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Hospitalization Rates and Associated Factors Among Older Adults With HIV in the United States

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Introduction: Literature on hospitalization incidence and risks among people with HIV (PWH) in the current antiretroviral therapy era is limited.

Methods: Using data (2017–2021) on PWH ≥ 40 years of age from the Advancing Clinical Therapeutics Globally HAILO Study, cumulative probabilities of first hospitalization were estimated using Kaplan–Meier plots. Cox proportional hazards regression was used to identify factors associated with first hospitalization.

Results: Among 891 participants (median age 50 years; 80% male), 38 with prevalent hospitalization at baseline were excluded. The remaining 853 participants had a follow-up of 2721 person-years, during which 170 (20%) had at least 1 hospitalization event (incidence rate, 6.2 per 100 person-years [95% confidence interval [CI] = 5.4–7.3]). The leading causes of hospitalization included infections (14%), elective surgery (13%), cardiovascular conditions (12%), and lung problems (12%). Former and current smokers had higher hospitalization risk (adjusted hazard ratio [aHR] 1.51 [95% CI = 1.03–2.20], aHR 1.85 [95% CI = 1.24–2.76], respectively) than never smokers. Hospitalization risk was higher for participants who were frail (aHR 2.31 [95% CI = 1.38–3.86]) compared with those who were robust (not frail), and lower in the Western region compared with the Northeast region (hazard ratio = 0.55, 95% CI: 0.32–0.93). Hospitalization risk was also higher for participants with diabetes (aHR 1.69 [95% CI = 1.13–2.52]).

Conclusion: We observed a lower hospitalization risk than in previous studies among PWH. Interventions to reduce smoking, prevent frailty, and improve diabetes management may further lower hospitalization risk.

Key Words: hospitalization, HIV, older people with HIV

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INTRODUCTION

The average age of people with HIV (PWH) has been increasing, largely because of the success of antiretroviral therapy (ART).[1–3] However, even with effective ART, HIV continues to contribute to increased comorbidity burden, elevated risk for some infections, and mortality.[4,5] Likewise, advancing age is associated with increased susceptibility to disease.[6,7] Thus, the combination of chronic HIV and advanced age is likely to result in an increased risk of severe disease requiring hospitalization.

Data on hospitalization patterns among older adults with HIV in the current ART era, however, remain limited. Among a US military cohort (mean [SE] age 37 [10] years), the hospitalization rate was 13.7 per 100 person-years between 1999 and 2007.[8] Another study in a similar timeframe (1997–2003), which included 1338 PWH (median age 38 years), reported a hospitalization rate of 21 per 100 person-years.[9] Conversely, among 28,057 PWH (median [IQR] age 41 [33–48] years), all-cause hospitalization rates decreased from 22 per 100 person-years in 2005 to 13 per 100 person-years in 2015.[10] These studies on hospitalization trends among PWH were conducted when guidelines recommended initiation of ART at a much lower $CD4^+$ T-lymphocyte cell count threshold.[11,12] They were also largely conducted before introduction of newer ART regimens containing integrase strand transfer inhibitors and tenofovir alafenamide that appear to be associated with a greater prevalence of obesity but fewer renal and bone toxicities.[13–15] Finally, the demographics and comorbidity

Table 1. Baseline (enrollment into HAILO, A5322) Demographic and Clinical Characteristics of Study Participants

Characteristics	Total (N = 891), %
Age group, years	
40–49	396 (44.4)
50–59	367 (41.2)
≥60	128 (14.4)
Missing	0 (0.0)
Sex	
Female	178 (20.0)
Male	713 (80.0)
Missing	0 (0.0)
Race and ethnicity	
Non-Hispanic White	426 (47.8)
Non-Hispanic Black	266 (29.9)
Hispanic/other*	198 (22.2)
Missing	1 (0.1)
Education	
<High school	129 (14.5)
High school	202 (22.7)
>High school	560 (62.9)
Missing	0 (0.0)
Body mass index, kg/m^2	
<25	281 (31.5)
25 to <30	350 (39.3)
≥30	247 (27.7)
Missing	13 (1.5)
Medical insurance	
Private	387 (43.4)
Public	236 (26.5)
Medicare	101 (11.3)
None/unknown	165 (18.5)
Missing	2 (0.2)
Smoking status	
Never	373 (41.9)
Former	285 (32.0)
Current	222 (24.9)
Missing	11 (1.2)
Alcohol use	
None	322 (36.1)
Light	320 (35.9)
Moderate/heavy	202 (22.7)
Missing	47 (5.3)
Substance use (tobacco and alcohol excluded)	
Never	387 (43.4)
Former	273 (30.6)
Current	186 (20.9)
Missing	45 (5.1)
Physical activity, weekly	
<3 days of moderate/vigorous activity	397 (44.6)
≥3 days of moderate/vigorous activity	443 (49.7)
Missing	51 (5.7)
Frailty status	
Robust	494 (55.4)
Prefrail	341 (38.3)
Frail	53 (5.9)
Missing	3 (0.3)
Duration of ART, years	
<5	288 (32.3)
5 to <8	188 (21.1)
8 to <11	137 (15.4)
≥11	278 (31.2)
Missing	0 (0.0)
CD4 count, cells/mm^3	
<500	268 (30.1)
≥500	612 (68.7)
Missing	11 (1.2)
HIV RNA, copies/mL	
<50	815 (91.5)
≥50 (nonsuppressed)	70 (7.9)
Missing	6 (0.7)
US region of entry site	
Northeast	204 (22.9)
Midwest	256 (28.7)
South	176 (19.8)
West	255 (28.6)
Missing	0 (0.0)
Participant-reported comorbidities	
Diabetes	89 (10.0)
Hypertension	460 (51.6)
Renal disease	67 (7.5)
Cardiovascular disease	59 (6.6)

Participants with missing information on chronic conditions were assumed not to have any chronic conditions.

*Other included Asian, Pacific Islander, American Indian, Alaskan Native, or >1 race.

burden of PWH has shifted over the last 10 years, potentially affecting reasons for hospitalization.[16]

The goal of this study was to determine the incidence and causes of hospitalization in a well-characterized contemporary cohort of older US adults with HIV, leveraging data from the Advancing Clinical Therapeutics Globally HIV infection, Aging, and Immune Function Long-term Observational (HAILO) Study.

METHODS

Study Population

HAILO is a longitudinal, multisite cohort study of older PWH who enrolled participants aged ≥40 years old between 2013 and 2014, with follow-up through 2021. All eligible participants lived in the United States and initiated their first ART treatment in Advancing Clinical Therapeutics Globally randomized clinical trials.[17] Participants provided written informed consent before enrollment, and the local institutional review boards at each site provided ethical clearance.

Study Procedures

HAILO included bi-annual visits initially and annual visits in the last year of the study for clinical events, medical

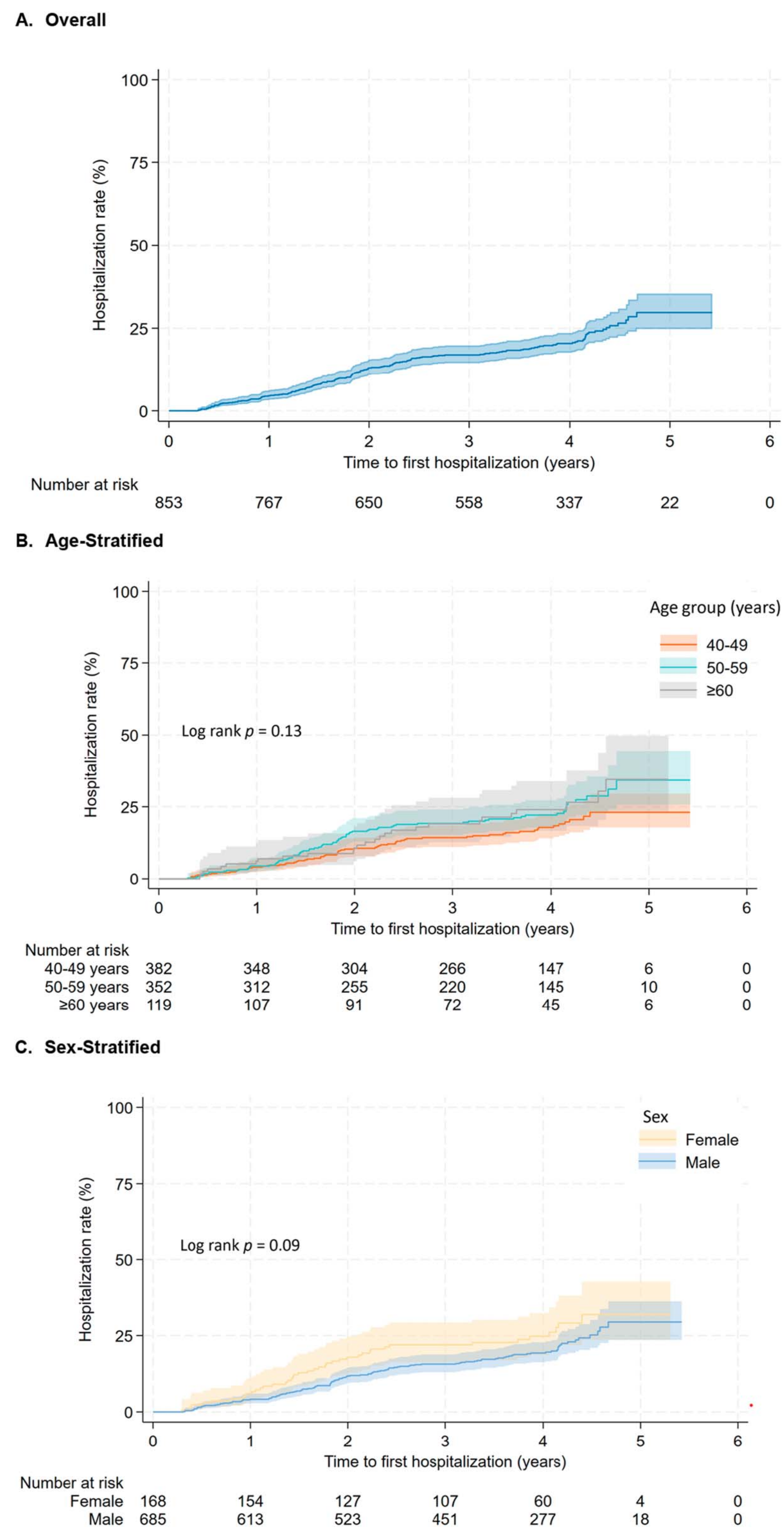

FIGURE 1. Time to first hospitalization among people with HIV, HAILO 2017–2021. Panel A: Overall. Panel B: Age stratified. Panel C: Sex stratified.

chart abstraction, and hospitalization questionnaires, whereas physical measurements (blood pressure, weight, hip, mid-waist, and mid-arm circumference), behavioral questionnaires, and frailty evaluations were conducted annually.

Outcomes

The primary outcome was the first hospitalization, assessed by participant report on a questionnaire introduced in 2017. Secondary outcomes included participant-reported

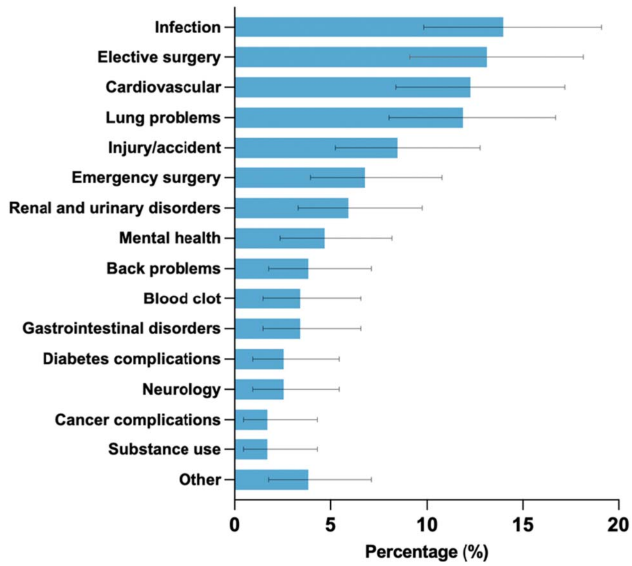

FIGURE 2. Causes of the first hospitalizations during study follow-up, HAILO 2017–2021: lung problems exclude blood clots. Of the 208 participants with a first-time hospitalization event, 206 reported the cause of hospitalization.

reasons for hospitalization and length of stay. Hospitalization was defined by an affirmative response to the question: "In the past 6 months, have you been hospitalized overnight for any reason?" Those who responded "Yes" to hospitalization were then asked to specify the total number of nights hospitalized by selecting 1 of the following categories: 1–2 nights, 3–6 nights, or 7 or more nights. Reasons for hospitalization were categorized into 16 domains[1]: heart or blood vessel problems[2]; blood clots[3]; lung problems (excluding blood clots)[4]; diabetes or diabetes-related complications[5]; liver, gallbladder, or gastrointestinal problems[6]; kidney or bladder problems/infections[7]; urgent or emergency surgery[8]; planned or scheduled surgery[9]; cancer or complications of cancer treatment[10]; neurological issues[11]; infections[12]; back problems[13]; psychological or mental health conditions[14]; injuries or accidents[15]; substance use; and[16] other (see Table S1, Supplemental Digital Content, http://links.lww.com/QAI/C683). Each category was mutually exclusive.

Assessment of Covariates

Sociodemographic characteristics included age, sex, race/ethnicity, education, and medical insurance. Lifestyle behaviors included smoking status, alcohol use, substance use, and physical activity. Frailty status (robust, prefrail, frail) was assessed using the Fried frailty phenotype,[18] which includes the 5 components of weak grip, slow gait speed on a 4-meter walk, and self-reported weight loss, exhaustion, and low activity.[19] Individuals were categorized as frail if they met 3–5 criteria, prefrail if they met 1–2 criteria, or robust if they did not meet any criteria.[20] HIV-related characteristics included CD4 count, HIV-RNA level, and duration of ART. Comorbidities assessed included diabetes (defined by a medical diagnosis, use of diabetes medication or hemoglobin A1C $\geq$ 6.5%), hypertension (defined by systolic blood pressures $\geq$140 mm Hg, diastolic blood pressures $\geq$90 mm Hg at 2 consecutive visits, or use of antihypertensive medication), renal disease (defined by estimated glomerular filtration rate <60 mL/minute per 1.73 m^2 or proteinuria with urinary protein-to-creatinine ratios $\geq$0.2 mg/mg), and cardiovascular disease (defined by a chart-abstracted medical diagnosis of myocardial infarction, stroke/transient ischemic attack, angina pectoralis, congestive cardiac failure, peripheral artery disease, thrombosis/embolism, arrhythmia, and coronary artery disease).[21] Laboratory test results ($CD4^+$ and $CD8^+$ T-lymphocyte cell counts [CD4 and CD8], HIV-1 RNA) were abstracted from medical charts.

Statistical Analysis

Participant characteristics at HAILO enrollment were summarized as frequencies and percentages. The baseline for this analysis was defined as the first visit at which the hospitalization questionnaire was administered during 2017–2018. Data collected before this baseline were not used in the time-to-event analyses. Time under follow-up was defined as the number of years from the initiation of hospitalization data collection to the first hospitalization, the time of death, or the last follow-up visit. We further censored participants who reported hospitalization at the baseline visit. For participants with missing covariates at their defined baseline, data were imputed using the last observation carried forward method, from their most recent visit before the baseline.

The number of first hospitalizations and the incidence rate per 100 person-years were calculated overall and stratified by age and sex; 95% confidence intervals (CI) were calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter.[22] The cumulative probabilities of the first hospitalization were estimated using the Kaplan–Meier method overall and stratified by age and sex, with the log-rank test used for group comparisons. The associations of sociodemographic and major clinical risk factors with first hospitalization were assessed using Cox proportional hazards regression models. All covariates were measured at analytic baseline and treated as fixed over time.

Results were presented as hazard ratios (HR) with corresponding 95% CI. We used the Schoenfeld residuals test to check the assumption of proportional hazards. After univariable Cox modeling, an adjusted Cox proportional hazards model was performed to identify independent predictors of hospitalization. Age, sex, race, and ethnicity were included in the adjusted model, and variables that were significantly associated with first hospitalization in the crude analysis. The adjusted model included adjustment for age, sex, race and ethnicity, education, BMI, medical insurance, smoking status, frailty status, region of residence, diabetes, renal disease, and cardiovascular disease.

Causes of first hospitalization were summarized as percentages in the overall study population and stratified by sex and age. The length of stay was summarized as frequencies in the overall population and stratified by sex and age.

TABLE 2. Cox Proportional Hazards Regression Analysis of Risk Factors for Hospitalization, HAILO 2017–2021

	Crude Model		Adjusted Model	
Characteristic	**Hazard ratio (95% CI)**	***P*-value***	**Hazard ratio (95% CI)**	***P*-value***
Age group, years		0.14		0.40
40–49	Ref.		Ref.	
50–59	1.37 (0.99–1.91)		1.21 (0.86–1.69)	
≥60	1.37 (0.88–2.14)		0.92 (0.54–1.57)	
Sex		0.10		0.39
Male	Ref.		Ref.	
Female	1.35 (0.95–1.92)		1.19 (0.80–1.78)	
Race and ethnicity		0.005		0.53
White, non-Hispanic	Ref.		Ref.	
Black, non-Hispanic	1.20 (0.86–1.66)		0.91 (0.63–1.30)	
Hispanic/other	0.53 (0.34–0.85)		0.73 (0.42–1.26)	
Education		0.02		0.07
<High school	Ref.		Ref.	
High school	0.95 (0.61–1.48)		0.80 (0.49–1.31)	
>High school	0.63 (0.42–0.93)		0.58 (0.35–0.95)	
Body mass index, kg/m^2		0.14		
<25	Ref.		—	
25 to <30	0.72 (0.50–1.05)		—	
≥30	1.00 (0.70–1.45)		—	
Medical insurance		0.005		0.20
Private	Ref.		Ref.	
Public	1.40 (0.99–1.97)		0.96 (0.63–1.47)	
Medicare	1.87 (1.23–2.85)		1.29 (0.79–2.11)	
None/unknown	0.58 (0.25–1.35)		0.48 (0.21–1.12)	
Smoking status		<0.001		0.008
Never	Ref.		Ref.	
Former	1.61 (1.12–2.31)		1.51 (1.03–2.20)	
Current	2.22 (1.53–3.25)		1.85 (1.24–2.76)	
Alcohol		0.74		—
Abstainer	Ref.		—	
Light drinker	0.87 (0.61–1.24)		—	
Moderate/heavy drinker	0.94 (0.64–1.38)		—	
Substance use (tobacco excluded)		0.14		—
Never	Ref.		—	
Former	1.43 (1.00–2.03)		—	
Current	1.10 (0.75–1.60)		—	
Physical activity, weekly		0.006		0.18
<3 days of moderate/vigorous activity	Ref.		Ref.	
≥3 days of moderate/vigorous activity	0.65 (0.48–0.89)		0.80 (0.58–1.11)	
Frailty status		<0.001		0.001
Robust	Ref.		Ref.	
Prefrail	1.22 (0.88–1.69)		0.92 (0.65–1.32)	
Frail	3.88 (2.45–6.16)		2.31 (1.38–3.86)	
Duration of ART, years		0.40		—
<5	Ref.		—	
5 to <8	0.76 (0.50–1.15)		—	
8 to <11	0.72 (0.45–1.16)		—	
≥11	0.80 (0.55–1.16)		—	
CD4 count, cells/mm^3		0.89		—
<500	Ref.		—	
≥500	0.97 (0.69–1.38)		—	
HIV RNA, copies/mL		0.14		0.18
<50	Ref.		Ref.	

TABLE 2. (*Continued*) Cox Proportional Hazards Regression Analysis of Risk Factors for Hospitalization, HAILO 2017–2021

	Crude Model		Adjusted Model	
Characteristic	**Hazard ratio (95% CI)**	***P*-value***	**Hazard ratio (95% CI)**	***P*-value***
≥50	1.56 (0.86–2.84)		1.49 (0.83–2.66)	
US region of entry site		<0.001		0.06
Northeast	Ref.		Ref.	
Midwest	0.98 (0.68–1.44)		1.15 (0.77–1.70)	
South	0.80 (0.51–1.25)		0.91 (0.58–1.43)	
West	0.37 (0.23–0.60)		0.55 (0.32–0.93)	
Participant-reported comorbidities				
Diabetes	1.91 (1.33–2.74)	<0.001	1.69 (1.13–2.52)	0.01
Hypertension	0.84 (0.62–1.13)	0.25	—	—
Renal disease	1.68 (1.08–2.61)	0.03	1.38 (0.85–2.24)	0.19
Cardiovascular disease	1.70 (1.11–2.58)	0.01	1.36 (0.87–2.12)	0.18

*Hypothesis tests for group comparisons used the Wald test with a significance level set at α = .05.

We also conducted a stratified analysis to examine predictors of initial hospitalization by sex. In addition, several sensitivity analyses were conducted to examine the robustness of the primary findings. First, to minimize potential bias introduced by planned procedures, we excluded elective surgeries. Second, to address potential bias from the shift from biannual to annual hospitalization assessment in the final study year, we censored participants at their last biannual visit. Third, to account for recurrent hospitalizations, we performed a negative binomial regression to estimate incidence rate ratios. Finally, we conducted a sensitivity analysis on the Cox regression model by assigning the date of first hospitalization to the midpoint between the first reported hospitalization visit and the prior visit. Data analyses were performed using Stata/MP 18 (StataCorp, College Station, TX). All statistical tests were two-sided, and P <0.05 was considered statistically significant.

RESULTS

Among 1035 participants enrolled in HAILO, 891 participants completed at least 1 hospitalization questionnaire. Most of the participants were male (80%), 40–59 years of age (86%), had virally suppressed HIV at <50 copies/mL (92%), had hypertension (52%), and were robust (55%). Additional demographic and clinical characteristics are shown in Table 1.

Time to First Hospitalization

During 5 years of follow-up, 208 (20%) participants had at least 1 hospitalization event, including 139 with 1 hospitalization and 69 with multiple hospitalizations (51 with 2, 11 with 3, 5 with 4, 2 with 5 hospitalizations). After excluding 38 participants with prevalent hospitalization at baseline, 170 incident hospitalizations occurred during 2721 person-years of follow-up among the remaining 853 participants (incidence rate, 6.2 per 100 person-years [95% CI = 5.4–7.3]) (see Table S2, Supplemental Digital Content, http://links.lww.com/QAI/C683). Six participants died during follow-up. The proportion of people hospitalized increased steadily over time (Fig. 1A). There was no statistically significant difference by age group (P = 0.13; Fig. 1B) and sex group (P = 0.09; Fig. 1C).

Causes of Hospitalization

Overall, the most common participant-reported causes of hospitalization were infections (14.0%), elective surgery (13.1%), cardiovascular conditions (12.3%), and lung problems (11.9%) (Fig. 2). Among elective surgeries, orthopedic and joint procedures were the most frequent, accounting for 32%, followed by spine surgeries (23%), cardiovascular interventions (16%), gastrointestinal or abdominal surgeries (13%), urologic surgery (6%), and other procedures (10%). The leading causes of hospitalization varied by age group (see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/C683). Among individuals aged 40–49 years, infections (17.4%) and lung problems (16.3%) were most common. In the 50–59 age group, elective surgery (17.0%) and cardiovascular conditions (17.0%) were the most frequently reported. Among those aged ≥60 years, infections and injury/accident were the most common causes of hospitalization, accounting for 18.4% and 15.8%, respectively.

Hospitalization causes differed by sex (see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/C683). Among women, the most common causes were lung problems (19%), infections (15%), and elective surgery (13%), whereas in men, the most common causes were infections (14%), cardiovascular conditions (14%), and elective surgery (13%).

Length of Stay

Thirty-six percent of participants reported being hospitalized for 1–2 days, 38% for 3–6 days, and 25% for 7 or more days. When stratified by age, those aged 40–49 years were more commonly hospitalized for 3–6 days, those aged 50–59 years for 1–2 days, and participants aged ≥60 years were also most frequently hospitalized for 3–6 days (P = 0.03). However, no significant difference in the length of hospital stay was observed between men and women (P = 0.96) (see Figure S2, Supplemental Digital Content, http://links.lww.com/QAI/C683).

Factors Associated With Hospitalization

In the adjusted model, risk of hospitalization was significantly higher among former smokers (HR = 1.51, 95% CI: 1.03–2.20) and current smokers (HR = 1.85, 95% CI: 1.24–2.76) compared with never smokers, higher among those that were frail (HR = 2.31, 95% CI: 1.38–3.86) compared with those who were robust, and lower in the Western region compared with the Northeast region (HR = 0.55, 95% CI: 0.32–0.93). In addition, diabetes (HR = 1.69, 95% CI: 1.13–2.52) was associated with a higher risk of hospitalization (Table 2). When hospitalizations for elective surgery were excluded, the above associations remained (see Table S3, Supplemental Digital Content, http://links.lww.com/QAI/C683). Results were largely consistent when adjusting for recurrent hospitalization (see Table S5, Supplemental Digital Content, http://links.lww.com/QAI/C683), using an alternative date of hospitalization definition (Supplementary Table 6), and censoring at the last biannual visit (see Table S7, Supplemental Digital Content, http://links.lww.com/QAI/C683).

DISCUSSION

In this large, well-characterized US cohort of PWH age ≥40 years, 20% of participants had at least 1 hospitalization over 5 years of follow-up, with an incidence rate of 6.2 per 100 person-years. The most common causes of hospitalization were lung problems, elective surgery, infections, and cardiovascular conditions. The risk factors for hospitalization were former or current smoking status, frail status, region of residence, and diabetes.

A direct comparison of the hospitalization risk in our study with other studies among PWH is challenging because of different definitions of hospitalization and differing methods for assessing hospitalization.[9,10,23–25] The hospitalization rate we observed (6.2 persons per 100 person-years) is lower than that observed in a US military cohort between 1999 and 2007 (13.7 per 100 person-years),[8] New York City in 2013 (36.7 per 100 person-years),[26] the Calgary region in Canada between 1997 and 2003 (21 per 100 person-years), and the observed trend among US and Canadian cohorts (from 22 per 100 person-years in 2005 to 13 per 100 person-years in 2015).[10] However, a UK study with a similar timeframe (2011–2018) reported a similar incidence rate (5.8 per 100 person years).[27] Most studies on hospitalization among PWH have been conducted in younger populations and before 2015 and reported declines in hospitalization over their follow-up period.[9,10,23,24] The results we observed were consistent with an expected lower hospitalization rate given advances in HIV treatment, including highly effective and well-tolerated ART, lower pill burden, and early treatment initiation that has contributed to better virological control and immune function preservation.[11] In the general population in the United States, substantial differences in hospitalization by region have been reported because of differences in patient health status, treatment preferences, physician practice patterns, access to and availability of services, and wages/cost of living.[28] These differences might also explain the observed lower rate of hospitalization in the Western region.

Excluding elective surgical procedures, we found that the most common causes of hospitalization were infections, cardiovascular disease, and lung problems consistent with prior literature,[9,10,24,29] and is what is expected with age. We did see differences in causes of hospitalization by age, with lung problems and infections more common among 40–49, planned surgery and cardiovascular conditions most common for the 50- to 59-year age group, and infections and injury/accident for the ≥60-year age group. This could be a chance finding or reflect differences in other factors in these age groups (vaccination, smoking, use of statins). Most hospital stays were for less than a week, comparable with other studies.[9,30]

About hospitalization risk factors, we found more hospitalizations in the older age groups and among women (see Table S4, Supplemental Digital Content, http://links.lww.com/QAI/C683), similar to previous studies,[8] although neither difference was statistically significant. Prior studies, including younger age groups, have also reported more hospitalizations among women, likely reflecting pregnancy-related factors or greater willingness to seek care among women; however, only 19% of women in this study were premenopausal. We also identified many modifiable risk factors that may have contributed to hospitalization including smoking, frailty, and diabetes. Not surprisingly, smoking was associated with hospitalization, similar to studies in the general population,[31,32] and likely additionally reflected in the increased comorbid disease burden seen among smokers. We did not see increased risk with alcohol use or substance use. Frailty has also been associated with increased risk for disease[20] and hospitalization.[33,34] Cardiovascular, endocrine, respiratory, gastrointestinal, and other disorders are associated with a greater frequency in people with diabetes,[35,36] likely contributing to the increased risk of hospitalization.

Strengths of this study include the large, well-characterized cohort with sites across the United States and 7 years of follow-up. Limitations should also be noted: we had a low proportion of women, many variables were self-reported, and specific times of the hospitalization were not reported. If death occurred during the hospitalization, the hospitalization visit would not have been subsequently reported; this limitation could have affected both the estimate of the hospitalization rate and the factors associated with hospitalization. Reasons for hospitalization were not adjudicated, so we could not rule out errors in reporting.

In summary, we observed a lower risk of hospitalization compared with previous studies of PWH, with infection-related and cardiopulmonary problems the leading causes of hospitalization. We also identified several potentially modifiable factors, suggesting that interventions for smoking cessation, preventing or attenuating frailty, and managing comorbidities such as diabetes may further reduce hospitalization among older PWH.

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