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ORIGINAL RESEARCH

Frailty Syndrome, pulmonary and functional capacity in patients with HIV/AIDS

Síndrome da fragilidade, capacidade pulmonar e funcional em pacientes infectados pelo HIV/AIDS

Síndrome de fragilidad, capacidad pulmonar y funcional en pacientes infectados por el VIH/SIDA

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ABSTRACT | This study aims to evaluate the prevalence of frailty syndrome and its relationship with lung function, functional capacity, and disease-related variables in HIV-infected patients. This is a cross-sectional and descriptive study, with quantitative data analysis. The sample consisted of individuals diagnosed with HIV/AIDS, without previous locomotion limitations. The frailty syndrome was evaluated by the frailty phenotype, punctuated in the following items: unintentional weight loss, fatigue, reduced gait speed, physical activity level, and hand grip strength. Pulmonary function and ventilatory muscle strength were assessed by spirometry and manovacuometry, while functional capacity was assessed by the six-minute walk test. Data analyses were performed with comparison tests, with a 5% significance level. All patients included in this study were scored on the frailty criterion. In total, 70% were fragile and 30% were classified as pre-fragile. There was a relation between impaired functional capacity, the prevalence of restrictive ventilatory disorder, and comorbidities in the fragile population when compared with the pre-fragile group. The findings of this study conclude that frailty syndrome affects the health of individuals with HIV/AIDS, with spirometry impairment, reduced functional capacity, and presence of comorbidities.

Keywords | HIV Infections; Frailty; Spirometry; Walk Test.

RESUMO | O objetivo deste estudo foi avaliar a prevalência da síndrome da fragilidade e a sua relação com a função pulmonar, a capacidade funcional e as variáveis relacionadas à pacientes infectados pelo vírus HIV. Trata-se de um estudo transversal e descritivo, com análises quantitativas de dados. A amostra foi composta por indivíduos diagnosticados com HIV/AIDS e sem limitações prévias de locomoção. A síndrome da fragilidade foi avaliada pela aplicação do fenótipo da fragilidade, pontuado nos seguintes itens: perda de peso não intencional, fadiga, redução da velocidade da marcha, redução do nível de atividade física e redução da força de preensão palmar. A função pulmonar e a força muscular ventilatória foram avaliadas por meio de espirometria e manovacuometria. A capacidade funcional foi mensurada pelo teste de caminhada de seis minutos (TC6). A análise dos dados foi realizada com testes estatísticos de comparação, adotando-se o nível de significância de 5%. Todos os pacientes incluídos neste estudo encontravam-se dentro dos critérios de fragilidade. Destes, 70% eram frágeis e 30% pré-frágeis. Verificou-se uma relação entre o comprometimento da capacidade funcional, a prevalência de distúrbio ventilatório restritivo e a presença de comorbidades na população frágil comparado com a pré-frágil. Os achados desst estudo permitem a conclusão de que a síndrome da fragilidade impacta a saúde de indivíduos com HIV/AIDS,

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com comprometimento da espirometria, redução da capacidade funcional e presença de comorbidades.
Descritores | Infecções por HIV; Fragilidade; Espirometria; Teste da Caminhada.

RESUMEN | El objetivo de este estudio fue evaluar la prevalencia del síndrome de fragilidad y su relación con la capacidad pulmonar, la capacidad funcional y las variables relacionadas a pacientes infectados por el VIH. Este es un estudio transversal y descriptivo, con análisis de datos cuantitativos. La muestra estuvo constituida por personas diagnosticadas con VIH/SIDA y sin limitaciones previas de locomoción. Para evaluar el síndrome de fragilidad, se aplicó el fenotipo de fragilidad, que se puntuó en los siguientes ítems: pérdida de peso involuntaria, fatiga, reducción de la velocidad de la marcha, reducción del nivel de actividad física y reducción de la fuerza de agarre. La capacidad pulmonar y la fuerza de los músculos ventilatorios se evaluaron mediante espirometría y manovacuometría. La capacidad funcional se midió mediante la prueba de caminata de seis minutos (PC6). El análisis de los datos se realizó mediante pruebas de comparación estadística, adoptando un nivel de significancia del 5%. Todos los pacientes incluidos en este estudio se encontraban dentro de los criterios de fragilidad. De estos, el 70% eran frágiles y el 30% prefrágiles. Hubo una relación entre la capacidad funcional deteriorada, la prevalencia de trastorno ventilatorio restrictivo y la presencia de comorbilidades en la población frágil en comparación con la población prefrágil. Los hallazgos de este estudio muestran que el síndrome de fragilidad afecta la salud de las personas con VIH/SIDA, con deterioro de la espirometría, reducción de la capacidad funcional y presencia de comorbilidades.
Palabras clave | Infecciones por VIH; Fragilidad; Espirometría; Prueba de Caminata.

INTRODUCTION

The recognition of similarities between the clinical and the biological phenotypes of older adults and individuals infected with the HIV virus has increased the scientific interest in studying frailty syndrome (FS)[1]. The literature reports that 19% of HIV-infected patients may develop this syndrome[2]. The first study that investigated the relationship of FS with this population observed a strong association of viral infection with frailty[1]. Subsequent studies showed a significant association with severe HIV infection, specifically related to low levels of CD4 and uncontrolled infection[2,3].

Frailty is a syndrome marked by a decrease in physiological reserve and greater vulnerability to stress, predisposing the individual to major adverse outcomes including hospitalization, institutionalization, disability, and death. Although FS is related to aging, it has been characterized as a distinct process from chronological age[1,4-6].

The pathophysiological mechanisms responsible for the development of FS in HIV-infected patients are not yet clear. Piggott, Erlandson and Yarasheski [4] and Walston et al.[5] present hypotheses regarding FS in people with HIV, considering that HIV infection and the use of antiretroviral therapy may contribute to the emergence of molecular alterations, comorbidities, psychosocial, and behavioral changes. Such disorders are closely related to altered energy metabolism, chronic inflammation status, immune system activation, and neuroendocrine dysfunction—whose release of inflammatory mediators contribute to the development of insulin resistance, lipodystrophy/obesity, sarcopenia, anorexia, osteoporosis, cognitive impairment, anemia, and thrombophilia[4,5].

As a result, these patients may experience reduced gait speed, muscle weakness, weight loss, and fatigue. The set of these aspects may lead to mobility limitations, impairment of functional capacity, increased number of falls, social isolation, and hospitalizations[4].

Recent studies have shown a growing interest regarding frailty syndrome in HIV-infected individuals due to the high disability of affected patients[1,5]. To date, studies relating FS and HIV infection in the Brazilian population are scarce. Most studies only address FS in relation to aspects of the disease, time of diagnosis, CD4 levels, and presence of comorbidities. The influence of frailty on functional capacity and pulmonary function in HIV individuals is still little explored[3,6-8].

Thus, this study aims to evaluate the presence of frailty in individuals with HIV/AIDS and to understand its relationship with pulmonary function, functional capacity, and disease-related variables.

METHODOLOGY

This is a cross-sectional and descriptive study conducted at the Infectious Diseases Outpatient

Clinic of the Hospital Dia Professora Esterina Corsini da Universidade Federal de Mato Grosso do Sul (UFMS), in Campo Grande (MS), Brazil. This study was approved by the Research Ethics Committee of the Universidade Federal de Mato Grosso do Sul, opinion No. 1.086.017.

The study included individuals diagnosed with HIV/AIDS, older than 18 years old, of both sexes, oriented, responsive and clinically stable, without cognitive impairment, without medical contraindication to perform efforts, absence of motor limitations that interfered in locomotion or other clinical conditions that could be worsened by physical exertion. Hospitalized patients and those who were unable to attend the evaluation were excluded.

Initially, the researchers analyzed the patients' medical records. The individuals were invited to participate in the study, after reading and signing the informed consent form. Next, the evaluations were performed, divided into two moments: at first, anamnesis and anthropometric evaluation were performed; levels of viral load (VL) and CD4 T lymphocytes were collected; the international physical activity questionnaire (IPAQ) and the Center for Epidemiological Studies – Depression (CES-D) scale were applied; pulmonary function and respiratory muscle strength were also evaluated. In the second moment, the six-minute walk test (6MWT), gait speed test, and hand dynamometry were performed. Data collection was divided in these two moments due to the possibility of stress tests causing fatigue and interfering in the results.

References proposed by the Brazilian Ministry of Health[9] were used to evaluate viral load and CD4 T-cell count. Regarding the pulmonary function and respiratory muscle strength test, spirometry and manovacuometry were performed (maximal inspiratory pressure, MIP, and maximal expiratory pressure, MEP).

The pulmonary function test was performed using the IQTeQ spirometer®, following the recommendations for test standardization of the American Thoracic Society (ATS)[10]. The evaluated parameters were compared with the predicted values for the Brazilian population[11]. The evaluation of MIP and MEP (manovacuometry) was performed with the MVD300 – Globalmed®, equipped with a mouth adapter and an escape valve[12]. The method and the normality references respected the description of Neder et al.[13]. To evaluate functional capacity (FC), the 6MWT was used, respecting the ATS guideline [14] and following the parameters of normality in the Brazilian population[15].

The FS was evaluated by applying the frailty phenotype (FP)[16], in which the following items were verified: unintentional weight loss, muscle weakness, exhaustion report, low level of physical activity, and decreased gait speed. Individuals who presented three or more components of the phenotype were classified as fragile. Those with one or two components were classified as pre-fragile and those with no phenotype components were classified as non-fragile. The item 'weight loss' was evaluated by questioning individuals regarding the unintentional loss of 4.5 kg or more than 5% of body weight in the last 12 months (without diet or exercise). To verify exhaustion, two CES-D[17]questions were applied: "I felt that I had to make an effort to do usual tasks" and "I could not carry on my things." Participants who scored 2 or 3 for either of the two questions, scored on the frailty criterion[16].

The level of physical activity of the participants was measured using the short version of the IPAQ questionnaire[18]. Individuals classified as sedentary or insufficiently active scored on the frailty criterion.

Muscle strength was evaluated by measuring hand grip strength, in Kgf, with a Saehan® dynamometer. The test was performed according to the method proposed by Fess[19]. The final result was obtained by calculating the arithmetic mean of the three recorded values and comparing them with the reference value, according to sex and age[20]. The walking speed was evaluated by the time the patient spent to travel the distance of 4.6m on flat ground. Speed greater than 0.80m/s was considered "preserved gait speed[21]."

This study was carried out in compliance with the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[22] – as appropriate for cross-sectional observational epidemiological studies. For result analysis, data were submitted to descriptive statistical analysis, followed by tests of association with the chi-square test for categorical variables; Student's *t*-test or Mann-Whitney test were used to compare the continuous variables. The adopted significance level was 5% ($p<0.05$).

RESULTS

In total, 35 patients were screened in the study. Out of these, five were excluded: four did not show up

at the second moment of evaluation and one presented difficulty in locomotion. Out of the 30 patients who completed the study, 27 were male and three female, with a mean age of 41±11 years. Table 1 presents the sample characterization.

Table 1. General data of the studied population

Characteristic	Groups		p value
	Pre-fragile (n=9) % (n)	Fragile (n=21) % (n)	
Age	37.33±11.9	44.52±10.19	0.104
Sex			
Male	100% (9)	86% (18)	0.232
Female	0	14% (3)	
BMI			
Eutrophic	55.5% (5)	28.5% (6)	
Underweight	11% (1)	43% (9)	
Pre-obese	22.5% (2)	14% (3)	0.391
Obese (n=14)	11% (1)	9.5% (2)	
Obese II	0	5% (1)	
Time since HIV diagnosis			
<2 years	22% (2)	19% (4)	
2 to 4 years	56% (5)	38% (8)	0.547
>4 anos	22% (2)	43% (9)	
Smoker			
Yes	22% (2)	33.5% (7)	0.543
No	78% (7)	66.5% (14)	
Drinks Alcohol			
Yes	11% (1)	9.5% (2)	0.894
No	89% (8)	90.5% (19)	
Comorbidities			
Present	0% (0)	30% (8)	0.031*
Absent	100% (9)	70% (13)	
Co-infection**			
One	89% (8)	91% (19)	
Two	11% (1)	4.5% (1)	0.667
Three	0% (0)	4.5% (1)	

The results are presented onaverage ±standard deviation and in relative frequency (absolute frequency). BMI: body mass index; **Description of one to three co-infections; *p<0.05.

Regarding viral load and CD4 T levels, visualized in Table 2, the groups showed similar results.

Table 2. Viral load and CD4 T levels in the two studied groups

Characteristic	Groups		p value
	Pre-fragile (n=9) % (n)	Fragile (n=21) % (n)	
Viral Load			
Not detected	22% (2)	33.5% (7)	
Below the minimum limit	22% (2)	28.5% (6)	0.762
Low	34% (3)	28.5% (6)	
High (%)	22% (2)	9.5% (2)	
T CD4			
Recommended	34% (3)	24% (5)	
Low	22% (2)	38% (8)	0.860
Very Low	22% (2)	19% (4)	
Moderate	22% (2)	19% (4)	

The results are presented onaverage ± standard deviation and in relative frequency (absolute frequency).

Regarding the spirometry report, the two groups were statistically different, with predominance of restrictive ventilatory defect (RVD) in fragile individuals. The mean MIP value in the pre-fragile group was –103.5±33.45cmH_2O and, in the fragile group, –103.28±46.67cmH_2O. The MEP values between groups were, respectively, 110.5±26.5cmH_2O and 97.5±27.5cmH_20. In this comparison, there was no statistically significant difference between the two studied groups. When analyzing FC, the groups were different: a greater impairment was found in individuals considered fragile (Table 3).

Table 3. Pulmonary function, ventilatory muscle strength, and functional capacity of the studied population

Characteristic	Groups		p value
	Pre-fragile (n=9) % (n)	Fragile (n=21) % (n)	
Spirometry			
Normal	55.5% (5)	4.7% (1)	
Mild RVD	33.3% (3)	42.8% (9)	0.011*
Moderate RVD	0% (0)	23.8% (5)	
Severe RVD	11.1% (1)	28.5% (6)	
MIP			
Normal	66.6% (6)	52.3% (11)	0.469
Reduced	33.3% (3)	47.6% (10)	
MEP			
Normal	33.3% (3)	28.5% (6)	0.794
Reduced	66.6% (6)	71.4% (15)	
TC6'			
Normal	55.5% (5)	4.7% (1)	0.001*
Below expected	44.4% (4)	95.2% (20)	

The results are in relative frequency (absolute frequency). RVD: restrictive ventilatory defect; MIP: Maximum inspiratory pressure; MEP: Maximum expiratory pressure; 6MWT: six-minute walk test. *p<0.05.

DISCUSSION

A high prevalence of frailty was observed in the studied individuals. To date, few studies address frailty in the Brazilian population with HIV/AIDS. Recent studies suggest that HIV-infected individuals have reduced physical function and are at higher risk of frailty[23,24]. In fact, some patients infected with the virus manifested characteristics of frailty at a much younger age compared with non-infected patients[23].

The presence of co-infections and comorbidities was higher in fragile individuals in our study. The statistical difference, however, remained only in the comorbidity variable. Some studies have shown that such complications can occur both in young patients and older adults[24,25].

Although the literature has associated the occurrence of frailty in HIV with low levels of CD4, clinical control of the disease, and high levels of CV[2], this association between physical function and CD4+ lymphocyte count may be controversial. Some suggest that clinical classification is more important than laboratory classification to determine physical disability in AIDS[26].

Since the introduction of ART, some studies have reported predominance of chronic respiratory diseases. However, it is difficult to determine to what extent HIV infection interferes with this finding; it may be due to patients' longevity increase, since the introduction of ART. The association of HIV with smoking can also contribute to the increased prevalence of respiratory diseases[7].

Restrictive ventilatory disorders were predominant. The findings in the literature regarding pulmonary function of people with HIV are limited in relation to the extent and types of abnormalities[7], still, most studies report a predominance of obstructive ventilatory disorders[8,27,28]. However, due to the high occurrence of respiratory co-infections in people with AIDS and the simultaneous existence of chronic respiratory diseases and/or smoking, it is difficult to describe the real respiratory effects of HIV infection. A probable explanation for our findings was the low prevalence of smokers in the studied sample.

Regarding respiratory muscle strength, no statistically significant difference was observed between the groups. However, studies suggest that respiratory muscle impairment in HIV can occur due to three main factors: (1) HIV infection itself; (2) side effects caused by prolonged ART use; or (3) metabolic and infectious processes, and vasculitis [29,30]. Of the three mentioned hypotheses, mitochondrial toxicity, reduced oxidative enzyme activity, increased production of reactive oxygen species and lipodystrophy occurrence directly interfere with cardiorespiratory function[29-31]. The sample size of this research may have been a limiting factor to study muscle impairment related to HIV infection.

The FC (assessed through the 6MWT) was more clearly compromised in the fragile group. HIV infection is prone to involve multiple organs and systems, producing a wide variety of debilitating conditions that can compromise patients' functional independence—this is especially true when considering the number of neurological, neuromuscular, cardiac and pulmonary complications associated with symptomatic HIV infection[26].

The physical weakness resulting from the disease can compromise the patients' independence, their professional life and productivity, generating social and economic problems[26]. However, few studies have addressed functional disability and/or the evolution of functional performance according to the time since diagnosis[32-34]. Richert et al.[6] longitudinally evaluated FC, locomotion, and muscle performance of the lower limbs of 354 people with HIV. The authors concluded that lower limbs muscle performance and functional capacity were compromised and associated with falls. These results suggest that motor alterations are of clinical relevance in the studied profile; however, unlike our study, these individuals were not evaluated by the frailty phenotype.

An intervention study[35], performed in a rehabilitation program for HIV patients, evaluated the performance in the 6MWT, flexibility, upper limbs strength, and quality of life upon admission. Out of the 20, seven (35% of the sample) were unable to complete the 6MWT.

Erlandson et al.[36] reported that moderate functional impairment is common among middle-aged HIV-infected individuals. The FC was analyzed with three instruments: (1) evaluation of the frailty phenotype, (2) physical performance test and (3) the 400m walking test. Another study[37] with HIV-infected children, resulted in a worst performance in the 6MWT when compared with non-infected children, and the highest percentage of CD4 was associated with longer distances covered in the test.

Our study has limitations, such as the small sample. Data collection presented some issues due to the need to perform the tests at two different moments, the specificity of the population, and a short collection period. However, it is worth mentioning that this study was one of the first to investigate the association between HIV infection and frailty syndrome in a Brazilian sample.

CONCLUSION

Frailty syndrome affected all HIV-infected individuals. Fragile participants had greater impact on spirometry, functional capacity, and comorbidities, without association with the variables related to HIV infection.

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