Human Immunodeficiency Virus Infection and Risk of Heart Failure Rehospitalizations

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Human Immunodeficiency Infection (HIV) is associated with increased risk for heart failure (HF). Outcomes of HF in patients living with HIV (PWH) are poorly understood. We sought to identify the risk of HF rehospitalizations (30 and 90 days) among PWH versus uninfected controls admitted with HF. Using the 2016 Nationwide Readmissions Database, we identified all patients (≥18 years) who were discharged alive with a primary diagnosis of HF (ICD10 I50.xx) with or without secondary diagnosis of HIV (ICD 10 Z21, B20, O98.7, or B97.35). Propensity score matching was used to match PWH with controls (1:1) based on 45 patient characteristics (demographics, hospitalization characteristics, and comorbidities). Cox regression models were used to compare rates of HF rehospitalization (primary ICD10 I50.xx) within 30 and 90 days after discharge from the index HF hospitalization. A total of 312,264 patients with HF were identified, of whom 1,112 (0.4%) had HIV. After propensity score matching, 1,112 PWH were matched with 1,112 uninfected controls. The standard mean difference for each variable was <10% postmatching. Overall, HF rehospitalization rates were 11.2% and 19.2% at 30 and 90 days, respectively. The 2 groups (PWH and controls) were not different statistically with respect to all 45 covariates. Compared with controls, PWH had a higher risk of HF rehospitalization within 30 days (hazard ratio 1.45, 95% confidence interval 1.13 to 1.87, p = 0.004) and 90 days (hazard ratio 1.41, 95% CI 1.16 to 1.71, p <0.001). This risk was consistent across age groups, gender, types of HF, presence or absence of coronary artery disease, or chronic kidney disease. In conclusion, in this propensity-matched national cohort of patients admitted with HF, patients with HIV had increased risk of HF rehospitalizations compared with uninfected controls at 30 days and 90 days. **(Am J Cardiol 2019;124:1232−1238)**

The global prevalence of Human Immunodeficiency Infection (HIV) is estimated at 36.9 million subjects with an annual incidence of 1.8 million cases.[1] Access to ART has transformed HIV infection into a treatable chronic disease, and the life expectancy of patients living with HIV (PWH) is now approaching that of the general population.[2] Most deaths in PWH are due to noncommunicable illnesses, and it is well documented that PWH are at increased risk for cardiovascular disease and heart failure (HF)[3−6] despite appropriate ART.[7] HF is a global pandemic and affects an estimated 26 million subjects worldwide. It accounted for nearly 1 million hospitalizations in the United States in 2010 and health care costs of HF exceed $30.7 billion annually.[8] Hospitalizations account for 75% of the cost, and rehospitalization rates remain near 20% placing a large burden on patients, hospitals, and third-party payers.[9,10] To improve patient outcomes and lower healthcare costs, it is pivotal to identify patients at highest risk of rehospitalization to allow for targeted intervention.[11] As PWH grow older, the prevalence of HF in HIV is expected to increase.[12] It is important to understand the risk of HF hospitalizations in this population. We therefore conducted a propensity-matched study to examine the risk of HF rehospitalizations (30 and 90 days) among PWH versus uninfected controls.

Methods

Data for our study were obtained from the 2016 Nationwide Readmissions Database (NRD) which was developed for the Healthcare Cost and Utilization Project. The 2016 NRD includes a calendar year of data with diagnoses and procedure codes reported using the ICD-10-CM/PCS coding system. It was constructed with data from the Healthcare Cost and Utilization Project State Inpatient Databases with reliable, verified patient linkage numbers. It includes discharge data from 27 geographically dispersed states accounting for 57.8% of the total resident population and 56.6% of all US hospitalizations. It contains more than 100 clinical and nonclinical variables for each hospital stay, including demographics, payment source, total hospital cost, and variables essential for rehospitalization analyses. All data were obtained whereas adhering to strict privacy guidelines.

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We identified patients (≥18 years) who were discharged alive with a primary diagnosis of HF (ICD10 I50.xx) with or without secondary diagnosis of HIV (ICD 10 Z21, B20, O98.7, or B97.35). The index hospitalization was defined as the first hospitalization with a primary diagnosis of HF. Any subsequent hospitalization was considered a rehospitalization. Patients who died during the index hospitalization and patients with missing demographics were excluded from this analysis. Patients discharged in December were excluded to allow sufficient time for follow-up as NRD contains data from only one calendar year. ICD10 codes for covariates are listed in Supplemental Table 1. Patients with combined systolic and diastolic HF were considered to have systolic HF.

The study outcomes were all-cause rehospitalization and HF rehospitalization (primary discharge diagnosis, ICD10 I50.xx) within 30 and 90 days of discharge from the hospital.

Propensity score matching was used to match PWH with controls (1:1) based on 45 patient characteristics (demographics, hospitalization characteristics, and comorbidities) using "MatchIt" Package in R. Baseline characteristics are compared using chi-squared tests or *t* tests. Cox regression models were used to compare rates of all-cause and HF rehospitalization within 30 and 90 days after discharge from the index HF hospitalization between HIV and control. Survival curves were generated using the Kaplan-Meier method. Factors associated with all-cause and HF rehospitalizations among PWH were examined using cox regression with forward conditional selection of variables at $p = 0.05$. Analyses were performed using Statistical Package for Social Sciences (version 20) and R Package 3.4.2. All tests were 2 sided, and $p < 0.05$ was considered statistically significant.

Results

A total of 312,264 patients with HF were identified, of whom 1,112 (0.4%) had HIV. After propensity score matching, 1,112 PWH were matched with 1,112 uninfected controls. The standard mean difference for each variable was <10% postmatching (Supplemental Figure 1). Figure 1 shows propensity scores for matched and unmatched patients. Table 1 lists the baseline characteristics of PWH and controls. There were no statistically significant differences between groups. Briefly, the PWH group was characterized by a mean (standard deviation) age of 55.6 (11) years, 31% were women, 63% had systolic HF, 41% had coronary artery disease (CAD), 54% had chronic kidney disease (CKD), 52% are smokers, 36% had diabetes, 38% had hypertension, 4% used opioids, 4.4% used cannabinoids, and 7.8% used cocaine.

Overall, HF rehospitalization rates were 11.2% and 19.2% at 30 and 90 days, respectively; and all-cause rehospitalizations were 29% and 48% at 30 and 90 days. Compared with controls, PWH had higher risk of HF rehospitalization within 30 days (hazard ratio [HR] 1.45, 95% confidence interval [CI] 1.13 to 1.87, $p = 0.004$) and 90 days (HR 1.41, 95% CI 1.16 to 1.71, $p < 0.001$), Figure 2. PWH also had higher risk of all-cause rehospitalizations at 30 days (HR 1.43, 95% CI 1.23 to 1.67, $p < 0.001$) and 90 days (HR 1.38, 95% CI 1.22 to 1.56, $p < 0.001$). This risk was consistent across age groups (≤65 vs >65 years), gender, HF subtype (diastolic vs systolic HF), CAD versus no CAD, CKD versus no CKD, and median income of the ZIP code of residence (below vs above median) for all-cause and HF rehospitalizations, Figures 3 and 4.

Among PWH, factors associated with 90-day HF rehospitalization were female gender (HR 1.36, 95% CI 1.05 to 1.77, $p = 0.021$), depression (HR 1.41, 95% CI 1.01 to 1.98,

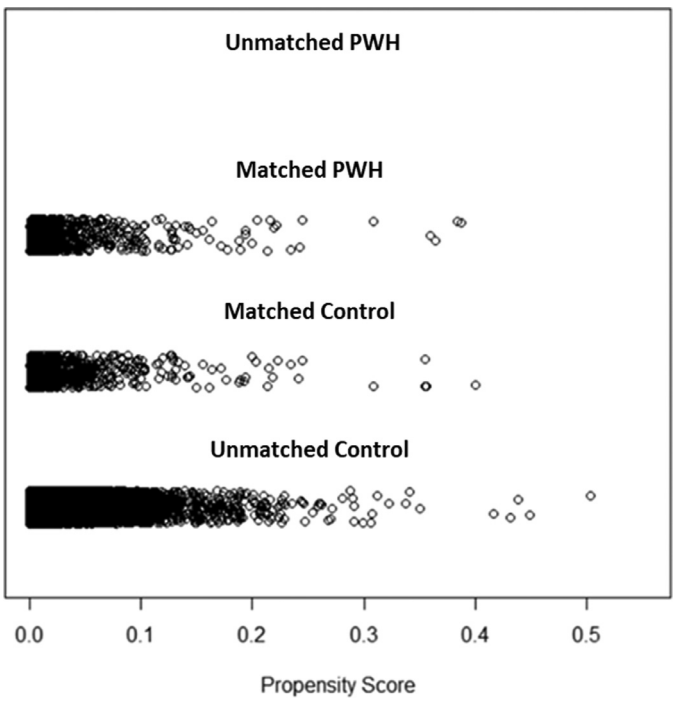

Figure 1. Propensity scores of matched and unmatched patients.

Table 1
Characteristics of patients with HIV and controls after propensity score matching

	PWH	Control	p Value
Age	55.6 ± 11.0	55.7 ± 14.5	0.97
Female	347 (31.2%)	315 (28.3%)	0.14
LOS index hospitalization	5.3 ± 5.9	5.4 ± 7.5	0.84
Weekend admission	277 (24.9%)	280 (25.2%)	0.88
Disposition location			0.73
Home	784 (70.5%)	810 (72.8%)	
Transfer to short-term hospital	6 (0.5%)	4 (0.4%)	
Transfer other*	82 (7.4%)	72 (6.5%)	
Home Health Care (HHC)	187 (16.8%)	173 (15.6%)	
Against Medical Advice (AMA)	53 (4.8%)	53 (4.8%)	
Discharge month			0.98
January	151 (13.6%)	158 (14.2%)	
February	138 (12.4%)	138 (12.4%)	
March	130 (11.7%)	126 (11.3%)	
April	97 (8.7%)	96 (8.6%)	
May	110 (9.9%)	100 (9%)	
June	89 (8%)	107 (9.6%)	
July	109 (9.8%)	104 (9.4%)	
August	102 (9.2%)	98 (8.8%)	
September	104 (9.4%)	104 (9.4%)	
October	50 (4.5%)	54 (4.9%)	
November	32 (2.9%)	27 (2.4%)	
Elective admission	24 (2.2%)	21 (1.9%)	0.65
Primary payer			0.89
Medicare	559 (50.3%)	542 (48.7%)	
Medicaid	342 (30.8%)	359 (32.3%)	
Private	131 (11.8%)	138 (12.4%)	
Self-pay	38 (3.4%)	33 (3%)	
No charge	5 (0.4%)	3 (0.3%)	
Other	37 (3.3%)	37 (3.3%)	
NCHS county categorization			0.80
Central	456 (41%)	458 (41.2%)	
Fringe	280 (25.2%)	270 (24.3%)	
Metro medium	212 (19.1%)	213 (19.2%)	
Metro small	72 (6.5%)	63 (5.7%)	
Micropolitan	57 (5.1%)	63 (5.7%)	
Other	35 (3.1%)	45 (4%)	
Income Quartile by ZIP code			0.56
First Quartile	611 (54.9%)	635 (57.1%)	
Second Quartile	244 (21.9%)	219 (19.7%)	
Third quartile	165 (14.8%)	171 (15.4%)	
Fourth quartile	92 (8.3%)	87 (7.8%)	
HF diagnosis	(0%)	(0%)	0.78
Diastolic HF	260 (23.4%)	264 (23.7%)	
Systolic HF	704 (63.3%)	711 (63.9%)	
HF-NOS	148 (13.3%)	137 (12.3%)	
Coronary Artery Disease	455 (40.9%)	454 (40.8%)	0.97
Valvular heart disease	125 (11.2%)	115 (10.3%)	0.49
Chronic kidney disease	604 (54.3%)	599 (53.9%)	0.83
Peripheral arterial disease	188 (16.9%)	189 (17%)	0.96
Diabetes mellitus	405 (36.4%)	413 (37.1%)	0.73
Stroke	132 (11.9%)	133 (12%)	0.95
Hypothyroidism	81 (7.3%)	74 (6.7%)	0.56
Anemia	74 (6.7%)	74 (6.7%)	>0.99
Coagulopathy	98 (8.8%)	113 (10.2%)	0.28
Pulmonary embolism	10 (0.9%)	12 (1.1%)	0.67
Depression	145 (13%)	153 (13.8%)	0.62
Atrial arrhythmia	201 (18.1%)	179 (16.1%)	0.22
Obstructive sleep apnea	131 (11.8%)	108 (9.7%)	0.12
Obesity	205 (18.4%)	206 (18.5%)	0.96
Liver disease	150 (13.5%)	135 (12.1%)	0.34
Acute kidney injury	302 (27.2%)	314 (28.2%)	0.57

(continued)

Table 1 (***Continued***)

	PWH	Control	p Value
Chronic obstructive pulmonary disease	28 (2.5%)	26 (2.3%)	0.78
Hyperlipidemia	400 (36%)	383 (34.4%)	0.45
Hypertension	428 (38.5%)	434 (39%)	0.79
Psychosis	46 (4.1%)	37 (3.3%)	0.31
Palliative care	20 (1.8%)	19 (1.7%)	0.87
Dementia	12 (1.1%)	14 (1.3%)	0.69
Connective tissue disease	21 (1.9%)	15 (1.3%)	0.31
Blood transfusion	43 (3.9%)	44 (4%)	0.91
Hemodialysis	191 (17.2%)	180 (16.2%)	0.53
Alcohol	62 (5.6%)	65 (5.8%)	0.78
Smoker	580 (52.2%)	595 (53.5%)	0.52
Opioid use	45 (4%)	37 (3.3%)	0.37
Cannabinoid use	49 (4.4%)	59 (5.3%)	0.32
Cocaine use	87 (7.8%)	81 (7.3%)	0.69

NCHS = National center for health statistics; NOS = heart failure, not otherwise specified.

* Includes Skilled Nursing Facility (SNF), Intermediate Care Facility (ICF), Another Type of Facility.All diagnoses are derived from ICD 10 codes (see Supplemental Table 1 for Implantable cardioverter-defibrillator (ICD) code dictionary).

p = 0.046), and systolic HF versus HF-NOS (HR 1.25, 95% CI 1.04 to 1.51, p = 0.017), whereas diastolic HF was associated with lower risk of admission (HR 0.74, 95% CI 0.59 to 0.94, p = 0.015) versus HF-NOS. All-cause rehospitalizations were associated with CKD (HR 1.25, 95% CI 1.05 to 1.50, p = 0.015), hemodialysis (HR 1.35, 95% CI 1.08 to 1.67, p = 0.008), and cocaine use (HR 1.43, 95% CI 1.09 to 1.88, p = 0.01), whereas living in the third quartile of median ZIP code (vs first quartile) income was associated with a lower risk of rehospitalization (HR 0.69, 95% CI 0.54 to 0.89, p = 0.004).

Discussion

In our propensity-matched national cohort of patients admitted with HF, PWH were found to have an increased risk for HF and all-cause rehospitalization after HF admission compared with uninfected controls at both 30 and 90 days. These findings are supported by data derived from recent studies. A previous single-center cohort study showed significantly increased 30-day HF rehospitalization for PWH (49% vs 32%),[13] whereas a separate cohort study showed HIV was associated with 3.4-fold higher odds of rehospitalization for HF.[14]

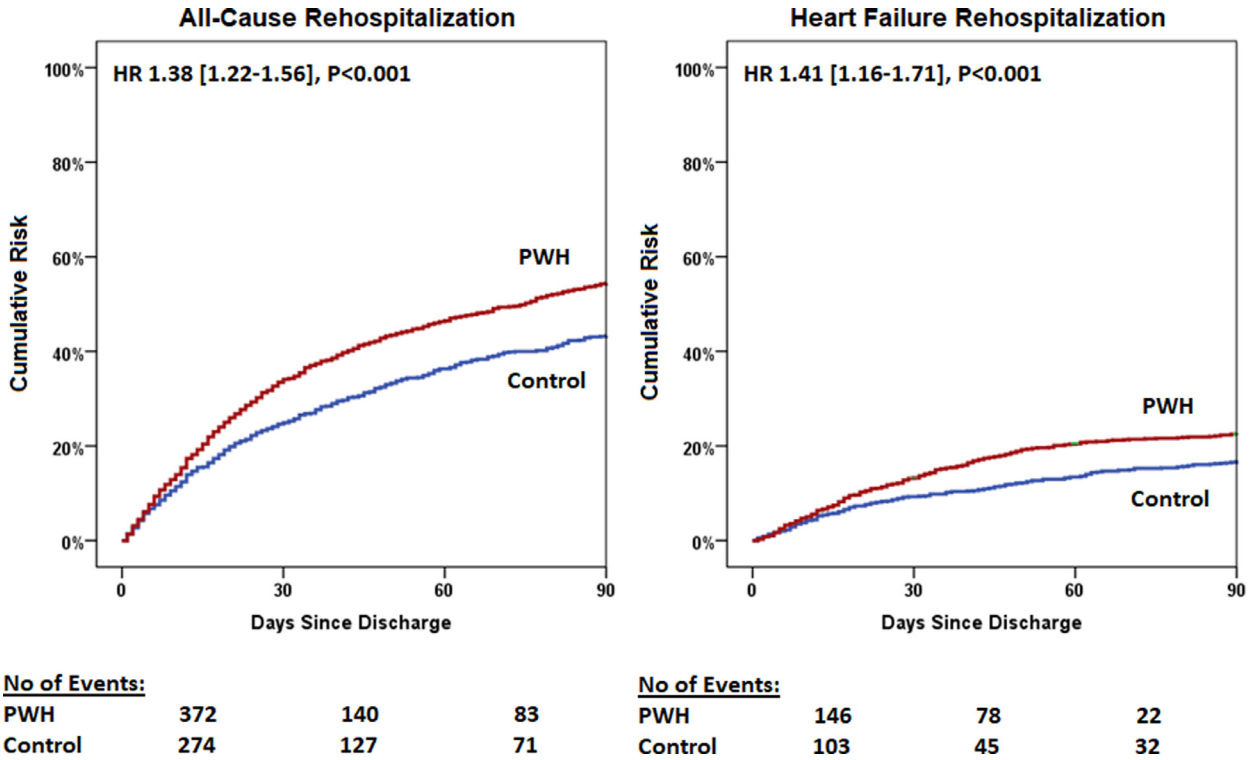

Figure 2. Kaplan-Meier plot of the of all-cause and heart failure rehospitalization in persons living with HIV (PWH) and matched uninfected controls. Hazard ratios (HR) and 95% confidence intervals are estimated using cox-proportional hazard models.

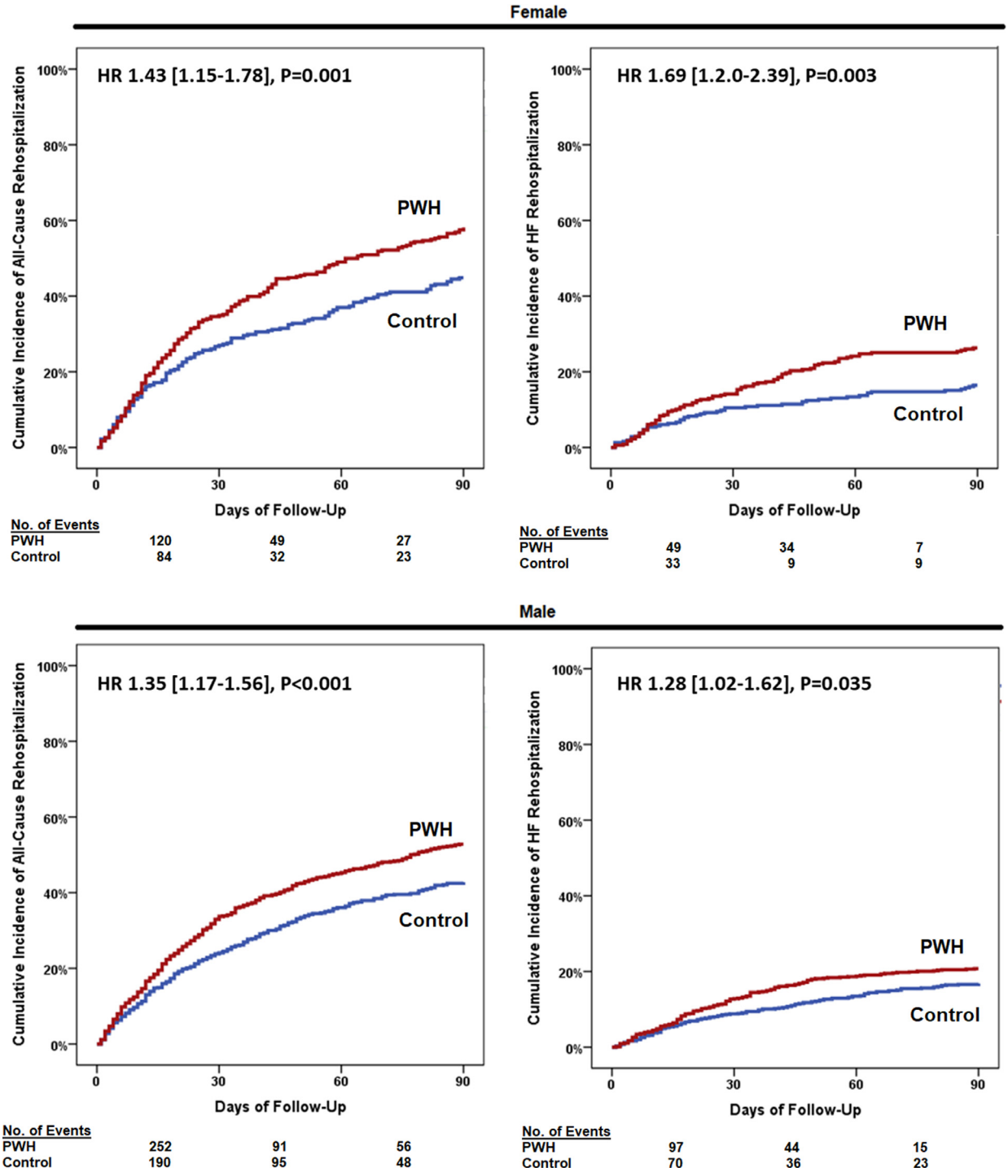

Figure 3. Kaplan-Meier plot of the of all-cause and heart failure rehospitalization in persons living with HIV (PWH) and matched uninfected controls, stratified by gender. Hazard ratios (HR) and 95% confidence intervals are estimated using cox-proportional hazard models.

As effective ART has become more accessible, the phenotype of overt left ventricular (LV) systolic dysfunction is being replaced by an insidious course of LV diastolic dysfunction and varying degrees of systolic dysfunction which develop at significantly younger ages than uninfected controls.[15] In a recent meta-analysis of PWH on ART, the prevalence of systolic dysfunction was 8.3% whereas that of diastolic dysfunction was 43.4%.[16] The Veteran Aging Cohort Study Virtual Cohort provides evidence of an increased risk of incident HF in PWH with a HR of 1.81 (95% CI 1.39 to 2.36) after adjusting for traditional risk factors.[17] A more recent study supports that PWH are at increased risk of HF with a relative risk of 1.66 (CI 1.60 to 1.72, p <0.0001).[8] Proposed pathophysiological causes of HF in PWH include direct HIV-induced myocardial damage,[18] autoimmune responses and systemic inflammation,[19] accelerated myocardial fibrosis,[20] increased risk of CAD and myocardial infarction,[21,22] nutritional deficiencies,[23]

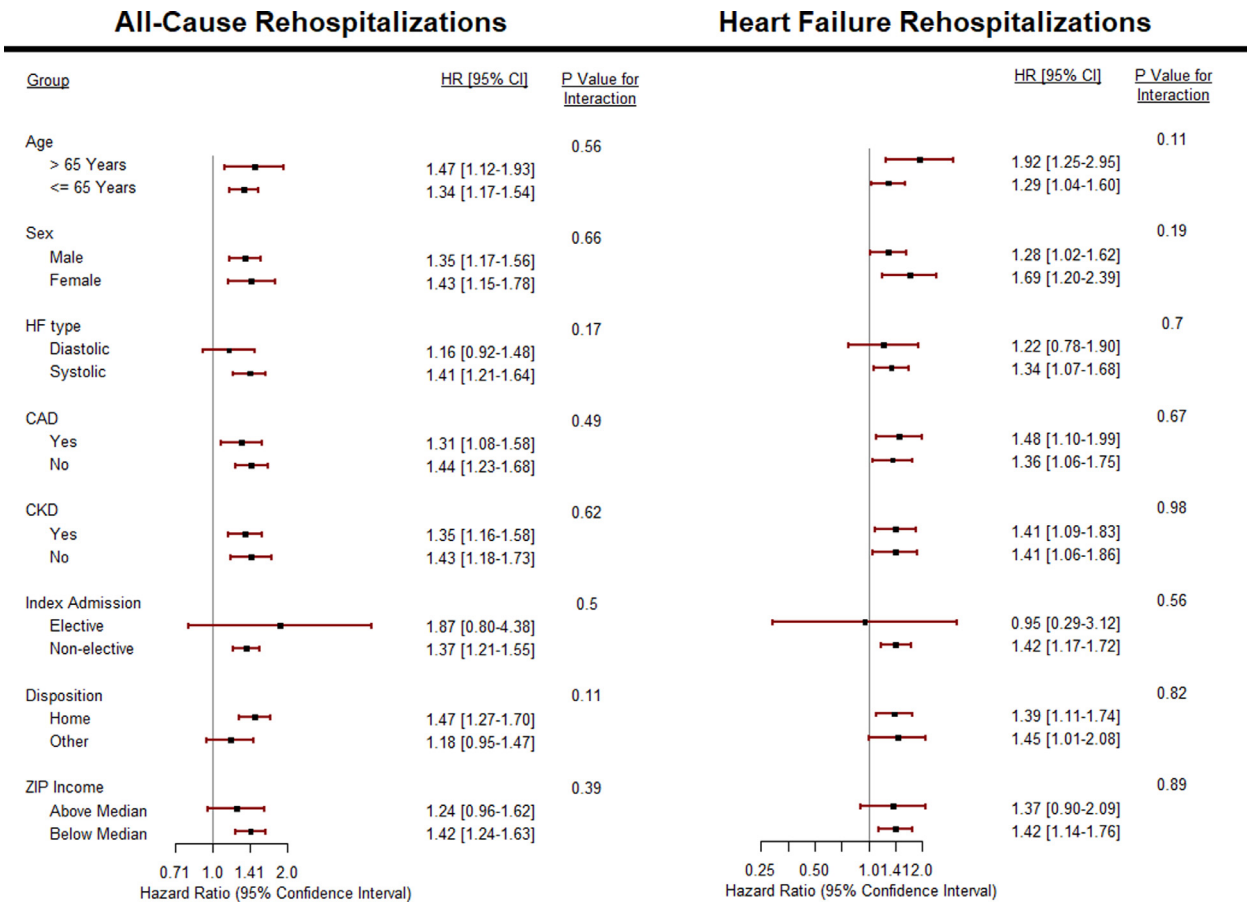

Figure 4. Association between HIV with all-cause and HF rehospitalization among subgroups. Values to the right of the line of unity represent increased risk in PWH. CAD = coronary artery disease, CKD = chronic kidney disease.

altered lipid metabolism,[24] and toxicity from HIV medications themselves.[25]

The etiology of increased HF rehospitalizations among PWH has not yet been studied; however, it is likely a multifactorial phenomenon. PWH develop HF at an earlier age and with more rapid progression than uninfected controls.[15–17] Rapid progression of disease leads to earlier hospitalizations, and a recent study shows that a single previous HF admission independently increases risk of HF rehospitalizations with a HR of 1.51 (95% CI 1.18 to 1.92). The HR increases to 1.90 (95% CI 1.47 to 2.44) with multiple past HF admissions.[26] PWH are more likely to have medical co-morbidities such as diabetes, hypertension, peripheral vascular disease, CAD, and hepatitis B and C. In addition, they are more likely to use tobacco, alcohol, cannabinoids, and cocaine.[7] PWH diagnosed with HF require management of at least two complicated chronic illnesses which leads to drug-drug interactions, polypharmacy, and expenses which reduce compliance.[14] Finally, in comparison to healthy counterparts, PWH are less likely to be prescribed diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β blockers, and antiplatelet agents.[7] Our propensity-matched analysis accounted for many of these factors, suggesting they do not fully explain the increased risk of rehospitalization for PWH.

In the modern ART era, by 2030 it is anticipated that 73% of PWH will be 50 years or older.[27] This is clinically significant given the increased risk of HF in this population. The current optimal medical therapy for PWH and HF is unknown because no randomized trials have been performed, and HIV status is not regularly collected in clinical trials or registries. Therapy is therefore guided by consensus and data derived from studies of uninfected individuals.[15] General recommendations include standard guideline-driven therapy including lifestyle modifications and pharmacologic treatmentsl.[12] Pharmacologic treatments, according to AHA/ACC/HFSA guidelines,[28] include diuretics, β blockers, angiotensin converting enzyme, or angiotensin receptor blockers. For those with Heart Failure with Preserved Ejection Fraction (HFpEF), aldosterone antagonism may reduce HF hospitalizations.[29] The clinical effectiveness of advanced therapies such as implantable devices and cardiac transplantation has not been well-studied in PWH as HIV is still seen as a relative contraindication in many centers. There may be reluctance to offer these options due to lack of safety data, perceived limited life expectancy, and theoretical risk of infection.[12,15] It is important to note that multiple studies have shown HF[7,12,17] and HF rehospitalizations[14] are associated with viral control as measured by CD4+ count and viral load. As such, PWH should receive ART to attain viral control.

This study has some limitations. For instance, the NRD does not have information on important variables such as CD4+ count, viral load, and discharge medications after index hospitalization. Additionally, our diagnoses of HF and HIV were dependent on administrative claims data recorded by physicians or hospitals, and these may have been misclassified. An important strength of our study, however, was the use of propensity-score matching to reduce the risk of residual confounding. Furthermore, generalizability is enhanced through contemporary data (2016) from a large sample that is nationally representative of the United States.

In conclusion, in this propensity-matched national cohort of patients admitted with HF, patients with HIV had an increased risk of HF rehospitalizations compared with uninfected controls at 30 and 90 days.

Disclosures

DB, NT, and SGA have no conflicts of interest pertinent to this manuscript. CTL has received a research grant from Gilead Sciences.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.034.

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