Frailty and Cause-Specific Hospitalization Among Persons Aging With HIV Infection and Injection Drug Use

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Received April 12, 2016; Accepted July 6, 2016

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background: Hospitalization events exact a substantial toll across the age spectrum. Frailty is associated with all-cause hospitalization among HIV-uninfected adults aged 65 years and older. Limited data exist on the frailty relationship to hospitalization among HIV-infected persons or those aged less than 65 years. Comparative investigation of the frailty relationship to specific classes of hospitalizations has rarely been reported among adults of any age. This study sought to determine the frailty relationship to three distinct classes of hospitalization events among HIV-infected persons and their uninfected counterparts.

Methods: Frailty was ascertained semiannually among persons with prior injection drug use using the five Fried phenotypic domains. Hospitalization events were categorized using Agency for Healthcare Research and Quality clinical classification software into chronic, infectious, and nonchronic, noninfectious conditions. Cox proportional hazards models were used to examine the frailty relationship to time to first hospitalization event.

Results: Among 1,303 subjects, mean age was 48 years; 32% were HIV-infected. Adjusting for sociodemographics, comorbidity, substance use, and HIV disease stage, time-updated frailty status was associated with risk for all hospitalization classes. Baseline frailty was significantly associated with all-cause (hazards ratio [HR] 1.41; 95% confidence interval [CI], 1.06, 1.87), chronic (HR 2.13; 95% CI, 1.46, 3.11), and infectious disease hospitalization (HR 2.51; 95% CI, 1.60, 3.91) but not with nonchronic, noninfectious hospitalization risk (HR 1.09; 95% CI, 0.74, 1.61).

Conclusion: The frailty phenotype predicts vulnerability to chronic and infectious disease-related hospitalization. Frailty-targeted interventions may mitigate the substantial burden of infectious and chronic disease-related morbidity and health care utilization in HIV-infected and uninfected populations.

Keywords: Chronic disease—HIV/AIDS—Infection—Injection drug use

Background

Hospitalization events often reflect the most severe stage of clinical disease, presaging severe disability and mortality. These events exact a substantial economic toll, with an estimated cost of $400 billion in 2011 in the United States alone (1,2). Hospitalizations can be broadly classified into chronic, infectious and nonchronic, noninfectious type events. Annually, chronic disease-related hospitalizations account for over $300 billion in costs (3). Of infectious disease hospitalizations, sepsis and pneumonia alone cost over $30 billion. Approximately 65% of all hospitalizations and 80% of chronic and infectious disease hospitalizations occur among persons 45 years or older (1–4). Reducing hospitalization events in aging populations is a significant clinical and economic imperative.
With combination antiretroviral therapy (cART), HIV-infected persons are living longer (5,6). With increasing age has come an increasing burden of adverse aging-associated phenotypes and heightened vulnerability to aging-associated morbidity, often manifest in hospitalization events. Thus, despite a concomitant decline in Acquired Immunodeficiency Syndrome (AIDS) conditions, hospitalization burden remains substantial with a shift toward non-AIDS comorbid disease (7–9). There have been limited direct studies of hospitalization events among HIV-infected persons relative to their HIV-uninfected counterparts in the cART era. However, the few studies that exist demonstrate persistently higher hospitalization rates in the HIV-infected population (9,10). Among HIV-infected persons, those with injection drug use remain at particularly heightened risk for hospitalization (7,11). Understanding pathways of increased vulnerability to hospitalization is crucial to developing interventions to reduce health care utilization and promote healthy outcomes for aging HIV-infected persons and their high-risk counterparts.

Frailty is an aging-related syndrome of increased vulnerability to adverse clinical outcomes, including hospitalization and death (12–14). Although initially characterized in the HIV-uninfected elderly population (adults 65 years and older), recent studies support its relevance to nonelderly and HIV-infected populations, with substantive data indicating a heightened frailty burden among HIV-infected persons (15–19). However, the relationship of frailty to clinical outcomes such as hospitalization has not been fully investigated in HIV-infected adults. Prior frailty studies have primarily focused on all-cause hospitalization. Pathophysiologic impairments in frailty, including dysregulated inflammation and immunity (20–22), would suggest that frailty may predispose to both chronic and infectious disease hospitalization; these relationships have been largely unexplored.

In this study, we sought to examine the relationship of baseline and time-updated frailty phenotype status to all-cause, chronic disease, infectious, and nonchronic, noninfectious hospitalization risk in a cohort of aging HIV-infected and uninfected adults with prior injection drug use.

Methods

Study Participants and Data Collection

The AIDS Linked to the IntraVenous Experience (ALIVE) cohort has prospectively followed persons aged 18 years or older with a history of injecting drugs in a community-recruited cohort since 1988. Participants were recruited through street-based efforts from 1988 through 2008 (23). At semiannual visits, ALIVE participants completed standardized questionnaires and underwent clinical examination. Detailed information obtained at each follow-up visit included socioeconomic, behavioral, and clinical parameters. Substance use including alcohol, tobacco, and illicit injection and noninjection drug use were assessed by participant self-report of behaviors in the prior 6-month period. Comorbid conditions ascertained included obesity (defined as a body mass index ≥30) and participant self-report of any provider diagnosis of diabetes, hypertension, or cerebrovascular, cardiovascular, renal, chronic lung, malignant, or liver disease. Hazardous alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT). Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale (17). The ALIVE study has been continually approved by the Johns Hopkins Institutional Review Board.

Frailty Assessment

Frailty assessments were performed semiannually in ALIVE from 2005 using the five Fried domains: slow gait, decreased grip strength, exhaustion, low physical activity, and weight loss (Supplementary Table 1) (13,17).

Hospital Ascertainment and Diagnostic Categories

Through June 2012, medical records were obtained for interval hospitalization events reported at each follow-up visit. Admission dates and ICD-9 diagnostic codes were abstracted. Agency for Healthcare Research and Quality (AHRQ) chronic condition indicator clinical classification software was utilized to first categorize each primary admission diagnosis as chronic or nonchronic. Separate AHRQ clinical classification software was used to further subcategorize diagnoses into 1 of 18 subcategories (24,25). Any infection assigned to a clinical classification software organ system category (e.g., pneumonia in the pulmonary category and cellulitis in the dermatologic category) was reassigned such that all infections were grouped into a single category. Nonchronic conditions were then subdivided into infectious or noninfectious. A separate category for AIDS-defining illnesses was created by reassigning ICD-9 codes per the 1993 Centers for Disease Control and Prevention revised classification (7,26). Mortality was assessed through linkage to the National Death Index (NDI) (17,27).

Statistical Analysis

Frailty was considered as a three-tier categorical variable: robust, 0; prefrail, 1–2; frail, ≥3 criteria. To evaluate the relationship between frailty and incident hospitalization over the study period 2005 through 2012, Cox proportional hazards regression models were performed. The index (baseline) visit, defined as the date of initial frailty assessment, was the time origin. Hospital-free survival times were determined to the date of first hospitalization during study follow up. Participants who remained event-free for the study duration were censored as of the date of their last follow-up visit. Separate Cox regression analyses were performed to assess the independent contribution of frailty to all-cause, chronic disease, infectious disease and nonchronic, noninfectious hospitalization events. In separate models, frailty was considered both as a fixed baseline and as a time-varying covariate. Substance use variables, homelessness, unemployment, comorbidity, and HIV-specific factors (HIV status, CD4 count, HIV viral load, prior AIDS diagnosis, and cART status) were considered as time-varying covariates. All models were a priori adjusted for age, gender, race, and educational attainment. Log(-log) plots and Schoenfeld residuals were used to confirm the proportionality assumption. Analyses were repeated using competing risk models based on the methods of Fine and Gray, with death as the competing risk. Further sensitivity analyses were performed utilizing Cox proportional hazard models with delayed entry with individual age as the time scale. Analyses were performed using STATA (version 12; Stata Corp., College Station, TX).

Results

Study Population and Hospital Diagnoses

Among 1,303 participants, the mean age at baseline was 48 years (SD 7.8), with 96% of participants less than 65 years of age; 89% were African American and 32% HIV infected (Table 1). Over a median follow-up period of 4.5 years (interquartile range [IQR], 2.5, 5.8), 543 (42%) participants were hospitalized at least once; 300 (23%) had at least 1 chronic disease hospitalization, 216 (17%) had at least 1 infectious disease hospitalization, and 289 (22%) had at least 1 nonchronic, noninfectious hospitalization event.
Hospitalization events by clinical classification software diagnostic subcategory and hospitalization class are shown in Supplementary Tables 2 and 3. The most common overall primary hospital diagnoses were infection (30%), cardiovascular disease (16%), and psychiatric illness (13%). The most common chronic disease diagnoses were psychiatric illness (28%; predominantly depression or psychosis), cardiovascular disease (20%; predominantly malignant hypertension, acute myocardial infarction, stroke, and congestive heart failure), and pulmonary disorders (12%; predominantly chronic obstructive pulmonary disease or asthma exacerbation). The most common infectious diseases diagnoses were pneumonia (37%), skin and soft tissue infections (30%), and bacteremia/septicemia (5%). The most common acute, noninfectious disease conditions were non-cardiac chest pain (23%), gastrointestinal disease (16%; predominantly acute gastritis and acute pancreatitis), and fractures (9%).

Nonfrailty Risk Factors for Hospitalization

Univariate and multivariable associations with all-cause and cause-specific hospitalization are shown in Supplementary Table 4 and Table 2, respectively. In multivariable analyses, chronic disease hospitalization risk was associated with increased chronic comorbidity, homelessness, and hazardous alcohol use. Infectious disease hospitalization risk was associated with homelessness, prescription drug abuse, and active injection drug use. Acute, noninfectious hospitalization risk was associated with hazardous alcohol use. Unemployment was associated with increased risk for all three classes of hospitalizations.

In multivariable analyses (Supplementary Figure 1), a prior AIDS diagnosis was associated with increased risk for all three classes of hospitalizations. Having a CD4 nadir <50 cells/ml with a detectable viral load was associated with an increased nonchronic, noninfectious hospitalization risk. Dose response associations of lower CD4 count, HIV virologic status, and cART use were consistently observed with infectious disease hospitalization risk.

Frailty and Risk for All-Cause and Cause-Specific Hospitalization

Cox regression models for the association of frailty with incident hospitalization are shown in Supplementary Figure 2 and Table 2. The median time to hospitalization from baseline frailty assessment was 17 months (IQR 7.4, 34.3) and from the most proximal frailty measurement 4.7 months (IQR 2.7, 7). Adjusting for sociodemographics,
behavioral factors, comorbidity, and HIV/AIDS status, the baseline frailty measure was significantly associated with an increased risk of all-cause (HR 1.41; 95% CI, 1.01, 1.87), chronic (HR 2.12; 95% CI, 1.46, 3.11), and infectious disease (HR 2.51; 95% CI, 1.60, 3.91) hospitalization but not with acute, noninfectious hospitalization (HR 1.09; 95% CI, 0.74, 1.61). When treated as a time-varying covariate, frailty was significantly associated with all outcomes: all-cause hospitalization (HR 1.53; 95% CI, 1.16, 2.03), chronic disease (HR 2.27; 95% CI, 1.58, 3.27), infectious disease (HR 1.70; 95% CI, 1.11, 2.60), and nonchronic, noninfectious hospitalization (HR 1.50; 95% CI, 1.03, 2.18). The interaction terms between frailty and HIV status for all four outcomes were not significant.

**Table 2. Frailty and Risk for All-Cause and Cause-Specific Hospitalization**

<table>
<thead>
<tr>
<th>Time-updated frailty models*</th>
<th>All-cause (HR 95% CI)</th>
<th>Chronic (HR 95% CI)</th>
<th>Infectious (HR 95% CI)</th>
<th>Nonchronic, Noninfectious (HR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 y)</td>
<td>1.03 (0.96, 1.10)</td>
<td>1.08 (0.99, 1.18)</td>
<td>0.99 (0.89, 1.09)</td>
<td>1.08 (0.98, 1.18)</td>
</tr>
<tr>
<td>Female</td>
<td>1.41 (1.17, 1.70)</td>
<td>1.43 (1.11, 1.84)</td>
<td>1.41 (1.06, 1.88)</td>
<td>1.25 (0.96, 1.61)</td>
</tr>
<tr>
<td>African American</td>
<td>0.88 (0.64, 1.21)</td>
<td>0.93 (0.59, 1.47)</td>
<td>0.93 (0.56, 1.56)</td>
<td>0.94 (0.59, 1.50)</td>
</tr>
<tr>
<td>Less than high school education</td>
<td>0.94 (0.79, 1.13)</td>
<td>0.95 (0.74, 1.21)</td>
<td>1.07 (0.80, 1.42)</td>
<td>0.93 (0.73, 1.19)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>1.92 (1.49, 2.48)</td>
<td>2.37 (1.62, 3.48)</td>
<td>1.85 (1.19, 2.87)</td>
<td>1.65 (1.18, 2.32)</td>
</tr>
<tr>
<td>Homeless</td>
<td>1.42 (1.10, 1.84)</td>
<td>1.59 (1.12, 2.25)</td>
<td>1.48 (1.02, 2.14)</td>
<td>—</td>
</tr>
<tr>
<td>Hazardous alcohol use</td>
<td>1.30 (1.06, 1.60)</td>
<td>1.37 (1.05, 1.80)</td>
<td>—</td>
<td>1.46 (1.11, 1.92)</td>
</tr>
<tr>
<td>Recent injection drug use</td>
<td>1.25 (1.03, 1.51)</td>
<td>—</td>
<td>2.32 (1.73, 3.11)</td>
<td>—</td>
</tr>
<tr>
<td>Prescription drug abuse</td>
<td>1.40 (1.05, 1.87)</td>
<td>—</td>
<td>1.66 (1.11, 2.48)</td>
<td>—</td>
</tr>
<tr>
<td>Number of comorbid conditions*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>HIV status</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HIV+, no AIDS</td>
<td>1.27 (1.03, 1.56)</td>
<td>0.89 (0.67, 1.20)</td>
<td>2.64 (1.93, 3.61)</td>
<td>1.10 (0.82, 1.47)</td>
</tr>
<tr>
<td>HIV+, AIDS</td>
<td>2.74 (2.05, 3.67)</td>
<td>1.55 (1.02, 2.34)</td>
<td>7.60 (5.30, 11.2)</td>
<td>2.10 (1.43, 3.09)</td>
</tr>
<tr>
<td>Frailty status—time updated*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Robust</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Prefrail</td>
<td>1.12 (0.91, 1.39)</td>
<td>1.19 (0.88, 1.61)</td>
<td>1.12 (0.79, 1.57)</td>
<td>1.14 (0.85, 1.52)</td>
</tr>
<tr>
<td>Fail</td>
<td>1.53 (1.16, 2.03)</td>
<td>2.27 (1.58, 3.27)</td>
<td>1.70 (1.11, 2.60)</td>
<td>1.50 (1.03, 2.18)</td>
</tr>
<tr>
<td>Baseline frailty models*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Frailty status—baseline*</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Robust</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Prefrac</td>
<td>1.00 (0.81, 1.23)</td>
<td>1.21 (0.90, 1.64)</td>
<td>1.32 (0.92, 1.90)</td>
<td>0.93 (0.70, 1.23)</td>
</tr>
<tr>
<td>Fail</td>
<td>1.41 (1.06, 1.87)</td>
<td>2.13 (1.46, 3.11)</td>
<td>2.51 (1.60, 3.91)</td>
<td>1.09 (0.74, 1.61)</td>
</tr>
</tbody>
</table>

**Note:** CI = confidence interval; HR = hazard ratio; y = years

*Data are adjusted HR (95% CIs).

*Multivariable models evaluating the relationship of frailty as a time-varying covariate with hospitalization.

*Multivariable models examining the relationship of the index (baseline) frailty measure with hospitalization, adjusting for the covariates listed in each respective time-updated model.

*Diabetes, hypertension, cerebrovascular accident, cardiovascular disease, renal disease, chronic obstructive pulmonary disease, cancer, obesity, and liver disease.

*Robust participants had a frailty score of 0; prefrail participants had a frailty score of 1–2; and frail participants had a frailty score of 3–5.

Level of significance for each boldface value: *p < .05.

Global p: †p = .11; ‡p = .69.

**Discussion**

This study provides evidence for the relationship of the frailty phenotype with distinct classes of hospitalization events. We show the strong relationship of the frailty phenotype with chronic and infectious disease hospitalization risk among aging HIV-infected and uninfected adults, independent of comorbidity and HIV disease stage, with an attenuated relationship observed with nonchronic, noninfectious hospitalization risk. With a median age of 48 years in this cohort, our findings provide further support for the clinical relevance of the frailty phenotype to nonelderly HIV-infected populations and their uninfected counterparts, suggesting earlier life-course opportunities for frailty interventions. More broadly, our findings suggest frailty may be a critical target to reduce the substantial burden of chronic and infectious disease-related hospitalization in HIV-infected and uninfected populations.
Prior studies strongly support a role for chronic comorbid disease in frailty onset (14,15,17). The frailty association with chronic disease hospitalization in this study provides support for frailty, not solely as a consequence but also as a putative driver of chronic disease progression and severity; congruent with the bidirectional relationship proposed in the HIV-uninfected elderly population (14). Dysregulated inflammation may be one significant shared pathway, with our previously observed association of inflammation with both chronic disease and frailty in this population (27,28).

The frailty association with infectious disease hospitalization, independent of HIV status or disease stage is particularly notable. Despite observations that older adults experience more frequent and severe infections, little data exist directly linking the frailty phenotype to infection. Studies have previously focused on how chronic infections, such as cytomegalovirus or HIV, promote frailty onset and progression (15–17,29). Few studies have explored susceptibility to infection once the frailty phenotype is already manifest. Dysregulation of innate and adaptive immune compartments, itself a putative feature of frailty may contribute to this risk, and recent observations of reduced influenza vaccine antibody responses among frail adults provides mechanistic support for our findings (30).

We observed a weaker association for the frailty phenotype with nonchronic, noninfectious hospitalization events, an association limited to frailty measured closer in time to the hospitalization. This weaker relationship could reflect a pathophysiology qualitatively different to the biological pathways that characterize frailty predisposing to chronic disease or infectious disease vulnerability. The differential association of time-updated frailty as compared to baseline frailty with nonchronic, noninfectious hospitalizations itself may also reflect a more transient window of vulnerability associated with these events. Frailty has been associated with speciﬁc acute events such as incident falls in HIV-uninfected populations (13), and fractures constituted a notable component of this class. With the observed association of both increased comorbidity and prior AIDS diagnosis with these events, these findings could also reflect greater heterogeneity in the frailty relationship with events in this class. Differential frailty relationships to distinct classes of hospitalization events may account in part for previously observed discordant results in the frailty phenotype relationship to all-cause hospitalization in the HIV-uninfected elderly population, with increased risk observed in some studies and no association in others (12,13).

Limited data exist on correlates of hospitalization events in the late cART era, particularly among persons with prior or current injection drug use. Thus, we make additional note of the nonfrailty-related relationships to hospitalization observed in this study. The observed sociobehavioral associations with hospitalization, including substance use and homelessness, are congruent with prior studies (10,11,31,32). There has been less data comparing hospitalization events for HIV-infected persons directly to HIV-uninfected persons (10,11,31,32). More recent reports have focused on how chronic disease hospitalization in this study provides support for frailty, not solely as a consequence but also as a putative driver of chronic disease progression and severity; congruent with the bidirectional relationship proposed in the HIV-uninfected elderly population (14). Dysregulated inflammation may be one significant shared pathway, with our previously observed association of inflammation with both chronic disease and frailty in this population (27,28).

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Prior AIDS diagnosis was the only HIV-specific factor associated with increased chronic disease hospitalization. There has been an increasing evidence base for the role of HIV, particularly advanced HIV infection, on the onset and progression of chronic non-AIDS disease (34,35). Our findings may reflect legacy effects of advanced HIV disease on chronic disease outcomes or potential lower thresholds for hospital admission despite similar acuity observed in HIV-infected populations (36).

There remains no gold standard for frailty assessment. However, the Fried phenotype has been the most commonly employed and widely validated instrument in the research literature to date (37). The frailty phenotype applied in this study cohort was based on the five frailty domains originally described by Fried and colleagues with minor modifications in operationalization. As reported in this and our prior studies, the epidemiologic correlates, biological relationships, and clinical outcomes with this phenotype in our cohort are similar to that observed for frailty in older HIV-uninfected populations (17,27). We utilized broad categories of hospitalization. However, we adopted a classification scheme derived and employed by the AHRQ that has been clinically meaningful and applicable to both HIV-infected and uninfected populations (24,25). This categorization scheme demonstrated significant face validity in the qualitative associations observed (ie, the association of increasing comorbidity with chronic disease hospitalization risk and the strong association of HIV/AIDS parameters with infectious disease hospitalization risk). There is still likely further heterogeneity in the frailty relationship within each class that would benefit from biologically informed, disease-focused investigation. Finally, this population was a predominantly African American, urban cohort of persons with prior injection drug use and heightened socioeconomic challenge; further evaluation of frailty relationships to cause-specific hospitalization in other populations will be beneficial. However, this population represents the patient subgroups with notably higher hospitalization rates, lower life expectancy, and recently demonstrated to suffer the most severe disparities in frailty burden and thus most likely to benefit from targeted intervention (38–40).

In conclusion, our findings suggest opportunities for frailty intervention earlier in aging trajectories to abrogate severe morbidity. Frailty-targeted interventions may prove relevant to reducing the substantial burden of chronic and infectious disease morbidity and health care utilization in higher risk populations. Further exploration of the relationship of frailty to disease-specific events may help guide targeted resource allocation and health care planning for frail adults. Elucidation of frailty-related biological pathways that promote susceptibility to chronic diseases and in parallel to infections will likely aid the development of biologically driven, frailty-targeted interventions. Such targeted frailty interventions may find significant utility in reducing the tremendous clinical and economic burden associated with hospitalization and promote healthy aging outcomes for HIV-infected and -uninfected populations alike.

Supplementary Material
Please visit the article online at http://gerontologist.oxfordjournals.org/ to view supplementary material.

Funding
This work was supported by the National Institute of Allergy and Infectious Diseases and the National Institute on Drug Abuse at the National Institutes of Health (K23-AI-108357, RC1-AI-086053, U01-DA-023832, RO1-DA-12568, K24-AI-118591).

Acknowledgments
The authors would like to thank the ALIVE study participants and ALIVE study staff for their significant contributions to this work.


