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Effect of Hospitalization on Cognitive and Physical Function in People with HIV

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Abstract:

Background: Hospitalization contributes to cognitive and physical decline among older adults. We aimed to determine the impact of hospitalization on cognitive and physical function among people with HIV (PWH).

Methods: Participants who had been hospitalized and had cognitive or physical function assessments were included. Cognitive function (a composite of Z-scores for three cognitive tests; NPZ3), gait speed, and grip strength slope differences before and after hospitalization were adjusted for potential confounding variables.

Results: Of 892 participants, 208 had ≥1 hospitalization: 198 had NPZ3 scores and 197 had gait/grip measures. The median age was 58 years, 37% were Black, and 14% Hispanic; median CD4 was 656 cells/mm^3, 94% had HIV-1 <200 copies/ml. The NPZ-3 slope difference after versus before hospitalization was -0.071 per year (95% CI= -0.167, 0.026), with significant difference among those admitted for 3-6 days (-0.177 [95% CI -0.336, -0.018]) but not <3 or >6 days. The grip strength slope difference was -0.626 kg per year (95% CI -1.749, 0.497), with significant decline among those admitted for 3-6 days (-1.60 kg per year [95% CI -3.04, -1.52], p=0.03) but not <3 or >6 days. The gait speed increase was significant among those admitted for 3-6 days (0.044 m/s [0.005,0.083], p=0.03) but not for those with <3 or >6 days.

Conclusions: Intermediate duration of hospitalization was associated with modest declines in post-hospitalization cognitive function (predominantly psychomotor performance) and grip strength.

Key words: HIV, hospitalization, cognitive function, psychomotor performance, physical function

Background

Cognitive impairment (CI) is defined as a change in one or more cognitive domains (perceptual-motor function, language, memory and learning, executive function, attention, and social cognition) that is not attributable to delirium or other mental disorders. Hospitalization may result in CI or worsening of underlying cognitive function, particularly in older adults.[1-3] Cognitive changes may occur due to a variety of reasons during hospitalization including critical illness, delirium, medications, infectious processes, or surgical procedures.[1,4-8] Critical illness specifically contributes to a higher risk for long-term CI, occurring in up to 25% of patients requiring care in the intensive care unit.[9] Similarly, post-surgical cognitive dysfunction may occur in up to 10-20% of patients, varying by type of surgery and potentially persisting for months.[10] Other studies have suggested that nonelective hospitalization can lead to increased decline in cognitive function as compared to surgery or anesthesia.[2] However, any hospitalization can lead to cognitive decline particularly in older adults.[11] CI following hospitalization may improve over time but for some persons with additional risk factors (i.e., older age, prolonged hospitalization) may result in longer-term cognitive impairment. [3,12,13]

In addition to effects on cognition, hospitalization has been associated with long-term declines in gait speed, muscle strength, and development of frailty, which may profoundly affect populations with pre-existing impairment, such as older adults.[14-16] Over 30 million hospitalizations occur annually in the United States, of which 30-35% are among people over the age of 65. With a significant proportion of hospitalizations occurring in older individuals, any post-hospitalization cognitive and physical changes could have large-scale impacts on the health system.[17]

Compared to the general population, people with HIV (PWH) have a higher and earlier onset comorbidity burden, an increased prevalence of multimorbidity, and a greater burden of geriatric syndromes such as CI, frailty, and physical function impairments.[18,19] Hospitalization rates have generally declined among PWH with improvements in HIV care and access to antiretroviral therapy.[20,21] However, over 30% of PWH are projected to reach age 70 years or older by 2030, and hospitalization rates will likely increase as a result of the overall increases in age and comorbidity burden.[18,20] Furthermore, the combination of cognitive and physical function impairment in PWH creates an increased risk of adverse outcomes including falls, disability and death which may increase hospitalizations.

To our knowledge, no studies to date have explored the impact of hospitalization on changes in cognitive and physical function in PWH. The primary aim of this analysis was to compare the trajectories of cognitive and physical function before and after hospitalization. We hypothesized that hospitalizations would be associated with a decline in both cognitive and physical function, with longer hospitalization durations leading to the greatest decline.

Methods

Study Design and Participants

We performed an analysis of participants enrolled in the Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections (ACTG) longitudinal cohort study HAILO (HIV Infection, Aging, and Immune Function Long-Term Observational Study). [22,23]HAILO enrolled 1035 PWH aged 40 years or older in 2013-2014, with study visits initially every 6 months and then yearly through 2021. All HAILO participants who completed a hospitalization survey were included in a descriptive comparison of those with and without hospitalization. Those who had a hospitalization and measures of cognitive or physical function before or after hospitalization were included in the comparison of trajectories of cognitive and physical function before and after hospitalization. The ACTG HAILO Hospitalization Questionnaire self-reported on hospitalization through the following questions: 1) In the past 6 months have you been hospitalized overnight for any reason? 2) How many separate times did you stay in a hospital overnight? 3) How many total nights did you stay in a hospital overnight (1-2, 3-6, 7 or more nights), 4) For what condition or problem were you hospitalized?

The primary exposure variable, first hospitalization reported during HAILO follow-up, was collected using the hospitalization survey, beginning in 2015. Hospitalization was defined as at least one overnight hospital visit in the past 6 months. We also considered duration of hospitalization, and reasons for hospitalization (surgical [elective vs urgent/emergent] and non-surgical) as separate exposures. For this analysis, cognitive and physical function data available from 6 months prior to hospitalization data collection to up to 3 years after hospitalization were included to compare trajectories before and after hospitalization.

The outcome measures included 1) an abbreviated measure of cognitive function primarily assessing psychomotor speed and 2) physical function. The cognitive assessments were completed every 48 weeks using the Trail Making Test-Part A and B (TMA, TMB), and the Wechsler Adult Intelligence Scale-Revised Digit Symbol Test (DSY). The raw score for each test was standardized using demographic-adjusted normative means and combined in a summary z-score, the NPZ3 using a standardized protocol.[24,25] The TMA, TMB, and DSY mainly assess speeded executive control or psychomotor speed. Physical function was assessed using gait speed, the average of two assessments on a 4-meter walking course, and grip strength, the average of three measures using a Jamar dynamometer with the dominant hand.

Covariates included age, sex, race/ethnicity, education, body mass index (BMI), smoking history, substance use history, HIV-1 RNA, and CD4 T-cell count at the time point closest to hospitalization.

Statistical Analysis

Demographic, NPZ-3 score, physical function, and other covariates were summarized using descriptive statistics. Continuous variables were reported as means with standard deviations (SD) or medians with 1st and 3rd quartiles (Q1, Q3) as appropriate, and categorical variables as counts and percentages. The Wilcoxon test and chi-square test were used for statistical comparisons across subgroups for continuous and categorical variables, respectively. All analyses were conducted using SAS® 9×4 (SAS Institute, Cary, NC).

For the pre-post hospitalization analysis, baseline was defined as 3 months prior to the study visit during which the hospitalization was reported, to approximate the date of the first hospitalization during HAILO follow-up. Participants who reported more than one hospitalization were censored before the second hospitalization.

We first visually examined the pattern of change in the NPZ3 score, gait speed, and grip strength before and after hospitalization using LOESS plots. Piecewise generalized linear models using generalized estimating equations (GEE) with autoregressive working correlation were fit. Linear spline models with a single knot at baseline were fit to account for non-linear trends, allowing participants to serve as controls for estimation of changes in NPZ3, gait speed and grip strength before and after hospitalization.

We fit unadjusted GEE models for NPZ3, gait speed and grip strength and then added sex, age, race/ethnicity, education, smoking, BMI, substance use, CD4 T-cell count and HIV RNA viral load as confounding variables based on clinical considerations and if they changed the estimate of slope before or after baseline by 10% or more. Multiple GEE models from 6 months before hospitalization to 3 years after hospitalization were evaluated with and without confounding variables: 1) two-time variables: years from HAILO entry + years from baseline (i.e., slope difference between after versus before hospitalization); 2) time variables and number of nights of hospital stay and 3) time variables and reasons for hospitalization. We examined whether the duration of hospitalization (1-2, 3-6, ≥7 nights) and reasons (surgical vs non-surgical) for hospitalization modified the trajectory. In a sensitivity analysis, we also evaluated duration of hospitalization as 1-2 or ≥3 nights.

Results

Of the 1035 HAILO participants, 892 participants completed at least one hospitalization survey; 208 (23%) reported at least one hospitalization, over a median of 3.9 (Q1, Q3= 3.2, 4.2) years of follow-up. NPZ3 and physical function data were available for 198 and 197 participants (of the 208), respectively.

The characteristics of participants who were hospitalized are shown in Table 1. The median number of hospitalizations was 1 (Q1, Q3 = 1,2); 139 (67%) had one hospitalization, 51 (25%) had two hospitalizations, and 18 (9%) had three or more hospitalizations. Of the hospitalized participants, 78 were hospitalized for 1-2 nights, 79 for 3-6 nights and 51 for > 7 nights. Fifty-three (25%) participants were hospitalized for surgical reasons, including 17 for emergency surgeries.

Baseline characteristics among hospitalized and non-hospitalized persons

Among the hospitalized participants, the median age was 58 years (Q1, Q3 = 51-63), 25% were females, 37% were Black, and 14% were Hispanic. Hospitalized persons were more likely to be Black (37% vs. 28%), less likely to be Hispanic (14% vs. 21%), more likely to be currently smoking (31% vs. 21%) and have a history of recreational substance use (60% vs. 50%) compared to non-hospitalized participants (Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/QAD/D865).

Median NPZ3 scores at baseline were lower for those who were subsequently hospitalized (0.3; Q1, Q3 = -0.4, 0.9) than for those not hospitalized (0.5; Q1, Q3 = -0.2, 1.2); p = 0.005 (Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/QAD/D865).

The median baseline gait speed was 1.004 m/s (Q1, Q3= 0.854, 1.143) and grip strength was 33 kg (Q1, Q3 =26, 40). Gait speed and grip strength were significantly slower and weaker, respectively, among participants who were subsequently hospitalized (Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/QAD/D865).

Cognitive outcomes (Psychomotor performance) before and after hospitalization

Baseline NPZ3 scores differed by duration of hospitalization, with 16% of those hospitalized for 1-2 nights, 14% of those hospitalized for 3-6 nights and 25% of those hospitalized for > 7 nights demonstrating baseline impairment.

The adjusted slope of NPZ3 scores before hospitalization was 0.025 (95% CI= -0.022,0.071; p=0.3); the slope after hospitalization was -0.046 (95% CI= -0.122,0.030; p=0.2), resulting in a small and not statistically significant adjusted per year slope difference of -0.071 (95% CI= -0.167,0.026); p=0.1. The slope difference after versus before hospitalization varied by length of stay with the largest difference among participants hospitalized for 3-6 nights (-0.177 [95%CI= -0.336, -0.018]; p=0.03), and no significant differences for those with 1-2 (0.023 [95% CI=-0.105,0.150]; p=0.7) or ≥7 nights (-0.129 [95% CI=-0.391,0.133]; p=0.3) of hospitalization (Figure 1/Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/QAD/D865). In a sensitivity analysis comparing those hospitalized for 1-2 nights and ≥3 nights, the adjusted slope difference for those with ≥3 nights (-0.151 [95% CI= -0.288, -0.014], p= 0.03) was greater than that for those hospitalized for 1-2 nights (0.022 [95% CI= -0.105, 0.150), p= 0.7; Supplementary Table 5, Supplemental Digital Content, http://links.lww.com/QAD/D865).

The slope differences in NPZ3 scores did not appreciably differ between those admitted for non-surgical reasons (-0.078 [95% CI -0.194, 0.038]; p=0.2) and surgical reasons (-0.057 [95% CI= -0.226, 0.111]; p=0.5; Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/QAD/D865).

Gait speed and grip strength before and after hospitalization

Of 197 participants with at least one hospitalization and physical function data, 77 were hospitalized for 1-2 nights, 74 for 3-6 nights and 46 for > 7 nights.

The adjusted gait speed slope before hospitalization (-0.014 m/s per year [95% CI =-0.028,-0.000], p =0.04) and after hospitalization (0.000 m/s per year [95% CI= -0.016,0.017], p= 0.9) yielded an adjusted per year slope difference of (0.014 m/s ([95% CI= -0.010,0.039], p= 0.2; Supplementary Table 3, Supplemental Digital Content, http://links.lww.com/QAD/D865).

There was a non-significant decline in gait speed slope difference for participants hospitalized for >7 nights [slope difference =-0.025 m/s, 95%CI = -0.064,0.013, p=0.2] while gait speed slope difference yielded an increase after hospitalization for those with a 3-6 night hospital stay (slope difference = 0.044 m/s, 95% CI= 0.005,0.083 p=0.03; Figure 2; Supplementary Table 3, Supplemental Digital Content, http://links.lww.com/QAD/D865). For those hospitalized for non-surgical reasons, there were no appreciable changes in gait speed slope from before to after hospitalization. Among those hospitalized for surgical reasons, gait speed decreased in the period before hospitalization and increased after hospitalization (slope difference = 0.046 m/s, 95% CI= -0.105, 0.108, p=0.1). In the sensitivity analysis, the gait speed measures before versus after hospitalization gait speed were similar and not significant between those hospitalized for 1-2 nights and ≥3 nights (Supplementary Table 6, Supplemental Digital Content, http://links.lww.com/QAD/D865).

The slope of adjusted grip strength was -0.022 kg [95% CI =-0.604, 0.560] before and -0.648 kg [95% CI= -1.421,0.125] after hospitalization, with no appreciable slope difference (-0.626 kg [95% CI= -1.749,0.497]; p = 0.3; Figure 3; Supplementary Table 4, Supplemental Digital Content, http://links.lww.com/QAD/D865). There were differences by hospital duration: the adjusted slope difference in grip indicated a significant decline among those with 3-6 nights of stay (-1.596 kg [95% CI =-3.040,-0.152; p=0.03), but with no significant difference among those with 1-2 nights (-0.535 kg [95% CI =-2.599,1.530], p=0.6) or ≥7 nights (-0.217 kg [95% CI =-2.267,1.833], p=0.8; Figure 3/Table 4). There was a modest decrease in adjusted slope difference for grip strength for non-surgical reasons (slope difference= -0.328 kg, 95%CI = -1.631, 0.97; p=0.6) and surgical reasons (slope difference= -1.502 kg, 95% CI= -3.797,0.793; p=0.2). The sensitivity analysis showed that the decline in grip strength after versus before hospitalization was greater for those hospitalized 3 or more nights (-0.925 [95% CI -2.146,0.296], p=0.1) than for those hospitalized 1-2 nights (-0.540 [95% CI -2.598,1.518, p=0.6; Supplementary Table 7, Supplemental Digital Content, http://links.lww.com/QAD/D865)

Discussion

In a large, well-characterized observational cohort, we provide novel data on the impact of hospitalization on abbreviated cognitive battery (primarily psychomotor performance) and physical function among adult PWH (median age 58 years), which is considerably younger than many other older adult cohorts. We found that intermediate hospitalization duration (3-6 nights) was associated with decrease in NPZ3 scores and grip strength but not gait speed. Not surprisingly, participants who required hospitalization (particularly those with ≥ 7 days hospitalization) also tended to have lower baseline NPZ3, slower gait, and weaker grip compared to those with no hospitalization, suggesting pre-existing vulnerability. Considering that PWH may have a greater burden of cognitive and physical function impairment than populations without HIV, the impact of hospitalization may be particularly relevant to this population and underscores the value of understanding the functional impact of hospitalization on long-term outcomes.

Associations between hospitalization and subsequent cognitive and physical function impairment have been noted in large cohort studies of populations without HIV. Our data is unique in that 1) we have NPZ-3 and physical function measures both before and after hospitalization for most participants, 2) we provide the first data on the impact of hospitalization on these outcomes in PWH, and 3) our follow-up time of up to 3 years is much longer than that of many other cohort studies.[6,26,27]

Different and often more expansive assessments of cognition have been used in prior studies. A large longitudinal population-based study of community dwelling older adults (median age 73 years) found a 3-fold decrease in episodic memory and 1.7-fold decrease in executive function. A combination of tests including Mini-Mental State Examination score, episodic memory score and digit symptom substitution modalities test was used.[7] Analysis of hospitalizations from the Memory and Aging Project included a battery of 21 cognitive tests and demonstrated decline in scores for global cognition and specific domains of working memory, episodic memory, semantic memory, perceptual speed and visuospatial.[2] The cognitive testing used in this cohort was limited and focused on psychomotor performance. Future analyses should be conducted with a wider panel of cognitive testing in PWH.

Various factors contribute to cognitive decline following hospitalization in the general population, including infections, intensive care unit admissions, type of medications received, delirium, and anesthesia. Older age, multiple comorbidities, longer hospital stays, and increased severity of illness also correlate with post-hospitalization cognitive decline.[7,9,11] We observed a modest decline in cognitive function in persons with an intermediate duration of hospitalization. We did not observe a significant decline in cognitive function in participants admitted for ≥7 days. Smaller sample size and lower baseline cognitive function in this group could have affected the slope change with hospitalization.

Physical function decline is common in hospitalized adults, occurring in about 30% of inpatients and is associated with prolonged length of hospital stay, long-term care requirement, recurrent hospitalization and mortality.[28-34] Gait speed and grip strength have been shown to decrease post-hospitalization, resulting in decreased mobility and functional limitations in performing activities of daily living.[14,15,35-40] Hospitalization type (surgical vs non-surgical) may influence changes in physical function. We observed a greater, but non-significant, decline in handgrip strength with surgical hospitalizations. Grip strength has been used as a measure of muscle strength, frailty, and overall health during preoperative assessments to help predict post-operative recovery.[41-43] The observed decline in grip strength may be attributable to several factors, including residual neuromuscular effects from anesthesia, postoperative pain and analgesic use, postoperative fatigue related to systemic inflammation, surgery-related oxidative stress leading to mitochondrial dysfunction and perioperative nutritional deficits. [44-46] Even though the median age in our study was relatively young, we noted small declines in grip strength following hospitalization for intermediate duration. We had no information on physical therapy or rehabilitation during or after hospitalization and postulate that those with longer hospitalization may have received physical rehabilitation services which could affect the slope decline noted.

While ART has improved lifespan in PWH, acceleration or accentuation in the aging process occurs as a consequence of chronic comorbidities and elevated levels of inflammation, immune senescence, mitochondrial dysfunction, and epigenetic changes, amongst other factors.[47-50] Maintaining a high level of cognitive and physical function may not only prevent hospitalizations but also provide more resilience from the deconditioning and functional decline noted during hospitalizations. Screening PWH for cognitive and physical function during or shortly following hospitalization may help to identify patients at risk and incorporate appropriate rehabilitation programs earlier.

The strengths of this study include the utilization of a longitudinal cohort with baseline NPZ-3 and physical function measures and yearly assessments using standardized assessment tools. The limitations of the study include possible imperfect recall of self-reported hospitalization information. Annual visits may miss short-term recovery or transient declines following hospitalization. Smaller sample sizes of subgroups, including those hospitalized for over 7 nights, may have affected our ability to observe the effects of hospitalization in these groups. We had small numbers of patients with surgical reasons for hospitalization and hence did not analyze specifically by types of surgery but did describe elective and non-elective procedures. The TMA, TMB, and DSY used for cognitive assessment in this study reflect psychomotor performance and not general cognitive function. Hence, our assessment of other cognitive domains including working memory, episodic memory, attention, processing speed visuospatial functions may be limited. Lastly, our findings in this well-established longitudinal cohort with prior clinical trial involvement may not be generalizable to other populations of PWH.

In conclusion, the findings of this study demonstrate modest post-hospitalization declines in cognitive function (mainly psychomotor performance) and physical function in a middle-aged cohort of PWH. Assessment of cognitive and physical function following hospitalization may facilitate timely interventions such as early rehabilitation, exercise programs, and cognitive training to prevent long-term decline.

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Figure 1: LOESS curves with 95% confidence bands indicating change in NPZ3 scores over time. Timepoint 0 indicates hospitalization. The clustering of data points following timepoint 0 shows the first study visit following hospitalization.

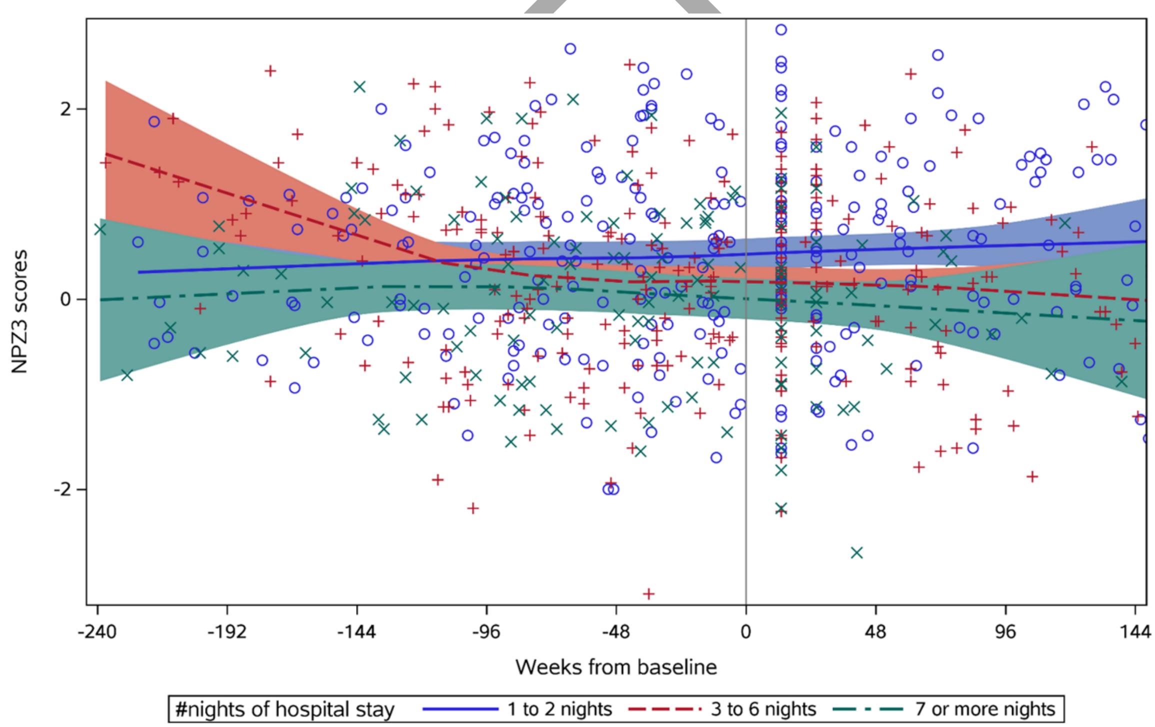

Figure 2: LOESS curves with 95% confidence bands indicating change in gait speed over time. Timepoint 0 indicates hospitalization. The clustering of data points following timepoint 0 shows the first study visit following hospitalization.

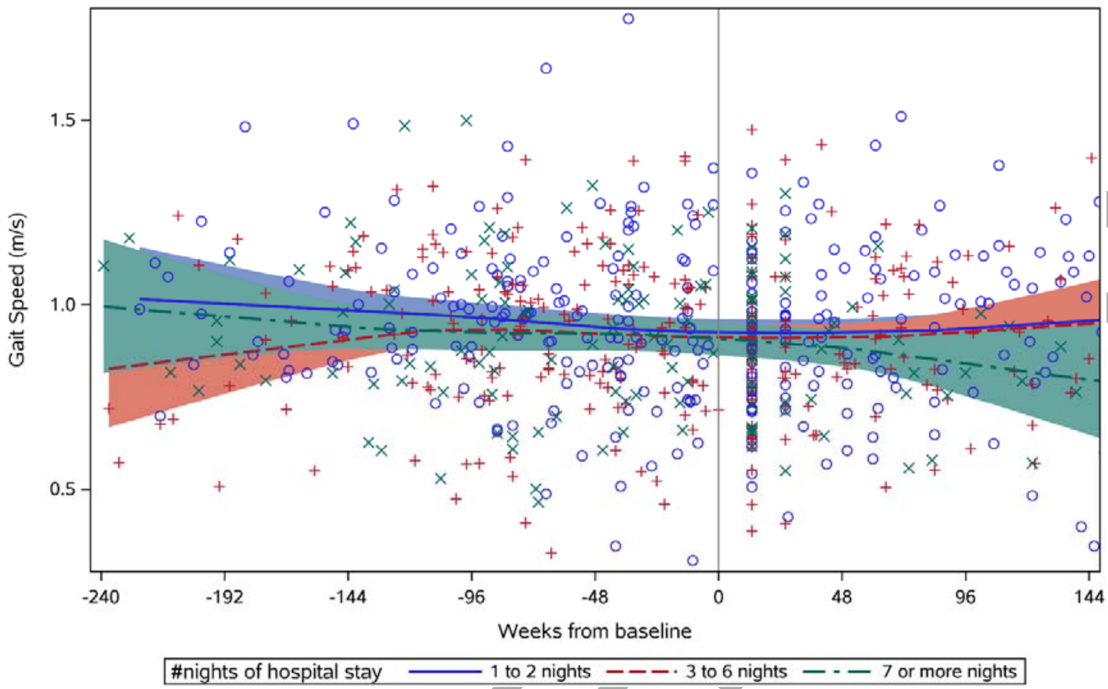

Figure 3: LOESS curves with 95% confidence bands indicating change in grip strength over time. Timepoint 0 indicates hospitalization. The clustering of data points following timepoint 0 shows the first study visit following hospitalization.

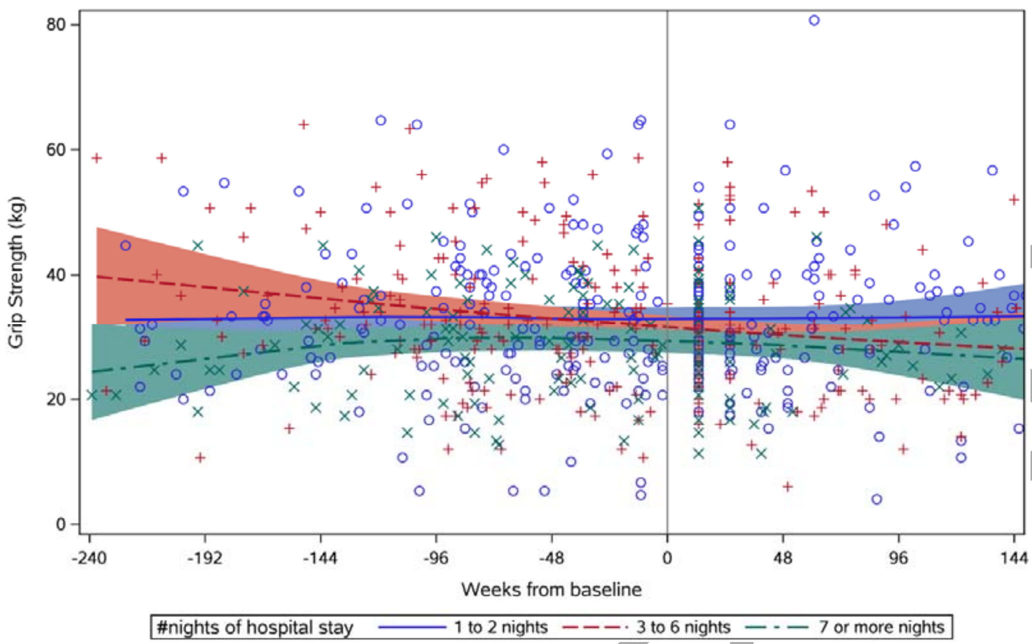

Table 1: Baseline demographics and clinical characteristics of participants who were hospitalized (N=208)

		Number of nights of hospital stay		
Characteristic		1-2 nights (N=78)	3-6 nights (N=79)	≥7 nights (N=51)
Age	Median (Q1, Q3)	58 (51, 63)	56 (51, 63)	59 (53, 63)
	Mean (s.d.)	58 (7)	57 (8)	59 (8)
Sex	Male	58 (74%)	59 (75%)	39 (76%)
	Female	20 (26%)	20 (25%)	12 (24%)
Race/Ethnicity	White	37 (47%)	44 (56%)	18 (35%)
	Black	29 (37%)	21 (27%)	27 (53%)

	Hispanic	10 (13%)	14 (18%)	6 (12%)
Total years of education	Median (Q1, Q3)	13 (12, 16)	13 (12, 15)	14 (12, 15)
	Mean (s.d.)	13 (4)	13 (3)	14 (3)
Number of hospitalizations	1	52 (67%)	53 (67%)	34 (67%)
	2	19 (24%)	19 (24%)	13 (25%)
	>=3	7 (9%)	7 (9%)	4 (8%)
Surgical reason for hospitalization		27 (35%)	16 (20%)	10 (20%)
HIV-1-RNA copies	Median (Q1, Q3)	<40 (20, <40)	<40 (<40, 40)	<40 (20, <40)
	Mean (s.d.)	37 (2.5)	55 (4.9)	41 (2.9)
BMI	Median (Q1, Q3)	28.0 (24.4, 32.2)	26.6 (23.6, 32.6)	26.5 (22.1, 29.6)
	Mean (s.d.)	28.9 (5.6)	29.4 (7.8)	27.2 (6.7)
	Obesity	26 (33%)	28 (35%)	10 (20%)
Smoking status	Never	30 (38%)	25 (32%)	11 (22%)
	Prior	27 (35%)	29 (37%)	22 (43%)
	Current	21 (27%)	25 (32%)	18 (35%)
Substance use	Never	39 (50%)	29 (37%)	15 (31%)
	Prior	19 (24%)	28 (35%)	22 (45%)
	Current	20 (26%)	22 (28%)	12 (24%)
Cardiovascular disorders		11 (14%)	8 (10%)	12 (24%)
Diabetes		4 (5%)	3 (4%)	2 (4%)
Cancer		1 (1%)	2 (3%)	3 (6%)
Neurologic diagnosis		1 (1%)	1 (1%)	4 (8%)

Mental health diagnosis		3 (4%)	5 (6%)	7 (14%)
NPZ3 scores at baseline (N=177)	Median (Q1, Q3)	0.5 (-0.3, 1.1)	0.2 (-0.4, 0.7)	0.1 (-0.8, 0.8)
	Mean (s.d.)	0.5 (1.0)	0.2 (1.0)	0.0 (0.9)
	Impaired	11 (16%)	9 (14%)	11 (25%)
Average of 3 grip strengths (in kg) (N=173)	Median (Q1, Q3)	30.7 (25.0, 40.7)	31.7 (26.0, 39.3)	28.7 (23.3, 36.7)
	Mean (s.d.)	32.9 (11.9)	32.9 (11.1)	29.3 (9.2)
Gait speed (m/s) (N=173)	Median (Q1, Q3)	0.936 (0.812, 1.107)	0.962 (0.785, 1.102)	0.892 (0.763, 1.042)
	Mean (s.d.)	0.949 (0.241)	0.945 (0.221)	0.902 (0.177)

Smoking status includes cigarette use, does not include other tobacco product use

Substance use includes marijuana, cocaine, heroin, amphetamines.