An Emerging Concern—High Rates of Frailty among Middle-aged and Older Individuals Living with HIV

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ABSTRACT

Background

The aim of the present study was to calculate a frailty index (FI) in older adults (≥50) living with HIV, search for cross-sectional associations with the FI, and investigate the association between the FI score and two-year mortality.

Methods

Cross-sectional study with a short-term prospective component for the determination of two-year mortality was performed. The study took place in an HIV outpatient clinic in Calgary, Canada between November 1, 2016 and December 31, 2018. Over 700 patients 50 years of age or older took part. We calculated a FI for each patient, examined associations between FI and select patient characteristics, and evaluated the association between FI value and two-year mortality.

Results

The mean FI was 0.303 (± 0.128). Mean FI did not differ between males and females, nor was it associated with either nadir or current CD4 cell count. It did increase with age, duration of ART, and duration of diagnosed HIV infection. Mean FI was higher among those who died compared to survivors (0.351 vs. 0.301; *p*=.033).

Conclusions

Frailty is highly prevalent in persons living with HIV and associated with a higher mortality rate. Health-care providers should be aware of the earlier occurrence of frailty in adults living with HIV.

Key words: frailty, frailty index, human immunodeficiency virus (HIV), geriatric syndrome, vulnerability, anti-retroviral therapy, accelerated aging, multimorbidity

INTRODUCTION

Frailty is conceptualized as a state of increased vulnerability to stressors due to a decline in physiological reserve and resiliency.[1] In geriatric medicine, frailty is used to identify patients at higher risk for adverse outcomes[1-4] and less tolerant of aggressive therapy.[5,6] At a population level frailty becomes more common as we age. In the Canadian Community Health Survey (CCHS), which is a national population-based survey that gathers health-related data, the estimated prevalence of frailty among those 65–74 years of age was 16%.[7]

With antiretroviral therapy (ART) persons living with HIV (PLWH) are now surviving longer, with many predicted to achieve a normal life expectancy.[8-12] The US Centers for Disease Control (CDC) reported that, in 2015, nearly half (47%) of PLWH in the United States were ≥50 years old.[13]

Frailty is common among PLWH,[14-21] with higher rates of frailty seen in PLWH compared to age-matched HIV individuals.[16-18,22] In a 2016 systematic review, the prevalence of frailty in HIV+ cohorts aged 40-50 years ranged from 5-28%, which is significantly higher than similarly aged populations without HIV.[17-24] In a Swiss HIV- population, for example, the prevalence of frailty among those 50-64 years of age was only 2.7%.[25] Frailty is predictive of adverse outcomes in PLWH populations. In the Veterans Aging Cohort Study, frailty increased the 5-year risks of hospitalization and mortality by 78% and 75%, respectively, in the HIV+ group.[20] In people who inject drugs (PWID), the combined effect of frailty and HIV on mortality was greater than the sum of their individual effects (HR 7.06; 95% CI 3.49-14.3).[24]

Among the numerous tools available for the detection of frailty, none has been shown to be superior. The two most frequently employed in general older populations are the frailty phenotype (often in a modified version)[2] and the frailty index (FI).[3] Both measures are associated with disability, poorer self-reported health, and higher health-care utilization, but the FI may better discriminate in the lower and middle ranges of the frailty continuum.[26] Most studies

in PLWH have employed the frailty phenotype (i.e., presence of 3 or more of unintentional weight loss, slow walking speed, self-reported exhaustion, weak grip strength, and low physical activity).[2] An FI (a ratio of health deficits present to total considered) has been previously used in at least one HIV+ cohort.[14] Their reported mean FI was 0.31 in a group of patients with an average age of 46. Population-based studies of HIV-negative individuals have used FI of ≥0.21 as the threshold for frailty, with ≥0.30 categorizing those more frail and ≥0.45 the most frail.[7] FIs derived from community-based samples typically increase with age, whereas values from clinical or institutional cohorts are less clearly associated with increasing age and tend to be higher.[27] FI scores ≥0.7 is a boundary beyond which further deficit accumulation is unlikely as death is imminent.[28] In the previously noted HIV+ study, higher values predicted mortality, incident multimorbidity,[14] and a bidirectional inverse association with successful cognitive aging.[15]

Providing optimal health care for this aging HIV population will require expertise not only in dealing with HIV infection but also in the management of multiple age-related comorbidities and geriatric syndromes. At the end of 2018 at the Southern Alberta Clinic (SAC) in Calgary, Canada, 41% of PLWH receiving care was ≥50 years of age, and the median age of the cohort was 50 years. It is estimated that by 2030, nearly three-quarters of PLWH in the Netherlands will be ≥50 years of age.[29]

Our primary study objective was to report on an FI based on health data routinely collected on HIV+ patients ≥50 years of age followed in a large geographically defined Canadian HIV program. Secondary objectives were to: a) assess which factors were associated with current FI scores; and, b) examine if two-year mortality rates were related to baseline FI score.

METHODS

Setting and Sample

The Southern Alberta Clinic (SAC) provides exclusive access to publicly funded ART and HIV related investigations (e.g., HIV viral load and CD4 measures) for its catchment population. SAC serves nearly two thousand PLWH. Patients attend SAC every 3–4 months and have blood testing prior to each visit. The cohort is geographically defined and longitudinal clinical data have been collected since 1989 on all PLWH in the southern half of the province of Alberta. All SAC patients who were ≥50 years of age between November 1, 2016 (when the clinic began to routinely assess for frailty) and December 31, 2018 were included in this cross-sectional study, with two-year follow-up data on mortality.

Frailty Index Calculation

Routinely collected health data at SAC were included in the 29-item FI developed for SAC patients (Table 1). The SAC

database includes both measured variables such as laboratory results, as well as self-reported and clinician-documented variables (e.g., medical diagnoses). While modeled after the 45-item FI previously employed for HIV+ patients, (see Table 2 for the variables included in the Modena FI),[14] the indices were not identical. Modifications from the prior Modena 45-item FI involved the elimination of 12 variables either because the information was not routinely collected (e.g., D-dimer, C-reactive protein) or due to missing values (e.g., presence of osteoporosis and steatohepatitis), and changes in the definition of three of the variables where typically it was broadened to increase sensitivity in the detection of a deficit. Table 2 provides the variables included in the FI used for SAC patients; differences from the prior FI are noted with an accompanying description of the alteration made in the footnotes. No new items were added. All deficits, including laboratory abnormalities, were treated as non-resolvable (if abnormal once they counted towards the FI score).

For the purpose of our study, variables associated with HIV infection and monitoring (e.g., HIV viral load and CD4 cell count) were not included in the FI. The index was calculated on 716 patients utilizing values recorded prior to December 31, 2018 or the death of the patient. For each patient, FI values were included if the item was ever abnormal for the particular patient. The FI of a patient was the ratio of the number of health deficits present in a given patient divided by the total number evaluated (i.e., the denominator was 29). The resultant FI is a continuous value between 0 and 1, with higher values associated with increasing frailty.

We examined the completeness of data collection for the FI variables by determining the proportion with missing values, and screened for errors in the dataset by performing range checks. Data distributions were assessed for normality to identify outliers. Data were recoded as 0=absent and 1=present for binary variables.

All data used in this study were drawn from the SAC electronic database. Missing data were recorded as absent, but over 70% of patients had complete data for the laboratory variables. We reviewed the prevalence estimates for comorbidity data and compared these values to the expected prevalence in an HIV+ population. If the prevalence was lower than would have been expected, we either broadened the definition (e.g., hypertension was more broadly defined as either a clinical diagnosis or the prescription of one or more antihypertensive medications) or removed the item from the index (e.g., osteoporosis was removed because the prevalence estimate even when we included pharmacotherapy for this condition was 1.8%, which is well below what we would have expected).

Patient-level variables potentially associated with frailty and not included in our FI, along with other variables of interest that had been considered in prior studies of frailty in PLWH including age (categorized by strata),[17,18,21] sex,[17,18] duration of diagnosed HIV infection[16] and of ART,[18,21,23] nadir (lowest ever measured) and current CD4 cell count,[17,18,21,23]

TABLE 1.
Health deficits included in frailty index at southern Alberta clinic

	Deficits Included at SAC	Description of Included Deficits
1	Lipodystrophy	Lipo-atrophy and lipo-hypertrophy
2	High or low body mass index	<18 or >25 kg/m^2 (calculated)
3	High total cholesterol	>200 mg/dl
4	High low density cholesterol	>100 mg/dl
5	Low high density cholesterol	<40 mg /dl
6	High triglycerides	>150 mg/dl
7	Abnormal white blood cell counts	<4000 cells/μL
8	Anemia	If female: <100g/L, if male: <120g/L
9	Hepatitis C co-infection	Positive
10	Hepatitis B co-infection	Hepatitis B antigen positive
11	Polypharmacy	>5 drug classes currently in use (excluding antiretroviral therapy)
12	Hyponatremia	<125 mmol/L
13	Hypoalbuminemia	<33gL
14	Elevated aspartate transaminase	>31 U/L
15	Elevated alanine transaminase	>31 U/L
16	Abnormal alkaline phosphatase	<38 or >126
17	Elevated gamma glutamyl transphosphatase	>55 U/L
18	Low platelets	<150 cells/μL
19	Abnormal potassium	> 3.5 or >5.3 mEq/L
20	Abnormal phosphorus	<2.5 or >5.1 mg/dL
21	Abnormal thyroid stimulating hormone	<0.27 or > 4.2 μIU/mL
22	Elevated total bilirubin	>1.1 mg/dl
23	Cardiovascular disease[a]	Record of cardiovascular disease in clinic relevant problem list or prescription of nitroglycerin spray
24	Hypertension	Record of hypertension in the clinic relevant problem list or on treatment, or by prescription for a blood-pressure lowering medication
25	Diabetes mellitus type II[a]	Hemoglobin A1c>6.5% or on diabetic treatment
26	Chronic kidney disease	2 estimated glomerular filtration rates GFR <60ml/min
27	Cirrhosis	FIB-4 score >3.25
28	Chronic obstructive pulmonary disease/Asthma[a]	Record of COPD or Asthma in the clinic relevant problem list or prescription for a medication used to treat COPD or Asthma
29	Any cancer	Clinical diagnosis with biopsy confirmation

[a]Indicates deficits with a modified definition compared to the frailty index employed in Modena, Italy (see Table S1 for frailty index deficits and descriptions employed in Modena).

and current determination of HIV viral load,[20,21] were obtained from the SAC electronic health record.

Deaths

We examined both the number and the causes of death employing CoDe methodology for PLWH[30] during the two-year study period. We compared the mean FI in patients who died compared to those who survived, and the proportion who died for each of the FI strata (non-frail [FI < 0.21], frail [0.21–0.29], and more-frail [0.30–0.44], most-frail [0.45+]).[7]

Analysis

STATA version 14.2 (StataCorp LLC, College Station, TX) was used to perform statistical analysis. Descriptive statistics were utilized to describe the study population including demographics and baseline features. For continuous variables, mean (± standard deviation (SD)) and median (interquartile range) values were calculated. Two-sample, two-tailed *t*-tests were used to compare between group mean FIs. We calculated a Spearman's correlation coefficient for nonparametric measures of correlation between FI and age, duration of HIV

TABLE 2.
Health deficits included in the frailty index employed in Modena, Italy

Deficits Included in Modena	Description of Included Deficit
1 Lipoatrophy	Multicenter AIDS Cohort Study (MACS) criteria
2 Lipohypertrophy	MACS criteria
3 Nonalcoholic fatty liver disease[a]	Liver/spleen ratio <1.1
4 Menopause or male hypogonadism[a]	If female: FSH>30 IU/L and LH <30IU/L and/or absence of menstruation >1 year
	If male: testosterone <300 ng/dL
5 High or low body mass index	<18 or >25 kg/m^2
6 High waist circumference[a]	If female: >88 cm, if male: >102 cm
7 High visceral adipose tissue[a]	VAT >130 cm^2 or VAT/TAT ratio >0.5
8 Sarcopenia or presarcopenia[a]	Fat-free mass index <-1 SD
9 Insulin resistance[a]	Homeostasis Model Assessment-Insulin Resistance >2.8
10 High total cholesterol	>200 mg/dl
11 High low density cholesterol	>100 mg/dl
12 Low high density cholesterol	<40 mg /dl
13 High triglycerides	>150 mg/dl
14 High homocysteine[a]	If female: >10 μmol/L, if male: >15 μmol/L
15 Abnormal white blood cell counts	<4000 cells/μL
16 Anemia	If female: <100 g/L, if male: <120 g/L
17 Hepatitis C co-infection	Positive
18 Hepatitis B co-infection	Hepatitis B antigen positive
19 Vitamin D insufficiency[a]	<30 ng/mL
20 Polypharmacy	>5 drug classes (excluding antiretroviral therapy)
21 Abnormal parathyroid hormone[a]	>60 pg/mL
22 Abnormal D-dimer[a]	>Sample mean (358)
23 Elevated C-reactive protein[a]	>0.7mg/L
24 Sedentary lifestyle[a]	<3h/week physical activity
25 Atherosclerosis[a]	Coronary artery calcium score >100 or intima media thickness >0.85mm
26 Hyponatremia	<125 mmol/L
27 Proteinuria or albuminuria	>5 mg/mmol
28 Elevated aspartate transaminase	>31U/L
29 Elevated alanine transaminase	>31 U/L
30 Abnormal alkaline phosphatase	<38 or >126 U/L
31 Elevated gamma glutamyl transphosphatase	>55 U/L
32 Low platelets	<150 billion/L
33 Abnormal potassium	> 3.5 or >5.3 mEq/L
34 Abnormal phosphorus	<2.5 or >5.1 mg/dL
35 Abnormal thyroid stimulating hormone	<0.27 or > 4.2 mIU/L
36 Elevated total bilirubin	>1.1 mg/dl
37 Unemployment[a]	Self-report
Comorbidities	
1 Cardiovascular disease	Clinical diagnosis
2 Hypertension	Measured blood pressure or on treatment
3 Diabetes mellitus type II	Fasting blood glucose >125 mg/dL or on treatment
4 Chronic kidney disease	2 estimated glomerular filtration rate measurements <60ml/min/1.73m^2
5 Cirrhosis	FIB-4 score >3.25
6 Chronic obstructive pulmonary disease/Asthma	Spirometry: FEV1/FVC ratio <0.7
7 Osteoporosis[a]	Dual-energy absorptiometry *T*- or *Z*-score <-2.5 or fragility fracture
8 Any cancer	Clinical diagnosis with biopsy confirmation

[a]Deficits not included in the Southern Alberta Clinic Frailty Index.
FSH = follicle stimulating hormone; LH = luteinizing hormone; VAT = visceral adipose tissue; TAT = total adipose tissue; FIB = fibrosis-4 score; FEV1/FVC = forced expiratory volume in one second/forced vital capacity.

infection and of ART, and nadir and current CD4 cell count. Confidence intervals were 95% intervals, and significant *p* values were defined as < .05.

Ethics

The University of Calgary Research Ethics Board granted approval for this study (REB-16-1009).

RESULTS

Demographic and clinical characteristics of the SAC cohort are presented in Table 3. Study patients were predominantly males (85%) between 50 and 64 years of age (82.4%). Most had been living with HIV and receiving ART for many years

TABLE 3.
Patient characteristics

Total number of patients	717
Age, mean years (± SD)	59.2 (6.5)
Age, range years	50 to 92
Number of patients between 50–64 years (%)	591 (82.4)
Number of patients ≥ 65 years (%)	126 (17.6)
Number of male patients (%)	610 (85.2)
Duration of known HIV infection, mean years (± SD)	18.4 (8.1)
Duration of known HIV infection, range years	2 to 37
Duration of ART, mean years (± SD)	14.9 (7.5)
Duration of ART, range years	1 to 32
Current CD4 cell count, mean cells/μL (± SD)	593.5 (287.9)
Current CD4 cell count, range cells/μL	2 to 1,832
Number of patients with CD4 cell count ≤200 (%)	49 (6.8)
Number of patients with CD4 cell count >200 (%)	668 (93.2)
Nadir CD4 cell count, mean cells/μL (± SD)	351.7 (266.6)
Nadir CD4 cell count, range cells/μL	1 to 1,715
Number of patients with nadir CD4 cell count ≤200 (%)	234 (32.6)
Number of patients with nadir CD4 cell count > 200 (%)	483 (67.4)
Number of patients with current undetectable viral load (%)	668 (93.2)
Number of patients with current detectable viral load (%)	49 (6.8)
Deaths, number (%)	24 (3.35)
Deaths, mean age years (± SD)	63.9 (9.7)
Survivors, mean age years (± SD)	59.1 (6.3)

SD = standard deviation; IQR = interquartile range; ART = antiretroviral therapy.

(mean 18.4 and 14.9 years, respectively). At the time of FI assessment, the majority of patients had CD4 cell counts within the expected range of 500 to 1,500 cells/μL[31] (mean 594 cells/μL) and 93% had undetectable HIV viral loads defined as ≤40 copies/mL.

The mean FI was 0.303 (SD 0.128, range 0 to 0.69; see Table 4). The distribution of values was approximately normal (Figure 1). Nearly 75% of patients had FI values ≥ 0.21, (n=535; 74.6%), over half of the cohort ≥ 0.30 (n=391; 54.5%), and nearly 10% ≥ 0.45 (n=68; 9.5%).

Patients aged ≥65 had statistically significant higher mean FI values than those 50–64 (0.342 vs. 0.295; *p* = .0001). FI values were also significantly higher among those with both nadir and current CD4 cell counts below 200 cells/μL, with the difference greater for low nadir CD4 cell (*p* < .0001) than low current CD4 cell counts (*p* = .0472). Males had a modestly higher mean FI value of 0.306 compared to 0.289 for women that was not statistically significant (*p* = .109).

There were statistically significant, but weak, positive linear relationships between FI and duration of ART, duration of diagnosed HIV infection, and age (*r* = 0.238, *p* < .0001 for duration of ART; *r* = 0.212, *p* < .0001 for duration of diagnosed HIV infection; and *r* = 0.162, *p* < .0001 for age). The relationship between FI and age is shown in Figure 2, which includes the line of best fit and 95% confidence intervals. There was no significant relationship between FI and current CD4 cell count (*r* = -0.036; *p* = .3418), but there was a modest inverse relationship between FI and nadir CD4 count that approached statistical significance (*r* = -0.074; *p* = .0523).

Deaths

Twenty-four patients (3.3%) died during the study period. Mean age was greater among those who died compared to survivors (63.9 vs. 59.1 years; *p* = .0002) (Table 5), as was mean FI (0.351 vs. 0.302; *p* = .033). Current CD4 cell counts were significantly lower in patients who died (341 cells/μL) than those who survived (602 cells/μL) (*p* < .0001), and there were significantly more deaths in patients with a current CD4 cell count <200 cells/μL than in those with a current CD4 cell count ≥200 cells/μL (10 vs. 14; χ^2 = 47.3; *p* < .001). There was no significant difference in the number of deaths in patients with a low nadir CD4 cell count (<200 cells/μL) compared to those with a nadir CD4 cell count ≥200 cells/μL (9 vs. 15; χ^2 = 0.289; *p* = .591). With respect to HIV viral load, there was no significant difference in the number of deaths in patients with currently detectable versus undetectable HIV viral loads. Three deaths occurred in those with currently detectable HIV viral load and 21 deaths occurred in those with currently undetectable HIV viral load (χ^2 = 1.25; *p* = .263).

Based on FI values, approximately one-quarter (n=182; 25.4%) were non-frail (FI<0.21), a fifth (n=144; 20.1%) were frail (FI ≥0.21), close to a half (n=323; 45.1%) more-frail (FI ≥0.30), and nearly one in ten (n=67; 9.4%) most-frail (FI ≥0.45), employing cut-offs suggested by Hoover *et al.*[7] Five

TABLE 4.
Frailty index values

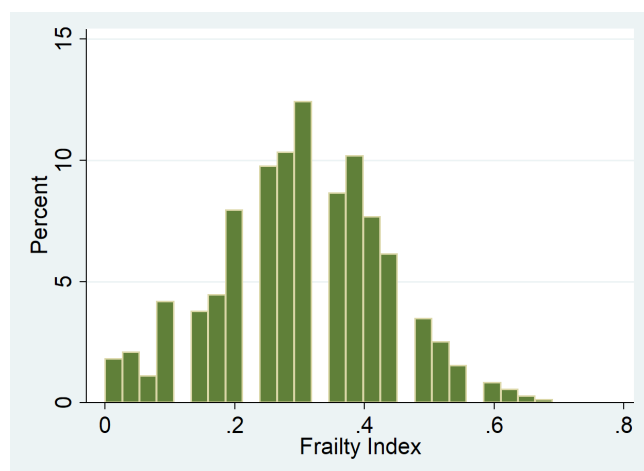|		
Frailty Index, mean (± SD)	0.303 (0.128)	
Frailty Index, range	0 to 0.69	
Frailty Index, males mean (± SD)	0.306 (0.127)	$p = .1088$
Frailty Index, females mean (± SD)	0.289 (0.134)	
Frailty Index, ≥ 65 years of age, mean (± SD)	0.342 (0.135)	$p = .0001$
Frailty Index, aged 50–64 years, mean (± SD)	0.295 (0.125)	
Frailty Index, mean (± SD) for current CD4 cell count ≤ 200 cells/μL	0.333 (0.155)	$p = .0472$
Frailty Index, mean (± SD) for current CD4 cell count >200 cells/μL	0.301 (0.126)	
Frailty Index, nadir CD4 cell count ≤200 cells/μL (± SD)	0.332 (0.125)	$p < .0001$
Frailty Index, nadir CD4 cell count >200 cells/μL (± SD)	0.289 (0.128)	
Number of patients with FI ≥0.21 "frail" (%)	535 (74.6)	
Number of patients with FI ≥0.30 "more-frail" (%)	391 (54.5)	
Number of patients with FI ≥0.45 "most frail" (%)	68 (9.5)	
Frailty Index, 75th percentile	0.379	
Frailty Index, 90th percentile	0.448	
Frailty Index, 95th percentile	0.517	

SD = standard deviation; IQR = interquartile range.

FIGURE 1. Distribution of frailty index values; mean 0.303, median 0.310, range 0 to 0.690

FIGURE 2. Relationship between frailty index and age at time of screening (years) including line of line of best fit and 95% CI

deaths occurred in the non-frail (5/182, 2.7%), three in the frail (3/144, 2.1%), ten in the more-frail (10/323, 3.1%) and six in the most-frail (6/67, 9%) groups.

Cause of death as determined by CoDe methodology for HIV patients[30] was available for 22/ 24 patients. Cancer was most common (9/22; 40.9%), followed by cardiovascular causes (myocardial infarction, stroke, ischemic heart disease, or other heart or vascular causes) (6/22; 27.3%), acute intoxication (4/22; 18.2%), and other causes (3/22; 13.6%). The mean FI of the five patients who died suddenly from acute intoxication or accident/other violent cause was 0.29 compared to a mean FI of 0.39 in the 17 patients who died of cancer, cardiovascular and other causes.
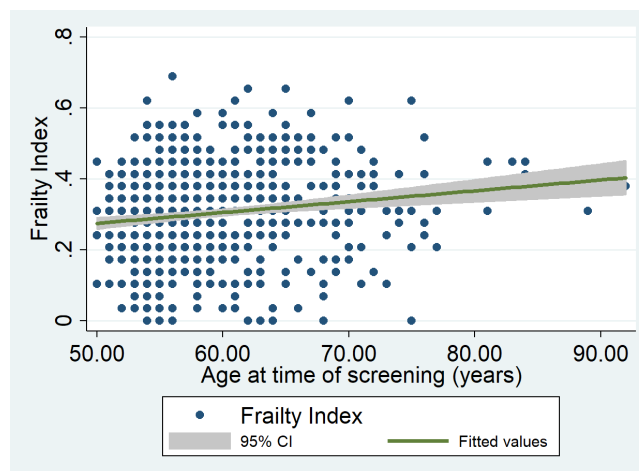
DISCUSSION

Previous studies have identified a broad range of prevalence estimates for frailty in HIV,[19] which may be at least partly due to the variability in the method of identification. In this cross-sectional study with two-years of follow-up data on mortality, the mean FI in over 700 PLWH ≥50 years of age attending SAC was more than 2-fold higher than HIV-negative participants with a mean age of 75 in a Canadian population-based study.[7] FI scores are known to be higher in clinical versus population-based cohorts, and the increase in FI with age tends to be more modest compared to population-based cohorts.[27] Our results are similar to these prior observations.

TABLE 5.
Characteristics of patients who died

	Deceased	Survived	p value
Number of patients (%)	24 (3.3)	693 (96.7)	
Age, mean years (± SD)	63.9 (9.7)	59.1 (6.3)	p = .0002
Duration of known infection, mean years (± SD)	21.3 (7.5)	18.3 (8.1)	p = .038
Duration of ART, mean years (± SD)	18.6 (5.8)	14.8 (0.3)	p = .01
Frailty Index, mean (± SD)	0.351 (0.164)	0.302 (0.127)	p = .033
Current CD4 cell count, mean (± SD)	340.8 (252.9)	602.3 (285.2)	p < .0001
Nadir CD4 cell count, mean (± SD)	289.0 (179.0)	353.8 (268.9)	p = .126

SD = standard deviation.

Similarly, our mean-calculated FI (0.303) approximates that observed in another HIV cohort that employed a FI (mean 0.31).[14] This finding supports potential generalizability of the FI to other HIV cohorts, which would permit comparisons and collaborative frailty studies across cohorts and sites. In constructing FIs, investigators do not have to use exactly the same variables in order to have comparable results as long as item selection follows certain rules.[3,4,27] Frailty indices made up of different variables have been shown to produce similar results in predicting patient outcomes.[32]

Despite evidence of effective ART confirmed by suppressed HIV viral loads and normal CD4 cell counts, PLWH in our cohort were at a high frailty risk. The weak positive association between FI and duration of ART and, to a lesser extent, the duration of diagnosed HIV infection, requires further study. Proposed cellular mechanisms by which ART may accelerate aging and possibly the development of frailty in PLWH include mitochondrial dysfunction and oxidative stress (nucleotide reverse transcriptase inhibitors, NRTIs), telomere shortening (NRTIs), and accumulation of the immature nuclear envelope protein prelamin A (protease inhibitors, PIs).[33] Although in linear regression, there was only a weak and nonstatistically significant negative association between FI and both nadir and current CD4 cell counts, when evaluated as binary variables (≤200 vs. >200 cells/μ), the negative association with FI was significant for both low nadir and low current CD4 cell counts. Low nadir CD4 cell count had a greater association than did low current CD4 cell count ($p < .0001$ and $p = .0472$). In a previous study of PLWH, nadir CD4 count was modestly associated with FI, but current CD4 count was not.[14]

Further work is needed on identifying contributing factors to the development of frailty in PLWH. The earlier onset and higher prevalence of frailty in HIV patients compared to HIV-negative individuals also raises the possibility of unique mechanisms such as the role of HIV infection itself, long-term toxicity of ART, delayed diagnosis of HIV infection and initiation of ART (suggested by the association with low nadir CD4 cell count), psychosocial factors or the common comorbidities observed in PLWH. Based on these findings, potentially modifiable factors that are associated with FI include both low nadir and low current CD4 cell counts. Earlier diagnosis of HIV and initiation of ART, and support and reinforcement of adherence to therapy, are mechanisms to decrease the frequency of these risk factors in our patients.

We observed a relationship between FI and death during the study period. Those who died had a mean FI of 0.35 compared to 0.30 in individuals who survived ($p = .033$). This relationship was also found in the Italian cohort.[14] The most common causes of death were cancer (9/22) and cardiovascular disease (6/22). Both cancer and cardiovascular disease are deficits in the FI we utilized, but each could only contribute an increment of 0.03 to an individual's FI. A number of patients (5/22) died suddenly from drug overdoses, accidents, or through violence. They tended to have lower FI values. This is an area requiring additional research. Deaths from drug use, accidents, and violence are not often addressed in studies of older adults

While community-based cohorts have used FI cut-off values ≥0.21 to identify frailty,[7] this threshold at SAC this would identify nearly 75% of patients ≥50 years of age as frail. We are exploring whether a FI ≥ 0.30 based on routinely collected health data can be used to identify HIV+ patients who should have a confirmatory clinical frailty assessment. Instruments such as the Clinical Frailty Scale[6] or the frailty phenotype,[4] as has been suggested for older patients in the United Kingdom,[34] could be used. Those confirmed as frail could then undergo a comprehensive geriatric assessment to identify modifiable contributing factors, determine prognosis, and develop a management plan.[7] In our cohort, a cut-off value of ≥0.30 would approach the 50th percentile of all patients (0.310), but would be below the mean FI of patients who died (0.351). Identifying those who might benefit from more resource-intensive services and/or interventions is an urgent need in clinical practice.

Further research is needed to inform the management of frailty in the HIV population. Longitudinal studies are required to determine the trajectory of frailty in this population and the strength of associations with clinical outcomes such as mortality and disability. Cognitive and physical training,

nutritional supplementation, or combination treatment may improve frailty status in HIV- populations.[35] One study suggested that adherence to a Mediterranean diet was associated with reduced incidence of frailty in HIV- older adults (OR 0.44; 95% CI 0.29 to 0.66).[36] It is as yet not clear what specific intervention may improve the frailty status of HIV+ individuals. We know lifestyle factors (i.e., smoking, obesity, low physical activity) and specific ART agents are associated with frailty. Addressing them may prevent or ameliorate frailty when present in this population.[37]

Limitations

The main limitation of the study is the cross-sectional design, which prohibits drawing conclusions of causality and the directionality of the associations found. Another potential limitation of the study is that the FI was based on data collected for purposes other than the determination of frailty. This would raise questions about comprehensiveness and accuracy, but missing values for the items included in the FI were relatively infrequent and our range checks allowed us to correct clearly aberrant values. Using data routinely collected for clinical care has the potential advantages of making this index both more feasible and generalizable to large HIV populations. The calculation of an FI could be automated with the requirement of no additional time, resources or specialized equipment. Our FI consisted of only 29 variables, which is at the lower end of the range of items required for the creation of an FI.[3] While we were unable to replicate exactly the FI index employed in another HIV cohort, the similarity of our results and the flexibility in the construction of the FI would allow its more widespread adoption across HIV care programs. Though our study was based on those receiving care at a single clinic, our study population is likely representative of aging PLWH across Canada with a high proportion of men receiving active ART and showing suppressed viral loads. Finally, as with the electronic FI used by NHS England,[38] we treated all deficits including laboratory abnormalities as non-resolvable. This would tend to inflate FI scores for those followed for longer periods of time. The impact of modifying this approach, especially for laboratory values (e.g., determination based on frequency of the abnormality and/or using only most recent value), should be explored.

CONCLUSION

We confirmed the high prevalence of frailty occurring at relatively young ages that have been seen in another HIV+ cohort using an FI.[14] Calculating an FI in PLWH based on routinely collected data would help in identifying potentially vulnerable patients who could benefit from a more in-depth, geriatric-based evaluation. In our study, despite evidence that the HIV infection was being well managed with suppressed HIV viral loads and normal CD4 cell counts, high levels of frailty were seen compared to HIV- populations. Studies are urgently needed to understand the underlying pathophysiology of frailty in PLWH, how to prevent its occurrence, and the best way to manage it should the condition occur.

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CONFLICT OF INTEREST DISCLOSURES

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