3(6)
Age at HAART ≥ 50 years			
Yes (40)	5 (12)	27(68)	8 (20)
No (61)	8 (13)	47 (77)	6 (10)
Age on HAART at frailty diagnosis ≥ 50 years			
Yes (49)	8 (16)	34 (60)	7(14)
No (52)	5 (10)	40 (77)	7 (13)
Age at frailty diagnosis ≥ 50 years			
Yes (34)	4 (12)	21 (62)	9 (26)
No (69)	10 (14)	54 (78)	5 (8)*
CD4 T at HIV diagnosis (≥ 200 cells/μL)			
Yes (30)	6 (20)	21 (70)	3 (10)
No (70)	8 (11)	54 (74)	11 (15)
CDC clinical stage			
A1 (11)	2 (18.2)	8 (72.7)	1 (9.1)
A2 (6)	1 (16.7)	5 (83.3)	0
A3 (5)	0	5 (100)	0
B1 (8)	1 (12.5)	6 (75)	1 (12.5)
B2 (10)	3 (30)	5 (50)	2 (20)
C1 (18)	3 (16.7)	12 (66.7)	3 (16.7)
C2 (26)	1 (3.8)	21 (80.8)	4 (15.4)
C3 (19)	3 (15.8)	13 (68.4)	3 (15.8)

*P<0.05

and health-related characteristics of participants. Diabetes and hypertension were the most frequent chronic diseases (21% and 27%, respectively); 34% of participants were aged 50 years or more at the time of HIV-diagnosis. At time of HIV-diagnosis, 71% had <200 CD4+ T cells/μL, 66% had <14% of CD4+ T cells, the viral load median was 63650 copies/mL (IQR: 434-278323), CD4+ T cells/μL count nadir median was 99.9 (IQR: 41-205), with a CD4+ T cells percentage median of 9.1% (IQR: 5-15), and CD8+ T cells/μL count nadir with a median of 624 (IQR: 297-1086), and a CD4/CD8 ratio media of 0.27, 19% had a detectable VL and 7.8% had virologic failure.

Nineteen percent presented a related-HIV neurological disease and 30% a cardiovascular disease. The prevalence of co-infection with hepatitis B virus was 11% and 9% for hepatitis C virus.

14% of participants were classified as frail. Nevertheless, the comparison between groups showed no differences regarding HIV-clinical stage, sex, and immunological variables.

The univariate linear regression (Table 2) showed that variables with lowers *P*-values were age at the time of HIV-diagnosis and age at initiation of HAART. The CD4/CD8 ratio was not significant at this level of analysis.

The immunological profile model: CD4+ T cells/μL, CD8+ T cells/μL and viral loud nadir, did not reach statistically significance in the multivariate linear regression.

Discussion

In the present study, CD4+ T cells/μL, CD8+ T cells/μL and viral loud nadir were no independently associated with frailty. Our results demonstrated no association between scores on the four immunological variables and FS in OALHIV. Multivariate linear regression analyses cannot account the variance of the frailty score, and the prevalence of frailty was 14%.

Strong association has been observed between HIV infection and frailty. The findings most pronounced have been demonstrated among men with low CD4+ T lymphocyte count (<350 cells/μL), high viral load (>100,000 copies/mL), clinically defined AIDS, longer duration of HIV infection and older age [17]. Association between frailty and low CD4+ T lymphocyte count has been replicated in other cohorts. In the Women's Interagency HIV Study (WIHS), frailty was higher among HIV-infected women with AIDS (12%) or with a CD4+ T lymphocyte count <100 cells/μL (20%) compared to HIV-uninfected women (8%), HIV-infected women without AIDS (7%), or HIV-infected women with CD4 count >500 cells/μL (6%) [18].

However, our result showed that neither the viral load level nor baseline CD4 cells/μL lower scores explained the FS, as demonstrates by other studies [10]. We believe that variations in the cut-off to measure immunologic profile among all studies may explain the absence of statistical significance of our results between low CD4+ T lymphocyte count, viral load, and FS.

Table 2: Coefficients (95%CI) for the effects of a standard deviation increase in frailty scores at baseline on change in predictor variables scores.

Predictor variables, per SD	Univariate Regression	Multivariate Regression
	β (SE), *P-value*	**β (SE), *P-value***
Age	0.276 (0.011), *0.003*	
Sex	-0.039 (0.221), *0.676*	
Co-morbid	0.143 (0.074), *0.124*	
Age at the time of HIV-diagnosis	0.206 (0.009), *0.027*	
Age at initiation of HAART	0.227 (0.009), *0.014*	
Years living with HIV-diagnosis	-0.087 (0.013), *0.355*	
Years living with HAART	-0.100 (0.015), *0.285*	
CD4	-0.036 (0.001), *0.698*	0.083 (0.001), *0.575*
CD8	-0.009 (0.000), *0.923*	-0.032 (0.000), *0.751*
Viral loud nadir	0.047 (0.000), *0.617*	0.049 (0.000), *0.605*

Thus, to the best of our knowledge, this is one of the first studies to identify frailty among OALHIV through the Fried Score in Latin America. Studies have reported a prevalence of frailty between 5-33% in routine HIV care [20-25]. In our study we found a prevalence of fragility of 14%. Variations in the frailty definition limit the comparisons of frailty prevalence between study populations. This study also it is the first in which the FP subtypes have been described in OALHIV so we don't know if they are similar from other regional studies.

Now it is clear that OALHIV suffer from an accelerated aging due to the persistent and chronic activation of the immune system that leads to immune exhaustion and accelerated immunosenescence, even in the presence of virological control [23-25]. Several associations between frailty and HIV infection have been suggests in previous research [26-28]. A clinical expression of this is an increased prevalence of GS. Thus, HIV-infected patients are biologically older than their chronological age, and they suffer from aging-related problems, such as frailty [26,27].

Ávila-Funes evaluated a sample in Mexico City, with similar characteristics to our patient population: all the participants were receiving HAART at the time of the study. One of the main differences is the better immunological status and the youthness of our sample [28].

Although CD4 count is a strong predictor of frailty, some studies have shown a lack of association between nadir CD4 cell count and frailty [22,25]. A study found that frail participants had immune restoration as indicated by higher CD4 count and suppressed viral load [29]. Another study described that the viral load was not associated with the frailty in the model that included CD4 cell count [21]. These results can be the evidence that frailty manifestations in OALHIV could be a final common pathway of diseases associated with wasting as seen in the geriatrics syndromes [17]. In some studies, the presence of frailty in OALHIV has shown an association not only with age or with immunological variables, but also with conditions considered geriatric syndromes [10,20,30].

In summary, the results of the present study show that the presence of worse scores in some immunological variables had no association with frailty in OALHIV.

Our study has several limitations. This is a cross-sectional design and is not possible to know the direction of the associations found and this is a non-probabilistic sample. Patients were recruited consecutively to participate in the study in a HIV-AIDS clinic, thus the sample was consisted of individuals with heterogeneous characteristics (e.g. higher self-care levels, better immunological profile).

The main strengths of our study are FS screening, which was done with standardized CGA, patient sample is one of the largest in the region, and our analysis considers covariates. However, these results must be replicated in a more extensive cohort with a longitudinal approach.

Conclusions

This study shows that the prevalence of frailty is 14% in the studied population OALHIV. The combination of 3 immunological variables cannot explain the variation in the dependent variable (FS). The presence of frailty and its potential negative effects are some of the challenges of this time in which HIV infection has become a disease with which it is possible to grow old. The results of the present study suggest the importance of monitoring other covariates that potentially could have an impact on health status of the elderly population with HIV.

Acknowledgment

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Conflict of Interest

None.

Financial Disclosure

All authors state no financial interest, stock, or derived direct financial benefit.

Previous presentations

None.

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