Development of Frail RISC-HIV: a Risk Score for Predicting Frailty Risk in the Short-term for Care of People with HIV

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Objective: Frailty is common among people with HIV (PWH), so we developed frail risk in the short-term for care (RISC)-HIV, a frailty prediction risk score for HIV clinical decision-making.

Design: We followed PWH for up to 2 years to identify short-term predictors of becoming frail.

Methods: We predicted frailty risk among PWH at seven HIV clinics across the United States. A modified self-reported Fried Phenotype captured frailty, including fatigue, weight loss, inactivity, and poor mobility. PWH without frailty were separated into training and validation sets and followed until becoming frail or 2 years. Bayesian Model Averaging (BMA) and five-fold-cross-validation Lasso regression selected predictors of frailty. Predictors were selected by BMA if they had a greater than 45% probability of being in the best model and by Lasso if they minimized mean squared error. We included age, sex, and variables selected by both BMA and Lasso in Frail RISC-HIV by associating incident frailty with each selected variable in Cox models. Frail RISC-HIV performance was assessed in the validation set by Harrell's C and lift plots.

Results: Among 3170 PWH (training set), 7% developed frailty, whereas among 1510 PWH (validation set), 12% developed frailty. BMA and Lasso selected baseline frailty score, prescribed antidepressants, prescribed antiretroviral therapy, depressive symptomology, and current marijuana and illicit opioid use. Discrimination was acceptable in the validation set, with Harrell's C of 0.76 (95% confidence interval: 0.73–0.79) and sensitivity of 80% and specificity of 61% at a 5% frailty risk cutoff.

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Conclusions: Frail RISC-HIV is a simple, easily implemented tool to assist in classifying PWH at risk for frailty in clinics.

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Introduction

Frailty is commonly used to measure physical well being and vulnerability to health stressors, including mortality, among aging adults [1,2]. It is well studied in the general population, and there is a growing body of literature focused on people with HIV (PWH) [3–10]. Findings show that frailty is a risk factor for poor health outcomes such as falls, hospitalization, and mortality in studies among the general population as well as PWH [1,3,4,6,10–13]. An expanded focus on risk factors that predict frailty development is important to improve care practices for healthy aging [3,6,8]. Improved identification of individuals at risk of frailty could aid in implementing early interventions to prevent frailty incidence, progression, and other related adverse health outcomes. This may be particularly important among PWH, since this population experiences frailty more often and at younger ages than those without HIV [5,6,9,14].

Frailty among PWH is commonly attributed to HIV-related factors (e.g. depletion of $CD4^{+}$ cells and accelerated aging due to chronic inflammation from HIV), non-HIV comorbidities, and greater polypharmacy, including medications for HIV [3–5,9,10,14–21]. These HIV-related factors can add to the aging process that adults without HIV experience. Earlier initiation of antiretroviral therapy (ART) and improvements in ART medications leading to greater viremic control and reduced inflammation may change the impact of HIV-related factors on frailty development [22]. There remains a gap in the literature addressing early detection despite multiple calls emphasizing the need for a transition from characterizing frailty to focusing on screening and interventions among PWH [1,8,23]. Although some studies have assessed risk factors for frailty, they have often been limited by small size and lack of consideration of risk behaviors that are more common among PWH (e.g. substance use) [4,16,20,24,25]. To overcome these limitations, we developed a clinical care decision-making risk score through modeling factors that predicted development of frailty in the short-term among PWH.

Methods

Setting and participants

We created the frailty risk in the short-term for care of PWH (frail RISC-HIV) score within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) [26]. CNICS is a clinical cohort of PWH aged ≥18 in care at eight academic sites across the United States; seven with relevant data were included in this study. CNICS integrates and harmonizes clinical data across the cohort from electronic health records and other data sources, including laboratory, diagnosis, medication, and demographic information. Also, PWH in CNICS complete a clinical assessment of patient reported outcomes (PROs), comprised of validated survey instruments, such as the HIV Symptom Index and 9-item Patient Health Questionnaire (PHQ-9) [27]. PWH completed this PRO assessment every ∼4–6 months as part of routine care visits.

PWH were included in this study if they met the following criteria: completed two or more PRO assessments between January 2011 and March 2021, had complete data on candidate predictor variables at first PRO assessment (within the study period) and frailty measures at all follow-up assessments, and were not frail at baseline. Time was measured as years since first, or baseline, PRO assessment, and PWH were followed until developing frailty or 2 years as we were specifically interested in short-term risk of frailty. PWH were separated into two groups: the training and validation set. The training set included PWH at six sites, and the seventh site was set aside during risk score development to be used as the validation set to evaluate the risk score. The validation site was chosen based on sample size (the site with the most recorded events) and representing all ranges of predictors assessed. This is a standard approach that we use, rather than selecting a random subset of PWH from all sites, to ensure independence of subpopulations for discrimination and calibration. Institutional review boards at each site approved CNICS protocols and participants completed informed consent prior to entry into CNICS.

Frailty

Frailty was defined using a modified version of Fried's Frailty Phenotype, an approach often used in studies of frailty among PWH [2,14,21,28]. We scored PWH from 0 to 4 based on four of Fried's five components measured in the PRO assessment, with a modified phenotype that is highly correlated ($\rho = 0.81$) with Fried's original phenotype [29]. These components included fatigue, unintentional weight loss, inactivity, and poor mobility

(the fifth criteria, grip strength, is not assessed in CNICS). Only PWH who reported 0–2 of these four components at baseline (i.e. not frail or prefrail) were included in the risk score development and validation. We considered someone frail during follow-up if they reported the presence of three or more components [2].

Candidate predictor variables

We included demographic, clinical, and behavioral characteristics as potential frailty predictors. Age and sex were included in the risk score *a priori* due to well known associations with frailty [9,30,31]. Race/ethnicity was considered as an additional potential demographic predictor. HIV-related clinical variables included: $CD4^+$ cell count (lowest and current), HIV viral load, self-report of currently taking ART, ever-prescribed didanosine (DDI), and ever-prescribed stavudine (D4T). Diagnoses included: hepatitis C virus (HCV) coinfection (defined by any lifetime positive result from an HCV antibody, RNA, or genotype test), hepatitis B virus (HBV) coinfection (defined by any lifetime positive result from a HBV surface antigen, e-antigen, or DNA test), and diabetes [any of the following criteria: hemoglobin A1c $\geq$6.5; use of a diabetes-specific medication, such as insulin; or use of a diabetes-related medication not exclusively used to treat diabetes (e.g. biguanides) in the setting of also having a diabetes diagnosis] [32]. Dyslipidemia (defined as lipid abnormalities severe enough to require lipid-lowering medications, such as statins) was also included. Additional clinical characteristics considered were baseline frailty score, body mass index [weight (kg)/height (m^2)], systolic and diastolic blood pressure, self-reported body morphology abnormalities (lipohypertrophy and lipoatrophy), kidney function [measured by estimated glomerular filtration rate (eGFR)], and liver function (measured by fibrosis-4) [33,34]. In addition, depression was included in two ways: antidepressant medication prescription, and depressive symptomology measured by a modified PHQ-9, which excluded sleep-related items yielding in a seven-item measure, from hereafter referred to as PHQ-7. The sleep questions (items 3 and 4 on the PHQ-9) were excluded to limit collinearity between depressive symptomology and frailty since the frailty phenotype includes fatigue as a component. Finally, substance use behaviors included current use of marijuana, cocaine/crack, methamphetamine, illicit opioids, and tobacco cigarettes, tobacco cigarettes smoked per day, years smoking cigarettes, pack-years smoking, alcohol use (AUDIT-C score), and frequency of use measured by days per month of alcohol, binge drinking, marijuana, methamphetamine, cocaine/crack, and illicit opioids [35].

Statistical analysis

We used two machine learning techniques with Cox proportional hazards (PH) models to select variables from the list of candidate predictors defined above for inclusion in Frail RISC-HIV. First, we used Bayesian Model Averaging (BMA) and designated selection criteria at having a greater than 45% probability of being in the best fitting model. We came to this decision due to the nuances in BMA results, in which predictors on the cusp of selection at 50% likelihood (a common cutoff) may provide important information in a prediction model, thus we also allowed for some clinical judgment in our variable selection for these on the cusp and considered our selection criterion at >45% likelihood [36]. Second, we used least absolute shrinkage and selection operator (Lasso) regression with five-fold cross-validation to select variables from the candidate predictors. Variables selected by *both* BMA and Lasso were included in frail RISC-HIV, in addition to age and sex. We selected BMA and Lasso due to their robust approach to variable shrinkage and our successful implementation of these techniques in prior analyses [37–39].

We then used a Cox PH model to estimate the hazard ratio (HR) of developing frailty associated with each selected variable. The baseline estimated survival and the HRs were used to calculate the risk score by multiplying each HR coefficient by the value of its respective predictor (e.g. HR for baseline frailty score multiplied by an individual's baseline frailty score) and adding each product together.

Frail RISC-HIV performance was assessed in the validation cohort. Discrimination was assessed by calculating Harrell's C, evaluating risk score cut points with sensitivity and specificity, and using lift plots. We considered Harrell's C statistic values of <0.70, 0.70 to 0.80, and >0.80 as inadequate, acceptable, and excellent levels of discrimination, respectively [38]. Lift plots were made by calculating the event rate per decile of frail RISC-HIV using cutoffs from the training set. Calibration was assessed by comparing the predicted vs. observed probability of developing frailty for both the training and validation sets. Analyses were performed using Stata version 16.1 (StataCorp, College Station, Texas, USA) and R version 4.1.1 [40–42].

Results

Cohort description

The analytic cohort included 4680 PWH, separated into training ($n = 3170$) and validation sets ($n = 1510$). There were not significant differences between PWH who had complete case data and those who did not, with the exception of a lower proportion of Hispanic PWH included and younger average age (43 years vs. 45 among PWH excluded) in the training set (Table 1, Supplemental Digital Content, http://links.lww.com/QAD/C804). Both groups were followed for a mean of 1.6 years (maximum 2 years by definition) and 220 PWH (7%) became frail in the training set, while 186 (12%) became frail in the validation set. Comparisons of the training and validation set for all candidate predictors are presented in Table 1. Among the entire cohort, 14% of PWH were

Table 1. Candidate predictor variables at baseline among PWH included in the training and validation sets for the Frail RISC-HIV.

Variable % or mean (SD)	Everyone $n = 4680$	Training set $n = 3170$	Validation set $n = 1510$
Female sex	14%	16%	9%
Age (years)	43 (11)	43 (11)	44 (11)
Active ART prescription	86%	91%	76%
Race/ethnicity			
Black	30%	38%	13%
Hispanic	15%	8%	31%
Other	6%	5%	8%
White	48%	48%	48%
Baseline frailty score	0.7 (0.8)	0.7 (0.8)	0.7 (0.8)
Active antidepressant prescription	51%	53%	49%
PHQ-7 score	3.1 (4.0)	3.0 (3.9)	3.4 (4.2)
Taking statins	18%	19%	16%
Body mass index (kg/m^2)	27 (6)	28 (6)	26 (4)
Hepatitis C virus coinfection	11%	11%	11%
Hepatitis B virus coinfection	4%	4%	4%
Systolic blood pressure (mmHg)	126 (10)	126 (10)	125 (10)
Diastolic blood pressure (mmHg)	79 (7)	80 (6)	77 (6)
Lipohypertrophy score	2.2 (3.8)	2.4 (3.9)	1.7 (3.5)
Lipoatrophy score	1.2 (3.3)	1.1 (2.7)	1.6 (4.2)
Diabetes	9%	10%	7%
Kidney function (eGFR, ml/min per 1.73 m^2)	95 (22)	94 (22)	96 (21)
Liver function (fibrosis-4 score)	1.2 (1.2)	1.1 (1.1)	1.3 (1.4)
Nadir CD4$^+$ cell count (cells/μl)	318 (250)	312 (243)	332 (262)
Current CD4$^+$ cell count (cells/μl)	579 (314)	610 (318)	512 (295)
HIV viral load	18 331 (145 120)	7887 (46 663)	40 257 (244 985)
Ever-prescribed DDI	9%	9%	9%
Ever-prescribed D4T	13%	12%	15%
Current substance use			
Marijuana	33%	35%	29%
Cocaine	6%	6%	5%
Methamphetamine	10%	9%	12%
Illicit opioids	2%	2%	2%
Tobacco cigarette	30%	30%	30%
Cigarettes per day	3.6 (7.0)	3.7 (7.1)	3.4 (6.6)
Years smoking cigarettes	7.0 (8.2)	7.0 (8.2)	6.9 (8.2)
Cigarette pack-years	5.0 (8.1)	5.1 (8.2)	4.8 (7.9)
Alcohol use (AUDIT-C) score	2.3 (2.4)	2.4 (2.4)	2.2 (2.5)
Frequency of substance use (days per 30)			
Drinking alcohol	4.0 (5.9)	4.1 (6.0)	3.6 (5.7)
Binge drinking	0.8 (3.4)	0.8 (3.4)	0.7 (3.6)
Marijuana	3.9 (9.5)	3.8 (9.4)	3.9 (9.8)
Methamphetamine	0.6 (3.8)	0.6 (4.0)	0.6 (3.6)
Cocaine	0.1 (1.3)	0.1 (1.5)	0.1 (0.8)
Illicit opioids	0.1 (2.0)	0.2 (2.2)	0.1 (1.3)
Frail (event)	8%	7%	12%

D4T, stavudine; DDI, didanosine; frail RISC-HIV, frailty risk in the short-term for care of people with HIV; PWH, people with HIV.

female, 48% were White, 30% were Black, and the average age at baseline was 43 years. There were 140 (3%) PWH aged 65 or older and 1,494 (32%) aged 50 or older.

Risk score development

In BMA, six variables exceeded 45% likelihood of being in the best model: baseline frailty score, PHQ-7 score, antidepressant prescription, current illicit opioid use, taking ART, and current marijuana use (Table 2). These variables, in addition to lipohypertrophy, tobacco cigarette pack-years, and frequency of illicit opioid use were selected by Lasso regression. Full variable selection results are presented in Table 2. Sex, age, and variables selected by both BMA and Lasso (baseline frailty score, PHQ-7 score, prescribed antidepressants, illicit opioid use, taking ART, and marijuana use) were included in Frail RISC-HIV. Estimated HRs for frailty among the selected variables are presented in Table 3. The predictor with the largest weight was baseline frailty score, with an HR of 2.9 per additional component of frailty. The next largest weight was illicit opioid use, with a 2.3 times greater risk of frailty. The average predicted risk of frailty in the training set was 8.6% [interquartile range (IQR): 2.0–10.1%].

Risk score validation

Discrimination was acceptable in the validation set, with Harrell's C of 0.76 [95% confidence interval (CI): 0.73–0.79]. The receiver operator characteristics for risk score values, which represent the percentage likelihood of

Table 2. Variable selection results for Bayesian Model Averaging (BMA) and Lasso regression, bold = selected.

Variable % or mean (SD)	BMA Likelihood	Lasso coefficient[a]
Female sex[b,c]	29.1	0.36
Age (years)[b,c]	3.2	0.01
On ART[c]	**48.4**	**0.12**
Race/ethnicity		
Black	0.1	–
Hispanic	0.1	–
Other	1.7	–
Baseline frailty score[c]	**100.0**	**0.93**
Taking antidepressants[c]	**77.5**	**0.17**
PHQ-7 score[c]	**99.8**	**0.05**
Taking statins	0.6	–
Body mass index (kg/m^2)	22.7	–
Hepatitis C virus coinfection	0.5	–
Hepatitis B virus coinfection	0.3	–
Systolic blood pressure (mmHg)	0.7	–
Diastolic blood pressure (mmHg)	2.9	–
Lipohypertrophy score	31.7	0.02
Lipoatrophy score	0.1	–
Diabetes	0.1	–
Kidney function (eGFR, ml/min per 1.73 m^2)	0.5	–
Liver function (fibrosis-4 score)	0.3	–
Nadir CD4$^+$ cell count (cells/μl)	0.1	–
Current CD4$^+$ cell count (cells/μl)	0.1	–
HIV viral load	10.4	–
Ever-prescribed DDI	0.1	–
Ever-prescribed D4T	0.8	–
Current substance use		
Marijuana[c]	**46.6**	**0.19**
Cocaine	0.7	–
Methamphetamine	0.2	–
Illicit opioids[c]	**56.4**	**0.42**
Tobacco cigarette	0.8	–
Cigarettes per day	1.2	–
Years smoking cigarettes	5.3	–
Cigarette pack-years	39.1	0.01
AUDIT-C score	0.1	–
Frequency of substance use (days per 30)		
Drinking alcohol	1.3	–
Binge drinking	0.2	–
Marijuana	0.2	–
Methamphetamine	0.2	–
Cocaine	0.1	–
Illicit opioids	6.5	0.004

D4T, stavudine; DDI, didanosine; SD, standard deviation.
[a]Lasso coefficients are the model coefficients (in this case the shrunk log hazard ratios) for variables that are in the model for the lambda value that minimizes the mean cross-validated error and are only reported for selected variables.
[b]Forced into risk score regardless of selection.
[c]Included in risk score.

becoming frail within 2 years, are displayed in Fig. 1, with notable frailty risk cut points indicated at 5 and 10% risks of frailty. At 5% risk, the sensitivity of Frail RISC-HIV was 80% and specificity was 61%, whereas at 10% risk, the sensitivity was 58% and specificity was 81%. Most of the risk of frailty was observed in the top three risk score deciles according to lift plots; risk was five times greater in the top three deciles vs. the bottom seven (Fig. 2). In terms of calibration, the risk score underpredicted overall risk of frailty in the validation set, with predicted risk of 7.9% (IQR: 1.8–9.7%) vs. observed risk of 14.7%.

Table 3. Hazard ratios of frailty for variables included in Frail RISC-HIV in the training set ($n = 3170$).

Variable	Hazard ratio	95% Confidence interval	*P*-value
Baseline frailty score	2.9	2.4–3.6	<0.001
Depressive symptomology	1.1	1.0–1.1	<0.001
Current illicit opioid use	2.3	1.3–4.2	0.01
Current marijuana use	1.4	1.1–1.9	0.01
Prescribed antidepressants	1.4	1.1–2.0	0.02
Not prescribed ART	0.6	0.3–0.97	0.04
Female sex	1.5	1.1–2.1	0.02
Age (per decade)	1.1	0.96–1.2	0.2

ART, antiretroviral therapy; frail RISC-HIV, frailty risk in the short-term for care of people with HIV.

Discussion

We developed Frail RISC-HIV, a short-term frailty risk score for PWH in clinical care, with acceptable validation properties. Frail RISC-HIV is a simple, easily implemented tool to aid in identifying PWH at the greatest risk of transitioning to being frail in the near future and can be used to target early interventions to support healthy aging. We identified cutoffs on frail RISC-HIV at 5 and 10% risk of becoming frail within 2 years, with good-fair diagnostic properties (e.g. sensitivity and specificity). Both cutoffs, including the tradeoffs between them, may be useful to consider as part of care, and it is important to note that they have nearly opposite sensitivity and specificity values (80 and 61% vs. 58 and 81%). Furthermore, the predictors selected by our machine learning approach were consistent with prior studies and highlight characteristics that may be important to carefully watch throughout long-term care of PWH [4,18,19,25,43,44].

A frailty risk score is a valuable tool to incorporate into care as it integrates various domains of data and translates those factors/behaviors to suggest the likelihood of future frailty. This prediction can be used to guide treatment, identify individuals or groups for monitoring, or suggest potential interventions best aligned with someone's frailty risk. Specifically, Frail RISC-HIV highlights the complexities of frailty among PWH, including factors other than age (which is often used as a singular screening characteristic) that may impact someone's likelihood of becoming frail, especially when these factors (e.g. depression, certain substance use) are present among younger PWH who otherwise may not be considered at high risk for frailty. Notably, Frail RISC-HIV was developed including follow-up time, so its utility is heightened as a tool for early interventions. We also suggest potential cutoffs for implementing the score, and there is flexibility in selecting these values, allowing for adaptation to optimize effectiveness in the clinical use of this tool (i.e. varying sensitivity and specificity). Additional validation work may improve Frail RISC-

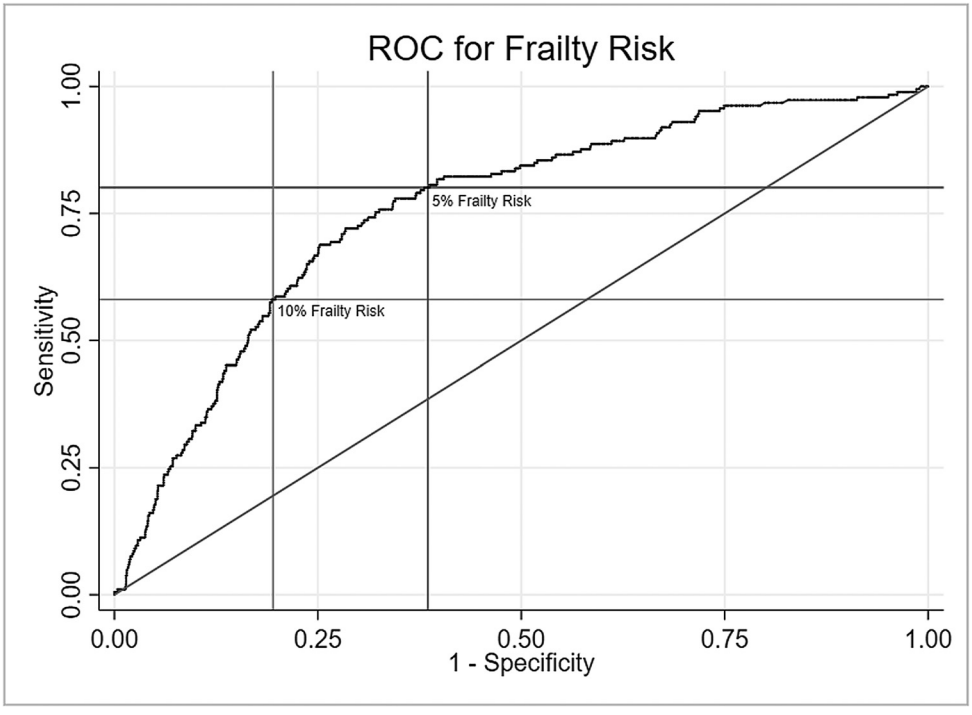

Fig. 1. Receiver operating characteristics (ROC) curve for the Frail RISC-HIV, with notable cutoffs indicated for percentage risk of becoming frail. RISC-HIV, risk in the short-term for care of people with HIV.

HIV, for example, by recalibrating within a different population to allow for utility in settings other than HIV primary care or by including biomarkers into future risk profiles.

Our study builds on the findings of another frailty screening tool recently developed, the FUNCFRAIL Score [45]. However, in contrast to the prior instrument, we examined variables prior to the development of frailty

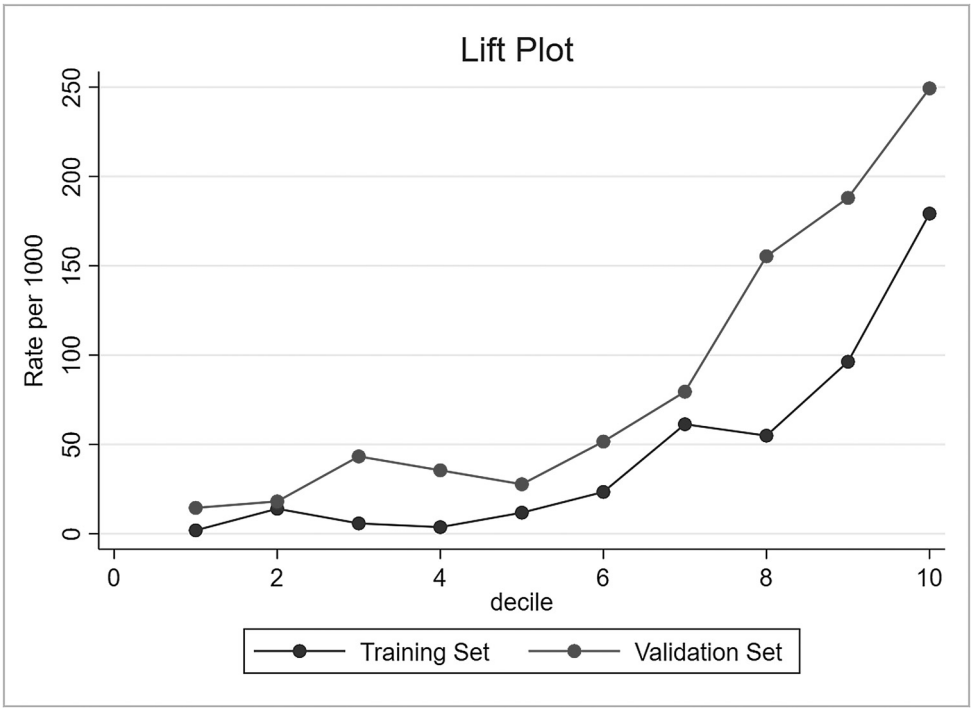

Fig. 2. Lift plot (by decile) of frailty risk per 1000 in the validation set vs. training set.

and had a much larger number of PWH (4680 vs. 798) [45]. The FUNCFRAIL Score was developed using cross-sectional data, while we were able to expand on that and incorporate 2 years of follow-up to predict future frailty. This was important because it enabled us to consider the presence of frailty components among PWH who are not yet frail. In particular, baseline frailty score is an important predictor of future frailty and our finding that baseline score was the strongest predictor underscores the need for interventions to mitigate progression. While recovery in frailty has been observed, this suggests that progression occurs relatively quickly in this population, and highlights the importance of directing interventions, such as physical activity, toward early prevention [19]. Further research on predictors of prefrailty or ways to slow frailty progression should be of utmost importance.

Moreover, both depressive symptomology and antidepressant prescription were identified as predictors, highlighting the important relationship between depression and frailty. Depression and frailty have a complex relationship; both are common among PWH and may exacerbate the symptoms of one another [43,46–49]. There is overlap in the symptomology of depression and frailty, particularly in exhaustion and low daily activity, but the two remain distinct syndromes in clinical practice [46,47]. To alleviate some concern of collinearity in our own consideration of depression as a predictor of frailty, we measured depressive symptomology via PHQ-7, a modified version of the PHQ-9 which excludes the sleep-related items [50]. Still, depressive symptomology was an important predictor in Frail RISC-HIV. Furthermore, clinical depression, or other reasons such as anxiety, that warrants pharmacological intervention with antidepressants increases polypharmacy burden [17,18]. Despite excluding two items in the depression symptoms assessment, both symptomology and treatment of depression were identified as predictors. This provides further evidence of the association between frailty and depression and underscores need to focus research on understanding and ultimately reducing their co-occurrence.

Recently, a new syndemic, Opioids and other substances, Aging, Alcohol, Tobacco, and HIV (OATH), was introduced to draw attention to links between important biological, behavioral, and psycho-social issues and to demonstrate co-occurring and interacting mechanisms that impact the health of PWH [25]. Accelerated aging, chronic inflammation, multimorbidity, and polypharmacy are established and well researched areas of care among PWH, and OATH integrates substance use into the context of each of these [25]. Our work highlights the short-term predictive ability of certain substance use variables, and emphasizes illicit opioid and marijuana use as important areas of focus. In the context of OATH, opioid use can impair and suppress the immune system, whereas there is mixed evidence regarding marijuana as it may have both pro- and anti-inflammatory properties [25,51,52]. Studies on substance use and frailty are extremely limited among PWH, however, adverse health outcomes associated with opioid use, such as cardiovascular disease, have been noted [53]. Further research on the consequences of substance use has been suggested, particularly to investigate the impact of substance use treatment.

Furthermore, there is some published evidence on relationships between frailty, substance use, and pain. One study of formerly incarcerated homeless women found drug dependence to be associated with physical frailty [54]. This study and others have also found associations between bodily pain and physical frailty [54–56]. Additional research is warranted to confirm these findings, but it is important to note that these mechanisms align with our results. Specifically, illicit opioid and marijuana use were selected as predictors in Frail RISC-HIV and could be signs of early self-management of frailty (i.e. for pain and/or discomfort) [57–61]. This may be especially relevant for Frail RISC-HIV since we focused on short-term risk, and these behaviors could be signs of early frailty.

Taking ART was also selected as a predictor, with the HR showing being on ART conferring an increased risk of developing frailty, potentially indicating longer duration of HIV infection. The time period of this study (2011–2021) is representative of the era with updated recommendations for HIV treatment, including immediate initiation of ART following HIV diagnosis [22]. Furthermore, within CNICS, almost all PWH are prescribed ART (>96% in 2019–2020) [62]. Therefore, we suspect this HR may indicate PWH not taking ART having more recently diagnosed HIV, and less time living with HIV to impact the development of frailty. It is worth noting that this variable was an indicator of self-reporting taking ART, not adherence to ART. Additionally, it is important to note that this study was designed to only identify predictors of transitioning to frailty, not causal factors associated with frailty, so while the HRs are useful to understand the weight of each predictor in the risk score, they should not be interpreted as causal.

With the aforementioned exception of ART, other HIV-related factors are absent from Frail RISC-HIV. There is a well characterized association between HIV-factors, such as current $CD4^+$ cell count, and frailty, however, they may be a representation of eventual immune exhaustion rather than a predictor of future frailty, that is, they correlate well with current frailty, but less so as a precursor [63]. Another study evaluating predictors of transitions in frailty by Brothers and colleagues identified mostly HIV-related factors as predictors, but their results are from 2004–2014, mostly preceding the current treatment recommendations [19]. The differences between our findings regarding HIV-related factors may be due to a shift in HIV care in the current treatment era to improved medications and early ART initiation [22]. In addition, Brothers *et al.* measured frailty via frailty index, which may not confer comparability with our frailty phenotype

given the difference in scope between defining frailty by presence of comorbidities, symptoms, and other factors vs. components of frailty as defined by Fried.

This study has many strengths worth highlighting, including the size and diversity of CNICS. We were able to follow PWH for up to 2 years to observe transitions to frailty, which has not been done for a frailty risk score among PWH. We also examined a broad and extensive list of candidate predictors for Frail RISC-HIV. Substance use in particular is an important area of research among aging PWH, and an evaluation of these behaviors has been lacking in recent literature. Finally, we used advanced techniques and methodologies in our machine learning approach to select predictor variables to develop a robust risk score. There are also limitations to note. CNICS is a clinic- and US-based cohort, therefore our results may not be generalizable to PWH who are not engaged in clinical care or PWH outside the United States. Although the large majority of PWH in the United States are male, the proportion of female PWH in this study is slightly low (15%), however, this number is likely representative of PWH engaged in care. Our risk score is also a short-term predictor of frailty, and longer follow-up would be useful. Finally, there is no universal definition of frailty, which makes it difficult to precisely compare across different studies. However, many studies, particularly among PWH, use Fried's phenotype or a modified version as we did.

Conclusion

The prevention and slowing of frailty among PWH may prolong healthy living time, quality of life, and overall survival. Frail RISC-HIV can aid in identifying PWH at risk of developing frailty and suggest areas for targeted interventions to slow progression. Further research focusing on biomarkers and longer-term predictors of frailty as well as prefrailty is warranted to improve our understanding of the development and progression of frailty.

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Conflicts of interest

There are no conflicts of interest.

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