Increased Echocardiographic Pulmonary Pressure in HIV-infected and -uninfected Individuals in the Veterans Aging Cohort Study

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Abstract

Rationale: The epidemiology and prognostic impact of increased pulmonary pressure among HIV-infected individuals in the antiretroviral therapy era is not well described.

Objectives: To examine the prevalence, clinical features, and outcomes of increased echocardiographic pulmonary pressure in HIV-infected and -uninfected individuals.

Methods: This study evaluated 8,296 veterans referred for echocardiography with reported pulmonary artery systolic pressure (PASP) estimates from the Veterans Aging Cohort study, an observational cohort of HIV-infected and -uninfected veterans matched by age, sex, race/ethnicity, and clinical site. The primary outcome was adjusted mortality by HIV status.

Measurements and Main Results: PASP was reported in 2,831 HIV-infected and 5,465 HIV-uninfected veterans (follow-up [mean $\pm$ SD], 3.8 $\pm$ 2.6 yr). As compared with uninfected veterans, HIV-infected veterans with HIV viral load greater than 500 copies/ml (odds ratio, 1.27; 95% confidence interval [CI], 1.05–1.54) and those with CD4 cell count less than 200 cells/ μ l

(odds ratio, 1.28; 95% CI, 1.02–1.60) had a higher prevalence of PASP greater than or equal to 40 mm Hg. As compared with uninfected veterans with a PASP less than 40 mm Hg, HIV-infected veterans with a PASP greater than or equal to 40 mm Hg had an increased risk of death (adjusted hazard ratio, 1.78; 95% CI, 1.57–2.01). This risk persisted even among participants without prevalent comorbidities (adjusted hazard ratio, 3.61; 95% CI, 2.17–6.01). The adjusted risk of mortality in HIV-infected veterans was higher at all PASP values than in uninfected veterans, including at values currently considered to be normal.

Conclusions: HIV-infected people with high HIV viral loads or low CD4 cell counts have a higher prevalence of increased PASP than uninfected people. Mortality risk in HIV-infected veterans increases at lower values of PASP than previously recognized and is present even among those without prevalent comorbidities. These findings may inform clinical decision-making regarding screening and surveillance of pulmonary hypertension in HIV-infected individuals.

Keywords: human immunodeficiency virus; pulmonary hypertension; patient outcome assessment; electronic health records; echocardiography

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At a Glance Commentary

Scientific Knowledge on the

Subject: Little is known about the risk factors and impact of pulmonary pressure on outcomes in HIV, particularly in comparison with demographically and behaviorally similar uninfected people. Furthermore, no data exist to guide risk stratification or to inform the optimal threshold for recommending invasive hemodynamic evaluation in this population.

What This Study Adds to the

Field: This work provides a contemporary examination of the epidemiology of increased pulmonary pressure among a national sample of HIV-infected and -uninfected individuals referred for echocardiography. HIV infection with unsuppressed viral control was independently associated with increased pulmonary pressure. HIV-infected individuals are at higher risk of adjusted mortality than uninfected individuals, and risk factors for pulmonary hypertension differ by HIV status. We observed that mortality risk in HIV-infected individuals was significantly increased at pulmonary pressure values currently considered normal and well below the threshold at which consideration of invasive evaluation is recommended. These findings have implications for pulmonary hypertension screening, surveillance, and risk factor modification in HIV-infected individuals.

HIV-infected people have an increased risk of cardiovascular disease, including pulmonary hypertension (PH) (1–6). Important knowledge gaps remain in our understanding of PH in the HIV population, in part because most studies have focused on pulmonary arterial hypertension (PAH), which is rare. Little is known about the risk factors and impact of pulmonary pressure

on outcomes in HIV. Presently, no data exist to guide risk stratification or to inform the optimal threshold for recommending invasive hemodynamic evaluation in this population. These questions are important because the prevalence of HIV infection is increasing, especially among older and minority populations (7).

To address these knowledge gaps, we present data from the largest contemporary cohort of HIV-infected and -uninfected individuals with pulmonary artery (PA) pressure estimates, detailed comorbidity profiles, and mortality outcomes. We investigated mortality risk across a spectrum of echocardiographic PA pressure estimates in a large, nationwide cohort of HIV-infected and -uninfected veterans treated in a single healthcare system. This study builds on our prior work in the Veterans Aging Cohort Study (VACS) by using echocardiographic estimates of PA pressure rather than International Classification of Diseases (ICD) codes for PH (8). Increased pulmonary pressure in this study refers to an estimated PASP greater than 40 mm Hg on echocardiography, not a specific disease entity such as PAH. The aims of this study were to examine the prognostic impact of PA pressure, to identify clinical features associated with increased pulmonary pressure, and to ascertain the PA pressure threshold at which mortality risk increases in HIV-infected and -uninfected veterans. Some of the results of these studies have been previously reported in the form of an abstract (9).

Methods

The VACS is a prospective observational longitudinal cohort of HIV-infected and -uninfected veterans matched 1:2 for age, race/ethnicity, sex, and clinical site and enrolled in the same calendar year (10). Clinical and demographic data are extracted from the Veterans Affairs (VA) Corporate Data Warehouse and the VA electronic medical record Health Factor dataset (10). The Vanderbilt University Medical Center, Yale University, and West Haven VA Medical Center institutional

review boards approved this study. The VACS has a waiver of informed consent.

We included all VACS participants enrolled on or after April 1, 2003 who had been referred for a transthoracic echocardiogram and had a reported pulmonary artery systolic pressure (PASP). The baseline was a participant's first PASP measurement on or after April 1, 2003. The prevalence of all covariates and laboratory measurements were based on measures ascertained closest to the date of the baseline echocardiogram. All participants were followed from their baseline date to death or censored on September 30, 2012, if living.

A custom rule-based information extraction system was built using Leo framework to provide PASP and left ventricular ejection fraction data for the study (11, 12). On manual validation, the accuracy of extracted PASP values across different report formats was 95 to 100%. PASP values less than 12 mm Hg or greater than 152 mm Hg were assumed to be nonphysiologic or due to data entry errors (e.g., PASP of -10 mm Hg) and were excluded (13). Right atrial pressure estimation was nonstandardized. PASP values were extracted directly from the echocardiogram reports, which integrated the interpreting physician's estimation of right atrial pressure. Increased PASP was defined as PASP greater than 40 mm Hg (14, 15). For secondary analyses, we extracted left atrial (LA) size and left ventricular (LV) thickness to better understand drivers of elevated PASP. LA enlargement was defined as anterior–posterior diameter greater than 40 mm, and LV hypertrophy was defined as interventricular septal thickness greater than 11 mm. As our data extraction tool was not designed *a priori* to extract data on LA and LV size, we were not able to completely capture these variables.

HIV status was determined based on a validated metric including at least one inpatient or two or more outpatient ICD ninth revision (ICD-9) codes for HIV and if the participant was included in the VA Immunology Case Registry (10). Our

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analyses included the following outcomes: 1) all-cause mortality; 2) increased PASP; and 3) incident heart failure (HF). For the latter, we used the presence of one or more inpatient or two or more outpatient VA, VA fee for service, or Medicare ICD-9 codes to identify HF events within and outside the VA healthcare system, as previously described (11, 16). Mortality was determined from the VA vital status file, which is compiled from combined sources including inpatient mortality, social security data, and national death benefits data, a method previously shown to provide excellent mortality ascertainment (17).

We determined age, sex, and race/ethnicity using administrative data. Comorbid hypertension, diabetes mellitus, dyslipidemia, renal disease, hepatitis C infection, chronic obstructive pulmonary disease (COPD), alcohol abuse, smoking status, coronary heart disease, stroke, atrial fibrillation, cancer, and anemia were ascertained using a combination of clinical, laboratory, and/or ICD-9 code data collected closest to the date of the baseline echocardiogram, as previously described (18–22). We also calculated the VACS index, a score that assesses mortality risk using indicators of HIV disease and organ system injury (23). Hypertension was categorized as absent (blood pressure < 140/90 mm Hg and no antihypertensive medication) or present ($\geq 140/90$ mm Hg or on antihypertensive medication) (24). We collected CD4⁺ lymphocyte counts (CD4 cell counts) and HIV viral load value closest to and within 180 days from the date of the baseline echocardiogram. Baseline antiretroviral therapy (ART) was categorized by regimen of ART within 180 days before baseline: protease inhibitors plus nucleoside reverse transcriptase inhibitors (NRTI); nonnucleoside reverse transcriptase inhibitors (NNRTI) plus NRTI; other (i.e., use of protease inhibitors, NRTI, or NNRTI medications, but not in combination as described in other two categories); and no ART use (referent group). All ART medications that were on VA formulary during the study period were included. We have previously demonstrated in a nested sample that 98% of HIV-infected veterans obtain their ART medications from the VA (10).

Statistical Analysis

Descriptive statistics for all variables by HIV and increased pulmonary pressure were

analyzed using Wilcoxon tests for continuous variables and the χ^2 test for categorical variables. We used logistic regression models to identify clinical associations with increased pulmonary pressure. We used Cox proportional hazards models to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) to examine mortality risk by HIV and increased pulmonary pressure in adjusted analyses. Secondary analyses were restricted to participants without significant comorbidities. Similar analyses were used to assess the risk of incident HF, except that the follow-up was through December 31, 2011, when we were last able to ascertain HF events from Medicare data. All models included age, sex, race/ethnicity, established cardiovascular risk factors, and other relevant comorbidities selected *a priori*. For models involving only HIV-infected participants, we further adjusted for baseline HIV viral load, CD4 count, and ART regimen. To visually inspect the association between PASP and all-cause mortality, we stratified by HIV status and plotted the risk of all-cause mortality by PASP (modeled with restricted cubic splines). To assess whether the impact of HIV on mortality risk differed at various values of PASP, we included an interaction term between HIV status and PASP, and at each PASP value we plotted the mortality risk for an HIV-infected veteran versus an uninfected veteran. Missing covariate data were accounted for using multiple imputation techniques, where continuous variables were imputed using predictive mean matching to produce biologically plausible values and categorical variables were imputed using a discriminate function with a noninformative Jeffreys prior. Using multiple imputation, we created five complete datasets. Analyses were performed in each of the five datasets and results were combined across imputations according to Rubin's rules.

Results

We identified 8,296 (2,831 HIV-infected and 5,465 HIV-uninfected veterans) with reported PASP values on echocardiography. Increased PASP was observed in 782 HIV-infected and 1,478 HIV-uninfected veterans. PASP values were similar between HIV-infected and -uninfected veterans (mean $\pm$ SD, 36 ± 15 mm Hg vs. $36 \pm$

14 mm Hg; $P = 0.99$) as was the prevalence of increased PASP (28 vs. 27%, respectively; $P = 0.58$). HIV-infected veterans with increased PASP had a lower CD4 cell count, higher HIV viral load, and were less likely to have been exposed to any ART than HIV-infected veterans without increased pulmonary pressure (Table 1). In addition to established PH risk factors (diabetes, COPD, HF), black race was associated with increased PASP in HIV-infected and -uninfected veterans (Table 2). Current or former smoking status was associated with increased PASP among HIV-infected but not uninfected veterans (P for interaction = 0.037). In contrast, male sex (P for interaction = 0.056) and obesity (P for interaction = 0.10) were only associated with increased PASP among uninfected veterans. All ART regimens were associated with a protective point estimate in adjusted analyses but did not reach statistical significance.

Veterans with HIV viral load greater than or equal to 500 copies/ml and those with CD4 cell counts less than 200 cells/ μ l were significantly more likely to have increased PASP than uninfected veterans (odds ratio, 1.27; 95% CI, 1.05–1.54; and odds ratio, 1.28; 95% CI, 1.02–1.60, respectively; see Table E1 in the online supplement).

In this study, 2,656 participants died (42% among HIV-infected veterans) during 3.8 ± 2.6 years of follow-up. Mortality rates per 1,000 person-years were highest in HIV-infected veterans with increased pulmonary pressure (Table 3). This finding persisted in secondary analyses adjusting for prevalent LA enlargement and left ventricular hypertrophy (Table E2). As compared with uninfected veterans with normal PASP, veterans with increased PASP, regardless of HIV status, had at least a 50% higher mortality rate (Table 3). Among HIV-infected veterans, increased PASP was associated with a significant increased risk of death even after adjusting for demographics, comorbidities, viral load, CD4 count, and ART regimen (HR, 1.30; 95% CI, 1.14–1.49; $P < 0.001$). In veterans without prevalent stroke, heart failure, COPD, diabetes, or renal disease, increased PASP was associated with at least double the mortality risk, regardless of HIV status (Table 3) and was highest in HIV-infected veterans with increased PASP (HR, 3.61; 95% CI, 2.17–6.01; $P < 0.001$). Incident HF rates and risk increased among

Table 1. Baseline Characteristics of Veterans Stratified by HIV and Pulmonary Artery Systolic Pressure Status

Baseline Characteristics *†‡	HIV-infected (n = 2,831)		HIV-uninfected (n = 5,465)	
	No PH (PASP ≤ 40 mm Hg [n = 2,049])	PH (PASP > 40 mm Hg [n = 782])	No PH (PASP ≤ 40 mm Hg [n = 3,987])	PH (PASP > 40 mm Hg [n = 1,478])
Age, yr				
Mean (SD)	56.7 (9.8)	57.9 (10.0)	57.5 (9.4)	59.2 (9.3)
Median	56.0	57.0	57.0	58.0
Age category				
<40 yr	3.5	2.3	2.4	0.8
40–64 yr	77.7	76.0	78.9	75.1
≥65 yr	18.8	21.7	18.7	24.1
Male sex	97.3	98.1	96.2	98.9
Race/ethnicity				
African American	48.1	60.7	46.8	59.1
White	40.0	31.7	40.0	32.7
Hispanic	9.0	4.9	11.0	6.5
Other	2.8	2.7	2.2	1.7
Framingham risk factors				
Hypertension	89.2	94.6	95.8	97.4
Diabetes mellitus	33.0	44.3	41.7	55.9
Dyslipidemia	68.8	66.5	60.3	57.9
Smoking				
Current	46.7	52.3	42.6	42.3
Former	22.3	25.1	25.3	28.0
Never	31.0	22.6	32.2	29.7
Other risk factors				
VACS index				
Mean (SD)	41.4 (24.7)	50.5 (27.0)	27.4 (18.9)	34.9 (20.7)
Median	37.0	47.0	22.0	33.0
HCV infection	40.8	43.4	19.5	21.2
Renal disease, ml/min/1.73 m ²				
eGFR ≥ 60	78.7	66.7	81.7	65.9
eGFR 30–59	14.7	16.4	13.4	21.8
eGFR < 30	6.6	16.9	4.9	12.4
BMI, kg/m ²				
BMI < 18.5	5.1	7.0	2.0	2.7
18.5 ≤ BMI < 30	74.7	74.1	55.9	50.6
BMI ≥ 30	20.1	18.8	42.1	46.7
Anemia, g/dl				
Hb ≥ 14	36.1	28.0	50.5	36.0
Hb 12–13.9	37.1	34.4	33.4	35.1
Hb 10–11.9	19.3	25.8	12.5	20.7
Hb < 10	7.6	11.8	3.6	8.2
History of alcohol abuse	37.5	41.7	36.5	37.3
COPD	30.6	41.6	31.0	44.9
HF				
EF > 50%	3.1	8.6	3.7	9.1
EF ≤ 50%	7.7	17.1	6.9	13.1
No EF	10.9	24.3	14.7	35.2
No HF	78.3	50.0	74.7	42.6
Left atrial enlargement	30.7	53.5	41.7	63.0
Left ventricular hypertrophy	35.5	49.8	43.5	52.2
Stroke	6.2	6.7	7.5	8.3
Coronary heart disease	35.5	46.0	48.2	61.2
Atrial fibrillation	11.4	15.9	16.3	25.4
Cancer	11.0	13.6	9.0	11.0
HIV-specific variables [§]				
CD4 cell count, mm				
CD4 ≥ 500	34.6	32.5	—	—
200 ≤ CD4 < 500	45.4	43.0	—	—
CD4 < 200	19.9	24.5	—	—
HIV-1 RNA, copies/ml				
HIV-1 RNA < 500	68.6	61.0	—	—
500 ≤ HIV-1 RNA < 1,000	3.0	4.4	—	—
HIV-1 RNA ≥ 1,000	28.4	34.6	—	—

(Continued)

Table 1. (Continued)

Baseline Characteristics *†‡	HIV-infected (n = 2,831)		HIV-uninfected (n = 5,465)	
	No PH (PASP ≤ 40 mm Hg [n = 2,049])	PH (PASP > 40 mm Hg [n = 782])	No PH (PASP ≤ 40 mm Hg [n = 3,987])	PH (PASP > 40 mm Hg [n = 1,478])
ART regimen				
NRTI + PI	40.7	36.7	—	—
NRTI + NNRTI	18.8	17.8	—	—
Other	6.2	6.1	—	—
No ART	34.4	39.4	—	—

Definition of abbreviations: ART = antiretroviral therapy; BMI = body mass index (calculated as weight in kilograms divided by height in meters squared); COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EF = ejection fraction; HCV = hepatitis C virus; HF = heart failure; NNRTI = nonnucleoside reverse-transcriptase inhibitor; NRTI = nucleoside reverse-transcriptase inhibitor; PASP = pulmonary artery systolic pressure; PH = pulmonary hypertension; PI = protease inhibitor; VACS = Veterans Aging Cohort Study.

Data are presented as percentage unless otherwise noted.

*All characteristics were statistically different among HIV-infected veterans ($P < 0.05$) using χ^2 test or Wilcoxon rank sum test except the following: age ($P = 0.07$), sex ($P = 0.22$), dyslipidemia ($P = 0.25$), HCV infection ($P = 0.21$), BMI ($P = 0.13$), stroke ($P = 0.62$), cancer ($P = 0.06$), and ART regimen ($P = 0.09$).

†All characteristics were statistically different among HIV-uninfected veterans ($P < 0.05$) using χ^2 test or Wilcoxon rank sum test except the following: dyslipidemia ($P = 0.11$), smoking status ($P = 0.09$), HCV infection ($P = 0.16$), alcohol dependence ($P = 0.59$), and stroke ($P = 0.34$).

‡All variables had complete data except the following: hypertension data were available on 2,829 (HIV-infected) and 5,462 (uninfected); dyslipidemia data were available on 2,699 (HIV-infected) and 5,244 (uninfected); smoking data were available on 2,549 (HIV-infected) and 5,023 (uninfected); VACS Index data were available on 2,285 (HIV-infected) and 5,396 (uninfected); eGFR data were available on 2,818 (HIV-infected) and 5,421 (uninfected); BMI data were available on 2,824 (HIV-infected) and 5,458 (uninfected); anemia data were available on 2,817 (HIV-infected) and 5,405 (uninfected); left atrial data were available on 1,489 (HIV-infected) and 2,195 (uninfected); interventricular septum thickness data were available on 995 (HIV-infected) and 1,807 (uninfected); CD4 cell count data were available on 2,374 (HIV-infected); and HIV-1 RNA data were available on 2,376 (HIV-infected).

§Because uninfected veterans do not have HIV-specific biomarkers or ART regimens, these cells contain only dashes.

individuals with increased PASP regardless of HIV status (Table E3).

When we modeled PASP as a continuous variable stratified by HIV status using a PASP value of 15 mm Hg as the reference, the adjusted risk of death in HIV-infected veterans began to increase at a lower PASP than uninfected veterans and with a larger effect size at all PASP values (Figure 1). For example, an HIV-infected individual with a PASP of 30 mm Hg has an HR of 1.40 (95% CI, 1.18–1.67) for mortality, whereas the corresponding HR for uninfected individuals is 1.21 (95% CI, 1.04–1.41). HIV-infected veterans had an increased risk of mortality as compared with uninfected veterans across all PASP values (Figure 2). The difference in risk between HIV-infected and -uninfected veterans was highest at values currently considered normal or modestly elevated.

Discussion

In this national sample of veterans referred for echocardiography, HIV-infected people with unsuppressed HIV virus or low CD4 cell counts had a higher prevalence of increased PASP than uninfected people. As compared with participants with either HIV infection or increased PASP, participants

with both conditions had the highest rates and risk of death. Although mortality risk increased with increasing PASP, HIV-infected people had significantly increased mortality risk at PA pressure values currently considered normal and well below the threshold at which consideration of invasive evaluation is recommended (14). Although risk factor profiles for increased PASP varied by HIV status, black race was independently associated with increased PASP in both HIV-infected and HIV-uninfected veterans.

Increased PASP in individuals with HIV has been well described, particularly in the pre-ART era (1, 2, 25, 26). Our study adds to this field by examining PASP in the ART era in a national sample that includes demographically and behaviorally similar uninfected individuals. Unlike prior studies that were limited by small sample sizes, missing covariate data, or lacked outcome data, this study was powered to examine how mortality risk changes across a wide distribution of PASP values.

Although this study was unable to discriminate precapillary PH from PH due to left heart disease because echocardiographic estimates of PASP do not inform on the etiology of increased pulmonary pressure, we presume that most of the increased PASP in VACS is due to

left heart disease or parenchymal lung disease, given the high prevalence of cardiovascular risk factors and COPD in our cohort.

Although the high burden of comorbid disease was undoubtedly a major driver of outcomes in our study, increased PASP was significantly associated with mortality even among those veterans without prevalent comorbidities (Table 3). Similarly, increased PASP was also associated with increased risk of incident HF regardless of HIV status. Interestingly, there was no increased risk of heart failure among HIV-infected individuals without PH, which is inconsistent with prior reports, including from VACS (11). This likely reflects an increased risk of HF in the reference population (uninfected individuals with normal pulmonary pressure) who were referred for echocardiograms, rather than a lack of an association between HIV and HF. Taken together, these data suggest that HIV confers risk for increased PASP and mortality beyond that expected from chronically elevated LV pressure. Differences in the ability of the right ventricle to adapt to elevated afterload may explain higher mortality in HIV-infected veterans, but these data are not available in our cohort. These findings are important because PH due to LV disease is far more

Table 2. Clinical Features Associated with Increased Pulmonary Artery Systolic Pressure Stratified by HIV Status

Characteristic	HIV-infected (n = 2,831)		HIV-uninfected (n = 5,465)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age, per 10 yr	1.14 (1.05–1.24)*	1.13 (1.01–1.26)*	1.21 (1.13–1.28)*	1.06 (0.98–1.14)
Male sex	1.44 (0.81–2.56)	1.28 (0.66–2.45)	3.59 (2.14–6.04)*	3.16 (1.84–5.44)*
Race/ethnicity				
African American vs. white	1.59 (1.33–1.91)*	1.38 (1.11–1.71)*	1.55 (1.36–1.76)*	1.48 (1.28–1.72)*
Hispanic vs. white	0.68 (0.47–0.99)	0.62 (0.41–0.94)*	0.72 (0.57–0.92)*	0.84 (0.65–1.08)
Other vs. white	1.20 (0.71–2.01)	1.52 (0.86–2.69)	0.94 (0.60–1.48)	1.27 (0.78–2.06)
Hypertension	2.15 (1.53–3.02)*	1.48 (0.98–2.24)	1.69 (1.18–2.41)*	0.73 (0.50–1.07)
Diabetes mellitus	1.61 (1.36–1.90)*	1.23 (1.01–1.50)*	1.77 (1.57–2.00)*	1.24 (1.08–1.42)*
Dyslipidemia	0.89 (0.74–1.07)	0.98 (0.80–1.20)	0.90 (0.79–1.02)	0.81 (0.71–0.94)*
Smoking				
Current vs. never	1.51 (1.22–1.86)*	1.41 (1.11–1.81)*	1.06 (0.91–1.24)	1.02 (0.84–1.23)
Former vs. never	1.50 (1.15–1.94)*	1.36 (1.04–1.79)*	1.18 (1.00–1.40)*	1.06 (0.88–1.27)
VACS Index, 5 points	1.07 (1.05–1.08)*	†	1.10 (1.08–1.11)*	†
HCV infection	1.11 (0.94–1.31)	0.91 (0.74–1.12)	1.11 (0.96–1.29)	1.04 (0.87–1.23)
Renal disease, ml/min/1.73 m ²				
eGFR 30–59 vs. ≥60	1.31 (1.04–1.65)*	1.08 (0.84–1.41)	2.00 (1.71–2.34)*	1.37 (1.15–1.64)*
eGFR < 30 vs. ≥60	3.02 (2.33–3.92)*	2.04 (1.50–2.79)*	3.13 (2.52–3.88)*	1.65 (1.28–2.13)*
BMI, kg/m ²				
BMI < 18.5 vs. 18.5–29.9	1.37 (0.98–1.93)	1.28 (0.86–1.89)	1.48 (1.01–2.18)*	1.32 (0.86–2.01)
BMI ≥ 30 vs. 18.5–29.9	0.94 (0.76–1.16)	0.94 (0.74–1.20)	1.22 (1.08–1.38)*	1.21 (1.05–1.39)
Anemia, g/dl				
Hb 12–13.9 vs. ≥14	1.20 (0.98–1.48)	0.97 (0.77–1.22)	1.48 (1.28–1.70)*	1.14 (0.98–1.33)
Hb 10–11.9 vs. ≥14	1.73 (1.38–2.17)*	1.05 (0.80–1.38)	2.32 (1.95–2.75)*	1.42 (1.17–1.73)*
Hb < 10 vs. ≥14	2.03 (1.51–2.74)*	1.05 (0.72–1.52)	3.15 (2.42–4.08)*	1.69 (1.25–2.29)*
Alcohol dependence/abuse	1.19 (1.01–1.41)*	1.05 (0.86–1.29)	1.03 (0.91–1.17)	0.98 (0.85–1.14)
COPD	1.61 (1.36–1.91)*	1.28 (1.05–1.56)*	1.81 (1.60–2.05)*	1.40 (1.22–1.61)*
HF				
EF > 50 vs. no HF	4.30 (3.00–6.16)*	3.32 (2.25–4.88)*	4.38 (3.41–5.62)*	2.96 (2.27–3.85)*
EF ≤ 50 vs. no HF	3.50 (2.71–4.52)*	2.90 (2.19–3.84)*	3.33 (2.72–4.08)*	2.74 (2.21–3.40)*
No EF vs. no HF	3.50 (2.80–4.37)*	2.77 (2.14–3.59)*	4.20 (3.63–4.86)*	3.08 (2.61–3.64)*
Stroke	1.09 (0.78–1.52)	0.85 (0.58–1.24)	1.11 (0.89–1.39)	0.84 (0.66–1.06)
Coronary heart disease	1.55 (1.31–1.83)*	1.07 (0.88–1.32)	1.70 (1.51–1.92)*	1.03 (0.89–1.19)
Atrial fibrillation	1.46 (1.16–1.85)*	0.97 (0.74–1.29)	1.76 (1.52–2.03)*	1.16 (0.98–1.36)
Cancer	1.27 (0.99–1.63)	1.30 (0.99–1.71)	1.25 (1.03–1.52)*	1.05 (0.85–1.31)
CD4 cell count, mm				
200–499 vs. ≥500	1.03 (0.82–1.28)	0.87 (0.69–1.11)	—	—
<200 vs. ≥500	1.35 (1.06–1.73)*	1.14 (0.85–1.52)	—	—
HIV-1 RNA copies, ml				
500–999 vs. <500	1.51 (0.96–2.37)	1.53 (0.93–2.49)	—	—
≥1,000 vs. <500	1.33 (1.06–1.66)*	1.19 (0.89–1.58)	—	—
ART regimen				
NRTI + NNRTI vs. no ART	0.83 (0.65–1.05)	0.83 (0.63–1.10)	—	—
NRTI + PI vs. no ART	0.79 (0.65–0.95)*	0.93 (0.74–1.16)	—	—
Other vs. no ART	0.87 (0.61–1.25)	0.98 (0.66–1.46)	—	—

Definition of abbreviations: ART = antiretroviral therapy; BMI = body mass index (calculated as weight in kilograms divided by height in meters squared); CI = confidence interval; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EF = ejection fraction; HCV = hepatitis C virus; HF = heart failure; NNRTI = nonnucleoside reverse-transcriptase inhibitor; NRTI = nucleoside reverse-transcriptase inhibitor; OR = odds ratio; PI = protease inhibitor; VACS = Veterans Aging Cohort Study.

Adjusted analyses include age, sex, race/ethnicity, hypertension, diabetes, dyslipidemia, HCV infection, smoking status, renal disease, BMI, anemia, alcohol dependence or abuse, COPD, congestive heart failure, stroke, coronary heart disease, atrial fibrillation, and cancer. Analyses in the HIV-infected group also include HIV-specific biomarkers and ART regimens. Because of concerns regarding collinearity, VACS Index was not included in the adjusted model. * $P < 0.05$.

†VACS Index cannot be calculated for uninfected individuals.

common than PAH. Thus, studies investigating the mechanisms of HIV-associated PH should also focus on PH in patients with LV disease, not just PAH.

Understanding why the combination of HIV and increased PASP is associated with higher mortality may lead to mechanistic

insights in pulmonary vascular disease in uninfected individuals. Some studies report an association between HIV-specific biomarkers and ART (e.g., higher viral load) and PH (5, 27–31). Reports for the latter association are conflicting and typically involve patients with confirmed

or presumed PAH (32–34). In this study, high viral load and lower CD4 cell count were associated with increased PASP. This is consistent with our prior work in VACS linking high HIV viral loads and immunodeficiency with an increased risk of acute myocardial infarction and HF

Table 3. Mortality Rates and Risk According to HIV and Increased Pulmonary Artery Systolic Pressure Status

Group	N	Deaths	Rate/1,000 PY (95% CI)	Mortality Risk Fully Adjusted (95% CI)*	Mortality Risk VACS Index Adjusted (95% CI) [†]	Mortality Risk Fully Adjusted and FIB4 (95% CI) [‡]
HIV−, PASP ≤ 40 mm Hg	3,987	887	54 (51–58)	1.00	1.00	1.00
HIV−, PASP > 40 mm Hg	1,478	645	127 (117–137)	1.51 (1.36–1.68)	1.88 (1.70–2.08)	1.51 (1.36–1.68)
HIV+, PASP ≤ 40 mm Hg	2,049	698	92 (86–99)	1.37 (1.24–1.53)	1.14 (1.03–1.27)	1.35 (1.21–1.50)
HIV+, PASP > 40 mm Hg	782	426	178 (162–196)	1.81 (1.60–2.05)	1.70 (1.50–1.93)	1.78 (1.57–2.01)
Subanalysis In subset with no prevalent comorbidities [§]						
HIV−, PASP ≤ 40 mm Hg	689	58	18 (14–24)	1.00	1.00	1.00
HIV−, PASP > 40 mm Hg	79	15	43 (24–70)	2.00 (1.12–3.58)	1.66 (0.94–2.93)	2.04 (1.14–3.65)
HIV+, PASP ≤ 40 mm Hg	460	101	52 (42–63)	2.10 (1.48–2.98)	1.40 (0.99–1.98)	2.06 (1.45–2.94)
HIV+, PASP > 40 mm Hg	66	24	99 (64–148)	3.49 (2.10–5.80)	2.07 (1.25–3.42)	3.61 (2.17–6.01)

Definition of abbreviations: CI = confidence interval; FIB4 = Fibrosis 4 index; PASP = pulmonary artery systolic pressure; PY = patient years; VACS = Veterans Aging Cohort Study.

*Adjusted for age, sex, race/ethnicity, hypertension, diabetes, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides, hepatitis C virus infection, smoking status, renal disease, body mass index, anemia, alcohol dependence or abuse, chronic obstructive pulmonary disease, congestive heart failure, stroke, coronary heart disease, atrial fibrillation, and cancer.

[†]Adjusted for VACS Index.

[‡]Adjusted for everything in * as well as the FIB4.

[§]In these analyses, we removed individuals with a prevalence of any of the following: diabetes, renal disease, chronic obstructive pulmonary disease, congestive heart failure, stroke, or coronary heart disease, and thus the mortality risk is not adjusted for these characteristics.

(11, 16, 35, 36). ART exposure or specific regimen was not associated with adjusted risk of increased pulmonary pressure; however, our cross-sectional study does not

account for the intensity of duration of ART use.

Consistent with prior studies (37), increased PASP was significantly associated

with diabetes, COPD, and renal function. The magnitude of association between some clinical features (smoking, obesity, male sex) differed significantly

Figure 1. Adjusted risk of mortality according to pulmonary artery systolic pressure (PASP) value and HIV status. Restricted cubic spline plots of all-cause mortality according to PASP value and (A) HIV-infected, and (B) uninfected veterans. The reference group for HIV-infected individuals are HIV-infected subjects with a PASP value of 15 mm Hg and similar for uninfected individuals. There is a nonlinear relationship between PASP and mortality in HIV-infected veterans and higher risk at lower values compared with uninfected veterans. Adjusted for age, sex, race/ethnicity, hypertension, diabetes, dyslipidemia, hepatitis C virus infection, smoking status, renal disease, body mass index, anemia, alcohol dependence or abuse, chronic obstructive pulmonary disease, congestive heart failure, stroke, coronary heart disease, atrial fibrillation, and cancer. Values in brackets are 95% confidence intervals. HR = hazard ratio.

by HIV status. Black veterans accounted for 61% of the HIV-infected subjects with increased PASP but only 51% of the total HIV-infected cohort. Black race was associated with a higher prevalence of PASP in uninfected veterans. These findings suggest that PASP risk factor profiles differ by HIV status and that black individuals are particularly vulnerable, which may aid clinician decision-making regarding PH screening and surveillance intervals in this high-risk population.

Our findings related to pulmonary pressure and mortality have important implications for HIV-infected patients and their providers. The prevalence of elevated PASP in referral populations using echocardiographic estimates ranges from 6 to 57% (4, 5, 31, 38–41). Given this broad range, it is unclear whether a cutoff applied to the general population for recommending invasive evaluation (e.g., 40 mm Hg) is appropriate for HIV-infected individuals or others at risk for PH. Current recommendations are largely empiric, vary based on expert

opinion, and do not specifically relate to risk in specific PH causes. In VACS participants, the adjusted risk of death increases at a lower PASP value in HIV-infected versus HIV-uninfected veterans. Moreover, lower PASP values were associated with a high risk of mortality in HIV-infected veterans. In contrast to uninfected veterans, the effect of PASP in HIV-infected veterans was nonlinear, with disproportionate risk occurring between values of roughly 30 to 50 mm Hg. Accordingly, these data should prompt reconsideration of the current approaches to PH diagnosis, screening, and surveillance in HIV-infected individuals. Echocardiographic estimates of PASP are particularly relevant for HIV-infected individuals and their providers in endemic areas where catheterization laboratories are rare and risk projection is necessarily based on echocardiographic data. One speculation for the observation of increased mortality among HIV-infected individuals with PH is that HIV may lower the threshold for right ventricular decompensation because of effects on the

immune system, HIV medications, or both. The relative hazard of mortality between HIV-infected and uninfected veterans declined at higher PASP estimates in our cohort (Figure 2). This may reflect the inability of the right ventricle to compensate at high afterload regardless of HIV status. These findings require validation, ideally in cohorts with a greater proportion of women, but suggest that the spectrum and magnitude of risk may differ between infected and uninfected individuals.

Limitations

We studied an echocardiography referral population; therefore, we are unable to comment on the prevalence of PH in the general HIV community. PASP estimates were not collected according to a common protocol or interpreted by a central laboratory. Nonetheless, our study involves a large nationwide sample with clinically interpreted echocardiograms from which management decisions are made, making our findings highly generalizable. The correlation between Doppler PASP estimates and invasive hemodynamics is imperfect, which may lead to misclassification of PH status (42). Unfortunately, hemodynamic data in the HIV VA population are sparse (43). We do not have data on right ventricular function, which is an important mediator of mortality in the setting of increased pulmonary pressure. This is an important focus of future work as we refine our data extraction tool. Similarly, data on exposure to PAH-specific therapies are not currently available in VACS. We did not have access to data on self-reported substance use, including exposure to cocaine and methamphetamine, which are risk factors for PH. We were unable to ascertain the indication for echocardiography. Although indications may have differed between HIV-infected and -uninfected veterans, the distribution of PASP between groups was nearly identical, suggesting lack of a systematic bias. Finally, an inherent limitation to a veteran population is the relative paucity of women.

Conclusions

HIV-infected people with high HIV viral loads or low CD4 cell counts have a higher prevalence of elevated PASP

Figure 2. Incremental change in adjusted risk by pulmonary artery systolic pressure (PASP) value. Point estimates and 95% confidence intervals represent the hazard ratios of death at each PASP comparing HIV-infected to uninfected veterans. Incremental risk is highest at lower values and remains higher in HIV-infected veterans at all values. This model includes PASP, HIV status, and the interaction between PASP and HIV status, along with adjustment for age, sex, race/ethnicity, hypertension, diabetes, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides, hepatitis C virus infection, smoking status, renal disease, body mass index, anemia, alcohol dependence or abuse, chronic obstructive pulmonary disease, congestive heart failure, stroke, coronary heart disease, atrial fibrillation, and cancer.

than uninfected people. In HIV-infected people, mortality risk increases with increasing PASP values and is present even at lower values of PASP than previously recognized. These findings support the need for future work examining

the mechanisms of developing increased PASP in HIV-infected people as well as the causes driving the associated mortality risk. Importantly, these findings may provide rationale for HIV-specific thresholds for invasive evaluation and

inform future recommendations for screening and surveillance of HIV-infected individuals for PH. ■

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