Original Article

Frailty assessment: An emerging concept in aged People Living with HIV (PLHIV)

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Abstract

Introduction: As the life expectancy of People Living with HIV (PLHIV) has improved with effective antiretroviral treatment (ART), they now face the challenges of accelerated ageing. Frailty is an emerging concept in the management of PLHIV and up to 28% of PLHIV are identified as frail. Frailty is a determinant of adverse clinical outcomes and is a complex clinical endpoint that has not been studied in India. This exploratory study was done to evaluate frailty and its determinants among PLHIV in India. **Materials and Methods:** This was a cross-sectional study in 76 PLHIV aged 50 years or more. All the study subjects underwent a comprehensive clinical assessment. The Fried's criteria and Veterans Aging Cohort Study (VACS) Index were used to evaluate for frailty. Socio-demographic, clinical, immunological, and virological variables were assessed for their association with frailty. The study was registered under Clinical Trials Registry-India (ICMR-NIMS): REF/2019/05/025616. **Results:** The mean age of the subjects was 56.05 ± 5.8 years (range 50-76), and males constituted 81.57% (62/76) of the subjects and majority (60.53%) were underweight. On frailty assessment, 57.89% of the PLHIV were identified as prefrail/frail. Frailty had a significant association with low CD4 count ($P = 0.0001$) and number of comorbidities ($P = 0.017$) especially when comorbidities ≥2 ($P = 0.04$) and polypharmacy ($P = 0.033$). VACS index, polypharmacy, and low CD4 count ≤200 cells/mm^3 were strong predictors of frailty. On multivariate regression analysis, CD4 count ≤200 emerged as the strongest independent predictor of frailty. **Conclusion:** The study highlighted the high prevalence of frailty and under nutrition among aged PLHIV. The study emphasizes the need for a shift away from traditional clinical endpoints to other outcome measures for a holistic approach to PLHIV.

Keywords: Aged PLHIV, ageing, frailty, HIV

Introduction

With the universal access to effective antiretroviral treatment (ART), people living with HIV (PLHIV) experience longer life expectancy and lower mortality and thus the increase in the prevalence of aged PLHIV. The incidence of people acquiring HIV infection in older ages has also increased, adding on to the burden of aged PLHIV. Of the estimated 35.6 million PLHIV worldwide, 3.6 million are over the age of 50 years and their numbers increasing steadily.[1,2] Different studies have defined the criteria for "aged PLHIV" differently; however, the most common consensus is PLHIV who are more than 50 years of age.[3] Aged PLHIV face a unique set of challenges that might be due to immune deficiency due to HIV and HIV-associated non-AIDS conditions such as geriatric syndromes (falls, incontinence, dementia, confusion, malnutrition, sarcopenia, and disability), frailty, social neglect, psychological issues, decreased adherence, polypharmacy, and increased risk of multimorbidities.

Frailty is defined as an "age-related condition characterized by increased vulnerability to stressors, thought to be due to multisystem dysregulation."[4] There is a lack of uniformity while defining frailty, and there is no universally accepted model for measuring frailty. There is a need for recognizing and identifying

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frail individuals since frailty can predict morbidity and represents a poor quality of life. As HIV care is now being handled more by primary care physicians, it is important for primary care clinicians to be aware of these concepts. Furthermore, many aspects of comprehensive care of PLHIV can be integrated with primary care and delivered by individualized interventions. There is paucity of studies on aged PLHIV in developing countries, including India. This study aims to determine the prevalence of frailty in PLHIV and explore the complex interplay between frailty and aging, to assess its risk factors among aged PLHIV.

Materials and Methods

Study design and sample

This was an observational, cross-sectional study on aged PLHIV attending the ART center at the Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi. The study was approved by the Institutional Ethics Committee of Maulana Azad Medical College wide approval number F.No. 17/IEC/MAMC/2018/02. The study was registered under Clinical Trials Registry-India (ICMR-NIMS): REF/2019/05/025616.

The study 76 recruited aged PLHIV (PLHIV >50 years of age) who gave informed consent to participate. All subjects underwent a detailed history and a comprehensive clinical assessment. Demographic, socioeconomic, and lab parameters were collected.

Frailty assessment

All subjects were subjected to frailty assessment by evaluating the Frailty phenotype (Fried's phenotype/Fried's criteria) and the Veterans Aging Cohort Study (VACS) Index. Fried's phenotype[5] was based on assessment of five criteria as developed by Fried *et al.*: (1) weight loss, (2) low physical activity, (3) exhaustion, (4) slowness, and (5) weakness.

Unintentional weight loss defined by >10-pound (>4.5 kg) weight loss documented in the last year or ≥5% of the previous body weight. For patients who had attended center for <12 months, unintentional weight loss was defined as >5 pounds (>2.25 kg) in the last 6 months or ≥2.5% of the previous year's body weight.

Physical inactivity was defined by subjects answering 3 when asked whether their health limits vigorous activities such as participating in strenuous sports: 1 = not at all, 2 = yes, limited running, lifting heavy objects, a little, or 3 = yes, limited a lot.

Exhaustion was defined when subjects answering 2 or 3 to either one of two statements: How often have you felt that: (a) everything you did was an effort or (b) I could not "get going" 0 = rarely (<1 day), 1 = some of the time (1–2 days), 2 = occasionally (3–4 days), or 3 = most of the time (5-7 days).

Weak grip strength: hand grip strength was measured using the Jamar Hand Dynamometer, an isometric, hydraulic hand dynamometer. The patient's hand grip strength was compared to reference values for grip strength for healthy Indians.[6]

Slowness was objectively measured by walking speed along 15-feet (4.57 m) distance, with average of two measurements being taken. A time of ≥7 s in men with a height of ≤173 cm, or ≥6 s in height of >173 cm, or ≥7 s in women with a height of ≤159 cm, or ≥6 s in height of >159 cm were defined as slow.

Patients were classified into three categories: not frail, prefrail, and frail.

Frailty index was evaluated using the Veterans Aging Cohort Study (VACS) Risk Index,[7] which included the following: 1) Age, 2) CD4 count, 3) Hemoglobin, 4) FIB-4 (a measure of liver fibrosis): (years of age × AST)/platelets in 100/L × square root of ALT), 5) Estimated glomerular filtration rate, 6) Hepatitis C status. Accordingly, the score was noted [Table 1] and was included in further analysis.

The study subjects were interviewed for social and demographic variables, which included their age, gender, relationship status, occupation, education, monthly income, family/social support, history of opportunistic infections (OI), route of acquisition of HIV, any history of high-risk behavior (substance abuse, alcohol use, smoking, IV drug abuse, MSM behavior). History regarding HIV and its treatment was taken such as time from HIV diagnosis, history related to ART regimen like duration of ART, type of regimen, any history of drug toxicity, ART switch, ART adherence based on pill count over the past four weeks. Their absolute CD4+ T cells/μL count, plasma viral

Table 1: VACS risk index

Variable	Value	Points
Age (years)	<50	0
	50-64	12
	≥65	27
CD4 (cells/mm^3)	≥500	0
	350-499	6
	200-349	6
	100-199	10
	50-99	28
	<50	29
HIV-1 RNA (copies/ml)	<500	0
	500-1×10^5	7
	≥1×10^5	14
Hemoglobin (g/dl)	≥14	0
	12-13.9	10
	10-11.9	22
	<10	38
FIB-4	<1.45	0
	1.45-3.25	6
	>3.25	25
eGFR (ml/min)	≥60	0
	45-59.9	6
	30-44.9	8
	<30	26
HCV Infection		5

load and HIV-clinical stage were noted. Further information regarding history of chronic diseases like diabetes, hypertension, dyslipidemia, malignancy, coronary artery disease, cerebral vascular accident and stroke, chronic obstructive pulmonary disease, chronic liver disease, hepatitis (B, C) coinfection, osteoarthritis, chronic kidney disease, falls or any other comorbidity identified/reported from their previous medical records, were noted.

Statistical analysis

The analysis was performed using the Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov–Smirnov test. Quantitative variables were compared using Independent t test/Mann–Whitney test (when the data sets were not normally distributed) between the two groups. Qualitative variables were correlated using Chi-square test/Fisher's exact test. A *P* value of <0.05 was considered statistically significant.

Results

The mean age of the subjects was 56.05 ± 5.8 years (range 50-76 years) and males constituted 81.57% (62/76) of the subjects. The majority of study subjects (69.74%) self- reported acquisition of HIV through heterosexual route and 77.63% of the subjects were married. The average duration of HIV infection in the subjects at the time of enrolment was 8.25 ± 4.9 years and 14.47% were recently diagnosed. 50% of the subjects had history/were currently abusing alcohol/tobacco/drugs. The mean BMI of the subjects was 18.04 ± 3.51 kg/m^2, and 60.53% of them were underweight (BMI <18.5 kg/m^2).

The mean CD4 count was 356.43 ± 240.14 cells/mm^3 (median 253.5). 64.47% of the study subjects had CD4 >200 cells/mm^3. The mean CD4 count among the recently diagnosed (≤12 months) subjects was 148.09 ± 76.2 cells/mm^3, and the mean count among the rest was 391.69 ± 240.7 cells/mm^3. All subjects were on ART, 65.79% of the subjects were on ART for ≥5 years. 73.68% of the subjects were on 1st line ART, 18.42% were on 2nd line, and 7.89% were on 3rd line ART. Polypharmacy was defined as the study subjects consuming ≥5 drugs other than ART in a day. 26.32% (20/76) of the subjects had polypharmacy by this definition. Out of these, 80% study subjects were male.

Frailty was evaluated using the Fried's phenotype. Those fulfilling none of the criteria were classified as "not frail"; those fulfilling 1 or 2 criteria as "prefrail" and ≥3 criteria as frail. For the purpose of comparison, subjects were divided into two categories: frail and prefrail versus not frail. In our study, 57.89% of the study subjects were prefrail/frail; 42.11% of the study subjects were not frail. 42.86% of the females were frail, in comparison with 27.42% of the male (*P* = 0.366). Among the subjects, 56.52% of those <65 years were frail, in comparison with 71.43% of those ≥65 years (*P* = 0.692). With the decrease in CD4 count, the prevalence of frailty increased (*P* = 0.0001). This was especially evident at CD4 count ≤200 cells/mm^3 (*P* < 0.0001). The mean CD4 count among frail/prefrail was 304.34 ± 250.52 cells/m^3 in comparison with 428.06 ± 208.14 cells/m^3 among those without frailty (*P* = 0.0007). No significant relationship could be determined between frailty and viral load. Mean BMI among frail individuals was 17.84 ± 3.72 kg/m^2 in comparison with mean BMI of 18.3 ± 3.24 kg/m^2 among the not-frail study subjects. (*P* = 0.396). 100% of the subjects with clinical stage 4 illness were prefrail/frail (*P* = 0.07).

Frailty had significant relationship with number of comorbidities with the median number of comorbidities, in prefrail/frail PLHIV, being 2 (*P* = 0.017). The risk of frailty increased significantly when the comorbidities were ≥2 (*P* = 0.04). Frailty also had a significant relationship with polypharmacy (*P* = 0.033). Mean number of drugs (excluding ART) consumed by frail/prefrail individuals was significantly higher in comparison to a subject who is not frail (3.32 ± 2.9 v/s 1.53 ± 2.03; *P* = 0.003).

The mean VACS index calculated for the study subjects was 45.75 ± 24.26 with a median of 41. Frail individuals had a higher VACS index in comparison with nonfrail individuals. (51.8 ± 27.43 v/s 37.44 ± 16.01 median: 50 v/s 34.5) (*P* = 0.022).

Univariate logistic regression analysis was performed to determine the predictors of frailty [Table 2]. Among all parameters, VACS, polypharmacy and low CD4 count ≤200 cells/mm^3 emerged as strong predictors of frailty. After removal of confounding factors on multivariate regression analysis, CD4 count ≤200/mm^3 emerged as the strongest independent predictor of frailty.

Discussion

Our study highlights that some frailty is observed among nearly 60% of aged PLHIV in India. Our results were similar to other studies in the world. Kristine M. Erlandson *et al.* reported that of 1016 subjects, 6% were frail, and 38% prefrail.[8] Díaz-Ramos *et al.* from Mexico reported the prevalence of frailty and prefrailty in 87.93% of the 116 PLHIV (≥50 years) recruited in the study.[9] Jose ´-Ramo ´n Blanco *et al.* in a study from Spain with 248 PLHIV reported the prevalence of prefrailty of 39.1% and frailty of 4.4%.[10] Wulunggono W *et al.* from Indonesia[11] reported the prevalence of prefrailty/frailty as 54.9%, most of whom (51.2%) were prefrail and 3.7% were frail among the 164 PLHIV they recruited.

With the decrease in CD4 count, the prevalence of frailty increased (*P* = 0.0001). This was especially evident at CD4 count ≤200 cells/mm^3 (*P* < 0.0001). CD4 count ≤200/mm^3 emerged as the strongest independent predictor of frailty. This highlights the importance of achieving immune reconstitution. Arpi S. Terzian *et al.* recognized low CD4 count as a "strong independent predictor" of frailty, slower gait and lower grip

Table 2: Univariate logistic regression for significant risk factors of frailty

Variable	Beta coefficient	Standard error	*P*	Odds ratio	Odds ratio lower bound (95%)	Odds ratio upper bound (95%)
VACS	0.028	0.012	0.020	1.028	1.004	1.053
Number of pills/medications taken in a day	0.100	0.067	0.134	1.106	0.970	1.261
Age in years						
50-60				1.000		
>60	0.034	0.558	0.951	1.035	0.347	3.089
Gender						
Female				1.000		
Male	0.052	0.598	0.931	1.053	0.327	3.398
Body mass index (kg/m²)						
≥18.5 kg/m²				1.000		
<18.5 kg/m²	0.522	0.476	0.272	1.686	0.663	4.283
CD4 count (cells/mm≥)						
>200				1.000		
≤200	2.770	0.736	0.0002	15.954	3.772	67.469
VL						
<1000				1.000		
≥1000	-0.399	0.565	0.481	0.671	0.222	2.032
Education						
Secondary and above				1.000		
Illiterate/Primary	-0.099	0.471	0.833	0.905	0.360	2.279
Marital status						
Married				1.000		
Single/Widowed/Divorced	0.999	0.618	0.106	2.714	0.809	9.110
Clinical stage						
1				1.000		
4	2.203	1.636	0.178	9.051	0.367	223.299
Anemia	-0.627	0.800	0.433	0.534	0.111	2.564
Number of comorbidities						
<2				1.000		
≥2	0.940	0.485	0.053	2.561	0.989	6.629
Addiction	-0.210	0.465	0.651	0.810	0.326	2.016
Polypharmacy	1.299	0.607	0.032	3.667	1.116	12.048
Number of pills/medications taken in a day						
<5				1.000		
≥5	0.762	0.485	0.116	2.143	0.829	5.541
Duration of HIV (in years)						
<5				1.000		
≥5	-0.672	0.656	0.306	0.511	0.141	1.846
ART Duration (in years)						
<5				1.000		
≥5	-0.222	0.597	0.710	0.801	0.248	2.582

strength (weakness).[12] Desquilbet L *et al.*[13,14] also reported in the MACS (Multicenter AIDS Cohort Study) that a low CD4 T-cell count was an independent and a significant predictor of the frailty phenotype. It was also found that the association between CD4 T-cell count and the frailty phenotype continued even after the study was confined to ART-treated men with a good virological response, or hepatitis B or C status and depression. There are no published Indian studies on the determinants of frailty. Elderly people are already facing ageing-related immunosenescence. When HIV associated immune depletion occurs additionally, the results are catastrophic. This emphasizes the need to start ART early so that early and optimum immune reconstitution can be achieved. No significant relationship could be determined between frailty and viral load. This might be explained due to the heterogeneous selection of patients with highly variable plasma viral load. Also, viral load and CD4 counts determine two different things though they are mutually related.

WHO clinical staging and frailty did have a fairly strong relationship ($P = 0.07$). It has been suggested that frailty may in part be reversible especially after treatment of OIs. Since OI's lead to weakness, poor endurance, decrease physical activity, fatigue or even cognitive decline; its treatment can lead to improvement in all of the mentioned factors and can partially reverse frailty. Frailty had significant relationship with number of comorbidities with the median number of comorbidities in prefrail/frail PLHIV

being 2 ($P = 0.017$). The risk of frailty increased significantly when the comorbidities were ≥2 ($P = 0.04$). Frailty also had a significant relationship with polypharmacy ($P = 0.033$). Stronger association of frailty with comorbidities can be explained, since having more comorbidities leads to worsening of muscular strength; increase in levels of fatigue, exhaustion and neurocognitive impairment. Polypharmacy can lead to drug–drug interactions, poor adherence and toxicity: all of them contributing to decreased efficacy of ART and further leading to frailty. These findings corroborate with the findings of Michael Ssonko *et al.*[15] from Uganda.

Kristine M. Erlandson *et al.* reported a significant correlation of frailty with lower level of education, advanced age, initial use of efavirenz, smoking, obesity and neurocognitive impairment; the protective factors were physical activity and alcohol use. No such correlation could be determined in our study.[8] Wulunggono W *et al.* also demonstrated that depression was significantly associated with prefrailty/frailty ($P = 0.038$).[11]

The VACS Index is a clinical risk index that is similar to a frailty index: It reflects the "absolute risk of all-cause mortality, hospitalization, intensive care unit admission, and functional performance." VACS has been used as a surrogate marker in a few other studies such as by Womack *et al.* who assessed physiologic frailty by the VACS Index score and determined its strong association with risk of fragility fracture.[16] In our study, the VACS index significantly correlated with frailty (median: 50 v/s 34.5) ($P = 0.022$). Similar results were reported by Jose ´-Ramo ´n Blanco *et al.*[10] Frail patients had an advanced age ($P = 0.006$), increased prevalence of sensory deficits (visual or auditory) ($P = 0.002$), increased falls in the previous year ($P = 0.0001$), a higher Charlson comorbidity index (P 0.001), and a higher VACS index ($P = 0.001$). Similar to our findings, the subjects with >2 comorbidities and treatment with >5 non ARV drugs, were more frail ($P = 0.0001$ and $P = 0.004$, respectively). Several independent frailty predictors in men (VACS index, C-reactive protein [CRP], and falls) were different from women (CRP, AIDS, and menopause).[10] In our study, due to low percentage of female study subjects (18.42%), such differences could not be explored. Gerome V Escota *et al.* reported that prefrail/frail participants had higher median VACS Index scores when compared with nonfrail participants (18 versus 10, $P < 0.001$). In multivariate analysis, prefrailty/frailty was independently associated with a higher VACS Index score (OR: 1.025, $P = 0.019$). This supports the view that the VACS index may be also used to identify prefrailty and frailty in PLHIV.[17]

The significance of frailty lies in the fact that it often identifies individuals more vulnerable to unfavorable health outcomes. There is now overwhelming proof of the significance of frailty as a marker in identifying vulnerable or at-risk PLHIV, and it may be an important clinical target for improving outcomes among PLHIV. One challenging situation in the clinical application of frailty in HIV is the lack of interventions to target frailty, once it has been identified. Few suggested interventions include management of polypharmacy, exercise, and balanced nutrition. Souza *et al.* found that resistance training two times a week was linked to equivalent improvements in strength, lipid levels, and glycemic control in a small sample of PLHIV and HIV-negative men older than 60.[18] Julian Falutz *et al.* found that in treated PLHIV, even low levels HIV replication leads to activation of immunological reactions and chronic inflammation, which can cause destabilization of normally autoregulated physiological systems in response to environmental and biological challenges which expedites frailty.[19] Lellouche *et al.* conducted a study regarding the prevalence of frailty among persons with and without HIV infection. It was found that prefrailty and frailty was associated more with HIV infection. In PLHIV, prefrailty/frailty was associated with depressive symptoms, kidney disease and duration of HIV infection.[20] Eveline Verheij *et al.* reported that mortality rate was greater among the frail subjects (95% CI 14.2-46.4) compared with prefrail (95% CI 4.7-11.2) and robust (95% CI 1.1-4.9). Frailty was found to be significantly associated with death (hazard ratio, 4.6) and incident comorbidity (OR 1.9).[21] Anita Edwards *et al.* in a study in rural Kwazulu-Natal, South Africa compared the prevalence of frailty and bio markers related to frailty among older population with and without HIV infection. They found that the prevalence of frailty was not increased in PLHIV and that it was similar for PLHIV and people without HIV (17.7% vs 14.7%, $P = 0.72$). The prevalence of frailty was more among women (18.3% vs 13.04%, $P = 0.16$).[22] In the multivariable analysis, the prevalence of frailty was more in people who were 70 years or more compared to those between 50 and 59 years ($P < 0.001$). The only other Indian study that has attempted to study frailty was done by Talukdar *et al.*[23] Their study used weight loss as the only parameter for assessing frailty. By this definition of evaluation, frailty or unexpected weight loss was seen in 31% of the men and 14% of the women. Weight loss alone does not completely define frailty, as frailty is a complex parameter that denotes diminished physiologic reserve and increased vulnerability to stressors, predisposing to major adverse clinical outcomes. Frailty in HIV gives us scope for more research work for better management and help us to cater to the needs of this vulnerable population. A comprehensive care for the aged PLHIV will have to encompass facets of healthcare interventions that extend beyond clinical care and ART.[24]

Care for PLHIV is getting integrated into primary care globally, and it is no longer confined to "specialist care." In such a scenario, it is very important for primary care physicians to be aware of emerging concepts like frailty that are an important determinant of outcome. Identifying frail PLHIV is important as they are the most vulnerable among this group. Incorporation of frailty assessment into routine care with the development of simpler tools and instruments will result in a more holistic approach to care for PLHIV.

Limitations

Our study had some limitations. The cross-sectional study design was a one-time observation and the study could not establish

any causal or temporal relationship between HIV-1-related risk factors and frailty. Furthermore, frailty was not longitudinally followed up for critical outcomes, such as disability and death. The sample size was small, restricted by the time frame of this study. More studies with a larger data size and follow-up are required to study the impact of frailty in the long run and to strengthen the findings of our study. A serious effort is also needed to assess the impact of frailty interventions including managing the individual components of frailty.

Key findings and summary

Yet, our study findings highlighted the need to address this complex issue in this vulnerable population. It emphasizes the importance of management of comorbidities and polypharmacy among aged PLHIV. Undernutrition was highly prevalent in the aged PLHIV. This suggests that nutritional rehabilitation should be incorporated in the management of the older PLHIV and the National Programme must make serious efforts to tackle it. As low CD4 count emerged as an independent predictor of frailty, measures must be taken to achieve immune reconstitution early in the older PLHIV. It can also be concluded that VACS index can be used as an objective surrogate marker for frailty. Most of the focus of the HIV programs has been on the 15- to 49-year age group. Age, presence of frailty, functional, cognitive status, and comorbidities should be taken into account while determining the optimal regimen for the older patients. It is time to address the requirements of the older PLHIV and strategize approaches tailored to the special needs of this unique, vulnerable population.

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Conflicts of interest

There are no conflicts of interest.

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